Successful treatment of a Malignant Hyperthermia (MH) crisis depends on early diagnosis and aggressive treatment. The onset of a reaction can be within minutes of induction or may be more insidious. Previous uneventful anaesthesia does not exclude MH. The steps below are intended as an aide memoire. Presentation may vary and treatment should be modified accordingly. Know where the dantrolene is stored in your theatre. Treatment can be optimised by teamwork.

**Diagnosis - consider MH if:**
1. Unexplained, unexpected increase in end-tidal CO\(_2\) together with
2. Unexplained, unexpected tachycardia together with
3. Unexplained, unexpected increased in oxygen consumption

Masseter muscle spasm, and especially more generalised muscle rigidity after suxamethonium, indicate a high risk of MH susceptibility but are usually self-limiting.

**Take measures to halt the MH process:**
1. Remove trigger drugs, turn off vapourisers, use high fresh gas flows (oxygen), use a new, clean non-rebreathing circuit, hyperventilate. Maintain anaesthesia with intravenous agents such as propofol until surgery completed.
2. Dantrolene; give 2-3 mg.kg\(^{-1}\) i.v. initially and then 1 mg.kg\(^{-1}\) PRN.
3. Use active body cooling but avoid vasoconstriction. Convert active warming devices to active cooling, give cold intravenous infusions, cold peritoneal lavage, extracorporeal heat exchange.

**Monitor:**
ECG, \(\text{SpO}_2\), end-tidal CO\(_2\), invasive arterial BP, CVP, core and peripheral temperature, urine output and pH, arterial blood gases, potassium, haematocrit, platelets, clotting indices, creatine kinase (peaks at 12-24h).

**Treat the effects of MH:**
1. Hypoxaemia and acidosis: 100% O\(_2\), hyperventilate, sodium bicarbonate.
2. Hyperkalaemia: sodium bicarbonate, glucose & insulin, i.v. calcium chloride (if in extremis).
3. Myoglobinemia: forced alkaline diuresis (aim for urine output >3 ml.kg\(^{-1}\).h\(^{-1}\), urine pH >7.0).
5. Cardiac arrhythmias: procainamide, magnesium, amiodarone (avoid calcium channel blockers - interaction with dantrolene).

**ICU management:**
2. Assess for renal failure and compartment syndrome.
3. Give further dantrolene as necessary (recrudescence can occur for up to 24h).
4. Consider other diagnoses, e.g. sepsis, phaeochromocytoma, myopathy.

**Late management:**
1. Counsel patient and/or family regarding implications of MH.
2. Refer patient to MH Unit.
Guidelines for management of a malignant hyperthermia (MH) crisis

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INTRODUCTION
Malignant hyperthermia (MH) is a rare pharmacogenetic autosomal dominant disease. This is generally unmasked when a susceptible individual is exposed to general anaesthesia and it can present during or after delivery of anaesthesia. The common precipitants are volatile anaesthetic agents and succinylcholine (suxamethonium). In these individuals there is increased skeletal muscle oxidative metabolism leading to increased oxygen consumption, increased production of carbon dioxide and increased body temperature. Circulatory collapse and death frequently follow if the condition is not recognised and treated promptly.

EPIDEMIOLOGY
The incidence of MH is 1 in 4500 to 1 in 60000 under general anaesthesia. It occurs worldwide and in all racial groups.

PATHOGENESIS
Sixty to seventy per cent of cases are due to a mutation in ryanodine receptor (RYR1) in the sarcoplasmic reticulum (SR), the site of calcium storage in skeletal muscle cells. In health RYR1 receptors mediate release of calcium from the SR into the muscle cell cytoplasm, causing muscle contraction. Defective RYR1 receptors allow exaggerated calcium release and also have a higher threshold for deactivation and muscle relaxation. Other mutations have also been recognised to cause MH.

Various musculoskeletal abnormalities like scoliosis, hernias or strabismus have been stated to be associated with MH susceptibility, but an analysis of over 2500 patients has not supported this. Based on a recent review, the association of MH in patients with dystrophies (Duchenne muscular dystrophy and Becker dystrophy) has been found to be very weak. There is also a very weak link to disorders such multiple sclerosis, myasthenia gravis, and other neuromuscular disorders and enzymopathies.

COMMENTARY ON ALGORITHMS

1 – Clinical features of MH
The clinical features of MH are not specific. Prompt diagnosis depends on knowledge of features and recognising those in a pattern consistent with an evolving MH reaction and exclusion of other differential causes. Increasing end-tidal CO₂ is usually the first sign of MH. Tachycardia, mixed respiratory and metabolic acidosis are present due to the hypermetabolic state. There is an accompanied increase in oxygen consumption. Total body or truncal rigidity could be an isolated presentation. Masseter spasm may be an isolated feature after succinylcholine. Increased temperature is usually a delayed sign.

Masseter spasm
In the absence of a positive family history, susceptibility to MH may be suspected by exaggerated increase in the tension of the jaw muscles. Jaw stiffness after succinylcholine may be present in most individuals and is often more pronounced in children. When the jaw stiffness is prolonged and severe the condition is termed masseter spasm. There are reports showing a relationship between masseter spasm and MH susceptibility. When presented with this situation one should avoid the trigger agents mentioned below and follow the MH treatment guidelines. If the surgical procedure is non-urgent it should be aborted. The patient should be referred for testing and the family should be counselled.

2 - Trigger agents for MH

<table>
<thead>
<tr>
<th>Inhaled agents</th>
<th>Depolarising muscle relaxants</th>
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<tbody>
<tr>
<td>Desflurane</td>
<td>Succinylcholine</td>
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<tr>
<td>Enflurane</td>
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</tr>
<tr>
<td>Halothane</td>
<td></td>
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<tr>
<td>Isoflurane</td>
<td></td>
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<tr>
<td>Sevoflurane</td>
<td></td>
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<tr>
<td>Ether</td>
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</table>

Summary
Malignant hyperthermia (also termed as malignant hyperpyrexia) is a life threatening emergency.

More appropriately it is a “malignant hypermetabolic” disorder.

Increase in temperature is a hallmark of MH but it may be a late sign.

The operating room area and recovery area should be equipped with appropriate resuscitative measures and equipment.

Practice drills and simulation training are strongly recommended due to the rarity of this condition.

The importance of teamwork and communication is paramount to successful management of an MH crisis.
The breathing circuit should be changed and fresh gas flows increased. Hyperventilate with 100% oxygen at flows of 10 l.min$^{-1}$ or more. Consideration should be given to stopping the procedure unless it is an emergency.

3A - Dantrolene

This is the only available specific and effective treatment for MH.

Mechanism of action

Dantrolene is a skeletal muscle relaxant and has been shown, via action on the ryanodine receptor, to inhibit the calcium release channel of the skeletal muscle sarcoplasmic reticulum. This prevents the increase in intracellular calcium concentration. The molecular mechanism of action is unclear.

Presentation and reconstitution

Pharmacologically it is a hydantoin derivative, highly lipophilic and poorly soluble in water – it is therefore advisable to dedicate one to two members of staff with the specific role of preparing the dantrolene. It is available as 20mg lyophilized dantrolene sodium added to 3 grams of mannitol to improve water solubility. The contents of the vials have to be dissolved in 60ml of water. Prewarming the water (<39°C) may improve the solubility of dantrolene. This gives a final concentration of 0.33 mg.ml$^{-1}$ with a pH of 9.5. The prepared solution should be protected from light and stored at 15-25°C. Once reconstituted it should be used with 6 hours.

Mode of administration

The alkaline nature of the solution makes it irritant to veins and it should be injected through a large vein or a fast flowing infusion. Before administering the solution should be clear and devoid of any particles. Consider central venous access once the initial crisis is under control. A lot of help is needed to reconstitute dantrolene in a crisis. Call for help as soon as possible.

Pharmacokinetics and pharmacodynamics

Dantrolene is metabolized by liver microsomes to an active metabolite and excreted via urine and bile. The mannitol present in the formulation causes an osmotic diuresis and fluid shifts. A urinary catheter is usually necessary and helps monitoring of output and fluid balance. Watch carefully for rhabdomyolysis and renal failure.

Other indications for dantrolene

Dantrolene is also used in the management of neuroleptic malignant syndrome (NMS), spasticity, and ecstasy intoxication.

In patients with high risk for MH, prophylaxis with dantrolene is no longer recommended because oral therapy does not guarantee reliable plasma concentrations.

Side effects

These include muscle weakness, phlebitis, respiratory failure and gastrointestinal discomfort. It may prolong the duration of neuromuscular blockade and ventilatory support post-crisis is frequently needed.

Table 2. Safe anaesthetic agents for MH patients

<table>
<thead>
<tr>
<th>Intravenous anaesthetics</th>
<th>Narcotics (opioids)</th>
<th>Muscle relaxants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etomidate</td>
<td>Alfentanil</td>
<td>Atracurium</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Codeine</td>
<td>Cisatracurium</td>
</tr>
<tr>
<td>Methohexital</td>
<td>Diamorphine</td>
<td>Mivacurium</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Fentanyl</td>
<td>Vecuronium</td>
</tr>
<tr>
<td>Propofol</td>
<td>Hydromorphone</td>
<td>Pancuronium</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Meperidine</td>
<td>Rocuronium</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Methodone</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Morphin</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Naloxone</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oxycodone</td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled non-volatile agents</strong></td>
<td>Remifentanil</td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Sufentanil</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Neostigmine</td>
<td></td>
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<tr>
<td></td>
<td>Atropine</td>
<td></td>
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<tr>
<td></td>
<td>Glycopyrrolate</td>
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<td></td>
<td>Ephedrine</td>
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</tbody>
</table>

Figure 2. Dantrolene
3B - Active cooling
Commence active cooling of the patient if their core temperature is greater than 39°C. Consider cold intravenous fluids and lavage of the stomach, bladder or rectum, and body cavities that are open for surgery. Stop cooling once the core temperature is below 38°C to prevent a fall to less than 36°C.

4 - Monitoring
Monitoring during and after the MH crisis is very important. Core temperature, ECG (electrocardiogram), blood pressure (continuous and invasive if available), capnography, urine output, and observation of urine colour (for myoglobinuria) are essential. Blood gas analysis is useful, where available, to identify acidosis and initiate treatment with bicarbonate and hyperventilation to compensate for hypocapnia. Where available monitor the creatine kinase (CK) level during the crisis and every 6 hours for 36 hours.

5 – Treat the effects of MH
CK levels of more than 10,000IU.l\(^{-1}\) indicate significant rhabdomyolysis (skeletal muscle breakdown) and myoglobinuria and you can predict that acute kidney injury (AKI) is likely. AKI may be prevented or limited by aggressive hydration aiming to maintain a urine output of greater than 3ml.kg\(^{-1}\).h\(^{-1}\). Alkalization of the urine with a bicarbonate infusion may improve the solubility of myoglobin and is advocated in the algorithm, aiming to achieve a urine pH of greater than 7.0. Watch for hyperkalaemia.

Management of hyperkalaemia
Treat hyperkalaemia if the blood concentration is >5.5mmol.l\(^{-1}\) or there are ECG changes.

Treatment of hyperkalaemia involves:
- Infusion of glucose and insulin - 10 units of short-acting insulin (e.g. Actrapid) in 50ml 50% dextrose given over 30 minutes (monitor blood sugar),
- Calcium chloride or calcium gluconate 10ml of the 10% solution injected intravenously over 10 minutes,
- 1-2mEq.kg\(^{-1}\)sodium bicarbonate IV – (an 8.4% solution of sodium bicarbonate contains one mEq per ml),
- A \(\beta\)-agonist such as nebulised salbutamol (2.5-5mg).

Avoid calcium channel blockers, which may increase potassium levels or cause cardiac arrest in the presence of dantrolene.

6 – ICU and late management
After the initial management of the crisis, continuing intensive care is very important. Watch for signs for disseminated intravascular coagulation (DIC) and compartment syndrome. Supportive and symptomatic treatment is essential. Dantrolene treatment may be required for up to 24 hours post crisis (1mg.kg\(^{-1}\) every 4-6 hours). Consider differential diagnoses.

Neuroleptic malignant syndrome (NMS)
MH may be confused with NMS. The clinical features include the triad of pyrexia, rigidity and raised CK levels (indicating rhabdomyolysis). The presentation is usually over 24-72 hours and is the result of the central ant dopaminergic effects of major tranquilizer drugs. The most important clue to diagnosis is a careful patient history with particular emphasis on the medications being taken around the time of presentation. Most often it follows administration of neuroleptic drugs. It is postulated that dopamine D\(_2\) receptor antagonism by the neuroleptic drugs either block the heat loss pathway or produce heat due to extrapyramidal rigidity.

Treatment involves stopping the neuroleptic drug and is predominantly supportive and intensive care therapy. Dantrolene and dopamine agonists such as bromocriptine and amantidine, may be beneficial. Dantrolene is used intravenously in the same dose used for MH.

7 - Follow up and MH testing
An alert bracelet or information regarding this condition should always be carried by the susceptible patients. The patient and their family should be referred to an MH unit for testing and biopsy.

### Table 3. Differential diagnosis of suspected MH\(^{3}\)

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Neuroleptic malignant syndrome</td>
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<tr>
<td>Inadequate anaesthesia and analgesia</td>
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<tr>
<td>Inappropriate breathing circuit, fresh gas flow or ventilation</td>
</tr>
<tr>
<td>Infection or sepsis</td>
</tr>
<tr>
<td>Tourniquet ischaemia</td>
</tr>
<tr>
<td>Anaphylaxis</td>
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<tr>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td>Thyroid storm</td>
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<tr>
<td>Heat stroke</td>
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<tr>
<td>Other muscle disease</td>
</tr>
</tbody>
</table>

### ANAESTHESIA FOR MH SUSCEPTIBLE PATIENTS
- Consider alternatives to general anaesthesia.
- Schedule these patients as the first case on the operating list.
- Vaporizers should be removed from the anaesthesia machines.
- Breathing circuits should be new.
- The anaesthesia machine should be flushed at 10l.min\(^{-1}\) oxygen for at least 20 minutes. In addition the circuit may be used to ventilate a bag until there is no volatile agent is detected in the circuit.
- Avoid potential trigger agents for MH.
- MH crisis resuscitation drugs should be readily available in the vicinity of the operating room area.

### MANAGEMENT OF MH SUSCEPTIBLE PARTURIENT OR A POTENTIAL MH SUSCEPTIBLE FETUS\(^{6}\)
- Review history of the both parents to ascertain the risk for MH.
- The mother should be treated as MH susceptible until delivery of the fetus.
- The anaesthesia provider should be notified immediately when the patient arrives in the delivery unit.
• Epidural/spinal anaesthesia is strongly recommended if caesarean section or operative intervention is needed.
• If regional anaesthesia is contraindicated or general anaesthesia is indicated, non-trigger anaesthesia should be administered.
• Suxamethonium should be avoided and alternative muscle relaxants should be considered. Careful airway assessment should be performed. With the potential risk for aspiration, modified rapid sequence induction with non-depolarizing relaxant should be considered. Rocuronium in dose of 1mg.kg\(^{-1}\) can provide good intubating conditions within 60 seconds. If the facilities for awake intubation are available, it should be considered if difficult airway management is anticipated.
• Nitrous oxide in the form of Entonox may be used for labour analgesia.

**POSTOPERATIVE MONITORING OF MH SUSCEPTIBLE PATIENTS**
The presentation of MH varies in onset and course. It can be evident within ten minutes of administration of a trigger agent but may present up to several hours later. Care should be taken for monitoring these patients carefully in the recovery area. Studies advise that between three to six hours is safe.\(^3\) MH susceptible patients can be safely managed as day case patients.

**MH TROLLEY**
A dedicated MH trolley or box is worth considering and this must be restocked on a regular basis. A careful log of stocking and restocking should be maintained. There should be a dedicated person or group of people responsible for maintaining the contents of the trolley. This should contain adequate dantrolene, sterile water for mixing, sodium bicarbonate, glucose, insulin, calcium chloride, mannitol and temperature probes.

A flow chart diagram in laminated printed format should be available in the operating room environment for easy access and reference to follow treatment guidelines.

**SUMMARY**
• Adequate knowledge and a guideline-based approach is key to successful outcomes following unanticipated MH crisis.
• Management of known MH susceptible patient involves avoidance of trigger agents and adequate preparation. Consideration should be given to regional/local anaesthesia if feasible.
• MH susceptible patients should be observed in the recovery area for three hours.\(^3\)
• The operating room and recovery area should have dantrolene readily available and this must be restocked on a regular basis.
• Physicians and nurses should know where it is stored.

**REFERENCES AND FURTHER READING**