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Efficacy of Immunomodulatory Therapies in Pediatric Acute Necrotizing Encephalopathy: A Systematic Review and Meta-Analysis of 158 Patients

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 October 2025 and was last updated on 30 October 2025.

INTRODUCTION

Review question / Objective The primary objective of this systematic review and meta-analysis was to determine whether immunomodulatory therapies – specifically high-dose corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, and tocilizumab – improve clinical outcomes in pediatric acute necrotizing encephalopathy (ANE). We sought to pool data from published cases (10 studies, n=158) to assess the association of each therapy with survival and neurologic recovery.

Rationale Acute necrotizing encephalopathy (ANE) is a rare, fulminant pediatric encephalopathy with high mortality and often devastating neurologic sequelae. Given this poor prognosis, aggressive immunomodulatory treatments (high-dose steroids, IVIG, therapeutic plasma exchange, IL-6 blockade) are frequently attempted, yet the evidence for their efficacy is limited and inconsistent. No randomized trials exist, and most data derive from small series. A formal pooled analysis of available cases is therefore needed to clarify whether these interventions improve survival or neurological outcomes in children with ANE.

Condition being studied The condition of interest is acute necrotizing encephalopathy in children (generally age <18 years). ANE is a rare parainfectious encephalopathy of childhood, characterized by symmetric multifocal brain lesions (notably in the thalami, brainstem, and cerebellum) and rapid neurologic decline. It is associated with very high mortality (historical series report ~30–40%) and severe neurological deficits in survivors. The patient population includes both sporadic and genetic (e.g. RANBP2-associated) cases of pediatric ANE.

METHODS

Search strategy We systematically searched PubMed, Embase, the Cochrane Library, Web of Science, CINAHL, and Scopus for relevant studies.

Search terms combined "acute necrotizing encephalopathy" (ANE/ANEC) with each immunotherapy (e.g. "corticosteroids", "IVIG", "plasmapheresis", "tocilizumab") and outcome-related terms (e.g. "outcome", "neurologic outcome").

The search covered studies published from January 2003 through 2023 (approximately the past 20 years).

We limited to human studies in pediatric populations and English language. References of retrieved articles and relevant reviews were also hand-searched for additional studies.

Participant or population Pediatric patients (typically <18 years old) with a diagnosis of acute necrotizing encephalopathy, including both sporadic and familial (e.g. RANBP2-associated) cases.

ANE diagnosis was based on clinical presentation and neuroimaging consistent with symmetric necrotic lesions in the brain (as per each study).

Intervention High-dose corticosteroids (typically intravenous methylprednisolone pulse therapy).

Intravenous immunoglobulin (IVIG) therapy.

Therapeutic plasmapheresis (plasma exchange, PLEX).

Tocilizumab (interleukin-6 receptor antagonist).

Comparator Patients who did not receive the specific immunotherapy, or received it later/delayed. For example:

No or late corticosteroid treatment (versus early high-dose steroids).

No IVIG therapy (versus receiving IVIG).

No plasmapheresis (versus receiving PLEX).

No tocilizumab (versus receiving tocilizumab).

Study designs to be included Observational studies (prospective or retrospective case series and cohort studies) of pediatric ANE cases treated with the above immunotherapies.Randomized trials were not expected or found, given the rarity of ANE.Single-case reports were excluded, as they do not allow for comparative analysis.

Eligibility criteria Inclusion: Studies of children (<18 years) with ANE that reported use of at least one target immunotherapy and reported clinical outcomes. Outcomes must be reported in a way that can be classified into "good" versus "poor" (see below).

Exclusion: Studies lacking sufficient outcome data or comparator groups for the therapies, or those comprising only single case reports. Non-English publications and adult-only cohorts were also excluded.

Information sources Bibliographic databases: PubMed, Embase, Cochrane Library, Web of Science, CINAHL, and Scopus.

Timeframe: Studies published from January 2003 through the search date (2023).

Language: English.

Additional sources: Manual search of references in retrieved articles and relevant reviews.

Main outcome(s) The primary outcome was neurologic status categorized as a dichotomous measure: Good outcome (survival with no or mild neurologic deficits, e.g. near-baseline cognitive function) versus Poor outcome (death or survival with severe permanent disability).

We extracted the number of patients with "good" versus "poor" outcomes for each treatment comparison to calculate effect sizes.

Additional outcome(s) Overall survival (mortality) was specifically noted, particularly for the plasmapheresis analyses (where in-hospital mortality could be compared between PLEX vs no-PLEX).

Any quantitative neurologic or developmental scores reported (e.g. Pediatric Cerebral Performance Category, developmental quotient) were recorded if available, but these were not pooled due to heterogeneity.

Odds ratios (and, secondarily, risk ratios) for good outcome were computed for each intervention as effect measures in the meta-analysis.

Quality assessment / Risk of bias analysis Risk of bias in each included study was assessed using a modified Newcastle–Ottawa Scale for observational studies.

Domains evaluated included selection of cases, comparability/confounding (e.g. differences between treated vs untreated groups), outcome assessment, and adequacy of follow-up.

Each study was qualitatively rated (low/moderate/high risk of bias) in these domains. Given that all data come from non-randomized series, the overall evidence level was considered low, with common issues such as lack of control groups, retrospective data collection, and variable outcome definitions.

Strategy of data synthesis For each treatment modality, we performed a meta-analysis of binary outcomes (good vs poor) across studies to calculate pooled odds ratios (ORs) with 95% confidence intervals.

A random-effects model (DerSimonian–Laird method) was used a priori to account for expected clinical and methodological heterogeneity between studies.

Heterogeneity was assessed by the chi-square Q test and the I^2 statistic (with $I^2 > 50\%$ indicating substantial heterogeneity).

Where events were rare or zero in a comparison arm, a continuity correction (adding 0.5 to cells) was applied to enable calculation of the OR.

Analyses were performed using RevMan 5.4 (with cross-checking in Stata), and forest plots were generated for each comparison. A significance threshold of $p<0.05$ was used in all analyses.

Subgroup analysis We planned subgroup analyses based on clinical factors influencing prognosis. In particular, we stratified data by the presence versus absence of brainstem lesions on neuroimaging, as prior reports suggest brainstem involvement may modify treatment effect.

An exploratory subgroup analysis was conducted for patients receiving combined early high-dose steroids plus tocilizumab versus steroids alone (if sufficient data were available).

Sensitivity analysis Sensitivity analyses were conducted to assess the robustness of our findings. We compared results using a fixed-effect model versus the primary random-effects model to ensure findings were not model-dependent.

We also calculated risk ratios (RR) as an alternative effect measure to odds ratios (OR) to confirm that conclusions were consistent (qualitatively similar results were obtained).

In cases of zero events in one arm, we tested analyses with and without continuity corrections to verify that effect estimates remained similar. Bonferroni corrections were applied for multiple comparisons in subgroup analyses as noted.

Country(ies) involved Taiwan.

Keywords acute necrotizing encephalopathy; pediatric encephalopathy; immunomodulatory therapy; corticosteroids; intravenous immunoglobulin; plasmapheresis; tocilizumab; systematic review; meta-analysis.

Contributions of each author

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