Epidemiology of Meningitis and Encephalitis in the United States, 2011–2014

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Background. Large epidemiological studies evaluating the etiologies, management decisions, and outcomes of adults with meningitis or encephalitis in the United States (US) are lacking.

Methods. Adult patients (≥18 years) with meningitis or encephalitis by International Classification of Diseases, Ninth Revision codes available in the Premier Healthcare Database during 2011–2014 were analyzed.

Results. A total of 26,429 patients with meningitis or encephalitis were identified. The median age was 43 years; 53% were female. The most common etiology was enterovirus (13,463 [51.6%]), followed by unknown (4,944 [21.4%]), bacterial meningitis (3,692 [14.1%]), herpes simplex virus (2,184 [8.3%]), noninfectious (921 [3.5%]), fungal (720 [2.7%]), arboviruses (291 [1.1%]), and other viruses (214 [0.8%]). Empiric antibiotics, antivirals, and antifungals were administered in 85.8%, 53.4%, and 7.8%, respectively, and varied by etiologies. Adjunctive steroids were utilized in 15.9% of all patients and in 39.3% of patients with pneumococcal meningitis, with an associated decrease in mortality (6.67% vs 12.5%, P = .0245). The median length of stay was 4 days, with the longest duration in those with fungal (13), arboviral (10), and bacterial meningitis (7). Overall inpatient mortality was 2.9% and was higher in those with bacterial (8.2%), fungal (8.2%), or arboviral (8.9%) disease. Overall readmission rate at 30 days was 3.2%; patients with arboviral (12.7%), bacterial (6.7%), and fungal (5.4%) etiologies had higher rates.

Conclusions. Viruses are the most common cause of meningitis and encephalitis in the United States and are treated with antibiotic therapy in the majority of cases. Adjunctive steroid treatment is underutilized in pneumococcal meningitis, where it has shown to decrease mortality.

Keywords. meningitis; encephalitis; adjunctive corticosteroids; epidemiology; United States.

Meningitis and encephalitis are caused by a wide variety of infectious and noninfectious etiologies, creating diagnostic and treatment challenges to clinicians [1–3]. Furthermore, the majority of patients continue to have unknown etiologies, with some pathogens requiring urgent antimicrobial therapy for cure and survival [4, 5]. Although autoimmune causes of encephalitis such as the anti-N-methyl-D-aspartate receptor antibody encephalitis have to be considered in the differential diagnosis, the majority of the identified etiologies in meningitis and encephalitis are infectious [3–5]. Some viral pathogens such as West Nile virus (WNV), herpes simplex virus (HSV), and varicella zoster virus (VZV) can cause either a meningitis or encephalitis presentation [5, 6].

Three recent studies using the Nationwide Inpatient Sample (NIS) have evaluated the burden, costs, and etiologies of encephalitis and bacterial meningitis in the United States from 1997 to 2010 [7–9]. A major limitation with these studies is the lack of clinical information available through the NIS database. The purpose of our study was to utilize the Premier Healthcare Database (PHD) to evaluate the epidemiology, management, and outcomes of adults with all types of meningitis and encephalitis in the United States from 2011 to 2014.

METHODS

Study Population
Adult patients (≥18 years of age) with an admitting or discharge diagnosis (primary and/or secondary) of meningitis or encephalitis determined by International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes (see Supplemental Appendix A) that were discharged between 1 January 2011 and 31 December 2014 were eligible for the study. If patients had multiple admissions for the same diagnosis, only the first hospitalization was included for analysis. Patients were excluded from the study if the lumbar puncture was done 2 days before or after admission to the hospital, or patients were electively admitted or had a trauma-related admission, had chronic meningitis (ICD-9 diagnosis code: 322.2), or had possible nosocomial meningitis.
(cerebrospinal fluid [CSF] shunt, craniotomies, spinal procedures, or head trauma with CSF leaks during the 30 days prior to admission and at time of admission). All data were de-identified, and no individual data were reported, in accordance with the Health Insurance Portability and Accountability Act.

Data Source
Data for the study were derived from the de-identified PHD, the largest hospital discharge database in the United States. It currently contains data from >619 million patient encounters, or 1 in every 5 hospital discharges in the United States since January 2000 through June 2016. The PHD is a complete census of inpatient and hospital-based outpatient encounters from nearly 700 hospitals in all 50 states in the nation. Hospitals of all sizes, from large tertiary hospitals to small community hospitals in both rural and urban areas, are included in the database. PHD data includes patient demographics, admission and discharge diagnoses and dates, etiologies of meningitis and encephalitis, inpatient mortality, and discharge status. PHD also contains a date-stamped log of billed items, including procedures, medications, laboratory test results, and diagnostic and therapeutic services at the individual patient level. All procedures and diagnoses are captured for each patient, as well as all drugs and devices received. Drug utilization information is available by day of stay and includes quantity, dosing, strength used, and cost.

Data Analysis
Descriptive data were summarized using frequencies and percentages for categorical variables and using mean (standard deviation) or median (interquartile range) for each subgroup. The $\chi^2$ or Fisher exact test was used to compare the differences between subgroups for categorical variables. Two-sample paired $t$ tests was used for comparing differences in continuous variables. All analyses were performed using SAS software version 9.4.

RESULTS

Cohort Assembly
A total of 46,828 adults with an admitting or discharge diagnosis of meningitis or encephalitis were identified. We excluded 4291 patients with repeated admission for the same diagnosis. Among the 42,537 unique adult patients, 31,495 (74%) had a lumbar puncture performed. A total of 26,429 adult patients were included in the study after we excluded patients who had the lumbar punctures done 2 days before or after admission (n = 4620), who had nosocomial meningitis (n = 336), or who had chronic meningitis (n = 110).

Baseline Demographics, Comorbidities, and Site of Care
As seen in Table 1, there was a slight female predominance (53.3%), and the median age of the cohort was 43 years (range, 18–101 years). Non-Hispanic white (49.9%) was the most common race and ethnicity group. A Charlson comorbidity score $>1$ was seen in 16.4% of the patients. The most common comorbidities seen in the study population included diabetes mellitus (15.4%), chronic pulmonary disease (12.8%), renal disease (6.0%), and cerebrovascular diseases (5.8%). Human immunodeficiency virus (HIV) infection/AIDS was seen in 1120 (4.2%). A total of 24,091 (91.2%) patients were admitted to the hospital either through the emergency department (21,013 [87.2%]), from outpatient clinics (2210 [9.2%]), or as a transfer from another facility (868 [3.6%]).

Frequency and Duration of Antimicrobial Therapies
A total of 22,684 (89.7%) patients were treated with intravenous antibiotics, 13,791 (57.2%) with intravenous antivirals, and 2042 (8.5%) with intravenous antifungal therapies (Table 2). Antibiotics were universally administered in bacterial meningitis (99%), but were also given to the majority of patients with viral (enterovirus [EV], herpes viruses [including cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, VZV], arboviruses, other viruses), fungal, and unknown etiologies. The median duration of antibiotic therapy ranged from 3 days in EV meningitis to 8 days in bacterial meningitis. Antiviral therapy (mainly intravenous acyclovir) was frequently administered in viral etiologies (HSV/VZV, 94.6%; arboviruses, 74.2%; EV, 56.6%) and also given in a significant proportion of unknown cases (56.8%), and in patients with bacterial (41.6%) and fungal etiologies (32.9%). Lastly, antifungal was given in 82.8% of patients with fungal meningitis and infrequently (14%) given in other etiologies.

Utilization of Adjunctive Steroids
Intravenous steroids administered on the first day of antibiotic therapy were documented in 4190 (15.9%) of all patients with meningitis and encephalitis with a median duration of 2 days (Table 3). All etiologies received adjunctive steroids empirically, ranging from 10.1% in fungal meningitis to 39.3% in pneumococcal meningitis. The median duration of steroids was higher in those with proven bacterial meningitis (4 days). Only patients with pneumococcal meningitis had a mortality benefit with the use of steroids (6.7% vs 12.5%, $P = .0245$).

Length of Stay, Readmission Rates, and Outcomes
The majority of patients (91.2%) were admitted to the hospital for evaluation and treatment. The median lengths of stay varied by etiologies ranging from 3 days for EV to 13 days for fungal meningitis (Table 4). The length of stay was shorter for EV compared to all other etiologies ($P < .05$). The inpatient mortality (0.5%) for EV was lower than that for all other etiologies except for noninfectious causes ($P < .05$). The highest mortality was observed in patients with bacterial meningitis (8.2%), arbovirus (8.9%), other viruses (11.7%), and fungal meningitis (8.2%). Readmission rates to the hospital within 30 days with
inpatient mortality in the study was low (3.2%), 4188 (17.4%) of patients were discharged to a nursing home/rehabilitation facility or to hospice. A minority of patients were transferred to a different hospital (0.4%).

**DISCUSSION**

This is the largest study to date evaluating the epidemiology, management, and outcomes of adults with meningitis or encephalitis in the United States. The median age of the patients was 43 years; half of them were nonwhite and 16.4% had a significant number of comorbidities, with 4.2% having HIV coinfection. As seen in other studies, patients with meningitis and encephalitis have high rates of hospitalization and empiric antimicrobial use [1, 4, 7]. The majority of the patients were evaluated and admitted through the emergency departments, but up to 22.5% of lumbar punctures were done as an inpatient. This could potentially be explained due to a trend toward interventional radiologists performing the lumbar punctures instead of the treating physicians [10].

Empiric intravenous antibiotic therapy was administered to 22,648 (85.8%) patients even though only 3656 (14%) had bacterial meningitis. This is commonly done as CSF cultures may take up to 72 hours to grow even though clinical models can help clinicians identify with 100% sensitivity a subgroup of patients with zero risk for having an urgent treatable etiology such as bacterial meningitis [4]. Similarly, 14,109 (53.4%) patients received empiric intravenous antiviral therapy, but only 2184 (8.3%) had HSV infection. Intravenous acyclovir is clearly indicated and lifesaving in the subset of patients with HSV encephalitis (approximately 20%) but not in the meningitis cases [6]. The median duration of antiviral therapy in those with HSV was short (5 days), most likely representing the predominance of meningitis cases vs encephalitis [6]. Empiric intravenous antifungal therapy was given only in 2055 (7.8%) of...
all the patients and was given appropriately to the majority of patients with proven fungal meningitis (81.7%) with a median duration of 9 days. This low rate of empiric antifungal therapy is probably due to the low incidence of HIV coinfection (4.2%), where cryptococcal meningitis is more likely.

This is the only study to date that documents the use of adjunctive intravenous steroids in adults with meningitis or encephalitis in the United States. Approximately 15% of all cases received adjunctive steroids on the first day of antibiotic therapy. All the etiological groups received steroids empirically, ranging from 10.1% in fungal meningitis to 39.3% in pneumococcal meningitis. Adjunctive dexamethasone decreases mortality in pneumococcal meningitis and is recommended by several guidelines [2, 11, 12]. In the Netherlands, compliance with this recommendation is excellent as 89% of patients with bacterial meningitis receive adjunctive dexamethasone and has been associated with a nationwide reduction in the mortality of pneumococcal meningitis [13]. A recent population-based study in the United States showed a reduction in the mortality in pneumococcal meningitis cases, but the authors did not report on adjunctive steroids [9]. In this study, even though compliance was low, the use of adjunctive steroids in pneumococcal meningitis was associated with a reduction in mortality (6.7% vs 12.5%, \( P = .0245 \)). Adjunctive steroids are not indicated in viral etiologies [2] and can be harmful in fungal meningitis by increasing disability, side effects, and affecting microbiological clearance [14]. Despite this, 10.1% of fungal cases of meningitis received inappropriately intravenous steroids, which may be associated with a trend toward an increased rate of mortality (13.7% vs 7.6%, \( P = .0705 \)). Additionally, intravenous steroids were not associated with any mortality benefit in other etiologies including HSV, where there is some evidence in the literature suggesting improved outcomes in the subset of patients with encephalitis [15].

### Table 3. Frequency, Duration, and Impact on Inpatient Mortality of Adjunctive Intravenous Steroids in Adults With Meningitis or Encephalitis in the United States, 2011–2014 (N = 26 429)

<table>
<thead>
<tr>
<th>Etiology (No.)</th>
<th>No. (%)</th>
<th>Median Days (IQR)</th>
<th>Mortality(^b) With Steroids</th>
<th>Mortality(^b) Without Steroids</th>
<th>( P ) Value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall sample</td>
<td>4 190 (15.85)</td>
<td>2 (3)</td>
<td>130/4190 (3.10)</td>
<td>643/22239 (2.89)</td>
<td>.5105</td>
</tr>
<tr>
<td>Enterovirus etiology (13 463)</td>
<td>1 905 (14.15)</td>
<td>1 (2)</td>
<td>7/1905 (0.37)</td>
<td>58/11558 (0.50)</td>
<td>.4431</td>
</tr>
<tr>
<td>Unknown etiology (4 944)</td>
<td>638 (12.90)</td>
<td>3 (4)</td>
<td>22/638 (3.45)</td>
<td>225/4306 (5.23)</td>
<td>.0545</td>
</tr>
<tr>
<td>Bacterial meningitis (3 692)</td>
<td>1 121 (30.36)</td>
<td>4 (3)</td>
<td>84/1121 (7.49)</td>
<td>215/2571 (8.36)</td>
<td>.3734</td>
</tr>
<tr>
<td>Pneumococcal meningitis (5 72)</td>
<td>225 (39.33)</td>
<td>4 (2)</td>
<td>15/225 (6.67)</td>
<td>43/344 (12.5)</td>
<td>.0245</td>
</tr>
<tr>
<td>Herpes viruses(^c) (2 184)</td>
<td>267 (12.23)</td>
<td>2 (2)</td>
<td>2/267 (0.75)</td>
<td>43/1917 (2.24)</td>
<td>.1034</td>
</tr>
<tr>
<td>Fungal meningitis (7 20)</td>
<td>73 (10.14)</td>
<td>2 (5)</td>
<td>10/73 (13.70)</td>
<td>49/647 (7.57)</td>
<td>.0705</td>
</tr>
<tr>
<td>Non-ME diagnosis (9 21)(^e)</td>
<td>142 (15.41)</td>
<td>1 (2)</td>
<td>2/142 (1.41)</td>
<td>5/779 (0.64)</td>
<td>.2950</td>
</tr>
<tr>
<td>Arbovirus (291)</td>
<td>26 (8.93)</td>
<td>2 (5)</td>
<td>3/26 (11.54)</td>
<td>23/242 (8.68)</td>
<td>.7149</td>
</tr>
<tr>
<td>Other viruses (2 14)</td>
<td>18 (8.41)</td>
<td>3 (4)</td>
<td>0/18 (0.00)</td>
<td>25/196 (12.76)</td>
<td>.1069</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; ME, meningitis/encephalitis.

\(^a\)First dose of intravenous steroids given on the same day of the intravenous antibiotic therapy.

\(^b\)Mortality comparing etiologies by receipt of intravenous steroids on the first day of antibiotic therapy.

\(^c\)Comparing inpatient mortality in different etiologies by receipt of intravenous steroids on the first day of antibiotic therapy.

\(^e\)Includes herpes simplex virus types 1, 2, and 6; cytomegalovirus; Epstein-Barr virus; and varicella zoster virus.

\(^d\)Final diagnosis not meningitis or encephalitis.

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### Table 4. Length of Stay, Inpatient Mortality, and Readmission Rates\(^a\) in Adults With Meningitis or Encephalitis in the United States, 2011–2014

<table>
<thead>
<tr>
<th>Etiology (No.)</th>
<th>No. (%)</th>
<th>Median Length of Stay (d)</th>
<th>Inpatient Mortality, No. (%)</th>
<th>Readmission Rate, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall sample</td>
<td>26 429 (100)</td>
<td>4 (5)</td>
<td>776 (2.9)</td>
<td>845 (3.2)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>13 463 (51.6)</td>
<td>3 (2)</td>
<td>65 (0.5)</td>
<td>164 (1.2)</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>4 944 (21.4)</td>
<td>5 (7)(^b)</td>
<td>247 (5.1)(^b)</td>
<td>253 (5.1)(^b)</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>3 692 (14.1)</td>
<td>7 (6)(^b)</td>
<td>302 (6.2)(^b)</td>
<td>245 (6.7)(^b)</td>
</tr>
<tr>
<td>Herpes viruses(^c)</td>
<td>2 184 (8.3)</td>
<td>5 (6)(^b)</td>
<td>45 (2.1)(^b)</td>
<td>79 (3.6)(^b)</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>720 (2.7)</td>
<td>13 (12)(^b)</td>
<td>59 (8.2)(^b)</td>
<td>39 (5.4)(^b)</td>
</tr>
<tr>
<td>Arbovirus</td>
<td>281 (1.1)</td>
<td>10 (11)(^b)</td>
<td>26 (8.9)(^b)</td>
<td>37 (12.7)(^b)</td>
</tr>
<tr>
<td>Other viruses</td>
<td>214 (0.8)</td>
<td>8 (9)(^b)</td>
<td>25 (11.7)(^b)</td>
<td>13 (6.1)(^b)</td>
</tr>
<tr>
<td>Noninfectious</td>
<td>921 (3.5)</td>
<td>3 (3)(^b)</td>
<td>7 (0.8)</td>
<td>15 (1.6)</td>
</tr>
</tbody>
</table>

Abbreviation: d, days; ME, meningitis/encephalitis.

\(^a\)Readmission rate within 30 days with the same diagnosis.

\(^b\)Comparing in patients to the enterovirus group (\( P < .05 \)).

\(^c\)Includes herpes simplex virus types 1, 2, and 6; cytomegalovirus; Epstein-Barr virus; and varicella zoster virus.

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### Table 5. Discharge Status and Outcomes in Adults With Meningitis or Encephalitis in the United States, 2011–2014 (n = 24 091)

<table>
<thead>
<tr>
<th>Disposition</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home/home health</td>
<td>18 640 (77.4)</td>
</tr>
<tr>
<td>Nursing home/rehabilitation</td>
<td>39 091 (16.3)</td>
</tr>
<tr>
<td>Hospice</td>
<td>279 (1.2)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>773 (3.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>322 (1.3)</td>
</tr>
<tr>
<td>Transfer to another hospital</td>
<td>106 (0.4)</td>
</tr>
</tbody>
</table>

\(^a\) Among inpatients only.
The median length of stay for the EV cases was 3 days and was lower than the duration of hospitalization for the other etiologies ($P < .05$). This is consistent with the practice of admitting patients with meningitis to await final CSF bacterial cultures [1]. This group was also the one associated with the lower mortality and readmission rates with the exception of the noninfectious cases. The long duration of hospitalization and high rates of mortality and readmission rates in the arboviral cases could be due to a diagnostic bias. A recent large study documented that patients who were sicker or had encephalitis were more likely to be tested for WNV [16]. Bacterial meningitis was also associated with a prolonged length of stay and high readmission rates but the mortality was lower than reported for the years 1998–2007 (8.2% vs 14.8%) [17].

Our study had several limitations. First, the diagnosis of the etiologies was solely based on ICD-9 diagnosis codes in hospital discharge data and was not corroborated with diagnostic tests. Misclassification of etiologies may exist and several etiologies such as VZV and arboviruses are underrepresented, due most likely to lack of testing. Second, available clinical data were limited. This prevented us from evaluating the impact of the independent effect of steroids on mortality controlling for other prognostically significant variables. Despite these limitations, our study had several advantages. First, this is a large study of adults with meningitis or encephalitis in the United States evaluating underlying baseline demographics, site of care, etiologies, and outcomes. Furthermore, this is the first study to report on the use of antimicrobial therapies and adjunctive steroids by different etiologies. It is also the first study to evaluate the impact of adjunctive steroids on mortality in the United States.

In conclusion, meningitis and encephalitis in the United States remain a challenging syndrome to clinicians, with the majority of patients being admitted to the hospital and receiving empiric antimicrobial therapy pending identification of the causative agent. Adjunctive steroids are given in a minority of patients with documented pneumococcal meningitis, and its use is associated with a reduction of inpatient mortality. Earlier identification of the etiologic agents could aid clinicians in better selecting their empiric therapy choices in the future.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
Author contributions. N. R. and J. S. did the data collection, analysis, and interpretation. R. H., S. D., C. C. G., L. Z., J. M. B.-L., and S. B. participated in the data interpretation and literature search and edited the manuscript. R. H. wrote the first draft of the manuscript and made all the changes suggested by the coauthors.

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Potential conflicts of interest. bioMérieux paid for the Premier Database analysis and paid S. D., R. H., and J. M. B.-L. as consultants on the project. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References