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INFOGRAPHIC

GUIDELINES

2025 ESAIC and ESPA Guidelines on neuromuscular block in anaesthetised children

Indications, monitoring and reversal

Francis Veyckemans, Sophie Debouche, Jost Kaufmann, Nicola Disma, Angela Amigoni, Giulia Bonatti, Michelle Icka Christensen, Thomas Engelhardt, Alexander Fuchs, Thomas Fuchs-Buder, Tom G. Hansen, Jacob Karlsson, Maren Kleine-Brueggeney, Andrea Clarissa Lusardi, Thomas Riva, Jean-Philippe Salaün, Vera Saldien, Rita Saynhalath, Mikkel Scavenius, Denis Schmartz, Luc E. Vanlinthout, Ricardo Carlos Vieira, Britta S. von Ungern-Sternberg, Carolina S. Romero and Arash Afshari

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Keywords

neuromuscular block, paediatric, neuromuscular blocking agents, neuromuscular monitoring, reversal

Summary

Question 1 - Is a neuromuscular block necessary to facilitate tracheal intubation in children, including specific considerations for some subgroups?

- We recommend the use of a neuromuscular blocking agent (NMBA) to facilitate tracheal intubation in children under general anaesthesia in the operating room when maintaining spontaneous breathing is not required. (*Strong recommendation with moderate level of evidence*)
- Outside the operating room, we suggest using a NMBA for tracheal intubation, considering patient safety, availability of necessary devices and drugs, provider competency and the presence of auxiliary support. *(Conditional recommendation with very low level of evidence)*

From the UCLouvain Medical School (FV); European Society of Anaesthesiology and Intensive Care (ESAIC), Research & Clinical Trial Coordinator, ESAIC Headquarters, Brussels, Belgium (SD); Department for Pediatric Anaesthesia, Children's Hospital Cologne, Cologne, Germany & Faculty for Health, University of Witten/Herdecke, Witten, Germany (JK); Unit for Research in Anaesthesia, IRCCS Istituto Giannina Gaslini, Genova (ND); Pediatric Intensive Care Unit, Department of Mother's and Child's Health University Hospital of Padova, Padova (AA); Unit for Research in Anaesthesia, IRCCS Istituto Giannina Gaslini, Genova, Italy (GB); Department of Pediatric and Obstetric Anaesthesia, University of Copenhagen, Rigshospitalet, Denmark (MIC); Department of Anaesthesia, McGill University, & Department of Anesthesia, Montreal Children's Hospital, Montreal, Quebec, Canada (TE); Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (AF); Department of Anaesthesia, Critical Care and Perioperative Medicine, CHRU Nancy, University of Lorraine, Nancy, France (TFB); Department of Anaesthesiology & Intensive Care, Akershus University Hospital, Lørenskog, Norway & Institute of Clinical Medicine, University of Oslo, Oslo, Norway (TGH); Karolinska Institute Department of Physiology and Pharmacology (FYFA), C3, Section of Anaesthesiology and Intensive Care, Stokholm, Sweden (JK); Deutsches Herzzentrum der Charité (DHZC), Department of Cardiac Anaesthesiology and Intensive Care Medicine (MKB); Charité - Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, (MKB); German Center for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany (MKB); Unit for Research in Anaesthesia, IRCCS Istituto Giannina Gaslini, Genova, Italy (ACL); Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland (TR); Department of Anaesthesiology and Critical Care Medicine, Centre Hospitalier Universitaire Caen Normandie; Normandie Université, UNICAEN, Université Caen Normandie, INSERM, GIP CYCERON, Institut Blood and Brain @Caen-Normandie (BB@C), UMR-S U1237, Physiopathology and Imaging of Neurological Disorders (PhIND), Caen, France (JPS); Department of Anaesthesiology, Antwerp University Hospital, Edegem, Faculty of Medicine and Health Science, University of Antwerp, Antwerp, Belgium (VS); The University of Texas Southwestern Medical Center and Children's Health, Dallas (RS); Outcomes Research Consortium, Houston, Texas, USA (RS); Department of Paediatric and Obstetric Anaesthesiology, Juliane Marie Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark (MS); H.U.B - Hôpital Érasme, Université libre de Bruxelles, Department of Anaesthesiology, Reanimation, Perioperative Medicine and Algology, Brussels, Belgium (DS); Department of Anaesthesiology, Erasmus MC Sophia Children's Hospital University Medical Centre Rotterdam, Rotterdam, The Netherlands (LEV); Universidade de São Paulo, Faculdade de Medicina, Disciplina de Anestesiologia (RCV); Universidade de São Paulo (HC-FMUSP), Faculdade de Medicina, Hospital das Clínicas, Instituto da Criança e do Adolescente, São Paulo, SP, Brazil (RCV)); Department of Anaesthesia and Pain Medicine, Perth Children's Hospital, Child and Adolescent Health Service, Nedlands (BvUS); Division of Emergency Medicine, Anaesthesia and Pain Medicine (BvUS); Institute for Paediatric Perioperative Excellence, The University of Western Australia, Perth (BvUS); Perioperative Medicine Team, The Kids Research Institute Australia, Nedlands, Western Australia, Australia (BvUS); ESAIC Guidelines Committee, Anesthesia and Intensive Care Department, University General Hospital Valencia, Universidad Europea de Valencia, Valencia, Spain (CSR); Department of Paediatric and Obstetric Anaesthesia, Rigshospitalet and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark;, European Society of Anaesthesiology and Intensive Care Guideline Committee (ESAIC), Brussels, Belgium (AA)

Correspondence to Francis Veyckemans, MD, UCLouvain Medical School, Belgium
E-mail: veyckemansf@gmail.com

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- We recommend the use of a NMBA to facilitate tracheal intubation in neonates and infants in the OR, when maintaining spontaneous breathing is not required. *(Strong recommendation with moderate level of evidence)*
- Should, for any reason, the decision be made not to use an NMBA for intubation, we recommend achieving sufficient depth of anaesthesia, including high-dose opioids or different adjuvants, such as opioids and/or sevoflurane in addition to propofol, and having a skilled and experienced clinician perform the intubation. (*Strong recommendation with moderate level of evidence*)
- We suggest considering the use of a NMBA for tracheal intubation in children in the emergency room to improve intubation conditions, decrease the number of attempts, and reduce the risk of complications (*Conditional recommendation with very low level of evidence*)
- For rapid sequence induction and intubation, we recommend using rocuronium rather than succinylcholine. *(Strong recommendation, moderate level of evidence)*
- The panel abstained from providing recommendations for intubation in the neonatal ICU and paediatric ICU

Question 2: Does neuromuscular block affect surgical conditions in children?

- We recommend a selective approach to NMB in paediatric abdominal surgery, avoiding deep NMB for minor procedures such as inguinal hernia repair, and establishing deep NMB for major procedures such as hepatobiliary surgery, when necessary. Deep NMB should be considered for enhancement of the surgical conditions and ventilation when indicated. (*Conditional recommendation based on moderate level of evidence).*
- We suggest that NMB can improve surgical and ventilatory conditions when a second-generation supraglottic airway is used for abdominal surgery (*Conditional recommendation based on low level of evidence*)

Question 3 - What are the strategies for the diagnosis and treatment of residual neuromuscular block in children?

- We recommend, whenever an NMBA is used, quantitative neuromuscular monitoring be applied to modulate the level of neuromuscular block and to rule out a residual neuromuscular block before extubation. (*Strong recommendation based on moderate level of evidence*)
- We suggest neuromuscular monitoring at the adductor pollicis site as the first choice and the flexor hallucis brevis as an alternative if the adductor pollicis site is not accessible (*Conditional recommendation based on very low level of evidence*)
- We suggest electromyography-based rather than acceleromyography-based quantitative neuromuscular monitoring and calibrating the device before administering a NMBA (*Conditional recommendation based on very low level of evidence*)
- We recommend sugammadex over neostigmine for the reversal of aminosteroid NMBA in children due to its faster recovery time, shorter time to extubation, and more effective reversal of moderate and deep block. *(Strong recommendation based on moderate level of evidence)*
- In children under the age of 2 years, sugammadex can be safely used for reversal of aminosteroid NMBA at the same dose range as for children and adults. *(Strong recommendation based on moderate level of evidence)*
- To prevent residual neuromuscular block or recurarisation, we suggest avoiding excessive doses of rocuronium and using systematic quantitative neuromuscular monitoring to ensure adequate recovery before extubation. (*Conditional recommendation based on very low level of evidence*)
- In children aged less than 2 years or when a large total dose of rocuronium or vecuronium has been used, we suggest an extended observation period in the post anaesthesia care unit (PACU) if sugammadex was used for reversal. (*Conditional recommendation based on very low level of evidence*)
- To exclude a prolonged duration of action of succinylcholine, we suggest using clinical assessment (e.g. return of spontaneous breathing and movements) and NMB monitoring to evaluate recovery after its administration. *(Conditional recommendation based on very low level of evidence)*

Question 4: Neuromuscular block in special conditions.

- We recommend avoiding succinylcholine in children with any neuromuscular disease due to an increased risk of rhabdomyolysis and resistance to its effects (myasthenic syndromes). Instead, nondepolarising NMBA should be preferred, including for rapid sequence induction and intubation
- If an NMBA is necessary, rocuronium or vecuronium is preferred, as they can be reversed with sugammadex. Sugammadex should be preferred over neostigmine for reversal to provide a more predictable and safer recovery profile.
- Regardless of the NMBA used, its dose should be titrated according to the child's level of NMB, as evaluated with quantitative neuromuscular monitoring.
- When using a nondepolarising NMBA in children with a myopathy, we suggest evaluating the baseline train of four (TOF) ratio before NMBA administration.
- Neostigmine should not be used in children with myasthenic disorders as it can contribute to postoperative cholinergic or myasthenic crises and is even contraindicated in some forms of congenital myasthenia.

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- Due to the delayed onset and prolonged recovery of NMB, we suggest using titrated doses of all nondepolarising NMBA (e.g. rocuronium $\leq$0.3 mg kg^{-1}) in children with muscular dystrophy to minimise the risk of residual NMB at the end of the intervention.
- We suggest the use of a NMBA in children with cerebral palsy, taking into account their altered pharmacodynamic and/or pharmacokinetic state, and suggest quantitative neuromuscular monitoring to minimise complications related to resistance or sensitivity to NMBA.
- We suggest quantitative monitoring of NMB in children with chronic use of anticonvulsants, as these children may need higher doses or more frequent administration of aminosteroid NMBA to maintain NMB.
- As giving succinylcholine shortly after neostigmine can result in a prolonged duration of action, we suggest quantitative monitoring of NMB if succinylcholine is given after administration of neostigmine
- In case NMB is required less than 2 h after reversal of rocuronium with sugammadex, we suggest using a nonsteroidal NMBA or titrating the rocuronium dose based on quantitative monitoring to achieve sufficient NMB.

GRADE for all of the above statements: *Conditional recommendations based on low or very low level of evidence*

Introduction

Neuromuscular blocking agents (NMBAs) are a common component of balanced anaesthesia that can be used at induction to facilitate airway management, and during maintenance to improve surgical conditions or ventilation. Data from the European APRICOT study showed that 60.8% of tracheal intubations were performed with a NMBA.[1] Moreover, neuromuscular block (NMB) NMB is not always monitored in children, especially in neonates and infants, as illustrated by the same study, where only 16% of the children who had received a NMBA had neuromuscular monitoring; however, there is significant institutional variation.[2] This picture appears to be similar in North America.[3] Absence of monitoring has been reported to increase the risk of residual neuromuscular block and postoperative respiratory complications, or even recurarisation.[4,5] The recent availability of paediatric electromyography-based monitors might contribute to a change in practice.[6,7]

The recommended dosage of the reversal agent neostigmine is based on few studies, and the dose of sugammadex for rocuronium reversal is the same as for adults and based on limited age-specific data.[8–10]

In the recent 'Peri-operative management of neuromuscular blockade. A guideline from the European Society of Anaesthesiology and Intensive Care', the authors issued an informal call for a specific paediatric guideline to be produced.[11] As there is no previous guideline on the use of NMBA in anaesthetised children, a Task Force for this guideline was appointed and approved by the ESAIC guideline committee in February 2024. It was subsequently decided to provide three separate parallel publications:

- a formal clinical guideline following the ESAIC guideline committee standards
- a systematic review assessing the effects of avoidance vs. the use of NMBA for the facilitation of tracheal intubation in children and infants
- a publication on the development of the neuromuscular junction and the pharmacology of the current NMBA and their antagonists.[12] Professors Vera Saldien (Belgium) and Tom G. Hansen (Denmark/Norway) were invited to write the latter manuscript and to participate in the Delphi rounds of the clinical guideline manuscript.

This proposal was subsequently accepted by the Editor-in-Chief of the *European Journal of Anaesthesiology*. A Task Force meeting was organised in Munich on 27 May 2024, during the annual ESAIC Euroanaesthesia Congress and was officially presented in the ESAIC Newsletter of July 2024.

Materials and methods

The Task Force developed clinical queries in the form of four questions: the first three questions were adapted from the adult guidelines and included emergency and intensive care:

(1) Is NMB necessary to facilitate tracheal intubation in children?,
(2) Does the intensity of NMB affect surgical conditions in children during abdominal surgery, and outcomes in the paediatric ICU (PICU) or neonatal ICU (NICU)?
(3) What are the strategies for the diagnosis and treatment of residual NMB in children?
(4) The fourth clinical question emphasises specific comorbidities such as the presence of a neuromuscular disease or cerebral palsy, which are otherwise rarely considered in guidelines.

These four questions were adapted to the Population/Intervention/Comparison/Outcome (PICO) approach by the methodologist (AA) and information specialist Janne Vendt (JV) (Copenhagen University Hospital, Copenhagen, Denmark) to facilitate the search strategy. The initial list of PICOs was further revised and approved by the Task Force. PICOs were based on the research questions to be addressed.

The main clinical queries and related PICOs were as follows:

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(1) Is NMB necessary to facilitate tracheal intubation in children, including specific considerations for some subgroups?
   - PICO1: NMB for children undergoing general anaesthesia in the operating room and outside it?
   - PICO2: NMB for intubation of neonates and infants?
   - PICO3: Which NMBA for rapid sequence induction and intubation in children (RSII)?
   - PICO4: NMB for intubation in the emergency room?
   - PICO5: NMB for intubation in the PICU?
   - PICO6: NMB for intubation in the NICU?
   - PICO7: Are intubation conditions equivalent between NMB and high-dose remifentanil/alfentanil to facilitate tracheal intubation?
   - PICO8: Are intubation conditions equivalent between NMB and propofol to facilitate tracheal intubation?

(2) Does the depth of neuromuscular block affect outcomes in children?
   - PICO1: Does NMB affect surgical conditions during abdominal surgery?
   - PICO2: Does NMB affect outcomes in the PICU?
   - PICO3: Does NMB affect outcomes in the NICU?

(3) What are the strategies for the diagnosis and treatment of residual NMB in children?
   - PICO1: Does the use of quantitative neuromuscular monitoring at the adductor pollicis muscle allow diagnosis of residual NMB, and does a train of four (TOFr) ratio at least 0.9 allow ruling it out? Are there any alternative sites for the use of quantitative neuromuscular monitoring in children?
   - PICO2: Is there any difference in efficacy between neostigmine and sugammadex when reversing rocuronium or vecuronium?
   - PICO3: What is the risk of residual NMB or recurarisation after the administration of sugammadex?
   - PICO4: Can succinylcholine be associated with prolonged NMB?
   - PICO5: Monitoring of NMB in PICU/NICU?

(4) Special conditions: children with a neuromuscular disease, children with cerebral palsy, children on anticonvulsant drugs
   - PICO1: Children with neuromuscular disease
   - PICO2: Children with cerebral palsy
   - PICO3: Children on anticonvulsant drugs
   - PICO4: Need for NMB following reversal with neostigmine or sugammadex

Types of studies

Data analysis included all randomised, parallel and quasi-randomised studies (including crossover studies) and observational studies performed in children that addressed any of the above queries. Previous meta-analyses and systematic reviews were considered when available and met the inclusion criteria. Data from quasi-randomised and observational, and large retrospective studies were included for those PICOs where only a few randomised controlled trials (RCTs) or high-quality data were available to provide a trustworthy recommendation. Narrative reviews, case series, and case reports were only considered if there were no other available data from studies mentioned above. Published abstracts from conference proceedings and registered but not completed studies were excluded.

Study participants

The qualitative and quantitative analysis of the literature was confined to children (< 18 years old) in whom an NMBA was used to perform tracheal intubation with general anaesthesia, or during maintenance of anaesthesia to improve surgical conditions or ventilation, or to ensure adequate ventilation in the PICU or NICU.

Types of interventions

We included the following interventions: NMB (type of NMBA: succinylcholine, atracurium, cisatracurium, mivacurium, vecuronium and rocuronium), quantitative neuromuscular monitoring [defined as acceleromyography (AMG) or electromyography (EMG) -based], neostigmine or sugammadex-based reversal. We also considered the different settings and circumstances (operating room, PICU and NICU, emergency department, RSII) where NMBA can be used in children.

Types of comparators

We included the following comparators: no or any degree of NMB, neostigmine-based or sugammadex-based reversal, the use of quantitative neuromuscular monitoring, the presence of a neuromuscular disorder, the presence of cerebral palsy and the use of anticonvulsants.

Types of outcomes

The main outcomes studied varied with the clinical question and specific PICOs. The main outcome was the first attempt intubation rate for Question 1, the quality of surgical conditions or ventilation for Question 2, the incidence of residual NMB or recurarisation for Question 3, and a specific outcome for each PICO in Question 4.

Search method for identification of studies

The literature search strategy was developed by the trial search and information specialist JV in close collaboration with the author FV and the ESAIC group methodologist and Cochrane editor AA. We systematically searched for eligible studies in the following databases: Medline (Ovid SP, 1946 – search date, 6 PICO-specific searches), Central (Cochrane Database Systematic Reviews, 5 PICO-specific searches) and Epistemonikos (https://www.epistemonikos.org/en/advanced_search) for the systematic reviews. A combination of subject headings and free-text terms was used for the topic search. We

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added filters for study types inspired by National Institute for Health and Care Excellence (NICE) but adapted to our use (https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literaturesearching-and-evidence-submission#developing-searchstrategies). These search strategies are presented in Appendix 1, http://links.lww.com/EJA/B252. The bibliographic references and citations of included studies and systematic reviews were checked for other eligible studies. During the screening process, the search was limited to the period from 1995 to 2024, and only references published in this period were screened. The Task Force members were also encouraged to add any missing articles of interest that they were aware of and to conduct additional searches themselves. The titles resulting from the searches were allocated to the above four question groups via the Ryyan review system (https://www.rayyan.ai) and screened by respective Task Force members as follows: Q1: AA, FV, BvUS, JoK, JaK, LV, RV, RS; Q2: JoK, LV, MS, TR, MKB, TE, AF; Q3: ND, BvUS, DS, J-PS, RV, RS, TF-B, GB, AL; and Q4: FV, JaK, JoK, MS, TE, TR, ND, AF. The electronic searches for the guideline were run in June 2024.

Search results

Out of a total number of 21 017 articles initially detected through the electronic search in the three aforementioned databases, 411 were finally selected following three steps of screening based on the title, abstract, and finally the full content of each article. This selection process was completed by 19 October 2024. The distribution of these studies according to the PICOs is described in Appendix 2, http://links.lww.com/EJA/B252. A few papers published after October 2024 and until October 2025, as identified by members of the Task Force, were added during the data analysis process. However, there was no comprehensive systematic additional search like the initial one.

Assessment of risk of bias in included studies

For each PICO, a pair of review authors were supplied with literature for assessment of risk of bias by SD. They extracted the relevant data of the included papers and summarised them in Excel tables with their respective risk of bias and overall study quality evaluated using a SIGN checklist specific for the type of study (RCT, observational study) (https://www.sign.ac.uk/using-our-guidelines/methodology/checklists/). For our systematic review (Q1 PICO1) (M.I. Christensen, A. Creutzburg, M. Vested, in press), we used the Cochrane Risk of Bias tool (first edition). Disagreement regarding assessment of risk of bias was settled in discussion with the methodologist (AA).

Assessment of quality of the evidence

The recommendations were formulated based on the findings of the included studies in conjunction with their methodological quality. Decisions to assess the level of evidence for a recommendation were based on the calibre and type of the literature, observed inconsistencies, indirectness or directness of the evidence, overall impression of the quality of the evidence, the presence of publication bias, magnitude of effect, dose–response gradient and plausible residual confounding.

Initially, we used the classification of recommendations and level of evidence criteria of the American Heart Association and of the Grading of Recommendations Assessment Development and Evaluation (ref : https://www.ighg.org/international-guideline-harmonization-group/methods/grading-system/). However, due to changes in the ESAIC guideline policies in 2025, moving towards implementation of evidence synthesis and grading as outlined by GRADE methodology, our recommendations have been revised accordingly. (Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook).

Development of recommendations

The recommendations developed for the clinical questions and PICOs followed GRADE methodology (their significance is illustrated in Fig. 1). These recommendations were then discussed and re-discussed as required with the entire expert panel in light of the data synthesis, the risk of bias and the quality of the evidence.

Every single recommendation or suggestion was subject to the voting and consensus following a four-step Delphi process. This also allowed discussion of the methodological quality of the supporting literature when the quality of evidence was low or when rephrasing of recommendations was needed. A recommendation or suggestion was adopted when the approval rate was at least 75%.

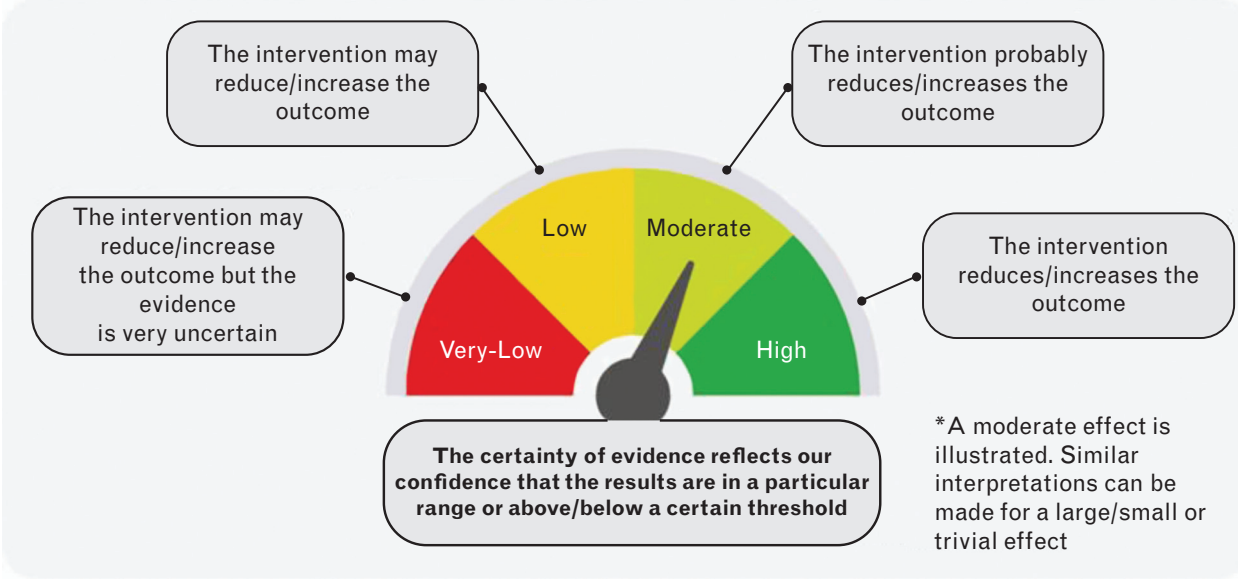
The first round was organised in April 2025: 41/52 proposals were approved at the end of the first round. The second round was performed in May 2025: 44/52 proposals were approved.

The third was organised as a hybrid meeting (face-to-face at EuroAnaesthesia 2025 in Lisbon and videoconferencing for Task Force members not present) to obtain a consensus on the eight remaining recommendations or clinical practice statements.

The recommendations suggestions and their respective rationale were then merged into a single document shared on Sharepoint by the lead author (FV). The final version of the document was subsequently reviewed several times and finally endorsed by all members of the expert panel in October 2025 after a last Delphi vote.

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Fig. 1 Interpretation of the levels of certainty of evidence for intervention effects. The figure illustrates the interpretation of the certainty of evidence on a moderate effect. Similar interpretations can be made for a large effect (e.g. the intervention results in a large reduction/increase), for a small effect (e.g. the intervention results in a slight reduction/increase) or for no important effect (the intervention results in no important difference. (reprinted with permission from https://book.gradepro.org/guideline/overview-of-the-grade-approach).



Guidelines:

Question 1 - Is neuromuscular block necessary to facilitate tracheal intubation in children, including specific considerations for some subgroups?

PICO1: Neuromuscular block for children undergoing general anaesthesia in the operating room and outside it

Recommendation

- **We recommend the use of a NMBA to facilitate tracheal intubation in children under general anaesthesia in the operating room when maintaining spontaneous breathing is not required.**
  GRADE: *Strong recommendation with moderate level of evidence*
- **Outside the operating room, we suggest using a NMBA for tracheal intubation, considering patient safety, availability of necessary devices and drugs, provider competency and the presence of auxiliary support.**
  GRADE: *Conditional recommendation with very low level of evidence*

Rationale:

There were four systematic reviews summarised in Appendix 3, Table 1, http://links.lww.com/EJA/B252: First, in a systematic review conducted following Cochrane recommendations for the purpose of this guideline the avoidance of NMBA significantly increased the incidence of difficult intubation [relative risk (RR) 3.47; 95% CI 2.52 to 4.77, $I^2 = 18\%$, random effect model] and incidence of failed intubation in children (RR 5.12; 95% CI 2.49 to 10.53; $I^2 = 0\%$, random effects model).[13] The authors included 30 RCTs involving children undergoing orotracheal or nasotracheal intubation using direct laryngoscopy or video-laryngoscopy for any type of procedure requiring general anaesthesia. A total of 2276 participants were included, with five trials studying solely neonates and infants, while the remaining 25 trials included infants and children aged 3 months to 14 years.[14–43] In 28 trials, the operating room was the setting for elective surgery, and children had an ASA physical status score of I-II. Only four trials included patients with difficult airways. Midazolam was the most frequently used premedication. The overall findings were consistently observed across all settings, ages, types of induction agents, types of anaesthetic agents, and NMBA and dose regimen employed, and were independent of risk of bias domains, indicating consistency and precision.

To adjust for the risk of random error and multiple testing, and in order to calculate the required information size to accept or refute the findings of the conventional meta-analyses, trial sequential analysis was applied with continuity correction for the primary outcome, and with the inclusion of zero event trials in the α-adjusted meta-analysis. For the primary outcome, the incidence of difficult tracheal intubation, an α-spending adjusted

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RR of 3.68 (95% CI 2.22 to 6.11; $\alpha = 5\%$, $\beta = 90\%$, continuity correction factor = 0.01, random effects model) was obtained in favour of using NMBA in children and infants. In addition, boundaries and futility were crossed, indicating firm evidence supporting the use of NMBA.

Second, a recently published systematic review further supports the use of NMBA in children (0 to 12 years old).[44] The use of NMBA significantly increased the likelihood of both excellent and acceptable intubating conditions. The authors found strong evidence that the risk of unacceptable intubation conditions (RR = 0.35; 95% CI 0.22 to 0.46, $I^2 = 23\%$) and failed first intubation attempts (RR = 0.25; 95% CI 0.14 to 0.42; $I^2 = 0\%$) was significantly lower when using an NMBA. Children aged 24 months or less had higher rates of unacceptable intubation conditions (difficult laryngoscopy, vocal cords closed or closing, strong body movements or sustained coughing) and failed first pass attempts compared to those more than 24 months, in both the NMBA and muscle relaxant-free groups. In the younger group (≤24 months), the NMBA group had 15.8% unacceptable conditions and 3.2% failed attempts, while the relaxant-free group had 26.9 and 15.6%, respectively. Among older children (>24 months), these rates were lower: 9.2 and 1.3% in the NMBA group, and 16.2 and 5.6% in the relaxant-free group. This suggests younger children are at higher risk for suboptimal intubation outcomes regardless of NMBA use. In addition, the review identified a higher incidence of adverse respiratory events (26%) and arterial desaturation (14%) at induction in the control groups compared to those receiving rocuronium (0%).[44]

Across both systematic reviews, rocuronium was the most studied and preferred drug, with dose regimens of 0.25 to 1.5 mg kg^{-1}, and succinylcholine (2 mg kg^{-1}) was the second most studied drug. However, the evidence for atracurium, cisatracurium, and mivacurium in children remains limited.

Third, a systematic review from 2012 of tracheal intubation without NMBA in children aged 1 to 10 years assessed the role of adjuvants in various combinations when propofol (14 studies, 807 children) or sevoflurane (nine studies, 696 children) was used for induction.[45] A weighted average of 80.5% of excellent intubation conditions with propofol and succinylcholine in five studies (123 children) was used as a comparator. For sevoflurane induction, they found a weighted average of excellent intubation conditions of 41% with sevoflurane alone, 84% with sevoflurane with 2 mg kg^{-1} lidocaine, 88.7% for sevoflurane with propofol 2 mg kg^{-1} and 75 or 81.2% with sevoflurane with 1 or 2 μg kg^{-1} remifentanil, respectively. Of note, ventilation was assisted before intubation in most studies. The end-tidal concentration of sevoflurane at the time of intubation varied from 3.7 to 5.7%. In case of induction with 2.5 to 4 mg kg^{-1} propofol, they found a weighted average of excellent intubation conditions of 81% with alfentanil 15 to 20 μg kg^{-1}, 29 to 85% with remifentanil 1 to 4 μg kg^{-1}, and 60% with fentanyl.

Fourth, the intubation conditions and haemodynamic responses produced by various types and doses of NMBA in paediatric anaesthesia were compared using a network meta analysis.[46] One hundred and five articles (94 RCTs and 11 controlled clinical trials) published between 1986 and 2024 were included with a total of 8008 children 0 to 12 years old undergoing elective or emergency tracheal intubation under direct laryngoscopy with or without an NMBA. Using network meta-analysis and meta-regression, the use of an NMBA significantly increased the likelihood of achieving excellent (OR: 5.05, 95% CI 2.43 to 10.48) and acceptable (OR: 6.23, 95%CI 3.35 to 11.58) intubation conditions compared with no NMBA. This study showed that intubation without NMBA is the most challenging in neonates and infants, tending to become easier up to approximately the age of 4, then becoming increasingly difficult again as children grow older, indicating that NMBA use may become more beneficial as children grow older. However, the authors acknowledge that low to moderate confidence can be assigned to the recommendations from this meta-analysis mainly due to concerns about the risk of bias, incomplete reporting and clinical heterogeneity among the included studies.[46]

No trials were found that directly assessed the impact of NMBA in the nonoperating-room anaesthesia setting.

PICO2: Neuromuscular block for intubation of neonates and infants

Recommendation

- **We recommend using an NMBA to facilitate tracheal intubation in neonates and infants in the operating room when maintaining spontaneous breathing is not required.**

GRADE: *Strong recommendation with moderate level of evidence*

Rationale

Recent systematic reviews,[19,46–48] with high[18] to moderate-quality RCTs[33,49–51] and observational studies[53–56] support the use of NMBA to facilitate tracheal intubation in neonates and infants when spontaneous breathing is not required.[47,48,53] (Appendix 3, Table 2, http://links.lww.com/EJA/B252) Using meta regression, a meta-analysis showed that, with similar NMBA treatment and anaesthesia induction, younger children, mean age 1.66 years [1.15 to 2.17] had better intubation conditions with an NMBA than older children, mean age 5.95 years [5.65 to 6.26] for both excellent (OR: 2.97, 1.82 to 5.10) and acceptable intubation conditions (OR: 2.29, 1.14 to 4.39).[46] NMB can

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improve glottic visualisation, suppress airway reflexes, optimise intubation conditions,[18,47–49,52,55] and reduce oxygen desaturation during airway management.[48,51–54] This is particularly important given the unique airway anatomy of both neonates and infants. By reducing complications such as laryngospasm,[18,47] airway trauma[33,47,48] and multiple intubation attempts,[52–55] the use of an NMBA can facilitate smoother airway management with a higher first attempt success rate.[18,33,47,48,52]

PICO 3: Which neuromuscular blocking agent should be used for rapid sequence induction and intubation in children?

Recommendation

- **For RSII, we recommend using rocuronium rather than succinylcholine.**
  GRADE: *Strong recommendation with moderate level of evidence*

Rationale

The dose of succinylcholine recommended for RSII varies, ranging from 2 to 3 mg kg^{-1} in neonates and infants, and 1.5 to 2 mg kg^{-1} in children.[57,58] Although succinylcholine is considered to be ultra short-acting, its average duration of action of 4.7 min could potentially cause a problem in a cannot intubate-cannot oxygenate situation. The hypothesis that a dose lower than 1 mg kg^{-1} could be efficient in children was tested in one RCT: acceptable intubation conditions were obtained with a lower dose (0.5 vs. 1 mg kg^{-1}) at 60 s (28/30 in 0.5 group 29/30 in 1 group), but excellent conditions were more often obtained with 1 mg kg^{-1} (25/30 vs. 16/30, $P = 0.043$).[59] The main difference was a longer apnoea time in the 1 mg kg^{-1} group. However, the findings of this small study do not justify an adjustment of the previous dose recommendations for succinylcholine in children.

Rocuronium is increasingly replacing succinylcholine due to the increased availability of sugammadex, which allows for rapid reversal when clinically needed. Although using a high dose of rocuronium (0.9, 1 or 1.2 mg kg^{-1}) is often reported for RSII, only a few small comparative studies have been published to support this dose range. Most of the published trials used a simulated classic RSII scenario with either thiopentone[60–62] or propofol[63,64] and monitoring with acceleromyography[60,63,64] or EMG.[62] The results are summarised in Appendix 3, Table 3, http://links.lww.com/EJA/B252. In short, the onset of relaxation and intubation conditions at 60 s were similar between rocuronium 0.9 and succinylcholine 1.5 mg kg^{-1},[60] and between rocuronium 0.6 mg kg^{-1} and succinylcholine 1 mg kg^{-1}.[63,64] However, intubation conditions at 30 s were better or similar to succinylcholine 1.5 mg kg^{-1} with rocuronium 0.9 mg kg^{-1} and better than rocuronium 0.6 mg kg^{-1}.[61] Finally, similar rates of excellent/good intubation conditions were observed at 60 s after the administration of rocuronium 0.9 and 0.6 mg kg^{-1}, although the mean onset time was shorter in the 0.9 mg kg^{-1} group (118 ± 27 vs. 193 ± 47 s, $P < 0.01$).[62]

PICO 4: Neuromuscular block for intubating children in the emergency room

Recommendation

- **We suggest considering the use of an NMBA for tracheal intubation in children in the emergency room to improve intubation conditions, decrease the number of attempts and reduce the risk of complications**
  GRADE: *Conditional recommendation with low level of evidence*

Rationale:

Two studies (one retrospective, one prospective observational) analysed the use of NMB for intubation of children in the emergency room and its impact on success rates, patient outcomes, and complications. These studies included children in emergency and critical care settings, focusing on traumatic brain injury and emergency airway management (Appendix 3, Table 4, http://links.lww.com/EJA/B252).

A retrospective analysis on tracheal intubation of children aged 2 to 15 years with severe traumatic brain injury found first attempt intubation success in 89% using an NMBA vs. 64% without ($P = 0.02$).[65] In addition, tracheal intubation without NMB led to significantly higher rates of intracranial pressure spikes (>20 mmHg) in 68% compared to 32% when a NMBA was used ($P < 0.01$).

In a prospective observational study of paediatric emergency airway management, analysing 452 intubations, the use of an NMBA was associated with improved first-pass success rates (72% without to 91% with NMBA, $P < 0.001$).[66] The study also documented a reduction in oxygen desaturation events ($SpO_2 < 80\%$) from 30% in the no NMBA group compared with 14% in the NMBA group ($P = 0.004$).

PICO 5: For children undergoing tracheal intubation in the paediatric ICU, should a neuromuscular agent be used?

The panel abstained from providing recommendations.

The literature search revealed very limited evidence regarding this PICO. Furthermore, the guidelines Task Force mainly consists of anaesthesiologists rather than PICU physicians. It was hence decided to refrain from issuing recommendations and leave this task to a more

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interdisciplinary panel involving PICU specialists. In the meantime, we refer to general recommendations from PICO 1.

PICO 6: For children undergoing tracheal intubation in the neonatal ICU, should a neuromuscular blocking agent be used?

The panel abstained from providing recommendations.

The guidelines Task Force mainly consists of anaesthesiologists rather than NICU physicians. It was hence decided to refrain from issuing recommendations and leave this task to a more interdisciplinary panel involving NICU specialists. In the meantime, we refer to general recommendations from PICO 1.

Literature review

Four RCTs compared the use of NMB with an alternative sedation regimen or no sedation for tracheal intubation in the NICU (Appendix 3, Table 5, http://links.lww.com/EJA/B252).[19,33,51,52,67,68] All studies evaluated elective or semi-emergency intubation; four studies discussed nasotracheal intubation, and one oral intubation. Studies were included if they addressed intubation conditions, number of attempts and/or complications sustained during intubation.

Two RCTs assessed the use of an NMBA vs. propofol for sedation. In infants with a corrected postmenstrual age younger than 45 weeks and aged less than 10 days, no significant difference was found for frequency of prolonged desaturations less than 80% (59.6% in the atropine-propofol group vs. 65.9% in the atracurium-atropine-sufentanil group, adjusted risk difference, -6.4; 95% CI -21.0 to 8.1) or in the median [IQR]number of attempts, 2 [1 to 2] vs. 1 [1 to 2], absolute difference 0, between the two groups.[19] However, there was better quality of sedation (excellent in 51.7% of the propofol group vs. 92.6% in the atracurium group) but more severe adverse events (thoracic rigidity 13.8 vs. 3.6%, 4 of which were associated with bradycardia <100 beats per minute lasting more than 60 s) in the group receiving atracurium. In neonates born at 27 to 28 weeks of gestation and 3 to 4 days-old, the use of propofol led to a decrease in median time to achieve intubation, 120 s [60 to 180] vs. 260 s [60 to 435]; $P = 0.007$) and higher median oxygen saturations during tracheal intubation, 80% [67 to 88] vs. 60% [43 to 82] than in the morphine, atropine and succinylcholine group. Intubation-related bleeding in the oropharynx occurred in two infants (6%) in the propofol group vs. seven infants (23%) in the succinylcholine group ($P = 0.117$).[51]

Two RCTs compared the use of an NMBA with sedation only. The use of thiopentone, succinylcholine and remifentanil was compared with morphine and atropine in 34 prematures (median gestational age around 27 weeks of gestation) intubated during the first week [33]: the NMB group had superior intubation conditions (16/17 vs. 1/17, $P < 0.001$) and a shorter procedure duration of 45 s [35 to 154] compared with 97 s [49 to 365], ($P = 0.031$). The morphine group had prolonged heart rate decrease and higher mean ± SD arterial blood pressure increase (% change: mean 21% ± 23% vs. -2% ± 22%, $P < 0.007$) during the intubation. In another study involving premature neonates (mean gestational age 30 weeks) intubated when a mean of 9.65 days old, the administration of atropine, fentanyl and mivacurium compared with atropine and fentanyl was associated with less episodes of desaturation 60% or less (11/20; 55% vs. 5/21; 24%; $P = 0.041$) and more frequent success in two or less attempts (7/20; 35% vs. 15/21; 71%; $P = 0.019$).[52] However, both studies were underpowered.

PICO7: To facilitate tracheal intubation in children, are intubation conditions equivalent between neuromuscular block and high-dose remifentanil/alfentanil?

Recommendation

- **Should, for any reason, the decision be made not to use an NMBA for intubation, high doses of opioids can provide similar intubation conditions in children.**
  GRADE: *Strong recommendation with moderate level of evidence*

Rationale

Although the use of an NMBA is generally recommended for intubation, there are circumstances where the anaesthesiologist may opt not to use an NMBA, for example due to intra-operative nerve monitoring, maintenance of spontaneous ventilation, allergy, lack of availability or other reasons. We reviewed the literature to propose alternative options for providing the best possible intubation conditions in this setting. There are a large number of RCTs (Appendix 3, Table 6a, http://links.lww.com/EJA/B252)[69–84] assessing intubation conditions and complications following various doses of remifentanil or alfentanil compared to NMB. Issues in assessing this PICO were that the definition of 'high-dose' opioids remains unclear and that various opioids in various doses are compared amongst each other or against various NMBA in various doses. Although low-dose opioids are associated with inferior intubation conditions, coughing and body movements, in the majority of studies, high-dose opioids are comparable with NMB for intubation conditions, first attempt success rates, and rate of complications, with a low risk of thoracic rigidity. The clear dependence on the dose used is also highlighted by a

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range of RCTs (Appendix 3, Table 6b, http://links.lww.com/EJA/B252) [82,83] and dose-finding studies using just opioids in the absence of NMB. Intubation conditions, including success rates, ease of laryngoscopy, cardiovascular stability and adverse events, are similar during intubation with an NMBA compared to high-dose opioids in healthy children without difficult airways.

Generally, a dose of alfentanil more than 10 $\mu g\,kg^{-1}$ combined with propofol or a dose of remifentanil 2 to 3 $\mu g\,kg^{-1}$ combined with sevoflurane, propofol, or ketamine can provide satisfactory intubation conditions with a low risk of thoracic rigidity.

PICO 8: Are intubation conditions following propofol equivalent with and without a neuromuscular blocking agent?

Recommendation

- **Should, for any reason, the decision be made not to use an NMBA for intubation, we recommend achieving sufficient depth of anaesthesia, including high-dose opioids or different adjuvants, such as opioids and/or sevoflurane in addition to propofol, and having a skilled and experienced clinician perform the intubation.**
  GRADE: *Strong recommendation with moderate level of evidence*

Rationale

As stated in PICO 1, we recommend the use of an NMBA for intubation, as it appears superior to other strategies, including propofol alone, for providing optimal intubation conditions. Much of the evidence assessing the efficacy of a strategy using propofol as a substitute for an NMBA is derived from indirect comparisons (Appendix 3, Table 7, http://links.lww.com/EJA/B252). In a small RCT, comparable intubating conditions in children were found with 1.5 $mg\,kg^{-1}$ of propofol compared to 0.6 $mg\,kg^{-1}$ of rocuronium in addition to 8% sevoflurane.[23]

Another RCT compared alfentanil (14 $\mu g\,kg^{-1}$), rocuronium (0.3 $mg\,kg^{-1}$) and propofol 2 $mg\,kg^{-1}$. Rocuronium 0.3 $mg\,kg^{-1}$ or alfentanil 14 $\mu g\,kg^{-1}$ with 3.7% end tidal concentration of sevoflurane resulted in significantly better intubating conditions compared to 2 $mg\,kg^{-1}$ propofol.[34]

A systematic review from 2012 assessing tracheal intubation without NMBA in children aged 1 to 10 years, evaluated the role of adjuvants in various combinations when propofol (14 studies, 807 children) or sevoflurane (nine studies, 696 children) was used for induction.[45] They used a weighted average of 80.5% of excellent intubation conditions with propofol and succinylcholine in five studies (123 children) as a comparator. With sevoflurane induction, they found a weighted average of excellent intubation conditions of 41% with sevoflurane alone, 84% with sevoflurane with 2 $mg\,kg^{-1}$ lidocaine, 88.7% of sevoflurane with propofol 2 $mg\,kg^{-1}$ and 75 or 81.2% with sevoflurane with 1 or 2 $\mu g\,kg^{-1}$ remifentanil. Of note, ventilation was assisted before intubation in most studies, and the end-tidal concentration of sevoflurane at the time of intubation varied from 3.7 to 5.7%. For induction with 2.5 to 4 $mg\,kg^{-1}$ propofol, they found a weighted average of excellent intubation conditions of 81% with alfentanil 15 to 20 $\mu g\,kg^{-1}$, 29 to 85% with remifentanil 1 to 4 $\mu g\,kg^{-1}$ and 60% with fentanyl 3 $\mu g\,kg^{-1}$.

Other trials have evaluated different doses of propofol (1 to 3.5 $mg\,kg^{-1}$) in combination with fentanyl and sevoflurane, showing better efficacy with the higher doses of propofol.[83–86]

In a small RCT in neonates, 2.5 $mg\,kg^{-1}$ of propofol was found to be superior to morphine, atropine, and succinylcholine.[51] However, this study had several methodological limitations, making its findings difficult to contextualise within current practice. Another small RCT comparing fentanyl with propofol vs. propofol and succinylcholine found almost similar results.[36] It should be emphasised that most of these studies did not evaluate the haemodynamic effects of the drug regimes.

Question 2: Does neuromuscular block affect outcomes in children?

PICO1: Does neuromuscular block affect surgical conditions in abdominal surgery

Recommendation:

- **We recommend a selective approach to NMB in paediatric abdominal surgery, avoiding deep NMB (post-tetanic count: 1 to 2 responses) for minor procedures (e.g. inguinal hernia repair), and establishing deep NMB for major procedures (e.g. hepatobiliary surgery) when necessary. Deep NMB should be considered for enhancement of surgical conditions and ventilation when indicated.**
  GRADE: *Conditional recommendation based on moderate level of evidence*

Rationale

High-quality studies demonstrate that NMB is advantageous in paediatric laparoscopic surgery.[43,87,88] A low-quality study suggests that for short, minor procedures such as laparoscopic inguinal hernia repair, deep NMB with post tetanic count (PTC) 1 to 2 offers no advantage,

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as it does not significantly enhance surgical conditions compared to moderate NMB (TOFc: 1-2).[89] Two moderate-quality studies indicate that acceptable surgical conditions for these minor procedures can even be achieved without NMB and with the use of a supraglottic airway (SGA).[91,93] (Appendix 3, Table 8a and 8b, http://links.lww.com/EJA/B252)

For abdominal surgery without an NMBA, surgical conditions tend to worsen with age.[88] This can explain why neither shallow nor moderate NMB significantly improved surgical conditions in neonates and younger infants, given their immature abdominal wall muscles. Indeed, as children grow older, increased muscle tone and reduced abdominal cavity compliance make the use of an NMBA more beneficial for optimising surgical conditions.

A high-quality RCT showed that for major procedures, such as hepatobiliary surgery, deep NMB lowers intra-abdominal pressure, creating a safer and more controlled environment. The lower peak inspiratory airway and abdominal pressures facilitate better visualisation and manipulation, leading to improved surgical conditions. When reversal of deep NMB with rocuronium is performed with sugammadex, recovery times are not prolonged.[43,89]

The necessity of NMB for laparoscopic surgery in neonates and small infants remains controversial.[88,92] A high-quality RCT found that NMB did not significantly improve surgical conditions, as assessed by the Leiden-Surgical Rating Scale.[43] In the same study, however, NMB reduced the incidence of adverse events during induction of anaesthesia and maintenance, particularly by improving tracheal intubation conditions.

A retrospective study of laparoscopic pyloromyotomy found no significant differences in surgical conditions, extubation time, or peri-operative complications between neonates and young infants who received NMBA and those who did not.[92] Another retrospective comparison of succinylcholine and rocuronium in this group showed a slight variation in recovery times but no effect on overall outcomes.[90] Considering the need to balance the risks and benefits of NMBA administration, we suggest that shallow NMB (TOFr: minimal fade or > 0.4) might be the optimal choice for minor laparoscopic surgery in neonates and small infants.

A retrospective cohort study of 6507 children under 10 years of age undergoing surgery with general anaesthesia assessed whether high intra-operative NMBA doses are associated with an increased risk of postoperative respiratory complications.[94] The children were divided into three groups: no intra-operative NMBA; a low multiple of age-adapted ED95 of NMBA dosing; and a high multiple of age-adapted ED95 NMBA dosing. Of note, only neostigmine was used for reversal, and only 23.6% of the patients received TOF monitoring. Propensity score matching was used to adjust for confounders. The OR for postoperative respiratory complications was highest in children who received the highest intra-operative doses of NMBA: 2.27 (95% CI 1.12 to 4.59, $P = 0.022$) by comparison with no NMBA. Subgroup analysis showed that age less than 1 year (OR 3.84; 95%CI 1.35 to 10.94), duration of surgery less than 90 min (OR 4.25; 95% CI 1.19 to 15.18) and ASA score more than 1 (OR 3.17; 95% CI 1.13 to 7.04) were significant risk factors. A similar but nonsignificant trend for an increased incidence of adverse respiratory events in the PACU was observed in a RCT involving 103 infants, despite monitored reversal of rocuronium with neostigmine or sugammadex.[43] Infants who had had a moderate NMB (TOFc = 1 or 2) presented more complications in the PACU (26.5%) than those with either no NMB (11.4%) or shallow NMB (TOFr>0.4) (9.1%; $P = 0.103$). Therefore, when an NMBA is used, particular caution has to be placed on the monitoring and appropriate reversal to reduce the risk for peri-operative respiratory adverse events.

- **We suggest that NMB can improve surgical and ventilation conditions when a second-generation SGA is used for abdominal surgery**
  GRADE: *Conditional recommendation based on low level of evidence*

A SGA without NMB is occasionally used for short laparoscopic procedures and leads to faster recovery and fewer airway complications compared to a tracheal tube and NMB.[43,91,93] Studies show that a second-generation SGA that has a gastric drainage port can be safely used during laparoscopic surgery.[88,91] However, proper patient selection is essential, as intubation may be required in the presence of gastroesophageal reflux or a high aspiration risk.[91] Inadequate muscle relaxation can adversely affect surgical conditions by elevating airway pressure, leading to increased intra-abdominal pressure, patient movement and reduced surgical field visibility.[88,93] The use of an NMBA with a second-generation SGA significantly improved surgical conditions and reduced the incidence of intra-operative adverse events during short laparoscopic procedures.[88,91] Although the use of a SGA without NMB is a viable alternative to a tracheal tube with NMB, careful monitoring is necessary to manage risks such as gastric distention, regurgitation and airway complications.[91,93]

PICO2 and PICO3: Does neuromuscular block affect outcomes in PICU and NICU?

The panel abstained from providing recommendations.

Given the paucity of clinical studies, and since the guidelines Task Force mainly consists of anaesthesiologists

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rather than PICU and NICU physicians, we refrain from issuing recommendations.

Literature review

PICU

o RCT assessing the effects of continuous NMB on ventilated children on the PICU could be identified. Several prospective and retrospective observational studies assessed the effects of various regimes of NMB in children with medical problems in PICU,[95,96] following surgery,[97,98] trauma[99] or in mixed PICU admissions.[100–102] The risk of bias of these studies is generally high, given the retrospective or observational design with unclear allocation of patients to the various treatment groups, which often results in a selection bias with 'higher risk' patients in the NMB group. (Appendix 3, Table 9, http://links.lww.com/EJA/B252)

In acute respiratory distress syndrome, mixed results were not only reported with a possible reduction in mortality but also longer duration of mechanical ventilation and lower oxygenation indices when using NMB.[95,96] In children after tracheostomy[97] or cardiac surgery,[98] the postoperative use of NMB in the PICU was associated with prolonged mechanical ventilation,[98] prolonged PICU stay[97] and postoperative ileus,[97] but children receiving NMB were sicker. Studies of mixed PICU patients suggested prolonged mechanical ventilation and PICU stay with the use of NMB,[100,101] and one study identified the use of NMB as a predictor for in-hospital mortality.[102] But it has also been reported that NMB reduces oxygen consumption and energy expenditure as measured by indirect calorimetry[103] and that oversedation, defined by low processed EEG values, commonly occurs in mechanically ventilated children receiving NMB in the PICU.[104] Furthermore, the use of NMB might be indicated in the PICU in special clinical circumstances such as following repair of oesophageal atresia to decrease tension on the anastomosis, in the setting of a hypothermia protocol, in the presence of an open chest or a traumatic brain injury, and if there is a high risk of a pulmonary hypertensive crisis.

NICU

Ventilated newborns are susceptible to barotrauma and face risks such as pneumothorax, interstitial emphysema, intraventricular haemorrhage and death. Breathing asynchronously with the ventilator might increase those risks. Historical data of neonates paralysed with pancuronium in the 1980s and 1990s suggest that the use of NMB may reduce these risks.[105,106] However, these are historical data, and other studies did not demonstrate improved outcomes with NMB, indicating that the differences might be attributable to other factors.[107] Also, prolonged NMB in newborns might itself be associated with complications. It is unclear if these data are transferable to current settings with modern ventilators and advanced neonatal care in general.

Question 3 - What are the strategies for the diagnosis and treatment of residual neuromuscular block in children?

PICO 1: Does the use of quantitative neuromuscular monitoring at the adductor pollicis allow diagnosis of residual NMB, and does a TOF ratio of 0.9 allow ruling out residual NMB? Are there alternative sites in children for neuromuscular monitoring?

Recommendation

- **We recommend quantitative neuromuscular monitoring whenever an NMBA is used to modulate the level of neuromuscular block and to rule out residual NMB before extubation.**
  GRADE: *Strong recommendation based on moderate level of evidence*

Rationale

In adults, guidelines recommend the use of ulnar nerve stimulation and quantitative neuromuscular monitoring at the adductor pollicis to exclude residual NMB.[11] This is based on evidence from five randomised clinical trials and one retrospective observational study that include a total of 788 patients, resulting in good evidence with intermediate risk of bias.[108–113] In contrast to adults, few studies exist on the incidence of residual NMB and the influence of qualitative neuromuscular monitoring in children. One prospective paediatric trial investigated clinical assessment in comparison with qualitative monitoring at the adductor pollicis followed by neostigmine reversal (0.05 mg kg^{-1}) or sugammadex, in 73 children.[114] With this approach, 29.7% of the children who received neostigmine still presented with residual NMB, defined as TOFr less than 0.9 by a quantitative EMG monitoring, in the PACU while those reversed by sugammadex using the same clinical or qualitative monitoring showed no residual NMB in the PACU. However, care should be taken when interpreting the results of comparative studies between sugammadex and neostigmine because, in most studies, NMB was too deep at the time of neostigmine administration according to the recommendations from adult settings (ESAIC guideline TOFr > 0.2,[11] ASA guideline TOFr> 0.4).[115] The definitions of the different depths of NMB are given in Table 1.

A comparison of a dose of 0.02 mg kg^{-1} of neostigmine administered either after return of spontaneous ventilation or when the TOFr was between 0.4 and 0.9 did not find a difference in residual NMB (TOFr <0.9 by quantitative monitoring) at extubation: 75% in the spontaneous breathing group and 73.3% in the monitored group

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Table 1 Depth of neuromuscular block: definitions

According to response to train-of-four stimulation (TOF):
- shallow block: TOF ratio (TOFr) $>$ 0.4
- moderate block: TOF count (TOFc) $>$ 1 or 2
- deep block: posttetanic count (PTC) $>$ 1
- complete decurarisation : TOFr $\geq$ 0.9

Warning : if baseline TOFr $\geq$ 1.10 with acceleromyography-based monitoring, there is a risk of underestimation of residual neuromuscular block[126]

(RR 1.02; 95% CI 0.83 to 1.26).[116] However, the low dose of neostigmine and the short time of 8.9 min (control group) and 9.6 min (monitored group) between neostigmine administration and measurement of the final TOFr can explain these results. Neostigmine has been shown to need more time to achieve its effect. (Appendix 3, Table 10, http://links.lww.com/EJA/B252)

A prospective quality assurance study involved 39 children less than 3 years old undergoing elective cleft lip and palate surgery with 0.1 mg kg^{-1} cisatracurium with either sevoflurane or propofol and remifentanil.[117] Quantitative AMG-based neuromuscular monitoring was performed at the tibial nerve. Upon conclusion of anaesthesia, 3/39 patients (8%) had a TOFr less than 0.9; all were infants and had received sevoflurane for maintenance of anaesthesia. This study confirms the potentiation of NMB by halogenated agents: the mean $\pm$ SD duration of action of the single dose of cisatracurium was 119 $\pm$ 40 min in the sevoflurane group vs. 73 $\pm$ 29 min in the TIVA group ($P < 0.001$).[117]

In the database of the Danish Cholinesterase Research Unit, neuromuscular monitoring reduced awakening while the patient was still paralysed from 100 to 29%, while concomitantly reducing pulmonary complications from 25 to 10%.[118] In this study, any type of monitoring (qualitative or quantitative) was considered.

Lastly, a TOFr more than 0.9 assessed at the adductor pollicis does not necessarily indicate sufficient neuromuscular recovery of the upper airway muscles and may even not indicate complete neuromuscular recovery as part of the acetylcholine receptors are still occupied by the NMBA.[12] It should thus be interpreted according to the patient's age and comorbidity as well as the pharmacology of the NMBA used.

Recommendation

- **We suggest neuromuscular monitoring at the adductor pollicis site as the first choice and the flexor hallucis brevis as an alternative if the adductor pollicis site is not accessible**
  GRADE: *Conditional recommendation based on very low level of evidence*

Rationale

A recent trial using EMG-based monitoring identified delayed onset and recovery of NMB when monitoring the lower extremity (foot) compared with the upper extremity (hand).[119] Similar differences were observed with acceleromyography-based monitoring (AMG) and could be explained by morphological differences between the adductor pollicis and flexor hallucis brevis muscle.[120] Quantitative neuromuscular monitoring of muscle relaxation at the level of the corrugator supercilii muscle is difficult due to the small size of the muscle.

Recommendation

- **We suggest quantitative electromyography-based rather than acceleromyography-based neuromuscular monitoring and calibrating the device before administering an NMBA.**
  GRADE: *Conditional recommendation with very low level of evidence*

Rationale

Until recently, only AMG was used for neuromuscular monitoring in children. However, this monitor is difficult to secure on small hands, is rather bulky, and necessitates calibration, which can be difficult in neonates and infants, contributing to the less frequent use of neuromuscular monitoring in young children.[121] Novel and easier to use EMG-based monitoring devices are now available for neonates, infants, and children.[6,122,123] These devices have expanded the possible clinical applications of accurate TOF monitoring in children, including those less than 6 months of age, and the potential to better evaluate the degree of NMB and its reversal, even when access to the upper extremities is limited or impossible. In addition, contrary to AMG, EMG-based devices are characterised by the absence of twitch response potentiation (also called overshoot, staircase phenomenon or reverse fade),[12,124] which is also observed in infants,[125] and a need for lower supramaximal current intensity.[126] However, whatever the type of neuromuscular monitoring device used, calibration before administering a NMBA is important to improve the reliability of subsequent TOF monitoring.[127]

Q3 PICO 2: Are there differences in efficacy between neostigmine and sugammadex when reversing rocuronium or vecuronium?

Recommendation

- **We recommend sugammadex over neostigmine for the reversal of aminosteroid NMB in children due to its faster recovery time, shorter time to extubation and more effective reversal of moderate and deep block.**

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GRADE: *Strong recommendation with moderate level of evidence*

- **In children under the age of 2 years, sugammadex can be safely used for reversal of aminosteroid NMBAs at the same dose per kg bodyweight as in older children and adults.**
  GRADE: *Strong recommendation with moderate level of evidence*

Rationale

On the basis of the available studies, there is growing evidence that sugammadex is superior to neostigmine for reversal of steroidal NMBA in children. A meta-analysis of RCTs with trial sequential analysis with data from 18 studies involving 1065 children showed that sugammadex is associated with shorter intervals from administration of reversal agents to TOFr more than 0.9 (MD = -14.42, with 95% CI -17.08 to -11.75) and to extubation (MD = -13.98, with 95% CI -16.70 to -11.26) compared with the control groups (acetylcholinesterase inhibitors for 16/18 studies, placebo for 2/18).[128] Additionally, administration of sugammadex was associated with a reduced incidence of postoperative nausea and vomiting, bradycardia, and dry mouth, compared with the control groups. The trial sequential analysis indicated that the current sample sizes were sufficient. (Appendix 3, Table 11, http://links.lww.com/EJA/B252)

In summary, when sugammadex is compared with neostigmine, it provides:

- Faster recovery and extubation:
  - Multiple RCTs show significantly shorter recovery and extubation times[129–133]
  - Sugammadex 4 mg kg^{-1} provides rapid reversal of deep rocuronium-induced NMB[132]
  - Sugammadex 2 mg kg^{-1} is also effective but may be more suitable for moderate NMB [129]
  - A recent phase 3 RCT involving children less than 2 years old at the request of the FDA confirms the above findings[10]
- Better haemodynamic stability
  - As a result of the simultaneous administration of an anticholinergic agent, neostigmine is associated with increased heart rate and blood pressure compared to sugammadex,[131] suggesting that sugammadex may be a safer choice for haemodynamically vulnerable patients.
  - No clinically significant differences in adverse events such as bradycardia, hypersensitivity, arrhythmias, hypotension, respiratory issues, postoperative residual paralysis or pulmonary complications.[130,134]
- Reduced need for additional doses:
  - More extra doses of neostigmine were needed compared to sugammadex, indicating better efficacy with sugammadex[131]
- At the time of writing, sugammadex is still used off-label in children less than 2 years-old

Sugammadex is thus superior to neostigmine for reversal of steroidal NMBA in children due to a faster recovery and more effective reversal of moderate and deep NMB. It should be the preferred choice, especially for those at risk of haemodynamic instability or requiring a rapid return to spontaneous breathing. The recommended NMB monitoring-based doses of neostigmine and sugammadex are presented in Table 2.

Q3 PICO 3: What is the risk of residual neuromuscular block or recurarisation when sugammadex is used for reversal?

Recommendation

- **To prevent residual NMB or recurarisation, we suggest avoiding excessive doses of rocuronium and using systematic quantitative neuromuscular monitoring to ensure adequate recovery before extubation.**
  GRADE: *Conditional recommendation based on very low level of evidence*
- **In children aged less than 2 years or when a large total dose of rocuronium or vecuronium has been used, we suggest an extended observation period in PACU if sugammadex was used for reversal.**
  GRADE: *Conditional recommendation based on very low level of evidence*

Rationale

Recurarisation, or recurrent NMB, refers to the appearance of direct signs of NMB (quantitative and qualitative monitoring: TOFc less than 4/4 or TOFr less than 0.8 over three consecutive measurements) or indirect signs (respiratory failure, hypoxaemia), after a free interval during which effective (TOFr $\geq$ 0.9) recovery of NMB was confirmed.[135,136] Confusion may arise with residual NMB, which is differentiated from recurarisation by the absence of such a free interval of recovery of NMB. The frequent absence of systematic quantitative neuromuscular monitoring of NMB in clinical practice and in the scientific literature often makes it difficult to distinguish between recurarisation and residual NMB because respiratory failure and hypoxaemia can be caused by both. Two retrospective studies suggest a higher risk of recurarisation in children

Table 2 Dosage of reversal agents

For aminosteroid muscle relaxants
TOFc $\geq$ 2 : sugammadex 2 mg kg^{-1}
PTC $\geq$ 1 : sugammadex 4 mg kg^{-1}
For all nondepolarising muscle relaxants :
When TOFr $\geq$ 0.2 (ESAIC)[11] or $\geq$ 0.4 (ASA)[117]
Neostigmine 20 to 50 μg kg^{-1} with half dose of atropine or glycopyrrolate

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younger than 2 years after sugammadex reversal of rocuronium (Appendix 3, Table 12, http://links.lww.com/EJA/B252).

The first study, conducted at a tertiary medical centre (2018 to 2021), analysed records of 2923 children under 2 years of age who underwent surgery with rocuronium as the sole NMBA.[4] In 123 cases (4.2%), a second dose of sugammadex had to be administered because of residual NMB. Factors such as increasing age and weight were associated with a reduced likelihood of redosing ($P < 0.01$). However, only 40.7% of patients who received a second dose had intra-operative qualitative TOF monitoring. The median [IQR] time to redose was 7 min [4 to 17], but without quantitative TOFr data before redosing, the study cannot confirm whether the redose was due to residual NMB or recurarisation.

The second study is a review of seven case reports of children under 2 years of age who had received sugammadex after rocuronium administration.[5] In 6/7 cases, extubation occurred based on clinical signs of adequate recovery of NMB (3/6 with neuromuscular monitoring, including one quantitative). Direct (2/7 with neuromuscular monitoring) or indirect (respiratory distress) signs of NMB and recurarisation appeared 17 to 50 min after sugammadex administration, and these signs resolved quickly with a second dose of sugammadex. The authors note that the initial dose of rocuronium was excessive (2.4 to 9.2 times the ED95) or repeated in at least 5/7 cases, while the sugammadex dose was inadequate. Based on these findings, the authors recommend strategies to minimise the risk of postsugammadex residual NMB/recurarisation: using a rocuronium induction dose ≤ 2 x ED95 for age, applying systematic quantitative neuromuscular monitoring, and extending PACU stay for at least 60 min after sugammadex administration, especially when a large total dose of rocuronium has been administered.

Recurarisation can be due to either a too small dose of sugammadex being administered or because of 'rebound NMB' due to redistribution of unbound rocuronium molecules from peripheral compartments back into central and effect compartments.[137]

Implementing effective strategies to prevent, diagnose, and manage both residual NMB and recurarisation is crucial for ensuring patient safety. These strategies should include the routine use of quantitative neuromuscular monitoring to adjust the dose of rocuronium or neostigmine according to the TOFc or TOFr (according to the adult guidelines, neostigmine should not be administered before TOFr $>$ 0.2 or 0.4) and to confirm adequate recovery of NMB (TOFr $>$0.9) before extubation.[11,115]

A prospective cohort study was performed in 189 adults with rocuronium-induced NMB using the following protocol and an AMG-based neuromuscular monitoring: no reversal if TOFr was more than 0.9; neostigmine + glycopyrrolate if TOFr was more than 0.4 and less than 0.9; sugammadex 2 mg kg^{-1} if TOFc was more than 2 but TOFr less than 0.4 and sugammadex 4 mg kg^{-1} if TOFc was 0 and PTC more than 1.[138] No case of residual NMB was observed which means that the upper 95% CI for the incidence of residual NMB was 1.9% using this approach. This also means that residual NMB can occur despite careful monitoring and adherence to guidelines, and that controlling the adequate reversal of NMB before extubation should be standard practice.

Finally, upper airway reflexes should be confirmed along with a TOF ratio more than 0.9 prior to extubation to ensure adequate neuromuscular recovery.

Q3 PICO 4: Can succinylcholine be associated with residual neuromuscular block?

- **To exclude a prolonged duration of action of succinylcholine, we suggest using clinical assessment (return of spontaneous breathing and movements) and monitoring to evaluate recovery after its administration.**
  GRADE: *Conditional recommendation based on very low level of evidence*

Rationale:

Succinylcholine is associated with high variability in duration, and occasionally with prolonged NMB. Two clinical situations may affect the duration of NMB after administration of succinylcholine: a deficiency in pseudocholinesterase (butyrylcholinesterase) the enzyme responsible for breaking down succinylcholine[139] (congenital: prevalence homozygous 1/2800, heterozygous 1/300 individuals with a severe or moderate prolongation of action, respectively), or acquired: liver insufficiency, and/or administration of high or repeated doses resulting in a so-called phase II, desensitisation or dual block, which is a nondepolarising block. The supporting evidence is based on case reports in adults,[140] children[141,142] and a paediatric survey in the UK,[143] in which prolonged apnoea was reported by 36% of respondents. To mitigate this risk, it is important to monitor neuromuscular function or look for clinical signs of muscular recovery (return of spontaneous breathing movements) after administering succinylcholine. This will ensure complete NMB recovery before administering a nondepolarising NMBA, especially in patients with a known or suspected pseudocholinesterase deficiency[118] or after repeated doses of succinylcholine in a short period of time. Standard TOF monitoring cannot be used to evaluate a depolarising block due to the absence of fade, and only the decrease in height of the single twitch can be observed.[144] However, the ratio of T4 to Tr (which is the ratio between T4 and a reference twitch (Tr), calculated as the mean value of the four twitches in a TOF-sequence

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[Tr = (T1 + T2 + T3 + T4)/4] obtained before the establishment of the NMB) can be used instead, but has not been tested in children so far.[145] On the contrary, in the presence of a phase II block, fading is present during TOF and tetanic stimulation.

Q3 PICO 5: Monitoring of neuromuscular block in the PICU/ NICU

The panel abstained from providing recommendations

Given the paucity of specific studies on monitoring of NMB in a PICU/NICU environment, the available research evidence does not allow any recommendation on this topic. However, there is convincing evidence that:

- AMG and EMG monitoring is feasible and nonhazardous even in neonates and small infants.[121,146]
- Neuromuscular recovery is highly variable and may be modified by the patient's age and comorbidity.[147,148]
- Residual NMB at the time of extubation may negatively affect outcome in the same way as after general anaesthesia.

Question 4: Neuromuscular block in special conditions.

Literature on the anaesthetic management of rare diseases is scarce, and data on the use of NMBA and their reversal are even rarer. Thus, only experts' opinions are justified. When considering the anaesthetic management of children with a neuromuscular disease, we refer to the European Neuromuscular Centre consensus statement on anaesthesia in patients with neuromuscular disorders.[149]

When caring for children with neuromuscular diseases or other rare diseases and syndromes, we refer also to specialised websites such as ORPHANET (https://www.orpha.net), NORD (https://rarediseases.org), ORPHANANESTHESIA (https://www.orphananesthesia.eu) or Syndromes and Rare Diseases in Pediatrics: Anesthesia (http://tinyurl.com/PED-RARE) for futher information if required. These sites can also be accessed through the European Society of Paediatric Anaesthesiology (ESPA) and Society of Pediatric Anesthesiology websites.

Q4 PICO1: Neuromuscular block in children with a known or suspected neuromuscular disease

Q4 PICO1a: Children with myasthenic syndromes

Recommendation

- **Succinylcholine should not be used in children with myasthenic disorders. If NMB is necessary, rocuronium or vecuronium is prefered as they can be reversed with sugammadex.**
- **If rocuronium or vecuronium are not available or contraindicated (e.g. allergy), atracurium, cisatracurium or mivacurium can be used.**
- **Neostigmine should not be used in children with myasthenic disorders, as it can contribute to postoperative cholinergic or myasthenic crises and is contraindicated in some forms of congenital myasthenia.**
- **Regardless of the NMBA used, the dose should be titrated according to the level of NMB, as evaluated with quantitative neuromuscular monitoring.**

GRADE for all of the above statements: *Conditional recommendation based on very low level of evidence*

Rationale

In children, myasthenic syndromes include juvenile myasthenia gravis, transient neonatal myasthenia and congenital myasthenia.

Juvenile myasthenia gravis has the same pathophysiology as in adults: it is caused by auto-antibodies against acetylcholine receptors (85%), the MuSK or LRP4 protein. Transient neonatal myasthenia occurs in 10 to 20% of neonates born to mothers with myasthenia gravis following the transplacental passage of maternal auto-antibodies and resolves within 2 months after birth. Anticholinesterases (pyridostigmine) are the basis of the symptomatic treatment of myasthenia gravis and transient neonatal myasthenia.

Congenital myasthenia is a group of syndromes caused by mutations of one of 34 genes resulting in dysfunction at the presynaptic, synaptic or postsynaptic level: their treatments are various (e.g. ephedrine, salbutamol), and anticholinesterases are contraindicated in some.[150]

There are almost no publications on the use of NMBA in children presenting with a myasthenic syndrome. Consequently, mainly evidence from the adult literature is considered.

Adults with myasthenia gravis are classically considered resistant to succinylcholine. However, no new data have been published during the past 20 years. For children with myasthenia gravis, most publications report anaesthetic management without an NMBA. One report on the use of a small dose of atracurium (0.2 mg kg^{-1}), as recommended at that time, showed a prolonged duration of action.[151] In adults, the use of titrated doses of rocuronium or vecuronium, followed by reversal with sugammadex, appears effective and well tolerated, notably because it reduces the postoperative occurrence of residual muscle weakness, as well as cholinergic and myasthenic crises, which can occur when neostigmine is used.[152,153] (Appendix 3, Table 13, http://links.lww.com/EJA/B252). Two large retrospective studies using propensity-score matching compared the incidence of postoperative

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myasthenic crises in adults with myasthenia gravis receiving rocuronium and sugammadex in comparison with no NMBA. Their results are contradictory: one showed a reduced incidence of myasthenic crises in patients undergoing thymectomy (4.3 vs. 8.7%, OR 0.48; 95% CI 0.25 to 0.91; $P = 0.02$),[154] while the other showed no difference in patients undergoing a wide range of procedures (32% thymectomies; 6.2 vs. 5.3% RR = 1.14 95% CI 0.70 to 1.85).[155] The major limitations of these studies are that neither the severity of myasthenia nor the use of neuromuscular monitoring were documented. These results highlight the importance of careful dosing of peri-operative anticholinesterase treatment in myasthenia gravis patients, even when rocuronium and sugammadex are used. However, a few cases of failure of total reversal of rocuronium-induced NMB with sugammadex have been reported[156]; their cause is undetermined. Thus, verification of the effective reversal of NMB with quantitative monitoring is warranted.

The safe use of sugammadex following NMB with rocuronium has been described in one infant with transient neonatal myasthenia.[157]

Mivacurium may have a prolonged duration of action in the presence of pre-operative pyridostigmine because of plasma cholinesterase inhibition. However, a prospective series in adults with myasthenia gravis showed that it can be used if rocuronium and vecuronium are not available or contraindicated.[158]

So far, the well tolerated and efficient use of rocuronium and sugammadex has been described in only two cases of congenital myasthenia.[159,160]

Q4 PICO 1B: Children with muscular dystrophy

Recommendation

- **Succinylcholine should be avoided in patients with Duchenne and Becker Muscular Dystrophy due to the risk of severe rhabdomyolysis and fatal hyperkalaemic cardiac arrest. Instead, a nondepolarising NMBA, such as rocuronium or cisatracurium, should be preferred, including for rapid sequence induction and intubation.**
  GRADE: *Conditional recommendation based on low level evidence*
- **Due to the delayed onset and prolonged recovery of NMB, doses of all nondepolarising NMBA (e.g. rocuronium $\leq$ 0.3 mg kg^{-1}) should be titrated in patients with muscular dystrophy to minimise the risk of residual NMB at the end of the intervention.**
  GRADE: *Conditional recommendation based on very low level evidence*
- **Due to increased sensitivity and prolonged recovery times, neuromuscular function should be monitored using quantitative techniques. Sugammadex is preferred over neostigmine for reversal to provide a more predictable and safer recovery profile.**
  GRADE: *Conditional recommendation based on very low level evidence*

Rationale

Muscular dystrophies are a group of genetic disorders characterised by dystrophin deficiency and progressive muscle weakness. Among the dystrophinopathies, Duchenne and Becker muscular dystrophy represent the most common forms and present significant peri-operative challenges due to altered neuromuscular physiology, increased sensitivity to anaesthetic agents and a high risk of life-threatening complications. As literature is limited and mainly consists of case reports, except for Duchenne and Becker muscular dystrophy, dystrophinopathies often serve as a paradigm for other muscular dystrophies.

Succinylcholine is strictly contraindicated in patients with muscular dystrophy as it can trigger massive potassium efflux from damaged muscle cells, leading to hyperkalaemia, severe arrhythmias, and cardiac arrest. A retrospective study analysing paediatric cardiac arrests during anaesthesia found that 72% involved succinylcholine, and 64% occurred in previously undiagnosed Duchenne Muscular Dystrophy patients, with a mean potassium level of 7.4 mmol l^{-1} confirming hyperkalaemia as the primary cause of arrest.[161] Case reports reinforce this risk, demonstrating fatal hyperkalemia following succinylcholine administration in children with undiagnosed neuromuscular disorders,[162,163] and also the risk of acute succinylcholine-induced rhabdomyolysis in children with dystrophinopathy. This was confirmed in a systematic review.[164] (Appendix 3, Table 14, http://links.lww.com/EJA/B252).

Patients with dystrophinopathies exhibit a delayed onset and prolonged duration of NMB due to altered receptor sensitivity and neuromuscular junction physiology. Duchenne Muscular Dystrophy sufferers receiving rocuronium (0.3 mg kg^{-1}) experience significantly prolonged onset (mean 315 vs. 195 s, $P < 0.01$) and recovery (mean 40.3 vs. 9.8 min, $P < 0.01$) compared to controls, especially if older than 10 years.[165] Similarly, standard doses of rocuronium (0.6 mg kg^{-1}) lead to a markedly prolonged mean recovery time (132 min in Duchenne muscular dustrophy vs. 39 min in controls).[166] In another study, patients with Duchenne muscular dystrophy experienced a prolonged NMB with both rocuronium and mivacurium, probably due to altered receptor pharmacodynamics.[167] Mivacurium, though rapidly metabolised, exhibits prolonged recovery, suggesting altered cholinesterase activity in Duchenne muscular dystrophy. Given these altered pharmacodynamics, qualitative neuromuscular monitoring (e.g. TOF count) is insufficient. Instead, quantitative monitoring with AMG or EMG is recommended for precise dosing and recovery assessment.[168] In

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dystrophinopathies, for aminosteroid NMBA reversal, sugammadex is preferred over neostigmine due to its more predictable and faster recovery profile, reducing the risk of prolonged NMB and associated complications.[169]

Q4 PICO 1C: Muscle relaxation and reversal in children with a myotonic disorder

Recommendation

- **We suggest avoiding succinylcholine due to the risk of myotonic contractures. We suggest considering reversal options before NMBA administration, as neostigmine may worsen myotonia.**
- **We suggest that sugammadex might be the safest reversal agent.**

GRADE for all the above statements: *Conditional recommendation based on very low level of evidence*

Rationale

Children with myotonic disorders present significant challenges during anaesthestic care due to altered neuromuscular physiology, including increased sensitivity to NMBA and unpredictable responses to reversal agents. While myotonic disorders cover a broad spectrum, the reports are predominantly on congenital myotonic dystrophy type 1 (Steinert disease). Most data are either case reports, case series or (retrospective) observational studies, and some reports do not specifically address the paediatric cohort. Considering these methodological limitations, we refrain from issuing recommendations for or against specific medications. However, succinylcholine should be avoided due to a potential risk of myotonic crisis. It has been used uneventfully in 113 adults,[170] and one case of myotonia was observed in a child.[171] In children undergoing muscle biopsy for suspected neuromuscular disease, succinylcholine was used only in two out of 877 neonates, reflecting widespread avoidance[172] (Appendix 3, Table 15, http://links.lww.com/EJA/B252). The European Neuromuscular Centre (ENMC) consensus statement on anaesthesia in patients with neuromuscular disorders strongly advises against its use.[149]

Cisatracurium and atracurium are preferred due to Hofmann elimination, which reduces the risk of prolonged paralysis. Atracurium has similar pharmacological properties but lacks direct clinical studies. Rocuronium and vecuronium warrant caution due to a risk of prolonged NMB. For example, prolonged rocuronium-induced NMB reversed with sugammadex has been described in a 14-month-old child,[173] but the use of rocuronium has also been reported in a few cases without complications.[176]

According to a comparative study in adults, EMG-based neuromuscular monitoring is more precise than acceleromyography.[174]

Neostigmine was associated with increased respiratory complications in myotonic patients, but with a very low evidence base for a causal relationship.[170] On the other hand, in a retrospective paediatric series, risk of postoperative respiratory complications was associated with the use of NMBA without reversal (RR = 24.9; 95% CI 4.3 to 148.5, $P < 0.0001$).[175] No case of neostigmine-induced myotonic crisis has been published so far.

Sugammadex might be the preferred antagonist for aminosteroid NMBA due to direct encapsulation. A review of 386 patients, including 19 with a myotonic disorder, confirmed its effectiveness, though some cases showed transient myotonia.[176]

Q4 PICO 1D: Muscle relaxation and reversal in children with mitochondrial and metabolic disorders

Recommendation

Mitochondrial disorders

- **Although no hazardous effect of succinylcholine has been reported in children with mitochondrial disorders, we suggest avoiding its use in children with a myopathy associated with a mitochondrial disorder.**
- **When using a nondepolarising NMBA in children with a myopathy associated with a mitochondrial disorder, we suggest evaluating the baseline TOF ratio before NMBA administration.**
- **We suggest using steroidal nondepolarising NMBA, because of reversal options with sugammadex, thus avoiding the side effects of neostigmine**

GRADE for all the above statements: *Conditional recommendation based on very low level of evidence*

Rationale

The literature on the anaesthetic management of children with a mitochondrial disorder deals mainly with intravenous (i.v.) fluids, prevention of hypoglycaemia and the potential risks of propofol-based total intravenous anaesthesia.[149,177] Data regarding NMB are scarce. In a retrospective series of nine patients undergoing 20 procedures (12 before the diagnosis of a mitochondrial cytopathy was established), the following NMBA and reversal agents were used uneventfully: succinylcholine four times, a nondepolarising NMBA 14 times and neostigmine six times.[178] The same results were observed in a retrospective series of 38 children.[177] Increased sensitivity to mivacurium was observed in one patient whose baseline TOF ratio was 0.59, indicating a preexisting muscular involvement.[179] Sugammadex has been used uneventfully in a few cases.[176] (Appendix 3, Table 16a, http://links.lww.com/EJA/B252) We suggest a preference

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for steroidal NMBA with the option of sugammadex reversal, thus avoiding side-effects of neostigmine while evaluating the baseline TOFr before its administration to achieve appropriate dose titration of the NMBA.

Recommendation

Metabolic myopathies

- **We suggest avoiding the use of succinylcholine in children with a myopathy caused by a glycogen-storage or lipid metabolism disorder because of an increased risk of rhabdomyolysis.**
- **When using a nondepolarising NMBA in children with a myopathy caused by a glycogen-storage or lipid metabolism disorder, we suggest evaluating the baseline TOF ratio before NMBA administration.**
- **We suggest using steroidal nondepolarising NMBA because of reversal options with sugammadex, thus avoiding the side effects of neostigmine.**
  GRADE for the above statements: *Conditional recommendation based on very low level of evidence*

Rationale

The literature on the anaesthetic management of children with a myopathy caused by a glycogen-storage (e.g. McArdle disease or glycogenosis type V) or lipid metabolism (e.g. carnitine disorders) disorder is scarce,[149,180] with only one series of 41 procedures (mainly muscle biopsies) published. The uneventful use of succinylcholine (three cases) and of unspecified nondepolarising NMBAs (16 cases) is reported without further details. As children with these myopathies are at high risk for spontaneous rhabdomyolysis due to fever or hypoglycaemia, we suggest avoiding succinylcholine. Moreover, due to the variable severity of muscle involvement, we suggest using quantitative neuromuscular monitoring and titrated doses of a nondepolarising NMBA. (Appendix 3, Table 16b, http://links.lww.com/EJA/B252)

Q4 PICO1E: Other neuromuscular conditions

Recommendation

- **We suggest considering rocuronium or vecuronium due to the reversal option with sugammadex. Neostigmine is more unpredictable pharmacodynamicly compared to sugammadex, which might be of disadvantage in some settings.**
- **Regardless of the NMBA used, dose titration according to effect is advised, as evaluated with quantitative neuromuscular monitoring while considering the possible influence of the pathology itself.**
  GRADE for the above statements: *Conditional recommendation based on very low level of evidence*

Rationale

Regarding the use of sugammadex in children with these very rare conditions, we encourage readers to look for case reports in the supplemental Table S1, https://doi.org/10.1016/j.bja.2024.05.015 of the systematic review by Schneider *et al.*[176]

We present two examples to highlight clinical issues that could be relevant in other rare neuromuscular diseases. (Appendix 3, Table 17, http://links.lww.com/EJA/B252)

In the presence of inflammatory myopathy (e.g. myositis), perivascular inflammation, fibrin thrombi and obliteration of capillaries may slow access of the NMBA and the reversal agent to the neuromuscular junction. This could result in a slower onset and reversal of NMB even in the absence of increased sensitivity to the NMBA *per se* and should be considered before a rapid sequence induction and intubation.[181,182]

In the case of a neuropathy, defective nerve conduction may result in difficult monitoring of the NMB, and muscle atrophy resulting from demyelination can cause increased sensitivity to nondepolarising NMBA. To illustrate the complexity of this issue, Charcot-Marie-Tooth disease serves as an example. It has at least 40 genetic causes with varying degrees of nerve demyelination and conduction delays, which could explain the variability in the reported cases. For instance, a normal response to mivacurium was observed in children with Charcot-Marie-Tooth 1,[183] but prolonged NMB following vecuronium in an adult.[184] Moreover, a case of rocuronium-induced relaxation refractory to sugammadex has been reported in an adult with the Charcot-Marie-Tooth 1A variant.[185] Most reports suggest neuromuscular monitoring using a rarely affected peripheral nerve, such as the facial nerve.[185,186] There remains some controversy on the choice of AMG or EMG-based neuromuscular monitoring for these cases.[185]

Q4 PICO 2: Use of NMBA in children with Cerebral Palsy

Recommendation

- **We suggest the use of NMB in children with cerebral palsy, taking into account their altered pharmacodynamic and/or pharmacokinetic status.**
- **We suggest quantitative neuromuscular monitoring to minimise complications related to resistance or sensitivity to NMBA**
  GRADE for the above statements: *Conditional recommendation based on very low level of evidence*

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Rationale

Six studies evaluated the effects of NMB in children with cerebral palsy, assessing pharmacodynamic differences, dosing requirements and peri-operative outcomes (Appendix 3, Table 18, http://links.lww.com/EJA/B252). These studies suggest that children with cerebral palsy often exhibit resistance to nondepolarising NMBA, altered responses to depolarising NMBA and potential benefits from adjunctive therapies like magnesium sulphate.

Succinylcholine's effect on plasma potassium levels was measured in children with cerebral palsy with no significant hyperkalaemic response being found, suggesting its relative safety for RSII in this disorder.[187] The dose–response relationship of succinylcholine at the adductor pollicis muscle was explored under propofol and nitrous oxide anaesthesia, with similar onset and duration in children with and without cerebral palsy, reinforcing its usability in this disorder.[188]

Two studies investigated vecuronium. The first study found that children with cerebral palsy required increased doses of vecuronium to achieve adequate NMB, probably due to upregulation of acetylcholine receptors.[189] The second study similarly demonstrated that vecuronium resistance was further influenced by concurrent anticonvulsant therapy, necessitating dose modifications and neuromuscular monitoring.[190]

Resistance to nondepolarising NMBA was confirmed in children with spastic cerebral palsy undergoing surgery for scoliosis with higher doses of rocuronium required for achieving adequate NMB.[191] On the basis of TOF monitoring, the mean ± SD intubation dose was greater in cerebral palsy patients than in controls (0.86 ± 0.09 vs. 0.6 ± 0.03 mg kg^{-1}) and even greater in the cerebral palsy patients receiving chronic anticonvulsant therapy (1.21 ± 0.13 mg kg^{-1}). In addition, the intubation dose of rocuronium increased with the severity of cerebral palsy regardless of anticonvulsant therapy. These findings emphasise the importance of individualised dosing strategies and real-time quantitative neuromuscular monitoring to optimise patient outcomes.

The effects of magnesium sulphate on NMBA requirements and postoperative analgesia were studied in children with cerebral palsy.[192] Magnesium sulphate significantly reduced the total NMBA dose required while also improving early postoperative pain control, suggesting its utility as an adjunct to enhance NMB and recovery.

Overall, these studies highlight the need for tailored NMB management in children with cerebral palsy. Although succinylcholine appears to be a viable option for RSII, resistance to nondepolarising NMBA like vecuronium and rocuronium requires dose adjustments. Magnesium sulphate may serve as a beneficial adjunct to optimise NMB and postoperative analgesia. Given these findings, we recommend that clinicians carefully consider pharmacodynamic alterations of NMBA in children with cerebral palsy and adjust their peri-operative approach accordingly. Objective neuromuscular monitoring on a limb with minimal contracture should be considered to ensure appropriate dosing, adequate paralysis and well tolerated recovery.

Q4 PICO 3: Use of an NMBA in children on anticonvulsants

- **We suggest quantitative monitoring of NMB in children with chronic use of anticonvulsants, as they may need higher doses or more frequent administration of aminosteroid NMBA to maintain NMB.**
  GRADE: *Conditional recommendation based on very low level of evidence*

Rationale

Although acute administration of anticonvulsants leads to an increased effect of NMBA, chronic anticonvulsive treatment with phenytoin and/or carbamazepine has been reported to result in resistance to long-acting aminosteroid NMBA in adults.[193] Very limited data are available in children that confirm these findings (Appendix 3, Table 19, http://links.lww.com/EJA/B252).

The time to abolish a twitch response for rocuronium and vecuronium is similar regardless of the agent or the combination of chronic anticonvulsants used.[194,195] However, the recovery from either rocuronium or vecuronium blockade is approximately twice as fast in children on either phenytoin or carbamazepine. The clearance of vecuronium is increased in children on chronic anticonvulsant treatment, suggesting a pharmacokinetic component.[194]

Chronic anticonvulsant therapy also results in a need to increase the dose of rocuronium in children with cerebral palsy (also refer to Q4PICO2).

There are so far no data on NMBA in children treated with more recently introduced anticonvulsant drugs such as sodium valproate, topiramate or levetiracetam.

Q4 PICO4: Need for neuromuscular block following reversal with neostigmine or sugammadex.

Recommendation

- **As the administration of succinylcholine shortly after neostigmine can result in a prolonged duration of action, we suggest quantitative monitoring of NMB if succinylcholine is given after administration of neostigmine** (see also Question 3 PICO4)
- **If NMB is required less than 2 h after reversal of rocuronium with sugammadex, we suggest using a nonsteroidal NMBA or titrating the rocuronium dose based on quantitative monitoring to achieve sufficient NMB.**

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GRADE for the above statements: *Conditional recommendation based on very low level of evidence*

Rationale

NMB may be needed following reversal of previous NMB with neostigmine or sugammadex, for example to treat severe laryngospasm following extubation or to restart surgery in cases of emergency such as bleeding. Theoretically, the inhibition of acetylcholinesterase by neostigmine should result in a prolonged duration of action of succinylcholine. This has been confirmed in one case report: the administration of a low dose succinylcholine (0.5 mg kg^{-1}) resulted in a prolonged NMB (50 min) in an infant who required re-intubation to relieve laryngospasm after receiving neostigmine.[196]

There are no publications on NMB early after administration of sugammadex in children. It is recommended that succinylcholine or a benzylisoquinoline (atracurium, cistatracurium, mivacurium) NMBA should be given in such a situation. In an open-label study of 16 adult volunteers rocuronium, 1.2 mg kg^{-1} was administered 5 to 60 min after reversal of deep NMB with 4 mg kg^{-1} sugammadex. Nonlinear model results showed that if a dose of 1.2 mg kg^{-1} rocuronium was given more than 30 min after a sugammadex dose of 4 mg kg^{-1}, NMB onset time is less than 2 min with 95% confidence.[197] If rocuronium was administered less than 25 min after sugammadex, NMB onset time varied between 1.92 and 4.42 min (< 4.25 min with 95% confidence). Moreover, the clinical duration of NMB was longer for the later rocuronium repeat dose times. This was confirmed in a multicentre observational study involving 11 adults who required rocuronium within 12 h after previous antagonism with sugammadex.[198] This study demonstrated that 0.6 mg kg^{-1} rocuronium can re-establish NMB within 3 min if the interval between the last sugammadex administration and re-administration of rocuronium was more than approximately 3 h. If sugammadex was administered less than 2 h previously, larger doses of rocuronium (0.9 to 1.2 mg kg^{-1}) were necessary to re-establish a NMB.

Adverse events

Adverse events associated with or caused by NMBA in children remain rare. In an extensive review of 47 RCTs, including 3086 children, performed to identify the most commonly reported severe adverse events as defined in the good clinical practice criteria of the the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), no statistically significant differences in the incidence of severe adverse events was found when comparing avoidance vs. use of NMBA for tracheal intubation: 0.8% in the NMB-free group vs. 1.5% in the NMB group (random-effects model, RR: 0.63; 95% CI 0.33 to 1.21, $P = 0.17$, $I^2 = 0\%$).[13] However, the certainty of evidence was very low due to risk of bias, indirectness and imprecision. Moreover, more common adverse events such as laryngospasm, cough, bucking or bronchospasm at intubation, which can result in significant morbidity, were not considered.

In a Japanese prospective cohort study involving 19 733 airway management procedures in children, the use of a NMBA significantly decreased the risk of any haemodynamic and respiratory adverse events except desaturation during airway management (adjusted OR 0.62; 95% CI 0.43 to 0.88, $P = 0.006$) if the NMBA was administered at the first airway securing attempt.[199]

Two cohort studies reported the incidence of postoperative respiratory complications when an NMBA is used. An increased risk of postoperative respiratory complications was found in a retrospective cohort study of 6507 children under 10 years undergoing surgery with general anaesthesia.[94] The children were divided into three groups: no intra-operative NMBA; a low multiple of age-adapted ED95 of NMBA dosing; and a high multiple of age-adapted ED95 NMBA dosing. Of note, only neostigmine was used for reversal, and only 23.6% of the patients received TOF monitoring. Propensity score matching was used to adjust for confounders. The OR for postoperative respiratory complications was highest in children who received the highest intraoperative doses of NMBA: 2.27 (95% CI 1.12 to 4.59, $P = 0.022$) by comparison with no NMBA. Subgroup analysis showed that age less than 1 year (OR 3.84; 95% CI 1.35 to 10.94), duration of surgery less than 90 min (OR 4.25; 95%CI 1.19 to 15.18) and ASA score more than 1 (OR 3.17; 95% CI 1.13 to 7.04) were significant risk factors. A similar but nonsignificant trend for an increased incidence of adverse respiratory events in 103 infants in the PACU was observed in a RCT, despite monitored reversal of rocuronium with neostigmine or sugammadex.[43] Infants with a moderate intraoperative NMB (TOFc = 1 or 2) presented more complications in the PACU (26.5%) compared to those with either no NMB (11.4%) or a shallow intraoperative NMB (TOFr>0.4) (9.1%, $P = 0.103$).

A secondary analysis of the NECTARINE prospective cohort showed that an NMBA was used in 58.7% of the 3840 infants studied. The most frequently used NMBA were rocuronium (33.5%), atracurium (32%), cisatracurium (16.5%) and succinylcholine (8.9%).[200] Only 29.8% of the infants receiving a nondepolarising NMBA received a reversal agent. In the subgroup of 2407 infants extubated in the operating room, the risk of postoperative pulmonary complications at 30 days was 8.4% in infants receiving no NMBA, but 16.6% among those receiving NMBA with no reversal and 2.5% if a reversing agent was administered (neostigmine in 85.6% of cases). Reversing NMB before tracheal extubation led thus to a reduced risk ratio for postoperative pulmonary complications (RR 0.43; 95%CI 0.26 to 0.70). These results highlight the

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importance of NMB monitoring and adequate reversal when using an NMBA.

Anaphylaxis following administration of an NMBA is the second most frequently reported cause of peri-operative anaphylactic reaction. In a retrospective study of 835 405 Japanese children anaesthetised between 2010 and 2016, a diagnosis of possible or probable anaphylactic reaction was issued in 545/606 410 (0.09%) children receiving rocuronium, 33/51 832 (0.06%) children receiving neostigmine and 297/367 724 (0.08%) children receiving sugammadex.[201] Using conditional logistic regression in nested case-control studies for both possible and probable anaphylaxis, the authors found no significant association between sugammadex and peri-operative anaphylaxis in children. In the US Wake Up Safe registry of 2 261 749 children anaesthetised between 2010 and 2017, a peri-operative anaphylactic reaction occurred in 0.003%. An NMBA or a reversal agent was involved in 11 and one out of the 62 cases reported, respectively.[202] Finally, in the US Wake Up Safe registry of 1 006 685 anaesthetics performed between 2010 and 2015, the use of an NMBA or a reversal agent was considered the cause of six and two cases out of the 329 anaesthesia-related cardiac arrests reported, respectively.[203]

Discussion

In accordance with ESAIC guideline policies, '*this guideline will not be intended to dictate clinical practice and clinicians should use this guideline as a guide when making patient-tailored decisions*'. The complete list of recommendations and suggestions is summarised in the accompanying summary.

Our aim and objective is to guide clinicians and researchers towards better and safer clinical practice and towards better and more extensive research in this area. We intend to update this extensive guideline regularly, as we anticipate significant evolution in monitoring, the widespread introduction of the ERAS concept (Enhanced Recovery After Surgery), which mandates neuromuscular monitoring, and an increasing number of pharmacological publications. Moreover, we acknowledge that one size does not fit all, and alternatives to NMB for intubation should be considered as required. This is reflected in our recommendations and clinical considerations throughout this collaborative work that includes colleagues from a wide range of countries around the world.

As with any guideline, one must be humble in acknowledging its limitations. We acknowledge that our recommendations may be subject to debate, given the heterogeneity of patient populations, variability in intubation techniques, and the potential risk of bias in some of the trials across different PICOs. Ideally, all recommendations should be based on high-quality systematic reviews; however, this is not the case for every PICO included. Moreover, the studies included in this guideline exhibit considerable heterogeneity in terms of age-related inclusion criteria and subgroup definitions. This variability may lead to confusion for readers. As a general framework, the age subgroups used across our assessments typically represent the following paediatric categories: neonates (<1 month), infants (1 to 12 months), toddlers (1 to 2 years), preschool children (2 to 6 years), school-age children (6 to 12 years) and adolescents (13 to 17 years). But these definitions often do not align with those reported in the trials included in our guideline. Despite these methodological limitations, following a thorough evaluation of the evidence, four Delphi rounds and extensive discussions among panel members, we are confident that our recommendations represent best clinical practice

There also other more clinical limitations. First, the success of tracheal intubation relies on the subtle interplay between anatomy and (patho-)physiology, NMB, depth of anaesthesia and intubator's skills or experience. This has been shown, for example, in a Swiss prospective study involving 755 children without respiratory tract infection aged 1 to 14 years: the risk for peri-operative respiratory adverse events was increased 1.7-fold if they were not looked after by a paediatric anaesthesiologist.[204] Similarly, in an Australian prospective cohort study of 2891 paediatric intubations, airway management by a specialist paediatric anaesthesiologist resulted in a significantly reduced risk of any peri-operative respiratory adverse effect compared to management by a registrar ($P < 0.0001$).[205] On the contrary, in the Japanese prospective cohort study involving 19 733 airway management procedures in children, the experience of the person in charge of airway management did not affect the risk of any adverse events: the reported OR was 0.80 (95% CI 0.59 to 1.09, $P = 0.159$) when comparing a trainee with a specialist and 0.88 (95% CI 0.57 to 1.37, $P = 0.577$) when comparing a frequent or occasional operator with a specialist, except for desaturation as an outcome.[199] However, these results were not adjusted for the child's age. These studies should be interpreted with caution as they considered experience in paediatric airway management, which includes intubation, but also other skills. In fact, the operator's experience was reported in less than 50% of the studies reviewed. This potential source of bias should be kept in mind when interpreting the rationales of Question 1.

Second, some concepts referred to in the text are either poorly defined or their definition varies depending on the publications. For instance, it remains a debatable question as to what the term '*adequate intubation conditions*' signifies in many of the included publications. An objective intubation score such as the Viby-Mogensen score should be systematically used in future studies.[206] An RCT in adults has indeed demonstrated that excellent intubating conditions are less frequently associated with postoperative hoarseness and vocal cord injury than acceptable conditions.[207] In the same way, the concepts of '*adequate depth of anaesthesia*', '*high-dose opioids*' and of '*skilled intubator*'

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should be clearly defined by consensus and used in future research protocols to facilitate comparison between studies. The lack of clear definitions is a particular problem and significantly limits the validity of any meta-analysis and reduces the reliability and generalisability of their findings, including the one carried out for this guideline.

Third, certain groups of patients are not covered by this guideline, such as burn patients.

Fourth, the use of NMB in cases of expected or unexpected difficult intubation is not considered in this guideline, although an NMBA was administered in 43% of the 1018 cases collected in the PeDi registry.[208] The decision to use an NMBA in case of difficult intubation should be based on the individual characteristics, the cause of the obstruction (functional vs. anatomical) and a local algorithm, and this is explained in previous publications.[209] The principles described in this guideline regarding NMB monitoring and reversal should of course be applied to this specific situation.

Moreover, the effect of administering an NMBA at induction of anaesthesia in children with an upper respiratory tract infection was not considered. A multicentre cohort study was performed in France with 621 children aged less than 18 years presenting for anaesthesia with a current upper respiratory tract infection or a history of such an infection within the preceding 4 weeks.[210] In the 489 who were actually anaesthetised, using an NMBA at induction significantly decreased the risk of peri-operative respiratory adverse events [3.7% in the NMBA group vs. 10.6% in the NMBA-free group ($P = 0.004$)].[209] This controversial issue deserves more attention in future studies.

Finally, although this document is mandated and supported by ESAIC and ESPA, no recommendations are proposed regarding the use of an NMBA for intubation or ventilation in the PICU and NICU. Regarding this issue, the members of the Task Force acknowledge the lack of high-quality evidence. Furthermore, there are significant differences in patient populations, settings and acute clinical care priorities between children cared for in the PICU and NICU as compared with those managed in the operating room, even if there are some overlaps. Recommendations on the use of an NMBA and monitoring of NMB in these patients should be made by an interdisciplinary panel involving NICU and PICU specialists. When NMBA are used, it is important to ensure an adequate level of sedation which may in future include processed EEG monitoring when available. Therefore, we can only suggest applying the general principles of this guideline and reiterate that the use of an NMBA should be supported by adequate sedation.

The members of the Task Force hope that this guideline will stimulate improved evidence-based practices, implementation of better monitoring, and foster more relevant research with more universal and patient-centred outcomes across all important settings, including emergency care, rare diseases, PICU and NICU.

Implementation

We acknowledge that beyond the complexity of devising and publishing clinical practice guidelines, the diffusion, dissemination and implementation of the messages of this document remains the real challenge. There will indeed be many obstacles to overcome. For example, introduction of quantitative neuromuscular monitoring requires education and training but also departmental and institutional (financial) support.

The challenge will be even greater in low income settings. To be realistic, one could propose the stepwise approach described in Table 3, the starting point of which will depend on the current clinical practice in individual departments.

A prospective qualitative study with a before/after design will be set up by members of the Task Force to evaluate the clinical impact of the publication of these guidelines.

Knowledge gaps and pathways for future research

During this extensive literature search and through numerous Task Force meetings, we identified some knowledge gaps that could act as a starting point for future clinical research in paediatric anaesthesia and intensive care. Several relevant domains and questions came to attention:

Physiology:

- What are the specificities of neuromuscular monitoring in neonates?
  - Is the baseline TOF ratio lower than 1 in this group?
  - How does the suppression of the ventilatory response to acute hypoxaemia induced by a NMBA recover as compared to TOFr in small children?[211]
- *Neuromuscular monitoring:*
  - What are the limitations of EMG-based monitoring? Is an EMG-based TOFr of at least 0.9 associated with improved paediatric outcomes ?
  - How do we monitor patients with amyotrophy?

Table 3 Suggested stepwise approach for the implementation and adoption of the guidelines

- Education on pharmacology of NMBA and reversal agents in children
- Increasing use of NMB for intubation in children
- Routine use of qualitative neuromuscular monitoring
- Use of neostigmine only when TOFc = 4
- Routine use of quantitative monitoring of neuromuscular block and achieving a TOFr $\geq$ 0.9 before extubation
- Introduction of sugammadex for reversal of deep NMB with steroidal NMBA
- Adoption of EMG-based neuromuscular monitoring

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  - Which is the best neuromuscular monitoring option in the presence of a nerve conduction defect?
  - Which is the best way to monitor the level of sedation during NMB?
- *Pharmacology:*
  - What is the dose–response curve of sugammadex when used to reverse a rocuronium-induced NMB in the different paediatric age groups?
  - Are there any interactions between the most recent anticonvulsants and nondepolarising NMBA or sugammadex?
- *Epidemiology:*
  - Could the increased use of nondepolarising NMBA (and sugammadex) in children result in an increased risk of hypersensitivity IgE-mediated reactions when administered to the same individuals as they grow older? Should an international registry be established?
- *Providing better care for muscle disease patients:*
  - Creating an international registry to collect data on the anaesthetic care (including NMB) of patients with a rare disease would be an important step forward for the improvement of the safety of anaesthetic management in a group at increased anaesthetic risk.

Conclusion

This guideline provides structured recommendations for the use use, monitoring and reversal of NMBAs in anaesthetised children. It reflects current best practice based on the available paediatric literature, expert consensus with a rigorous methodology aligned with ESAIC and ESPA standards. Key recommendations highlight the importance of NMB use to facilitate tracheal intubation in children, the benefits of quantitative neuromonitoring to rule out residual NMB before extubation, and the appropriate use and dosage of reversal agents when needed. Special attention is also given to neonates, children with neuromuscular or metabolic conditions, and those on chronic anticonvulsant therapy, underscoring the need for tailored approached in high-risk populations.

Although this guideline offer strong clinical direction, it also identifies significant knowledge gaps, particularly in neonatal and intensive care settings, rare diseases and advanced monitoring technologies, which demand further research. Last but not least, implementation of this guideline into clinical practice will require access to effective monitoring tools, professional education and training, and institutional commitment.

Finally and most importantly, this guideline is a resource to support individualised, safe and effective anaesthetic care. Our aim is to promote thought-full clinical decision making, stimulate research and ultimately improve outcomes for children requiring the use of NMB in anaesthesia and intensive care.

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Conflicts of interest: FV is one of the chairpersons of the Syndromes and Rare Diseases in Pediatrics: Anesthesia website and a reviewer for Orphananesthesia

TFB: Receipt of honoraria or consultation fees: Merck

TGH: Deputy Editor-in-Chief, European Journal of Anaesthesiology

JoK: Europe-wide patent for the paediatric emergency ruler (PaedER; www.paeder.com)

VS: Receipt of grants/research supports: MSD research support

BvUs: Receipt of grants/research supports: NHMRC and Stan Perron Charitable Foundation

AA: is a reviewer for Orphanaesthesia

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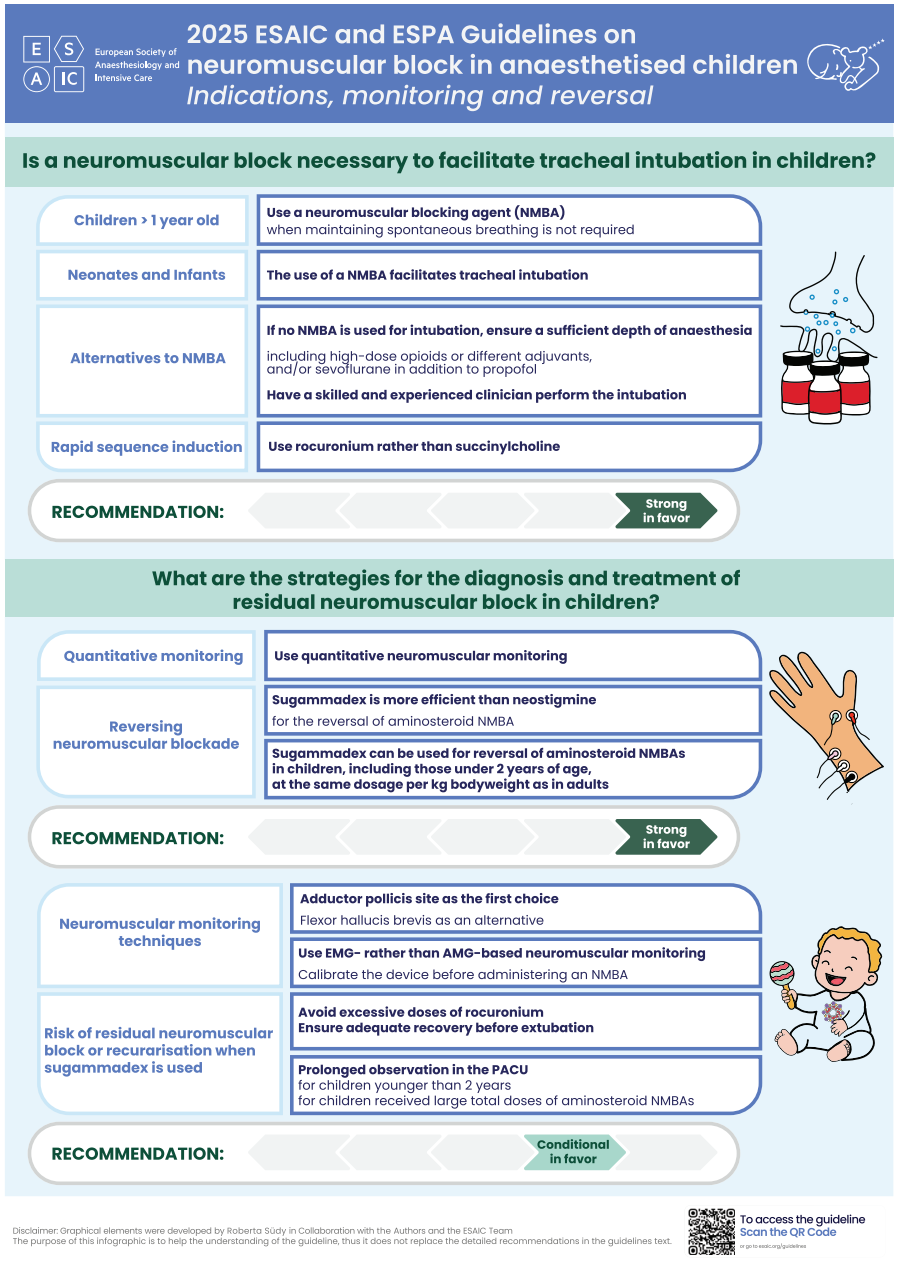
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GRAPHICAL ABSTRACT



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