

van den Bersselaar Luuk (Orcid ID: 0000-0001-7735-3267)  
Reimann Jens (Orcid ID: 0000-0003-3349-6877)  
Tasca Giorgio (Orcid ID: 0000-0003-0849-9144)  
Vilchez Juan J (Orcid ID: 0000-0002-0532-2872)  
Jungbluth H. (Orcid ID: 0000-0002-7159-3427)

## Title

The European Neuromuscular Centre Consensus Statement on Anaesthesia in Patients with Neuromuscular Disorders

## Authors

Luuk R van den Bersselaar<sup>1,2\*</sup>, Luc Heytens<sup>3\*</sup>, Helga CA Silva<sup>4</sup>, Jens Reimann<sup>5</sup>, Giorgio Tasca<sup>6</sup>, Óscar Díaz-Cambronero<sup>7</sup>, Nicoline Løkken<sup>8</sup>, Anna Hellblom<sup>9</sup>, Philip M Hopkins<sup>10</sup>, Henrik Rueffert<sup>11</sup>, Børge Bastian<sup>11</sup>, Juan Jesus Vilchez<sup>12</sup>, Robyn Gillies<sup>13</sup>, Stephan Johannsen<sup>14</sup>, Francis Veyckemans<sup>15</sup>, Tino Muenster<sup>16</sup>, Andrea Klein<sup>17,18</sup>, Ron Litman<sup>19</sup>, Heinz Jungbluth<sup>20, 21</sup>, Sheila Riazzi<sup>22</sup>, Nicol C Voermans<sup>2\*</sup>, Marc MJ Snoeck<sup>1\*</sup>

<sup>1</sup>Department of Anesthesiology, Malignant Hyperthermia Investigation Unit, Canisius Wilhelmina Hospital Nijmegen, the Netherlands

<sup>2</sup>Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

<sup>3</sup>Departments of Anesthesiology and Neurology, University Hospital Antwerp; Malignant Hyperthermia Research Unit, University of Antwerp and Born Bunge Institute, Belgium

<sup>4</sup>Department of Surgery. Discipline Anaesthesia, Pain and Intensive Care. Malignant Hyperthermia Unit. University Federal São Paulo, Brazil

<sup>5</sup>Department of Neurology, University of Bonn Medical Centre, Bonn, Germany

<sup>6</sup>UOC di Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

<sup>7</sup>Department of Anesthesiology, Malignant Hyperthermia Unit, Perioperative Medicine Research Group, Hospital Universitari I Politècnic la Fe, Valencia, Spain.

<sup>8</sup>Copenhagen Neuromuscular Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

<sup>9</sup>Department of Intensive and Perioperative Care, Skåne University Hospital Lund, Sweden

<sup>10</sup>Leeds Institute of Medical Research at St James's, University of Leeds and Malignant Hyperthermia Investigation Unit, St James's University Hospital, Leeds, UK

<sup>11</sup>Helios Klinik Schkeuditz; Department of Anaesthesiology, Intensive Care, Pain Therapy; Malignant Hyperthermia Investigation Unit, University Hospital Leipzig, Germany

<sup>12</sup>Neuromuscular Center, Hospital UIP La Fe and ERN EURO-NMD. Neuromuscular Research Group at IIS La Fe and CIBERER

<sup>13</sup>Department of Anaesthesia and Pain Management, Malignant Hyperthermia Diagnostic Unit, Royal Melbourne Hospital, Victoria, Australia

<sup>14</sup>Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Center for Malignant Hyperthermia, University Hospital Wuerzburg, Wuerzburg, Germany

<sup>15</sup>Clinique d'Anesthésie pédiatrique, Hôpital Jeanne de Flandre, CHU de Lille, Lille, France

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/ene.15526](https://doi.org/10.1111/ene.15526)

This article is protected by copyright. All rights reserved.

<sup>16</sup>Department of Anesthesia and Intensive Care Medicine, Hospital of the Order of St. John of God, Regensburg, Germany

<sup>17</sup>Department of Pediatric Neurology, University Children's Hospital UKBB, Basel, Switzerland

<sup>18</sup>Division of Neuropaediatrics, Development and Rehabilitation, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland

<sup>19</sup>Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

<sup>20</sup>Department of Paediatric Neurology, Neuromuscular Service, Evelina's Children Hospital, Guy's & St. Thomas' Hospital NHS Foundation Trust, London, UK.

<sup>21</sup>Randall Centre for Cell and Molecular Biophysics, Muscle Signalling Section, Faculty of Life Sciences and Medicine, King's College London, London, UK

<sup>22</sup>Department of Anesthesiology and Pain Medicine, Malignant Hyperthermia Investigation Unit, University Health Network, University of Toronto, Canada

*\*Shared first / last author*

**Corresponding author:**

Luuk R van den Bersselaar, MD

[luuk.vandenbersselaar@radboudumc.nl](mailto:luuk.vandenbersselaar@radboudumc.nl)

Malignant Hyperthermia Investigation Unit

Department of Anaesthesiology, C40-01

Canisius Wilhelmina Hospital

Weg door Jonkerbos 100

6532 SZ Nijmegen

The Netherlands

**Total word count (including title page, references, and structured abstract): 9483**

**Running title:** Anaesthesia and Neuromuscular Disorders

**Key words:** Anaesthesia, malignant hyperthermia, myopathy, neuromuscular disorders, peri-operative care.

#### **ACKNOWLEDGEMENTS**

We are thankful to the ENMC who financially supported the 259<sup>th</sup> ENMC workshop. Several authors are members of the Radboud-NMD, NL-NMD, EURO-NMD and the TREAT-NMD consortium.

We would like to dedicate this consensus statement to the late Professor Ron Litman, he participated and contributed to the first workshop session.

#### **CONFLICT OF INTEREST**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The ENMC did not influence the content of this consensus statement.

## **ABSTRACT (word count 250; maximum 250)**

**Background** Patients with neuromuscular conditions are at increased risk of suffering peri-operative complications related to anaesthesia. There is currently little specific anaesthetic guidance concerning these patients. Here we present the European Neuromuscular Centre (ENMC) consensus statement on anaesthesia in patients with neuromuscular disorders as formulated during the 259<sup>th</sup> ENMC workshop on Anaesthesia in neuromuscular disorders.

**Methods** International experts in the field of (paediatric) anaesthesia, neurology and genetics were invited to participate in the ENMC workshop. A literature search was conducted in PubMed and EMBASE whose main findings were disseminated to the participants and presented during the workshop. Depending on specific expertise, participants presented the existing evidence and their expert opinion concerning anaesthetic management in six specific groups of myopathies and neuromuscular junction disorders. The consensus statement was prepared according to the Appraisal of Guidelines for REsearch & Evaluation (AGREE II) reporting checklist. The level of evidence has been adapted according to the Scottish Intercollegiate Guidelines Network (SIGN) grading system. The final consensus statement was subjected to a modified Delphi process.

**Results** A set of general recommendations valid for the anaesthetic management of patients with neuromuscular disorders in general have been formulated. Specific recommendations were formulated for 1) neuromuscular junction disorders; 2) muscle channelopathies (non-dystrophic myotonia and periodic paralysis); 3) myotonic dystrophy (type 1 and 2); 4) muscular dystrophies; 5) congenital myopathies and congenital dystrophies and 6) mitochondrial and metabolic myopathies.

**Conclusion** This ENMC consensus statement summarizes the most important considerations for planning and performing anaesthesia in patients with neuromuscular disorders.

**Key words:** Anaesthesia, malignant hyperthermia, myopathy, neuromuscular disorders, peri-operative care.

## INTRODUCTION

Patients with neuromuscular disorders (NMDs) are at increased risk of peri-operative complications related to anaesthesia. The reasons for this include associated cardiorespiratory morbidity; altered pharmacodynamics of anaesthetics and neuromuscular blocking agents (NMBAs); impaired temperature and glucose regulation; and specific risks associated with certain underlying genetic defects, or a combination of the above [1-3].

Whilst in recent years comprehensive standards of care have been formulated for the more common NMDs such as Duchenne Muscular Dystrophy (DMD) [4] and Spinal Muscular Atrophy (SMA) [5] there is lack of consensus guidance focusing on the anaesthetic management of NMDs throughout the range of neuromuscular conditions. Neurologists are often asked to share the specific considerations regarding their neuromuscular patients requiring surgery, anaesthesia or procedural sedation. Furthermore, neurologists who provide follow-up for patients with NMDs are well-placed to alert them to any perioperative risks specifically associated with their NMD, and the particular precautions to be taken in close liaison with anaesthesiologists [1].

We therefore present the European Neuromuscular Centre (ENMC) consensus statement on anaesthesia in patients with NMDs as discussed and formulated during the 259<sup>th</sup> ENMC Workshop on Anaesthesia in Neuromuscular Disorders [6]. This consensus statement provides a comprehensive and accessible overview with the aim to guide neurologists and anaesthesiologists, and to improve perioperative safety, optimize risk assessment and appropriate management of these patients.

## METHODS

Our approach to developing this consensus statement was performed according to the Appraisal of Guidelines for REsearch & Evaluation (AGREE II) reporting checklist [7].

### ENMC workshop

For the 259<sup>th</sup> ENMC workshop on Anaesthesia in NMDs, 30 international experts in the field of (paediatric) anaesthesia, neurology and genetics were selected by the workshop organisers (NV, MS, SR, HJ) based on their particular expertise in anaesthesia and/or NMDs and geographic balance. The ENMC research board approved the participants list. The virtual workshop consisted of three parts:

- I. Anaesthetic management of various NMDs (December 11<sup>th</sup>, 2020);
- II. New developments in the field of MH and increasing awareness (May 28<sup>th</sup>, 2021);
- III. Genetic counselling in patients with MH, rhabdomyolysis and related congenital myopathies (May 29<sup>th</sup>, 2021).

The comprehensive workshop report has been published separately [6] but did not allow for the inclusion of the full anaesthesia considerations included in this paper.

In preparation for the ENMC workshop, the organisers conducted a literature search covering the period January 1<sup>st</sup>, 2000 to July 14<sup>th</sup>, 2021 in PubMed and EMBASE using the methodological framework for scoping reviews [8]. The main findings of this literature search were disseminated to the participants and presented during the first part of the workshop. Furthermore, six couples of workshop participants were invited to present the existing evidence and their expert opinion for anaesthetic management in specific groups of NMDs (see below). These participants provided a written summary of their recommendations, which were merged to a preliminary version of this consensus statement. The presenters were subsequently invited to participate in a virtual meeting to discuss the preliminary consensus statement. After the initial evaluation, a revised version was distributed as a basis for discussion during the second part of the ENMC workshop. Subsequently, the preliminary consensus statement document was modified according to the discussion at the second workshop session and distributed by email. Consensus regarding the consensus statement content was reached after further communication by email. Finally, the consensus statement content was subjected to a modified Delphi process [9]. The whole process description is summarized in **Figure 1**.

### Modified Delphi process

The consensus statement drafted following the ENMC workshop and subsequent meetings was distributed among its co-authors (n = 22). They were asked to indicate their agreement for each recommendation on a 9-point scale (score 1: absolutely disagree, score 9: absolutely agree). Given the variable and specific expertise of the workshop participants, for some of them the full content of this consensus statement was not completely within their area of expertise. The participants were asked to withhold from voting if a specific

recommendation was not within their area of expertise. The level of agreement for each recommendation is presented as the median score and the percentage of participants who scored  $\geq 7$ . Consensus was defined as a median score of  $\geq 7$  and at least 70% of the respondents scoring the recommendation  $\geq 7$ .

### Focus and approach

This consensus statement entails general recommendations applicable to all patients with NMDs who need anaesthesia or procedural sedation and group-specific recommendations for:

- Neuromuscular junction disorders;
- Muscle channelopathies (non-dystrophic myotonia and periodic paralysis);
- Myotonic dystrophy (type 1 and 2);
- Muscular dystrophies;
- Congenital myopathies and dystrophies;
- Mitochondrial and metabolic myopathies.

Suggested relevant topics were risks, myopathy-related treatment, preoperative diagnosis and management, specific recommendation for anaesthesia including non-anaesthetic drugs used in the peri-operative phase and specific recommendations for postoperative care.

We restricted detailed clinical information concerning the six main groups of NMDs to what was essential for our purpose. For complementary disease-specific anaesthesia considerations we refer to the following databases:

- OrphanAnesthesia (<https://www.orphananesthesia.eu/en/>);
- Syndromes and rare diseases in paediatric anaesthesia (<http://tinyurl.com/PED-RARE>).

As we consider the ASA physical status classification [10] too unspecific for this particular patient population, we devised a practical risk assessment tool with a scoring matrix based on the “NARCO-SS-risk assessment tool” [11] and the matrix model developed by *Schieren et al.* [2].

### Level of evidence

The level of evidence for each recommendation has been adapted from the Scottish Intercollegiate Guidelines Network grading system [12] and is indicated in each paragraph:

- Level 1+ high quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with very low risk of bias;
- Level 1- meta-analyses, systematic reviews or RCTs with high risk of bias;
- Level 2+ systematic reviews or case control or cohort studies with low risk of bias;
- Level 2- case control or cohort studies with high risk of bias, animal studies;
- Level 3 case reports, case series;
- Level 4 expert opinion.

## RESULTS

### Modified Delphi process

A total of 20 participants (90.9%) responded. During the modified Delphi process, consensus was reached for all recommendations.

### **LEVEL 1: General recommendations for patients with neuromuscular disorders**

#### Surgery setting

Surgery and the associated need for sedation and/or anaesthesia pose a burden on the neuromuscular patient. They should only receive anaesthesia or sedation in settings with 24-hour high care facility [1-3].

Level of evidence: 4.

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 18 of 19 (94.7%), one respondent abstained from voting.

#### Anaesthesia technique

Surgery or diagnostic procedures should be performed using regional anaesthesia if possible, preferably as a single technique or alternatively in combination with general anaesthesia [1-3].

Level of evidence: 4

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 18 of 19 (94.7%), one respondent abstained from voting.

#### Preoperative assessment

A clear understanding of the confirmed or suspected neuromuscular diagnosis, degree of muscle weakness, current treatment and awareness of associated cardiorespiratory manifestations are paramount for the preoperative assessment. Cardiomyopathy or cardiac conduction defects can be part of certain NMDs [13-17]. Due to respiratory muscle weakness and spinal deformities there is an increased risk of restrictive lung disease [16, 18-20]. Furthermore, chronic hypoxaemia and pulmonary hypertension may lead to cor pulmonale, which must be considered during the preoperative examination [13]. This information can be partly obtained from the history or physical examination, but ancillary assessments may be necessary.

A careful preoperative examination, multisystem evaluation and clear communication among anaesthesiologists, surgeons, cardiologists, pneumologists and neurologists are crucial. During the preoperative assessment, specific attention should be paid to craniofacial abnormalities indicating a difficult airway [21]. Depending on the procedure, additional preoperative investigations may include ECG, chest X-ray, echocardiography, Holter examination, lung function tests (in the sitting and supine position), polysomnography and



blood tests including arterial blood gases, haemoglobin, electrolytes, lactate, creatine kinase (CK), liver and kidney function tests [1-3, 13-20, 22].

Some neuromuscular patients are treated with anticholinesterase inhibitors, anti-arrhythmic drugs, antisense oligonucleotides, steroids or other immunosuppressive agents [4, 23]. This needs to be recorded and evaluated during the preoperative assessment.

Level of evidence: 2+

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 19 of 19 (100%), one respondent abstained from voting.

#### Premedication

Patients with NMDs have an increased sensitivity to sedatives and anaesthetics [1-3]. Premedication with benzodiazepines may result in central respiratory depression, airway obstruction and/or worsening of muscle weakness. Premedication should therefore be avoided, and if absolutely required only be used in reduced doses with concurrent pulse oximetry (SpO<sub>2</sub>) and respiratory rate monitoring [1-3].

Level of evidence: 4

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 19 of 19 (100%), one respondent abstained from voting.

#### Preoperative fasting

Patients with NMDs should be scheduled for surgery as the first case of the day since prolonged fasting may cause hypoglycaemia, in particular in patients with reduced muscle mass [24-26].

Level of evidence 2+

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 14 of 16 (87.5%), four respondents abstained from voting.

Some NMDs are associated with gastro-intestinal dysmotility and dysphagia and the patient may not have an empty stomach [27]. Gastric ultrasound imaging could be used to evaluate the volume of gastric content before anaesthesia and adapt the induction technique accordingly [28].

Level of evidence 2+

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 12 of 16 (75%), four respondents abstained from voting.

#### Body temperature management

Anaesthesia causes drop in body temperature due to vasodilation and blunting of thermoregulatory reflexes. This effect is more pronounced in neuromuscular patients because of their reduced muscle mass. Moreover, hypothermia further increases sensitivity to sedatives, anaesthetics and non-depolarising NMBAs [29]. Preoperative warming reduces the fall in core temperature following induction of anaesthesia in the general population [30] and will be even more beneficial in patients with NMDs.

Level of evidence: 4

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 19 of 19 (100%), one respondent abstained from voting.

On the other hand, increased muscle activity (cramps, myotonia) or excessive external heating can result in hyperthermia with increased muscle tone, cramps and rhabdomyolysis. Therefore, continuous temperature monitoring is recommended.

Level of evidence: 4

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 18 of 18 (100%), two respondents abstained from voting.

#### General anaesthesia

Short-acting opioids, sedatives and hypnotics are preferred to minimize respiratory depression on emergence from anaesthesia [1-3].

Level of evidence: 4

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 18 of 18 (100%), two respondents abstained from voting.

#### Neuromuscular blocking agents

Based on their mechanisms of action, NMBAs can be divided into depolarising NMBAs and non-depolarising NMBAs [1]. Patients with an NMD are at greatest risk for succinylcholine-induced hyperkalaemia [31-34]. Hence, succinylcholine should not be used in patients with a known or suspected NMD.

Level of evidence: 2-

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 19 of 19 (100%), one respondent abstained from voting.

Most neuromuscular patients have an increased sensitivity to non-depolarising NMBAs because of the reduced muscle mass and strength. A lower initial dose may be sufficient to achieve adequate muscle relaxation. Duration of action is often prolonged and effects of residual relaxation are more severe than in normal patients [35-38]. The effect of NMBAs

should be measured by quantitative neuromuscular monitoring to prevent residual neuromuscular blockade following emergence from anaesthesia and extubation.

Level of evidence: 2+

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 18 of 18 (100%), two respondents abstained from voting.

When a non-depolarising NMBA is used, extubation and emergence from anaesthesia should be guided by a Train-Of-Four (TOF) ratio of 1.0. Any residual and potentially clinically relevant muscle relaxation at the end of the intervention should preferably be reversed with sugammadex as a specific pharmacological antagonist of rocuronium and vecuronium [39-41]. Due to the effectiveness of sugammadex, the latter two non-depolarising NMBAs should be given preference. When there is residual neuromuscular blockade after use of other NMBAs or sugammadex is unavailable, extubation and emergence from anaesthesia should be postponed until baseline muscular strength has recovered spontaneously. In this scenario, postoperative sedation and ventilatory support is necessary.

Level of evidence: 2-

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 14 of 15 (93.3%), five respondents abstained from voting.

Reversal of muscle relaxation using cholinesterase inhibitors is contra-indicated because of side-effects in myotonic dystrophies [42, 43] and some congenital myasthenic syndromes. Cholinesterase inhibitors (*e.g.* neostigmine) are undesirable in other neuromuscular patients because of the unpredictable pharmacodynamics and the increased sensitivity to NMBAs.

Level of evidence: 2-

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 12 of 16 (75%), four respondents abstained from voting.

#### Volatile anaesthetics

Volatile anaesthetics are only strictly contraindicated in patients with NMDs with variants in the *RYR1* gene because of the possibility of MH-susceptibility [44-50], unless the specific variant has been classified as benign for MH according to the ClinGen Variant Curation Expert Panel recommendations for *RYR1* pathogenicity classifications in MH-susceptibility [51]. Patients with variants in the *CACNA1S* and/or *STAC3* genes should be referred to an MH investigation centre for advice on the risk of MH before exposure to volatile anaesthetics.

Level of evidence: 2+

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 11 of 15 (73.3%), five respondents abstained from voting.

NMDs without these specific genetic backgrounds might be associated with other, rare adverse effects, such as anaesthesia-induced rhabdomyolysis (AIR) in DMD or Becker muscular dystrophy (BMD) patients [33, 34]. The prolonged effect of NMBAs when used in combination with volatile anaesthetics also has to be taken into account [52].

Level of evidence: 2+

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 18 of 18 (100%), two respondents abstained from voting.

Hence anaesthesiologists are advised against the prolonged use of volatile anaesthetics in patients with NMDs. Although often recommended as an alternative, total intravenous anaesthesia (TIVA, most frequently based on a propofol, short-acting benzodiazepines or dexmedetomidine-based technique in combination with short-acting potent opioids) has other risks [53-56]. This is an important consideration as part of a comprehensive risk-benefit assessment between TIVA and volatile anaesthetic-based techniques.

Specific indications for use of volatile anaesthetics (which can be administered through a face mask) in patients with an NMD might include situations where awake intravenous access is not tolerated or may be difficult or impossible, e.g. in anxious children.

Level of evidence: 4

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 16 of 17 (94.1%), three respondents abstained from voting.

#### Postoperative period

After general anaesthesia or sedation, up to 24 hours monitoring (including ECG, SpO<sub>2</sub>, preferably CO<sub>2</sub> monitoring, as well as surveillance for signs of ongoing rhabdomyolysis) may be necessary [1, 2].

Level of evidence: 4

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 16 of 18 (88.9%), two respondents abstained from voting.

Early mobilisation and feeding after surgery should be pursued. Respiratory physiotherapy can improve breathing and facilitate coughing.

Level of evidence: 4

Median score modified Delphi process: 8. Respondents who scored  $\geq 7$ ; 17 of 18 (94.4%), two respondents abstained from voting.

#### Medical alert cards, apps and warnings in electronic patient files

Many patient advocacy organizations provide medical alert cards to patients with NMDs. These cards improve patient safety, supporting individuals and their families in relaying information to emergency services and other medical professionals. Specific and personalized disease information, possible complications and their specific treatments should be recorded in such formats.

Neurologists and rehabilitation specialists who provide follow-up for patients with NMDs are in an excellent position to alert their patients regarding perioperative risks and the specific precautions to be taken. Through annual review at follow-up visits, medical professionals can contribute to the improved use of medical alert cards. Medical alerts should be clearly visible in electronic health records, and recommendations for essential peri-operative precautions should be included in correspondence with other healthcare providers.

Level of evidence: 4

Median score modified Delphi process: 9. Respondents who scored  $\geq 7$ ; 19 of 19 (100%), one respondent abstained from voting.

## LEVEL 2: Group-specific recommendations

In addition to the general recommendations summarized above, this section gives disease-specific recommendations concerning the six groups of NMDs.

### 1. Neuromuscular junction disorders

Disorders of the neuromuscular junction may be caused by pathogenic antibodies, genetic defects [57], specific drugs and/or toxins that interfere with the normal signalling between the presynaptic nerve ending and the postsynaptic muscle membrane [58].

Acquired autoimmune disorders of the neuromuscular junction are the most common and include myasthenia gravis [58, 59] and Lambert-Eaton Myasthenic Syndrome (LEMS). LEMS is frequently associated with an underlying malignancy or another autoimmune process.

Congenital myasthenic syndromes are a phenotypically heterogeneous group of disorders due to a variety of genetic defects resulting in impaired neuromuscular transmission. Muscle weakness typically begins in early childhood, but presentation may be delayed until adolescence or adulthood. Facial muscles, including (extra)ocular and bulbar muscles, are the most consistently affected. Due to muscle weakness, affected infants may have feeding difficulties. Motor development may be delayed. The severity of the myasthenia varies greatly, ranging from an inability to walk to only minor weakness. Weakness may be exacerbated by fever or infection [57, 58]. Specific anaesthesia considerations for patients with neuromuscular junction disorders are summarized in **Table 1**.

### 2. Muscle channelopathies

Skeletal muscle channelopathies are rare clinically and genetically heterogeneous diseases. They are characterized by altered muscle fibre excitability caused by mutations affecting voltage gated ion channels such as chloride channel (ClC-1), sodium channel (NaV1.4), calcium channel (CaV1.1), or potassium channels (Kir2.1, Kir2.6, Kir3.4). The clinical manifestations vary from an inability to relax after voluntary contraction (myotonia) to transient attacks of generalized or focal flaccid muscle weakness (periodic paralysis). Fluctuation of symptoms are strongly affected by environmental triggers such as exercise, temperature changes, pain, emotional factors, fasting or alterations in serum potassium concentration [63]. The non-dystrophic myotonias include myotonia congenita (due to variants in *CLCN1*), paramyotonia congenita (due to variants in *SCN4A*), and sodium channel myotonia (*SCN4A*) [23]. Periodic paralyses include hyperkalaemic periodic paralysis (hyperPP) caused by variants in *SCN4A* and hypokalaemic periodic paralysis (hypoPP) caused by variants in *CACNA1S*, *SCN4A* [23, 64] or rarely *RYR1* [65], and Andersen-Tawil syndrome caused by variants in *KCNJ2* [66]. Andersen-Tawil syndrome is associated with ECG abnormalities (long Q-T interval and U-waves) and predisposition to life-threatening ventricular arrhythmias [14].

Up to 31% of patients with muscle channelopathies report worsening of symptoms and a prolonged recovery time after general anaesthesia [67]. There are reports of myotonic crises in patients with myotonias and prolonged paralysis (hyperkalaemic triggered by

succinylcholine or other potassium-releasing agents in patients with *SCN4A* variants and hypokalaemic related to hypokalaemia and hyperglycaemia following anaesthesia) [67, 68]. Variants in *CACNA1S* and, very rarely, *RYR1* are associated with hypoPP and while none of these *RYR1* variants has been shown to predispose to MH, the risk is difficult to disprove [65, 67, 69]. A patient with known hypoPP who had a confirmed episode of MH [69] has subsequently been found to harbour a *CACNA1S* variant pathogenic for hypoPP but also a second variant in *CACNA1S* and two variants in *RYR1* [48]; (unpublished data, PH). Specific anaesthesia considerations for patients with muscle channelopathies are summarized in **Table 2**.

### **3. Myotonic dystrophy type 1 and 2**

Myotonic dystrophy type 1 (DM1) is a frequent adult muscular dystrophy caused by DNA triplet repeat expansion in the *DMPK* gene. Larger expansions lead to the infantile or more severe, congenital form resembling a congenital muscular dystrophy, with often profound associated weakness, hypotonia, bulbar and respiratory involvement. A second form of myotonic dystrophy, type 2 (DM2), results from a different repeat expansion in the *CNBP* gene, showing more proximal weakness [71].

Both disorders have autosomal dominant inheritance and multisystem features, including a myotonic myopathy, cataract, cardiac conduction defects, central and obstructive sleep apnoea, and a range of endocrine abnormalities including diabetes mellitus [71]. Respiratory impairment is more common and more pronounced in DM1.

Much of the available literature does not differentiate the congenital form of DM1 from its other forms, despite the facts that CTG repeat analysis [72] as well as grading by presence of proximal weakness [72, 73] argue for a higher risk of complications in the congenital form. Furthermore, myotonia is usually absent in the early life of patients with this form. Specific anaesthesia considerations for patients with myotonic dystrophy type 1 and 2 are summarized in **Table 3**.

### **4. Muscular dystrophies**

Several different skeletal muscle disorders, with very different degrees of severity and characterized by various pathophysiological mechanisms, are classified under the definition of muscular dystrophies. These disorders vary widely with regards to age of onset, degree of motor impairment, and associated cardiorespiratory involvement [80]. Classification is based on the underlying gene defect. This paragraph will focus on the most common forms, the dystrophinopathies, limb girdle muscular dystrophies (LGMDs), facioscapulohumeral muscular dystrophy (FSHD) and oculopharyngeal muscular dystrophy (OPMD).

Dystrophinopathy refers to DMD and BMD due to hemizygous X-linked variants in the *DMD* gene, encoding dystrophin. Ventilatory support and steroid treatments has improved survival in boys with DMD significantly and has prolonged ambulation, reduced the risk of developing scoliosis and improved cardiac health [80]. Severe cardiorespiratory involvement is common and needs thorough evaluation during the pre-operative assessment [13, 17]. Macroglossia and neck muscles contracture can cause problems for intubation. CNS

Accepted Article

involvement manifesting as cognitive deficits, speech problems and psychiatric comorbidities such as anxiety and depression may complicate pre-operative counselling [81]. LGMDs are a genetically heterogeneous group of disorders characterized by predominantly proximal muscle weakness and onset after becoming able to walk [80]. Specific forms (e.g., sarcoglycanopathies and alpha-dystroglycanopathies) may be associated with cardiac involvement, usually dilated cardiomyopathy or rarely, arrhythmogenic heart disease which is frequent in *POPDC1*-related LGMDR 25 [15, 16]. Respiratory failure may be a feature of the most severe forms or of those with spinal deformities, such as the *COL6*-related LGMDs. Significant tongue enlargement, that can cause problems for intubation, is occasionally present in *FKRP*-related LGMD R9, DMD and sarcoglycanopathies [16, 21].

Facioscapulohumeral muscular dystrophy (FSHD) is caused by skeletal muscle misexpression of the *DUX4* retrogene and represents the third most common form of muscular dystrophy in adults after DMD and DM1. Phenotypes may be variable and not immediately apparent in presymptomatic carriers [80].

Oculopharyngeal muscular dystrophy (OPMD) is another late-onset mostly autosomal dominant disorder caused by a trinucleotide repeat expansion in the first exon of the polyadenylate-binding protein nuclear 1 gene (*PABPN1*). The main clinical issues are ptosis and dysphagia, although patients may later also develop proximal muscle weakness. Specific anaesthesia considerations for patients with muscular dystrophies are summarized in **Table 4**.

### **5. Congenital myopathies and congenital muscular dystrophies**

Congenital myopathies and congenital muscular dystrophies are disorders with early-onset muscle weakness. Both groups give rise to proximal, axial and often facial weakness with slow progression, cardiorespiratory impairment as well as joint contractures and scoliosis. Despite some overlap anaesthetic implications are different.

#### **Congenital muscular dystrophies**

Congenital muscular dystrophies are classically defined as a group of disorders characterized by onset in the first six months of life and muscle biopsy evidence of a muscular dystrophy with histopathological features of de- and regeneration [85]. Depending on the underlying disease, cardiorespiratory involvement can be prominent, while some forms may have associated CNS involvement with epilepsy. The genes associated can be classified according to the cellular localization of the encoded protein into the following groups. Proteins of the plasma membrane–extracellular matrix interface such as collagen 6 (*COL6A 1,2,3*), merosin or laminin  $\alpha 2$  (*LAMA2*), integrin  $\alpha 7$  (*ITGA7*), proteins involved in O-glycosylation of the dystrophin-associated glycoprotein (DAG) (*POMT1*, *POMT2*, *POMGnT1*, *LARGE*, *FKTN*, *FKRP*, *ISPD*) and other intracellular proteins such as lamin A/C (*LMNA*), an intermediate filament located at the inner nuclear membrane, and selenoprotein N (*SELENON*), a protein with redox and calcium level regulation function [80].



It should be noted that the clinical phenotype of congenital DM1 (see paragraph above) is more similar to this group of diseases than to the adult forms of myotonic dystrophy. Specific anaesthesia considerations for patients with congenital muscular dystrophies are summarized in **Table 5A**.

### **Congenital myopathies**

Congenital myopathies are a heterogeneous group of early-onset inherited disorders. The different subtypes are traditionally based on the predominant histopathological finding; nemaline rods, cores, central nuclei, or fibre type disproportion. There is, however, overlap between these findings and there is an emerging trend to define the conditions according to which gene is involved. There are over 20 genes associated with congenital myopathies. The overall prevalence is estimated at 2-4/100 000. [86-88] with *RYR1*-related myopathies the most common, followed by those due to variants in *NEB* and *ACTA1*. *TTN*-related myopathies are increasingly diagnosed and represent an important subgroup. The genes causing congenital myopathies predominantly encode proteins implicated in skeletal muscle  $\text{Ca}^{2+}$  homeostasis, excitation–contraction coupling, myofilament assembly and interaction, and other mechanisms [88]. Specific anaesthesia considerations for patients with congenital myopathies are summarized in **Table 5B**.

## **6. Mitochondrial and metabolic myopathies**

### **Mitochondrial myopathies**

Mitochondrial myopathies are caused by variants in either nuclear or mitochondrial DNA leading to impairment of oxidative phosphorylation or fatty acid metabolism in mitochondria. The accumulation of Acyl-CoA might result in a secondary carnitine deficiency and impair the citrate cycle, gluconeogenesis, the urea cycle, fatty-acid oxidation, resulting in a deficit in energy production in the form of adenosine triphosphate, particularly in skeletal muscle [22, 89]. In addition, patients with a mitochondrial myopathy can also present with multisystemic symptoms. Anaesthetic preparation should therefore always be case-specific and include a multisystemic assessment. Circumstances causing metabolic disturbance should be avoided in all mitochondrial myopathies whenever possible [22, 25, 89, 90]. Specific anaesthesia considerations for patients with mitochondrial myopathies are summarized in **Table 6A**.

### **Metabolic myopathies**

Metabolic myopathies present with either permanent (fixed) muscle symptoms or episodic abnormalities, such as exercise-intolerance, activity induced myalgia, muscle contractures and muscle damage that can progress to rhabdomyolysis. Metabolic myopathies can be classified further as muscle glycogen storage diseases (GSD) (or muscle glycogenosis) and lipid metabolism disorders [22, 91, 92].

Muscle GSD are a group of inherited disorders that cause glycogen to be improperly stored or utilized in the body. Symptoms and comorbidities are highly diverse, some GSDs only affect skeletal muscle, while others feature involvement of other organs (including the heart and liver). This needs special focus as patients can be severely affected multi-systemically [22, 91, 92]. For instance, patients with GSD type II may present as classic Pompe disease with cardiomegaly, juvenile oligo-symptomatic cases or late-onset cases with weakness and often severe respiratory involvement. Specific anaesthesia considerations for patients with GSDs are summarized in **Table 6B**.

Muscle lipid metabolism disorders can also manifest in organs other than skeletal muscle. Abnormalities in enzyme processing fats can result in accumulation of fatty acid and its derivatives including triglycerides, and sterol-containing metabolites such as cholesterol. This can be harmful to the heart and liver and may result in cardiomyopathy, arrhythmias, hepatomegaly, hypoglycaemia and hyperammonaemia [92]. Specific anaesthesia considerations for patients with muscle lipid metabolism disorders are summarized in **Table 6C**.

### LEVEL 3: Risk prediction matrix and safety of non-anaesthetic drugs used in the perioperative period

#### Risk prediction matrix

**Table 7** illustrates a preoperative assessment matrix designed as a practical tool based on Schieren *et al.* [2] which can be used to make an inventory of the multisystem features in patients with NMDs. A grey box in the risk prediction matrix indicates that at least a subset of this group of NMDs is associated with this specific condition/complication or disease manifestation. A white box indicates that this NMD is not specifically associated with this specific condition/complication or disease manifestation.

After obtaining the relevant information, the peri-operative risk can be obtained using the modified NARCO-SS tool. [11]. In this risk assessment tool, a score of 0, 1 or 2 is given for each organ system and/or specific scenario in the NARCO-SS acronym. A score of 0 indicates no signs or symptoms, a score of 1 indicates mild to moderate and a score of 2 indicates moderate to severe symptoms in the specific organ system. For the surgical severity (or “SS” in the acronym) a score of 0 is given for non-invasive or superficial elective procedures. A score of 1 is allocated for minimally invasive, elective procedures of up to 60 minutes duration with anticipated moderate blood loss. A score of 2 is given for major surgery/interventions or any type of surgery in an emergency setting.

- **N:** Neurological signs & muscular impairment? [0 – 1 – 2]
- **A:** Difficult Airway? [0 – 1 – 2]
- **R:** Symptoms of Respiratory disease? [0 – 1 – 2]
- **C:** Symptoms of Cardiac disease? [0 – 1 – 2]
- **O:** Other co-morbidity or metabolic concerns? [0 – 1 – 2]
- **SS:** Surgical Severity? [0 – 1 – 2]

#### Result risk assessment, based on modified NARCO-SS:

1. Low risk: total score 0-4 with no individual score > 1;
2. Moderate risk: total score 5-6 with no individual score > 1;
3. High risk: total score 7-9 or any individual score of 2;
4. Seriously reconsider the indication for surgery and anaesthesia when total score above 9.

#### Unsafe non-anaesthetic drugs

Anaesthetists are often asked by surgeons or other physicians to administer other drugs *e.g.* antibiotics or antiepileptics. However, several of these drugs are possibly harmful for patients with NMDs. The following drugs should only be used with caution:

- Neuromuscular junction disorders
  - Oxazolidinone antibiotics (myasthenic crisis) [59, 102]
  - Aminoglycoside antibiotics (myasthenic crisis) [59, 102]

- Accepted Article
- Beta blocking agents (myasthenic crisis) [102]
  - Botulinum toxin (myasthenic crisis) [102]
  - Fluoroquinolone antibiotics (myasthenic crisis) [59, 102]
  - Intravenous magnesium (myasthenic crisis) [58, 102]
  - Macrolide antibiotics (myasthenic crisis) [59, 102]
  - Muscle channelopathies
    - Potassium releasing agents (hyperkalaemic periodic paralysis) [23, 63]
    - $\beta$ -agonist (hypokalaemic periodic paralysis) [63]
    - Insulin (hypokalaemic periodic paralysis) [63]
  - Mitochondrial myopathies
    - Aminoglycoside antibiotics (ototoxicity) [95, 103]
    - Linezolid antibiotics (lactic acidosis) [95]
    - Metformin (lactic acidosis) [95, 103]
    - Valproic acid (liver failure) [95, 103]

### Open questions

Because of the low prevalence of most NMDs, there is a lack of prospective clinical studies with a high level of evidence on the anaesthetic management of patients with NMDs resulting in several urgent open questions [8]. Observational multicentre studies can be of great value to study the prevalence of perioperative complications in patients with NMDs and the association with certain anaesthetic agents. One of the open questions is the future role of remimazolam, a recently introduced short-acting benzodiazepine. In patients with NMDs, neither propofol or volatile anaesthetics are ideal and short-acting benzodiazepines might be useful in this respect.

Another open question is how to manage a patient suspected of a yet undefined myopathy presenting for a procedure requiring anaesthesia (e.g. surgery, muscle biopsy, MRI). If it is a diagnostic procedure, it is worth establishing if lower-risk diagnostic options, especially DNA testing, have been exhausted.

Some recommend that volatile anaesthetics are best avoided. However, there is no high-level evidence on this topic, and this remains a matter of debate. Anaesthesiologists should exercise their own professional expertise and judgement to assess the disease-inherent and circumstantial risks to determine the most appropriate anaesthetic technique.

The following considerations may be helpful:

- Infants with congenital myopathies, the group at risk for MH [45, 46, 49, 50], and X-linked muscular dystrophies due to variants in the dystrophin gene, the group at risk for AIR [33, 34] usually have delayed motor milestones but cognitive development is usually normal [19, 20, 49, 88].
- Infants with hypotonia due to a metabolic disease, the group at risk for propofol infusion syndrome [54-56], usually present with global developmental delay or other neurological signs e.g. epilepsy and spasticity [22, 91, 92].

- Accepted Article
- Although non-specific, an increased baseline CK level, possibly points to a congenital myopathy or dystrophy. Therefore, these patients might be prone to AIR or MH susceptibility, and TIVA might be the preferred option.
  - Laboratory evidence of metabolic derangements (*e.g.* elevated basal lactates) favour a metabolic, in particular mitochondrial myopathy [22, 92]. Volatile anaesthesia might be the preferred option in such cases as there is an increased risk of propofol infusion syndrome [54, 55].
  - Although the balance of risks may be judged to favour a TIVA-technique for a particular child, an intravenous induction in an infant can be very challenging or impossible even when using nitrous oxide for sedation and topical local anaesthesia. The use of a short inhalation induction is an option in this situation, subsequently changing to TIVA once the intravenous line has been secured.

Nitrous oxide, barbiturates, benzodiazepines, ketamine, opioids, rocuronium, vecuronium and local anaesthetics are not linked to MH, AIR, propofol infusion syndrome, or other adverse events specifically linked to certain NMDs [104]. However, one must realize that there are no risk-free anaesthetic agents since each agent has its own specific risks, especially in patients with several and severe comorbidities such as neuromuscular patients [105].

### **Conclusion**

This consensus statement summarizes the most important recommendations concerning anaesthesia in patients with NMDs. Since there have been no RCTs and only few large retrospective studies on this topic, most evidence is based on small case series and expert opinion, highlighting the need for future research. Prospective, observational studies using common databases would be of great value and may provide answers to several unresolved questions. However, carefully curated expert opinion-based recommendations can still be of value for health care professionals in the field of anaesthesia, NMDs and genetics. Given the low level of evidence, we expect an update of this consensus statement will be necessary in ten years or earlier in case of new highly relevant evidence outdates the content of this consensus statement.

## LEGEND TO FIGURES AND TABLES:

**Figure 1: A summary of the process description to developing this consensus statement document.**

ENMC = European Neuromuscular Centre

### **Table 1: Specific anaesthesia recommendations for neuromuscular junction disorders**

For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result  $\geq 7$ .

SIGN = Scottish Intercollegiate Guidelines Network

### **Table 2: Specific anaesthesia recommendations for muscle channelopathies**

For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result  $\geq 7$ .

SIGN = Scottish Intercollegiate Guidelines Network

### **Table 3: Specific anaesthesia recommendations for myotonic dystrophy type 1 and 2**

For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result  $\geq 7$ .

SIGN = Scottish Intercollegiate Guidelines Network

### **Table 4: Specific anaesthesia recommendations for muscular dystrophies**

For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result  $\geq 7$ .

SIGN = Scottish Intercollegiate Guidelines Network

### **Table 5: Specific anaesthesia recommendations for congenital muscular dystrophies (5A) and congenital myopathies (5B)**

For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result  $\geq 7$ .

SIGN = Scottish Intercollegiate Guidelines Network

**Table 6: Specific anaesthesia recommendations for mitochondrial myopathies (6A), metabolic myopathies (6B) and lipid metabolism disorders (6C).**

For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result  $\geq 7$ .

SIGN = Scottish Intercollegiate Guidelines Network

**Table 7: A risk prediction matrix to assess the multi-system features of patients with neuromuscular disorders.**

A grey box in the risk prediction matrix indicates that at least a subset of this group of neuromuscular disorders is associated with this specific condition/complication or disease manifestation. A white box indicates that this neuromuscular disorder is not specifically associated with this specific condition/complication or disease manifestation.

## REFERENCES

- [1]. van den Bersselaar LR, Snoeck MMJ, Gubbels M, *et al.* Anaesthesia and neuromuscular disorders: what a neurologist needs to know. *Pract Neurol.* 2020.
- [2]. Schieren M, Defosse J, Böhmer A, Wappler F, Gerbershagen MU. Anaesthetic management of patients with myopathies. *Eur J Anaesthesiol.* 2017 **34**: 641-649.
- [3]. Katz JA, Murphy GS. Anesthetic consideration for neuromuscular diseases. *Curr Opin Anaesthesiol.* 2017 **30**: 435-440.
- [4]. Kinnett K, Rodger S, Vroom E, Furlong P, Aartsma-Rus A, Bushby K. Imperatives for DUCHENNE MD: a Simplified Guide to Comprehensive Care for Duchenne Muscular Dystrophy. *PLoS Curr.* 2015 **7**.
- [5]. Mercuri E, Finkel RS, Muntoni F, *et al.* Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord.* 2018 **28**: 103-115.
- [6]. Van den Bersselaar LR, Riazi S, Snoeck MMJ, Jungbluth H, Voermans N. 259th ENMC International Workshop: Anaesthesia and neuromuscular disorders, December 11th, 2020 and May 28-29, 2021. *Neuromuscul Disord.* 2021 **Online ahead of print.**
- [7]. Brouwers MC, Kho ME, Browman GP, *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *Cmaj.* 2010 **182**: E839-842.
- [8]. van den Bersselaar LR, Gubbels M, Riazi S, *et al.* Mapping the current evidence on the anesthetic management of adult patients with neuromuscular disorders-a scoping review. *Can J Anaesth.* 2022.
- [9]. Hohmann E, Brand JC, Rossi MJ, Lubowitz JH. Expert Opinion Is Necessary: Delphi Panel Methodology Facilitates a Scientific Approach to Consensus. *Arthroscopy.* 2018 **34**: 349-351.
- [10]. American Society of Anesthesiologists. <https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system-2021>.
- [11]. Malviya S, Voepel-Lewis T, Chiravuri SD, *et al.* Does an objective system-based approach improve assessment of perioperative risk in children? A preliminary evaluation of the 'NARCO'. *Br J Anaesth.* 2011 **106**: 352-358.
- [12]. 50 SIGNS. A guideline developer's handbook. 2008.
- [13]. Cripe LH, Tobias JD. Cardiac considerations in the operative management of the patient with Duchenne or Becker muscular dystrophy. *Paediatr Anaesth.* 2013 **23**: 777-784.
- [14]. Mazzanti A, Guz D, Trancuccio A, *et al.* Natural History and Risk Stratification in Andersen-Tawil Syndrome Type 1. *J Am Coll Cardiol.* 2020 **75**: 1772-1784.
- [15]. Schindler RF, Scotton C, Zhang J, *et al.* POPDC1(S201F) causes muscular dystrophy and arrhythmia by affecting protein trafficking. *J Clin Invest.* 2016 **126**: 239-253.
- [16]. Ten Dam L, Frankhuizen WS, Linssen W, *et al.* Autosomal recessive limb-girdle and Miyoshi muscular dystrophies in the Netherlands: The clinical and molecular spectrum of 244 patients. *Clin Genet.* 2019 **96**: 126-133.
- [17]. Ogiso M, Isogai T, Kato K, Tanaka H, Tejima T, Isozaki E. Electrocardiographic and echocardiographic findings in muscular dystrophy patients with heart failure. *Heart Vessels.* 2018 **33**: 1576-1583.
- [18]. Herman GE, Finegold M, Zhao W, de Gouyon B, Metzenberg A. Medical complications in long-term survivors with X-linked myotubular myopathy. *J Pediatr.* 1999 **134**: 206-214.
- [19]. Yiu EM, Kornberg AJ. Duchenne muscular dystrophy. *J Paediatr Child Health.* 2015 **51**: 759-764.



- [20]. Klein A, Lillis S, Munteanu I, *et al.* Clinical and genetic findings in a large cohort of patients with ryanodine receptor 1 gene-associated myopathies. *Hum Mutat.* 2012 **33**: 981-988.
- [21]. Muenster T, Mueller C, Forst J, Huber H, Schmitt HJ. Anaesthetic management in patients with Duchenne muscular dystrophy undergoing orthopaedic surgery: a review of 232 cases. *Eur J Anaesthesiol.* 2012 **29**: 489-494.
- [22]. Cohen BH. Mitochondrial and Metabolic Myopathies. *Continuum (Minneapolis Minn).* 2019 **25**: 1732-1766.
- [23]. Stunnenberg BC, LoRusso S, Arnold WD, *et al.* Guidelines on clinical presentation and management of nondystrophic myotonias. *Muscle Nerve.* 2020 **62**: 430-444.
- [24]. Hayes LH, Yun P, Mohassel P, *et al.* Hypoglycemia in patients with congenital muscle disease. *BMC Pediatr.* 2020 **20**: 57.
- [25]. Taroni F, Uziel G. Fatty acid mitochondrial beta-oxidation and hypoglycaemia in children. *Curr Opin Neurol.* 1996 **9**: 477-485.
- [26]. Ørngreen MC, Zacho M, Hebert A, Laub M, Vissing J. Patients with severe muscle wasting are prone to develop hypoglycemia during fasting. *Neurology.* 2003 **61**: 997-1000.
- [27]. Hilbert JE, Barohn RJ, Clemens PR, *et al.* High frequency of gastrointestinal manifestations in myotonic dystrophy type 1 and type 2. *Neurology.* 2017 **89**: 1348-1354.
- [28]. Van de Putte P, Perlas A. Ultrasound assessment of gastric content and volume. *Br J Anaesth.* 2014 **113**: 12-22.
- [29]. Heier T, Caldwell JE, Sessler DI, Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *Anesthesiology.* 1991 **74**: 815-819.
- [30]. Horn EP, Bein B, Böhm R, Steinfath M, Sahili N, Höcker J. The effect of short time periods of pre-operative warming in the prevention of peri-operative hypothermia. *Anaesthesia.* 2012 **67**: 612-617.
- [31]. Larach MG, Rosenberg H, Gronert GA, Allen GC. Hyperkalemic cardiac arrest during anesthesia in infants and children with occult myopathies. *Clin Pediatr (Phila).* 1997 **36**: 9-16.
- [32]. Gronert GA. Cardiac arrest after succinylcholine: mortality greater with rhabdomyolysis than receptor upregulation. *Anesthesiology.* 2001 **94**: 523-529.
- [33]. Gurnaney H, Brown A, Litman RS. Malignant hyperthermia and muscular dystrophies. *Anesth Analg.* 2009 **109**: 1043-1048.
- [34]. Segura LG, Lorenz JD, Weingarten TN, *et al.* Anesthesia and Duchenne or Becker muscular dystrophy: review of 117 anesthetic exposures. *Paediatr Anaesth.* 2013 **23**: 855-864.
- [35]. Fujimoto M, Terasaki S, Nishi M, Yamamoto T. Response to rocuronium and its determinants in patients with myasthenia gravis: A case-control study. *Eur J Anaesthesiol.* 2015 **32**: 672-680.
- [36]. Caron MJ, Girard F, Girard DC, *et al.* Cisatracurium pharmacodynamics in patients with oculopharyngeal muscular dystrophy. *Anesth Analg.* 2005 **100**: 393-397.
- [37]. Wick S, Muenster T, Schmidt J, Forst J, Schmitt HJ. Onset and duration of rocuronium-induced neuromuscular blockade in patients with Duchenne muscular dystrophy. *Anesthesiology.* 2005 **102**: 915-919.
- [38]. Muenster T, Schmidt J, Wick S, Forst J, Schmitt HJ. Rocuronium 0.3 mg x kg<sup>-1</sup> (ED<sub>95</sub>) induces a normal peak effect but an altered time course of neuromuscular block in patients with Duchenne's muscular dystrophy. *Paediatr Anaesth.* 2006 **16**: 840-845.

- [39]. Wefki Abdelgawwad Shousha AA, Sanfilippo M, Sabba A, Pinchera P. Sugammadex and reversal of neuromuscular block in adult patient with duchenne muscular dystrophy. *Case Rep Anesthesiol*. 2014 **2014**: 680568.
- [40]. Gurunathan U, Kunju SM, Stanton LML. Use of sugammadex in patients with neuromuscular disorders: a systematic review of case reports. *BMC Anesthesiol*. 2019 **19**: 213.
- [41]. Mouri H, Jo T, Matsui H, Fushimi K, Yasunaga H. Effect of Sugammadex on Postoperative Myasthenic Crisis in Myasthenia Gravis Patients: Propensity Score Analysis of a Japanese Nationwide Database. *Anesth Analg*. 2020 **130**: 367-373.
- [42]. Mangla C, Bais K, Yarmush J. Myotonic Dystrophy and Anesthetic Challenges: A Case Report and Review. *Case Rep Anesthesiol*. 2019 **2019**: 4282305.
- [43]. White RJ, Bass SP. Myotonic dystrophy and paediatric anaesthesia. *Paediatr Anaesth*. 2003 **13**: 94-102.
- [44]. Hopkins PM, Rüffert H, Snoeck MM, *et al*. European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. *Br J Anaesth*. 2015 **115**: 531-539.
- [45]. Murayama T, Kurebayashi N, Ogawa H, *et al*. Genotype-Phenotype Correlations of Malignant Hyperthermia and Central Core Disease Mutations in the Central Region of the RYR1 Channel. *Hum Mutat*. 2016 **37**: 1231-1241.
- [46]. 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**: 1832-1841.
- [47]. Monnier N, Krivosic-Horber R, Payen JF, *et al*. Presence of two different genetic traits in malignant hyperthermia families: implication for genetic analysis, diagnosis, and incidence of malignant hyperthermia susceptibility. *Anesthesiology*. 2002 **97**: 1067-1074.
- [48]. Miller DM, Daly C, Aboelsaod EM, *et al*. Genetic epidemiology of malignant hyperthermia in the UK. *Br J Anaesth*. 2018 **121**: 944-952.
- [49]. Dowling JJ, Lillis S, Amburgey K, *et al*. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. *Neuromuscul Disord*. 2011 **21**: 420-427.
- [50]. van den Bersselaar LR, Hellblom A, Gashi M, *et al*. Referral indications for malignant hyperthermia susceptibility diagnostics in patients without adverse anesthetic events in the era of next-generation sequencing. *Anesthesiology*. 2022.
- [51]. Johnston JJ, Dirksen RT, Girard T, *et al*. Variant curation expert panel recommendations for RYR1 pathogenicity classifications in malignant hyperthermia susceptibility. *Genet Med*. 2021.
- [52]. Ye L, Zuo Y, Zhang P, Yang P. Sevoflurane enhances neuromuscular blockade by increasing the sensitivity of skeletal muscle to neuromuscular blockers. *Int J Physiol Pathophysiol Pharmacol*. 2015 **7**: 172-177.
- [53]. Hemphill S, McMEnamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth*. 2019 **122**: 448-459.
- [54]. Savard M, Dupré N, Turgeon AF, Desbiens R, Langevin S, Brunet D. Propofol-related infusion syndrome heralding a mitochondrial disease: case report. *Neurology*. 2013 **81**: 770-771.
- [55]. Vanlander AV, Jorens PG, Smet J, *et al*. Inborn oxidative phosphorylation defect as risk factor for propofol infusion syndrome. *Acta Anaesthesiol Scand*. 2012 **56**: 520-525.

- [56]. Shimizu J, Tabata T, Tsujita Y, *et al.* Propofol infusion syndrome complicated with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a case report. *Acute Med Surg.* 2020 **7**: e473.
- [57]. Finsterer J. Congenital myasthenic syndromes. *Orphanet J Rare Dis.* 2019 **14**: 57.
- [58]. Ciafaloni E. Myasthenia Gravis and Congenital Myasthenic Syndromes. *Continuum (Minneap Minn).* 2019 **25**: 1767-1784.
- [59]. Cata JP, Lasala JD, Williams W, Mena GE. Myasthenia Gravis and Thymoma Surgery: A Clinical Update for the Cardiothoracic Anesthesiologist. *J Cardiothorac Vasc Anesth.* 2019 **33**: 2537-2545.
- [60]. Woodcock T, Barker P, Daniel S, *et al.* Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency: Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK. *Anaesthesia.* 2020 **75**: 654-663.
- [61]. Fujita Y, Moriyama S, Aoki S, *et al.* Estimation of the success rate of anesthetic management for thymectomy in patients with myasthenia gravis treated without muscle relaxants: a retrospective observational cohort study. *J Anesth.* 2015 **29**: 794-797.
- [62]. Della Rocca G, Coccia C, Diana L, *et al.* Propofol or sevoflurane anesthesia without muscle relaxants allow the early extubation of myasthenic patients. *Can J Anaesth.* 2003 **50**: 547-552.
- [63]. Phillips L, Trivedi JR. Skeletal Muscle Channelopathies. *Neurotherapeutics.* 2018 **15**: 954-965.
- [64]. Wang XY, Ren BW, Yong ZH, Xu HY, Fu QX, Yao HB. Mutation analysis of CACNA1S and SCN4A in patients with hypokalemic periodic paralysis. *Mol Med Rep.* 2015 **12**: 6267-6274.
- [65]. Matthews E, Neuwirth C, Jaffer F, *et al.* Atypical periodic paralysis and myalgia: A novel RYR1 phenotype. *Neurology.* 2018 **90**: e412-e418.
- [66]. Vivekanandam V, Munot P, Hanna MG, Matthews E. Skeletal Muscle Channelopathies. *Neurol Clin.* 2020 **38**: 481-491.
- [67]. Raja Rayan DL, Hanna MG. Managing pregnancy and anaesthetics in patients with skeletal muscle channelopathies. *Neuromuscul Disord.* 2020 **30**: 539-545.
- [68]. Bandschapp O, Iazzo PA. Pathophysiologic and anesthetic considerations for patients with myotonia congenita or periodic paralyses. *Paediatr Anaesth.* 2013 **23**: 824-833.
- [69]. Marchant CL, Ellis FR, Halsall PJ, Hopkins PM, Robinson RL. Mutation analysis of two patients with hypokalemic periodic paralysis and suspected malignant hyperthermia. *Muscle Nerve.* 2004 **30**: 114-117.
- [70]. Ruffert H, Bastian B, Bendixen D, *et al.* Consensus guidelines on perioperative management of malignant hyperthermia suspected or susceptible patients from the European Malignant Hyperthermia Group. *Br J Anaesth.* 2021 **126**: 120-130.
- [71]. Thornton CA. Myotonic dystrophy. *Neurol Clin.* 2014 **32**: 705-719, viii.
- [72]. Sinclair JL, Reed PW. Risk factors for perioperative adverse events in children with myotonic dystrophy. *Paediatr Anaesth.* 2009 **19**: 740-747.
- [73]. Mathieu J, Allard P, Gobeil G, Girard M, De Braekeleer M, Bégin P. Anesthetic and surgical complications in 219 cases of myotonic dystrophy. *Neurology.* 1997 **49**: 1646-1650.
- [74]. Reimann J, Kornblum C. Towards Central Nervous System Involvement in Adults with Hereditary Myopathies. *J Neuromuscul Dis.* 2020 **7**: 367-393.
- [75]. Imison AR. Anaesthesia and myotonia--an Australian experience. *Anaesth Intensive Care.* 2001 **29**: 34-37.

- [76]. Veyckemans F, Scholtes JL. Myotonic dystrophies type 1 and 2: anesthetic care. *Paediatr Anaesth*. 2013 **23**: 794-803.
- [77]. Kim CS, Park JM, Park D, Kim DH, Park JS. Opioid use may be associated with postoperative complications in myotonic dystrophy type 1 with high-grade muscular impairment. *Sci Rep*. 2021 **11**: 8.
- [78]. Kirzinger L, Schmidt A, Kornblum C, Schneider-Gold C, Kress W, Schoser B. Side effects of anesthesia in DM2 as compared to DM1: a comparative retrospective study. *Eur J Neurol*. 2010 **17**: 842-845.
- [79]. Weingarten TN, Hofer RE, Milone M, Sprung J. Anesthesia and myotonic dystrophy type 2: a case series. *Can J Anaesth*. 2010 **57**: 248-255.
- [80]. Mercuri E, Bönnemann CG, Muntoni F. Muscular dystrophies. *Lancet*. 2019 **394**: 2025-2038.
- [81]. Latimer R, Street N, Conway KC, *et al*. Secondary Conditions Among Males With Duchenne or Becker Muscular Dystrophy. *J Child Neurol*. 2017 **32**: 663-670.
- [82]. Wang S, Peng D. Cardiac Involvement in Emery-Dreifuss Muscular Dystrophy and Related Management Strategies. *Int Heart J*. 2019 **60**: 12-18.
- [83]. Schorling DC, Müller CK, Pechmann A, *et al*. Coagulation disorders in Duchenne muscular dystrophy? Results of a registry-based online survey. *Acta Myol*. 2020 **39**: 2-12.
- [84]. Turturro F, Rocca B, Gumina S, *et al*. Impaired primary hemostasis with normal platelet function in Duchenne muscular dystrophy during highly-invasive spinal surgery. *Neuromuscul Disord*. 2005 **15**: 532-540.
- [85]. Schorling DC, Kirschner J, Bönnemann CG. Congenital Muscular Dystrophies and Myopathies: An Overview and Update. *Neuropediatrics*. 2017 **48**: 247-261.
- [86]. Amburgey K, McNamara N, Bennett LR, McCormick ME, Acsadi G, Dowling JJ. Prevalence of congenital myopathies in a representative pediatric united states population. *Ann Neurol*. 2011 **70**: 662-665.
- [87]. Witting N, Werlauff U, Duno M, Vissing J. Phenotypes, genotypes, and prevalence of congenital myopathies older than 5 years in Denmark. *Neurol Genet*. 2017 **3**: e140.
- [88]. Jungbluth H, Treves S, Zorzato F, *et al*. Congenital myopathies: disorders of excitation-contraction coupling and muscle contraction. *Nat Rev Neurol*. 2018 **14**: 151-167.
- [89]. Ahmed ST, Craven L, Russell OM, Turnbull DM, Vincent AE. Diagnosis and Treatment of Mitochondrial Myopathies. *Neurotherapeutics*. 2018 **15**: 943-953.
- [90]. Mtaweh H, Bayır H, Kochanek PM, Bell MJ. Effect of a single dose of propofol and lack of dextrose administration in a child with mitochondrial disease: a case report. *J Child Neurol*. 2014 **29**: Np40-46.
- [91]. Finsterer J. Update Review about Metabolic Myopathies. *Life (Basel)*. 2020 **10**.
- [92]. Angelini C, Marozzo R, Pegoraro V, Sacconi S. Diagnostic challenges in metabolic myopathies. *Expert Rev Neurother*. 2020 **20**: 1287-1298.
- [93]. Miyamoto Y, Miyashita T, Takaki S, Goto T. Perioperative considerations in adult mitochondrial disease: A case series and a review of 111 cases. *Mitochondrion*. 2016 **26**: 26-32.
- [94]. Footitt EJ, Sinha MD, Raiman JA, Dhawan A, Moganasundram S, Champion MP. Mitochondrial disorders and general anaesthesia: a case series and review. *Br J Anaesth*. 2008 **100**: 436-441.
- [95]. De Vries MC, Brown DA, Allen ME, *et al*. Safety of drug use in patients with a primary mitochondrial disease: An international Delphi-based consensus. *J Inherit Metab Dis*. 2020 **43**: 800-818.

- [96]. Conover ZR, Talai A, Klockau KS, Ing RJ, Chatterjee D. Perioperative Management of Children on Ketogenic Dietary Therapies. *Anesth Analg*. 2020 **131**: 1872-1882.
- [97]. Stettner GM, Viscomi C, Zeviani M, Wilichowski E, Dutschmann M. Hypoxic and hypercapnic challenges unveil respiratory vulnerability of Surf1 knockout mice, an animal model of Leigh syndrome. *Mitochondrion*. 2011 **11**: 413-420.
- [98]. Bollig G, Mohr S, Raeder J. McArdle's disease and anaesthesia: case reports. Review of potential problems and association with malignant hyperthermia. *Acta Anaesthesiol Scand*. 2005 **49**: 1077-1083.
- [99]. Hopkins PM, Ellis FR, Halsall PJ. Comparison of in vitro contracture testing with ryanodine, halothane and caffeine in malignant hyperthermia and other neuromuscular disorders. *Br J Anaesth*. 1993 **70**: 397-401.
- [100]. Martin JM, Gillingham MB, Harding CO. Use of propofol for short duration procedures in children with long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiencies. *Mol Genet Metab*. 2014 **112**: 139-142.
- [101]. Justiz AC, Mayhew JF. Anesthesia in a child with medium-chain Acyl-CoA dehydrogenase deficiency. *Paediatr Anaesth*. 2006 **16**: 1293-1294.
- [102]. Myasthenia Gravis Foundation of America Medical/Scientific Advisory Board. [www.Myasthenia.org/cautionary-drugs](http://www.Myasthenia.org/cautionary-drugs) November 25th 2021).
- [103]. Orsucci D, Ienco EC, Siciliano G, Mancuso M. Mitochondrial disorders and drugs: what every physician should know. *Drugs Context*. 2019 **8**: 212588.
- [104]. Trevisan CP, Accorsi A, Morandi LO, *et al*. Undiagnosed myopathy before surgery and safe anaesthesia table. *Acta Myol*. 2013 **32**: 100-105.
- [105]. Hopkins PM. Anaesthesia and the sex-linked dystrophies: between a rock and a hard place. *Br J Anaesth*. 2010 **104**: 397-400.

**Table 1: Specific anaesthesia recommendations for neuromuscular junction disorders**

Specific considerations for Myasthenia gravis	SIGN	Median score modified Delphi process	Respondents who scored $\geq 7$	Abstained from voting ( <i>n</i> )
<ul style="list-style-type: none"> <li>Elective surgery should preferably be performed when the condition is stable with the patient requiring low doses of immunomodulatory medication and preferably as first case of the day when the weakness is least pronounced [59].</li> </ul>	4	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>Consider postoperative complications:               <ul style="list-style-type: none"> <li><i>Myasthenic crisis</i>: severe respiratory muscle weakness that requires intubation or causes delayed extubation after surgery, linked to cholinergic deficit. Urgent therapy is needed with intravenous pyridostigmine, plasma exchange, immunoglobulins and/or supportive care [59].</li> <li><i>Cholinergic crisis</i>: identified by the mnemonic "SLUDGE": Salivation, Lacrimation, Urination, Defecation, Gastrointestinal distress, and Emesis. Antimuscarinic (atropine) drugs must be given [59].</li> </ul> </li> </ul>	4	9	18/19 (94.7%)	1
<b>Preoperative recommendations</b>				
<ul style="list-style-type: none"> <li>An intravenous hydrocortisone stress regimen should be considered in patients who are or were recently (&lt; 1 year) on a course of corticosteroids (prednisolone <math>\geq 5\text{mg/day}</math> for &gt; 1 month) [60].</li> </ul>	4	8	15/17 (88.2%)	3
<ul style="list-style-type: none"> <li>Anticholinesterase agents should be continued until prior to surgery but stopped during anaesthesia.</li> </ul>	4	9	17/19 (89.5%)	1
<ul style="list-style-type: none"> <li>Any immunosuppressive therapy other than steroids can be withheld on the day of surgery.</li> </ul>	4	8	16/17 (94.1%)	3
<ul style="list-style-type: none"> <li>Inform the patient about the increased risk for perioperative complications, mainly postoperative pulmonary complications, myasthenic crisis and postoperative residual neuromuscular blockade [59].</li> </ul>	4	9	19/19 (100%)	1
<b>Intraoperative recommendations</b>				
<ul style="list-style-type: none"> <li>TIVA and volatile anaesthetics have both been used effectively and safely and should be adapted to the case and surgery in question [59, 61, 62].</li> </ul>	2-	9	15/15 (100%)	5
<ul style="list-style-type: none"> <li>Use of sugammadex rather than neostigmine is associated with a lesser risk of myasthenic crisis after thymectomy in adult myasthenia gravis patients [41].</li> </ul>	2-	8.5	14/14 (100%)	6
<b>Postoperative recommendations</b>				
<ul style="list-style-type: none"> <li>Restart oral medication as soon as possible [59].</li> </ul>	4	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>If intravenous administration of anticholinesterase agents is required, the dose should be adjusted:               <ul style="list-style-type: none"> <li>Dose of oral pyridostigmine: intravenous pyridostigmine = 30:1 [59];</li> <li>Dose of oral pyridostigmine: intravenous neostigmine = 60:0.5 [58].</li> </ul>               However, caution is needed since there are large inter-individual differences in bioavailability.             </li> </ul>	4	9	16/16 (100%)	4
<ul style="list-style-type: none"> <li>Pyridostigmine can also be administered by continuous infusion when the dose is adjusted accordingly. Following dose conversion as outlined above, the infusion can be terminated, and oral anticholinergics restarted at any point.</li> </ul>	4	9	13/13 (100%)	7

**Table 2: Specific anaesthesia recommendations for muscle channelopathies**

<b>Preoperative recommendations</b>	<b>SIGN</b>	<b>Median score modified Delphi process</b>	<b>Respondents who scored <math>\geq 7</math></b>	<b>Abstained from voting (n)</b>
• Perform ECG and 24-hour Holter monitoring in patients with Andersen-Tawil syndrome and other patients treated with antiarrhythmic drugs [14].	2+	9	18/18 (100%)	2
• Inform the patient that the procedure might exacerbate and/or precipitate an attack resulting in prolonged post-surgical recovery [67].	2+	9	19/19 (100%)	1
• In patients with <i>RYR1</i> and/or <i>CACNA1S</i> variants, referral to an MH investigation centre, if possible, is recommended for advice on the risk of MH and use of volatile anaesthetics [44]. In case it is not possible to contact an MH investigation centre before surgery, <i>e.g.</i> in case of emergency surgery, use of volatile anaesthetics and/or succinylcholine is contra-indicated in patients with <i>RYR1</i> and/or <i>CACNA1S</i> variants [70].	2+	9	18/19 (94.7%)	1
• Succinylcholine should be avoided irrespective of the risk of MH [23, 68].	2+	9	18/18 (100%)	2
<b>Intraoperative recommendations</b>				
• Potassium supplementation in patients with paramyotonia congenita can trigger myotonia and should be avoided. In case of fasting, regular control of potassium serum levels is recommended.	3	9	17/17 (100%)	3
• Avoid hypothermia, shivering and agitation as these can cause myotonia [68].	3	9	19/19 (100%)	1
• Avoid high glucose levels and hyperventilation (potentially causing alkalosis) in hypoPP [68].	3	9	16/16 (100%)	4
• Avoid hyperkalaemia and hypoventilation (potentially causing acidosis) in hyperPP.	3	9	16/16 (100%)	4
• Patients treated with mexiletine should not receive class I antiarrhythmics due to the risk of conduction block.	3	9	13/13 (100%)	7
• Succinylcholine and/or acetylcholinesterase inhibitors should be avoided as these may induce myotonia [68].	3	9	18/18 (100%)	2

**Table 3: Specific anaesthesia recommendations for myotonic dystrophy type 1 and 2**

<b>Preoperative recommendations</b>	<b>SIGN</b>	<b>Median score modified Delphi process</b>	<b>Respondents who scored ≥7</b>	<b>Abstained from voting (n)</b>
<ul style="list-style-type: none"> <li>Preoperative screening should include ECG, echocardiography and lung function tests (in sitting and the supine position), with review of current medication and therapies (e.g. pacemakers, non-invasive ventilation etc.). A neurological examination should be performed to document the degree of muscle weakness, as proximal weakness indicates a greater risk of complications in myotonic dystrophy type 1 [72, 73].</li> </ul>	2-	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>Central nervous system (CNS) involvement manifesting as lack of initiative and compliance may complicate pre-operative counselling [74].</li> </ul>	2-	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>Consider antacid treatment as aspiration prophylaxis due to gastrointestinal dysmotility [42, 43].</li> </ul>	4	7	13/17 (76.5%)	3
<b>Intraoperative:</b>				
<ul style="list-style-type: none"> <li>Regional anaesthesia, TIVA and volatile anaesthetics have been used effectively and safely, although rigidity cannot always be prevented [42, 43, 75, 76].</li> </ul>	3	9	15/15 (100%)	5
<ul style="list-style-type: none"> <li>Use of opioids should be avoided if possible, as there is increased sensitivity to such drugs, with an increased risk of respiratory [77] (and possibly intestinal) complications [72], in case this is not possible, use short-acting opioids.</li> </ul>	3	8	14/17 (82.4%)	3
<ul style="list-style-type: none"> <li>Pain, cold, electrical or mechanical stimulation and drugs that increase muscle membrane excitability may occasionally trigger myotonia [76] which may be resistant to pharmacological treatment.</li> </ul>	3	8.5	18/18 (100%)	2
<b>Postoperative:</b>				
<ul style="list-style-type: none"> <li>Avoid the use of opioids if possible [77] [72].</li> </ul>	4	9	17/19 (89.5%)	1
<ul style="list-style-type: none"> <li>Monitoring should include CO<sub>2</sub> measurements as the hypercapnic response is diminished, also considering that excessive sleepiness may be part of the disease spectrum [74].</li> </ul>	4	9	16/19 (84.2%)	1
<ul style="list-style-type: none"> <li>Early home discharge is not recommended as there is an increased risk of having prolonged ileus due to intestinal dysmotility.</li> </ul>	4	9	16/18 (88.9%)	2
<b>Specific considerations for Myotonic dystrophy type 2</b>				
<ul style="list-style-type: none"> <li>The same recommendation as for DM1 as outlined above apply, however, the overall complication rate appears to be lower [78, 79].</li> </ul>	2-	9	15/15 (100%)	5
<ul style="list-style-type: none"> <li>In a few cases, a postoperative CK rise and increased muscle complaints have been reported [78].</li> </ul>	2-	9	14/14 (100%)	6



**Table 4: Specific anaesthesia recommendations for muscular dystrophies**

<b>Preoperative recommendations</b>	<b>SIGN</b>	<b>Median score modified Delphi process</b>	<b>Respondents who scored <math>\geq 7</math></b>	<b>Abstained from voting (n)</b>
<ul style="list-style-type: none"> <li>There is a need for a thorough preoperative evaluation: consideration of the exact molecular diagnosis, extent of muscle weakness, and specific assessment of cardiorespiratory involvement depending on the specific genetic background [13, 15-17, 82]. FSHD and OPMD are only exceptionally associated with cardiorespiratory involvement.</li> </ul>	2-	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>Pre-operative airway assessment in patients with DMD at an advanced disease stage (i.e. wheelchair-bound patients) requires special attention [21].</li> </ul>	2-	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>In DMD patient, CNS involvement manifesting as cognitive deficits, speech problems and psychiatric comorbidities such as anxiety and depression may complicate pre-operative counselling [81].</li> </ul>	2+	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>An intravenous hydrocortisone stress regimen should be considered in patients who are or were recently (&lt; 1 year) on a course of corticosteroids (prednisolone <math>\geq 5\text{mg/day}</math> for &gt; 1 month) [60].</li> </ul>	2-	8.5	16/18 (88.9%)	2
<b>Intraoperative:</b>				
<ul style="list-style-type: none"> <li>AIR seems to be a specific complication of general anaesthesia in dystrophinopathies, especially in the paediatric age. AIR can cause life-threatening hyperkalaemia, and the risk of occurrence is possibly linked to the use of succinylcholine and/or volatile anaesthetics [33, 34]. This is an important consideration in the choice of anaesthetic drugs as part of a comprehensive risk-benefit comparison between alternative techniques for the individual patient.</li> </ul>	2+	9	18/18 (100%)	2
<ul style="list-style-type: none"> <li>There is no association with MH [33].</li> </ul>	2+	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>Impaired primary haemostasis and increased blood loss has been reported in DMD due to impaired vessel reactivity [83, 84].</li> </ul>	2-	9	17/17 (100%)	3
<ul style="list-style-type: none"> <li>We have not found any reports of AIR associated with dystrophies other than DMD and BMD but cannot exclude the hypothetical risk of AIR when exposed to volatile anaesthetics, particularly in LGMDs where genetic variants affect proteins involved in sarcolemmal stability [33].</li> </ul>	4	9	19/19 (100%)	1
<b>Postoperative:</b>				
<ul style="list-style-type: none"> <li>Restart oral medication (e.g., steroids in DMD) as soon as possible.</li> </ul>	4	9	19/19 (100%)	1

**Table 5A: Specific anaesthesia recommendations for congenital muscular dystrophies**

<b>Preoperative recommendations</b>	<b>SIGN</b>	<b>Median score modified Delphi process</b>	<b>Respondents who scored ≥7</b>	<b>Abstained from voting (n)</b>
• Evaluate the need for fiberoptic tracheal intubation in the presence of craniofacial abnormalities. In some forms with spinal rigidity and markedly reduced neck movement (in particular those due to variants in <i>LMNA</i> , <i>COL6A</i> , <i>LAMA2</i> , or <i>SELENON</i> ) [80], intubation may be difficult.	3	9	17/17 (100%)	3
• Specific attention to potential cardiac involvement should be paid in forms due to variants in <i>LAMA2</i> , and the alpha-dystroglycanopathies.	3	9	16/16 (100%)	4
• Respiratory involvement should be considered in patients with variants in <i>SELENON</i> , <i>COL6</i> , <i>LAMA2</i> and the alpha-dystroglycanopathies [80].	3	9	15/15 (100%)	5
<b>Intraoperative:</b>				
• More specific considerations depend on the underlying pathology.	4	9	17/17 (100%)	3
• There is no association with MH.	4	9	18/18 (100%)	2
• We have not found any reports of AIR associated with dystrophies other than DMD and BMD but cannot exclude the hypothetical risk of AIR when exposed to volatile anaesthetics. TIVA and volatile anaesthetics have both been used effectively and safely and should be adapted to the case and surgery in question.	4	8	17/17 (100%)	3
<b>Postoperative:</b>				
• Nutrition needs to be monitored as reduced muscle mass can cause postoperative hypoglycaemia up to several days after surgery [24, 26].	3	9	15/15 (100%)	5

**Table 5B: Specific anaesthesia recommendations for congenital myopathies**

<b>Preoperative recommendations</b>	<b>SIGN</b>	<b>Median score modified Delphi process</b>	<b>Respondents who scored ≥7</b>	<b>Abstained from voting (n)</b>
• Evaluation of the need for fiberoptic tracheal intubation in the presence of craniofacial abnormalities. In some forms with spinal rigidity and markedly reduced neck movement (in particular those due to variants in <i>SELENON</i> and <i>NEB</i> ), intubation may be difficult.	3	9	17/17 (100%)	3
• In X-linked myotubular myopathy (XLMTM), liver function tests and coagulation studies should be performed preoperatively because of potentially associated hepatic involvement [18].	3	9	14/14 (100%)	6
• Cardiac involvement is common in <i>TTN</i> -related myopathies and the much rarer forms due to variants in the <i>MYH7</i> gene.	3	9	16/16 (100%)	4
• More specific considerations depend on the underlying pathology. Special attention to relevant respiratory involvement should be given in patients with variants in <i>MTM</i> , <i>NEB</i> , <i>ACTA1</i> , <i>TTN</i> and <i>RYR1</i> (in particular recessive variants) [20, 87]. In contrast to the muscular dystrophies, respiratory impairment may be out of proportion to the degree of limb girdle weakness (for example in <i>NEB</i> - and <i>SELENON</i> -associated forms) and must be anticipated with a high degree of suspicion [87, 88].	3	9	16/16 (100%)	4
<b>Intraoperative recommendations</b>				
• An increased bleeding tendency due to a coagulopathy has been described in patients with myotubular myopathy [18].	3	9	15/16 (93.8%)	4

<ul style="list-style-type: none"> <li>MH is mainly associated with <i>RYR1</i> variants [48] that are found in dominantly or recessively inherited <i>RYR1</i>-related myopathies [45] and the King-Denborough syndrome [49]. Less frequently, MH has also has been described in association with variants in <i>CACNA1S</i> [47] or <i>STAC3</i> [46]. In case of (presumed) MH-susceptibility, use of volatile anaesthetics and/or succinylcholine is strictly contra-indicated [70].</li> </ul>	2+	9	19/19 (100%)	1
<ul style="list-style-type: none"> <li>Nutrition needs to be monitored as reduced muscle mass can cause postoperative hypoglycaemia up to several days after surgery. [24, 26]</li> </ul>	3	9	17/17 (100%)	3

**Table 6A: Specific anaesthesia recommendations for mitochondrial myopathies**

<b>Preoperative recommendations</b>	<b>SIGN</b>	<b>Median score modified Delphi process</b>	<b>Respondents who scored ≥7</b>	<b>Abstained from voting (n)</b>
• Fasting for more than four hours should trigger a glucose drip, to be continued until oral intake is resumed [25].	4	9	19/19 (100%)	1
• Measurement of blood lactate levels, glucose and serum electrolytes at baseline and during the procedure is important to monitor perioperative metabolic homeostasis.	4	9	19/19 (100%)	1
<b>Intraoperative:</b>				
• Mitochondrial disorders are considered to increase the risk of propofol infusion syndrome [54-56] although there are case series reporting no complications [93, 94]. The cases of propofol infusion syndrome in patients with mitochondrial disorders occurred after 3-5 days of propofol infusion [54-56]. However, propofol infusion syndrome has also been reported after under an hour of infusion in healthy children and after two hours in healthy adults [53].	3	8.5	17/18 (94.4%)	2
• Propofol as an induction agent is safe [95] but should not be used for maintenance of anaesthesia. However, precaution is needed in case of preoperative metabolic deterioration [90].	3	9	16/16 (100%)	4
• Although patients may be hypersensitive, volatile anaesthetics are considered safe [1, 2, 95].	4	9	15/15 (100%)	5
• Etomidate, barbiturates and ketamine are considered safe as induction agents [95].	4	9	15/15 (100%)	5
• Intravenous fluids administered during periods of fasting (especially in paediatric patients) should contain at least 5% glucose (except if the patient is on a ketogenic diet to control seizures). Infusion solutions should be lactate-free, electrolyte solutions containing acetate rather than lactate are preferred [96].	4	9	17/18 (94.4%)	2
• Avoid hypo- and hyperthermia.	4	9	18/18 (100%)	2
<b>Postoperative:</b>				
• In case of post-operative ICU admission and/or mechanical ventilation, the use of propofol should be limited as there is an increased risk for propofol infusion syndrome [54-56].	3	9	18/18 (100%)	2
• Abnormal response to both hypoxaemia and hypercapnia has been observed in Leigh's syndrome [97].	3	9	13/13 (100%)	7

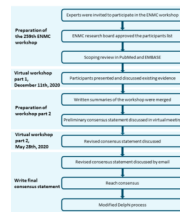
**Table 6B: Specific anaesthesia recommendations for muscle glycogen storage diseases**

<b>Preoperative recommendations</b>	<b>SIGN</b>	<b>Median score modified Delphi process</b>	<b>Respondents who scored ≥7</b>	<b>Abstained from voting (n)</b>
• Avoid circumstances that may increase metabolic burden (e.g. hypo/hyperthermia, hypoglycaemia, hypovolaemia).	4	9	19/19 (100%)	1
• Fasting for more than four hours should trigger a glucose drip, to be continued until oral intake is resumed.	4	9	19/19 (100%)	1
<b>Intraoperative recommendations</b>				
• Volatile anaesthetics are considered safe in all GSDs. Positive <i>in vitro</i> contracture tests have been reported in patients with GSDV [98] but these	4	9	19/19 (100%)	1

tests are known to be non-specific in a range of neuromuscular disorders [99]. There are no clinical reports of MH in patients with GSDV.				
• Avoid use of tourniquets, prolonged use of positions associated with rhabdomyolysis and high frequent cycling of intermittent non-invasive blood pressure measurements due to risk of rhabdomyolysis (especially in GSDV).	4	9	19/19 (100%)	1
• Short term TIVA with propofol is considered safe in most GSDs but should be avoided in GSDII, especially in case with severe cardiac involvement.	4	8.5	14/14 (100%)	6
• Monitor glucose, pH, ammonia, lactate, body temperature. Urinary catheter to monitor for myoglobinuria is also recommended.	4	8.5	17/18 (94.4%)	2
<b>Table 6C: Specific anaesthesia recommendations for muscle lipid metabolism disorders</b>				
<b>Preoperative recommendations</b>				
• Avoid circumstances that may increase metabolic burden and provoke catabolic states (e.g. hypo/hyperthermia, hypoglycaemia, hypovolemia).	4	9	20/20 (100%)	0
• Fasting for more than four hours should trigger a glucose drip, to be continued until oral intake is resumed.	4	9	18/18 (100%)	2
• Evaluation for the presence of a cardiomyopathy and coagulopathy (in particular in the presence of hepatomegaly).	4	9	19/19 (100%)	1
<b>Intraoperative recommendations</b>				
• If applicable, propofol should be avoided because of its elevated lipid content in the setting of impaired fatty acid oxidation; however short term use of propofol has been reported in a number of these disorders (MCAD, LCHAD, MTP and VLCAD without complications [100, 101].	3	9	16/16 (100%)	4

**Table 7:** Risk prediction matrix: multi-system features of patients with neuromuscular disorders.

	Neuromuscular junction disorders	Muscle channelopathies	Myotonic dystrophies	Muscular dystrophies	Congenital muscular dystrophies	Congenital myopathies	Mitochondrial myopathies	Metabolic myopathies	Lipid metabolism disorders
<b>Neurological signs &amp; muscular impairment</b>									
Ataxia							■		
Cerebral thrombosis							■		
Cognitive impairment			■	■					
Epilepsy					■		■		
Encephalopathy			■				■		■
Myoclonus							■		
Stroke-like episodes							■		
Weakness	■	■	■	■	■	■	■	■	■
<b>Airway</b>									
Aspiration	■		■	■	■	■	■	■	■
Difficult intubation				■	■	■		■	
Dysphagia	■		■	■	■	■	■	■	■
Macroglossia				■	■			■	
<b>Respiratory</b>									
Respiratory insufficiency	■		■	■	■	■	■	■	■
<b>Cardiac</b>									
Arrhythmias		■	■	■	■	■	■	■	■
Cardiomyopathy		■	■	■	■	■	■	■	■
Risk of sudden death		■	■	■	■	■	■		
<b>Other</b>									
Increased bleeding tendency				■		■			
Diabetes			■				■		
Exercise intolerance	■	■	■	■	■	■	■	■	■
Hypoglycaemia				■			■	■	■
Lactic acidosis							■		■
Rhabdomyolysis				■	■	■	■	■	■
Spinal deformity				■	■	■	■	■	
Malignant hyperthermia susceptibility		■				■			
Myotonia		■	■						



ENE\_15526\_220329\_Figure 1\_R1.tif

# MANAGE-PD

Tool for Making Informed Decisions to  
Aid Timely Management of Parkinson's Disease



**MANAGE-PD** allows you to:

- Identify PD patients inadequately controlled on oral medications
- Determine which patients with PD may be adequately controlled on their current treatment regimen or may require changes to their treatment regimen



Scan the QR code to  
access to the web

Click here to  
access to the web



MANAGE-PD is an AbbVie Inc. registered Medical Device. It is a collaborative research and development effort between AbbVie Medical Affairs and Health Economics and Outcomes, the Parkinson's Foundation and an international panel of Movement Disorder Specialists.

©2022 AbbVie Inc. All rights reserved. The Parkinson's Foundation logo is the sole property of the Parkinson's Foundation used with written permission. Any use of the Parkinson's Foundation name or logo without Foundation permission is prohibited. All content in <https://www.managepd.eu/> is intended only for informational use by healthcare professionals and is not offered as or intended to be medical advice for any particular patient. This information is not intended for patients. Only a healthcare professional exercising independent clinical judgement can make decisions regarding appropriate patient care and treatment options considering the unique characteristics of each patient.

PD: Parkinson's Disease