



High-dose methylprednisolone and tocilizumab improve survival of patients with high-risk pediatric acute necrotizing encephalopathy

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Background: Acute necrotizing encephalopathy (ANE) is a rare but devastating neurological disorder in children that is typically triggered by viral infections such as influenza, sudden acute respiratory syndrome coronavirus 2, and human herpesvirus-6. ANE is characterized by cytokine storm and associated with high mortality; however, optimal immunomodulatory strategies remain undefined.

Purpose: To evaluate the effectiveness of multiple immunomodulatory strategies, including high-dose methylprednisolone (MP), plasma exchange (PLEX), and tocilizumab, at reducing short-term mortality among pediatric patients with ANE stratified by disease severity using the ANE severity score (ANE-SS).

Methods: We retrospectively reviewed 65 pediatric patients (median age, 4.8 years; interquartile range, 2.8–7.7 years) diagnosed with ANE at Beijing Children's Hospital from 2016 to 2024. Patients were stratified by ANE-SS at admission into low- to medium-risk (ANE-SS<5) and high-risk (ANE-SS≥5) groups. Immunomodulatory treatments included different doses of MP, intravenous immunoglobulin, PLEX, and tocilizumab. The primary outcome was the 28-day postdischarge mortality. Multivariate logistic regression was used to identify the treatment strategies that were independently associated with improved survival.

Results: The overall 28-day postdischarge mortality rate was 45.9%, significantly higher in patients with ANE-SS ≥5 (65.7%) than in those with ANE-SS<5 (16.7%; $P<0.001$). A notable decline in mortality has been observed since 2022, coinciding with the increased use of high-dose MP (20 and 30 mg/kg/day) and tocilizumab. The annual mortality rate will drop to 38.9% in 2022, 36.8% in 2023, and 16.7% in

2024. In low- to medium-risk patients (ANE-SS<5), both 20-mg/kg/day and 30-mg/kg/day MP were associated with improved outcomes. In high-risk patients (ANE-SS≥5), the combination of 30-mg/kg/day MP and tocilizumab provided the greatest survival benefit. Multivariable logistic regression analysis identified that this combined therapy was independently associated with reduced mortality (odds ratio, 0.04; 95% confidence interval, 0.01–0.18; $P<0.001$). No significant survival benefit was observed following PLEX treatment.

Conclusion: In low- to moderate-risk patients, the 20- and 30-mg/kg/day MP regimens were effective. In high-risk patients with ANE, high-dose MP (30 mg/kg/day), particularly when combined with tocilizumab, may improve survival and possibly long-term neurological recovery. These findings support the use of a severity-based immunotherapy strategy for pediatric patients with ANE.

Key words: Acute necrotizing encephalopathy, Immunotherapy, Tocilizumab, Methylprednisolone, Mortality, Children

Key message

Question: Which immunomodulatory strategies can reduce mortality in children with acute necrotizing encephalopathy (ANE)?

Finding: High-dose methylprednisolone (30 mg/kg/day) significantly improved the survival of high-risk patients, particularly when combined with tocilizumab.

Meaning: These findings support the use of a severity-based immunotherapy approach to optimize the outcomes of pediatric ANE.

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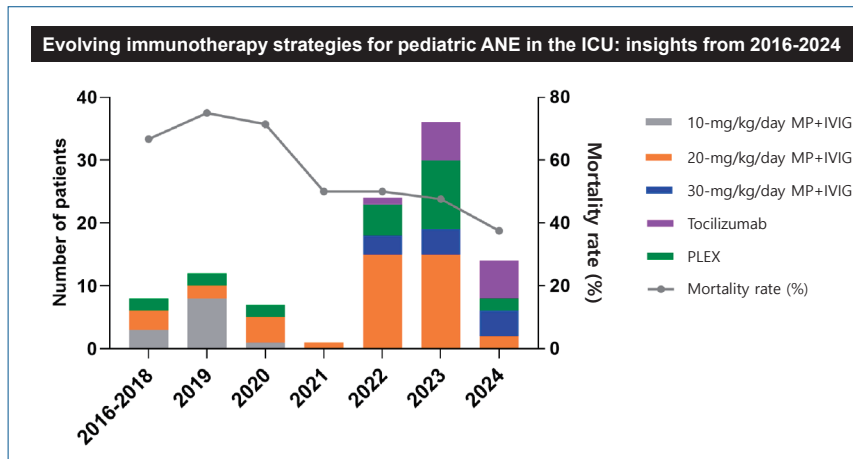
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Graphic abstract. Changes in Immunotherapy treatment and mortality for ANE in pediatric intensive care unit: 2016–2024. The percentage (%) represents the number of patients receiving a specific immunotherapy treatment, divided by the total number of patients receiving immunotherapy in that year. ANE, acute necrotizing encephalopathy; ICU, intensive care unit; MP, methylprednisolone; IVIG, intravenous immunoglobulin; PLEX, plasma exchange.

Introduction

Acute necrotizing encephalopathy (ANE) is a rare but devastating pediatric neurological disorder, most commonly triggered by viral infections such as influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and human herpesvirus-6.¹ The estimated annual incidence ranges from 0.17 to 1 per million children, with ANE accounting for approximately 6.1% to 50% of all influenza-associated encephalopathy cases.^{2–4} The disease rapidly progresses with bilateral thalamic and brainstem lesions, often resulting in a poor prognosis before treatment can be effectively initiated.^{5,6}

The pathophysiology of ANE is thought to involve an infection-induced cytokine storm, with excessive production of proinflammatory mediators such as interleukin-6 (IL-6). This hyperinflammatory response leads to disruption of the blood-brain barrier, cerebral edema, and neuronal injury.^{7,8} Immunomodulatory therapies, including high-dose methylprednisolone (MP), intravenous immunoglobulin (IVIG), and plasma exchange (PLEX), have been used empirically in clinical practice.⁹ More recently, IL-6 receptor blockade with tocilizumab has emerged as a potential therapeutic option for severe cases, although supporting evidence remains limited.^{10,11}

Early administration of MP at a dose of 30 mg/kg/day may be associated with improved outcomes in ANE. However, in clinical practices, particularly in China, lower doses (e.g., <20 mg/kg/day) have been more commonly used during the initial phase of treatment. This preference may reflect concerns regarding potential adverse effects of high-dose MP (e.g., secondary infections and stress-induced hyperglycemia) as well as limited experience in

treating ANE.^{8,9,12} To date, direct comparative evidence on the efficacy of different MP dosing strategies remains insufficient. Furthermore, the potential benefits of these regimens, especially when combined with adjunctive therapies such as tocilizumab, have not been systematically evaluated.

In this retrospective cohort study, we analyzed 65 pediatric ANE cases treated at Beijing Children's Hospital from 2016 to 2024. The objective was to evaluate the association between multiple immunomodulatory strategies and 28-day postdischarge mortality across distinct clinical risk groups, with the goal of informing evidence-based management in this high-risk population.

Methods

1. Study population

This retrospective cohort study included pediatric patients diagnosed with ANE who were admitted to the pediatric intensive care unit (PICU) of Beijing Children's Hospital, Capital Medical University, between January 2016 and December 2024. Diagnosis was established according to the modified Mizuguchi criteria,¹ which include: (1) acute encephalopathy following a febrile illness, with rapid deterioration in consciousness and seizures; (2) cranial imaging using computed tomography or magnetic resonance imaging demonstrating multifocal brain lesions, with required bilateral symmetric involvement of the thalamic; (3) cerebrospinal fluid (CSF) analysis typically revealing elevated protein without pleocytosis; (4) elevated serum aminotransferases levels in the absence of hyperammonemia. All cases were independently

validated by 2 attending pediatricians through review of clinical and neuroimaging records.

Eligible participants were aged between 29 days and 18 years diagnosed with virus-associated ANE. Patients with positive respiratory detection were included even if incomplete CSF data were available. Patients with alternative diagnoses, such as infectious encephalopathy, inherited metabolic encephalopathy, hypoxic-ischemic encephalopathy, autoimmune encephalitis, or other infection-triggered encephalopathy syndromes, were excluded.

2. Data collection

Clinical data were extracted from the electronic medical records and included: (1) demographic and baseline clinical characteristics; (2) clinical manifestations at admission; (3) neuroimaging findings and laboratory examination results, including serum cytokine and CSF routine before immunotherapy; (4) treatment regimens, including immunomodulatory therapies with MP, IVIG, PLEX, and tocilizumab, as well as supportive treatments (antiviral agents, anticonvulsants, and mechanical ventilation); (5) clinical outcomes.

3. Treatment

All patients initiated immunomodulatory therapy within 24 hours of admission. High-dose MP was defined as an initial dosage of ≥ 20 mg/kg/day; MP pulse therapy was administered for 3 days, followed by tapering over 7–10 days. IVIG is administered at 1g/kg/day for 2 days. Tocilizumab (< 30 kg: 12 mg/kg; ≥ 30 kg: 8 mg/kg) was infused in 100-mL saline over ≥ 1 hour, with a maximum dose of 800 mg. The administration of tocilizumab and PLEX was determined based on clinical deterioration or cytokine marker levels.

4. Outcome measures

The primary outcome was 28-day postdischarge mortality, chosen over in-hospital mortality to account for potential underestimation due to treatment abandonment. Secondary outcomes included the presence of neurological sequelae during a minimum follow-up period of 6 months. Survivors underwent structured neurological evaluation either in person at outpatient clinics or via standardized telephone interviews, using the Pediatric Overall Performance Category (POPC) scale.¹³ Outcomes were dichotomized into: good outcomes (POPC scores 1–2, indicating normal to mild disability) and poor outcomes (POPC scores 3–6, representing moderate disability to brain death).

5. Severity stratification: ANE-SS

The ANE severity score (ANE-SS) was used to stratify illness severity, with total scores ranging from 0 to 9 points

based on the following parameters: shock at onset (3 points), brainstem involvement (2 points), age > 48 months (2 points), platelet count $< 100,000/\mu\text{L}$ (1 point), and CSF protein > 60 mg/dL (1 point).¹⁴ Patients were categorized into 3 risk groups: low risk (0–1 point), intermediate risk (2–4 points), and high risk (5–9 points).

6. Ethics

All patients received with high-dose MP, PLEX, and tocilizumab, written informed consent was routinely obtained from their legal guardians as part of standard clinical practice. This study was reviewed by the Ethics Committee of Beijing Children's Hospital and classified as exempt.

7. Statistical analysis

Continuous variables were presented as mean \pm standard deviation for parametric data or as median with interquartile range (IQR) for nonparametric data. Categorical variables were expressed as counts and percentages. Student *t* test was used for parametric continuous variables, and the Mann-Whitney *U* test was employed for nonparametric continuous variables. Categorical variables were analyzed using the chi-square test or Fisher exact test. Statistical significance was set at $P < 0.05$. All the statistical analyses were conducted using IBM SPSS Statistics ver. 27.0 (IBM Co., USA).

Results

1. Patient characteristics and disease severity

The study cohort included 82 pediatric patients diagnosed with ANE. Seventeen patients, who died within 24 hours of admission with a Glasgow Coma Scale (GCS) of 2T, were excluded from subsequent analysis of immunotherapy efficacy. The remaining 65 patients were included in the efficacy analysis (Fig. 1). The median age of the cohort was 4.8 years (IQR, 2.8–7.7 years), with a nearly equal sex distribution (male-to-female ratio, 1:1.02). Influenza A and SARS-CoV-2 were identified as the predominant infectious pathogens.

At admission, 46.2% (30 of 65) were classified as low- to medium-risk (ANE-SS < 5), while 53.8% (35 of 65) were categorized as high-risk (ANE-SS ≥ 5). Patients in the high-risk group were significantly older (median age: 5.0 years vs. 3.0 years, $P = 0.020$) and exhibited more severe clinical manifestations compared to those in low-to-medium-risk group (ANE-SS < 5). Specifically, high-risk patients presented with deeper coma (GCS ≤ 5 : 76.9% vs. 33.3%, $P < 0.001$), a higher incidence of shock (69.2% vs. 6.7%, $P < 0.001$), and more frequent brainstem involvement (84.6% vs. 26.7%,

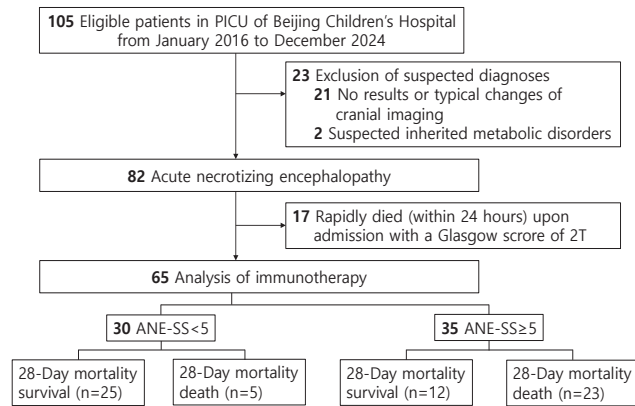


Fig. 1. Flow diagram of screening and enrollment of patients with pediatric acute necrotizing encephalopathy (ANE). A total of 105 children with suspected ANE were admitted to our hospital during the study period. Of them, 21 did not undergo imaging due to critical status or the absence of typical imaging findings, while 2 cases of suspected genetic metabolic encephalopathy were excluded. Finally, 82 children presented with clinically and radiologically confirmed ANE. Among them, 17 had a Glasgow Coma Score of 2T upon admission, exhibited dilated and fixed pupils, and died early during treatment or within 24-hour posttreatment. Consequently, 65 patients were included in the immunotherapy efficacy analysis. PICU, pediatric intensive care unit; ANE-SS, ANE severity score.

Table 1. Demographic and clinical characteristics by ANE-SS status

Variable	All patients (n=65)	ANE-SS<5 (n=30)	ANE-SS≥5 (n=35)	P value
Age (yr)	4.8 (2.8–7.7)	3.0 (1.9–6.0)	5.0 (4.0–8.3)	0.044
Male sex	29 (44.6)	14 (46.7)	15 (42.9)	0.758
Pathogen				
Influenza virus	33 (50.8)	13 (43.3)	20 (57.1)	0.267
SARS-CoV-2	18 (27.7)	10 (33.3)	8 (22.9)	0.347
HHV-6	3 (4.6)	1 (3.3)	2 (5.7)	1.000
Adenovirus	1 (1.5)	1 (3.3)	0 (0)	0.938
Unknown	10 (15.4)	5 (16.7)	5 (14.3)	1.000
Seizures	61 (93.8)	28 (93.3)	33 (94.3)	0.873
GCS≤5	36 (55.4)	10 (33.3)	26 (74.3)	<0.001
Shock	22 (33.8)	2 (6.7)	20 (57.1)	<0.001
MODS	24 (36.9)	3 (10)	21 (60)	<0.001
Coagulation disorders	40 (61.5)	12 (40)	28 (80)	<0.001
Brainstem involvement	40 (61.5)	10 (33.3)	30 (85.7)	<0.001
Mechanical ventilation	47 (72.3)	14 (46.7)	33 (94.3)	<0.001
Outcomes				
Survived	37 (56.9)	25 (83.3)	12 (34.3)	<0.001
Died	28 (43.1)	5 (16.7)	23 (65.7)	
POPC at the last follow-up				0.482
Poor	17 (45.9)	10 (40)	7 (58.3)	
Good	20 (54.1)	15 (60)	5 (41.7)	

Values are presented as median (interquartile range) or number (%). ANE-SS, acute necrotizing encephalopathy severity score; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HHV-6, human herpesvirus-6; GCS, Glasgow Coma Scale; MODS, multiple organ dysfunction syndrome; POPC, Pediatric Overall Performance Category.

Shock was defined as persistent hypotension despite fluid administration that required the initiation of vasoactive therapy. MODS was defined as the concurrent dysfunction of 2 or more organ systems, including respiratory, cardiovascular, hematological, neurological, gastrointestinal, hepatic, and renal.

The P value indicates the statistical comparison of the ANE-SS <5 and ANE-SS ≥5 groups.

Boldface indicates a statistically significant difference with $P<0.05$.

$P<0.001$) (Table 1). Additionally, levels of systemic inflammatory biomarkers, including procalcitonin, IL-6, IL-8, IL-10, as well as organ injury markers such as aspartate aminotransferase, lactate dehydrogenase, D-dimer were significantly elevated in high-risk group (all $P<0.05$) (Supplementary Table 1).

2. Trends in immunotherapy utilization and mortality (2016–2024)

An analysis of treatment trends from 2016 to 2024 revealed significant changes in immunotherapy strategies and associated mortality outcomes (Table 2). The use of first-line immunomodulatory therapy, defined as high-dose MP (≥ 20 mg/kg/day) combined with IVIG, increased steadily from 33.3% during 2016–2018 to 100% by 2021. Notably, the use of 30-mg/kg/day MP regimen rose sharply, from 15.4% in 2022 to 62.5% by 2024.

The application of PLEX gradually increased over the study period, ranging from 20.0% to 52.4%, with the exception of 2021, when it was not utilized. Tocilizumab, first introduced in 2023, was rapidly incorporated into clinical practice, with its use rising from 38.1% to 62.5% within 1 year.

Mortality rates range from 40% and 75%, peaking in 2019 when the use of immunotherapy was lowest. In subsequent years, mortality gradually declined with the increasing use of intensive immunotherapy regimens, particularly those combining 30-mg/kg/day MP, PLEX, and tocilizumab, reaching 38.9% in 2022, 36.8% in 2023, and 16.7% in 2024. Notably, indicators of disease severity, including ANE-SS≥5, brainstem involvement, and mechanical ventilation, remained relatively consistent over the study period.

3. Clinical outcomes of immunomodulation therapy by disease severity

All enrolled patients (n=65) in this study received first-line therapy with MP plus IVIG within 24 hours of admission. Based on this standardized combination, we further investigated the effect of different MP dosages and the additional use of second-line therapies, including tocilizumab and PLEX, across different disease severity.

1) Impact of MP dosage

In the low-risk group (ANE-SS<5), high-dose MP regimens demonstrated superior survival benefits. Treatment with 30-mg/kg/day MP achieved 100% survival rate, while 20 mg/kg/day resulted in 90.9% survival, compared to only 40% survival with lower doses (10–20 mg/kg/day) ($P=0.029$) (Table 3). In the high-risk patients (ANE-SS≥5), survival was clearly dose-dependent: 75% with 30 mg/kg/day, 25% with 20 mg/kg/day, and only 14.3% with 10–20 mg/kg/day.

Table 2. Composition of immunotherapy for ANE in pediatric intensive care unit: 2016–2024

Variable	2016–2018	2019	2020	2021	2022	2023	2024
Total number of patients	6	10	5	1	18	19	6
ANE severity							
ANE-SS \geq 5	2 (33.3)	6 (60.0)	4 (80.0)	0 (0)	8 (44.4)	10 (52.6)	5 (83.3)
Brainstem involvement	2 (33.3)	8 (80.0)	4 (80.0)	1 (100)	8 (44.4)	10 (52.6)	5 (83.3)
Mechanical ventilation	4 (66.7)	9 (90.0)	2 (40.0)	0 (0)	13 (72.2)	13 (68.4)	6 (100)
Different dosage of MP (mg/kg/day) +IVIG							
30	0 (0)	0 (0)	0 (0)	0 (0)	3 (16.7)	4 (21.1)	4 (66.7)
20	3 (50.0)	2 (20.0)	4 (80.0)	1 (100)	15 (83.3)	15 (78.9)	2 (33.3)
10 \leq 20	3 (50.0)	8 (80.0)	1 (20.0)	0 (0)	0 (0)	0 (0)	0 (0)
Tocilizumab	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)	6 (31.6)	6 (100)
PLEX	2 (33.3)	2 (20.0)	2 (40.0)	0 (0)	5 (27.8)	11 (57.9)	2 (33.3)
Mortality	3 (50.0)	7 (70.0)	3 (60.0)	0 (0)	7 (38.9)	7 (36.8)	1 (16.7)

Values are presented as number (%).

ANE, acute necrotizing encephalopathy; ANE-SS, ANE severity score; IVIG, intravenous immunoglobulin; MP, methylprednisolone; PLEX, plasma exchange.

Table 3. Clinical outcomes of children with ANE at 28 days postdischarge by clinical phenotype and immunotherapy regimen

Immunotherapy	ANE-SS<5		ANE-SS \geq 5		Brainstem involvement	
	Survived	Died	Survived	Died	Survived	Died
Different dosage of MP (mg/kg/day) +IVIG (n=65)						
30	3 (100)	0 (0)	6 (75)	2 (25)	7 (87.5)	1 (12.5)
20	20 (90.9)	2 (9.1)	5 (25)	15 (75)	11 (45.8)	13 (54.2)
10–<20	2 (40)	3 (60)	1 (14.3)	6 (85.7)	1 (12.5)	7 (87.5)
Combined second-line treatment (n=32)						
Tocilizumab						
Yes	2 (100)	0 (0)	9 (81.8)	2 (18.2)	9 (81.8)	2 (18.2)
No	10 (90.9)	1 (9.1)	1 (12.5)	7 (87.5)	6 (54.5)	5 (45.5)
PLEX						
Yes	10 (90.9)	1 (9.1)	6 (46.2)	7 (53.8)	9 (64.3)	5 (35.7)
No	2 (100)	0 (0)	4 (66.7)	2 (33.3)	6 (75)	2 (25)

Values are presented as number (%).

ANE, acute necrotizing encephalopathy; ANE-SS, ANE severity score; MP, methylprednisolone; IVIG, intravenous immunoglobulin; PLEX, plasma exchange
Second-line treatment: Patients received tocilizumab or therapeutic PLEX after the initial MP and IVIG treatment.

kg/day ($P=0.024$). These associations remained statistically significant in univariate Cox regression analysis ($P<0.001$), but lost significance in multivariate model ($P=0.321$), likely due to limited sample sizes in some subgroups (Table 4).

2) Efficacy of tocilizumab and PLEX

Tocilizumab and PLEX were typically administered as second-line interventions following initial steroid pulse therapy. Among this cohort, 13 patients were treated with tocilizumab, with 81.8% (11 of 13) administered within the first 24 hours of admission. PLEX were performed in 24 patients, all initiated within 72 hours of admission (Table 3).

Tocilizumab (8–12 mg/kg \times 1 dose) significantly improved survival in high-risk patients, with a survival rate of 81.8% compared to 12.5% in those who did not receive it ($P=0.005$) (Table 3). This effect was further confirmed in multivariate Cox regression analysis, which demonstrated a strong independent protective effect. (hazard ratio, 0.04; 95% confidence interval, 0.01–0.18) ($P<0.001$) (Table 4). While the

use of PLEX increased over time, it did not significantly reduce mortality in any subgroup ($P>0.05$ in univariate analysis) (Table 4).

4. Comparative efficacy of tocilizumab in high-risk patients with ANE

Among high-risk patients (ANE-SS \geq 5), those who received combination therapy with tocilizumab (n=11), had a better overall outcome compared to those who did not receive tocilizumab (n=8, Table 5).

Survival analysis revealed that in the tocilizumab group, survival rates were 80% for patients receiving 20-mg/kg/day MP and 83.3% for those receiving 30 mg/kg/day. In contrast, survival rates in the non-tocilizumab group were significantly lower, at 0% for the 20-mg/kg/day subgroup and 50% for the 30-mg/kg/day subgroup.

We further investigated neurological recovery at the 6-month follow-up after discharge. Among patients receiving combined tocilizumab with 30 mg/kg/day of MP, 60.0% had a good outcome (POPC score \leq 2), compared to 25% in

Table 4. Univariate and stepwise multivariate Cox hazard analysis of mortality by immunotherapy regimen at 28 days postdischarge

Variable	Univariate analysis		Multivariate analysis	
	ANE-SS<5	ANE-SS≥5	ANE-SS<5	ANE-SS≥5
Different dosage of MP (mg/kg/day) +IVIG (n=65)				
30	Reference	Reference	Reference	Reference
20	NA ^{a)}	9.00 (2.72–29.76)	NA ^{a)}	3.24 (0.70–15.12)
10≤20	NA ^{a)}	18.00 (3.10–104.53)	NA ^{a)}	2.16 (0.25–18.69)
<i>P</i> value	0.001	<0.001	0.002	0.321
Combined tocilizumab (n=13)				
Yes	NA ^{a)}	0.03 (0.01–0.11)	Reference	0.04 (0.01–0.18)
No	NA ^{a)}	31.50 (9.05–109.61)	NA ^{a)}	23.35 (5.58–97.79)
<i>P</i> value	NA ^{a)}	<0.001	NA ^{a)}	<0.001
Combined PLEX (n=24)				
Yes	0.38 (0.09–1.50)	0.77 (0.30–1.95)		
No	2.67 (0.67–10.67)	1.30 (0.51–3.30)		
<i>P</i> value	0.165	0.518		

Values are presented as hazard ratio (95% confidence interval).

ANE-SS, Acute Necrotizing Encephalopathy Severity Score; IVIG, intravenous immunoglobulin; MP, methylprednisolone; PLEX, plasma exchange; NA, not applicable.

^{a)}Not performed because of the small number of patients.

Boldface indicates a statistically significant difference with *P*<0.05.

Table 5. Clinical outcomes of tocilizumab plus corticosteroid immunomodulatory therapy in patients with high-risk ANE (ANE-SS ≥5): 28-day mortality and 6-month sequelae

Variable	With tocilizumab (n=11)		Without tocilizumab (n=8)	
	20-mg/kg/day MP + IVIG	30-mg/kg/day MP + IVIG	20-mg/kg/day MP + IVIG	30-mg/kg/day MP + IVIG
Outcomes				
Survived	4 (80)	5 (83.3)	0 (0)	1 (50.0)
Died	1 (20)	1 (16.7)	6 (100)	1 (50.0)
POPC at follow-up				
Good	1 (25.0)	3 (60.0)	0 (0)	1 (100)
Poor	3 (75.0)	2 (40.0)	0 (0)	0 (0)

Values are presented as number (%).

ANE, acute necrotizing encephalopathy; ANE-SS, ANE severity score; MP, methylprednisolone; IVIG, intravenous immunoglobulin; POPC, Pediatric Overall Performance Category.

the 20-mg/kg/day subgroup. In the nontocilizumab group, only one child survived in the 30-mg/kg/day subgroup. Although this observed difference was not statistically significant, likely due to the small sample size (Table 5). These results suggest that tocilizumab combined with high-dose MP (30 mg/kg/day) may enhance both survival and possibly long-term neurological recovery in high-risk patients with ANE.

5. Treatment-related adverse events

Three ANE patients treated with high-dose MP (1 at 20 mg/kg/day and 2 at 30 mg/kg/day) developed stress hyperglycemia. Two ANE patients with concomitant *Mycoplasma pneumoniae* infection receiving combined therapy (20-mg/kg/day MP, PLEX, and tocilizumab) developed cerebral arterial thrombosis, likely due to infection-induced hypercoagulability rather than procedural complications.

Discussion

Our study demonstrates a clear dose-response relationship of MP in the treatment of ANE. Both 20 and 30-mg/kg/day MP significantly reduced mortality in low- to medium-risk patients (ANE-SS<5). However, in high-risk cases (ANE-SS≥5), only the higher doses of 30mg/kg/day provided additional survival benefits. Notably, the combination of 30-mg/kg/day MP with tocilizumab achieved 83.3% survival rate in this high-risk subgroup, whereas lower-dose MP without tocilizumab resulted in poor outcomes, including 100% mortality in the 20 mg/kg/day MP group. Furthermore, PLEX exhibited limited therapeutic impact across all risk groups. These findings highlight the superior efficacy of high-dose MP, particularly when combined with tocilizumab, in improving survival outcomes in high-risk patients with ANE.

High-risk patients faced a 4.6-fold increased mortality risk compared to low- to medium-risk counterparts,^{14,15)} with brainstem involvement recognized as a poor pro-

gnostic factor.¹⁶⁾ Early administration of high-dose intravenous corticosteroids is crucial for optimizing treatment efficacy in ANE, with the typical international regimen of 30-mg/kg/day MP.^{6,17,18)} Previous studies in China frequently employed lower starting doses of less than 20 mg/kg/day due to the lack of international consensus guidelines for ANE. However, recent guidelines have recommended a dose range of 20–30 mg/kg/day, with 20 mg/kg/day being widely used.^{8,9,19)} Our analysis suggests that the initial 20-mg/kg/day MP pulse therapy appears sufficient for patients with low-to-medium-risk, whereas for high-risk patients, a higher dosage of 30 mg/kg/day may offer superior control of neuroinflammation and improved survival outcomes.

Furthermore, MP is generally administered in combination with intravenous IVIG, which may help alleviate neuroinflammation by inhibiting immune cell activity and reducing the release of proinflammatory cytokines. A meta-analysis indicated that the combined treatment of IVIG with high-dose MP and tocilizumab may enhance the survival outcomes in patients with ANE.¹⁵⁾ Other studies have reported limited clinical benefit from IVIG, whether used alone or in combination with corticosteroids.²⁰⁾ In our cohort, all patients received IVIG, preventing us from evaluating its standalone therapeutic effect. Therefore, the role of IVIG treatment in ANE remains unclear.

Tocilizumab, as an IL-6 receptor antagonist, exerts anti-neuroinflammatory effects by blocking IL-6-mediated signaling and restoring blood-brain barrier integrity.²¹⁾ Although retrospective studies have reported conflicting data regarding its mortality benefits, most evidence supports its role as a viable treatment for severe patients with ANE.^{22,23)} Our data show that high-risk patients treated with tocilizumab in combination with high-dose MP (30 mg/kg/day) had significantly better survival than those without tocilizumab. In contrast, high-dose MP alone showed limited benefit. These findings suggest tocilizumab may play a key therapeutic role, possibly synergizing with MP. Moreover, 6-month follow-up also indicated improved neurological outcomes with the combination. Given the small sample size, further prospective studies are needed to clarify their independent and combined effects. Overall, tocilizumab plus high-dose MP improves prognosis in high-risk patients with ANE.

PLEX may potentially reduce plasma inflammatory factors and reconstruct the concentration gradient between local infection foci and circulation, thereby enhancing leukocyte recruitment and pathogen clearance.¹⁰⁾ Although it appears theoretically beneficial for severe ANE cases, such as those with ANE-SS score \geq 2, including moderate to severe presentations, or for patients with a poor response to immunomodulatory therapy,²⁴⁾ the

current evidence remains limited.^{10,25)} In our study, 13 high-risk patients received PLEX, with 69.2% initiated within 24 hours. However, we observed no significant improvement in mortality or neurological outcomes compared to non-PLEX controls, highlighting the need for further research to define the role of PLEX in the management of ANE.

A major challenge in treating ANE lies in balancing therapeutic efficacy and safety—insufficient dosing may fail to control inflammation, while excessive treatment increases the risk of infection and metabolic disturbance. Currently, safety data on immunomodulatory therapy in ANE remain limited. High-dose corticosteroids may lead to complications such as infections, hypercoagulability, glucose metabolism disorders, and abnormal blood pressure, all of which warrant careful monitoring. Tocilizumab, while showing therapeutic promise, may induce hepatotoxicity, hypersensitivity reactions, or in rare cases, gastrointestinal perforation. In other inflammatory conditions, its most commonly reported adverse effects include neutropenia, thrombocytopenia, and elevated transaminases.²⁶⁾ No severe adverse effects were observed following short-term administration of high-dose MP or tocilizumab in this study. Cerebral arterial thrombosis occurred in 2 ANE patients with *Mycoplasma pneumoniae* infection in this study, which was likely related to infection-induced hypercoagulability rather than a procedural complication.

This study represents the largest reported cohort evaluating immunotherapies in pediatric ANE, featuring comprehensive treatment assessments and risk stratification based on ANE severity. However, several limitations must be acknowledged: (1) the retrospective design restricts causal inferences and may introduce selection bias; (2) few patients underwent genetic testing (RANBP2 mutations found in 5 cases), the efficacy of current immunotherapies for ANEI remains undetermined, and (3) the absence of epidemiological context hinders the interpretation of case fluctuations. These constraints underscore the need for prospective multicenter trials to validate our findings and address outstanding questions concerning optimal ANE management.

In conclusion, in low- to moderate-risk patients with pediatric ANE, pulse regimes of both 20- and 30-mg/kg/day MP are associated with improved outcomes. For high-risk patients, high-dose MP (30 mg/kg/day) combined with tocilizumab (8–12 mg/kg \times 1 dose) may improve survival and possibly long-term neurological recovery. These results highlight the importance of a risk-stratified immunotherapeutic strategy in the management of ANE.

Footnotes

Supplementary materials: Supplementary Tables 1 is available at <https://doi.org/10.3345/cep.2025.01431>.

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