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CLINICAL PRACTICE

Consensus guidelines on perioperative management of malignant hyperthermia suspected or susceptible patients from the European Malignant Hyperthermia Group

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Summary

Malignant hyperthermia is a potentially fatal condition, in which genetically predisposed individuals develop a hypermetabolic reaction to potent inhalation anaesthetics or succinylcholine. Because of the rarity of malignant hyperthermia and ethical limitations, there is no evidence from interventional trials to inform the optimal perioperative management of patients known or suspected with malignant hyperthermia who present for surgery. Furthermore, as the concentrations of residual volatile anaesthetics that might trigger a malignant hyperthermia crisis are unknown and manufacturers' instructions differ considerably, there are uncertainties about how individual anaesthetic machines or workstations need to be prepared to avoid inadvertent exposure of susceptible patients to trigger anaesthetic drugs. The present guidelines are intended to bundle the available knowledge about perioperative management of malignant hyperthermia-susceptible patients and the preparation of anaesthesia workstations. The latter aspect includes guidance on the use of activated charcoal filters. The guidelines were developed by members of the European Malignant Hyperthermia Group, and they are based on evaluation of the available literature and a formal consensus process. The most crucial recommendation is that malignant hyperthermia-susceptible patients should receive anaesthesia that is free of triggering agents. Providing that this can be achieved, other key recommendations include avoidance of prophylactic administration of dantrolene; that preoperative management, intraoperative monitoring, and care in the PACU are

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unaltered by malignant hyperthermia susceptibility; and that malignant hyperthermia patients may be anaesthetised in an outpatient setting.

Keywords: activated charcoal filter; ambulatory surgery; anaesthesia workstation; malignant hyperthermia; perioperative care

Editor's key points

- There is no evidence from interventional trials regarding optimal perioperative management of patients known or suspected malignant hyperthermia.
- These guidelines were developed by members of the European Malignant Hyperthermia Group based on available literature and a formal consensus process.
- Malignant hyperthermia-susceptible patients should receive anaesthesia that is free of triggering agents using a prepared anaesthetic workstation.
- Other key recommendations for malignant hyperthermia-susceptible patients include avoidance of prophylactic administration of dantrolene; applicability of standard preoperative, intraoperative, and post-anaesthesia care; and appropriateness of anaesthesia in an outpatient setting.

Malignant hyperthermia (MH) is a subclinical, potentially fatal pharmacogenetic disorder that manifests initially as skeletal muscle hyper-metabolism and sustained contraction, but which secondarily affects all organs when susceptible individuals are exposed to triggering agents. Triggering agents include *all* the potent inhalation anaesthetic agents available for general anaesthesia (e.g. desflurane, sevoflurane, isoflurane, halothane, and methoxyflurane) and the depolarising neuromuscular blocking agent succinylcholine.[1–3] The European Malignant Hyperthermia Group (EMHG) is the largest international multidisciplinary professional organisation for those with an interest in clinical and scientific aspects of MH, with members from South America, South Africa, Australia, and New Zealand, in addition to Europe. One of the aims of the EMHG is the development of guidelines to improve outcomes for MH-susceptible patients. Previous guidelines have been aimed at improving outcomes of MH crises, but we are frequently contacted for advice from anaesthesiologists tasked with providing anaesthesia for a known MH-susceptible patient.[2,3] Patients may be suspected of being at risk of developing MH based on a personal or family history: susceptibility may be confirmed through identification of genetic variants known to be pathogenic for MH or through *in vitro* muscle contracture tests.[4] Malignant hyperthermia-susceptible patients presenting for surgery require special precautions and perioperative preparations to minimise the likelihood of triggering an MH crisis.[5,6]

Therefore, the statements and recommendations of this practice guideline refer to those activities undertaken to care and prepare for anaesthesia of MH-suspected or known MH-susceptible patients. The purpose is to improve perioperative management to ensure the highest possible safety. The guidelines apply to patients of all ages with either proven MH susceptibility or patients who are at risk of being MH susceptible (i.e. untested relatives of known MH-susceptible individuals, patients with myopathies associated with MH, and patients with a personal or family history of a possible MH reaction that has not been formally investigated). Throughout the remainder of this guideline, all patients with known or suspected MH susceptibility are referred to as *MH-susceptible patients* irrespective of whether their MH status has been proved or not.

Methods

This guideline was conceived and developed by the members of the Executive Committee of the EMHG. A writing group was convened (for details, see the author list of this paper), and members of the Board of Directors of the EMHG, representing MH diagnostic centres around the world, were invited to be additional members of an expert consensus panel. Guideline development was informed by the Appraisal of Guidelines for Research & Evaluation proposals.[7,8]

The scope of the guideline was defined using the Population, Intervention, Comparator, and Outcome (PICO) framework. The PICO framework was used to inform a literature search up to and including July 2020 using the bibliographic databases MEDLINE (via PubMed) and Embase (via Ovid). Search terms (including MESH terms [PubMed] and EMTREE terms [Embase]) were malignant hyperthermia, workstation, preparation, perioperative management, and ambulatory. To identify 'grey literature', the authors and contributors were asked to search for publications outside MEDLINE and Embase that include relevant entries (guideline networks, congress abstracts and publications, and recommendations of scientific organisations). As a result, RCTs, analyses of registry data, non-randomised comparative and descriptive studies, case series, cohort studies, systematic reviews, experimental studies, expert opinion, manufacturers' instructions, presentations at the annual scientific meetings of the EMHG, and recommendations of national societies and organisations were evaluated.

Modified Delphi process

To generate consensus amongst members of the expert panel, a web-based adaptation[7] of the RAND/UCLA Appropriateness Method was used.[9] This approach includes a 9-point scale of appropriateness assigned to a series of statements: from '1=completely inappropriate' to '9=completely appropriate'. The level of agreement is expressed as the disagreement index (DI) that is based on the inter-percentile range (difference between the 66th and 33rd centiles appropriateness score) with a correction factor for asymmetry. A median score of 7 or more indicated an appropriate statement, whilst the lower the DI the greater was the consensus. To demonstrate strong agreement or consensus, the lower DI of <0.5 was compared with the generally accepted agreement DI <1.0. Besides rating of the statements, each panel member could submit additional

Table 1 Results of agreement to the statements after two rounds of the Delphi process by panel members. Median=median appropriateness score with range of 1 for 'completely inappropriate' to 9 for 'completely appropriate'; GRADE: assessment of strength of recommendation (1=strong; 2=weak) and quality of evidence (a=high, b=moderate, and c=low) according to the GRADE network definitions. GRADE, Grading of Recommendations Assessment, Development and Evaluation; MH, malignant hyperthermia.

Statement	Median		Disagreement index		Grade
	Round 1	Round 2	Round 1	Round 2	
1. The indications for pharmacological premedication are the same for MH-susceptible patients as those not predisposed to MH.	9	9	0	0	1c
2. Only trigger-free anaesthesia should be used in all MH-susceptible patients.	9	9	0	0	1a
3. Minimum monitoring for general anaesthesia for an MH-susceptible patient is electrocardiography, pulse oximetry, noninvasive blood pressure, inspired oxygen concentration, inspired/expired CO_2 with capnography, airway pressure, ventilatory frequency, minute ventilation, peripheral nerve stimulator when neuromuscular blocking agents are used, and continuous core body temperature measurement for procedures of any duration and (where available) depth of anaesthesia monitoring.	9		0.29		1c
3. If trigger-free anaesthesia is provided, an MH-susceptible patient will not need any extra monitoring during anaesthesia compared with a patient with the same condition and preoperative status, but not predisposed to MH.		9		0	1c
4. MH-susceptible patients can receive standard care in the recovery room (PACU) after surgery.	9	9	0	0	1c
5. MH-susceptible patients may be anaesthetised in an outpatient setting avoiding all volatile anaesthetics and succinylcholine whilst following national guidelines for ambulatory general anaesthesia.	9	9	0	0	1c
6. Specific pre- or postoperative blood tests are not necessary in MH-susceptible patients.	9	9	0.13	0	1c
7. A baseline (preoperative) serum creatine kinase measurement may be useful.	5	0.59			
7. Question was deleted for Round 2.					
8. The vaporisers should be removed before the anaesthesia machine is flushed.	9	9	0	0	1c
9. The anaesthetic breathing circuit (T-circuit, circle circuit, and reservoir bag) and soda lime should be changed for uncontaminated equipment before the anaesthesia machine is flushed.	9	9	0	0	1c
10. The anaesthesia machine and breathing circuit should be flushed with a maximum fresh gas flow of at least 10 L min^{-1} (oxygen, air, or any mixture) throughout the preparation period.	9	9	0	0	1c
11. The tidal volume should be set at 600 ml and ventilatory frequency at 15 bpm when mechanical ventilation is used during machine preparation.	7		0.44		2c
11. In the absence of alternative recommendations from the manufacturer, during machine preparation the tidal volume can be set at 600 ml and ventilatory frequency at 15 bpm for an adult patient when mechanical ventilation is used.		9		0	1c
12. When a new anaesthesia machine is supplied, the manufacturer should provide with it the period of flushing time required to decontaminate the machine of inhalation anaesthetic.	9		0		1c
12. When a new anaesthesia machine is supplied, the manufacturer should provide information on how the machine is decontaminated of inhalation anaesthetic.		9		0	1c
13. The anaesthesia machine should be flushed for the period of time recommended by the manufacturer.	9	9	0	0	1c
14. After the anaesthesia machine has been flushed for the recommended period of time, it should not be set to standby mode before use.	9	9	0	0	1c
15. Activated charcoal filters (licensed for this purpose), which effectively reduce volatile anaesthetic concentrations to <5 ppm, should be used.	9		0		1c
15. Anaesthetic charcoal filters, licensed for this purpose, which effectively reduce volatile anaesthetic concentrations to <5 ppm, may be used to minimise the anaesthesia machine preparation time.		9		0	1c

Continued

Table 1 Continued

Statement	Median		Disagreement index		Grade
	Round 1	Round 2	Round 1	Round 2	
16. Before siting the activated charcoal filters, the anaesthetic breathing circuit (T-circuit, circle circuit, and reservoir bag) and soda lime should be changed for uncontaminated equipment and the anaesthesia machine flushed.	9	9	0	0	1c
17. To flush the anaesthesia machine before siting the activated charcoal filters, use high flow (oxygen, air, or any mixture) >10 L min^{-1} for 90 s.	9	9	0	0	1c
18. Anaesthetic charcoal filters should be placed on the inspiratory and expiratory limbs of circle systems.	9	9	0	0	1c
19. The fresh gas flow should be maintained at 10 L min^{-1} for the first 30 min of clinical use, and then reduced to 3 L min^{-1}.	7		0.60		2c
19. We recommend reducing the fresh gas flow from >10 to 3 L min^{-1} when activated charcoal filters are placed and breathing circuit and soda-lime canister are changed.		9		0.29	1c
20. For clinical use, usual fresh gas flows can be used with a minimum of 1 L min^{-1}.	7		0.75		2c
20. After activated charcoal filters are placed and breathing circuit and soda-lime canister are changed, usual fresh gas flows can be used with a minimum of 1 L min^{-1}.		9		0.13	1c
21. The activated charcoal filters should be kept in place during the entire general anaesthesia procedure.	9	9	0	0	1c
22. There is no need to replace the activated charcoal filters after 12 h of use.	5	0.59			
22. Question was deleted for Round 2					

freehand comments. The writing group composed 22 statements for the first Delphi round based on the literature review and a preliminary survey of the consensus panel. The Delphi process was planned to continue until a stopping criterion (DI <0.5 or failure of the DI to improve by more than 15% between rounds) was reached for each statement. After each round, the median appropriateness score and DI for each statement were calculated and sent to panel members along with the de-identified raw scores and comments of other panel members. With successive rounds, the wording of statements could be adjusted in response to a high DI or freehand comments.

Guideline recommendations

The writing group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) network classification for strength of recommendation (1=strong; 2=weak) and for quality of evidence (a=high; b=moderate; c=low).[10] The maximum achievable quality of evidence is 'c' if the results are solely based on the consensus process. A median appropriateness score of >7.9 and DI <0.5 indicated a strong recommendation (GRADE 1c), whilst a median appropriateness score >6.9 and DI >0.5 but <1.0 indicated a weak recommendation.

Results

The first electronic literature search revealed 351 results, 322 of which were excluded after careful analysis. Additional guideline entries regarding relevant search terms, national guidelines, manufacturers' instructions, or congress abstracts were recruited from or contributed by the members of the expert consensus panel.[6,11,12]

The number of people invited to the Delphi process was 26 in each round, with 23 panel members (82%) responding in Round 1 and 25 (96%) in Round 2, before one of the stopping criteria was reached for each statement. In Round 1, 35 freehand comments on unclear or ambiguous statements were returned and later processed for the second Delphi round. Based on the resulting DI, appropriateness score, and suggested improvements, two statements concerning baseline measurement of serum creatine kinase and the duration of use of activated charcoal filters (ACFs) were deleted and six statements were modified for Round 2. After Round 2, 28 freehand statements were returned. The median appropriateness score, DI, and grade of evidence after each round are shown in Table 1. In using all results of the Delphi process to construct the guideline after Round 2, the writing group suggested to combine three statements (16–18) into a single recommendation to avoid repetitive content. A further three statements (12–14) regarding manufacturers' instructions in preparation of the anaesthesia machine were used to clarify the context of other statements/recommendations rather than being used as recommendations themselves. The resulting draft guideline, which included a total of 15 recommendations, was sent to all panel members who unanimously agreed with the guideline.

Figure 1 summarises the results of the consensus process that relate to the preparation of an anaesthetic workstation without and with ACFs.

Discussion

Preoperative evaluation and care

For safety reasons, it is always advisable to clarify the MH status of suspected patients according to the EMHG diagnostic guidelines through referral to an MH diagnostic centre.[4] However, anaesthesia should not be refused or postponed, regardless of definitive MH diagnostic testing, if this would risk progression of the surgical pathology. In these circumstances,

it may still be valuable to consult an MH expert who may be able to exclude the risk of MH based on the available history. Many MH diagnostic centres maintain a registry of cases and families that may also be helpful if the suspicion of MH arises from a family history. If an increased risk of developing MH under anaesthesia cannot be excluded, then the patient should *always* be treated as MH susceptible.

The standard anaesthetic assessment should be extended to include direct questioning for a history of rhabdomyolysis, which is more common in MH-susceptible individuals than the general population.[13,14] A small minority of MH-susceptible patients have an associated clinical myopathy.[15,16] In these cases, further preoperative evaluation and management will be dictated by the myopathy rather than MH susceptibility *per se*.

Indications for pharmacological premedication are the same for MH-susceptible patients as those not predisposed to MH

(Strong recommendation)

There is no evidence that psychological stress can trigger symptoms associated with MH in MH-susceptible patients. This means that specific or increased anxiolytic therapy before surgery is not necessary in these patients. The use of preoperative prophylactic treatment of MH patients with dantrolene, orally or intravenously, is unnecessary and associated with unpleasant side-effects of dantrolene.[17]

Choice of anaesthetic drugs

Only trigger-free anaesthesia should be used in all MH-susceptible patients

(Strong recommendation)

Regional anaesthesia (e.g. spinal, epidural, and peripheral nerve block) or local anaesthesia is a good choice for MH-susceptible patients. If unsuitable, trigger-free general anaesthesia, avoiding volatile anaesthetics and succinylcholine, is mandatory. Proper preparation of the anaesthetic machine (see standard practice or use of ACFs for preparation) before anaesthesia is also obligatory to avoid inadvertent exposure to volatile anaesthetics.[1]

Intraoperative monitoring

If trigger-free anaesthesia is provided, then an MH-susceptible patient will not need any extra monitoring during anaesthesia

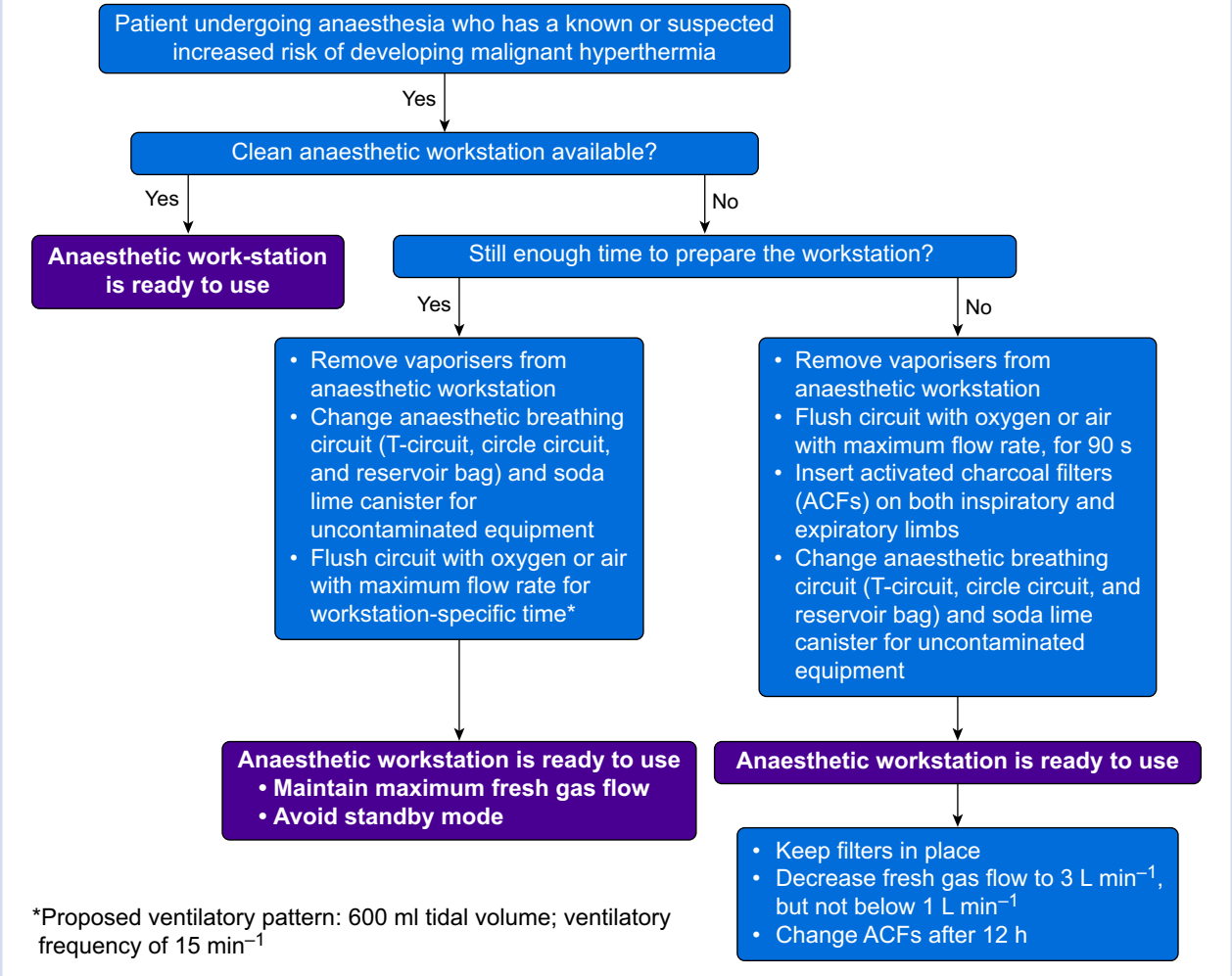

Fig 1. Schematic representation of the workflow required to prepare the anaesthetic workstation for a malignant hyperthermia-susceptible patient.

Table 2 Study recommendations for preparing anaesthesia machines for MH-susceptible patients and manufacturers' instructions. #Recommended preparation time according to manufacturers' instructions. ## with ABS™, Advanced Breathing System; D, desflurane; S, sevoflurane; I, isoflurane; PT, preparation time; VA, volatile anaesthetics; VF, ventilatory frequency.

Company	Type (reference)	Washout profile (VA)	Preparation time at fresh gas flow of 10 L min^{-1} (min)	Preparation time at maximum fresh gas flow (min)	Vaporiser	Breathing circuit	Carbon dioxide canister; absorbent	Special instructions	Activated charcoal filter investigation
GE Healthcare	Ohmeda Excel 210[27,28]	I; H	7		Remove	New	New absorbent	Replace ventilator, bellows, and tubing	No
GE Healthcare	Ohmeda Modulus I[29]	I; H	5		Remove	New	No change	Avoid previously used ventilator	No
GE Healthcare	Ohmeda Modulus II[30]	H	15		Remove	New	New absorbent	No reference to ventilator	No
GE Healthcare	Datex Ohmeda AS/3[31]	I	<30 (PT to reach 2 ppm)		Remove	New	New absorbent	Ventilator VT 1l; VF 10 bpm; I:E 1:2	No
GE Healthcare	Aestiva[32–34]	D; S; I	51 (S) 71 (D)	28 (S)## 35 (D)## 31 (I)##	Remove	New	New absorbent	Ventilator VT 500–700 ml; VF 10–12 bpm with ABS	Yes
GE Healthcare	Aisys[32–34]	D; S; I	55 (S) 69 (D)	13 (S)## 22 (D)## 11 (I)##	Remove	New	New absorbent	Ventilator VT 500–700 ml; VF 10–12 bpm with ABS	Yes
GE Healthcare	Avance, Amingo[32,35,36]	S	22 (S)	15 (D)## 5–37 (S)## 3 (I)##	Remove	New	New absorbent	Ventilator VT 500–600 ml; VF 15 bpm with ABS	Yes
Dräger	Narkomed GS[37]	S	18		Remove	New	New absorbent	Ventilator VT 600 ml; VF 10 bpm; I:E 1:2	Yes
Dräger	Primus[28,35,38]	S; I	74 (S) 12–70 (I)	42 (S) 52 (I)	Remove	New	New absorbent	Ventilator VT 500 ml; VF 15 bpm	No
	Primus[39]	D; S		3	Remove	New	New absorbent	Initial flush 90 s without vaporiser and additional 10 min flush between removal and replacement (including ventilator diaphragm)	Yes
Dräger	Apollo/Aestiva[40]	D; S; I	53/27 (D) 46/48 (S) 84/54 (I)		Remove	New	New absorbent	Replace with autoclaved ventilator diaphragm and integrated breathing system	Yes
Dräger	Fabius[37]	S	104		Remove	New	New absorbent	Ventilator VT 600 ml; VF 10 bpm; I:E 1:2	Yes
Dräger	Fabius GS[27,41]	I	50		Remove	New	New absorbent	Ventilator VT 500 ml; VF 15 bpm; replace with autoclaved ventilator diaphragm and tubing	No
Dräger	Fabius CE[41]	S	22		Remove	New	New absorbent	Ventilator VT 500 ml; VF 15 bpm	No
Dräger	Zeus[35,42,43]	D; S; I	36–85	16–34	Remove	New	New absorbent		Yes

Continued

Table 2 Continued

Company	Type (reference)	Washout profile (VA)	Preparation time at fresh gas flow of 10 L min^{-1} (min)	Preparation time at maximum fresh gas flow (min)	Vaporiser	Breathing circuit	Carbon dioxide canister; absorbent	Special instructions	Activated charcoal filter investigation
Dräger	Perseus[35]	S; I		14	Remove	New	New absorbent	Ventilator VT 500 ml; VF 15 bpm	No
Siemens	Kion[27]	I; H	23–25 (PT to reach 10 ppm)		Remove/off	New	Exclude	Ventilator VT 500 ml; VF 15 bpm	No
Maquet	Flow-i[35]	S		48 (120)[#]	Remove	New	New absorbent	Ventilator VT 500 ml; VF 15 bpm; PEEP 0	No
Air Liquide	Felix[35]	S		144	Remove	New	New absorbent	Ventilator VT 500 ml; VF 15 bpm	No
Heinen Löwenstein	Leon[35]	S		112	Remove	New	New absorbent	Ventilator VT 500 ml; VF 15 bpm	No

compared with a patient with the same condition and preoperative status, but not predisposed to MH

(Strong recommendation)

Most MH-monitoring guidelines recommend standard use of ECG, pulse oximetry, blood pressure, body core temperature, and (for general anaesthesia) capnography.[18–20] Use of further or extended monitoring depends on the type of anaesthesia or comorbidities.

Postoperative care

MH-susceptible patients can receive standard care in the recovery room (PACU) after surgery

(Strong recommendation)

There is no evidence to support elective ICU management of MH-susceptible patients after uneventful trigger-free anaesthesia. Factors other than MH susceptibility will determine the length of stay in the recovery room or the decision to transfer the patient to the ICU. Furthermore, environmental concentrations of volatile agents in the PACU are too low to trigger an MH event.[21]

Outpatient surgery

MH-susceptible patients may be anaesthetised in an outpatient setting avoiding all volatile anaesthetics and succinylcholine whilst following national guidelines for ambulatory general anaesthesia

(Strong recommendation)

As long as criteria of national guidelines for ambulant general anaesthesia are fulfilled, trigger-free anaesthesia (total i.v. or regional anaesthesia) is provided, and a 'clean' anaesthetic workstation is used, there is no reason to refuse outpatient surgery. For decades, several MH diagnostic centres have safely performed trigger-free general anaesthesia for diagnostic muscle biopsies in MH-susceptible patients in outpatient settings.[22–24]

Laboratory blood samples

Specific pre- or postoperative blood tests are not necessary in MH-susceptible patients

(Strong recommendation)

Specific blood tests for MH-susceptible patients are not routinely necessary. However, preoperative measurement of creatine kinase activity or serum potassium and myoglobin concentrations may be reasonable if there is a history of elevated resting creatine kinase concentration, muscular symptoms (cramps and myalgia), or rhabdomyolysis.

Preparation of the anaesthetic workstation for MH-susceptible patients

The lowest vapour concentration of volatile anaesthetic that can induce MH in humans remains unknown for ethical reasons. Even though the maximum safe concentration of 5 ppm for humans was defined arbitrarily, this threshold is generally accepted. In human muscle biopsies from MH patients, higher levels (up to 50 ppm) were tolerated in *in vitro* experiments, but the clinical anaesthetic vapour concentration of <5 ppm should be retained for forensic reasons until more valid data are available.[1]

There is no universal protocol that covers all workstations with consistent washout time to sufficiently remove volatile anaesthetic contamination in the breathing circuit. The

minimum preparation time is unknown for any workstation not reported in the literature or by its manufacturer. In some urgent situations (e.g. emergency operation in MH-susceptible patients), one may need to minimise preparation time of the anaesthetic workstation, which may pose a challenge with modern machines. Their complexity can make it difficult to reduce residual anaesthetic concentration in a simple and timely manner.

Standard practice for preparation

In cases of MH susceptibility, adequate preparation of the anaesthetic workstation is mandatory. This section of the guideline is valid for the standard preparation of modern anaesthetic workstations for all MH-susceptible patients. The aim is to keep inspired volatile anaesthetic concentration at 5 ppm or less. This threshold is commonly accepted to be 'safe' regardless of country-specific legal standards.

There are two traditional ways of obtaining an anaesthetic workstation free of residual volatile anaesthetics:

(i) Use of a dedicated clean machine never exposed to volatile anaesthetic agents
(ii) Flushing the workstation according to the manufacturer or expert recommendations

To store and maintain a dedicated 'vapour-free' workstation only for trigger-free anaesthesia are rarely an option because of the cost, storage, and servicing requirements of modern anaesthesia workstations. Because of complex internal components (plastic and rubber parts that are able to adsorb and release volatile anaesthetic substances), the time needed to flush the workstation differs from one model to another.[25] Modern, more complex anaesthetic workstations seem to require a prolonged time to wash out volatile agents compared with older generations of machines.[26] Preparing workstations should be planned well ahead, as it may be very time-consuming. When a new anaesthesia machine is supplied, the manufacturer should provide specific information on how the machine is decontaminated of inhalation anaesthetic. However, in some modern anaesthetic workstation manuals, there is insufficient information or only a 'health warning' that residual concentrations of volatile anaesthetics may affect MH patients.

Table 2 gives an overview of existing data from the literature of how to clean common anaesthetic workstations that are frequently used in European hospitals.[27–43]

Vaporisers should be removed before the anaesthesia machine is flushed

(Strong recommendation)

Most vaporisers have a significant reservoir for volatile anaesthetic agents that must be removed from the workstations when preparing it for use with MH-susceptible patients. This also prevents accidental misuse.

Anaesthetic breathing circuit (T-circuit, circle circuit, and reservoir bag) and soda lime should be changed for uncontaminated equipment before the anaesthesia machine is flushed

(Strong recommendation)

This recommendation is in accordance with almost all manufacturers' instructions and received a strong recommendation in the Delphi rounds, although there was also a suggestion to change the breathing circuit *after* the flushing process in order not to contaminate the new breathing circuit and to remove and leave out the soda-lime canister before and during the flushing period. From the theoretical point of view, this approach seems to be appropriate as well, but because of the complexity and high volume of the systems, it is recommended to replace the breathing circuits first. When available (e.g. in Ohmeda workstations), the fresh gas hose should also be replaced. Only a few workstations need replacement of the ventilator and bellows.[25,27,28]

Anaesthesia machine and breathing circuit should be flushed with a maximum fresh gas flow of at least 10 L min^{-1} (oxygen, air, or any mixture) throughout the preparation period

(Strong recommendation)

The anaesthesia machine should be flushed for the period of time recommended by the manufacturer. Each anaesthetic workstation requires a specific amount of time for removing residual volatile anaesthetic agents by fresh gas flushing (oxygen or air), which widely differs between the types of anaesthetic machines. Most companies and organisations recommend a time-specific flush of fresh gas (oxygen or air) at a flow of 10 L min^{-1}. However, there are also signs that rebound effects can occur when the maximal fresh gas flow of the machine (11–18 L min^{-1}) is decreased to 10 L min^{-1}. Therefore, we adapted the recommendation to a flow rate of >10 L min^{-1} and to the maximum flow of the workstation. After the anaesthesia machine has been flushed for the recommended period of time, flushing should be continued (it should not be set to 'standby mode' before use).[26–33,35–45]

In the absence of specific recommendations from the manufacturer, during machine preparation, the tidal volume can be set at 600 ml and ventilatory frequency at 15 bpm for an adult patient when mechanical ventilation is used

(Strong recommendation)

When a new anaesthesia machine is supplied, the manufacturer should provide information on how the machine is decontaminated of inhalation anaesthetic. The anaesthesia machine should be flushed for the period of time recommended by the manufacturer. Besides manufacturer's instructions, there are also different study recommendations concerning tidal volumes (500–700 ml) and ventilatory frequencies (10–15 bpm), which are not evidence based (Table 2).[27,28,32,33,35–38,41,42,45] For reasons of safety, we recommend a ventilatory pattern of 600 ml tidal volume and a ventilatory frequency of 15 bpm. Flow rates, tidal volume, and ventilatory frequency should be maintained for the entire period of flushing.

Use of ACFs to prepare an anaesthetic workstation

A third, more recent, option to prepare the anaesthetic workstation for MH patients is to use ACFs. Activated charcoal filters do not clean the complete workstation, but adsorb residual volatile anaesthetic in the breathing circuit. Commercially available filters containing 50 ml of granular activated charcoal have been shown to decrease quickly, safely, and cost-efficiently the concentration of anaesthetic vapours to <5 ppm in 2–3 min, and to guarantee this low concentration in the course of general anaesthesia.[12,34] Because of conflicts of interests (lack of nationwide availability and expenses), our guidelines do not mandate the stocking of ACFs, but if they are available, the EMHG suggests using them for the preparation of the anaesthetic workstation for an MH-susceptible patient.[34,39,40,46–50]

Activated charcoal filters licensed for this purpose, which effectively reduce volatile anaesthetic concentrations to <5 ppm, may be used to minimise anaesthesia machine preparation time

(Strong recommendation)

After the anaesthesia vaporiser has been turned off and the anaesthesia machine has been flushed using high flow (>10 L min^{-1}; oxygen, air, or any mixture) for 90 s, ACFs should be placed on the inspiratory and expiratory limbs. Afterwards, the breathing circuit (T-circuit, circle circuit, and reservoir bag) should be replaced and the soda-lime canister should be changed

(Strong recommendation)

This statement corresponds to the manufacturers' instructions for ACFs. The required anaesthetic vapour concentration of <5 ppm can be attained within 1–1.5 min after inserting just one ACF and flushing the breathing circuit for 90 s with 10 L min^{-1} fresh gas even without changing uncontaminated equipment. With the exception of the flushing time of only 90 s, we do recommend the same procedures as for the standard preparation of the workstation when using ACFs.

The capacity of only one charcoal filter, placed on the inspiratory limb, is sufficient to ensure the limit of <5 ppm in contaminated anaesthetic circuits, even without flushing or changing of the circuit. However, for safety reasons (e.g. ACF inserted on the wrong limb), ACFs should be placed on both inspiratory and expiratory limbs.

Reduce fresh gas flow from >10 to 3 L min^{-1} when ACFs are placed and breathing circuit and soda-lime canister are changed

(Strong recommendation)

Rebreathing from the circuit absorber system by reducing fresh gas flow may improve humidity and airway heat of inspired gases. It has been demonstrated that the concentration of sevoflurane remains unchanged (<2 ppm) despite decreasing fresh gas flow from 10 to 2 L min^{-1} (with only one ACF on the inspiratory limb of a changed circuit and breathing bag, without changing the soda-lime canister). Furthermore, it has been demonstrated that the concentrations of sevoflurane and desflurane remain <5 ppm when using a 1 L min^{-1} fresh gas flow over the course of 24 h.[50] This would conflict with the ACF manufacturer's instructions, but it shows that a 10 L min^{-1} fresh gas flow is not necessary.

After ACFs are placed and breathing circuit and soda-lime canister are changed, usual fresh gas flows can be used with a minimum of 1 L min^{-1}

(Strong recommendation)

Although a 3 L min^{-1} fresh gas flow is recommended by the manufacturer of ACFs, new data show that a 1 L min^{-1} fresh gas flow was also sufficient to keep trace amounts of volatile anaesthetic at safe levels. The higher soda-lime absorption of CO_2 may further improve air conditioning of the breathing gas (humidity and airway heat).[40,50]

Activated charcoal filters should be kept in place during the entire general anaesthesia procedure

(Strong recommendation)

Only by maintaining gas flow at 10 L min^{-1} will the volatile agent concentration remain <5 ppm if ACFs are removed after 1 h. There are no publications that assess long-term testing of ACFs for decontamination of anaesthetic workstations, but there are indications that ACFs are able to ensure anaesthetic vapour concentrations <5 ppm for 12 and 24 h (i.e. more than the duration of most operations).[34,51,52] The manufacturer's instruction is that the ACFs are changed every 12 h.[12]

Conclusions

These guidelines from the EMHG describe how to minimise the risk of triggering an MH reaction when preparing to anaesthetise MH-susceptible patients. This includes preparation of the anaesthetic workstation for safe and trigger-free general anaesthesia, with and without the use of ACFs. The guidelines are based on available evidence and the opinions of MH experts from a large group of laboratories studying MH around the world.

Disclaimer

These guidelines represent the views of the EMHG. It is based on careful consideration and interpretation of available evidence at the time on which they were agreed. The statements are intended principally for clinicians and hospital pharmacists involved in the management of MH, who are encouraged to take these statements into account when exercising their professional judgement. The guidelines do not override the individual responsibility for clinicians to make appropriate decisions and take actions according to the circumstances of individual patients.

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Authors' contributions

Data acquisition: PMH, KPEG, AH, DB, HR
Drafting of paper: HR, PMH, SH, BB, TG, KPEG
Final approval of the version to be published: all authors
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All authors substantially contributed to the conception and design of the work and the interpretation of data, critically revised the submitted material, approved the submitted version, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately resolved.

Declarations of interest

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References

1. Hopkins PM. Malignant hyperthermia: pharmacology of triggering. *Br J Anaesth* 2011; **107**: 48–56
2. Glahn KP, Ellis FR, Halsall PJ, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. *Br J Anaesth* 2010; **105**: 417–20
3. Glahn KPE, Bendixen D, Girard T, et al. Availability of dantrolene for the management of malignant

hyperthermia crises: European Malignant Hyperthermia Group guidelines. *Br J Anaesth* 2020; **125**: 133–40
4. Hopkins PM, Rüffert H, Snoeck MM, et al. The European Malignant Hyperthermia Group guidelines for the investigation of malignant hyperthermia susceptibility. *Br J Anaesth* 2015; **115**: 531–9
5. Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg* 2010; **110**: 498–507
6. Wappler F. S1-leitlinie maligne hyperthermie: update 2018 [S1 guidelines on malignant hyperthermia: update 2018]. *Anaesthesist* 2018; **67**: 529–32
7. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016; **352**: i1152
8. Hopkins PM, Cooke PJ, Clarke RC, et al. Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions. *Br J Anaesth* 2019; **123**: e29–37
9. Fitch K, Bernstein SJ, Aguilar MD, et al. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND Corp.; 2001
10. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924–6
11. Drägerwerk AG & Co. KGaA. *Instruction Manual Perseus A 500SW 2.0n*. Lübeck: Drägerwerk AG & Co. KGaA; 2020. p. 120
12. Dynasthetics. Prepare any anesthesia machine for susceptible patients in less than 90 seconds. Available from: https://www.dynasthetics.com; Accessed 28 July 2020.
13. Wappler F, Fiege M, Steinfath M, et al. Evidence for susceptibility to malignant hyperthermia in patients with exercise-induced rhabdomyolysis. *Anesthesiology* 2001; **94**: 95–100
14. Dlamini N, Voermans NC, Lillis S, et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. *Neuromuscul Disord* 2013; **23**: 540–8
15. Klingler W, Rueffert H, Lehmann-Horn F, Girard T, Hopkins PM. Core myopathies and the risk of malignant hyperthermia. *Anesth Analg* 2009; **109**: 1167–73
16. Stamm DS, Aylsworth AS, Stajich JM, et al. Native American myopathy: congenital myopathy with cleft palate, skeletal anomalies, and susceptibility to malignant hyperthermia. *Am J Med Genet A* 2008; **146A**: 1832–41
17. Hackl W, Mauritz W, Winkler M, Sporn P, Steinbereithner K. Anaesthesia in malignant hyperthermia-susceptible patients without dantrolene prophylaxis: a report of 30 cases. *Acta Anaesthesiol Scand* 1990; **34**: 534–7
18. Litman RS, Smith VI, Larach MG, et al. Consensus statement of the Malignant Hyperthermia Association of the United States on unresolved clinical questions concerning the management of patients with malignant hyperthermia. *Anesth Analg* 2019; **128**: 652–9
19. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. 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. *Anesth Analg* 2014; **119**: 1359–66
20. Jones PM, Allen BN, Cherry RA, et al. Association between known or strongly suspected malignant hyperthermia susceptibility and postoperative outcomes: an observational population-based study. *Can J Anaesth* 2019; **66**: 161–81
21. Heiderich S, Thoben C, Dennhardt N, et al. Low anaesthetic waste gas concentrations in postanaesthesia care unit: a prospective observational study. *Eur J Anaesthesiol* 2018; **35**: 534–8
22. Brandom BW. Ambulatory surgery and malignant hyperthermia. *Curr Opin Anaesthesiol* 2009; **22**: 744–7
23. Litman RS, Joshi GP. Malignant hyperthermia in the ambulatory surgery center: how should we prepare? *Anesthesiology* 2014; **120**: 1306–8
24. Yentis SM, Levine MF, Hartley EJ. Should all children with suspected or confirmed malignant hyperthermia susceptibility be admitted after surgery? A 10-year review. *Anesth Analg* 1992; **75**: 345–50
25. Targ AG, Yasuda N, Eger EI. Solubility of I-653, sevoflurane, isoflurane, and halothane in plastics and rubber composing a conventional anesthetic circuit. *Anesth Analg* 1989; **69**: 218–25
26. Kim TW, Nemergut ME. Preparation of modern anesthesia workstations for malignant hyperthermia-susceptible patients: a review of past and present practice. *Anesthesiology* 2011; **114**: 205–12
27. Petroz GC, Lerman J. Preparation of the Siemens KION anesthetic machine for patients susceptible to malignant hyperthermia. *Anesthesiology* 2002; **96**: 941–6
28. Prinzhausen H, Crawford MW, O'Rourke J, Petroz GC. Preparation of the Drager Primus anesthetic machine for malignant hyperthermia-susceptible patients. *Can J Anesth* 2006; **53**: 885–90
29. Beebe JJ, Sessler DI. Preparation of anesthesia machines for patients susceptible to malignant hyperthermia. *Anesthesiology* 1988; **69**: 395–400
30. McGraw TT, Keon TP. Malignant hyperthermia and the clean machine. *Can J Anesth* 1989; **36**: 530–2
31. Schönell LH, Sims C, Bulsara M. Preparing a new generation anaesthetic machine for patients susceptible to malignant hyperthermia. *Anaesth Intensive Care* 2003; **31**: 58–62
32. Kim TW, Wingate JR, Fernandez AM, Whitaker E, Tham RQ. Washout times of desflurane, sevoflurane and isoflurane from the GE Healthcare Aisys® and Avance®, Carestation®, and Aestiva® anesthesia system. *Paediatr Anaesth* 2013; **23**: 1124–30
33. Jones C, Bennett K, Kim TW, Bulger TF, Pollock N. Preparation of Datex-Ohmeda Aestiva and Aisys anaesthetic machines for use in malignant hyperthermia susceptible patients. *Anaesth Intensive Care* 2012; **40**: 490–7
34. Bilmen JG, Gillies RI. Clarifying the role of activated charcoal filters in preparing an anaesthetic workstation for malignant hyperthermia-susceptible patients. *Anaesth Intensive Care* 2014; **42**: 51–8
35. Cottron N, Larcher C, Sommet A, et al. The sevoflurane washout profile of seven recent anesthesia workstations for malignant hyperthermia susceptible adults and infants: a bench test study. *Anesth Analg* 2014; **119**: 67–75
36. Brünner HW, Pohl S, Grond S. Washout of sevoflurane from the GE Avance and Amingo Carestation anesthetic machines. *Acta Anaesthesiol Scand* 2011; **55**: 1118–23
37. Gunter JB, Ball J, Than-Win S. Preparation of the Dräger Fabius anesthesia machine for the malignant-hyperthermia susceptible patient. *Anesth Analg* 2008; **107**: 1936–45

38. Crawford MW, Prinzhausen H, Petroz GC. Accelerating the washout of inhalational anesthetics from the Drager Primus anesthetic workstation: effect of exchangeable internal components. *Anesthesiology* 2007; **106**: 289–94
39. Müller-Wirtz LM, Godsch C, Sessler DI, Volk T, Kreuer S, Hüppe T. Residual volatile anesthetics after workstation preparation and activated charcoal filtration. *Acta Anaesthesiol Scand* 2020; **64**: 851–6
40. Birgenheier N, Stoker R, Westenskow D, Orr J. Activated charcoal effectively removes inhaled anesthetics from modern anesthesia machines. *Anesth Analg* 2011; **112**: 1363–70
41. Shanahan H, O'Donoghue R, O'Kelly P, Synnott A, O'Rourke J. Preparation of the Drager Fabius CE and Drager Zeus anaesthetic machines for patients susceptible to malignant hyperthermia. *Eur J Anaesthesiol* 2012; **29**: 229–34
42. Neira VM, Al Madhoun W, Ghaffari K, Barrowman N, Berrigan P, Splinter W. Efficacy of Malignant Hyperthermia Association of the United States-recommended methods of preparation for malignant hyperthermia-susceptible patients using Dräger Zeus anesthesia workstations and associated costs. *Anesth Analg* 2019; **129**: 74–83
43. Cooper JB, Philip JH. More on anesthesia machines and malignant hyperpyrexia. *Anesthesiology* 1989; **70**: 561–2
44. Reber A, Schumacher P, Urwyler A. Effects of three different types of management on the elimination kinetics of volatile anaesthetics. Implications for malignant hyperthermia treatment. *Anaesthesia* 1993; **48**: 862–5
45. Whitty RJ, Wong GK, Petroz GC, Pehora C, Crawford MW. Preparation of the Drager Fabius GS workstation for malignant hyperthermia-susceptible patients. *Can J Anesth* 2009; **56**: 497–501
46. Jantzen JP, Eck J, Kleemann PP. An activated charcoal filter for eliminating volatile anesthetics. A contribution to the management of malignant hyperthermia. *Anaesthesist* 1989; **38**: 639–41
47. Martin JW, Welliver MD. Activated charcoal adsorption of volatile anesthetic agents for anesthesia machine preparation of malignant hyperthermia susceptible patients. *AANA J* 2013; **81**: 169–71
48. Martin TW, Block Jr FE. How will we ever know if our machine is adequately flushed? *Anesth Analg* 2014; **119**: 9–10
49. Sabouri AS, Lerman J, Heard C. Effects of fresh gas flow, tidal volume, and charcoal filters on the washout of sevoflurane from the Datex Ohmeda (GE) Aisys, Aestiva/5, and Excel 210 SE Anesthesia Workstations. *Can J Anaesth* 2014; **61**: 935–42
50. Choi YJ, Min SH, Park JJ, Cho JE, Yoon SZ, Yoon SM. Comparison of the temperature and humidity in the anesthetic breathing circuit among different anesthetic workstations: updated guidelines for reporting parallel group randomized trials. *Medicine (Baltimore)* 2017; **96**, e7239
51. Thoben C, Dennhardt N, Krauß T, et al. Preparation of anaesthesia workstation for trigger-free anaesthesia: an observational laboratory study. *Eur J Anaesthesiol* 2019; **36**: 851–6
52. Stoker R, Romankowski M, Kyle M, Burk JA. *12 Hour evaluation of filters to prepare an anesthesia machine for malignant hyperthermia susceptible patients*. San Francisco, CA: Proceedings of Anesthesiology 2013; 2013A4094

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