Corticosteroids for viral central nervous system infections

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Purpose of review
Viruses are frequent causes of central nervous system (CNS) infection. Lacking specific antiviral treatment or inadequate clinical response may lead to treatment with corticosteroids. This review describes the rationale for and clinical experience with the use of adjunctive corticosteroids for viral CNS infections.

Recent findings
Corticosteroids display anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive effects by genomic and nongenomic regulation of human cells. Recent population-based studies consistently show that empiric dexamethasone during diagnostic work-up for meningitis has neither been associated with improved outcome nor adverse effects in viral meningitis. Myelitis is most often due to noninfectious causes and standard empiric treatment includes high-dose methylprednisolone. There are no convincing data on viral myelitis to support a change of this approach. Corticosteroids have occasionally been employed in different types of viral encephalitis. Observational data and a few randomized clinical trials have not documented any substantial beneficial effects of adjunctive corticosteroids in viral encephalitis. Risks of harm with current treatment regimens remained low in published studies.

Summary
Except for myelitis, there are no data to support routine use of corticosteroids for viral CNS infections. Large, multidisciplinary syndromic platform trials of all-cause encephalitis may be a viable way to inform treatment guidelines.

Keywords
arbovirus, central nervous system infection, dexamethasone, encephalitis, herpes, management, meningitis, myelitis, treatment, viral central nervous system infections, virus

INTRODUCTION

Viruses are common causes of central nervous system (CNS) infections and can present as meningitis, myelitis, or encephalitis. They range in severity from a benign and self-limiting condition in viral meningitis to paraplegia in myelitis, and substantial neurocognitive impairment, focal neurological deficits, or death in encephalitis [1▪,2,3]. The application of corticosteroids for CNS infections usually has several arguments such as less collateral damage of neurons by the immune response and alleviation of edema [4,5]. On the other hand, concerns of immunosuppression and thereby untamed infection may offset any beneficial effects [6,7,8▪▪]. The effects of corticosteroids in viral CNS infections may also vary whether the clinical manifestation is part of a primary infection (e.g. flaviviruses or enteroviruses) or reactivation of viral latency (i.e. herpes viruses in adults).

In this review, we summarize the background and provide an update on current experiences with use of corticosteroids for treatment of viral CNS infections.

VIRAL CAUSES OF CENTRAL NERVOUS SYSTEM INFECTIONS

The underlying causes of viral CNS infections usually belong to the herpes virus family, flaviviruses,

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KEY POINTS

- Synthetic corticosteroid hormones exert a large variety of anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive effects by genomic (hours to days) and nongenomic regulation (minutes to hours).
- Overall, short-term treatment with corticosteroids appears to be without significantly increased risks of adverse effects and have been used for numerous CNS infections for more than half a century.
- Corticosteroids appear to be neither beneficial nor harmful in viral meningitis.
- Myelitis is most often noninfectious and empirical treatment with high-dose corticosteroids remains mandated considering lack of data suggesting harm in viral myelitis.
- Adjunctive dexamethasone has not been shown to be associated with an improved outcome in viral encephalitis so far.

enteroviruses in children or individuals with hypogammaglobulinemia, or rabies depending on the geographic location and exposures (Fig. 1) [9]. Yet, a plethora of different viruses have been implicated and the list is continuously expanding [9–11]. Importantly, recent developments in global travelling, climate changes, and increasing occurrences of extreme weather contribute to unpredictable distributions of pathogens and potential vectors of arthropod-borne viruses.

Several neurotropic viruses have direct cytolytic effects on neurons including Herpes simplex virus 1 and 2 (HSV-1 and HSV-2) [12▪▪], Varicella zoster virus (VZV) [13–15], West Nile Virus (WNV) [16–19], Japanese encephalitis virus (JEV) [20], and polio and nonpolio enteroviruses [21,22]. However, para and postinfectious immunological responses may also cause indirect damage or impairment of neurons and other cells within the CNS. This has resulted in numerous experimental adjunctive treatments such as ribavirin, interferons, immunoglobulins, and monoclonal antibodies. Still, corticosteroids

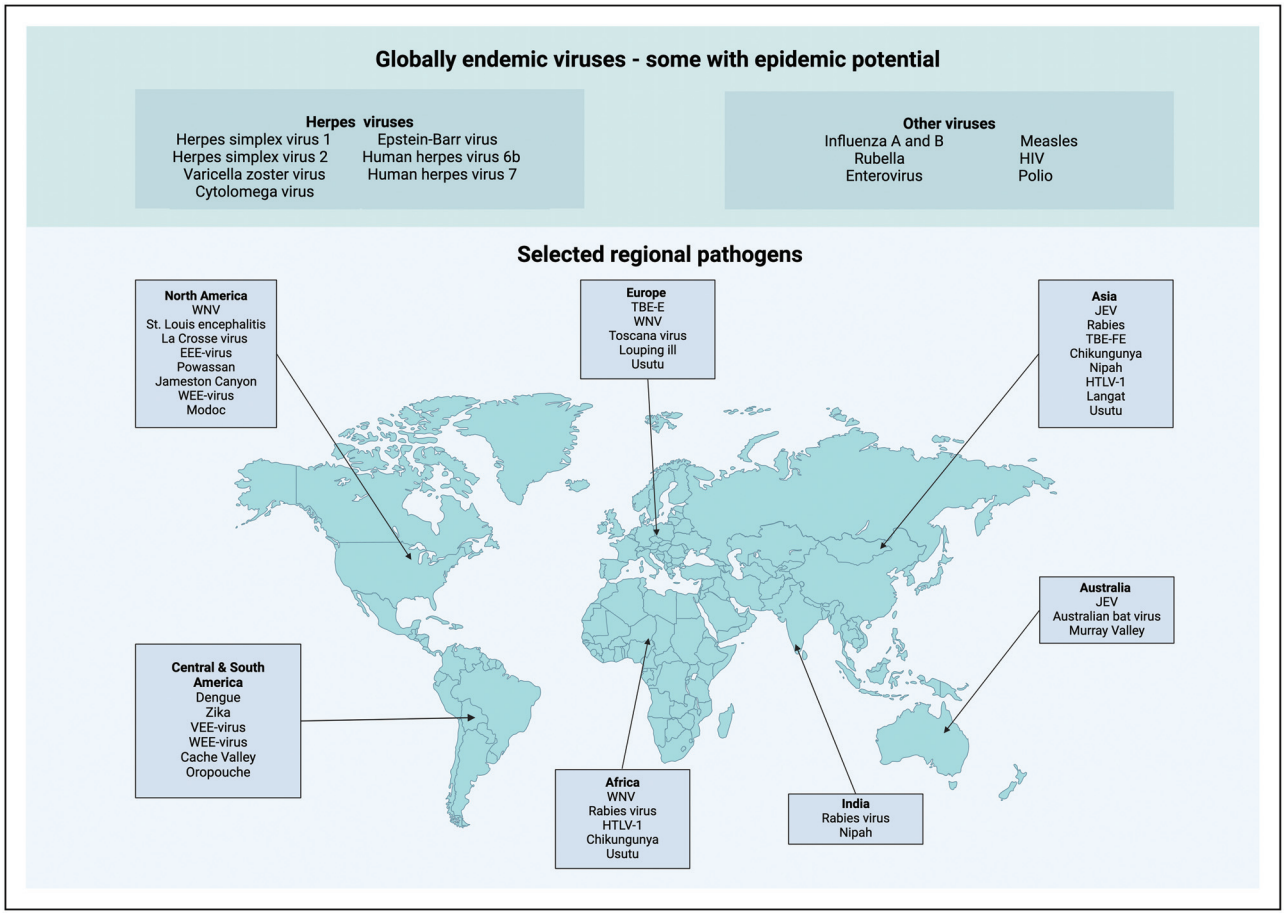

FIGURE 1. Selected viruses that may cause viral central nervous system infections in humans. EEE, Eastern equine encephalitis virus; HTLV-1, Human T-lymphotrophic virus-1; JEV, Japanese encephalitis virus; TBE, Tick borne encephalitis virus Europe (-E) or Far-East (-FE); VEE, Venezuelan equine encephalitis virus; WEE, Western equine encephalitis virus; WNV, West Nile Virus. [a]Created with biorender.com.

are by far the most commonly used anti-inflammatory agent for CNS infections.

CORTICOSTEROIDS

Synthetic corticosteroid hormones exert anti-inflammatory, immunosuppressive, antiproliferative, and vasoconstrictive effects [23]. They have been a tremendous success for treatment of numerous autoimmune and inflammatory conditions since 1948 [6]. Correspondingly, the Nobel Prize in Physiology or Medicine in 1950 was awarded to three scientists who discovered the hormones of the adrenal cortex and described their molecular structure and biological effects. In general, synthetic corticosteroids display limited mineralocorticoid activity, but they do differ in anti-inflammatory effect with dexamethasone as one of the most potent [6,7,24▪]. Common side effects include osteoporosis, suppression of the hypothalamic-pituitary-adrenal axis, Cushingoid features and weight gain, hyperglycemia, cardiovascular disease and dyslipidemia, myopathy, cataracts and glaucoma, psychiatric disturbances, gastrointestinal bleeding, and atrophic skin changes [23]. However, most of these potential harms usually require prolonged treatment over months and have not been more frequent compared with placebo in randomized controlled trials (RCTs) of short-term adjuvant dexamethasone treatment in bacterial meningitis [23,25].

GENOMIC REGULATION AND NON-GENOMIC EFFECTS OF CORTICOSTEROIDS

The anti-inflammatory effects of corticosteroids are complex and differ by cell types. The best-known mechanism is genomic regulation which usually takes hours to unfold. This regulation relies mainly on binding and activation of cytosolic glucocorticoid receptors that directly activate or suppress gene transcription involved in down- or upregulation of the inflammatory response (Fig. 2) [6,7]. However, cytosolic protein-protein interactions ("tethering") between activated glucocorticoid receptors and other transcription factors involved in the inflammatory response may also indirectly exert anti-inflammatory effects [6,26]. A third mechanism involves binding of corticosteroids to DNA segments that serve as receptors for both glucocorticoid response elements and other transcription factors of importance in the human inflammatory response.

Of special consideration for use in acute CNS infections, corticosteroids may also induce nongene regulatory anti-inflammatory effects that occur within seconds to minutes [6]. This includes a wide array of pathways by which corticosteroids or their cytosolic receptors interfere with overall cell functioning and downstream intracellular signal transduction.

ANTI-INFLAMMATORY EFFECTS OF CORTICOSTEROIDS

The administration of corticosteroids quickly results in decreased expression of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-11, IL-12, IL-13, IL-16, IL-17, interferon-γ, tumor-necrosis factor, and granulocyte-macrophage colony-stimulating factor [6,23]. Corticosteroids also mitigate edema by reduced production of mediators of vascular dilatation and permeability (i.e. prostaglandins, leukotrienes, and bradykinin) and improved responsiveness of endothelial cells to vasoconstrictors [6,27]. Extravasation and migration of leukocytes into infected tissue is attenuated by decreased expression of chemokines and adhesion molecules in vascular endothelial cells [6,27]. Corticosteroids also elicit a strong induction of apoptosis in immune cells, especially in lymphocytes. In some conditions, such as human T-lymphotrophic virus-1 (HTLV-1) associated myelopathy, corticosteroids may even hamper viral replication by down-regulating the host T-cell response [28,29]. Moreover, the adaptive cellular immune response is impaired by diminished T cell activity (e.g. T_H1 and T_H17), whereas effects of corticosteroids on humoral immunity are unclear and controversial [6].

Intriguingly, corticosteroids may enhance innate immune responses in some circumstances by improving sensitivity of pattern recognition receptors to exogenous pathogen-associated molecular patterns (PAMPs) by microorganisms and endogenous damage-associated molecular patterns (DAMPs) by human cells [6]. This adds to the complexity of analyses of potential benefit or harm within infectious diseases [6,7,30,31]. Some authors suggest that pro-inflammatory and anti-inflammatory effects of corticosteroids have a bi-phasic dose-response and temporal relationship. Low physiological doses of corticosteroids before infection were suggested to keep the innate immune system alert and rapidly responsive, whereas higher doses after onset of sepsis lead to strong anti-inflammatory effects to counter a disproportionate immunological response [6]. The evolutionary rationale would be that physiological danger is detected and managed early resulting in a shortened course of inflammation and improved outcome of disease.

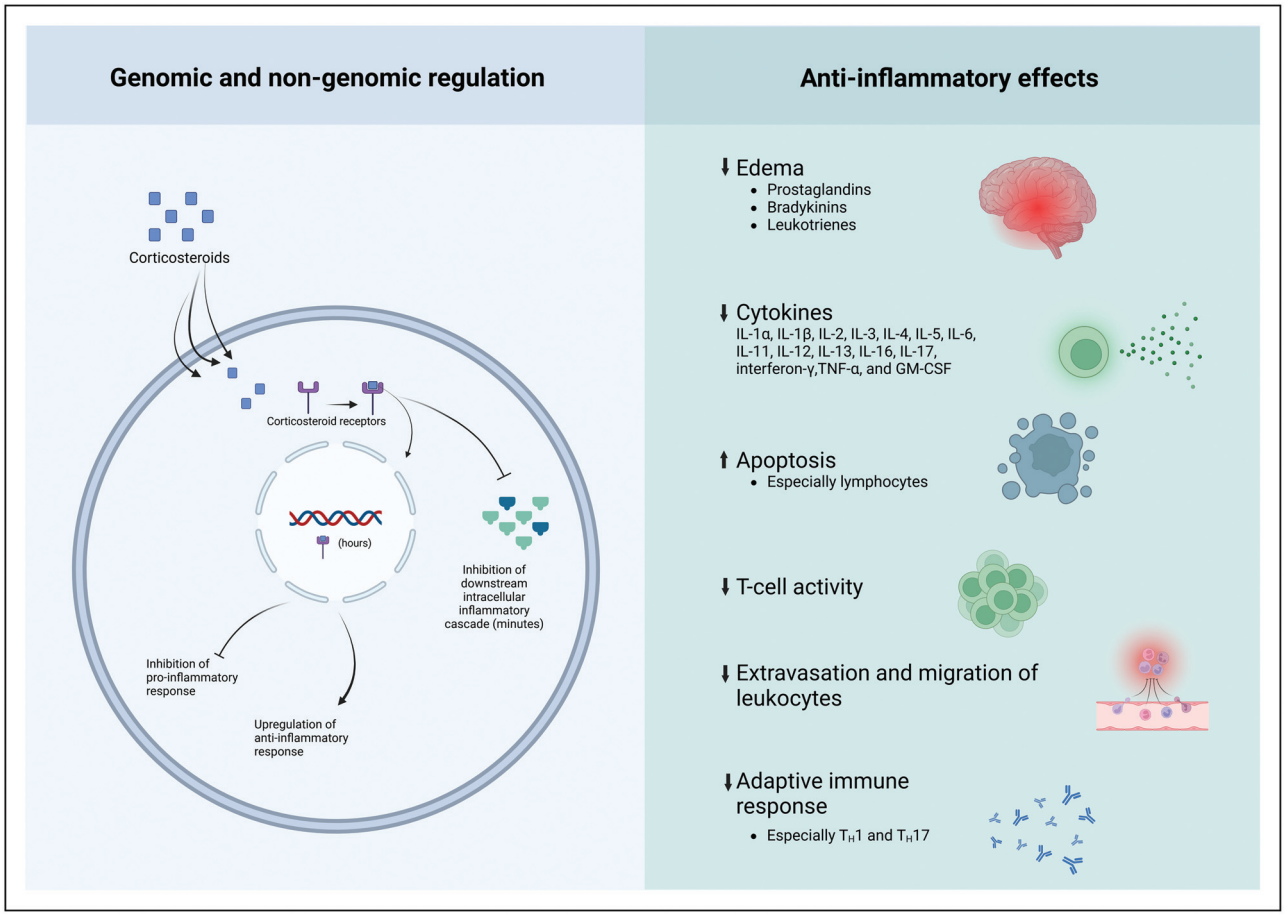

FIGURE 2. Genomic and nongenomic regulation of corticosteroids and their anti-inflammatory effects in humans. GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; TNF-α, tumor necrosis factor α. ªCreated with biorender.com.

CORTICOSTEROIDS FOR VIRAL AND OTHER CENTRAL NERVOUS SYSTEM INFECTIONS

Clinical experience with corticosteroids for bacterial and tuberculous meningitis dates back to the 1950s and for herpes simplex (HSV) encephalitis to the 1970s [25,32–39]. Interestingly, the used corticosteroids have differed in terms of specific drug, dosages, and durations of treatment, for example, intravenous (i.v.) methylprednisolone 40 mg q6 h for 12 days in a placebo-controlled trial of bacterial meningitis in the 1960 s [40]. The role of corticosteroids for pneumococcal meningitis was explored further in rabbit models in the 1980s using dosages of methylprednisolone corresponding to 1 g i.v. in humans [4,5]. They showed reduced outflow resistance with methylprednisolone [5] and also reduced edema and CSF lactate levels with dexamethasone compared with placebo and methylprednisolone [4]. A nonhuman primate model suggested that dexamethasone had favorable penetration into the CNS compared with prednisolone [41]. These and similar experimental animal models helped consolidate dexamethasone 0.15 mg/kg q6 h for four days (≈10 mg in a 70 kg adult) as the corticosteroid of choice in subsequent RCTs of bacterial meningitis in the 1980s and 1990s [25,42–44]. Considerations of a plasma half-life ($T^1/_2$) of 3.5–4.5 h and usual duration of increased intracranial pressure in bacterial meningitis may have inspired administration of dexamethasone four times daily for 4 days. From a pharmacodynamic point of view, the chosen regimen seems less logical given the duration of anti-inflammatory actions of dexamethasone of 36–72 h [24▪]. A prospective clinical study from 2013 also showed that the $T^1/_2$ of dexamethasone in plasma may be as long as 9 h in adults with pneumonia [45]. However, this knowledge was likely unknown at the time the studies were conducted and the current regimen has been proven effective in RCTs [25]. Dexamethasone in modified dosages according to disease severity and for prolonged duration have also been used in RCTs of tuberculous and cryptococcal meningitis with varying results [46–49].

Some of the first experiences of corticosteroids for HSV-1 encephalitis included two adults treated

with dexamethasone 5 mg q6 h for 14 and 22 days, respectively, with subsequent reductions to 4 mg q8 h for an unknown duration [39]. Clinical use of corticosteroids has since expanded into a broad array of viral CNS infections due to an unsatisfactory effect or lack of specific antiviral treatments for most neurotropic viruses.

VIRAL MENINGITIS

Corticosteroids are generally not recommended for viral meningitis but are sometimes used as part of empiric treatment for bacterial meningitis during the initial diagnostic work-up [50–53]. A recent large prospective population-based cohort study of 1025 adults hospitalized with viral meningitis in Denmark examined whether empiric dexamethasone 10 mg q6 h was associated with Glasgow Outcome Scale scores of 1 to 4 at 30 days after discharge [54▪▪]. A total of 36% of patients were treated with dexamethasone for initially suspected bacterial meningitis with a median of four dosages (IQR 2–5). Propensity-based analyses were conducted to account for confounding by disease severity. In alignment with previous reports from the same group, the study did not observe any overall or dose-dependent benefits or harms of empiric dexamethasone although more subtle neurocognitive effects were not assessed [1▪,55,56]. There was a slight signal of potential harm [weighted odds ratio 3.08, 95% confidence interval (95% CI) 1.36–6.94] in a supplementary analysis of patients with enterovirus meningitis treated with at least five doses of dexamethasone [54▪▪]. However, additional sensitivity analysis suggested that residual confounding by disease severity was the likely cause for this exploratory finding. Another study of 32 children ultimately diagnosed with viral or aseptic meningitis and empirically treated with dexamethasone for bacterial meningitis also found that all participants returned to normal daily activities within 3 days after discharge [57]. This contrasts the results of a few Chinese observational studies indicating an increased risk of harm and mortality in children with enterovirus 71 infection [58,59]. Finally, an experimental mouse model showed an increased viral load and higher mortality during treatment with dexamethasone within four days postinfection but not thereafter [60].

Ramsay-Hunt syndrome is caused by reactivation of VZV from the geniculate ganglion leading to facial nerve palsy and combined treatment with (val)aciclovir and corticosteroids is recommended [61–63,64▪,65,66]. A recent prospective population-based cohort study observed persistent facial nerve palsy at 30 days after discharge in 6/16 (38%) of patients treated with adjuvant corticosteroids for Ramsay-Hunt syndrome and concurrent VZV meningitis compared with 12/20 (60%, $P = 0.18$) in those treated solely with antivirals [61].

VIRAL MYELITIS

Viral myelitis is caused by direct infection of neurons or may occur as a para-infectious phenomenon likely due to molecular mimicry between pathogens and epitopes within the human CNS [67]. Several viruses have been described to manifest as myelitis such as enteroviruses, HTLV-1, WNV, Tick-borne encephalitis (TBE), VZV, HSV-2, Epstein–Barr virus, cytomegalovirus, Zika, and HIV. Acute transverse myelitis is the most severe clinical phenotype and may be partial, complete, or longitudinal. It usually occurs in adolescents and young adults with an annual incidence of approximately 1–4 per 1 000 000 persons [2]. Although viruses do cause myelitis, a large single-center retrospective cohort study found that the most frequent underlying conditions were vascular or systemic diseases, multiple sclerosis, idiopathic myelitis, and neuromyelitis optica spectrum disorder (NMOSD) [68▪].

Enteroviruses may cause acute flaccid myelitis, mainly in children and with certain strains such as D68, A71, D70, and polioviruses [22,69]. Corticosteroids have been used in several observational cohort studies without clear signals of benefit or harm [70–72].

HTLV-1 associated myelopathy (HAM) is treated with immunosuppressive therapies including corticosteroids [28,73]. Recently, a Japanese trial randomized patients with HAM to induction therapy with i.v. methylprednisolone 1 g for 3 days compared with standard treatment of oral prednisolone in eight patients with rapidly progressing disease (open-label, blinded endpoint assessment); and oral prednisolone compared with placebo in 32 patients with slowly progressing walking disabilities (double-blind) [74▪]. Primary endpoints comprised combinations of functional scores after 2 weeks (Group 1) and 24 weeks (Group 2), respectively. Although there were signals in favor of both i.v. methylprednisolone for induction among rapid progressors and oral prednisolone among slow progressors, the study was hampered by small sample sizes and showed no statistically significant differences in functional outcomes. There were some signs of improvement of CSF inflammatory markers in patients treated with prednisolone compared with placebo. Of note, an anti-CCR4 mAb has recently showed moderate efficacy in delaying disease progression in HAM and further studies are awaited [75,76].

Flaviviruses such as WNV and TBE occasionally lead to myelitis or acute flaccid paralysis and are sometimes treated with corticosteroids [77–79,80▪, 81–83]. A recent Italian retrospective observational cohort study of WNV neuroinvasive disease from five hospitals did not observe differences in in-hospital mortality or neurological sequelae at discharge according to corticosteroid treatment at any time during hospitalization ($n = 33$) or not ($n = 32$) [80▪]. However, the distribution between meningitis, myelitis, and encephalitis was unclear and the study did not sufficiently address confounding by indication and immortal time bias.

VZV also causes myelitis in rare cases, particularly in immunocompromised individuals [14,84–88]. It may occur by direct viral cytotoxic effects on the neuron or by VZV-mediated vasculitis [85,86]. Standard i.v. aciclovir 10–15 mg/kg thrice daily (t.i.d.) for 14 days combined with corticosteroids in the form of oral prednisone 1 mg/kg daily for 5 days without tapering has been recommended for VZV vasculitis based on expert opinion and a few observational cohort studies [14].

Elsberg's syndrome is defined as lumbo-sacral polyradiculitis with or without myelitis [89,90]. A population-based cohort study found that Elsberg's syndrome was diagnosed in approximately 1.2 per 1 000 000 adults per year, primarily young females [91▪]. The cause was HSV-2 in 19/28 (68%), VZV in 2/28 (7%), and unidentified in 7/28 (25%). Corticosteroids were used in 4/28 (14%), but data on outcome according to this exposure were lacking. Another study of 30 patients with suspected Elsberg's syndrome showed that 13 (43%) had been treated with corticosteroids without clear associations with outcome, although follow-up was only rudimentary [92].

VIRAL ENCEPHALITIS

A systematic review and meta-analysis of published studies on corticosteroids for viral encephalitis until 2020 has recently been reported [8▪▪]. Reports on progressive multifocal leukoencephalopathy, prion diseases, and subacute sclerosing panencephalitis were excluded. The authors identified 50 eligible studies (37 case reports on 43 patients) and added unpublished data on 155 patients from their own centers. This yielded a total of 281 persons with viral encephalitis of whom 120 (43%) had been treated with adjunctive corticosteroids. Only 10 observational cohorts qualified for inclusion in the meta-analysis. The involved pathogens were mainly HSV-1, WNV, measles, TBE, VZV, and JEV. The studies were heterogeneous in terms of pathogens, corticosteroid treatment regimens (type, dosage, duration), outcome assessment, degree of follow-up, and use of other adjuvant treatments. Funnel plots suggested publication bias of studies included in the meta-analysis and heterogeneity assessed by I^2 was 30%. Overall, no benefit or harm of adjunctive corticosteroids for viral encephalitis was found in the systematic review or in the meta-analysis using a random-effects analysis.

The inspiration for examining corticosteroids for HSV-1 encephalitis was derived from early case reports of improved outcome in patients [39,93] and some experimental studies suggesting reduced neuronal damage without increased viral load in brains of mice and rats whereas others did not [94–96]. This was followed by two retrospective observational cohort studies from the same Japanese group showing an improved outcome with corticosteroids in addition to aciclovir in HSV-1 [97,98]. However, limitations in study designs and sample sizes did not allow for sufficient adjustment for confounding by indication. The German trial on Aciclovir and Corticosteroids in Herpes simplex virus Encephalitis (GACHE) was a RCT that managed to enroll 41 patients with HSV encephalitis during six years before it was terminated due to insufficient recruitment [99]. This was followed by the DexEnceph RCT in the UK, which successfully completed enrolment of the planned 90 patients with HSV-1 encephalitis [100]. The primary outcome was improvement in the Auditory Memory Index of the 4th edition of the Wechsler Memory Scale. Eagerly awaiting formal publication, the results were presented at several international conferences and adjunctive dexamethasone was not associated with outcome or an increased risk of adverse effects.

Similarly, adjunctive corticosteroids were neither shown to be beneficial nor harmful in studies on encephalitis due to JEV [101–103], TBE [83,104,105], SLE [106], measles [107], and other viruses [8▪▪].

CONCLUSION AND PERSPECTIVES

Collectively, there is no apparent advantage or detrimental effects of using corticosteroids in viral meningitis given the current available literature. Viral myelitis is treated with antivirals (if relevant, e.g. herpes viruses) and high-dose adjuvant corticosteroids such as i.v. methylprednisolone 1 g for 3–5 days, which is also the backbone of treatment for idiopathic and noninfectious inflammatory acute transverse myelitis [2]. Considering the risks of inferior paraparesis and bladder/fecal dysfunction, no studies were identified that should prompt a change in current practice of management of myelitis. Finally, there are currently no convincing data to

support routine use of adjunctive corticosteroids for viral encephalitis.

Further studies are required to determine whether there might be any overall beneficial anti-inflammatory effects of corticosteroids in terms of timing of initiation since disease onset as well as type, dose, and duration of corticosteroid treatment for the different kinds of viral encephalitis. Moreover, autoimmune encephalitis may be triggered by preceding viral encephalitis, especially anti-NMDA following HSV-1 encephalitis, and whether adjunctive corticosteroids could reduce such risks also requires exploration.

The apparent lack of harm associated with short-term adjunctive corticosteroids supports the establishment of desperately needed large multidisciplinary syndromic platform trials of all patients with suspected infectious or autoimmune encephalitis to improve diagnosis and treatment of these challenging and life-threatening conditions.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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