INPLASY

Early vs Interval Appendectomy in Children With Complicated Appendicitis: A Meta-analysis

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective We aim to determine the efficacy of immunomodulatory therapies in children with acute necrotizing encephalopathy (ANE). Specifically, the review will address whether interventions such as high-dose corticosteroids, intravenous immunoglobulin (IVIG), plasma exchange (PLEX), and the interleukin-6 inhibitor tocilizumab improve clinical outcomes (survival and neurological recovery) in pediatric ANE. The objective is to synthesize available evidence from published cases and case series to identify which treatments (alone or in combination) are associated with better outcomes in this rare but often devastating condition.

Rationale Acute necrotizing encephalopathy is a rare, rapidly progressive encephalopathy in children that often follows a viral infection (commonly influenza). It carries a very high risk of death or severe neurological disability, yet there are no universally accepted treatment guidelines. Immunomodulatory therapies—especially high-dose intravenous corticosteroids started early—have been widely used based on pathophysiological rationale (ANE is thought to involve a "cytokine storm" causing brain inflammation) and small case series suggesting improved outcomes. Case reports and small series have also explored adjunctive treatments like IVIG, therapeutic plasma exchange, and tocilizumab (an IL-6 blocker), with some children achieving good recoveries. However, due to the rarity of ANE, no randomized trials exist and evidence is limited to observational studies. A systematic review and meta-analysis of published pediatric ANE cases is therefore warranted to pool data across studies. This will help clarify the potential be.

Condition being studied Pediatric acute necrotizing encephalopathy (ANE) is the condition of interest. ANE is a rare, life-threatening neuroinflammatory condition typically affecting

young children after an acute febrile illness. It is characterized by the sudden onset of encephalopathy (altered mental status, seizures, coma) accompanied by symmetric bilateral brain lesions, especially involving the thalami (often seen on MRI). The pathogenesis is not fully understood but is believed to involve an excessive immune response or cytokine storm triggered by infections (e.g. influenza, enterovirus, SARS-CoV-2), leading to blood–brain barrier disruption and brain edema. ANE has a high mortality rate (reported ~20–40%) and among survivors, a majority suffer significant neurological deficits. Due to its acute severity and lack of a definitive cure, ANE requires intensive care support and has motivated the use of various immunomodulatory therapies in an effort to improve outcomes.

METHODS

Search strategy We will perform a comprehensive literature search to identify studies addressing immunomodulatory treatment outcomes in pediatric ANE. The search will span multiple electronic databases, including PubMed, Ovid MEDLINE, Cochrane Library, CINAHL, Embase, and Scopus, from 2003 up to the latest available data (through April 2023). We will use a broad search string combining terms for acute necrotizing encephalopathy (e.g. "acute necrotizing encephalopathy" OR "ANEC") with terms for interventions (steroids, IVIG, plasma exchange, tocilizumab, etc.) and outcomes (e.g. "outcome", "neurological sequelae"). The search will be limited to full-text studies in English. We will exclude meeting abstracts and unpublished data. All titles and abstracts retrieved will be screened for relevance, and the references of pertinent articles will be hand-searched to ensure no relevant studies are missed.

Participant or population The population of interest is children with acute necrotizing encephalopathy. This includes pediatric patients (generally defined as ages 0–18 years) who meet clinical and radiographic criteria for ANE. Typical criteria are an acute encephalopathy with seizures or rapid neurological decline following a febrile illness, accompanied by characteristic neuroimaging findings (symmetric bilateral thalamic lesions, often with brainstem or white matter involvement). We will include both sexes and all ethnicities. Patients may be previously healthy or with predisposing factors (e.g. the RANBP2 gene mutation associated with familial ANE), as long as they are diagnosed with acute necrotizing encephalopathy. Essentially, any child reported in the literature with ANE and treated with immunomodulatory therapy will be considered for inclusion.

Intervention The interventions assessed in this review are immunomodulatory therapies used in the management of pediatric ANE. In practice, these include:

High-dose corticosteroids: typically intravenous methylprednisolone given in high doses (on the order of 20–30 mg/kg/day for 3–5 days or equivalent), usually initiated as early as possible once ANE is recognized. This is aimed at dampening the hyperinflammatory response in the brain.

Intravenous immunoglobulin (IVIG): administration of pooled immunoglobulins, which may modulate immune responses and has been used in some ANE cases to improve outcomes or halt disease progression.

Therapeutic plasma exchange (PLEX): also known as plasmapheresis, a procedure to remove and replace the patient's plasma, theoretically eliminating cytokines or autoimmune factors contributing to ANE.

Tocilizumab: an interleukin-6 (IL-6) inhibitor (monoclonal antibody) that targets a key cytokine implicated in ANE's pathogenesis. Tocilizumab has been used in a few cases as an adjunct to steroids to control the inflammatory cascade.

These interventions may be used singly or in combination as part of ANE treatment. Supportive care (ICU management, antivirals, etc.) is provided to all patients, but our review specifically focuses on the above immunomodulatory treatments and their impact on patient outcomes.

Comparator The comparator for each intervention will essentially be standard care without that specific immunomodulatory therapy, or an alternative timing/dose of therapy, depending on the analysis. Because no randomized trials exist, we will use between-group comparisons drawn from observational data. For example, in studies that include patients who received early high-dose steroids versus those who received late or no steroids, we will compare outcomes between those groups. Similarly, for IVIG, outcomes in patients given IVIG will be compared to those in patients who did not receive IVIG (i.e. managed with other therapies or steroids alone). For tocilizumab, outcomes of patients who received tocilizumab (in addition to other therapies like steroids) will be compared with those who did not

receive tocilizumab. In the analysis of plasma exchange, patients who underwent PLEX will be compared to those who did not. In summary, the review's analyses use patients not receiving a given immunomodulatory treatment (or receiving only the other treatments) as the comparator group to those who did receive the treatment, within the data available from the included studies.

Study designs to be included Given the rarity of ANE, we do not expect any randomized controlled trials. We will include observational studies that report on treatment and outcomes in pediatric ANE. Eligible study designs will primarily be retrospective or prospective case series and cohort studies. These may range from multi-patient case reports and case series to multicenter cohort analyses. We will include studies that had at least two or more ANE cases (since single-patient case reports are excluded) and that provided details on immunomodulatory treatments given and patient outcomes. If any systematic reviews or meta-.

Eligibility criteria Inclusion criteria: Studies will be included if they meet the following criteria – (1) The study population consists of pediatric patients (children or adolescents) diagnosed with acute necrotizing encephalopathy. (2) The study reports that these patients received one or more immunomodulatory interventions of interest (high-dose steroids, IVIG, plasma exchange, and/or tocilizumab) as part of their acute therapy. (3) Clinical outcomes are reported for the patients, such that it's possible to determine their neurological outcome or survival. Importantly, the study must provide patient-level data or clear outcomes for each treatment group (e.g. number of patients with good vs poor outcome in those who received a given therapy). (4) The study includes at least two patients (i.e. case series or larger; single case reports will not be included). (5) Publication is in English (full-text available) and published in or after the early 2000s (to reflect contemporary management, we focused on 2003–2023 literature).
Exclusion criteria: We will exclude articles that do not address treatment outcomes in ANE (for example, papers solely about neuroimaging or pathophysiology without discussing patient treatment results). Single-patient case reports are excluded, as noted, to focus on studies with multiple cases. We will also exclude studies that lack sufficient detail on treatments or outcomes – for instance, if a paper only mentions that steroids were used in all cases but does not specify timing or does not differentiate outcomes by treatment, it would not be usable for our analysis. Similarly, if a study does not report individual patient data (e.g. only provides aggregate outcomes without linking to specific treatments), it will be excluded because we require granular data to pool. Any non-English publications or abstracts without full text will be excluded as well..

Information sources We will gather data from a broad range of electronic databases to ensure comprehensive coverage of the literature. The primary information sources include: PubMed, Ovid MEDLINE, Cochrane Library, CINAHL, Embase, and Scopus. These databases were searched for relevant studies on ANE and immunomodulatory treatments, covering publications from 2003 up to April 2023. In addition to database searches, we reviewed the reference lists of all included papers (and key review articles) to identify any additional eligible studies that may have been missed by the electronic search. We restricted our sources to peer-reviewed, full-text articles; no unpublished manuscripts or conference-only abstracts were considered. All data extracted for the review ultimately come from these published sources.

Main outcome(s) The main outcomes of interest are the neurological and survival outcomes of children with ANE following treatment. In our analysis we categorize each patient's outcome into one of two broad categories: "good outcome" versus "poor outcome." A good outcome is operationally defined as survival with mild or no lasting neurological deficits (for example, the child recovers to a state of only minimal neurologic impairment or returns to essentially normal function for age). A poor outcome is defined as severe neurological impairment (significant neurological deficits such as motor, cognitive, or developmental disability) or death. Each included study may have used its own definitions or scales for outcome, but we will align them to this good/poor outcome framework for consistency.

Additionally, for the analysis of mortality, we specifically look at survival rates in relation to certain interventions. In particular, for plasma exchange (PLEX), since some studies only reported mortality and not detailed neurologic se.

Quality assessment / Risk of bias analysis We recognize that all included studies are observational (mostly case series) and thus carry a substantial risk of bias. To assess the quality of the evidence, we will perform a risk of bias evaluation tailored to case series data. Two reviewers will independently appraise each study using predefined criteria such as: clarity in the diagnosis of ANE, completeness of outcome reporting for all

cases, potential selection bias (e.g. consecutive cases or not), and any conflicts of interest. We will adapt tools like the Joanna Briggs Institute critical appraisal checklist for case reports/case series or similar guidelines for evaluating observational case series. This will involve checking whether each study clearly described its patient inclusion, interventions, follow-up, and outcomes. Since no standard risk-of-bias instrument perfectly fits these study designs, the assessment will be qualitative in nature. Any discrepancies between reviewers will be resolved by discussion.

Strategy of data synthesis We will synthesize the data by pooling individual patient outcome information from the included studies and performing comparative analyses between treatment groups. First, we will tabulate all relevant data (treatments given, presence of brainstem involvement, and outcome for each patient or group) to enable cross-study comparison. Then, we plan to conduct a quantitative descriptive analysis rather than a traditional meta-analysis with weighted effect sizes, due to the nature of the data. Specifically, for each therapeutic question, we will calculate the proportion of patients with a good outcome in each treatment group and compare these proportions.

For example, to evaluate early corticosteroid use, we will compare the percentage of children with good outcomes among those who received high-dose steroids within 24 hours of neurological decline versus those who received steroids later or not at all. Similar proportion comparisons will be done for IVIG vs no IVIG, for steroid+IVIG combination vs steroids alon.

Subgroup analysis We have planned a key subgroup analysis based on disease severity as indicated by brainstem involvement. Brainstem lesions on imaging are known to portend a worse prognosis in ANE. Therefore, for certain analyses (notably the steroid and IVIG effectiveness evaluations), we will stratify patients into two subgroups: those with brainstem involvement (B/S) and those without brainstem involvement. We will then examine whether the benefit of treatments differs between these subgroups. For instance, we will compare outcomes of early steroids vs. late/no steroids separately for patients with brainstem lesions and for those without, to see if early intervention is especially critical in the more severe (brainstem) cases. Similarly, IVIG outcomes will be compared within each subgroup. If a study did not report whether patients had brainstem involvement, those patients will be included in the overall analysis but excluded from the stratified subgroup comparison to avoid misclassification. Aside from brainstem involveme.

Sensitivity analysis To ensure the robustness of our findings, we will perform several sensitivity analyses. One planned approach is a leave-one-out analysis: we will remove each included study one at a time from the pooled data and re-run the key outcome comparisons to check if any single study unduly influences the results. This can highlight if one large series or outlier study is skewing the findings. Another sensitivity analysis will involve assessing the impact of study quality on the results – for example, we may repeat analyses including only the higher-quality studies (as determined by our risk of bias assessment) to see if the conclusions remain consistent. We will also examine whether altering any outcome definitions affects the results: since outcome classification (good vs poor) can be somewhat subjective, we might test a stricter or more lenient categorization (if data allow) to ensure our pooled results are not sensitive to how outcomes were defined. Additionally, given that we set a 24-hour threshold for “early” s.

Country(ies) involved Taiwan.

Keywords Acute necrotizing encephalopathy; Pediatric neurology; Immunomodulatory therapy; Corticosteroids; Intravenous immunoglobulin; Plasma exchange; Tocilizumab; Meta-analysis.

Contributions of each author

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