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ORIGINAL COMMUNICATION

Adjunctive steroids in adults with encephalitis: a propensity score analysis

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Abstract

Objective Adjuvant steroids have been used for the treatment of encephalitis, although there is limited data regarding its benefit. We described the use and impact of adjunctive steroids on adverse clinical outcomes (ACO) in adults with encephalitis.

Methods Retrospective observational study of 230 adults with encephalitis at two tertiary care hospital systems in Houston, Texas, between August 2008 and September 2017. An ACO was assessed at the time of death or discharge and defined as a Glasgow Outcome Scale 1–4. A propensity score analysis was performed.

Results Out of 230 adult encephalitis patients enrolled, 121 (52.6%) received steroids. Adjunctive steroids were given more frequently to those who had focal neurological deficits ($P=0.01$), required mechanical ventilation (MV) ($P=0.01$), had intensive care unit admission ($P<0.001$), had white matter abnormalities ($P=0.01$) or cerebral edema on magnetic resonance imaging of the brain ($P=0.003$). An ACO was seen in 135 (58.7%) of patients. The use of adjunctive steroids did not impact ACOs ($P=0.52$) on univariate analyses or after propensity score matching. Predictors for an ACO in logistic regression analyses included a Glasgow Coma Score (GCS) < 8, fever, MV, and cerebral edema.

Interpretation Adjunctive steroids are used more frequently in sicker patients and are not associated with improved clinical outcomes.

Keywords Encephalitis · Adjunctive steroids · Outcomes · Adults

Introduction

Encephalitis continues to be a challenging medical condition due to evasive etiologies, complicated guidelines for medical management for which compliance is suboptimal, and poor prognostic outcomes in the majority of patients [1, 2]. Even in the molecular diagnostic era and with awareness and testing for autoimmune etiologies, a large proportion of cases in adults with encephalitis remain unknown [2, 3]. In adults under the age of 65 years, the majority have unknown etiology making their management even more challenging [2]. Since 2008, five guidelines have been published to improve the diagnosis and management of patients presenting with encephalitis but compliance is suboptimal [1]. Finally, adverse clinical outcomes are seen approximately half of adults with encephalitis with in-hospital mortality rates varying between 5 and 15% [2, 4, 5]. Furthermore, survivors of *West Nile virus* (WNV), *Herpes simplex virus* (HSV) or other types of encephalitis can have long-term neurologic sequelae such as seizures, neurocognitive disorders, depression, and motor impairment [4, 5].

Adjunctive steroids have been utilized for the treatment of several causes of meningitis and encephalitis [6]. Even though steroids are associated with a reduction in mortality in adults with meningitis caused by *Streptococcus pneumoniae* and *Mycobacterium tuberculosis* [7, 8], they can also be associated with worse outcomes in patients with *Listeria*

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monocytogenes and *Cryptococcoccus neoformans* [7, 9, 10]. Adjunctive steroids are indicated in autoimmune encephalitis but data evaluating its effect on outcomes in patients with encephalitis of all causes remain limited.

As corticosteroids are often provided to patients prior to the exact etiology of their illness being determined, the objective of our study was to describe the use and potential impact of adjuvant intravenous corticosteroids on adverse clinical outcomes in adults diagnosed with acute encephalitis.

Methods

Ethical consideration

This study was approved by the University of Texas Health Committee for the Protection of Human Subjects, the Memorial Hermann Hospital Research Review Committee, and the Harris Health Research Committee.

Study population

Adults 18–65 years of age were enrolled between August 2008 and September 2017 at two tertiary care hospital systems in Houston, Texas. The study was conducted at 17 hospitals from the Memorial Hermann Health System (15 hospitals) and the Harris Health System (two hospitals). A total of 1241 patients were identified with an International classification of disease (ICD)-9 discharge diagnosis code of encephalitis. We excluded the following patients after reviewing the medical records: did not have encephalitis by the 2013 International Encephalitis Consortium definition ($n=580$), healthcare-associated ventriculitis or meningitis ($n=148$), community-acquired bacterial meningitis ($n=101$), aseptic meningitis ($n=72$), fungal meningitis ($n=68$), tuberculous meningitis ($n=25$), parasitic infection that did not meet the encephalitis definition ($n=3$), or had incomplete medical records ($n=14$). A total of 230 adults with encephalitis were included.

Case definition

We used the 2013 International Encephalitis Consortium definition of encephalitis, which includes the presence of one major criterion (presentation of altered mental status without alternative cause lasting more than 24 h), and the addition of at least two minor criteria (fever 72 h before or after the presentation; new-onset seizures; new-onset focal neurologic findings; white blood cell count $>5mm^3$ in the cerebrospinal fluid (CSF); neuroimaging findings consistent with encephalitis; or abnormal electroencephalogram (EEG) demonstrating changes consistent with encephalitis) [11]. An adverse clinical outcome (ACO) was assessed at the time of death or discharge and defined as a Glasgow Outcome Scale (GOS) 1–4 [11].

Statistical analysis

Data extraction from the medical record was performed with a standardized form. Extracted data included information on demographics, clinical presentation, diagnostic testing, and treatment.

Clinical risk factors (potential baseline confounders of the effect of interest) were evaluated by steroid treatment, and by AOC. *P*-values for the associations were calculated using Student's *t* test for continuous variables and chi-square tests/Fisher's exact tests for categorical variables. Univariate analysis underwent the Bonferroni correction to adjust the *P* value for multiple comparions. The effect of steroid use on AOC was assessed using unadjusted and adjusted logistic regression modeling. As a sensitivity analysis, propensity scores were also generated using generalized boosting models (GBM) provided the R package TWANG [12]. Specifically, 1000 random trees were constructed and assessed until convergence was met. The inverse probability treatment weight (IPTW) was calculated from the GBM model. The IPTW was used in a survey-weighted logistic regression outcome analysis to estimate the average treatment effect (ATE) of steroids on mortality. Covariate balance between groups before and after IPTW was assessed using the average standardized mean difference (SMD) before and after weighting and calculating the maximum Kolmogorov–Smirnov distance, which agreed with SMD. An average $SMD \leq 0.2$ after weighting for potential confounders was considered adequate. Residual confounding for those variables where $SMD > 2$ after weighting was accommodated by adjusting the outcome model for those variables. Statistical analysis was performed with SPSS version 25 (IBM, Austin, Texas, United States of America) and freeware R.

Results

Demographics and clinical presentation

A total of 230 adults with encephalitis were enrolled, of which 121 (52.6%) received steroids (Table 1). The median age of patients who received steroids was 41 years, with the majority of the patients being female (50.4%) and African American (40.0%). The most common presenting symptoms for all encephalitis patients were fever, headache, nausea, $GCS < 13$, and seizures. There was a trend of given adjunctive steroids more frequently to those who presented with focal neurological deficits (50.9% vs 34.0%, $P=0.01$).

Table 1 Baseline characteristics of 230 adults treated for encephalitis with or without steroids

Clinical features	Steroids given $n=121$ (%)	Steroids not given $n=109$ (%)	P value[b]
Median age in years	41	54	< 0.01
Male gender	60/121 (49.6)	66/108 (61.1)	0.07
Race			0.17
African American	36/90 (40.0)	30/88 (34.1)	
White	18/90 (20.0)	27/88 (30.7)	
Hispanics	27/90 (30.0)	21/88 (23.9)	
Asian	7/90 (7.8)	1/88 (1.1)	
Other	2/90 (2.2)	9/88 (10.2)	
Presenting symptoms			
Headache	45/90 (50.0)	40/77 (51.9)	0.80
Fever > 38.4 C	48/102 (47.1)	45/89 (50.6)	0.63
Focal neurologic deficits[d]	59/116 (50.9)	34/100 (34.0)	0.01
Seizures[c]	59/122 (48.4)	41/109 (37.6)	0.10
GCS < 13[a]	41/122 (33.6)	38/109 (34.9)	0.61
Nausea	29/89 (32.6)	24/76 (31.6)	0.89
GCS < 8[a]	25/121 (20.7)	24/108 (22.2)	0.77
Neck stiffness	10/70 (14.3)	8/65 (12.3)	0.74
Photophobia	5/64 (7.8)	8/62 (12.9)	0.35
Status Epilepticus	8/70 (11.4)	7/73 (9.6)	0.72

[a]*GCS* Glasgow Coma Scale

[b]*P* value adjusted by multiple comparisons using the Bonferroni correction and considered significant if < 0.003

[c]Seizure within one week of presentation

[d]Focal motor deficit, cranial nerve abnormality, or aphasia

Laboratory, radiological findings and management decisions

Laboratory results, radiological findings and management decisions are summarized in Table 2. The CSF profile consisted of a mild pleocytosis (median CSF serum WBC was 30 cells/mm^3) with a lymphocytic predominance, a normal glucose and mildly elevated protein. There was a trend of administrating adjunctive steroids more frequently to patients requiring mechanical ventilation (MV) (43.3%, $P=0.01$), having white matter abnormalities (54.1%, $P=0.01$), or cerebral edema on the brain magnetic resonance imaging (MRI) (76.1%, $P=0.003$) (Table 2). Patients that were admitted to the intensive care unit (ICU) received more frequently adjunctive steroids (63.6%, $P<0.001$), There was no difference in ACO between those who received steroids (60.7%) and those that did not (56.5%), ($P=0.52$). There was a trend in receiving less adjunctive steroids if a patient had a positive HSV PCR (5.0%, $P=0.01$).

Table 2 Laboratory, Radiological imaging and Management decision of 230 adults treated for encephalitis with or without steroids

In-hospital management	Steroids given $n=121$ (%)	Steroids not given $n=109$ (%)	P value[b]
Blood and CSF analysis			
Positive CSF bacterial culture	3/112 (2.7)	4/94 (4.3)	0.53
Positive HSV PCR	5/101 (5.0)	14/89 (15.7)	0.01
Positive VZV PCR	4/43 (9.3)	7/34 (20.6)	0.16
Positive enterovirus	1/66 (1.5)	1/49 (2.0)	0.83
Positive HIV	17/103 (16.5)	19/82 (23.2)	0.26
Positive arbovirus panel[d]	10/71 (14.1)	17/67 (25.3)	0.09
CSF protein > 120 mg/dL	34/118 (28.8)	29/105 (27.6)	0.84
CSF glucose < 40 mg/dL	15/118 (12.7)	13/104 (12.5)	0.96
WBC > 12,000 cells µL	39/116 (33.6)	30/100 (30.0)	0.57
Management decision			
Mechanical intubation	52/120 (43.3)	29/107 (27.1)	0.01
Needed ICU admission	77/121 (63.6)	42/106 (39.6)	< 0.001
Empiric antibiotics before LP	33/77 (42.9)	22/64 (34.4)	0.30
Charlson score > 1	51/122 (41.8)	55/109 (50.5)	0.19
Empiric antiviral given	75/115 (65.2)	71/92 (77.2)	0.06
Radiological findings			
White matter abnormalities[e]	60/111 (54.1)	33/90 (36.7)	0.01
Meningeal enhancement[e]	33/112 (29.5)	16/89 (18.0)	0.06
Cerebral edema[e]	86/113 (76.1)	54/95 (56.8)	0.003
EEG findings	92/103 (89.3)	60/75 (80.0)	0.82
Adverse outcome			
GOS = 1-4[c]	74/122 (60.7)	61/108 (56.5)	0.52

LP Lumbar puncture, *EEG* Electroencephalography, *GCS* Glasgow Coma Scale, *WBC* White cell count, *CSF* Cerebrospinal fluid, *Charlson score* Charlson comorbidity index, *HSV* Herpes Simplex virus, *VZV* Varicella Zoster Virus, *PCR* Polymerase chain reaction, *HIV* human immunodeficiency virus, *ICU* intensive care unit

[b]*P* value adjusted by multiple comparisons using the Bonferroni correction and considered significant if < 0.002

[c]GOS = 1 (Glasgow outcome scale from 1 to 4) 1 (death), 2 (persistent vegetative state), 3 (severe disability), or 4 (moderate disability) GOS = 0 (GOS score of 5) 5 (mild disability)

[d]Arbovirus panel = St. Louis encephalitis, West Nile virus, Eastern equine encephalitis virus, Venezuelan equine encephalitis virus, and La Crosse virus

[e]As seen in Magnetic Resonance Imaging

Etiologies

The most common etiology of adult encephalitis was found to be idiopathic (48.3% of cases), 49.5% of which received adjunctive steroids (Table 3). Viral pathogens were the second most common cause (28.2%), of which *HSV*, *WNV and*

Table 3 Etiologies in 230 adults with encephalitis and in 121 patients that received steroids

Etiologies, (*n*) (%) (*n* = 230)	*N* (%) (*n* = 230)	Patients that received steroids by etiology, *n* (%) (*n* = 121)
Unknown etiology	111 (48.3)	55 (49.5)
Viral etiology	65 (28.2)	26 (40.0)
West Nile virus	24	9
Herpes simplex virus	21	7
Varicella zoster virus	10	5
Cytomegalovirus	4	1
JC virus	1	1
Enterovirus	1	1
Autoimmune etiology	28 (12.1)	26 (92.8)
Anti-NMDA receptor antibodies	26	
Anti-VGKC antibodies	2	
Bacterial etiology	13 (5.6)	7 (53.8)
Mycobacterium tuberculosis	3	2
Treponema pallidum	2	0
Streptococci pneumonia	2	2
Beta hemolytic streptococci	1	0
Staphylococcus aureus	1	0
Coagulase negative Staphylococcus	1	1
Group A beta hemolytic streptococci	1	1
Brucella spp.	1	0
Rickettsia ricketsii	1	1
Parasitic etiology	5 (2.2)	5 (100.0)
Toxoplasma gondii	5	5
Fungal etiology	3 (1.3)	3 (100.0)
Cryptococcus neoformans	2	2
Coccidiodes immitis	1	1

NMDA anti-*N*-methyl-D-aspartate, *VKGC* voltage-gated potassium channel antibodies, *JC* John Cunningham virus

Varicella Zoster viruses were common etiologies. Autoimmune encephalitis accounted for 12.1% of cases with 92.8% of patients receiving steroids. Anti-*N*-Methyl-D-Aspartate (NMDA) receptor antibody encephalitis was the most common etiology. Bacterial causes of encephalitis were seen in the minority of patients (5.6%). *Streptococcus pneumoniae*, Group A beta-hemolytic streptococci, coagulase-negative staphylococcus and *Mycobacterium tuberculosis* were the more common etiologies. *Toxoplasma gondii* was the only parasite isolated in our population (2.2%), and *Cryptococcus neoformans and Coccidiodes immitis* were common fungal etiologies (1.3%).

Univariate and adjusted logistic regression analysis

An exploration of meaningful risk factors for ACO was performed by testing univariate associations between clinical characteristics and the ACO (Table 4). Univariate analyses revealed the following factors associated with an ACO: Glasgow Coma Score < 8, fever, seizures, focal neurological deficits, GCS < 15, presence of rash, status epilepticus, mechanical ventilation, intensive care admission, and meningeal enhancement or cerebral edema on MRI. Adjunctive steroids were not associated with ACOs ($P = 0.52$). On logistic regression, independent predictors for an ACO were cerebral edema on MRI, GCS < 8, mechanical ventilation and fever (Table 5).

Propensity score analysis

A propensity score model was used to confirm adjusted modeling results. Potential confounders of the treatment outcome relationship used in the GBM propensity score model were age, race, gender, fever, HSV, ICU admission, mechanical ventilation, focal neurological findings, GCS, white matter abnormalities, meningeal enhancement, cerebral edema, antibiotics, and antiviral therapy. Covariate balance before and after IPTW is presented in terms of average SMDs (Fig. 1). Adequate balance (SMD < 0.2) was achieved for more than half of the covariates and the remainder were

Table 4 Univariate analysis of factors associated with an adverse clinical outcomes in 230 adults with encephalitis

Clinical characteristics	Adverse clinical outcome[b] *n*, (%)	Odds ratio	95% confidence interval	*P* value[c]
Male gender	78/129 (60.5)	0.88	0.52–1.47	0.62
GCS < 8	44/50 (88.0)	6.88	2.80–16.92	< 0.001
Age > 60 years	44/70 (62.9)	1.30	0.73–2.30	0.38
Fever > 38.4 C	101/143 (70.6)	3.33	1.93–5.75	< 0.001
Seizures	72/105 (68.6)	2.06	1.21–3.50	0.008
Abnormal exam[d]	130/202 (64.4)	3.78	1.74–8.19	< 0.001
Status epilepticus	12/15 (80.0)	9.17	2.46–34.24	< 0.001
Charlson score > 1	59/111 (53.2)	0.63	0.37–1.06	0.08
Mechanical ventilation	85/125 (68.0)	2.13	1.25–3.60	0.005
ICU admission	85/124 (68.5)	2.22	1.31–3.77	0.003
Neck stiffness	3/12 (25.0)	1.28	0.32–5.18	0.73
CSF protein > 120 mg/dL	40/62 (64.5)	1.48	0.81–2.70	0.21
CSF glucose < 40 mg/dL	16/28 (57.1)	0.97	0.44–2.16	0.94
Thrombocytopenia < 50,000 µL	22/34 (64.7)	1.28	0.60–2.73	0.52
Leukopenia (WBC < 4000 µL)	11/18 (61.1)	1.09	0.41–2.92	0.86
Serum WBC > 12,000 µL	47/70 (67.1)	1.50	0.83–2.72	0.18
Cerebral edema[e]	28/30 (93.3)	11.35	2.62–49.14	< 0.001
Meningeal enhancement[e]	40/51 (78.4)	2.94	1.41–6.17	0.003
Received steroids[f]	74/122 (60.7)	1.19	0.70–2.01	0.52

GCS Glasgow Coma Scale, *WBC* White cell count, *Charlson* Charlson co-morbidity index, *CSF* Cerebrospinal fluid, *ICU* intensive care unit

[b]GOS = Glasgow Outcome Scale score from 1 to 4. 1 (death), 2 (persistent vegetative state), 3 (severe disability), or 4 (moderate disability) GOS = 0 (GOS score of 5) 5 (mild disability)

[c]*P* value adjusted by multiple comparisons using the Bonferroni correction and considered significant if < 0.002

[d]Abnormal exam refers to acute focal neurological deficits, GCS < 15 and/or presence of a rash

[e]Seen on Magnetic resonance imaging

[f]Steroids administered include prednisone, dexamethasone, methylprednisolone, or hydrocortisone; may have been oral or intravenous

slightly above 0.2 (Fig. 2). Those with SMD > 0.2 were age, race, ICU admission, antibiotics, and administration of antiviral therapy. These variables were included in a stepwise approach as adjusters to the IPTW logistic regression outcome model, which is interpreted in a sensitivity analytic framework (Table 6). The estimated ATE indicates steroids do not predict ACO (OR = 0.684, *P* = 0.16). The multiple sensitivity analyses adjusting for potential confounders that did not reach SMD < 0.2 showed similar insignificant findings. In fact, as more potential residual confounders were included in the outcome model, the effect of steroids on mortality decreased (in terms of the odds ratio), and became more insignificant (Table 6).

Discussion

Encephalitis continues to be a challenging medical diagnosis due to a variety of factors and can have devastating long-term consequences for patients afflicted with it. While steroids were used in ~ 50% of adults with encephalitis, studies have not clearly delineated their benefit [6, 9]. We found that steroids are more likely to be administered to patients who had a lower GCS on presentation, required mechanical ventilation, and had focal neurological deficits on presentation. Our logistic regression or the propensity scoring analysis did not show a benefit in reducing ACOs by the use of adjunctive corticosteroids.

Steroids in meningitis

Previous studies have elicited the effect of corticosteroids on long-term neurologic sequelae in patients suffering from meningitis. A recent Cochrane review (2015) evaluated 25 studies involving 4121 children and adults [13]. Use of corticosteroids led to lower risk of death when compared to placebo, though the results did not reach statistical significance. When considered by specific etiology, steroid administration has varying effects. When the etiology is pneumococcal meningitis, the most common bacterial cause, steroids

Table 5 Independent prognostic factors of an adverse clinical outcome in 230 adults with encephalitis by Logistic Regression

Clinical variable	Adjusted odds ratio	95% confidence interval	*P* value[b]
Cerebral edema[c]	6.55	1.37–31.40	**0.02**
Meningeal enhancement[c]	2.02	0.84–4.84	0.12
GCS < 8[d]	14.86	3.71–59.42	< **0.001**
Abnormal exam[e]	1.65	0.59–4.63	0.34
Seizures	1.10	0.53–2.29	0.80
Fever > 38.4 C	2.54	1.21–5.32	**0.01**
ICU admission[f]	1.85	0.75–4.58	0.18
Respiratory failure/intubation	0.24	0.08–0.70	**0.009**

Adverse clinical outcome defined by a Glasgow Outcome Scale (GOS) 1–4. GOS 1 (death), 2 (persistent vegetative state), 3 (severe disability), or 4 (moderate disability) or 5 (mild disability)

[b]All statistically significant outcomes signified by bolding the *P* value

[c]Seen on magnetic resonance imaging

[d]*GCS* Glasgow Coma Scale

[e]Abnormal examination = includes acute focal deficits, seizures, GCS < 15

[f]*ICU* intensive care unit

did reduce mortality, the rate of severe hearing loss (RR 0.67), any hearing loss (RR 0.74), and short-term neurologic sequelae (RR 0.83) when compared to placebo, though this benefit did not persist in long-term follow up [13]. The benefit of adjuvant corticosteroids also applies to patients suffering from *Mycobacterium tuberculosis* meningitis. A Cochrane Review in 2016 included nine studies in an analysis showing there was a 25% reduction in mortality (RR 0.75) when corticosteroids were administered, and a 10% absolute risk reduction (ARR) when corticosteroids were administered [14]. However, no long-term benefit was identified preventing disabling neurologic deficit (RR 0.92, 95% CI 0.71–1.20). In contrast steroids have been associated with worse outcomes in Listeria and in cryptococcal meningitis [9, 10]. A 4-year observational study showed in a subset of 252 patients with neurolisteriosis [9], the use of adjuvant dexamethasone was associated with higher mortality (OR 4.58, $P < 0.008$). A study investigating the effect of IV dexamethasone in HIV-positive patients with cryptococcal meningitis compared to standard-of-care regimen antifungal therapy was halted early due to adverse secondary outcomes in the dexamethasone group [10].

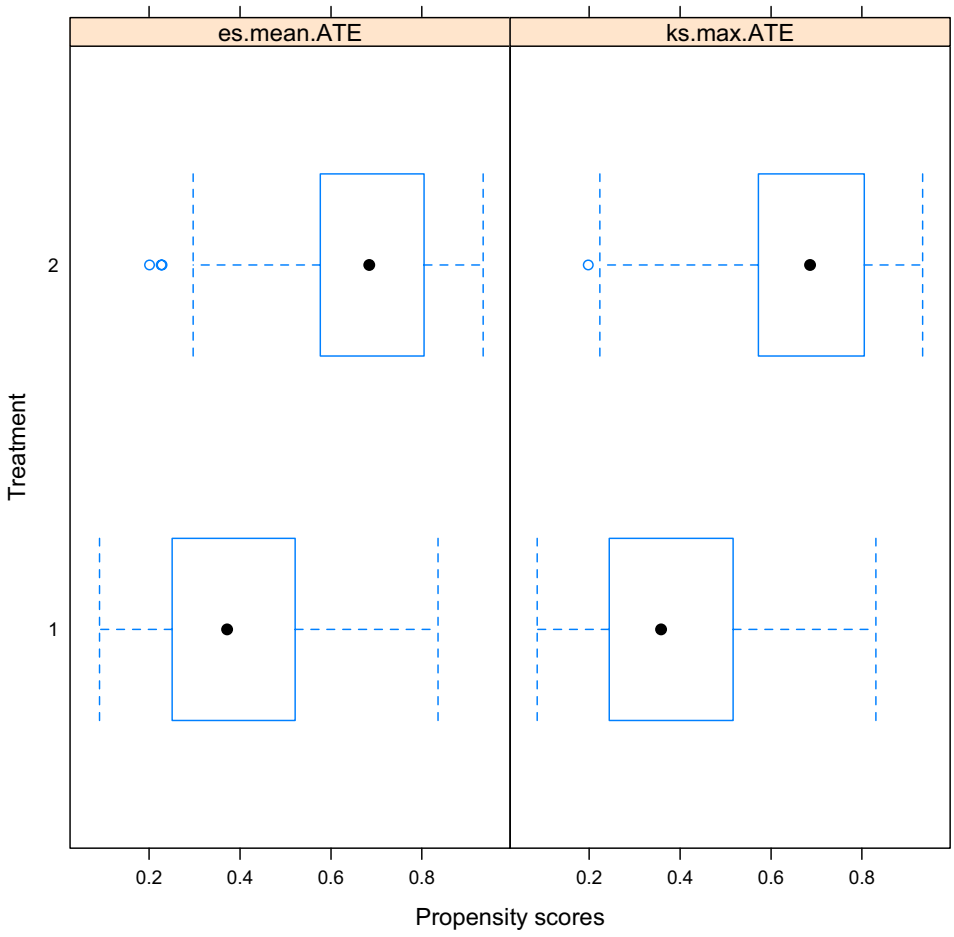

Fig. 1 Box plots demonstrating overlap in propensity score distributions between those treated steroids (bottom) and those not treated with steroids (top)

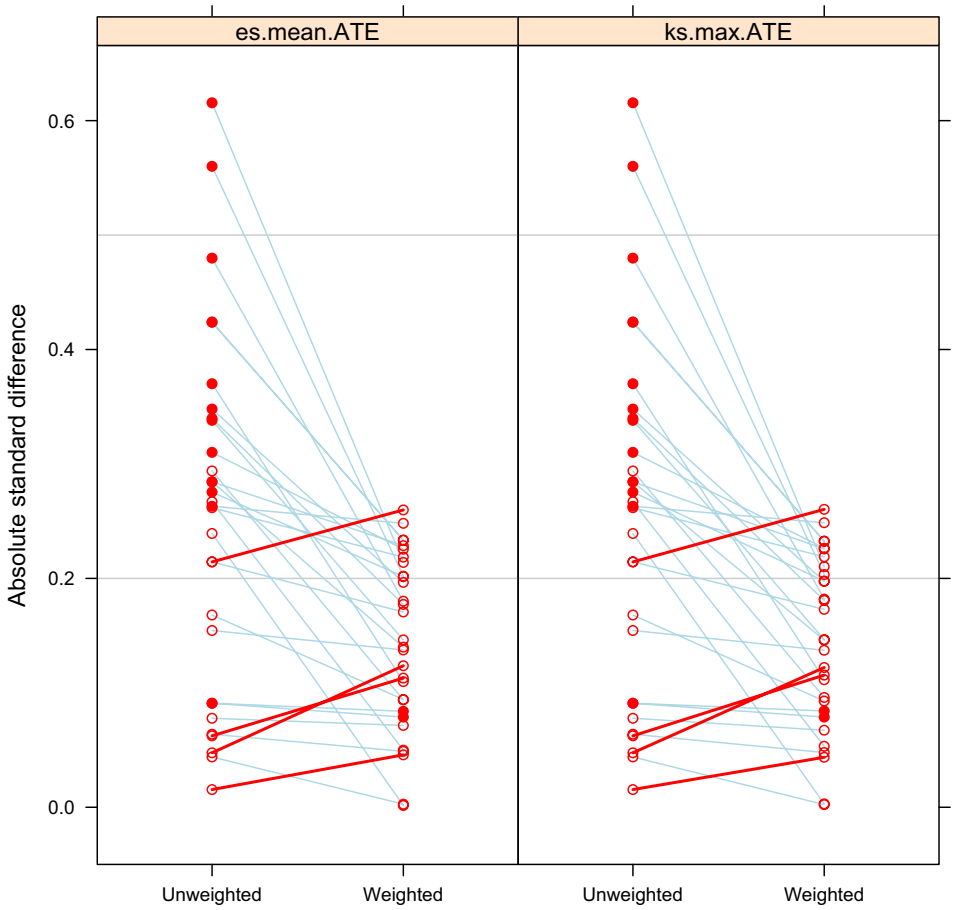

Fig. 2 Covariate balance in terms of standardized mean differences (left) and Kolmogorov–Smirnov distance (right)

Table 6 Confounding variables affecting adverse clinical outcomes after administration of intravenous corticosteroids

Model	Odds ratio	Standard error	*P* value
Unadjusted	0.83	0.44	0.06
IPTW	0.68	0.48	0.16
IPTW + age + ICU	0.74	0.57	0.19
IPTW + age + ICU + HSV	0.27	0.66	0.66
IPTW + age + ICU + HSV + race	0.36	0.64	0.58
IPTW + age + ICU + HSV + race + antibiotics + antivirals	0.31	0.68	0.65

Adverse clinical outcome defined by a Glasgow Outcome Scale (GOS) 1–4. GOS 1 (death), 2 (persistent vegetative state), 3 (severe disability), or 4 (moderate disability) or 5 (mild disability)

IPTW inverse probability treatment weight, *ICU* intensive care unit, *HSV* herpes simplex virus

Previous studies on the effect of corticosteroids on encephalitis

Prior to 2013, epidemiological studies regarding causative factors, mortality rates, and long-term sequelae of encephalitis were limited. Since then, studies have identified risk factors for mortality and poor neurological outcome for adults affected by acute encephalitis to include age 65 years or older, immunocompromised state, coma, mechanical ventilation, acute thrombocytopenia, CSF polymorphonuclear cell count in cases of viral encephalitis, cerebral edema, and autoimmune etiology of encephalitis [15, 16]. There are no prospective studies evaluating the effect of corticosteroid administration in patients suffering from all type of encephalitis. Our goal was to investigate the effect of corticosteroid administration in all etiologies of encephalitis.

Viral encephalitis

Causes of encephalitis are often not identified until later in hospitalization, leading first-line providers to prescribe corticosteroids without confirming the underlying etiology [6]. Although most cases of encephalitis are idiopathic [2], the most common identified causes of encephalitis are viral and autoimmune etiologies. In our study, we identified West Nile Virus, HSV, VZV, CMV, JC virus, as well as enterovirus as causes of encephalitis. HSV-1 is the most common cause of sporadic encephalitis in the United States and worldwide [17, 18]. A small retrospective study of 45 adults with HSV encephalitis found improved mortality on regression analysis when corticosteroids were administered [19]. Mortality in untreated HSV-1 encephalitis is near 70%, with 97% of survivors developing some long-term neurologic sequelae [20, 21]. One-year survival is improved to 85% with antiviral medications and supportive care [22]. There is limited data on adjunctive steroids in other viral etiologies. A small prospective study showed the use of IV dexamethasone did not improve mortality or neurologic sequelae at 3-month follow-up compared to placebo in patients suffering from Japanese encephalitis [23].

Autoimmune encephalitis

Consistent with previous studies, autoimmune etiologies were common causes of encephalitis among our study population [2]. In particular, anti-NMDA-receptor antibodies were found in 26 (93%) of 28 patients suffering autoimmune encephalitis. Studies have described the relationship between HSV-1 encephalitis and the development of anti-NMDA-receptor antibodies associated with recurrence of encephalitis symptoms, therefore immunomodulation from steroid administration is thought to lead to improved functional outcomes and quality of life [24]. In 2015, a small case series of 14 patients showed significant improvement in patients treated with IV corticosteroids and/or IV immunoglobulin therapy [25]. This may be why long-term outcomes are favorable in HSV encephalitis infected mice when glucocorticoids are administered later, rather than earlier [26].

A similar mechanism of illness is suggested in autoimmune disseminated encephalomyelitis (ADEM), classified as a demyelinating disease of the central nervous system (CNS), is similarly improved soon after administration of glucocorticosteroids [27]. The proposed mechanism of recurrent ADEM after the viral or bacterial infection is due to re-activation of T-cell clones against myelin epitopes that mimic the initial offending pathogen [28].

Steroids for encephalitis in our study

Between August 2008 and September 2017, we identified 230 patients with encephalitis, 121 (52.6%) of whom received IV corticosteroids. Our findings showed that patients had worse clinical outcome if they presented with obtundation (GCS < 8), fever, seizures, abnormal neurological exam, status epilepticus, respiratory failure, needed ICU admission, or with brain edema or meningeal enhancement seen on brain MRI (Table 4), consistent with previous studies. Steroids were more likely given to patients with more severe illness (mechanical ventilation, ICU admission, cerebral edema or white matter abnormalities) at the time of presentation. However, whether these patients received corticosteroids to treat severe illness or in response to the results of diagnostic tests remains unclear. As expected, patients suffering from autoimmune etiologies were more likely to receive corticosteroids than those with viral etiologies (92.8% vs 40%, respectively ($P < 0.001$) (Table 3), as one of the standard therapies for autoimmune encephalitis are steroids. An etiology was identified in 51.7% of patients, of which the leading causes were autoimmune, viral, bacterial, fungal and parasitic conditions (Table 3). Overall, there was no difference in ACO between patients who did or did not receive corticosteroids (Table 2).

Microbiology results

Of 230 patients diagnosed with encephalitis in our study, the most common identified infectious etiologies were viruses [65 (28.2%)] consistent with previous studies [3, 6]. All encephalitis guidelines uniformly recommend performing a CSF PCR for HSV, enteroviruses and VZV on all patients with encephalitis [3] but in our study they were only performed in 82.6, 50, and 33.5% of patients, respectively. Furthermore, only 60% of patients had arboviral serologies that could also contribute for a large proportion of undiagnosed viral etiologies. Similarly, bacterial etiologies were identified in 13 (5.7%) of all patients with encephalitis but as 39% of patients received antibiotic therapy before the lumbar puncture there is a possibility that more bacterial causes were not identified.

Predictors for ACO

The independent predictors for an ACO in our study included a Glasgow Coma Score (GCS) < 8, fever, mechanical ventilation, and cerebral edema. Adjunctive steroids were used in half of the patients in our study and did not have an impact ACOs ($P = 0.52$) either on univariate analyses or after propensity score matching. Further studies should determine the impact of steroids on specific etiologies.

Strengths, limitations and future studies

Our study had several strengths. First, this is the first study evaluating the use and impact of adjunctive steroids in adults with encephalitis. Second, our large sample size permitted us to perform a multivariable analysis that was confirmed by propensity score analysis, to evaluate the effect of steroids on ACO. Third, we used the international collaboration of encephalitis definition to only include patients with encephalitis. Finally, our study occurred during the time period that autoimmune etiologies were recognized and evaluated to increase the diagnostic yield of etiologies.

Despite the strengths, our study had limitations. First, due to the retrospective design of the study there was incomplete data and not all patients underwent uniform diagnostic testing leading to underdiagnosed etiologies for viral or autoimmune etiologies. Second, as this was an observational study the use of adjunctive steroids was not randomized introducing propensity bias. While the propensity score model did balance most of the potential confounders, it still showed no benefit of the use of adjunctive steroids. Finally, as this study was performed at one site in Houston and thus should be validated in other geographical areas.

Conclusion

Adults diagnosed with encephalitis continue to be afflicted with significant adverse clinical outcomes in the majority of patients. Adjunctive steroids are used in sicker adults with encephalitis and are not associated with improved clinical outcomes. Further studies should specifically delineate which forms of encephalitis, autoimmune or infectious, would benefit from adjuvant corticosteroid use.

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Compliance with ethical standards

Conflicts of interest RH is a speaker and has research support from Biofire®. All other authors do not have any conflicts of interest.

Ethical standard This study was approved by the University of Texas Health Committee for the Protection of Human Subjects, the Memorial Hermann Hospital Research Review Committee, and the Harris Health Research Committee.

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