doi.org/10.36721/PJPS.2026.39.7.199.1

REVIEW

Immunity-oriented drug strategies for viral encephalitis: Acyclovir, antiepileptics and corticosteroids in neurological intensive care

Liping Yu and Cheng Liang*
Neurological Intensive Care Unit, Lanzhou University Second Hospital, Lanzhou 730030, Gansu Province, China

Abstract: Viral encephalitis (VE), is a life-threatening neurological disorder marked by inflammation of brain parenchyma, driven by direct viral cytotoxicity and host immune-mediated injury. Globally, its incidence ranges from 1.4 to 13.8 cases per 100,000 individuals annually, with significant morbidity and mortality in endemic regions such as India, among children. Neurotropic viruses including herpes simplex virus (HSV), Japanese encephalitis virus (JEV) and West Nile virus, enter central nervous system via hematogenous or neuronal routes, triggering viral replication, cytokine release and blood–brain barrier disruption, resulting in seizures, cerebral edema and long-term neurological deficits. Current management in neurological intensive care relies on immunity-oriented strategies: Acyclovir as first-line antiviral for HSV and varicella-zoster virus, antiepileptics to control seizures and limit secondary neuronal injury and corticosteroids to modulate harmful neuroinflammation and cerebral edema. Emerging therapies, including novel antivirals (favipiravir, remdesivir, brincidofovir), monoclonal antibodies, cytokine inhibitors (tocilizumab, anakinra) and B-cell/plasma cell-targeted agents (rituximab, daratumumab), offer promise by simultaneously addressing viral replication and immune dysregulation. Personalized biomarker-guided integrating pathogen-directed and host-targeted therapies may optimize outcomes, reduce neuronal injury and improve recovery. This review underscores the importance of a multidimensional, immunity-oriented treatment paradigm, highlighting both established and emerging strategies to enhance prognosis and long-term neurological functions in patients with viral encephalitis.

Keywords: Acyclovir; Antiepileptics; Corticosteroids; Immunity-oriented therapy; Neuroinflammation; Viral encephalitis

Submitted on 21-10-2025 – Revised on 24-11-2025 – Accepted on 30-12-2025

INTRODUCTION

Viral encephalitis is a severe and potentially life-threatening condition characterized by inflammation of the brain tissue, or brain parenchyma, due to viral infections. It presents a significant global health challenge, with varying prevalence and impact across different regions. In India, the burden of viral encephalitis is notably high, with frequent outbreaks and substantial mortality, particularly among children (Boucher *et al.,* 2017). Understanding the pathophysiology of viral encephalitis is crucial for developing effective treatment strategies. This review aims to explore the mechanisms underlying viral encephalitis and discuss immunity-oriented drug strategies, including antiviral agents, corticosteroids and antiepileptic drugs, in the management of this condition (Ibrahim *et al.,* 2025). The global incidence of viral encephalitis varies, with reported rates ranging from 1.4 to 13.8 cases per 100,000 individuals per year (Claudette *et al.,* 2017). Herpes simplex virus (HSV) remains the most common cause of sporadic viral encephalitis. In contrast, arboviruses such as Japanese encephalitis virus (JEV) and West Nile virus contribute significantly to the disease burden in endemic regions (Al-Obaidi *et al.,* 2017). In India, the situation is particularly concerning. Between 2008 and 2014, there were more than 44,000 cases and nearly 6,000 deaths from encephalitis, especially in Uttar Pradesh and Bihar (Beckham *et al.,* 2021). Well-recognized etiological agents such as HSV, VZV, JEV and West Nile virus are discussed in detail due to their significant clinical and epidemiological burden. Opportunistic pathogens, including CMV, EBV and HHV-6, which are particularly relevant in immunocompromised populations, are also incorporated in Table 1.

Viral encephalitis arises from viral invasion, replication and the host immune response, leading to CNS inflammation and neuronal damage. Neurotropic viruses like HSV, JEV and West Nile virus enter the brain via hematogenous spread, crossing the blood–brain barrier through endothelial infection, transcytosis, or immune cell "Trojan horse" mechanisms or via neuronal retrograde transport (Wnek *et al.,* 2015). Within the CNS, viral replication causes neuronal death and activates glial cells, releasing pro-inflammatory cytokines that disrupt the BBB, promote edema and amplify injury (Fillatre *et al.,* 2017). While immune responses aid viral clearance, cytotoxic T-cell activity and excessive cytokine release contribute to oxidative stress, excitotoxicity and further neuronal dysfunction. Clinically, this manifests as fever, headache, seizures and altered consciousness, with severe cases progressing to coma. Long-term effects include cognitive decline, motor deficits and behavioural changes due to persistent neuronal loss and network disruption

**Corresponding author:* e-mail: snicu0504907@hotmail.com

(Reed *et al.,* 2019**)**. The mechanism of viral encephalitis is shown in Fig. 1.

The pathophysiology of viral encephalitis highlights the dual role of viral replication and host immune responses in driving neuronal injury, emphasizing the need for timely and targeted therapies (Marcocci *et al.*, 2022). Traditionally, management has relied on early intravenous acyclovir the gold standard for HSV encephalitis supported by intensive care measures, including seizure control with antiepileptics and reduction of cerebral edema. In select cases, corticosteroids are employed to modulate inflammation, while IVIG and plasmapheresis are used in autoimmune or para-infectious forms (Hidayat *et al.,* 2013). Limitations of these approaches have led to the development of emerging therapies, such as B-cell–depleting agents (rituximab, inebilizumab), cytokine inhibitors (tocilizumab, anakinra) and plasma-cell–targeting drugs (bortezomib, daratumumab) for refractory autoimmune encephalitis (Fugier *et al.,* 2014). Monoclonal antibodies against neurotropic viruses, repurposed antivirals like favipiravir and remdesivir and host-directed immunomodulators are also being explored to directly neutralize pathogens and fine-tune immune responses (Sacks *et al.,* 2011). These evolving strategies reflect a shift from purely symptomatic and antiviral management toward integrated pathogen- and immune-targeted therapies, aiming to prevent irreversible neurological damage and improve long-term outcomes. In neurological intensive care, immunity-oriented drug strategies primarily rely on a three-pronged approach: acyclovir, antiepileptics and corticosteroids (Lopes Pinheiro *et al.,* 2020). Acyclovir inhibits viral DNA polymerase, significantly reducing mortality and long-term sequelae in HSV encephalitis. Antiepileptics are essential to control seizures and status epilepticus, which can otherwise exacerbate neuronal injury. Corticosteroids, used selectively, reduce cerebral edema and dampen harmful immune-mediated inflammation within the CNS (Gao *et al.,* 2020).

The combined use of these agents represents both pathogen-directed and host-directed strategies, aiming to limit viral replication, stabilize neural activity and minimize immune-induced damage (Garber *et al.,* 2019). We focus on these drugs because they constitute the current standard of care, provide a foundation for newer immunomodulatory approaches and illustrate how integrated therapy can influence prognosis and long-term neurological outcomes. In summary, understanding the interplay between viral replication and host immune responses underscores the critical role of acyclovir, antiepileptics and corticosteroids in neurological intensive care, forming a cornerstone for both current practice and future immunomodulatory strategies.

Immunity-oriented drug strategies for viral encephalitis

The management of VE requires a dual approach that targets both the pathogen and the host's immune response. The combined use of antivirals, antiepileptics and corticosteroids represents an integrated strategy: antivirals directly suppress viral replication, antiepileptics stabilize neuronal activity and prevent secondary neuronal injury caused by seizures and corticosteroids modulate harmful immune responses, thereby reducing neuroinflammation (Garber *et al.,* 2019). These agents form the current standard of care and provide a framework for developing novel immunomodulatory therapies aimed at improving prognosis and long-term neurological outcomes. Understanding the interplay between viral replication and host immunity is critical to optimizing treatment strategies in the neurological intensive care unit (NICU) (Bai *et al.,* 2010).

In addition to standard antiviral and supportive treatments, recent research has highlighted the growing role of immunotherapy in the management of viral encephalitis. Since many neurotropic viruses trigger excessive immune activation leading to neuronal injury, immunomodulatory strategies aim to control both infection-driven inflammation and secondary autoimmune responses (Looker *et al.,* 2017). Emerging approaches include monoclonal antibodies with antiviral or anti-inflammatory properties, cytokine inhibitors targeting IL-6, TNF-α, and other key mediators of neuroinflammation and B-cell– or plasma-cell–directed therapies such as rituximab for refractory or immune-mediated cases (Garber *et al.,* 2019). Interferon-based therapies and novel immunomodulators targeting innate immune pathways are also under investigation. Incorporating these immunotherapeutic options may offer a more comprehensive and targeted approach to reducing neuronal damage and improving long-term outcomes in viral encephalitis (Soria *et al.,* 2010).

Antiviral therapy: Acyclovir

Acyclovir is a synthetic nucleoside analogue that selectively targets viral DNA polymerase and serves as the first-line therapy for HSV and varicella-zoster virus (VZV) encephalitis (Chou *et al.,* 2018). After phosphorylation by viral thymidine kinase, acyclovir is converted into its active triphosphate form, which competitively inhibits viral DNA polymerase and incorporates into viral DNA, leading to chain termination. This mechanism effectively halts viral replication in infected neurons while sparing host cells. Early administration of acyclovir, ideally within 24–48 hours of symptom onset, is critical, as it significantly reduces mortality and the risk of long-term neurological sequelae (Chou *et al.,* 2018). In HSV encephalitis, intravenous acyclovir decreases mortality from over 70% in untreated cases to approximately 20–30%, while in VZV-related central nervous system infections, it is particularly beneficial in immunocompromised patients or those presenting with severe neurological symptoms. Standard adult dosing is 10 mg/kg IV every eight hours for 14–21 days, with careful adjustment in patients with renal impairment. Hydration

and monitoring of renal function are essential to minimize the risk of nephrotoxicity, which can occur due to crystal deposition in renal tubules (Le-Vinh *et al.,* 2019). Although resistance is rare, it can develop in immunocompromised patients due to mutations in viral thymidine kinase or DNA polymerase. Delayed initiation of therapy is associated with poorer outcomes, highlighting the importance of rapid diagnosis and treatment. While acyclovir directly suppresses viral replication, optimal management of viral encephalitis also requires supportive care, seizure control and, in some cases, immunomodulatory therapy. Research continues to explore combination antiviral strategies and predictive biomarkers to improve efficacy and minimize complications. As illustrated in Fig. 2, acyclovir selectively inhibits viral DNA polymerase, blocking viral replication and reducing neuronal injury in HSV/VZV encephalitis (Karamitros *et al.,* 2016).

Although acyclovir is highly effective and remains the cornerstone of HSV encephalitis therapy, its use is associated with certain adverse effects, most notably acyclovir-induced nephrotoxicity (Topalis *et al.,* 2016). The reported incidence varies from 5–20%, with higher risk observed in patients receiving high-dose therapy, the elderly, those with baseline renal impairment, or individuals who are inadequately hydrated. Nephrotoxicity typically results from crystal-induced obstructive nephropathy, in which acyclovir precipitates within renal tubules, leading to an acute rise in serum creatinine, reduced urine output and, in severe cases, acute kidney injury (Thompson *et al.,* 2016). To minimize this risk, adequate intravenous hydration, avoidance of rapid infusion rates and regular monitoring of renal function (every 24–48 hours) are recommended throughout therapy. Dose adjustment according to creatinine clearance is essential, as failure to modify dosing in renally impaired patients significantly increases toxicity (Kimberlin *et al.,* 2024). In most cases, nephrotoxicity is reversible upon dose reduction or discontinuation of the drug, along with supportive management. Rarely, acyclovir may cause neurotoxicity, presenting as confusion, tremors, or hallucinations, particularly in patients with renal dysfunction due to drug accumulation. Early recognition, prompt dose adjustment and vigilant monitoring help ensure that the benefits of acyclovir therapy outweigh the risks, enabling safe and effective management of viral encephalitis (Becker *et al.,* 2018).

Antiepileptics in neurological ICU

Seizures are a frequent and serious complication in patients with viral encephalitis, resulting from direct viral neuronal injury, inflammatory cytokine release and disruption of neural networks. Effective seizure management is critical to prevent secondary neuronal damage and reduce morbidity (Perera *et al.,* 2021). Antiepileptic drugs (AEDs) are therefore a cornerstone of supportive care in the neurological ICU. Commonly used agents include levetiracetam, valproate and phenytoin, each with distinct mechanisms of action. Levetiracetam binds to synaptic vesicle protein 2A (SV2A) to modulate neurotransmitter release and reduce neuronal excitability, while valproate enhances gamma-aminobutyric acid (GABA)-mediated inhibition and may also exert mild anti-inflammatory effects. Phenytoin acts primarily by blocking voltage-gated sodium channels, stabilizing hyperexcitable neuronal membranes. Some studies suggest that certain AEDs, particularly levetiracetam and valproate, may modulate microglial activation and reduce neuroinflammatory responses, although clinical evidence remains limited. Dosing and monitoring are essential to optimize efficacy and minimize toxicity: levetiracetam is generally well tolerated with minimal drug interactions, valproate requires monitoring of liver function and platelet counts due to hepatotoxicity and thrombocytopenia and phenytoin requires careful serum-level monitoring to avoid arrhythmias, gingival hyperplasia and drug interactions (Perera *et al.,* 2021). Integrating AED therapy into VE management not only controls seizures but may also influence inflammatory pathways, contributing to improved neurological outcomes. Drugs for antiepileptics are outlined in table 2.

Corticosteroids

Corticosteroids have long been considered as adjunctive therapy in neuroinflammatory conditions due to their broad anti-inflammatory and immunosuppressive properties. In the context of viral encephalitis (VE), their role is complex and remains a subject of ongoing debate (Depla *et al.,* 2022). Corticosteroids act at multiple levels of the immune response. They inhibit transcription of proinflammatory cytokines such as IL-1β, TNF-α and IL-6, which are heavily implicated in neuronal injury during viral encephalitis. By reducing leukocyte adhesion and migration across the blood–brain barrier, corticosteroids limit immune cell infiltration into the central nervous system (CNS). Additionally, they stabilize vascular and neuronal membranes, thereby decreasing cerebral edema and reducing intracranial pressure. These effects are particularly valuable in cases of severe cerebral swelling, where uncontrolled inflammation can be as damaging as viral replication itself. (Chan-Tack *et al.,* 2021).

The use of corticosteroids in VE is supported by anecdotal evidence, case series and small observational studies, but randomized controlled trial data remain sparse and inconclusive. Some studies suggest benefits in reducing cerebral edema and improving neurological outcomes, especially in severe HSV encephalitis with high intracranial pressure (Griffiths and Reeves, 2021). Conversely, concerns exist that early or excessive immunosuppression may facilitate viral replication and worsen the primary infection (Leung *et al.,* 2019). This duality has made corticosteroid use controversial, with guidelines recommending individualized use rather than

universal application. Clinical scenarios where corticosteroids may be useful:

1. *Severe cerebral edema with raised intracranial pressure* – to prevent herniation and secondary ischemic injury (El Helou and Razonable, 2019).
2. *Post-infectious autoimmune encephalitis* – where immune-mediated pathology predominates rather than active viral replication.
3. *Refractory cases* – in patients who fail to improve on standard antiviral therapy and supportive care (Chen *et al.,* 2021).

When used, corticosteroids are generally given as adjunct therapy alongside antivirals. Dexamethasone is commonly preferred due to its potent CNS penetration and long half-life. Recommended dosing is 0.15–0.3 mg/kg/day IV for 3–5 days, though regimens vary across clinical settings. Initiation after or concomitant with antiviral therapy is strongly advised to ensure viral replication is already under control. Recent research suggests corticosteroids may also act by modulating microglial activation and attenuating excitotoxicity, offering neuroprotective effects beyond classical immunosuppression. Ongoing clinical trials are investigating their role in combination with antiviral and other immunomodulatory therapies, particularly in differentiating subgroups of patients who may benefit (e.g., severe edema, post-viral autoimmune encephalitis (Bai *et al.,* 2010). Biomarker-guided therapy, using cytokine profiles or imaging markers of inflammation, could eventually help stratify patients and optimize corticosteroid use. Corticosteroids increase the risk of secondary bacterial and fungal infections, can delay viral clearance and may worsen outcomes if administered too early in the course of illness. They may also cause metabolic complications, including hyperglycemia, gastrointestinal bleeding and psychiatric disturbances, which must be closely monitored in critically ill patients. As shown in fig. 3**,** corticosteroids exert their immunomodulatory effects by suppressing the transcription of proinflammatory cytokines such as IL-1β, TNF-α and IL-6, thereby reducing leukocyte infiltration across the blood–brain barrier, limiting cerebral edema and preserving neuronal integrity. This visual representation highlights the transition from a proinflammatory, neurotoxic state to a more controlled and protective CNS environment following corticosteroid therapy.

Clinical challenges in current management of viral encephalitis

Despite advances in neurocritical care and the availability of effective antivirals, the management of viral encephalitis continues to present substantial challenges. Mortality and morbidity remain high, with many survivors experiencing long-term neurological sequelae such as cognitive impairment, behavioural changes and epilepsy. The barriers to effective management can be broadly categorized into diagnostic delays, therapeutic limitations, drug-related complications and critical care constraints (Duerlund *et al*., 2025).

Delayed diagnosis and treatment initiation

A major obstacle in VE management is that its early-stage symptoms are fever, headache and altered sensorium, but seizures only appear after significant neuronal injury (Gundamraj and Hasbun, 2023). Neuroimaging and cerebrospinal fluid (CSF) analysis are important diagnostic tools in the early phase. Although the polymerase chain reaction (PCR) significantly improves accuracy (Yang *et al.,* 2023). As a result, treatment with acyclovir is often delayed, which directly correlates with poorer outcomes. Particularly, if we talk about the limitation in antiviral therapy, it is that Acyclovir, the gold standard for HSV encephalitis, has little to no activity against major arboviruses such as JEV and West Nile virus. Furthermore, acyclovir must be administered intravenously, requiring hospitalization and monitoring. Nephrotoxicity is a known risk, particularly in dehydrated or renally impaired patients and acyclovir resistance, though uncommon, is increasingly reported in immunocompromised individuals. complicating therapy and necessitating alternative antivirals that may be less effective or more toxic (Kalil Alves de Lima *et al.,* 2020).

Challenges in seizure management

Seizures are a common and serious complication of viral encephalitis (VE), occurring in approximately 60–70% of patients and frequently presenting as status epilepticus. Antiepileptic drugs (AEDs) such as levetiracetam, valproate, and phenytoin are routinely used in the neurological intensive care unit; however, their use in critically ill patients presents several challenges. Phenytoin requires close serum-level monitoring and is associated with significant risks, including cardiac arrhythmias and drug–drug interactions (Zhuangzhuang et al., 2019). Valproate, while effective as a broad-spectrum AED, carries risks of hepatotoxicity and thrombocytopenia, limiting its use in patients with hepatic dysfunction or coagulopathy. Levetiracetam is generally well tolerated and favored for its minimal drug interactions, but it may cause neuropsychiatric adverse effects such as agitation, irritability, and mood disturbances.

Importantly, none of the currently available AEDs are pathogen-specific, and their potential effects on neuroinflammation remain poorly defined in clinical practice. In parallel, corticosteroids—often used to reduce cerebral edema and suppress harmful inflammatory responses—pose additional challenges. Although corticosteroids may lower intracranial pressure, concerns persist regarding their potential to impair viral clearance. Evidence from randomized controlled trials remains limited and inconsistent, with some studies demonstrating reduced cerebral edema, while others report increased risks of secondary infections and prolonged viral persistence. Moreover, the lack of standardized protocols regarding the timing, dosing, and duration of corticosteroid therapy has resulted in substantial variability in clinical practice worldwide (Charise *et al*., 2019).

Table 1: Major, emerging and region-specific viral causes of encephalitis

S.No.	Virus	Classification	Geographical relevance	Clinical significance
1.	Herpes simplex virus (HSV-1, HSV-2)	Established major cause	Global	Most common cause of sporadic encephalitis
2.	Varicella-zoster virus (VZV)	Established	Global	Important in adults, immunocompromised
3.	Japanese encephalitis virus (JEV)	Arbovirus	India, Southeast Asia	Major cause in endemic regions, high mortality
4.	West Nile virus (WNV)	Arbovirus	Americas, Europe, Asia	Neuroinvasive disease, elderly at risk
5.	Zika virus	Emerging arbovirus	Americas, Southeast Asia	Neurological complications, congenital infection
6.	Chikungunya virus	Emerging arbovirus	India, Africa, Americas	Neurological involvement in outbreaks
7.	Dengue virus	Emerging arbovirus	India, Southeast Asia, Latin America	Immune-mediated encephalitis reported
8.	Enteroviruses (EV-71, coxsackie)	Established	Global, Asia	Major pediatric cause of encephalitis
9.	Rabies virus	Neglected zoonotic virus	Global, India high burden	Nearly 100% fatal encephalitis
10.	CMV, EBV, HHV-6	Opportunistic viruses	Global	Important in immunocompromised hosts
11.	Nipah virus	Emerging high-mortality pathogen	India (Kerala), Bangladesh	Causes severe encephalitis outbreaks
12.	Hendra virus	Emerging	Australia	Severe encephalitis and respiratory disease
13.	Mumps, measles (SSPE)	Vaccine-preventable viruses	Global	Rare but clinically important

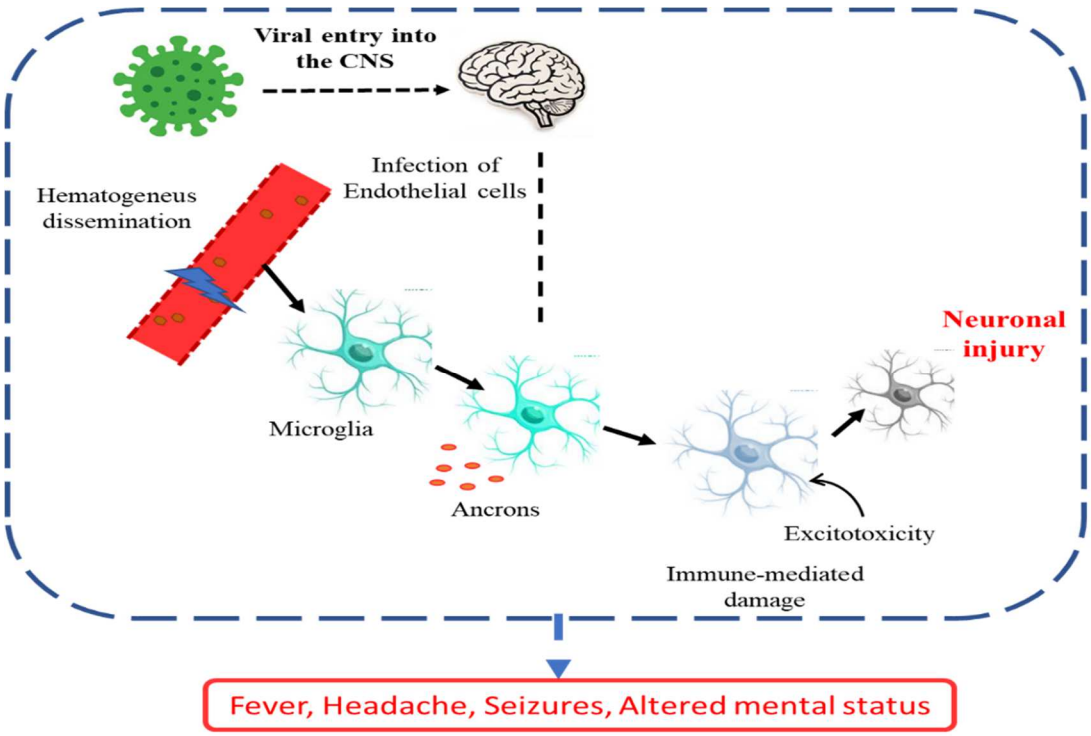

Fig. 1: Mechanism of viral encephalitis: Viral entry via blood or neurons triggers replication, immune activation, BBB disruption, edema, and neuronal injury, leading to seizures and long-term deficits.

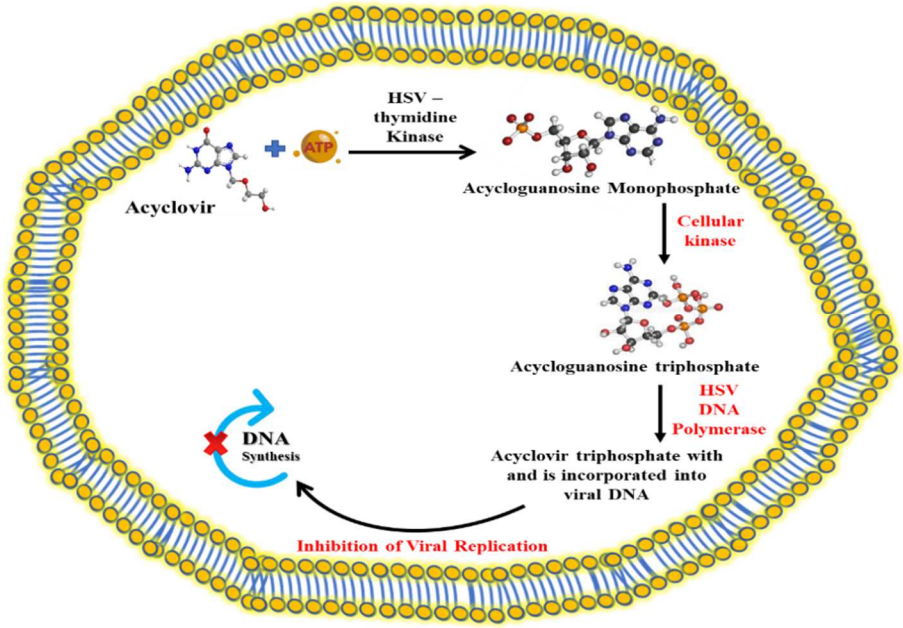

Fig. 2: Mechanism of action of acyclovir and its clinical effects in HSV/VZV encephalitis

Table 2: Antiepileptic drugs in viral encephalitis

S.No.	Drug	Mechanism of action	Typical dose (Adult)	Neuroinflammatory effects	Key adverse effects
1.	Levetiracetam	Modulates SV2A, reduces excitatory neurotransmission	500–1500 mg IV/PO twice daily	Possible microglial modulation	Somnolence, mood changes
2.	Valproate	Increases GABA, reduces neuronal excitability	20–30 mg/kg IV loading, then 10–15 mg/kg/day	Potential cytokine reduction	Hepatotoxicity, thrombocytopenia
3.	Phenytoin	Sodium channel blockade	15–20 mg/kg IV loading, then 100 mg TID	Limited evidence	Arrhythmia, gingival hyperplasia, interactions

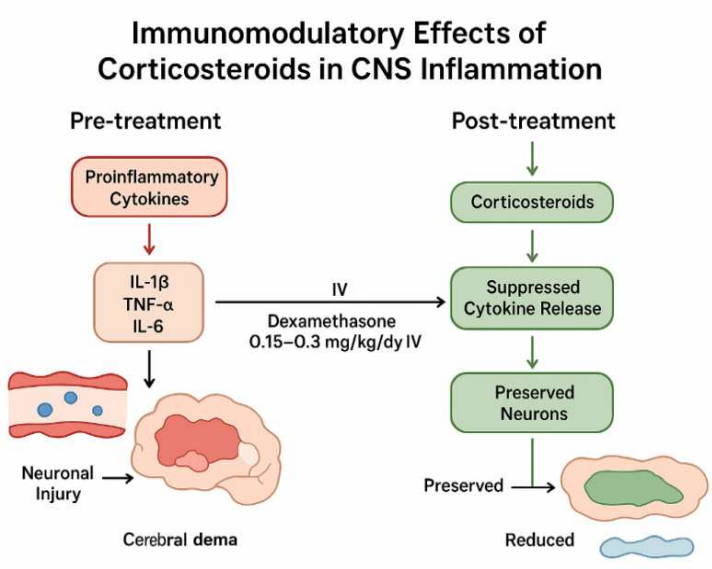

Fig. 3: Immunomodulatory effects of corticosteroids in CNS inflammation

Table 3: Clinical challenges and considerations in the management of viral encephalitis

S.No.	Challenge	Description	Clinical implications
1.	Delayed diagnosis	Non-specific symptoms, overlapping with other CNS infections.	Late initiation of antivirals increases morbidity and mortality.
2.	Limited antiviral coverage	Acyclovir mainly covers HSV/VZV; limited agents for other viral pathogens.	Treatment gaps for emerging or rare viruses; need for broader-spectrum agents.
3.	Seizure burden	High incidence of seizures in VE, requiring continuous EEG monitoring.	Increases risk of neuronal damage, ICU stay, and poor neurological outcomes.
4.	Corticosteroid controversy	Conflicting evidence on benefits in VE (edema vs. viral replication concerns).	Requires careful case-based decision-making; best used as adjunct therapy.
5.	ICU constraints	Limited resources for prolonged ICU care in severe VE.	Impacts management of ventilation, hemodynamics, and seizure control.
6.	Long-term sequelae	Cognitive, behavioral, and neurological deficits common in survivors.	Necessitates rehabilitation, neuropsychological follow-up, and long-term supportive care.

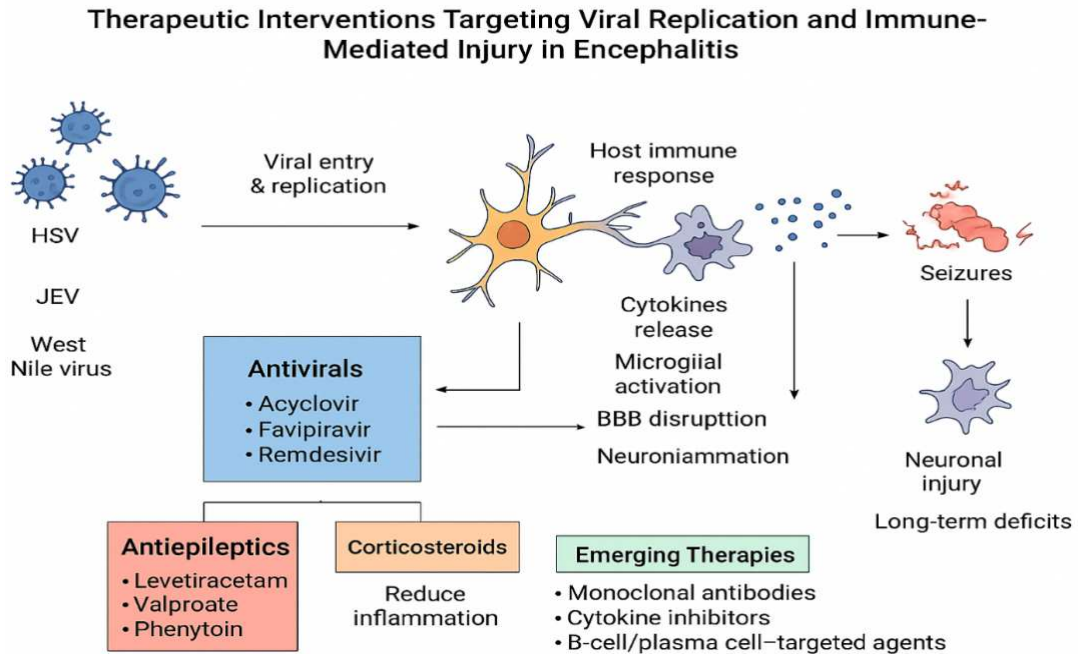

Fig. 4: Therapeutic interventions targeting viral replication and immune-mediated injury in encephalitis.

Critical care and resource limitations

VE often requires intensive supportive care, including ventilation, hemodynamic stabilization and management of multi-organ dysfunction. In LMICs, where outbreaks of JEV and other arboviruses are common, limited ICU capacity, ventilator availability and advanced neuroimaging access significantly worse mortality and long-term outcomes in endemic regions compared to high-income countries (Joseph, *et al*., 2017).

Long-term sequelae and rehabilitation

Despite appropriate treatment, many VE survivors experience neurological complications such as memory deficits, learning difficulties, psychiatric disorders and epilepsy. These long-term effects place significant strain on families and healthcare systems, especially in settings with limited access to rehabilitation services. The absence of structured follow-up and dedicated neurocognitive rehabilitation programs remains a major gap in VE management (Marrazzo *et al.,* 2021). As summarized in table 3, challenges including delayed diagnosis, limited antiviral options, high seizure burden, uncertain corticosteroid use and critical care constraints complicate acute management and contribute to chronic sequelae like cognitive impairment, behavioural changes and epilepsy. This highlights the need for pathogen-specific therapies and well-defined rehabilitation strategies to improve long-term outcomes (Depla *et al.,* 2023).

Emerging immunomodulatory and antiviral therapies

Given the limited effectiveness of current treatments, newer antiviral and immunomodulatory strategies are being explored to improve outcomes in VE (Kimberlin *et al.,* 2024).

Table 4: Emerging therapies in viral encephalitis

S.No.	Category	Examples	Mechanism	Clinical notes
1.	Novel antivirals	Favipiravir, Remdesivir, Brincidofovir	Inhibit viral RNA/DNA polymerases	Early evidence of activity; limited VE-specific trials
2.	Monoclonal antibodies	mAbs against rabies, JE, West Nile	Neutralize viral glycoproteins; block neuronal entry	Experimental, under clinical evaluation
3.	Cytokine inhibitors	Tocilizumab, Anakinra	Block IL-6 or IL-1 signaling → dampen cytokine storm	Case-based evidence; infection risk remains
4.	B-cell /Plasma cell–targeted	Rituximab, Daratumumab	Reduce autoantibody-producing cells	Effective in autoimmune/post-infectious encephalitis
5.	Adjunctive immunotherapies	IVIG, Plasmapheresis, Interferons	Immune modulation, antibody clearance, antiviral signaling	Supportive role; outcomes variable

VE caused by HSV, JEV, and West Nile virus progresses through viral entry, replication, and activation of the host immune response, leading to cytokine release, microglial activation, blood–brain barrier disruption, and neuronal injury that contributes to seizures and long-term neurological deficits (Thompson, *et al*, 2016). Current treatment focuses on reducing viral replication with antivirals (acyclovir, favipiravir, remdesivir), controlling seizures with antiepileptics (levetiracetam, valproate, phenytoin) and limiting inflammation with corticosteroids. Emerging approaches, including monoclonal antibodies, cytokine inhibitors, and B-cell/plasma cell-targeted therapies, aim to modulate harmful immune responses and prevent further neuronal damage.

Table 5: Recent trials and studies for emerging therapies

S.No.	Therapy	Clinical trial	Model	Key findings relevant to encephalitis / CNS	Limitations
1.	Favipiravir	Antiviral effect against Chandipura virus (CHPV) – in vitro + in vivo (NIV, India)	Mouse model of CHPV infection (causes encephalitis in children)	Oral favipiravir (300 mg/kg/day) until Day 7 post-infection achieved 100% survival in mice and reduced viral load *in-vitro*, indicating potential against encephalitic RNA viruses. (PubMed)	Preclinical only; human trials for encephalitis lacking; CNS penetration and pediatric dosing unknown.
2.	Favipiravir	Ebinur Lake Virus infection in mice (MDPI)	Lethal BALB/c mouse model of an encephalitic RNA virus	Favipiravir treatment significantly prolonged survival. (MDPI)	Preclinical; translation to humans, including CNS bioavailability, uncertain.
3.	Favipiravir	COVID-19 / pneumonia clinical trials (PLATCOV, FAVID)	Adults with mild/moderate COVID-19	Mixed outcomes: sometimes shortened recovery or improved symptoms; viral clearance not consistently significant. (BioMed Central)	Respiratory infections; CNS involvement minimal; relevance to encephalitis uncertain.
4.	Rituximab	Meta-analysis: second-line therapy in Autoimmune Encephalitis (AE)	277 AE patients across 14 studies	Favorable prognosis in ~80% of refractory AE cases; earlier treatment (<180 days) and younger patients (<18) associated with better outcomes. (ScienceDirect)	Focused on autoimmune encephalitis; not directly antiviral; safety during acute viral phase unclear.
5.	Rituximab	GENERATE Registry (Germany)	Patients with NMDAR-AE, LGI1, CASPR2, GAD65	Associated with improved long-term outcomes and earlier initiation benefits in NMDAR-AE. (PubMed)	Autoimmune encephalitis cohort; timing and patient selection crucial; viral replication phase not addressed.
6.	Tocilizumab	Institutional cohort in AE refractory to Rituximab	AE patients failing first- and second-line therapy	Better functional outcomes (mRS ≤2) at follow-up compared to observation; may benefit hyperinflammatory or delayed immune-mediated pathology. (PubMed)	Retrospective, small sample size; infection risk; not specific to viral encephalitis.
7.	Tocilizumab	Case reports in Limbic Encephalitis with anti-CASPR2 Abs	Single/few patients with refractory AE	Improvement in neurological symptoms and overall function reported. (Wiley Online Library)	Low-level evidence; heterogeneous dosing and timing; no RCTs.

Broad-spectrum antivirals such as favipiravir, remdesivir and brincidofovir show potential CNS penetration and activity against multiple RNA and DNA viruses, though robust VE-specific evidence is still lacking. Monoclonal antibodies are under investigation for rabies, Japanese encephalitis and West Nile virus by targeting viral entry mechanisms. Immunomodulators—including IL-6 inhibitors (tocilizumab), IL-1 blockers (anakinra) and B-cell–directed therapies like rituximab and daratumumab may help in hyperinflammatory or autoimmune-mediated disease. Adjunctive options such as IVIG, plasmapheresis and interferons offer additional immune modulation with variable efficacy. Overall, these pathogen- and host-directed therapies represent a promising shift in VE management, but their routine use awaits confirmation through controlled clinical trials. As summarized in table 4, emerging therapies encompass both pathogen-directed antivirals and host-targeted immunomodulators.

VE caused by HSV, JEV, and West Nile virus progresses through viral entry, replication, and activation of the host immune response, leading to cytokine release, microglial activation, blood–brain barrier disruption, and neuronal injury that contributes to seizures and long-term neurological deficits (Thompson *et al.,* 2016). Current treatment focuses on reducing viral replication with antivirals (acyclovir, favipiravir, remdesivir), controlling seizures with antiepileptics (levetiracetam, valproate, phenytoin) and limiting inflammation with corticosteroids. Emerging approaches, including monoclonal antibodies, cytokine inhibitors and B-cell/plasma cell-targeted therapies, aim to modulate harmful immune responses and prevent further neuronal damage.

Therapeutic strategies targeting viral and immune mechanisms in encephalitis

These preclinical and clinical studies, summarized in table 4, highlight the emerging landscape of antiviral and immunomodulatory strategies relevant to encephalitis. Favipiravir demonstrates promising antiviral activity against RNA viruses with CNS tropism in animal models, though human data remain limited, particularly regarding CNS penetration and pediatric dosing. Immunomodulatory agents such as rituximab and tocilizumab have shown efficacy in autoimmune-mediated encephalitis, emphasizing the importance of controlling immune dysregulation that can exacerbate neurological injury (Fig 4). Complementing this, immunomodulatory agents including rituximab and tocilizumab have demonstrated clinical benefits in autoimmune-mediated encephalitis, mitigating inflammation and promoting neurological recovery. Ongoing clinical trials and future research are critical to validate these approaches in human populations, optimize dosing and establish safety and efficacy profiles for CNS-targeted therapies**.** Together, the findings presented in table 5 of recent trials illustrate a dual therapeutic approach targeting viral replication and modulating immune responses that may inform future interventions for both viral and post-infectious encephalitis.

Standardized ICU management and antiepileptic drug considerations

Standardized neurocritical-care pathways for viral encephalitis emphasize immediate stabilization, prompt empiric antiviral therapy, rapid diagnostic testing (neuroimaging and CSF PCR), strict seizure protocols and active management of raised intracranial pressure. Protocolized seizure care follows ENLS/NCS algorithms (benzodiazepine → second-line AED → anesthetic escalation with EEG guidance), while ICP control uses head elevation, normocapnia, osmotherapy and neurosurgical input when required. Antiviral safety measures — particularly adequate IV hydration, dose adjustment by creatinine clearance and renal-function monitoring every 24–48 hours — are essential to prevent acyclovir nephrotoxicity and neurotoxicity (Atanasoff *et al.,* 2024**)**. Immunomodulatory therapies (corticosteroids, IVIG, plasmapheresis, anti-CD20 or cytokine inhibitors) are reserved for selected cases with evidence of immune-mediated injury and should be decided by a multidisciplinary team. These standardized elements can be adapted to local resources and are supported by ENLS, neurocritical-care and infectious-disease reviews and national JE/AES guidance.

Comparison of commonly used antiepileptic drugs (AEDs) in viral encephalitis further highlights the need for individualized seizure management. Levetiracetam is frequently preferred due to its favorable safety profile, minimal drug–drug interactions and absence of serum level monitoring requirements, although behavioral side effects such as agitation or mood alterations may occur. Valproate offers broad-spectrum seizure control but requires close monitoring of liver function and platelet counts due to risks of hepatotoxicity and thrombocytopenia, making it less suitable for patients with hepatic dysfunction. Phenytoin, while effective for status epilepticus, has a narrow therapeutic window, necessitating serum level monitoring and posing risks of arrhythmias, hypotension and significant drug interactions (Li *et al.,* 2024). These differences underscore the importance of selecting AEDs based on patient-specific factors, organ function and ICU resource availability, ensuring optimal seizure control while minimizing adverse events.

Future directions and key takeaways

Viral encephalitis remains a complex clinical challenge, with substantial morbidity and mortality despite established therapies such as acyclovir, antiepileptics and corticosteroids. Emerging evidence, summarized in table 5, highlights the potential of novel antiviral and immunomodulatory strategies to complement conventional care. Future research should prioritize well-designed clinical trials evaluating antivirals like favipiravir and

remdesivir in human encephalitis, with particular attention to CNS penetration, paediatric safety and optimal dosing regimens (Bock *et al.,* 2024). Immunomodulatory therapies, including rituximab, tocilizumab and other cytokine or plasma cell–targeted agents, require rigorous evaluation to define their role in both viral-triggered and autoimmune-mediated CNS injury. Personalized approaches are likely to become increasingly important. Integration of biomarker-guided therapy, such as cytokine profiling, neuroimaging markers of inflammation, or viral load assessments, may allow clinicians to tailor antiviral and immune-targeted treatments to individual patients, improving efficacy while minimizing adverse effects. Combination strategies that simultaneously address viral replication and immune dysregulation represent a promising avenue to limit neuronal injury and enhance long-term neurological recovery.

From this review, readers can take away several key lessons:

1. *Dual Pathogenesis Awareness:* Viral encephalitis involves both direct viral cytotoxicity and harmful immune responses, underscoring the need for therapies targeting both mechanisms.
2. *Early and Targeted Intervention:* Rapid initiation of antivirals, timely seizure control and judicious use of corticosteroids remain cornerstones of care and significantly influence outcomes.
3. *Emerging Therapies:* Novel antivirals, monoclonal antibodies, cytokine inhibitors and B-cell/plasma cell–directed therapies show promise but require validation in larger, controlled studies.
4. *Multidimensional Management:* Optimal care extends beyond drugs to include neurocritical support, long-term rehabilitation and monitoring for secondary complications.
5. *Future Research Priorities:* Translating preclinical findings into clinical practice will require carefully designed trials, integration of biomarkers and exploration of combination pathogen- and immune-targeted strategies.

Future progress in viral encephalitis management will depend on well-designed, multicenter clinical trials that evaluate both novel antivirals and immunomodulatory agents in diverse patient populations. Translational efforts should focus on defining optimal dosing, CNS penetration, pediatric applicability and long-term safety profiles. Integrating biomarkers, advanced neuroimaging and viral load monitoring into trial design will accelerate personalized treatment strategies. Ultimately, coordinated translational research pipelines bridging laboratory discoveries with clinical validation will be essential to establish effective combination therapies and improve neurological outcomes.

CONCLUSION

Viral encephalitis remains a significant neurological challenge, characterized by the dual impact of viral replication and immune-mediated neuronal injury. Despite advances in antiviral therapy, seizure management and supportive care, mortality and long-term neurological sequelae remain high, highlighting the limitations of conventional approaches. This review underscores the critical importance of an integrated, immunity-oriented therapeutic strategy that addresses both pathogen-driven and host-mediated mechanisms of injury. Established treatments such as acyclovir, antiepileptics and corticosteroids continue to form the foundation of care, yet emerging therapies—including novel antivirals, monoclonal antibodies, cytokine inhibitors and B-cell/plasma cell–targeted agents—offer promising avenues to improve outcomes, particularly in refractory or complex cases.

Future management of viral encephalitis will likely rely on personalized approaches that incorporate biomarkers, neuroimaging and careful patient stratification to guide therapy. Combination strategies targeting viral replication and dysregulated immune responses hold potential to minimize neuronal damage, reduce morbidity and enhance long-term recovery. Ultimately, advancing our understanding of the interplay between viral pathogens and host immunity, along with rigorous clinical evaluation of emerging therapies, will be essential to transform care, reduce mortality and improve quality of life for patients affected by this devastating condition.

Ultimately, this review emphasizes a shift from solely symptomatic or antiviral therapy toward integrated, immunity-oriented strategies, offering a roadmap for clinicians and researchers to improve both acute and long-term outcomes in patients with viral encephalitis. By understanding the interplay between viral replication and host immune responses, healthcare providers can adopt a more holistic, evidence-informed approach that minimizes neuronal injury and enhances recovery.

Acknowledgments
None

Authors' contribution
Liping Yu: Contributed to the conceptualization of the review, literature search, data interpretation and drafting of the manuscript; Cheng Liang: Supervised the overall project, provided critical revisions and approved the final version of the manuscript for submission. Both authors have read and approved the final manuscript.

Funding
There was no funding.

Data availability statement
All data generated or analysed during this study are included in this published article

Ethical approval

Ethical approval was not required for this study as it is a review article based on previously published literature and does not involve human participants or animal experiments.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

Al-Obaidi MMJ, Baharom N, Nor Rashid N, Othman I, Shueb RH and Sinniah M (2017). Japanese encephalitis virus disrupts blood–brain barrier and modulates apoptosis proteins in THBMEC cells. *Virus Res.*, **233**: 17-28.

Atanasoff KE, Parsons AJ, Ophir SI, Lurain N, Kraus T, Moran T, Duty JA and Tortorella D (2024). A broadly neutralizing human monoclonal antibody generated from transgenic mice immunized with HCMV particles limits virus infection and proliferation. *J Viro*l., **98**(7): e00213-24.

Bai F, Kong KF, Dai J, Qian F, Zhang L and Brown CR (2010). A paradoxical role for neutrophils in the pathogenesis of West Nile virus. *J. Infect. Dis.*, **202**(12): 1804-1812.

Beckham JD, Tyler KL, Haller IV, Durrant DM, Phares TW and Madden L (2021). A murine model of dengue virus infection in suckling C57BL/6 and BALB/c mice. *Anim. Models Exp. Med.*, **4**(1): 16-26.

Becker K, van Alen S, Idelevich EA, Schleimer N, Seggewiß J, Mellmann A, Kaspar U and Peters G (2018). Plasmid-encoded transferable mecB-mediated methicillin resistance. *Antimicrob. Agents Chemother.*, **62**(1): e01510-17.

Bock M, Schmid B and Lancaster MA (2024). Morphogenetic designs and disease models in central nervous system organoids. *Int. J. Mol. Sci.*, **25**(14): 7750.

Boucher A, Charrel R, Lepiller Q, Salinas S, Andre P and Henneton P (2017). Epidemiology of infectious encephalitis causes in 2016. *Med. Mal. Infect.*, **47**(3): 221-235.

Chan-Tack K, Harrington P, Bensman T, Choi SY, Donaldson E and O'Rear J (2021). Benefit–risk assessment for brincidofovir for the treatment of smallpox. *Antiviral Res.*, **195**: 105182.

Charise G, Soung A, Vollmer LL, Kanmogne M, Last A and Brown T (2019). T cells promote microglia-mediated synaptic elimination and cognitive dysfunction during recovery from neuropathogenic flaviviruses. *Nat. Neurosci.*, **22**(8): 1276-1288.

Chen Y, Li H, Yang J, Zheng H, Guo L and Li W (2021). A hSCARB2-transgenic mouse model for Coxsackievirus A16 pathogenesis. *Virol. J.*, **18**(1): 84.

Chen Z, Zhong D and Li G (2019). The role of microglia in viral encephalitis: A review. *J Neuroinflammation*., **16**(1):76.

Chou S, Ercolani RJ and Duan D (2018). Antiviral activity of maribavir in combination therapy. *Antiviral Res.*, **157**: 128-133.

Claudette LP, Scott HJ, Anderson K, Boucher MA, Li R and Nguyen T (2018). Antiviral therapies for herpesviruses: Current agents and new directions. *Clin. Ther.*, **40**(8): 1282-1298.

Depla JA, Mulder LA, de Sá RV, Wartel M, Sridhar A and Evers MM (2022). Human brain organoids as models for central nervous system viral infection. *Viruses*, **14**(3): 634.

Depla JA, Mulder LA, de Sá RV, Wartel M, Sridhar A and Evers MM (2023). Human brain microphysiological systems in the study of CNS viral infections. *Front. Cell. Neurosci.*, **17**: 1020567.

Duerlund LS, Nielsen H and Bodilsen J (2025). Current epidemiology of infectious encephalitis: A narrative review. *Clin. Microbiol. Infect.*, **31**(4): 515-521.

El Helou G and Razonable RR (2019). Letermovir for the prevention of cytomegalovirus infection and disease in transplant recipients. *Infect. Drug Resist.*, **12**: 1481-1491.

Fillatre P, Andre A, Cazals X, Sciarrino S, Martinot M and Cantin G (2017). Encéphalite infectieuse: Diagnostic étiologique et conduite à tenir. *Med. Mal. Infect.*, **47**(3): 236-251.

Fugier E, Morfin F, Thouvenot D, Lina B and Morand P (2014). Resistance of herpes simplex virus to acyclovir: A 10-year survey in France. *Antiviral Res.*, **111**: 36-41.

Gao Q, Bao L, Mao H, Wang L, Xu K, Yang M, Li Y, Zhu L, Wang N, Lv Z, Gao H, Ge X, Kan B, Hu Y, Liu J, Cai F, Jiang D, Yin Y, Qin C and Li J (2020). Development of an inactivated vaccine candidate for SARS-CoV-2. *Science*, **369**(6499): 77-81.

Garber C, Soung A, Vollmer LL, Kanmogne M and Brown T (2019). T cells promote microglia-mediated synaptic elimination. *Nat. Neurosci.*, **22**(8): 1276-1288.

Griffiths P and Reeves M (2021). Pathogenesis of human cytomegalovirus in the immunocompromised host. *Nat. Rev. Microbiol.*, **19**(12): 759-773.

Gundamraj VS and Hasbun R (2023). Viral meningitis and encephalitis: An update. *Curr. Opin. Infect. Dis.*, **36**(3): 177-185.

Hidayat A, Md Norefrina Shafinaz NN, Nazlina I, Rahman MA, Tan WL and Ahmad N (2013). Phenotypic and genotypic characterization of acyclovir-resistant HSV-1. *Antiviral Res.*, **100**(2): 306-313.

Ibrahim AM, Kallas EG, Arnal A, Lopez-Lopez MJ, Perez-Ramirez E and Rico-Sanchez A (2025). Epidemiology and surveillance of West Nile virus in the Mediterranean Basin during 2010–2023. *Curr. Res. Parasitol. Vector-Borne Dis.*, **7**: 100277.

Joseph O, Enose-A A, Lavi N, Harel A and Steiner I (2017). Roseolovirus-associated encephalitis in

immunocompetent and immunocompromised individuals. *J. Neurovirol.*, **23**(1): 625-639.

Kalil Alves de Lima L, Rustenhoven J and Kipnis J (2020). Meningeal immunity and its function in maintenance of the central nervous system in health and disease. *Annu. Rev. Immunol.*, **38**: 597-620.

Karamitros T, Magiorkinis E, Pliaka V, Beloukas A and Skoura L (2016). De novo assembly of the herpes simplex virus genome. *PLoS One*, **11**: e0157600.

Kimberlin DW, Whitley RJ, Ramers C, Lantos PM and Cantey JB (2024). Outcome and sequelae of infectious encephalitis. *J. Clin. Neurol.*, **20**(1): 23-36.

Le-Vinh B, Ducastelle-Lepretre S, Gautier-Veyret E, Morfin F and Foulongne V (2019). UL23 and UL30 characterization of HSV-1 strains. *Antiviral Res.*, **168**: 114-120.

Leung PYM, Tran T, Testro A, Paizis K, Kwong J and Whitlam JB (2019). Ganciclovir-resistant post-transplant cytomegalovirus infection due to combined deletion mutation at codons 595–596 of the UL97 gene. *Transpl. Infect. Dis.*, **21**(6): e13168.

Li M, Ostermann PN and Mulder LA (2024). Human brain organoids: Trends, evolution and remaining challenges. *Neural Regen. Res.*, **19**(11): 2387-2399.

Looker KJ, Magaret AS, Turner KME, Vickerman P and Newman LM (2017). Global and regional incidence of neonatal herpes. *Lancet Glob. Health*, **5**(3): e300-e309.

Lopes Pinheiro MA, Kooij G, Mizee MR, Kamermans A, Enzmann G, Lyck R, Schwaninger M, Engelhardt B and de Vries HE (2020). Meningeal immunity in central nervous system health and disease. *Annu. Rev. Immunol.*, **38**: 597-620.

Marcocci ME, Caccuri F, Fiorentini S, Palamara AT and Nencioni L (2022). Forty years after the registration of acyclovir: Do we need new anti-herpetic drugs? *Int. J. Mol. Sci.*, **23**(7): 3431.

Marrazzo P, Cricca M and Nastasi C (2021). Are organoid models an invaluable contribution to Zika virus research? *Pathogens*, **10**(10): 1233.

Perera MR, Wills MR and Sinclair JH (2021). Human cytomegalovirus antivirals and strategies to target the latent reservoir. *Viruses*, **13**(5): 817.

Reed C, Smith DR, Alcorn K, Rachal E and Hartman AL (2019). Neutrophil and macrophage influx in lethal Rift Valley fever encephalitis. *PLoS Pathog.*, **15**(6): e1001234.

Sacks CA, Spotswood LS, Hall CM, Williams G and Thompson RF (2011). Acyclovir and hydrocortisone cream for recurrent cold sores. *Virus Adapt. Treat.*, **3**: 1-6.

Soria B, Deback C, Agut H and Boutolleau D (2010). Genotypic characterization of UL23 thymidine kinase and UL30 DNA polymerase of clinical isolates of herpes simplex virus: natural polymorphism and mutations associated with resistance to antivirals. *Antimicrob. Agents Chemother.*, **54**(11): 4833-4842.

Tippin TK, Morrison ME, Brundage TM and Momméja-Marin H (2016). Brincidofovir is not a substrate for the human organic anion transporter 1: a mechanistic explanation for the lack of nephrotoxicity observed in clinical studies. *Ther Drug Monit*., **38**(6): 777-786.

Topalis D, Gillemot S, Snoeck R and Andrei G (2016). Distribution and effects of amino acid changes in drug-resistant α and β herpesviruses DNA polymerase. Nucleic Acids Res., **44**(20):9530-9554.

Wnęk G, Samorek-Salamonowicz E, Bancerz-Kisiel A, Pluta A and Osiński Z (2015). Animal herpesviruses and their zoonotic potential for cross-species infection. *Ann. Agric. Environ. Med.*, **22**(2): 191-194.

Yang D, Li XJ, Tu DZ, Li XL and Wei B (2023). Advances in viral encephalitis: Viral transmission, host immunity and experimental animal models. *Zool. Res.*, **44**(3): 525-542.