

Prevalence and Characteristics of Neuroinfectious Disease Inquiries Within the Emerging Infections Network: A 22-Year Retrospective Study

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Background. To monitor emerging infectious diseases, the Centers for Disease Control and Prevention and the Infectious Disease Society of America established the Emerging Infections Network (EIN), allowing infectious disease specialists to post inquiries about clinical cases. We describe the frequency and characteristics of neuroinfectious disease-related inquiries.

Methods. The EIN listserv was retrospectively reviewed from February 1997 to December 2019 using search terms associated with neurologic diseases. We recorded case summaries, disease type (ie, meningitis, encephalitis), inquiry type (diagnostic approach, result interpretation, management decisions), unique patient populations, exposures, pathogens, ultimate diagnosis, and change in clinical care based on responses.

Results. Of 2348 total inquiries, 285 (12.1%) related to neuroinfectious diseases. The majority involved meningitis (99, 34.7%) or encephalitis (56, 19.6%). One hundred fifteen inquiries (40%) related to management, 34 (12%) related to diagnostic workup, and 22 (8%) related to result interpretation. Eight (2.8%) specifically involved results of cerebrospinal fluid polymerase chain reaction testing. Sixty-three (22.1%) involved immunosuppressed patients (29 human immunodeficiency virus-positive cases [46%]). The most common pathogens were *Treponema pallidum* (19, 6.7%) and *Cryptococcus neoformans* (18, 6.3%). In 74 (25%) inquiries, patients had neurologic symptoms without a clear infection, 38 (51.3%) of which included noninfectious neurologic etiologies in the differential diagnosis.

Conclusions. This study demonstrates the significant challenges of diagnosis and management of neuroinfectious diseases within the field of infectious diseases. It also highlights the importance of curated forums to guide the approach of difficult cases, in particular instances that mimic infectious diseases. Finally, the EIN listserv may assist in identifying areas for research and training to address these complexities.

Keywords. EIN; education; listserv; neuroinfectious diseases; neurology.

Infectious diseases have the potential to affect the nervous system of millions of people worldwide [1]. For instance, approximately 3 million people contracted meningitis and 300 000 people died from the disease in 2016 [2]. With the discovery of new pathogens, a rise in the use of immunosuppressive therapy, improved diagnostics, and recent advances in infectious and autoimmune neurology, the field of neuroinfectious diseases is rapidly evolving [1, 3–7].

A 1992 landmark report by the Institute of Medicine addressed the critical threat posed to society by emerging infectious diseases [8]. This report highlighted infectious epidemics and pandemics and charged the infectious disease community to take steps to mitigate this threat. In response, the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA) launched the Emerging Infections Network (EIN) in 1997—a joint collaboration to identify and monitor new infectious diseases and syndromes [9]. It now comprises more than 2570 infectious disease physicians and members of the public health community located in the United States and abroad. The EIN listserv has 2 member types: infectious diseases physicians and members of the public health community. Infectious diseases physician members are all members of the IDSA or the Pediatric Infectious Diseases Society who see patients on a regular basis. These physician members practice in a variety of settings, including university hospitals, nonuniversity teaching hospitals, city/county public hospitals, community hospitals, and the Veterans' Affairs and

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Department of Defense hospital systems. Most members practice in the United States, with a small number of international members. Public health members include individuals working in a federal (eg, CDC, National Institutes of Health [NIH], US Food and Drug Administration [FDA], and other governmental entities), state, or local public health department and include veterinarians, microbiologists, epidemiologists, and pharmacists [10].

A major feature of this network is an exclusive, moderated listserv that allows physicians and members of the public health community, including CDC, FDA, NIH investigators and epidemiologists, to post inquiries related to challenging clinical issues, ranging from diagnostic dilemmas to management questions. Each post submitted to the listserv is reviewed by a moderator for appropriateness, edition, and removal of patient identifiers. Posts are then collated into a thread with an appropriate title and thread type (eg, clinical, epi, infection prevention, CDC update, FDA recall, etc) and sent out via the listserv platform on a once-daily basis (Monday through Friday only) with a disclaimer attached. Once the inquiry is published, other EIN members provide suggestions to resolve the case. In recent years, the FDA's Center for Drug Evaluation and Research/Drug Shortage group joined the listserv to provide information to its members and surveil antimicrobial drugs. The average number of total separate listserv discussions has been stable over the last decade at approximately 200 inquiries per year, with a total number of responses for all topics ranging from 760 to 976 per year [10].

This article describes the prevalence and characteristics of inquiries related to neuroinfectious disease cases discussed by infectious disease physicians on the EIN listserv. Our goals were to identify the spectrum of inquiries, the pathogens most often discussed, the populations most frequently affected, and finally to characterize recurring themes and unanswered questions to outline future opportunities on research and education in this complex field.

METHODS

Emerging Infections Network Listserv Methods

All members of the EIN community have access to post inquiries to the listserv. The listserv is moderated. All submissions are screened, potential patient identifiers are removed, and a disclaimer is attached to all posts.

Study Design and Setting

We conducted a retrospective study from June 2019 to December 2019. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies were followed.

Neuroinfectious Inquiries Selection

We retrospectively reviewed all inquiries published to the EIN clinical listserv from February 2, 1997 to December 31, 2019.

The EIN clinical listserv primarily consists of clinical queries in which infectious disease physicians present cases and ask questions about their patients to their colleagues. We compiled a list of search terms to broadly capture neuroinfectious disease-related cases, defined as conditions caused by a pathogen that affect the central and/or peripheral nervous system. The search terms were as follows: "meningitis," "encephalitis," "encephalopathy," "myelitis," "myelopathy," "neuropathy," "prion," "dementia," "rhombencephalitis," "neuromuscular," "neurodegeneration," "neurocognitive," "cognition," "demyelinating," "ADEM," "Guillain-Barre," "neurosyphilis," "spinal cord," "flaccid myelitis," "poliomyelitis," "transverse myelitis," "myelopathy," "leukoencephalopathy," "PML," "CJD," "JC virus," "IRIS," "Bell's palsy," "headache," "vasculopathy," "cranial nerves," "cranial neuropathy," "stroke," "radiculitis," "poliradiculitis," "hydrocephalus," "neurocysticercosis," "cerebral," "CSF." Search terms were divided among a group of study team members including neurology residents and fellows (E.M., L.D.-A., K.R., G.W., V.Y.).

The search initially resulted in 853 inquiries, 316 of which were duplicates. Of the remaining 537, 48 were excluded based on the thread category type, keeping only those that discussed clinical cases such as "EIN clinic," "EIN clinical peds," "EIN clinical HIV," and "EIN clinical transplant" and deleting those containing epidemiological information or announcements including "EIN epi," "EIN infection prevention," "CDC update," and "EIN abx stewardship." All remaining clinical inquiries were reviewed, and another 204 queries were excluded for not discussing neuroinfectious inquiries. The remaining 285 were included in the study (Figure 1).

Analysis and Classification of Inquiries

A standardized database was provided to study team members for data collection from each inquiry. We categorized queries to reflect whether the post was seeking advice on diagnostic approach, result interpretation, differential diagnosis, or management decisions. Diagnostic approach was defined as the diagnostic procedure including testing and imaging to discover a pathology; result interpretation was considered as the understanding of a test or imaging result; management decision was interpreted as treatment of a specific pathology or condition. Some inquiries were classified into 2 or more categories. In addition, we recorded whether cases involved specific patient populations (eg, immunosuppressed patients, pediatric cases, and pregnant women) or known exposures (eg, exposure to a particular animal species, patients with recent surgery/instrumentation, those from developing countries or with recent travel abroad). We also collected pathogen type (virus, bacteria, fungus, parasite, and unknown), specific pathogen when available, and ultimate syndromic or specific diagnosis if it was provided in the post. If the final diagnosis was not provided in the post or clinical data were limited to establish a diagnosis, the inquiry was classified as unknown diagnosis. In addition,

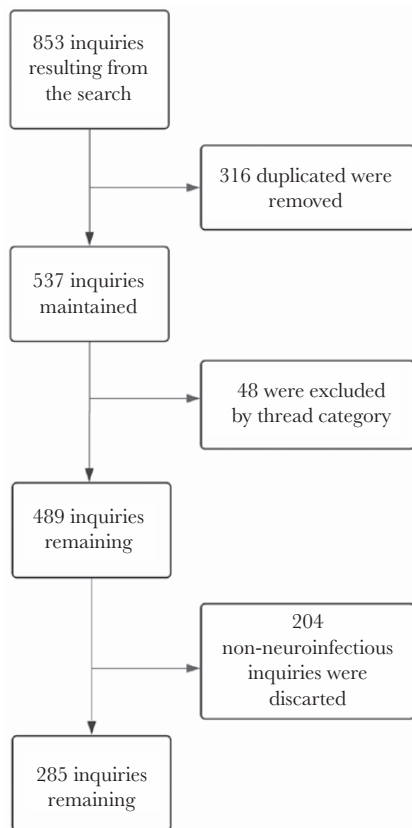


Figure 1. Flow chart of inquiries meeting search criteria, inquiries excluded during selection process and queries meeting inclusion criteria.

inquiries were categorized as to whether clinical care changed based on post responses. Finally, these data were reviewed for recurring questions and themes by the same study team members as well as 2 neuroinfectious disease-trained neurology attending physicians (K.T.T., A.V.); these themes are described under Results.

Statistical Analysis

Descriptive statistics including frequencies and percentages for categorical data were used to describe clinical inquiries. All data were analyzed using R version 3.6.3 (St. Louis, MO). Graphics and flowcharts were done using GraphPad Prism 7 (La Jolla, CA), MyDraw version 4.3.0 (Wilmington, DE), and LucidChart Software for Windows.

RESULTS

Of the 2348 total inquiries between February 1997 and December 2019, 285 (12.1%) cases were associated with neuroinfectious diseases. The majority related to meningitis (99 inquiries, 34.7%), encephalitis (56 inquiries, 19.6%), neurosyphilis (22 inquiries, 7.7%), peripheral neuropathy (12 inquiries, 4.2%), progressive multifocal leukoencephalopathy (PML) (6 inquiries, 2.1%), and brain abscess (5 inquiries, 1.7%), whereas

37 inquiries (12.9%) reported neurological symptoms, signs, or cerebrospinal fluid (CSF) abnormalities, but no definitive diagnosis (Figure 2A). The nature of clinical cases did not change over time (Figure 2B). One hundred fifteen inquiries (40%) related to management, 34 (12%) related to diagnostic workup, 31 (11%) related to other (eg, vaccination after Guillain-Barré syndrome [GBS] or encephalitis, immunosuppression for transplant after West Nile virus [WNV] encephalitis, association of WNV, and stroke), 22 (8%) related to result interpretation, and 83 inquiries (29.1%) were associated with multiple categories (Figure 3).

Many inquiries involved specific patient populations (Supplemental Table 2); 63 (22.1%) were immunosuppressed, 32 (11.1%) were pediatric cases, and 4 (1.4%) involved pregnant women. Among the immunosuppressed patients, 29 (46%) had human immunodeficiency virus (HIV), 21 (33%) were on immunosuppressive therapy (17 [26.9%] due to an underlying autoimmune or rheumatologic condition and 4 [6.3%] due to organ transplantation), 6 (10%) had hematologic malignancies, 2 (3%) had genetic immunodeficiency syndromes, 2 (3%) had undergone splenectomy, 2 (3%) had poorly controlled diabetes, and 1 (2%) had chronic kidney disease. The number of inquiries related to HIV and other mechanisms of immunosuppression remained stable over time, although the latter had a peak in 1998 (Figure 4). The pediatric cases ranged from healthy children with new-onset infections to critically ill children with multiple risk factors and exposures or resistant organisms. There were no clear themes or recurrent questions among the pediatric population.

Some inquiries also involved specific exposures; 9 (3.2%) had recent surgery/instrumentation; 8 (3.5%) had exposure to a particular vector or animal species including ticks (6, 2%), raccoons ([1, 0.3%), and pigs (1, 0.3%); 6 (2.1%) were from developing countries; and 4 (1.4%) had recent travel abroad. With respect to pathogen type, 90 (31.6%) cases involved bacteria, 72 (25.3%) involved viruses, 35 (12.3%) involved fungi, 12 (4.2%) involved parasites; 74 (26%) had no pathogen identified, and 2 (0.8%) involved multiple microorganisms. The most common causative pathogens were *Treponema pallidum* (19 cases, 6.7%), *Cryptococcus neoformans* (18 cases, 6.3%), herpes simplex virus ([HSV] 15 cases, 5.3%), *Borrelia burgdorferi* (12 cases, 4.2%), and WNV (12 cases, 4.2%). The full list of pathogens are available in Supplemental Figure 1.

Based on responses and follow-up posts, 37 (12.9%) inquiries resulted in a change in management. Many included suggestions for diagnostic testing that had not been performed. For example, 1 patient had tick exposure and a responder suggested testing for Powassan virus. This was performed and confirmed to be positive. Another patient had multiple cystic brain lesions with an initial nondiagnostic biopsy. Several responders recommended repeat tissue sampling, which was performed and confirmed glioma. Many also recommended a change in treatment

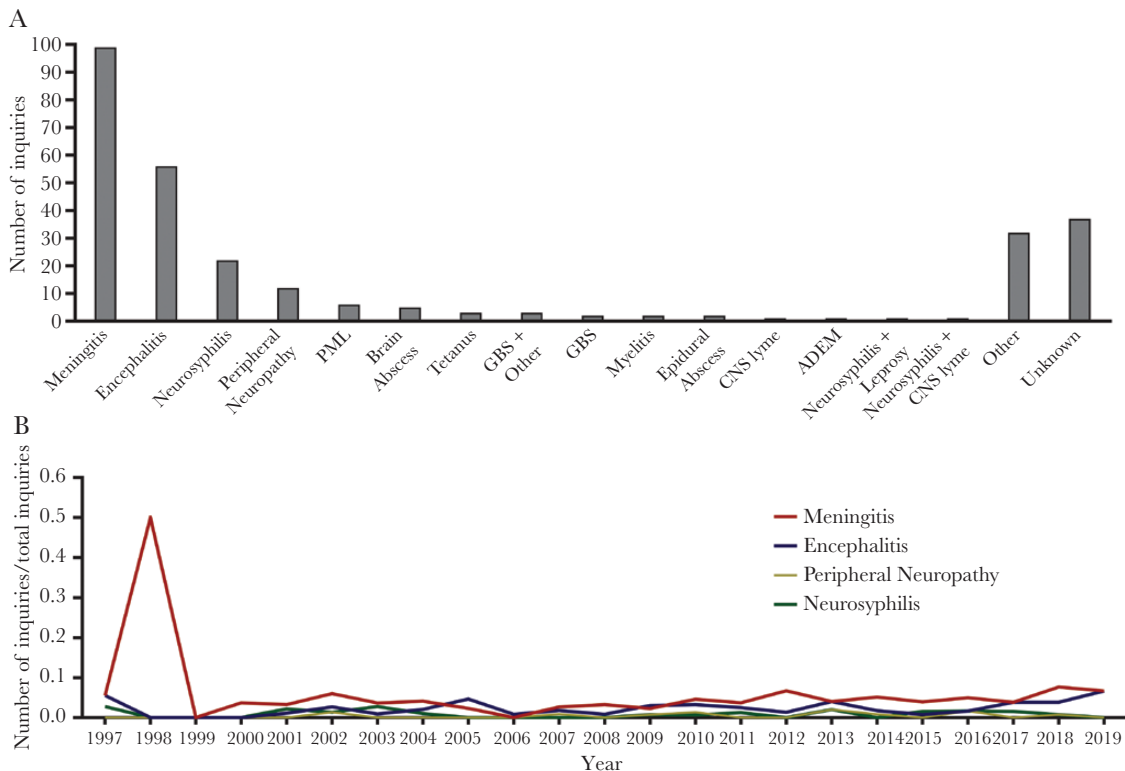


Figure 2. (A) Inquiries classified by disease category. (B) Inquiries by disease over time. ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; GBS, Guillain-Barré syndrome; PML, progressive multifocal leukoencephalopathy.

course (eg, broadening antibiotics, extending a course of antiviral therapy, stopping empiric coverage). In 12 (4.2%) inquiries, a follow-up post confirmed that there was no change in patient care based on responses. The majority of inquiries (236, 82.8%) lacked sufficient follow-up data to determine whether there was a change in management.

Several themes emerged from the data. Eight (2.8%) inquiries specifically related to results of CSF pathogen polymerase chain reaction (PCR) testing. Four (1.4%) of these involved positive

CSF human herpesvirus 6 (HHV6) PCR tests. The 2 early cases (in 2010 and 2011) were immunosuppressed patients with encephalitis who were tested for HHV6 due to high clinical suspicion and found to be positive. The 2 later cases (2017 and 2018) were immunocompetent patients presenting with encephalitis. Both of these patients were found to be HHV6 positive on the Biofire Film Array Meningitis Encephalitis PCR and were started on antiviral treatment. Repeat testing in these patients was persistently positive, and the inquiries requested guidance on whether to continue treatment. Although the final outcome was not available for these patients, there were numerous suggestions from responders to consider chromosomal integration of HHV6 given that HHV6 encephalitis is almost exclusively described in profoundly immunosuppressed patients. The other 4 (1.4%) inquiries involving pathogen PCR testing related to either HSV or varicella-zoster virus (VZV) PCR testing. Two were patients with persistently positive HSV1 PCR despite receiving treatment (one after 2 weeks, one after 5 weeks), both of whom had clinical improvement, and discussion was whether to continue treatment. Responses were mixed—all agreed with completing a 21-day course, but 3 of them (50%) suggested continuing acyclovir until the PCR was negative, whereas 3 (50%) favored stopping after 21 days based on clinical improvement alone. The third case involved a neonate with a fever and initial HSV1-positive PCR that was negative on repeat testing 1 day

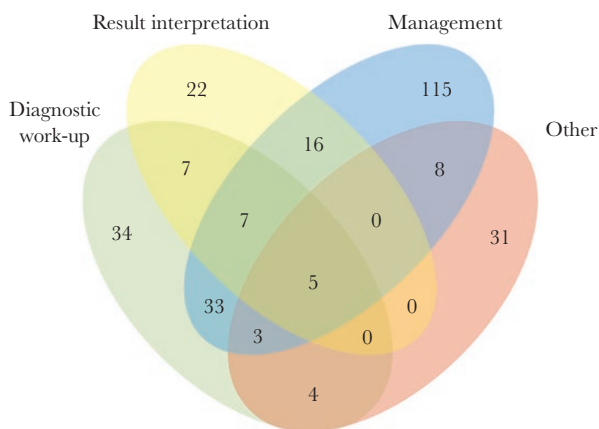


Figure 3. Ellipse Venn diagram of inquiry type.

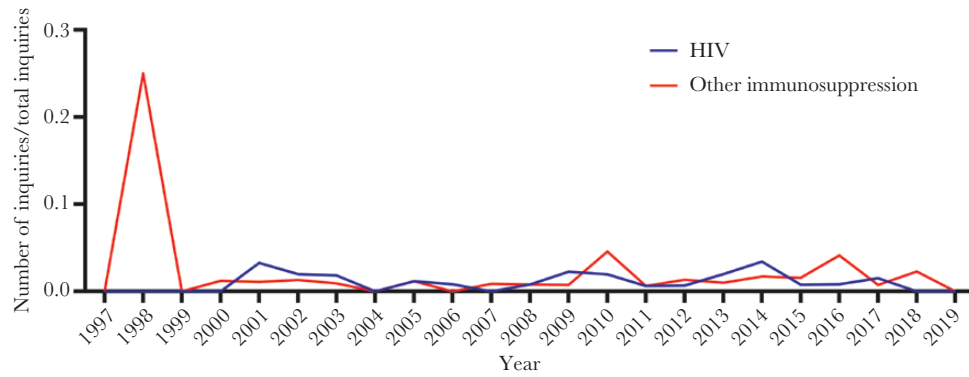


Figure 4. Mechanism of immunosuppression for inquiries related to immunosuppressed patients.

later. The clinical history did not support a diagnosis of HSV encephalitis, and the question was whether to continue treatment. Responses were mixed again: 1 (20%) recommended continuing treatment, 2 (40%) recommended stopping treatment and observing clinically, and 2 (40%) recommended additional testing to inform decision (HSV serologies, imaging, electroencephalogram). The final case involved a patient with clinical worsening and a persistent positivity VZV PCR despite 9 days of treatment, and the post was asking for suggestions for workup and management. There were no responses to this inquiry.

Another common theme in 74 (25.9%) inquiries was the diagnostic work-up and management of patients with neurologic symptoms without a clear infectious etiology. Thirty-eight (51.3%) of these inquiries had noninfectious neurologic etiologies on the differential (either in the initial post or in subsequent responses). The most common noninfectious differential diagnoses were sarcoidosis, lymphoma, acute demyelinating encephalomyelitis, *N*-methyl-D-aspartate (NMDA) encephalitis, neuromyelitis optica, multiple sclerosis, postinfectious encephalitis, Creutzfeldt Jakob disease, CSF leak, GBS, *Pseudotumor cerebrii*, and systemic lupus erythematosus. (Table 1) However, there were a total of 30 distinct etiologies suggested. (Supplemental table 1)

DISCUSSION

The EIN listserv is a forum for discussion of clinical aspects of emerging infectious diseases and new or unusual clinical events [10]. However, data related to neuroinfectious diseases have not been described. Our findings suggest the important and challenging components of neuroinfectious diseases in infectious disease physicians' practice, as demonstrated by the large number of clinical inquiries dedicated to infections affecting the central and peripheral nervous system. It is notable that analysis of this data enables the identification of research and educational priorities that may aid physicians in the diagnosis and management of these complex conditions.

First, the inquiries demonstrate the challenge of diagnosis of neurologic infections in the setting of immunosuppression. Neurologic complications of immunosuppression are increasingly common—approximately one third of patients with solid organ transplants develop neurologic complications, and up to one half of patients with rheumatologic conditions have neurologic manifestations, many of which have been attributed to immunosuppression as opposed to the condition itself [11–13]. Patients with malignancies are even more challenging diagnostically, because they may simultaneously be at risk for central nervous system (CNS) involvement of their malignancy, CNS infections due to immunosuppressive medications, and, more recently, neurologic immune-related adverse events due to novel immunotherapies [14, 15]. With a growing armamentarium of immunomodulatory medications, this challenge is likely to grow.

Table 1. Differential Diagnosis for Possible Noninfectious Cases

Noninfectious Neurologic Differential Diagnoses	Number of Inquiries Where Disease Was Proposed in the Differential Diagnosis ^a
Sarcoidosis	7
Lymphoma	6
Acute demyelinating encephalomyelitis	4
Anti-NMDA encephalitis	4
Primary angiitis of the CNS	4
Devic's disease/neuromyelitis optica	4
Multiple sclerosis	3
Postinfectious encephalitis	3
Autoimmune/paraneoplastic encephalitis	2
Creutzfeldt Jakob disease	2
CSF leak	2
Guillain-Barré syndrome	2
<i>Pseudotumor cerebrii</i>	2
Systemic lupus erythematosus	2

Abbreviations: CSF, cerebrospinal fluid; CNS, central nervous system; NMDA, *N*-methyl-D-aspartate.

^aA single case may have multiple noninfectious differential diagnoses.

The EIN listserv also highlights the complexity of broader pathogen testing through neuroinfectious disease-directed diagnostic panels. There were 2 inquiries related to HHV6 before the approval of the Biofire Film Array Meningitis Encephalitis PCR panel; both patients were tested for HHV6 due to their immunosuppressed status and a high clinical suspicion. However, 2 inquiries posted after the panel was approved involved immunocompetent cases in which the clinical suspicion for HHV6 was exceedingly low. After the panel revealed a positive result in these 2 cases, they both received treatment with antiviral agents. Numerous follow-ups suggested that these 2 results were likely clinically insignificant, perhaps related to chromosomal integration of the HHV6 genome [16]. Although the availability of a multiplex PCR panel has shown benefit in improved pathogen identification, there is also concern with overutilization in patients with low clinical suspicion for CNS infections [16, 17]. With more advanced diagnostics such as next-generation sequencing becoming available, dedicated training may be required to properly interpret testing results within the appropriate clinical context.

Also of interest were inquiries involving patients with neurologic symptoms but without a clear infectious cause. A broad range of noninfectious neurologic etiologies were considered in the differential diagnosis. Noninfectious encephalitis is increasingly being recognized, with autoimmune cases now constituting 20%–30% of all encephalitis cases [18]. This understanding was reflected in many inquiries suggesting anti-NMDA, postinfectious and paraneoplastic encephalitis as possible differential diagnoses. Given the broad range of neurologic disorders entertained, infectious disease specialists may benefit from dedicated training to recognize these processes. There is currently no mention of neurology or neuroinfectious diseases in the Accreditation Council for Graduate Medical Education (ACGME) infectious disease fellowship curriculum requirements [19]. Internal medicine residency curriculum requirements do include exposure to neurology as part of the training but do not specify type or length of exposure [20]. Neurologists would also likely benefit from training in infectious diseases. The ACGME currently requires “sufficient exposure . . . to faculty with special expertise in . . . infectious diseases” as part of the neurology residency training but does not require any infectious disease-related training itself [21]. As of July 2019, there were only 10 non-ACGME accredited fellowships dedicated to neuroinfectious diseases. Efforts are underway to standardize fellowship curricula for neurologists seeking training in neuroinfectious diseases, although there may be additional benefit in development of joint training opportunities for neurologists and infectious disease physicians [22, 23].

Limitations of this study include the retrospective study design. The broad search terms used were intended to comprehensively identify posts related to neuroinfectious diseases and

to try to minimize selection bias; however, it is possible that a few inquiries were missed. Although the classification of inquiries followed clear definitions and a standardized protocol to increase reliability of classification, differences could have arisen between raters. To minimize this issue, the entire database was reviewed by 2 study team members (E.M., L.D.-A.) to ensure consistency among all inquiries. The case summaries were scanned for themes, although based on the level of detail included, there may have been other important trends or themes that were missed. The listserv itself has inherent limitations as well. It reflects the queries and opinions of a small percentage of self-selected infectious disease and public health practitioners and does not necessarily reflect the practice of the infectious disease community as a whole. Moreover, given the nature of the listserv, it was not possible to independently verify the diagnoses, nor to ascertain how changing or updated case definitions may have influenced the reported diagnoses. Reporting bias in the listserv may impact our results and may, for example, account for the increased cases of non-HIV immunosuppression observed in 1998. Finally, although the listserv allowed us to focus on the perspectives of the infectious disease community, the data does not allow us to comment on the perspectives of neurologists and other physicians in approaching neuroinfectious disease cases.

Despite the limitations of the EIN listserv as a research tool, it can be beneficial for clinicians managing these complex cases. As we have shown, the tool can identify recurring questions and dilemmas, and these may be used to address gaps in education and evidence-based guidelines. For example, guidelines on when to send CSF pathogen PCR panels and how to interpret these results may help prevent the use of unnecessary antimicrobial medications. Education on the recommended evaluation and management of autoimmune conditions affecting the CNS (eg, autoimmune encephalitis) may help streamline diagnosis. In addition, understanding specific complications of various immunomodulatory therapies may help to guide diagnostic workup.

CONCLUSIONS

In summary, this retrospective study illustrates the significant and growing challenges related to the care of patients with neuroinfectious diseases in infectious disease physicians' practice, identifies priorities for research and training in the field, and highlights the utility of forums such as the EIN in guiding areas of priority.

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Disclaimer. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services. The Emerging Infections Network's listserv database does not contain any patient's confidential information. All data are deidentified before publication to ensure confidentiality.

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