



Roles of evidence synthesis studies and evidence-based clinical practice guidelines in pediatric perioperative outcomes research

Naoko Niimi^{1,2} · Evelina Pankiv^{1,2} · Ruxandra-Ioana Adam^{1,3} · Jason Hayes^{1,2} · Jason T. Maynes^{1,2,4} · Kazuyoshi Aoyama^{1,2,5} 

Received: 16 November 2024 / Accepted: 20 November 2024 / Published online: 18 December 2024
© The Author(s) under exclusive licence to Japanese Society of Anesthesiologists 2024, corrected publication 2025

Keywords Evidence synthesis study · Clinical practice guideline · Pediatric anesthesia

A randomized controlled trial (RCT) is generally considered to provide high-quality evidence for addressing a research hypothesis in clinical research [1, 2], such as trials comparing different fasting periods evaluated by ultrasound, or comparison of supraclavicular versus costoclavicular brachial plexus blocks [3–8]. However, many RCTs in anesthesiology are known to be fragile, mainly due to small number of participants and low outcome event rates [9, 10]. The fragility index (FI) is used to assess the robustness of RCT results, measuring the minimum number of patients whose result would have to change from a non-event to an event in order to convert a result from statistically significant to nonsignificant—a smaller FI indicates a less robust result [9, 11]. Hayes et al. recently reported that the median FI in pediatric anesthesiology is 3, indicating RCTs in pediatric anesthesiology are highly fragile, and that many pediatric anesthesiology trials were underpowered [9, 11]. One way to mitigate the limitations of an underpowered RCT is to conduct an evidence synthesis study by quantitatively pooling results from multiple RCTs to enhance statistical power.

Evidence synthesis study is a research method that allows researchers to identify, select, and qualitatively and quantitatively combine data from multiple relevant studies to address a research hypothesis. Evidence synthesis studies include the methodologies of scoping review (ScR), systematic review (SR), rapid review, and systematic review with meta-analysis (SR/MA) or network meta-analysis (NMA). Table 1 summarizes the key features of evidence synthesis studies and narrative reviews. A ScR follows a systematic and rigorous process outlined by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [12] and aims to identify gaps between what is known and what is not known in current studies by exploring broad research questions [13–16]. While both ScR and SR are types of evidence synthesis studies, ScR focuses on knowledge gaps, whereas SR aims to address specific research questions [17–19]. Typically, meta-analysis is conducted in addition to SR, which enables researchers to address research questions by quantitatively pooling effect sizes (e.g., mean difference, risk ratio) of eligible studies [20, 21]. Rapid review is a type of evidence synthesis study used to answer time sensitive or urgent questions, such as those seen in the context of COVID-19 [22]. The process of rapid review is omitted or simplified compared to SR with or without MA to expedite the process. NMA is an advanced type of SR/MA which allows for the comparison of three or more arms simultaneously, with direct and indirect evidence [23–25]. By conducting an evidence synthesis study, researchers will be able to qualitatively and quantitatively answer their research questions and may identify fields where evidence is lacking or where the quality of evidence remains low. The quality of evidence can be assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is a gold standard to systematically assess the quality

✉ Kazuyoshi Aoyama
kazu.aoyama@utoronto.ca

¹ Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, 555 University Ave, #2211, Toronto, ON M5G 1X8, Canada

² Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, ON, Canada

³ Department of Psychology, Queen's University, Kingston, ON, Canada

⁴ Program in Molecular Medicine, SickKids Research Institute, Toronto, ON, Canada

⁵ Program in Child Health Evaluative Sciences, SickKids Research Institute, Toronto, ON, Canada

Table 1 Features of evidence synthesis studies and narrative review

| | | Evidence Synthesis Studies | | |
|--------------------|--|----------------------------|----------------------------|-----------------------------------|
| | | Narrative Review | Scoping Review | Systematic Review + Meta analysis |
| Purpose | | Summarize | Identify gaps | Answer specific questions |
| Research Questions | | Broad/Undefined | Broad | Specific |
| Data Synthesis | | Qualitative | Qualitative | Quantitative |
| | | | ↓ Semi-formal Rapid review | ↓ Advanced Network Meta-Analysis |

of evidence and to determine strength of recommendations in an evidence synthesis study [26]. GRADE is an essential approach to provide evidence-based recommendations, especially when developing guidelines and is adopted by over 110 guideline organizations worldwide [27].

Evidence-based clinical practice guideline (CPG) provides best clinical practice recommendations for patient care. It is essential for improving and standardizing the quality of patient care, improving patient outcomes, and supporting clinical decision making. The development of a CPG is a rigorous process that involves synthesizing existing information from RCTs, observational studies, and expert opinions through systematic reviews, and assessing the quality of evidence by the GRADE approach to ensure recommendations are evidence-based [28]. The process requires external review by relevant clinical and scientific experts,

professional organizations, policy makers, patients, and other stakeholders to improve its quality. Regular updates, typically recommended every five years, help maintain its relevance. Figure 1 illustrates the hierarchy of evidence levels in research. Evidence-based CPGs represent the highest level of research evidence, making them more influential in clinical practice. At the same time, pre-clinical research, illustrated in the bottom of the pyramid, is also vital as it forms the foundation upon which further research and evidence synthesis are built.

Disma et al. have published an evidence-based CPG for airway management in neonates and infants, offering essential recommendations for this population [28]. Airway management requires anesthesiologists to respond rapidly because of their increased risk of critical hypoxia in this vulnerable population. The clinical strengths of

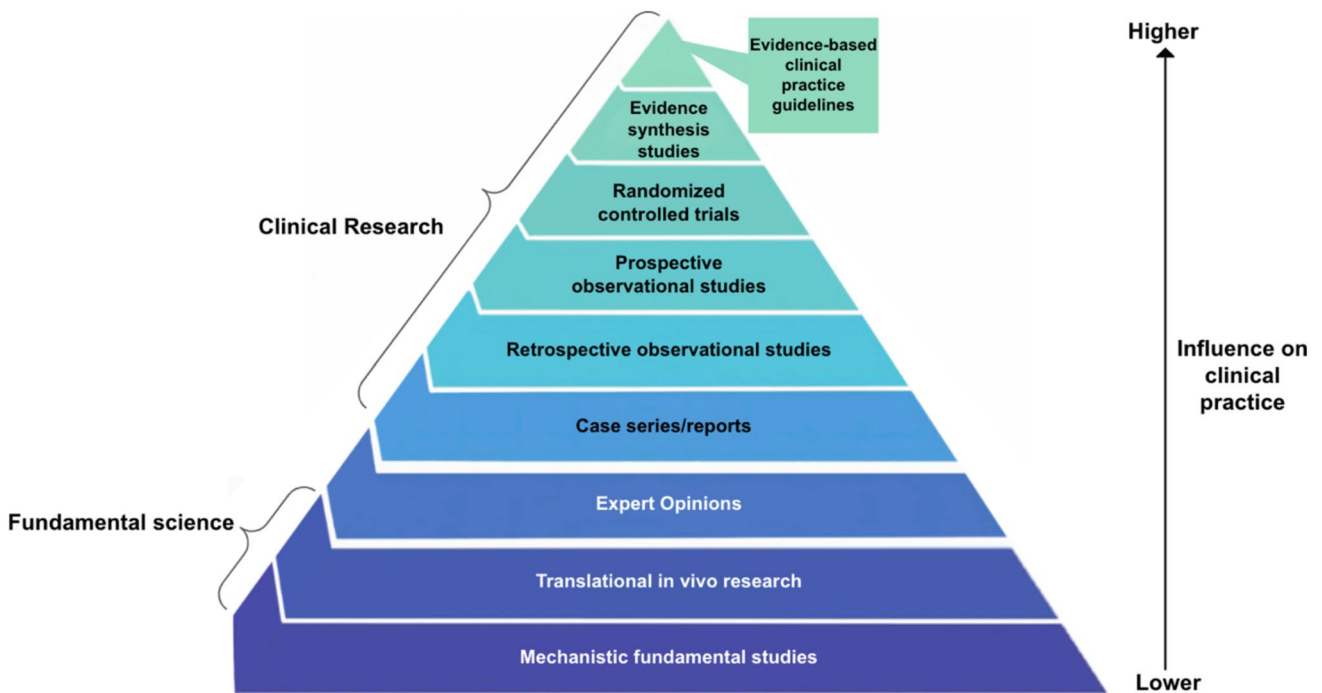


Fig. 1 Interpretations of level of evidence in research. The pyramid illustrates levels of evidence from pre-clinical to clinical research, highlighting the influence on clinical practice. Evidence-based clinical practice guidelines are positioned at the top, supported by all

other studies listed in the pyramid below. This does not imply that only the topmost level is important, fundamental science research and other types of clinical research are equally important in forming the foundation of evidence

this airway guideline are its ability to provide evidence based, standardized approaches tailored to these patients, including 13 specific recommendations for assessing airway difficulty, preparing equipment, and performing intubation and extubation. The guideline provides various techniques for effective airway management such as use of a video-laryngoscope and supplemental oxygenation during intubation, to improve success rates and minimize adverse events. From a methodological standpoint, the guideline demonstrates rigor in its development process. Recommendations were formulated through a literature search across multiple databases conducted by an information specialist, risk of bias assessment, and quality of evidence assessment according to the GRADE approach. Additionally, a multinational task force of 23 internationally recognized experts in pediatric airway management contributed to its development, which enables opinion from a broad perspective and specialized knowledge focused on airway management for neonates and infants. However, a CPG sometimes faces limitations due to the nature of its study design, such as lack of enough evidence for rare complex cases or specific patient comorbidities. A CPG may also not provide recommendations that are fully applicable to each facility, as each facility may have different available medications and equipment. To complement these gaps, narrative review can be valuable, incorporating quality improvement and educational perspectives. For instance, a narrative review can summarize the impact of aging on syndromic patients associated with difficult airway, which was briefly mentioned in the initial CPG. Thus, *Journal of Anesthesia* invited the authors of the airway CPG to publish a narrative review to provide additional information in areas where evidence was lacking in the previous guideline [29]. An example of such additional information is a physical assessment to predict difficult airway management and oxygen administration techniques during intubation, which were both not addressed in the previous guideline [29].

The editorial board of the *Journal of Anesthesia* often invites experts in anesthesiology, pain medicine, and critical care to publish invited narrative reviews. Unlike evidence synthesis studies, a narrative review does not have a clear methodology or protocol, but instead aims to summarize the topic. These invited reviews are expected to address timely topics, emerging areas of research, or updates in established fields. These reviews are valuable as they offer expert opinions and interpretations in the field in addition to up-to-date evidence. In the recent invited review of airway management in pediatrics [30], the use of a physical assessment to predict a difficult airway was detailed as it was not included in the CPG due to a lack of relevant prospective studies in neonates and infants. Likewise, some measurements used in adults (e.g. Mallampati score) are not feasible in this population as they require patient cooperation. Therefore, clinical

assessment and expert opinion remain the most reliable methods to predict a difficult airway [30], and the invited narrative review is well suited to provide the expert opinion that the CPG could not offer. Due to the limited number of RCTs on oxygenation methods and flow rates during intubation, the CPG states that “apneic oxygenation during intubation reduce the incidence of hypoxemia”, but lacks details on delivery methods and flow rates. This invited review provides detailed guidance on oxygen delivery methods, flow rates, equipment, and practical tips in the main text and online-only supplement videos, making this review an essential resource for expanding the CPG.

Evidence-based CPG and evidence synthesis study are cornerstones of evidence-based medicine, enabling the provision of high-quality healthcare. Supplemental reviews, such as invited reviews are an essential resource to organize information, highlight new findings, and provide updates. By offering expert insights and addressing areas where evidence may be limited, these reviews can guide clinical practice and facilitate advancements in medicine.

Acknowledgements JTM and KA acknowledges the Department of Anesthesiology and Pain Medicine, University of Toronto, and the Hospital for Sick Children, for secured academic time to conduct the current work as a recipient of a Merit Award 2023-2025.

Author contributions NN and KA wrote the initial and subsequent draft of the manuscript, which EP, RA, JH and JTM commented and edited. All authors approved the final version.

Funding This work was supported by Canadian Anesthesiologists’ Society Research Award 2022–2024 (KA), Canadian Anesthesiologists’ Society Career Scientist Award in Anesthesia 2024–2026 (KA), POS Summer Studentship Program, Hospital for Sick Children 2024 (RA, JH, KA), and Project Grants (PJX179857, PJT183603) 2022–2025, Canadian Institutes of Health Research (KA).

Declarations

Conflict of interest The authors declare that they have no competing interest related to this publication.

References

1. Zabor EC, Kaizer AM, Hobbs BP. Randomized controlled trials. *Chest*. 2020. <https://doi.org/10.1016/j.chest.2020.03.013>.
2. Niimi N, Yang A, Sumie M, Hayes J, Maynes JT, Aoyama K. Understanding three standard study designs for randomized controlled trials. *J Anesth*. 2024. <https://doi.org/10.1007/s00540-024-03355-z>.
3. Cho E, Kwak JH, Huh J, Kang IS, Ryu KH, Lee SH, Ahn JH, Choi HK, Song J. A comparative study using gastric ultrasound to evaluate the safety of shortening the fasting time before pediatric echocardiography: a randomized controlled non-inferiority study. *J Anesth*. 2024. <https://doi.org/10.1007/s00540-024-03360-2>.
4. Sakai W, Chaki T, Nawa Y, Oyasu T, Ichisaka Y, Nawa T, Asai H, Ebuoka N, Oba J, Yamakage M. Head cooling wrap could suppress the elevation of core temperature after cardiac surgery

- during forced-air warming in a pediatric intensive care unit: a randomized clinical trial. *J Anesth.* 2023. <https://doi.org/10.1007/s00540-023-03210-7>.
5. Guzel M, Bingul ES, Salviz EA, Senturk E, Cosgun MF, Savran KM. Comparison of ultrasound-guided supraclavicular and costoclavicular brachial plexus blocks in pediatric patients: a randomized clinical trial. *J Anesth.* 2023. <https://doi.org/10.1007/s00540-022-03143-7>.
 6. Masui K, Asai T, Saito T, Okuda Y. Efficacy of McGrath@MAC videolaryngoscope blade 1 for tracheal intubation in small children: a randomized controlled clinical study. *J Anesth.* 2023. <https://doi.org/10.1007/s00540-023-03207-2>.
 7. Ren Y, Nie X, Zhang F, Ma Y, Hua L, Zheng T, Xu Z, Gao J, Zhang J. Ultrasound-guided erector spinae plane block versus thoracic epidural block for postoperative analgesia in pediatric Nuss surgery: a randomized noninferiority trial. *J Anesth.* 2024. <https://doi.org/10.1007/s00540-024-03354-0>.
 8. Li H, Liu J, Xiong L, Duan G, Xu Y. Oxygen concentration titration guided by oxygen reserve index during pediatric laryngeal surgery with high-flow nasal cannula oxygen: a randomized controlled trial. *J Anesth.* 2024. <https://doi.org/10.1007/s00540-024-03348-y>.
 9. Hayes J, Zuercher M, Gai N, Roy Chowdhury A, Kazuyoshi AD. The Fragility Index of randomized controlled trials in pediatric anesthesiology. *Can J Anesth.* 2023. <https://doi.org/10.1007/s12630-023-02513-3>.
 10. Mazzinari G, Ball L, Serpa Neto A, Errando CL, Dondorp AM, Bos LD, Gama de Abreu M, Pelosi P, Schultz MJ. The fragility of statistically significant findings in randomised controlled anaesthesiology trials: systematic review of the medical literature. *Br J Anaesth.* 2018. <https://doi.org/10.1016/j.bja.2018.01.012>.
 11. Hayes J, Aoyama K. In reply: Comment on: the fragility index of randomized controlled trials in pediatric anesthesiology. *Can J Anesth.* 2024. <https://doi.org/10.1007/s12630-023-02659-0>.
 12. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, Weeks L, Hempel S, Akl EA, Chang C, McGowan J, Stewart L, Hartling L, Aldcroft A, Wilson MG, Garrity C, Lewin S, Godfrey CM, Macdonald MT, Langlois EV, Soares-Weiser K, Moriarty J, Clifford T, Tunçalp Ö, Straus SE. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med.* 2018. <https://doi.org/10.7326/M18-0850>.
 13. Pankiv E, Alfonso Albornoz FE, Nghiem J, Maria-Alexandra Petre F, Marina Englesakis F, Rana M, Mc Donnell C, Hayes J, Aoyama K. Prophylaxis for pediatric postoperative nausea and vomiting: a scoping review of clinical trials. *Can J Anesth.* 2023. <https://doi.org/10.1007/s12630-023-02560-w>.
 14. Pieri M, D'Andria Ursolo J, Di Prima AL, Bugo S, Barucco G, Licheri M, Losiggio R, Frau G, Monaco F. Remimazolam for anesthesia and sedation in pediatric patients: a scoping review. *J Anesth.* 2024. <https://doi.org/10.1007/s00540-024-03358-w>.
 15. Hatakeyama J, Nakamura K, Sumita H, Kawakami D, Nakanishi N, Kashiwagi S, Liu K, Kondo Y. Intensive care unit follow-up clinic activities: a scoping review. *J Anesth.* 2024. <https://doi.org/10.1007/s00540-024-03326-4>.
 16. Chen YYK, Soens MA, Kovacheva VP. Less stress, better success: a scoping review on the effects of anxiety on anesthetic and analgesic consumption. *J Anesth.* 2022. <https://doi.org/10.1007/s00540-022-03081-4>.
 17. Albornoz AE, Rana M, Hayes J, Englesakis M, Tsang M, Amin R, Gilfoyle E, Petre MA, Campisi P, Aoyama K. Perioperative clinical practice recommendations for pediatric tonsillectomy: a systematic review. *Can J Anesth.* 2024. <https://doi.org/10.1007/s12630-023-02668-z>.
 18. Pankiv E, Nghiem J, Albornoz AE, Rana M, Petre M-A, Englesakis M, Hayes J, Mc Donnell C, Aoyama K. Appraising and highlighting gaps among prophylactic intervention studies for reducing the incidence of postoperative nausea and vomiting in children: a systematic review. *BMJ Open.* 2024. <https://doi.org/10.1136/bmjopen-2022-070775>.
 19. Shioji N, Sumie M, Englesakis M, Gilfoyle E, Maynes JT, Aoyama K. Multisystem inflammatory syndrome in children: an Umbrella review. *J Anesth.* 2024. <https://doi.org/10.1007/s00540-024-03323-7>.
 20. Niimi N, Sumie M, Englesakis M, Yang A, Olsen J, Cheng R, Maynes JT, Campisi P, Hayes J, Ng WCK, Aoyama K. Effects of dexamethasone on opioid consumption in pediatric tonsillectomy: a systematic review with meta-analysis. *Can J Anesth.* 2024. <https://doi.org/10.1007/s12630-024-02817-y>.
 21. Gong T, Huang Q, Zhang Q, Cui Y. Postoperative outcomes of pediatric patients with perioperative COVID-19 infection: a systematic review and meta-analysis of observational studies. *J Anesth.* 2024. <https://doi.org/10.1007/s00540-023-03272-7>.
 22. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO, Legrand M, Deutschman CS. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med.* 2020. [https://doi.org/10.1016/S2213-2600\(20\)30404-5](https://doi.org/10.1016/S2213-2600(20)30404-5).
 23. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015. <https://doi.org/10.7326/M14-2385>.
 24. Yang A, Pechlivanoglou P, Aoyama K. Interpreting and assessing confidence in network meta-analysis results: an introduction for clinicians. *J Anesth.* 2022. <https://doi.org/10.1007/s00540-022-03072-5>.
 25. Petre MA, Levin DN, Englesakis M, Maynes JT, Pechlivanoglou P, Aoyama K. Dexmedetomidine vs. total intravenous anaesthesia in paediatric emergence delirium: a network meta-analysis. *Eur J Anaesthesiol.* 2021. <https://doi.org/10.1097/EJA.0000000000001490>.
 26. Zhang Y, Alonso-Coello P, Guyatt GH, Yepes-Nuñez JJ, Akl EA, Hazlewood G, Pardo-Hernandez H, Etxeandia-Ikobaltzeta I, Qaseem A, Williams JW Jr, Tugwell P, Flottorp S, Chang Y, Zhang Y, Mustafa RA, Rojas MX, Schünemann HJ. GRADE Guidelines: 19. Assessing the certainty of evidence in the importance of outcomes or values and preferences—Risk of bias and indirectness. *J Clin Epidemiol.* 2019. <https://doi.org/10.1016/j.jclinepi.2018.01.013>.
 27. Lima JP, Mirza RD, Guyatt GH. How to recognize a trustworthy clinical practice guideline. *J Anesth, Analg Crit Care.* 2023. <https://doi.org/10.1186/s44158-023-00094-7>.
 28. Handbook for Clinical Practice Guidelines Development. 2021. Available from: <https://www.idsociety.org/practice-guideline/clinical-practice-guidelines-development-training-and-resources/>
 29. Disma N, Asai T, Cools E, Cronin A, Engelhardt T, Fiadjoe J, Fuchs A, Garcia-Marcinkiewicz A, Habre W, Heath C, Johansen M, Kaufmann J, Kleine-Brueggeney M, Kovatsis PG, Kranke P, Lusardi AC, Matava C, Peyton J, Riva T, Romero CS, von Ungern-Sternberg B, Veyckemans F, Afshari A. Airway guidelines groups of the European Society of Anaesthesiology and Intensive Care (ESAIC), The British Society of Anaesthesia (BSA). Airway management in neonates and infants: European Society of Anaesthesiology and Intensive Care and British Journal of Anaesthesia joint guidelines. *Eur J Anaesthesiol.* 2024. <https://doi.org/10.1097/EJA.0000000000001928>.
 30. Zimmermann L, Maiellare F, Veyckemans F, Fuchs A, Scquizzato T, Riva T, Disma N. Airway management in pediatrics – Improving safety. *J Anesth.* <https://doi.org/10.1007/s00540-024-03428-z>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.