Brain & Development 48 (2026) 104594

Contents lists available at ScienceDirect

Brain and Development

journal homepage: www.elsevier.com/locate/braindev

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

Review Article

Key revisions in the 2023 guidelines for the diagnosis and treatment of acute encephalopathy in childhood☆

Jun-ichi Takanashi [a,b,*], Masashi Mizuguchi [a,c], Takashi Ichiyama [a,d], George Imataka [a,e], Akihisa Okumura [a,f], Tomohide Goto [a,g], Hiroshi Sakuma [a,h], Hiroaki Nagase [a,i], Kei Murayama [a,j], Hideo Yamanouchi [a,k], Taku Omata [a,b], Hiroko Tada [a,l], Yoshihiro Maegaki [m,n]

[a] *Working Group for the Revision of Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood, Japanese Society of Child Neurology, Tokyo, Japan*
[b] *Department of Pediatrics, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Japan*
[c] *Department of Developmental Medical Sciences, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
[d] *Division of Pediatrics, Tsudumigaura Medical Center for Children with Disabilities, Yamaguchi, Japan*
[e] *Department of Pediatrics, Dokkyo Medical University, Tochigi, Japan*
[f] *Department of Pediatrics, Aichi Medical University, Aichi, Japan*
[g] *Division of Neurology, Kanagawa Children's Medical Center, Kanagawa, Japan*
[h] *Department of Clinical Medical Sciences, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan*
[i] *Department of Pediatrics, Kobe University Graduate School of Medicine, Hyogo, Japan*
[j] *Department of Pediatrics, and Diagnostics and Therapeutics of Intractable Disease, Intractable Disease Research Center, Juntendo University Faculty of Medicine, Tokyo, Japan*
[k] *Department of Pediatrics, Comprehensive Epilepsy Center, Saitama Medical University, Saitama, Japan*
[l] *Department of Pediatrics, Chibaken Saiseikai Narashino Hospital, Narashino, Japan*
[m] *Committee for the Integration of Guidelines, Japanese Society of Child Neurology, Tokyo, Japan*
[n] *Division of Child Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan*

ARTICLE INFO

Keywords:
Acute encephalopathy
Guideline
Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)
Clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)
Targeted temperature management (TTM)

ABSTRACT

Background: New literature has accumulated since the publication of the guidelines for the diagnosis and treatment of acute encephalopathy in childhood 2016 (GL2016), necessitating the revision of these guidelines.
Methods: In 2020, the working group (WG) of the Japanese Society of Child Neurology began work on publishing a revised version of the GL2016. The WG formulated guidelines using the methodologies recommended by the Medical Information Network Distribution System (Minds).
Results: GL2023, published in 2023, includes clinical question 1 (CQ1), based on Minds 2020, and general and specific sections on acute encephalopathy (an update to GL2016) based on Minds 2007. In CQ1, early target temperature management at 36 °C within 24 h was weakly recommended for pediatric cases meeting certain criteria to reduce the risk of progression to acute encephalopathy with biphasic seizures and late reduced diffusion and its sequelae.
Conclusions: GL2023 provides updated recommendations that may improve the diagnosis and management of pediatric acute encephalopathy.

1. Introduction

Acute encephalopathy, which presents with acute central nervous system dysfunction, is characterized by acute onset of severe and long-lasting disturbances in consciousness and seizures, and is most often caused by infectious diseases, such as influenza and exanthema subitum. Acute encephalopathy consists of multiple syndromes, including acute necrotizing encephalopathy (ANE), acute encephalopathy with biphasic

☆ Given his role as Associate Editor-in-Chief, Hiroshi Sakuma had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Editor-in-Chief, Masafumi Morimoto

* Corresponding author at: Department of Pediatrics, Tokyo Women's Medical University Yachiyo Medical Center, Yachiyo, Japan. 477-96 Owadashinden, Yachiyo-Shi, Chiba 276-8524, Japan.
E-mail address: jtaka@twmu.ac.jp (J.-i. Takanashi).

https://doi.org/10.1016/j.braindev.2026.104594
Received 18 May 2026; Received in revised form 4 August 2026; Accepted 27 August 2026
Available online 23 September 2026
0387-7604/© 2026 The Japanese Society of Child Neurology. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

seizures and late reduced diffusion (AESD), and clinically mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). In the "Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood 2016" (GL2016) published in 2016 by the Japanese Society of Child Neurology (JSCN) [1,2], recommendations and comments were made on the general aspects of acute encephalopathy, and on individual syndromes with diagnostic criteria and therapies. Owing to the scarcity of studies with high levels of evidence, neither quantitative nor qualitative systematic reviews were conducted; instead, the recommendation grades were determined through discussions by the working group (WG). Following the publication of GL2016 and several papers on acute encephalopathy, a revised version of the GL was released in 2023 [3]. GL2023 identified the treatment of AESD, which is the most common encephalopathy in Japanese children (200–300/year), as a Clinical Question (CQ) based on a qualitative systematic review. Here, we present the main revisions from GL2016.

2. Methods

In 2020, the WG at the JSCN began work on publishing a revised version of the GL2016. Using the methodologies recommended by the Medical Information Network Distribution System (Minds) 2020 [4], the WG formulated guidelines, discussed the key clinical issues, and identified potential clinical questions (CQs). A systematic review was performed by two members of the WG in accordance with Minds 2020. English literature was retrieved from the PubMed database and Japanese literature from Ichushi-web, provided by the Japan Medical Abstracts Society, from May 2014 to January 2021. The general and specific descriptions of acute encephalopathy (excluding CQ) were revised and updated in accordance with Minds 2007, using the same method as in GL2016 [1].

In March 2022, the WG solicited public comments on the website from the other JSCN members and also invited the following organizations to review the drafts: the Japanese Pediatric Society, the Japanese Society for Pediatric Infectious Diseases, and the Japanese Society of Emergency Pediatrics. Based on the opinions and comments from the members and organizations, the GL2023 was published in January 2023 [3], and the guidelines were uploaded on the Minds homepage in July 2023.

3. Results

3.1. CQ

The WG determined the key clinical issues to be "treatment strategies for AESD, the most frequent and neurologically unfavorable type of acute encephalopathy." A systematic review was conducted using targeted temperature management (TTM) and high-dose steroid therapy as interventions. Although two retrospective cohort studies on TTM were identified for cases expected to progress to AESD [5,6], none were found on high-dose steroid therapy.

As a result of the qualitative systematic review, the following CQ related to TTM and AESD was presented.

Chapter 1 - CQ1.

In TTM-capable facilities, is TTM (target temperature 36 °C) useful for children suspected of having acute encephalopathy, considering the progression to AESD, sequelae, and serious adverse events?

Recommendation:

Early TTM (within 24 h) with a target temperature of 36 °C is weakly recommended for cases with fever that meet criterion 1) or 2), as well as criterion 3), of the following three criteria, as it reduces the risk of progression to AESD and its sequelae:

1) Intractable convulsive status epilepticus.

2) Impaired consciousness lasting more than 6 h.

3) No suspicion of multiple organ failure (e.g., aspartate aminotransferase [AST] < 90 U/L within 6 h of onset of neurological symptoms).

Recommendation level, weak; certainty of evidence (strength): very weak.

Comments:

Making an early diagnosis of AESD, a representative encephalopathy associated with excitotoxicity is challenging, because it cannot be confirmed until after late seizures (days 4–6) and the bright tree appearance (BTA) on MRI after day 3. However, TTM has been shown to potentially prevent progression to AESD when implemented early in the course of the disease. A systematic review of CQ1 yielded two retrospective cohort studies [5,6], both of which included cases with fever accompanied by (1) intractable convulsive status epilepticus, or (2) impaired consciousness lasting more than 6 h, and (3) no suspicion of multiple organ failure (e.g., AST < 90 U/L within 6 h of neurological symptom onset. The absence of multiple organ failure, as described in criterion 3, suggests the possibility of progression to AESD (excitotoxic encephalopathy) rather than to cytokine storm encephalopathy, such as ANE and hemorrhagic shock and encephalopathy syndrome (HSES) [7]. In both studies, high-risk cases expected to develop AESD were subjected to TTM within 24 h of symptom onset before a definitive diagnosis. However, the duration of TTM varied, namely at least 48 h (5) and 12–72 h (6). The progression to AESD was observed in 0/26 (0%) cases in the TTM group, and in 11/44 (25%) cases in the non-TTM group. No sequelae or serious adverse events were observed in any of the TTM groups. Because all available evidence derives from retrospective observational studies, the possibility of residual confounding cannot be excluded. Furthermore, the absence of randomized controlled trials limits the certainty of the recommendation. Therefore, although TTM under the above conditions was recommended, the recommendation strength was considered weak. Furthermore, the optimal duration for TTM remains unclear, and no recommendation is provided regarding this.

3.2. The general and specific descriptions of acute encephalopathy

Chapters 2–8 show the general and specific descriptions of acute encephalopathy.

GL2023 included no revisions to the grade of recommendation described in GL2016 [1].

This section lists the main points revised in GL2023. References in parentheses indicate the corresponding sections in GL2016 [1].

1) Definition of acute encephalopathy (2.1.1. in GL2016 [1]).
   The criterion for impaired consciousness has been changed to a Japan Coma Scale score of 20 or higher, or a Glasgow Coma Scale (GCS) score of less than 11. In GL2016, the criterion was "GCS 11 or lower".
2) Information on the epidemiology (including prognosis) of acute encephalopathy (2.1.2. in GL2016 [1]).
   The information has been updated to reflect the Japanese nationwide survey conducted from 2014 to 2017 [8]. In summary, the number of acute encephalopathy cases was 400–700 per year, and the median age of onset was 2 years. The causative pathogen was human herpes virus-6/7 in 16% of cases and influenza in 16% of cases. The involved syndromes were AESD (34%), MERS (18%), ANE (3%), HSES (2%), and acute encephalitis with refractory, repetitive partial seizures (AERRPS)/febrile infection-related epilepsy syndrome (FIRES) (1%). The overall prognosis for acute encephalopathy was a sequela rate of 36% and a mortality rate of 5%, with the syndrome-specific rates being AESD 61%/2% (sequelae/death), MERS 4%/0%, ANE 41%/25%, and HSES 47%/53%.
3) Imaging findings for AESD (2.2.3., 2.6.1. in GL2016 [1]).
   New findings have been added in GL 2023, suggesting that high b-value diffusion-weighted imaging (DWI) (b = 3000 s/mm2) may offer superior visualization of BTA than usual (b = 1000 s/mm2) [9], and that arterial spin labeling (ASL) may be useful for the early

diagnosis of AESD [10]. High b-value DWI has also been suggested to offer superior visualization in MERS.

Several reports of ASL have revealed that blood flow decreases within 8.5–22 h after an early seizure, followed by an increase afterward [10]. The distribution of these blood flow abnormalities was consistent with the later-appearing BTA, a characteristic MRI finding in AESD.

4) EEG findings for acute encephalopathy (2.2.4. in GL2016 [1]).

In addition to slow wave activity, the presence of seizures has been added as an abnormal finding on EEG in acute encephalopathy.

5) Treatment through mitochondrial rescue (2.4.3., 2.6.1. in GL2016 [1]).

There have been some reports that administering a mitochondrial vitamin cocktail (Vitamin B1, C, B7, E, CoQ_{10}, and L-carnitine) within 24 h improves the prognosis in AESD [11]. Because of its lower side effects, this therapy has been proposed as a potential treatment for acute encephalopathy in general.

6) Description of the early diagnostic score for AESD (2.6.1. in GL2016 [1]).

Since early diagnosis of AESD before late seizures or BTA on DWI is difficult, early AESD diagnostic scores, such as the Tada score [12] or Yokochi score [13], are described using clinical and laboratory data.

7) Therapy for AERRPS/ FIRES (2.6.2. in GL2016 [1]).

Anti-cytokine therapies, such as the interleukin1 (IL1)-receptor antagonist (anakinra) [14] and the IL6-receptor antibody (tocilizumab) [15], are listed as potentially effective treatments for AERRPS, in addition to ketogenic diet therapy.

8) New clinical and genetic findings related to MERS have been added (2.7.3. in GL2016 [1]).

It has been reported that urinary tract infections, particularly acute focal bacterial nephritis (AFBN), are frequent in MERS associated with bacterial infection [16]. Whole-exome sequencing analysis of familial cases of MERS type 2, which affects the corpus callosum and white matter, identified a common mutation in the *MYRF* gene [17]. MYRF, specifically expressed in the central nervous system oligodendrocytes, is involved in oligodendrocyte differentiation and maintenance, as well as the regulation of myelin-related gene expression. *MYRF* mutations are thought to cause transient myelin damage during infection or fever, leading to mild dysfunction, but have no effect under normal conditions.

4. Discussion

GL2023, published seven years after GL2016, consists of CQ1 (TTM for AESD), based on Minds 2020, and general and specific sections on acute encephalopathy (an update to GL2016), based on Minds 2007. A post-publication survey of GL2023 was conducted in 2025 by the Pediatric Acute Encephalopathy Research Group funded by the Ministry of Health, Labor and Welfare, and the data is currently being analyzed (under preparation for submission).

Acute encephalopathy in children is a serious illness, and conducting double-blind trials is difficult, making it challenging to perform quantitative systematic reviews. In fact, based on the results of systematic reviews, the usefulness of high-dose steroid therapy for AESD was not established as a CQ. The systematic review for CQ and the literature review for updating general and specific descriptions were conducted from 2014 to 2021; therefore, they do not include very recent publications.

The JSCN WG began revising the guidelines in 2025, aiming for publication in 2027–28. CQs to be considered include the effectiveness of (a) TTM for confirmed cases of AESD, (b) mitochondrial vitamin cocktail for AESD, and (c) high-dose steroid therapy for cytokine storm encephalopathy, including ANE.

Author contribution

JT, MM: Conceptualization and study design. JT, MM, TI, GI, AO, TG, HS, HN, KM, HY, YM: GL2023 revision work. JT, TO, HT: Manuscript drafting. JT, MM: Critical revision, review, editing, and supervision. All authors reviewed and approved the final version of the manuscript.

Ethics approval

Not applicable.

Funding

This study was funded in part by a Grant-in-Aid for Research on Measures for Intractable Diseases No. 24FC1010 from the Japanese Ministry of Health, Labor, Welfare, JSPS KAKENHI (Grant Number JP23K07192), and a grant from AMED (Grant Number 25ek0109800).

Declaration of competing interest

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

Acknowledgements

The authors are grateful to the Collaborative Research Supporting Committee of the Japanese Society of Child Neurology (JSCN) for promoting this study. We wish to thank all pediatricians for providing us with their patients' data, and the patients and their parents for participating in this study. We would like to thank Editage (www.editage.jp) for English language editing.

References

[1] Mizuguchi M, Ichiyama T, Imataka G, Okumura A, Goto T, Sakuma H, et al. Guidelines for the diagnosis and treatment of acute encephalopathy in childhood. Brain Dev 2021;43:2–31. https://doi.org/10.1016/j.braindev.2020.08.001.

[2] Committee for the Compilation of Guidelines for the Diagnosis and Treatment of Acute Encephalopathy in Childhood. In: Japanese society of child neurology, editor. Guidelines on the diagnosis and treatment of acute encephalopathy in childhood 2016. Tokyo: Shindan To Chiryo-sha; 2016. [Japanese].

[3] Working Group for the Revision of Guidelines for the Diagnosis and Treatment of Acute encephalopathy in Childhood. In: Japanese society of child neurology, editor. Guidelines for the diagnosis and treatment of acute encephalopathy in childhood 2023. Tokyo: Shindan To Chiryo-sha; 2023. Japanese, https://www.childneuro.jp/about/6443/.

[4] Japan Council for Quality Health Care. Minds manual for guideline development 2020 ver 3.0. Minds manual developing committee. https://minds.jcqhc.or.jp/methods/cpg-development/minds-manual/; 2021. accessed 7 May 2026.

[5] Nishiyama M, Tanaka T, Fujita K, Maruyama A, Nagase H. Targeted temperature management of acute encephalopathy without AST elevation. Brain Dev 2015;37:328–33. https://doi.org/10.1016/j.braindev.2014.06.005.

[6] Murata S, Kashiwagi M, Tanabe T, Oba C, Shigehara S, Yamazaki S, et al. Targeted temperature management for acute encephalopathy in a Japanese secondary emergency medical care hospital. Brain Dev 2016;38:317–23. https://doi.org/10.1016/j.braindev.2015.09.003.

[7] Nagase H, Nakagawa T, Aoki K, Fujita K, Saji Y, Maruyama A, et al. Therapeutic indicators of acute encephalopathy in patients with complex febrile seizures. Pediatr Int 2013;55:310–4. https://doi.org/10.1111/ped.12046.

[8] Kasai M, Shibata A, Hoshino A, Maegaki Y, Yamanouchi H, Takanashi JI, et al. Epidemiological changes of acute encephalopathy in Japan based on national surveillance for 2014–2017. Brain Dev 2020;42:508–14. https://doi.org/10.1016/j.braindev.2020.04.006.

[9] Tsubouchi Y, Itamura S, Saito Y, Yamashita E, Shinohara Y, Okazaki T, et al. Use of high b value diffusion-weighted magnetic resonance imaging in acute encephalopathy/encephalitis during childhood. Brain Dev 2018;40:116–25. https://doi.org/10.1016/j.braindev.2017.07.012.

[10] Uetani H, Kitajima M, Sugahara T, Muto Y, Hirai K, Kuroki Y, et al. Perfusion abnormality on three-dimensional arterial spin labeling in patients with acute encephalopathy with biphasic seizures and late reduced diffusion. J Neurol Sci 2020;408:116558. https://doi.org/10.1016/j.jns.2019.116558.

[11] Omata T, Fujii K, Takanashi JI, Murayama K, Takayanagi M, Muta K, et al. Drugs indicated for mitochondrial dysfunction as treatments for acute encephalopathy

with onset of febrile convulsive status epileptics. J Neurol Sci 2016;360:57–60. https://doi.org/10.1016/j.jns.2015.11.043.
[12] Tada H, Takanashi J, Okuno H, Kubota M, Yamagata T, Kawano G, et al. Predictive score for early diagnosis of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD). J Neurol Sci 2015;358:62–5. https://doi.org/10.1016/j.jns.2015.08.016.
[13] Yokochi T, Takeuchi T, Mukai J, Akita Y, Nagai K, Obu K, et al. Prediction of acute encephalopathy with biphasic seizures and late reduced diffusion in patients with febrile status epilepticus. Brain Dev 2016;38:217–24. https://doi.org/10.1016/j.braindev.2015.07.007.
[14] Kenney-Jung DL, Vezzani A, Kahoud RJ, LaFrance-Corey RG, Ho M-L, Muskardin TW, et al. Febrile infection-related epilepsy syndrome treated with anakinra. Ann Neurol 2016;80:939–45. https://doi.org/10.1002/ana.24806.
[15] Jun JS, Lee ST, Kim R, Chu K, Lee SK. Tocilizumab treatment for new onset refractory status epilepticus. Ann Neurol 2018;84:940–5. https://doi.org/10.1002/ana.25374.
[16] Maruyama Y, Sato M, Inaba Y, Fukuyama T. Comparison of mild encephalopathy with reversible splenial lesion with and without acute focal bacterial nephritis. Brain Dev 2020;42:56–63. https://doi.org/10.1016/j.braindev.2019.08.008.
[17] Kurahashi H, Azuma Y, Masuda A, Okuno T, Nakahara E, Imamura T, et al. *MYRF* is associated with encephalopathy with reversible myelin vacuolization. Ann Neurol 2018;83:98–106. https://doi.org/10.1002/ana.25125.