REVIEW ARTICLE

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Treatment strategies for paediatric autoimmune encephalitis – current evidence, limitations and future directions

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Abstract

Introduction and Objective. Autoimmune encephalitis (AE) is an inflammatory disorder in which the immune system attacks brain tissue, causing central nervous system *(CNS)* dysfunction. In children, it often manifests as seizures, behavioural changes, memory impairment and involuntary movements. The aim of the review is to summarise and discuss currently available treatment methods, their limitations, and the latest advances in the field.

Review Methods. A narrative literature review was conducted using PubMed and Google Scholar databases. The search strategy included combinations of the following key words and their variations: 'autoimmune encephalitis, 'AE' and 'paediatric' or 'children'. Priority was given to recent peer-reviewed studies published from January 2020 onwards in order to capture the most up-to-date evidence. However, selected earlier landmark studies were also included when considered essential for contextual understanding.

Brief description of the state of knowledge. Treatment of this condition primarily focuses on immunotherapy. First-line therapy includes high-dose corticosteroids, intravenous immunoglobulins and plasmapheresis. In cases refractory to first-line therapy, second-line treatments most commonly comprise rituximab and cyclophosphamide. Additional options include certain monoclonal antibodies, cytotoxic agents, as well as interleukin-2 *(IL-2)*. In addition to primary treatment, supportive therapy may be introduced.

Summary. AE is a serious neurological disorder that can cause irreversible *CNS* damage without prompt treatment. Its growing recognition in children highlights the need for early diagnosis and timely therapy. While immunotherapy is often effective, some patients remain refractory, underscoring the need for further research, paediatric-specific guidelines and new treatments.

Key words

autoimmune encephalitis, paediatric autoimmune encephalitis, autoimmune diseases of the central nervous system, immunotherapy, rituximab

INTRODUCTION

Autoimmune encephalitis *(AE)* represents a diverse group of inflammatory conditions in which the immune system targets the functional tissues of the brain, including the cerebral cortex and both white and grey matter. Furthermore, the inflammation can extend to the spinal cord and the protective membranes surrounding the brain [1–3]. These processes result in neurological dysfunction and neuronal cell death. In the paediatric population, the clinical manifestations of the disease are not well-defined and significant diagnostic challenges persist, which may delay diagnosis and the timely initiation of treatment [2]. Consequently, affected children may fail to regain their previous level of functioning [3]. Currently, randomized controlled trials and consensus guidelines for the management of paediatric patients are lacking [4]. The aim of this article is to summarise and discuss the currently available therapeutic approaches.

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The disease is associated with the presence of autoantibodies directed against neuronal cell-surface antigens, synaptic receptors, ion channels or intracellular neuronal proteins. These antibodies contribute to neuronal dysfunction and inflammation, resulting in a wide spectrum of neurological and psychiatric manifestations [5–6].

The immunopathogenesis of AE involves a complex interplay between humoral and cellular immune mechanisms. Activated B lymphocytes produce pathogenic autoantibodies directed against neuronal surface antigens, which can induce neuronal dysfunction through several mechanisms, including receptor cross-linking and internalisation, leading to synaptic and network alterations [7–8]. Increasing evidence indicates that both B and T lymphocytes play a crucial role in the development and progression of the disease through cytokine-mediated immune responses [9]. In addition, autoantibody-mediated immune reactions may trigger complement activation, which contributes to neuroinflammation and further amplification of the immune response within the central nervous system *(CNS)* [10].

Due to the functional rather than structural impact of these antibodies, prompt immunotherapeutic intervention often

leads to a full or partial reversal of deficits, correlating with a high rate of favourable prognostic outcomes [1]. AE currently includes a number of subtypes that may be classified according to the autoantibody found in the serum and/or cerebrospinal fluid (CSF). Antibodies associated with *AE* are broadly categorized into two groups based on the localization of their target antigens. Group I targets intracellular epitopes (e.g. anti-Hu, anti-Ma/Ta, anti-Yo, anti-GAD, anti-CV2/CRMP5), while group II is directed against cell-surface neuronal proteins (e.g. anti-NMDAR, anti-LGI1, anti-CASPR2, anti-GABAAR, anti-GABABR, and anti-AMPAR) [5, 11]. This classification is clinically relevant, because different antibodies are associated with specific phenotypes, prognoses, and treatment responses [5]. As a general rule, Group I AE is associated with a worse prognosis than Group II AE. Additionally, group I AE (also referred to as 'onconeural antibody') is associated with a more guarded prognosis and a higher probability of underlying malignancy compared to group II AE [11].

In paediatric patients, antibodies targetting neuronal surface antigens, particularly N-methyl-D-aspartate receptor (NMDAR), are the most frequently identified [5]. However, it is worth mentioning that there is an antibody-negative form of AE, that may have similar neuroimaging findings to, for example, N-methyl-D-aspartate (NMDA) type, and occurs with similar symptoms [5–6]. A diagnosis of seronegative encephalitis should be approached with caution, as limited antibody testing panels can lead to the misidentification of antibody-mediated cases as seronegative [12]. Over the last two decades, the identification of neuronal autoantibodies has significantly improved the understanding of pathogenesis, diagnosis and treatment of AE, particularly in the pediatric population [5–6]. The incidence of *AE* has also increased in recent years, partly due to improved recognition and diagnostic testing [6].

The diversity of clinical manifestations varies according to the type of autoantibody [13]. Common manifestations include seizures, behavioural and psychiatric disturbances, memory impairment, altered consciousness, autonomic dysfunction and abnormal movements. The clinical presentation may evolve over days to weeks and can mimic infectious encephalitis or primary psychiatric disorders, which often complicates early diagnosis [5–6]. Among children, seizures and behavioural changes are frequently the initial symptoms [5]. Manifestations such as fatigue and cognitive impairments may persist after the completion of treatment, even into adulthood [14–15].

OBJECTIVE

The aim of the review is to comprehensively synthesise and evaluate currently available therapeutic approaches for paediatric AE, ranging from established first-line immunotherapies to novel third-line interventions and supportive modalities. Specifically, the aim is to analyze the current clinical evidence supporting these treatments, delineate their primary operational limitations – such as safety profiles and delayed responses – and highlight future directions in paediatric-specific protocols. By addressing these critical gaps, the review seeks to provide clinicians with a structured overview to assist in early therapeutic decision-making and optimize long-term functional outcomes in affected children.

REVIEW METHODS

A comprehensive literature search was conducted across electronic databases, including PubMed and Google Scholar, to identify relevant studies on the treatment strategies for pediatric AE. A narrative review of the literature was conducted. The search strategy utilized combinations of the following Medical Subject Headings (MeSH) terms and key words: 'autoimmune encephalitis', 'AE', 'paediatric', 'children' and 'treatment'. To capture the most up-to-date and current evidence, the electronic search was primarily restricted to studies published from January 2020 onwards that were accessible through institutional subscriptions and open-access databases. Additionally, a manual review of high-impact neurological and pediatric journals was performed, and reference lists of relevant articles were screened to retrieve selected landmark studies essential for establishing contextual and historical understanding.

Inclusion criteria. 1) Peer-reviewed original research, clinical trials, cohort studies, case series and systematic reviews; 2) target population restricted to paediatric patients (aged 0–18 years) diagnosed with AE; 3) papers focusing on first-, second- or third-line immunotherapies, supportive care, or dietary interventions (e.g. the ketogenic diet).

Exclusion criteria. 1) Studies focusing exclusively on adult populations; 2) articles lacking specific data on therapeutic outcomes or limitations; 3) conference abstracts, editorials and non-peer-reviewed commentaries. The retrieved literature was then synthesized and discussed in a narrative format, organizing the evidence by treatment line and therapeutic modality.

Methodological qualities and limitations of sources. The literature collected possessed distinct methodological qualities, notably the inclusion of recent multi-centre retrospective studies and emerging clinical trial data (e.g. rituximab and bortezomib updates) that enhance the clinical relevance of the findings. However, several inherent limitations in the source publications must be acknowledged. A significant portion of the available evidence relies heavily on small case series, retrospective cohorts and anecdotal case reports, rather than large-scale, randomized controlled trials. This introduced potential selection bias and limited the generalizability of treatment efficacy. Furthermore, variations in institutional protocols, heterogeneous paediatric sample sizes and the frequent co-administration of therapies, complicated the isolation of individual drug effects, underscoring the need for standardized paediatric guidelines.

DESCRIPTION OF THE STATES OF KNOWLEDGE

FIRST-LINE THERAPY

Immunotherapy. The aim of immunotherapy is to suppress pathological autoimmune activity and reduce inflammation in the brain. First-line treatments include separate or combined use of high-dose intravenous corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis.

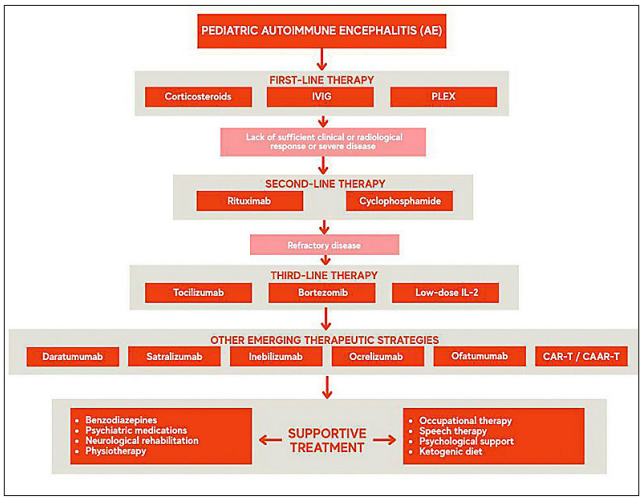

Figure 1. Summary of the treatment strategies for autoimmune encephalitis (AE) in children

Corticosteroids. Methylprednisolone exerts potent anti-inflammatory and immunosuppressive effects, including inhibition of immune cell activation and migration into the system CNS [16–17]. The recommended dose of intravenous methylprednisolone is 20–30 mg/kg i.v. for 3–5 days [18].

While methylprednisolone is the standard first-line corticosteroid treatment, other steroids such as dexamethasone may be used in selected cases. Dexamethasone is administered at a dose of 0.3–0.5 mg/kg/day intravenously for 5 consecutive days, followed by gradual tapering over 7–10 days [19].

Immunoglobulin. The key effects of IVIG in treating neurological diseases involve neutralizing specific harmful cytokines, reducing antibody production and modulating phagocytosis through Fc receptors [20].

To evaluate the impact of early intravenous immunoglobulin treatment in children with encephalitis a study was conducted – 'Intravenous immunoglobulin treatment in childhood encephalitis (IgNiTE): a randomised controlled trial'. The trial enrolled children with encephalitis of any etiology, and antibodies associated with AE were identified in only two paediatric patients. Participants randomized to receive IVIG were administered two 1 g/kg doses 24–36 hours apart, in addition to standard care, whereas control participants received placebo. In the descriptive analysis of the 18 enrolled children, similar proportions of 'good recovery' (defined as a score of ≤2 on the Paediatric Glasgow Outcome Score Extended at 12 months) were observed in the IVIG group (50%) and the placebo group (50%). New diagnoses of epilepsy occurred less frequently in the IVIG group (10%) than in the placebo group (25%). No serious adverse events were reported with IVIG administration. However, the trial was terminated early and was underpowered to demonstrate statistically significant differences in efficacy, underscoring the need for larger, adequately powered studies to clarify the role of IVIG in paediatric encephalitis [21].

Plasmapheresis. Plasmapheresis or Plasma exchange (PLEX) typically administered as 5–10 sessions every other day, represents an effective strategy for acute immunomodulation in *AE*, particularly when corticosteroids are contraindicated or insufficiently effective. Combining corticosteroids with PLEX may yield greater clinical improvement than corticosteroids alone, mirroring observations reported in other antibody-mediated disorders such as Neuromyelitis Optica Spectrum Disorder (NMOSD). PLEX may be particularly advantageous in *AE* accompanied by central demyelination or in cases with co-existing NMOSD and it is often considered when a fast immunomodulatory effect is desired in severe or fulminant presentations. Importantly, PLEX has no established psychiatric adverse effects and does not appear to increase thromboembolic risk beyond catheter-related thrombosis. Practical limitations include a higher bleeding risk, intravascular volume shifts (potentially problematic in patients with dysautonomia) and the need for central venous access in some settings, with its associated procedural complications; moreover, the procedure may be difficult to perform in markedly agitated patients [22].

SECOND-LINE THERAPY

Indications. Indications for second-line therapy include the lack of a sufficient clinical or radiological response to first-line therapy and severe disease [4, 22, 23].

Timing of second-line therapy. The optimal time to initiate second-line therapy is approximately 2 weeks after the initiation of first-line therapy, if no significant clinical improvement is observed or if only minimal improvement occurs [4, 22, 23].

Drugs used in second-line therapy. The most commonly used second-line drug chosen by specialists is rituximab. *This is due to its more favourable safety profile compared with cyclophosphamide* [4, 22, 24]. Another second-line treatment option is cyclophosphamide, which is used less frequently because it is more toxic than rituximab, and has a slower onset of action [4, 22, 24].

Mycophenolate mofetil is used for maintenance therapy and long-term disease control. This drug has a slow onset of action and is therefore used for maintenance therapy after disease control has been achieved [4].

Azathioprine and methotrexate are also used as maintenance therapy. However, there is insufficient data on the effectiveness of these medications, so there are no recommendations for their routine use [4].

Rituximab. Rituximab is a recombinant, chimeric monoclonal antibody directed against the CD20 antigen [23, 25], a transmembrane protein found on immature, mature and memory B cells. The mechanism of action of rituximab involves antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), phagocytosis, and induction of apoptosis [9]. The effect of rituximab is long-lasting due to the elimination of antigen-specific memory B cells and prevents the development of plasmablasts that secrete pathogenic antibodies [23]. Although rituximab acts primarily by reducing the number of B lymphocytes, it has an indirect effect on the response and activation of T lymphocytes. This results in a secondary inhibition of their cellular activity [22]. Due to its mechanism, rituximab is important in the treatment of *AE*, such as anti-NMDA receptor encephalitis. B lymphocytes producing autoantibodies directed against neuronal antigens are involved in the pathogenesis of

these diseases. Rituximab treatment leads to depletion of B lymphocytes, and consequently reduces antibody production and limits inflammatory activity in the *CNS* [4, 26].

Rituximab administration schedules include several dosing options. The first schedule is 375 mg/m² once weekly for 4 weeks. Alternatively, two doses are administered 2 weeks apart, at a dose of 500 mg in children weighing less than 40 kg and 1,000 mg in children weighing more than 40 kg. Another schedule involves 2 doses administered 2 weeks apart at a dose of 375–750 mg/m² (up to a maximum of 1 g) [4, 22, 23]. Adverse reactions to rituximab administration in children primarily include infusion-related reactions, including rash, fever and chills [27–28]. *In a study of 144 children treated with rituximab, infectious adverse events occurred in 11 patients (7.6%), including 2 deaths (1.4%) and 2 disabling or life-threatening infections (1.4%) [28]. The authors concluded that rituximab should be regarded as a broad-acting immunosuppressive agent and should be restricted to disorders with significant morbidity and mortality because of the risk of infectious complications [28].* Studies on the use of rituximab in children with anti-NMDA receptor encephalitis as second-line therapy indicate that this treatment may lead to clinical improvement and reduce the risk of disease relapse [27, 29].

Cyclophosphamide. An immunosuppressant belonging to the alkylating agent group. It works by alkylating DNA and disrupting cell replication, consequently inhibiting the production of immune cells. This leads to a reduction in the number of T and B lymphocytes and a decrease in autoantibody production. This mechanism is used in the treatment of autoimmune diseases [24,30]. In the recommendations, cyclophosphamide is used less frequently than rituximab due to its less favourable safety profile, but it is still considered a possible therapeutic option [4, 23, 24].

Cyclophosphamide therapy is recommended in patients who do not respond to rituximab, usually after approximately 6 weeks. The dosing regimen for cyclophosphamide includes intravenous administration of 500–1000 mg/m² in monthly pulses, usually for up to 6 months [4, 31, 32].

Cyclophosphamide may cause adverse effects related to its immunosuppressive activity. These include increased susceptibility to infections, an elevated risk of secondary malignancies and potential fertility impairment [31–32].

THIRD LINE THERAPY

In children with AE, satisfactory clinical improvement is sometimes not observed despite the use of standard first-line and second-line treatment therapies [31, 34, 35]. In patients who are refractory to these treatment methods, third-line therapy may be considered. This approach includes drugs with different mechanisms of action, that affect various components of the immune response, such as the production of autoantibodies or the activity of pro-inflammatory cytokines [24]. The third-line therapies most frequently described in the literature include monoclonal antibodies blocking interleukin-6 *(IL-6)* (e.g., tocilizumab), proteasome inhibitors such as bortezomib, as well as other immunomodulatory strategies, including the use of low doses of interleukin-2 *(IL-2)* [24, 31].

Tocilizumab. Tocilizumab is a humanised monoclonal antibody directed against the *IL-6* receptor that inhibits the signalling of this cytokine, and consequently reduces inflammatory processes and the activation of immune system cells. *IL-6* plays an important role in the regulation of the immune response, including the activation of B lymphocytes and the production of autoantibodies involved in the pathogenesis of *AE* [24,31,33]. Due to this mechanism of action, tocilizumab is considered a potential therapeutic option in children with AE refractory to standard first- and second-line immunotherapy. In available observational studies and case series, the use of this drug has been shown to lead to clinical improvement in some patients, particularly in cases of severe or relapsing disease [24].

Despite promising clinical results, data regarding the effectiveness of tocilizumab in the treatment of AE remain limited and are derived mainly from retrospective studies and case reports. Therefore, this drug is currently used primarily as part of third-line therapy in patients who have not improved after standard immunosuppressive treatment [24, 31, 35]. Tocilizumab appears to be well tolerated in children. Possible adverse effects include infusion reactions, infections, neutropenia, elevated liver enzymes, and the risk of gastrointestinal perforation. Therefore, regular monitoring of blood cell counts, liver function and lipid profile is recommended to enable early detection of potential toxicity [31].

Bortezomib. Bortezomib is a proteasome inhibitor that directly targets plasma cells, including long-lived plasma cells responsible for persistent autoantibody production [24,31,36]. For this reason, bortezomib is considered a potential therapeutic option in the treatment of *AE* refractory to standard immunotherapy.

Available data on the use of bortezomib in *AE* mainly come from case reports and small clinical series. Several clinical reports have demonstrated neurological improvement in patients with severe encephalitis associated with antibodies against the NMDA receptor who did not respond to first- and second-line therapies [34]. The literature also describes cases suggesting a beneficial effect of bortezomib in patients with severe anti-NMDA receptor encephalitis. In one case study including 5 patients with NMDAR encephalitis who received 1–6 doses of the drug, varying degrees of clinical response were observed, ranging from partial improvement of neurocognitive deficits to complete remission of disease symptoms [24, 31].

Reported adverse effects of bortezomib include infections, gastrointestinal disturbances, peripheral neuropathy, and haematological disorders. Therefore, careful monitoring of patients and assessment of the potential risk of adverse effects are required during treatment. Additionally, preclinical studies have shown that bortezomib may have a long-term impact on testicular function; therefore, particular attention should be paid to the potential effects of this therapy on the reproductive health of male children [24, 31, 36].

Despite promising results, the use of bortezomib in *AE* remains experimental and the available clinical data are limited and require confirmation in larger clinical studies [24, 31, 36].

Interleukin-2. *IL-2* is a cytokine that plays a key role in regulating the immune response by influencing the

proliferation and differentiation of T lymphocytes. Depending on the administered dose, IL-2 may produce different immunological effects – high doses primarily stimulate effector CD8+ T cells, whereas low doses preferentially activate regulatory T cells (Treg), which are responsible for maintaining immune tolerance and suppressing autoimmune reactions [24, 31, 36].

In recent years, increasing interest has focused on the use of low-dose IL-2 in the treatment of autoimmune diseases, including *AE*. This therapy aims to restore immune balance by increasing the number and activity of regulatory T cells, which may lead to suppression of the pathological immune response directed against neuronal antigens [24, 31, 36].

In clinical studies involving patients with *AE* refractory to standard immunotherapy, a low-dose IL-2 has been administered in small patient groups. In one study including 10 patients, clinical improvement was observed in approximately 60% of patients after 4 treatment cycles, while no deterioration of neurological status was reported in any of the participants [31].

The most commonly reported adverse effects include eosinophilia, neutropenia, subclinical hyperthyroidism, flu-like symptoms, and gastrointestinal complaints. Despite promising results, the available data on the use of IL-2 in AE remain limited and are mainly based on small clinical studies and case reports; therefore, further research is required to confirm the effectiveness of this therapy [24, 31, 36].

Other emerging third-line therapeutic strategies. In recent years, additional therapeutic strategies targetting different components of the immune response have also been considered in the treatment of refractory *AE*. One of these is daratumumab – a human monoclonal antibody directed against the CD38 antigen expressed on plasma cells responsible for the production of autoantibodies. Case reports have shown that the use of this drug in patients with refractory AE was associated with clinical improvement and a reduction in autoantibody titers [8, 24, 36].

Other monoclonal antibodies are also being investigated, such as satralizumab – an *IL-6* receptor inhibitor with a longer duration of action – and inebilizumab, which blocks the CD19 antigen and leads to the depletion of a broad range of B cells [8, 36]. The literature also describes isolated cases of the use of anti-CD20 antibodies such as ocrelizumab and ofatumumab, particularly in patients who are refractory to previous immunosuppressive therapy [8].

In addition, novel therapeutic approaches are being developed, including CAR-T or CAAR-T cell therapy, which involves the modification of T lymphocytes in order to selectively eliminate B cells producing autoantibodies. Despite promising results, most of these methods remain at the stage of clinical research or case reports, and their efficacy and safety require further evaluation in larger studies [8].

Tumour removal. In some cases, *AE* has a paraneoplastic nature and is associated with the presence of a tumour. This most commonly applies to encephalitis that may coexist with malignant tumors of the lungs, breasts, testes and ovaries [24]. In such situations, a key element of therapeutic management is treatment and the earliest possible removal of the tumour, as the presence of cancer may constitute a source of antigens triggering an autoimmune response. Therefore, in patients diagnosed with AE, appropriate diagnostic evaluation for neoplastic disease is recommended [24, 31]. However, fortunately, cases of tumour-related *AE* are extremely rare in childhood [1].

SUPPORTIVE TREATMENT

In addition to immunomodulatory therapy, an important component of the treatment of *AE* is symptomatic management, aimed at controlling neurological and psychiatric symptoms and improving patient functioning [31]. In some patients, the use of antiepileptic drugs and psychiatric medications is necessary, as seizures, behavioural disturbances and psychotic symptoms are common manifestations of the disease [24, 31, 33].

Benzodiazepines. Benzodiazepines are used in the early phase of the disease, particularly in the treatment of psychomotor agitation, seizures and catatonia, which is one of the more frequently observed symptoms in children with AE [31]. In cases where psychotic symptoms occur, antipsychotic medications such as olanzapine may also be used; however, careful differentiation between psychosis and catatonia is required before their introduction, as inappropriate use of antipsychotics may lead to the development of neuroleptic malignant syndrome [31].

Neurological rehabilitation. Additionally, an important component of management is neurological rehabilitation, including physiotherapy, occupational therapy and speech therapy, as well as psychiatric and psychological support. Comprehensive supportive care can significantly improve treatment outcomes and facilitate patients' return to daily functioning [31].

Ketogenic diet. The ketogenic diet *(KD)* is a restrictive dietary regimen characterized by a high intake of fats and proteins alongside a significant reduction in carbohydrates, leading to an increased concentration of ketone bodies in the blood [37]. Ketone bodies serve as both alternative energy substrates and signalling molecules, contributing to the biological effects of the *KD* [38]. This dietary intervention induces a metabolic state of ketosis, alters glycaemic levels, increases circulating fatty acids, and affects caloric restriction (CR)-related pathways [37].

The KD has demonstrated anti-inflammatory and neuroprotective properties in preclinical and mechanistic studies, prompting investigation in drug-resistant epilepsy and febrile infection-related epilepsy syndrome (FIRES) [37–39]. However, it is important to recognize that FIRES is classified as a subtype of new-onset refractory status epilepticus (NORSE) and is not considered AE; the diagnostic work-up in the FIRES literature explicitly excludes autoimmune causes [39]. Consequently, data from FIRES cannot be interpreted as direct evidence for the KD in *AE*, and reported outcomes are often confounded by concomitant immunomodulatory therapies, including anakinra [39].

The anti-inflammatory efficacy of the KD is based on a broad spectrum of mechanisms. Primarily, it modulates multiple inflammatory pathways, including TNF-α, IL-6, NF-κB and COX-2 signalling. The anti-inflammatory effect is also mediated through modulation of adenosine levels [37]. Ketone bodies activate cytoprotective pathways involving

Nrf2, sirtuins and AMPK, promoting anti-oxidant and anti-inflammatory responses [40]. β-hydroxybutyrate also modulates the NLRP3 inflammasome, a pathway implicated in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) [37]. It should be emphasized, however, that these findings derive from preclinical and mechanistic work and do not constitute clinical evidence of efficacy in AE.

Direct evidence specifically in paediatric *AE* remains exceptionally limited. A single case report described a 7-year-old child with anti-GAD65 antibody-mediated super-refractory status epilepticus in whom a classic KD was associated with seizure control after failure of multiple anti-seizure medications and immunotherapies [41]. The authors of that report noted that anti-GAD65 encephalitis is rare in children, and the case does not provide data supporting generalization to other antibody subtypes, such as surface-antibody encephalitides [41]. Regarding safety in paediatric populations, a Cochrane systematic review of KD in drug-resistant epilepsy identified constipation, diarrhea and vomiting as the most frequently reported adverse effects, and also documented potentially serious adverse events and tolerability limitations [42]. The same review found that KD may be effective in reducing seizure frequency in children with drug-resistant epilepsy, but rated the certainty of this evidence as low to very low [42].

Despite its mechanistic rationale and its established role in some forms of drug-resistant epilepsy, no direct evidence currently supports the use of KD as a routine adjunctive therapy in paediatric *AE*. The available evidence is limited to indirect data from FIRES and a single case report of anti-GAD65 encephalitis, neither of which provides a sufficient basis for general recommendations. In the authors' opinion, the KD remains an investigational approach; its application should be confined to carefully selected, highly refractory cases, ideally within the context of prospective clinical studies specifically designed to evaluate its efficacy and safety in paediatric *AE*.

CONCLUSIONS

AE is a neurological disorder that may lead to irreversible damage to the *CNS* if pharmacological treatment is not initiated at an early stage. It requires a specialized and comprehensive approach to ensure optimal patient recovery and the resolution of neurological deficits. Given the increasing recognition of this condition within the paediatric population, it is essential to adequately prepare medical personnel to establish a prompt and accurate diagnosis and to initiate appropriate treatment without delay.

Currently proposed therapeutic strategies, which typically begin with immunotherapy, are not effective in all patients. Therefore, further research on *AE* is warranted, including a greater number of randomized controlled trials assessing the efficacy of available treatments. Additionally, there is a need to develop consensus guidelines specifically tailored to the paediatric population and to introduce new therapeutic agents into clinical practice.

REFERENCES

1. Hiesgen J, Schutte C. Autoimmune encephalitis: Part 1 (Epidemiology, Pathophysiology and Clinical spectrum). S Afr Med J. 2023;113(3):116–121. Published 2023 Mar 2. https://doi.org/10.7196/SAMJ.2023.v113i3.780
2. Santoro JD, Demakakos P, He S, et al. A systematic review of the epidemiology of pediatric autoimmune encephalitis: disease burden and clinical decision-making. Front Neurol. 2024;15:1408606. Published 2024 Jul 2. https://doi.org/10.3389/fneur.2024.1408606
3. Ferreira JHF, Disserol CCD, de Freitas Dias B, et al. Recent advances in autoimmune encephalitis. Avanços recentes em encefalite autoimune. Arq Neuropsiquiatr. 2024;82(12):1–13. https://doi.org/10.1055/s-0044-1793933
4. Nosadini M, Thomas T, Eyre M, et al. International Consensus Recommendations for the Treatment of Pediatric NMDAR Antibody Encephalitis. Neurol Neuroimmunol Neuroinflamm. 2021;8(5):e1052. Published 2021 Jul 22. https://doi.org/10.1212/nxi.0000000000001052
5. Hardy D. Autoimmune Encephalitis in Children. Pediatr Neurol. 2022;132:56–66. https://doi.org/10.1016/j.pediatrneurol.2022.05.004
6. Dalmau J, Graus F. Diagnostic criteria for autoimmune encephalitis: utility and pitfalls for antibody-negative disease. Lancet Neurol. 2023;22(6):529–540. https://doi.org/10.1016/s1474-4422(23)00083-2
7. Papi C, Milano C, Spatola M. Mechanisms of autoimmune encephalitis. Curr Opin Neurol. 2024;37(3):305–315. https://doi.org/10.1097/wco.0000000000001270
8. Shang H, Shen X, Yu X, et al. B-cell targeted therapies in autoimmune encephalitis: mechanisms, clinical applications, and therapeutic potential. Front Immunol. 2024;15:1368275. Published 2024 Mar 18. https://doi.org/10.3389/fimmu.2024.1368275
9. Chen J, Qin M, Xiang X, et al. Lymphocytes in autoimmune encephalitis: Pathogenesis and therapeutic target. Neurobiol Dis. 2024;200:106632. https://doi.org/10.1016/j.nbd.2024.106632
10. Räuber S, Schroeter CB, Strippel C, et al. Cerebrospinal fluid proteomics indicates immune dysregulation and neuronal dysfunction in antibody associated autoimmune encephalitis. J Autoimmun. 2023;135:102985. https://doi.org/10.1016/j.jaut.2022.102985
11. Sanvito F, Pichiecchio A, Paoletti M, et al. Autoimmune encephalitis: what the radiologist needs to know. Neuroradiology. 2024;66(5):653–675. https://doi.org/10.1007/s00234-024-03318-x
12. Olivé-Cirera G, Fonseca E, Chen LW, et al. Differential diagnosis and comparison of diagnostic algorithms in children and adolescents with autoimmune encephalitis in Spain: a prospective cohort study and retrospective analysis. Lancet Neurol. 2025;24(1):54–64. https://doi.org/10.1016/s1474-4422(24)00443-5
13. Guasp M, Dalmau J. Autoimmune Encephalitis. Med Clin North Am. 2025;109(2):443–461. https://doi.org/10.1016/j.mcna.2024.09.001
14. de Bruijn MAAM, Aarsen FK, van Oosterhout MP, et al. Long-term neuropsychological outcome following pediatric anti-NMDAR encephalitis. Neurology. 2018;90(22):e1997–e2005. https://doi.org/10.1212/wnl.0000000000005605
15. Nguyen L, Yang JH, Goyal S, et al. A systematic review and quantitative synthesis of the long-term psychiatric sequelae of pediatric autoimmune encephalitis. J Affect Disord. 2022;308:449–457. https://doi.org/10.1016/j.jad.2022.04.027
16. Cheng L, Jia B, Wang C, et al. Immunotherapy for autoimmune encephalitis. Cell Death Discov. 2025;11(1):207. Published 2025 Apr 29. https://doi.org/10.1038/s41420-025-02459-z
17. Štěpánová E, Doležalová I, Sagan J, et al. Autoimunitní onemocnění centrálního nervového syndromu v dětském věku – diagnostika (MRI CNS), klinický průběh a léčba. Epidemiologie, mikrobiologie, imunologie. Epidemiol Mikrobiol Imunol. 2025;74(1):65–75. https://doi.org/10.61568/emi/11-6445/20250128/139688
18. Lee S, Kim HD, Lee JS, et al. Clinical Features and Treatment Outcomes of Seronegative Pediatric Autoimmune Encephalitis. J Clin Neurol. 2021;17(2):300–306. https://doi.org/10.3988/jcn.2021.17.2.300
19. Zhou X, Luo X, He Z, et al. Efficacy of dexamethasone combined with intravenous immunoglobulin for the treatment of pediatric autoimmune encephalitis. Front Neurol. 2025;16:1512908. Published 2025 Mar 12. https://doi.org/10.3389/fneur.2025.1512908
20. Dalakas MC. Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. Neurology. 1998;51(6 Suppl 5):S2–S8. https://doi.org/10.1212/wnl.51.6_suppl_5.s2
21. Hill M, Iro M, Sadarangani M, et al. Intravenous immunoglobulin treatment in childhood encephalitis (IgNiTE): a randomised controlled trial. BMJ Open. 2023;13(9):e072134. https://doi.org/10.1136/bmjopen-2023-072134

22. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. J Neurol Neurosurg Psychiatry. 2021;92(7):757–768. https://doi.org/10.1136/jnnp-2020-325300
23. Smets I, Titulaer MJ. Antibody Therapies in Autoimmune Encephalitis. Neurotherapeutics. 2022;19(3):823–831. https://doi.org/10.1007/s13311-021-01178-4
24. Yang J, Liu X. Immunotherapy for Refractory Autoimmune Encephalitis. Front Immunol. 2021;12:790962. Published 2021 Dec 16. https://doi.org/10.3389/fimmu.2021.790962
25. Thaler FS, Zimmermann L, Kammermeier S, et al. Rituximab Treatment and Long-term Outcome of Patients With Autoimmune Encephalitis: Real-world Evidence From the GENERATE Registry. Neurol Neuroimmunol Neuroinflamm. 2021;8(6):e1088. Published 2021 Oct 1. https://doi.org/10.1212/nxi.0000000000001088
26. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391–404. https://doi.org/10.1016/s1474-4422(15)00401-9
27. Zhang D, Li B, Li J, et al. Efficacy and Safety of Rituximab Treatment for Anti-N-Methyl-d-Aspartate Receptor Encephalitis Without Tumor in Children. Pediatr Neurol. 2024;161:85–90. https://doi.org/10.1016/j.pediatrneurol.2024.09.001
28. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014;83(2):142–150. https://doi.org/10.1212/wnl.0000000000000570
29. Dou X, Li D, Wu Y, et al. Efficacy and Safety of Rituximab in Chinese Children With Refractory Anti-NMDAR Encephalitis. Front Neurol. 2020;11:606923. Published 2020 Dec 14. https://doi.org/10.3389/fneur.2020.606923
30. Shin YW, Lee ST, Park KI, et al. Treatment strategies for autoimmune encephalitis. Ther Adv Neurol Disord. 2017;11:1756285617722347. Published 2017 Aug 16. https://doi.org/10.1177/1756285617722347
31. Stingl C, Cardinale K, van Mater H. An Update on the Treatment of Pediatric Autoimmune Encephalitis. Curr Treat Options in Rheum. 2018;4:14–28. https://doi.org/10.1007/s40674-018-0089-z
32. Garg D, Mohammad SS, Sharma S. Autoimmune Encephalitis in Children: An Update. Indian Pediatr. 2020;57(7):662–670.
33. Lee WJ, Lee ST, Moon J, et al. Tocilizumab in Autoimmune Encephalitis Refractory to Rituximab: An Institutional Cohort Study. Neurotherapeutics. 2016;13(4):824–832. https://doi.org/10.1007/s13311-016-0442-6
34. Yang JH, Liu EN, Nguyen L, et al. Survival Analysis of Immunotherapy Effects on Relapse Rate in Pediatric and Adult Autoimmune Encephalitis. Neurology. 2023;101(22):e2300-e2313. Published 2023 Nov 27. https://doi.org/10.1212/wnl.0000000000207746
35. Nosadini M, Eyre M, Molteni E, et al. Use and Safety of Immunotherapeutic Management of N-Methyl-d-Aspartate Receptor Antibody Encephalitis: A Meta-analysis. JAMA Neurol. 2021;78(11):1333–1344. https://doi.org/10.1001/jamaneurol.2021.3188
36. Dinoto A, Ferrari S, Mariotto S. Treatment Options in Refractory Autoimmune Encephalitis. CNS Drugs. 2022;36(9):919–931. https://doi.org/10.1007/s40263-022-00943-z
37. Di Majo D, Cacciabaudo F, Accardi G, et al. Ketogenic and Modified Mediterranean Diet as a Tool to Counteract Neuroinflammation in Multiple Sclerosis: Nutritional Suggestions. Nutrients. 2022;14(12):2384. Published 2022 Jun 8. https://doi.org/10.3390/nu14122384
38. Dyńka D, Kowalcze K, Paziewska A. The Role of Ketogenic Diet in the Treatment of Neurological Diseases. Nutrients. 2022;14(23):5003. Published 2022 Nov 24. https://doi.org/10.3390/nu14235003
39. Perulli M, Cicala G, Turrini I, et al. Fighting autoinflammation in FIRES: The role of interleukins and early immunomodulation. Epilepsy Behav Rep. 2022;18:100531. Published 2022 Feb 22. https://doi.org/10.1016/j.ebr.2022.100531
40. Kolb H, Kempf K, Röhling M, et al. Ketone bodies: from enemy to friend and guardian angel. BMC Med. 2021;19(1):313. Published 2021 Dec 9. https://doi.org/10.1186/s12916-021-02185-0
41. Sivathanu D, Kewalramani D, Kumar Manokaran R. Favorable response to classic ketogenic diet in a child with anti-GAD 65 antibody mediated super refractory status epilepticus. Epilepsy Behav Rep. 2022;19:100557. Published 2022 Jun 7. https://doi.org/10.1016/j.ebr.2022.100557
42. Martin-McGill KJ, Bresnahan R, Levy RG, et al. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020;6(6):CD001903. Published 2020 Jun 24. https://doi.org/10.1002/14651858.cd001903.pub5