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MAJOR ARTICLE

Perspectives on Diagnosis and Management of All-Cause Encephalitis: A National Survey of Adult Infectious Diseases Physicians

Marion Le Maréchal,[1] Luisa A. Diaz-Arias,[1] Susan E. Beekmann,[2] Philip Polgreen,[3] Kevin Messacar,[4] Allan R. Tunkel,[5] Kiran T. Thakur,[6] and Arun Venkatesan[1]

[1]Encephalitis Center, Johns Hopkins Hospital, Baltimore, Maryland, USA, [2]Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA, [3]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa, USA, [4]Department of Pediatric Infectious Diseases, Children's Hospital Colorado, Aurora, Colorado, USA, [5]Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA, and [6]Department of Neurology, Columbia University Irving Medical Center, New York, New York, USA

Background. Encephalitis is widely recognized as a challenging condition to diagnose and manage. The care of patients with encephalitis typically involves multiple disciplines, including neurologists and infectious disease (ID) physicians. Our objective was to describe the perspectives and needs of ID physicians regarding encephalitis, using a cross-sectional questionnaire survey.

Methods. We performed a survey among physician members of the Infectious Diseases Society of America's (IDSA) Emerging Infections Network (EIN).

Results. Response rate was 33% (480 among 1472 active EIN physician members). More than 75% of respondents reported caring for patients with suspected encephalitis. Although one-third were involved in the care of multiple patients with autoimmune encephalitis (AE) annually, comfort in diagnosing and managing encephalitis, and in particular AE, was low. Experience with advanced diagnostic tools was variable, as were approaches toward deployment of such tools. Respondents noted that training could be improved by incorporating a multidisciplinary approach taking advantage of online and virtual platforms. ID physicians report a heavy reliance on the 2008 IDSA guidelines for the management of encephalitis, and indicated strong support for a formal update.

Conclusions. ID physicians play an important role in the diagnosis and management of all-cause encephalitis. Despite exposure to AE, few ID physicians are comfortable in recognizing, diagnosing, and treating AE. Moreover, comfort with and use of advanced diagnostic tools for infectious encephalitis was highly variable. Training in encephalitis should include a focus on use and stewardship of advanced diagnostic tools and on collaborative approaches with neurologists and other practitioners on mechanisms and clinical presentations of AE. There is a need for a formal update of 2008 guidelines on the management of encephalitis.

Keywords. encephalitis; guidelines; NGS; training.

Encephalitis is widely recognized as a challenging condition to recognize, diagnose, and treat [1]. The incidence of encephalitis is approximately 5 cases per 100 000 per year [2], with more than half of patients presenting with moderate to severe symptoms [3], and associated with a mortality that is estimated between 5% and 12% [3–5]. Furthermore, survivors are typically left with substantial physical and cognitive disabilities [6, 7]. In addition to the burden on patients and families, the financial burden of encephalitis on the healthcare system is substantial, with total charges for encephalitis-associated hospitalizations in 2010 of $2.0 billion in the United States (US) [8].

Encephalitis can result from a myriad of identified etiologies that are comprised, broadly speaking, of either infectious or autoimmune causes. Therefore, physicians caring for patients with encephalitis need to be able to recognize a wide array of clinical entities. At the onset of illness in most patients, and for the duration of illness in some, it is unclear which category of disease is present. Cases of herpes simplex encephalitis, for example, can demonstrate substantial overlap with those of autoimmune limbic encephalitis, since in both situations an infectious prodrome may be present, there is evidence of a cerebrospinal fluid (CSF) pleocytosis, and there is temporal lobe involvement from a radiologic and clinical standpoint [9]. Moreover, the increasing use of both broad and targeted immunosuppressants for autoimmune conditions can also

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Correspondence: Marion Le Maréchal, MD, PhD, CHU Grenoble-Alpes, Boulevard de la chantourne, 38700 La Tronche, France (mlemarechal@chu-grenoble.fr); Arun Venkatesan, MD, PhD, Neurology Department, Johns Hopkins Hospital, 1800 Orleans St, Baltimore, MD 21287 (avenkat2@jhmi.edu).

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lead to situations in which there is lack of clarity as to whether the encephalitis is related to the primary autoimmune condition or whether it has arisen as an opportunistic infection in the setting of immunosuppression [10]. Thus, both neurologists and infectious disease (ID) physicians are often involved in the initial and ongoing evaluation of patients with suspected encephalitis [11].

As is evident, the care of patients with encephalitis is challenging and often involves multiple disciplines, including neurologists and ID physicians. Within neurology, training usually occurs as part of a neuro-ID fellowship, although such a pathway does not have formal accreditation status in the US. As a result, no formal curriculum exists for training in neuro-ID, although recently a group of neurologists with expertise in neuro-ID developed a consensus curriculum via a modified Delphi method [12]. In addition to guidelines regarding the clinical and laboratory evaluation of patients, the group highlighted the importance of a team-based approach to clinical care, with the involvement of ID physicians.

Little is known, however, about the specific training that ID specialists receive regarding encephalitis, nor of their perspectives regarding testing and evaluation of patients. Our main goal was to describe ID physicians' perspectives toward managing encephalitis, using a cross-sectional questionnaire survey.

METHODS

Participants and Emerging Infections Network

The Infectious Diseases Society of America's (IDSA) Emerging Infections Network (EIN) is a provider-based network developed by the Centers for Disease Control and Prevention to assist public health authorities with surveillance of emerging infectious diseases and related phenomena [13]. It is a flexible sentinel network composed of approximately 2400 ID specialists primarily from North America, including pediatric ID physicians and members of the public health community.

Eligible participants were physician members of the EIN with adult ID practices in the US.

Administration of Survey

Participants received an invitation via email including information about the study and a link to the online survey on 14 June 2022. Two reminders were sent to nonrespondents (first on 22 June 2022, and the second on 30 June 2022). The survey was open from June 14 to 8 July 2022.

Survey Tool Development

The survey was developed by a multidisciplinary team (composed of neurologists and ID physicians), based on the literature [12, 14]. The 11-item questionnaire (Supplementary Data 1) pilot was tested by 2 additional ID physicians (A. T. and K. M.), to assess for length and clarity. It was divided into 3 sections: (1) frequency of encephalitis diagnosis and management; (2) use of new tools for the diagnosis of encephalitis; and (3) resources used for encephalitis management.

Ethical Statement and Patient Consent Statement

The EIN has a standing institutional review board exemption for such surveys. Participation in the survey was voluntary, confidential, and without any financial compensation. No patient-level information was collected.

Data Analyses

Categorical variables were described as absolute numbers and frequencies. For univariate analysis, we used χ^2 test or Wilcoxon-Mann-Whitney test. R software (version 4.2.0) was used.

RESULTS

Participant Characteristics

Of 1472 active EIN physician members, 480 (32.6%) responded to the survey. All were adult ID physicians in North America, 6 of whom were in Canada (1.3%). More than 85% were in practice for ≥5 years, and one-third were in practice for >25 years. Sixty percent (288/480) practiced in a university or nonuniversity teaching hospital (Table 1).

Among the 480 respondents, 374 reported being involved in the care of patients with suspected encephalitis (77.9%). The other 106 respondents reported not caring for patients with

Table 1. Characteristics of the Participants (N = 480)

Characteristic	No. (%)
Adult ID practice	480 (100)
Region[a]	
New England	33 (7)
Mid-Atlantic	70 (15)
Central	169 (35)
South Atlantic	98 (20)
Mountain	24 (5)
Pacific	80 (17)
Canada	6 (1)
Years' experience since ID fellowship	
<5	67 (14)
5–14	155 (32)
15–24	90 (19)
≥25	168 (35)
Primary hospital type	
Community	134 (28)
Nonuniversity teaching	114 (24)
University	174 (36)
VA hospital or DOD	32 (7)
City/county	22 (5)

Abbreviations: DOD, Department of Defense; ID, infectious disease; VA, Veterans Affairs.

[a]For US states included in each region, see https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf.

Table 2. Respondents' Answers Based on Institutional Setting

Survey Item and Answer	University/ Nonuniversity Teaching Hospitals (n = 221) No.	(%)	Other Setting (Community, VA Hospital or DOD, City/ County) (n = 153) No.	(%)	*P* Value
Frequency in which respondents are involved in the care of suspected encephalitis					.164
Frequently	117	(52.9)	70	(45.8)	
Occasionally	78	(35.3)	55	(35.9)	
Rarely	26	(11.8)	28	(18.3)	
Never	0	(0.0)	0	(0.0)	
Frequency in which respondents are involved in the care of infectious encephalitis					.009
Frequently	81	(36.7)	34	(22.2)	
Occasionally	92	(41.6)	74	(48.4)	
Rarely	46	(20.8)	44	(28.8)	
Never	0	(0.0)	0	(0.0)	
Frequency in which respondents are involved in the care of AE					.012
Frequently	16	(7.2)	4	(2.6)	
Occasionally	65	(29.4)	36	(23.5)	
Rarely	123	(55.7)	90	(58.8)	
Never	14	(6.3)	22	(14.4)	
Person who is primarily responsible for a diagnostic evaluation of possible AE at your institution					.487
Only ID physician	4	(1.8)	1	(0.7)	
Only neurologist	125	(56.6)	79	(51.6)	
Combination of ID and neurologist	55	(24.9)	47	(30.7)	
Other	37	(16.7)	26	(17.0)	
Respondents are uncomfortable in					
Recognizing AE[a]	81	(36.7)	67	(43.8)	.213
Diagnosing AE[b]	122	(55.2)	90	(58.8)	.540
Treating AE[b]	195	(88.2)	131	(85.6)	.791
Experience with advanced NGS tools on the CSF					.385
Not aware of this test[c]	18	(8.1)	18	(11.8)	
Never used this test	107	(48.4)	75	(49.0)	
Sent these tests and found them useful	81	(36.7)	46	(30.1)	
Sent these tests, but have never found them useful	15	(6.8)	14	(9.2)	

Abbreviations: AE, autoimmune encephalitis; CSF, cerebrospinal fluid; DOD, Department of Defense; ID, infectious disease; NGS, next-generation sequencing; VA, Veterans Affairs.

[a]One missing data.

[b]Two missing data.

[c]$P = .286$ on subgroup analysis.

suspected encephalitis, and thus opted out of the remainder of the survey. Respondents who opted out had significantly more years of experience ($P < .001$) but otherwise did not differ.

Involvement in Encephalitis Care

Of the 374 respondents who reported involvement in the care of patients with suspected encephalitis, 187 (50.0%) reported involvement with >5 cases of suspected encephalitis per year, 133 (35.6%) with 3–5 cases per year, and 54 (14.4%) with ≤2 cases per year. While 75.1% of respondents indicated involvement with ≥3 cases of infectious encephalitis per year (281/374), 32.4% (121/374) were involved in the care of ≥3 cases of autoimmune encephalitis (AE) per year. Notably, there was no difference in the frequency of involvement in suspected encephalitis by hospital type ($P = .164$; Table 2). However, ID physicians from university hospitals, as compared to the other physicians, were more likely to report frequent involvement in infectious encephalitis care (36.7% vs 22.2%, $P = .009$) and in AE care (7.2% vs 2.6%, $P = .012$).

Most respondents (306/374 [81.8%]) answered that neurologists were primarily responsible for the diagnostic evaluation of possible AE in adult patients at their institution, and this did not differ by hospital type ($P = .487$; Table 2). The second most frequent situation was collaboration of an ID physician and a neurologist for the initial diagnostic evaluation of possible AE (102/374 [27.3%]).

Nearly 40% of respondents were not comfortable recognizing the clinical presentations associated with AE in adults

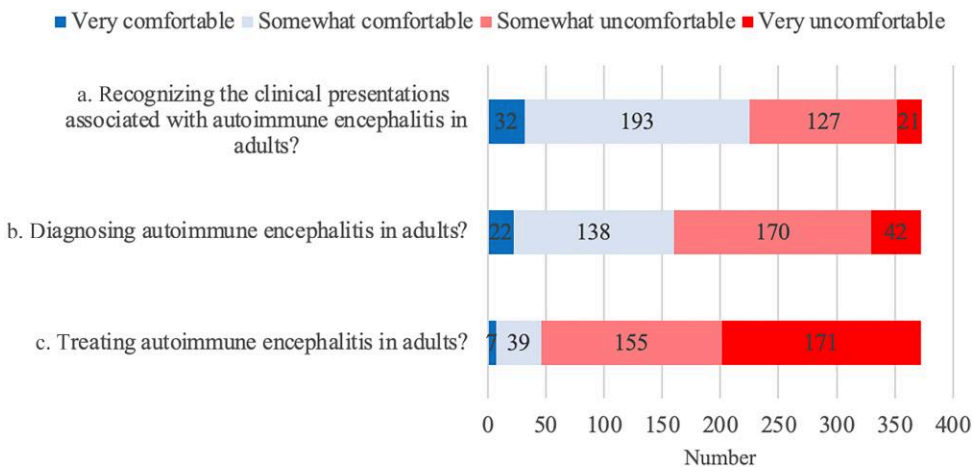

Figure 1. Confidence of respondents in recognizing, diagnosing, and treating autoimmune encephalitis.

(148/373 [39.7%]; 1 missing data), 57.0% were uncomfortable diagnosing AE in adults (212/372; 2 missing data), and 87.6% were uncomfortable treating AE in adults (326/372; 2 missing data) (Figure 1). This discomfort did not differ by hospital type (Table 2), nor by years of practice experience (Supplementary Data 2).

Use of New Tools for the Diagnosis of Encephalitis

Approximately 73% of respondents (272/374 [72.7%]) reported availability of multiplex polymerase chain reaction (PCR) testing on CSF at their local institution. Half of respondents reported no restrictions on the use of multiplex PCR testing on CSF in patients with suspected encephalitis (199/374 [53.2%]). About 20% reported requiring approval prior to testing, including 11.5% (43/374) who required ID and/or microbiology approval and 8.0% (30/374) who reported approved-use criteria (ie, CSF white blood cell count, patient's age); 11.0% (41/374) were not sure about PCR testing on CSF. There was no difference on the restriction for multiplex PCR testing depending on the hospital type ($P = .940$).

For patients with suspected encephalitis, 156 of 374 respondents (41.7%) reported having sent next-generation sequencing (NGS) tests for unbiased pathogen detection in the CSF, and 127 (81.4%) of those reported finding them useful. Half of the total respondents (182/374 [48.7%]) were aware of these tests but had never sent them. Responses did not differ by hospital type ($P = .385$; Table 2), nor by years of practice experience (Supplementary Data 2).

When asked how they would use advanced NGS testing if available with a reasonable turnaround time and covered by the patient's insurance, 83 of 374 (22.2%) stated that they would use this as part of the initial workup in patients with suspected encephalitis. The majority (253/374 [67.6%]) of respondents indicated that they would use such testing only if likely diagnoses were excluded by conventional testing (individual PCR or multiplex PCR, individual antigen/antibody test), slightly over half of whom would use it only if the patient was not improving (142/253 [56.1%]) (Figure 2).

Resources Used for Encephalitis Management

The preferred resources used when dealing with patients with suspected encephalitis were the IDSA clinical practice guidelines [15] (275/374 [73.5%]) and UpToDate (246/374 [65.8%]). The consensus statement of the International Encephalitis Consortium [16] was preferred by 82 of 374 (21.9%) respondents. There was no difference on the use of these resources depending on the years of experience.

Most respondents found a formal update of the 2008 IDSA guidelines for the management of encephalitis to be necessary (307/373 [82.3%]). Of the remainder, 46 of 373 (12.3%) had no opinion as to whether an update was needed, 17 of 373 (4.6%) were unaware of the guidelines, and only 3 of 373 (0.8%) did not find that an update was necessary (1 missing data). This did not differ by hospital type ($P = .544$) or years of practice ($P = .584$).

Improvements for Fellowship Training in Encephalitis

Respondents indicated that fellowship training was the major source of their training/knowledge of encephalitis (345/374 [92.2%]), followed by self-study (eg, journal articles, textbooks, online continuing medical education) (326/374 [87.2%]), and by "on-the-job" training during patient care (317/374 [84.8%]). Conferences were the least used source of training identified (55.6% vs >84% for all the other sources).

Free-response suggestions for improving fellowship training on encephalitis were given by 53 individuals (3 overlapping responses). The responses spanned 5 major themes: (1) suggestions on training on diagnostic methodology/stewardship related to new tools such as NGS or multiplex PCR (n = 16

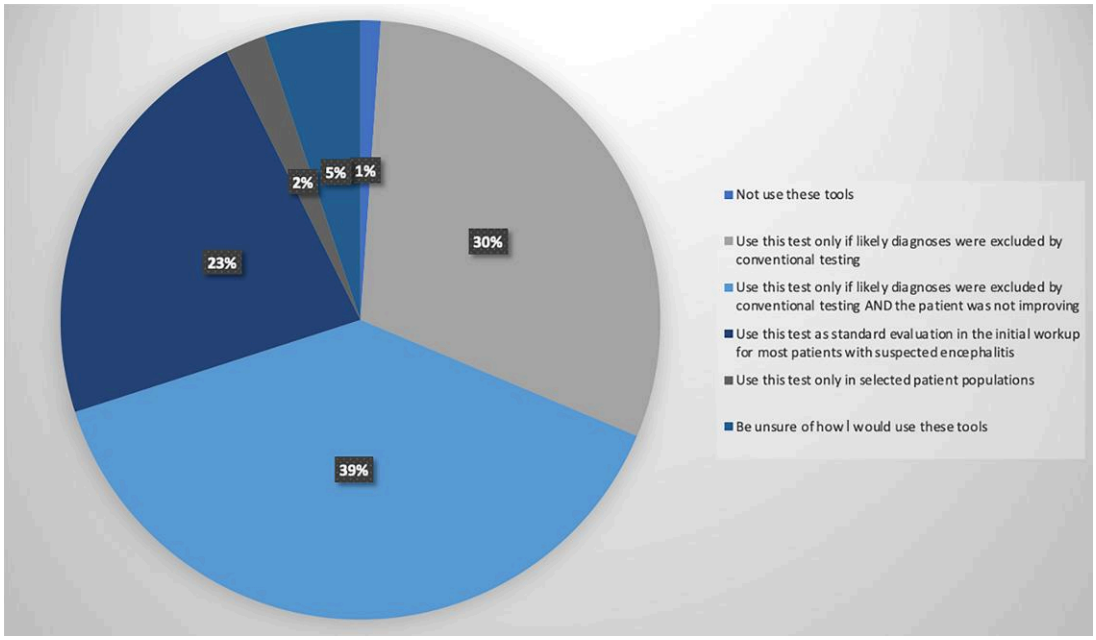

Figure 2. Anticipated and actual use of next-generation sequencing that respondents would have if this tool were available at their institution.

respondents); (2) collaborative training with other fields, including neurology, rheumatology, and radiology (n = 14); (3) suggestions for the format of training, with the inclusion of virtual and online formats (n = 14); (4) suggestions to train specifically on AE or associated mechanisms (n = 7); and (5) suggestions to train specifically on the epidemiology of encephalitis, especially on etiologies that are vector-borne (n = 5) (Supplementary Data 3).

Difficulties and Suggestions Concerning the Care of Patients With Encephalitis

Sixty respondents provided free-response comments regarding the diagnosis and treatment of encephalitis. Notably, 25 of them included terms such as "difficult," "challenging," and "frustrating," indicative of the challenges posed. Specific themes included (1) broad suggestions to improve encephalitis care in the US (n = 20 respondents); (2) comments on the diagnosis stewardship for testing of pathogens in encephalitis (n = 16); (3) difficulties in the treatment of encephalitis (n = 5); (4) challenges associated with the delay in results for antineuronal autoantibodies that were outside their utility window (n = 3); and (5) difficulties in the interpretation of testing, particularly concerning chromosomally integrated human herpesvirus 6 (HHV-6) (n = 3).

DISCUSSION

Summary of Findings

In this survey of nearly 500 ID physicians in North America, >75% reported caring for patients with suspected encephalitis, the majority of whom were involved in the care of numerous patients with infectious encephalitis annually. Although one-third were also involved in the care of multiple patients with AE annually, comfort in diagnosing and managing encephalitis was low. Experience with advanced diagnostic tools was variable, as were approaches on the deployment of such tools. Respondents noted that training could be improved by incorporating a multidisciplinary approach, taking advantage of online and virtual platforms, and focusing on AE, advanced NGS tools, diagnostic stewardship, and the changing epidemiology of encephalitis. Notably, ID physicians report a heavy reliance on the 2008 IDSA guidelines for the management of encephalitis [15] and indicated strong support for a formal update. Overall, encephalitis remains a challenging disease for adult ID physicians, despite improvements in diagnostics and management tools, warranting improved education and updated guidelines.

Role of the ID Physician in Encephalitis

Although the incidence of encephalitis overall is only 5 per 100 000 per year and that of the most common sporadic infectious cause, herpes simplex virus, is only 2–4 per 1 000 000 per year [1, 2], it was notable that the majority of ID physicians in university or other teaching hospitals reported frequent involvement with patients with infectious encephalitis. Even among those in nonuniversity/teaching settings, involvement was substantial. In comparison, involvement with AE was less, though still notable. A full one-third of ID physicians reported involvement with at least 3 cases of AE annually. Such involvement is

not entirely unexpected given the overlapping clinical presentations between infectious encephalitis and AE, since both result in an inflammatory condition of the central nervous system. In addition, the presence of prodromal infectious symptoms in AE, as has been reported in up to 70% of individuals with anti-*N*-methyl-D-aspartate receptor encephalitis [17], for example, can result in frequent and early involvement of ID physicians.

Perspectives on Autoimmune Encephalitis

Despite exposure to patients with AE in clinical practice, remarkably few ID physicians responded being "very comfortable" recognizing the clinical presentation, diagnosing, or treating AE, regardless of experience or practice setting. While comfort with recognition of clinical presentations of AE was higher, comfort levels in diagnosing AE were lower, and lower still for treating AE. The responses to comfort with the diagnosis of AE in adults in our survey were comparable to a recent survey of ID physicians on pediatric encephalitis, in which 45% of physicians were uncomfortable [14]. The identification of clinical characteristics that can distinguish autoimmune from infectious encephalitis—including psychiatric symptoms and tempo of disease [18]—may serve to ameliorate some of the discomfort among ID physicians regarding the diagnosis of AE. Additional training, as highlighted below, may also be of benefit.

Advanced NGS Tools in Encephalitis

We found marked heterogeneity in both experience with and approach to the use of advanced NGS in encephalitis. Despite the first report of the actionable use of NGS in encephalitis almost a decade ago [19], 1 in 10 respondents was unaware of advanced NGS tools for encephalitis and, of those who were aware, the majority had never used them. These figures are comparable to a recent survey in pediatric encephalitis [14]. Respondents' approaches to the use of advanced NGS tools were also quite variable. While advanced NGS tools have the potential to detect novel and potentially treatable pathogens in an unbiased fashion, and in some cases can contribute to excluding an infectious etiology and thus facilitate treatment for autoimmune etiologies, issues such as cost, availability, test characteristics, and interpretation of testing likely contribute to the varied experiences and approaches of ID physicians [20].

Training in Encephalitis

Our survey has identified a number of important facets of training that are in need of improvement. Regarding AE, a combined approach to training, in which ID physicians train along with neurologists, rheumatologists, and other practitioners, may be particularly beneficial given the frequent involvement of multiple disciplines in the clinical evaluation and treatment of patients with AE. In light of the rapid advancement and deployment of newer diagnostic tools such as multiplex PCR and NGS, respondents highlighted the need for training on these methodologies and on stewardship of such tools. This is particularly important given the potential for both false negatives and false positives on such testing, such as the notable example of detection of HHV-6 as a result of chromosomal integration, rather than active infection, via the BioFire assay [21]. In addition, given the ongoing identification of novel autoimmune causes, along with the recognition of emerging and reemerging infectious causes of encephalitis [22], suggestions also included training regarding the changing epidemiology of encephalitis, with a specific focus on etiologies that are vector-borne. Such training should incorporate newer formats to allow for online modules and broader access, a perspective that has been reinforced by the coronavirus disease 2019 pandemic [23].

Need for a Formal Update of 2008 IDSA Guidelines on the Management of Encephalitis

The 2008 IDSA clinical practice guidelines for the management of encephalitis were cited by three-fourths of respondents as a preferred resource when dealing with patients with suspected encephalitis. Surprisingly, fewer respondents cited UpToDate as the preferred resource despite this electronic resource being updated regularly, whereas the IDSA guidelines have not been updated in almost 15 years. The remarkable "staying power" of the IDSA guidelines highlights the important role of the IDSA in crafting and disseminating definitive guidelines that heavily influence the practice of ID physicians. Since 2008, however, innumerable advances have been made in the diagnoses and treatment of encephalitis. Multiplex PCR platforms have become increasingly used in the clinical setting of suspected encephalitis, and advanced NGS has been shown to be useful. Numerous new antibody-associated syndromes have been identified, and newer treatment options for AE—interleukin-6 inhibitors and proteasome inhibitors, among others—have been used [1]. The vast majority of respondents felt that a formal update of the guidelines is necessary. Notably, the need to update the guidelines has also been suggested by Dehority et al in a study of pediatric encephalitis [14], since IDSA guidelines also pertain to children and are widely used by pediatric ID physicians. In light of the strong consensus on updating the guidelines and the facets of training that respondents identified, we would propose that any update to the guidelines include discussion of the uses and limitations of multiplex PCR and advanced NGS, consideration of when to suspect and how to diagnose autoimmune etiologies, and updates to the epidemiology of encephalitis. In light of the multidisciplinary nature of the disease and proposed training, a broad consortium composed of ID physicians (adult and pediatric), neurologists, rheumatologists, microbiologists/laboratory pathologists, pharmacists, and radiologists may be best suited for the task.

Given the pace of discovery, the potential to address gaps in knowledge regarding technologies such as multiplex PCR and metagenomic NGS in coming years, and continual evolution of management, it would be reasonable to formally revisit such guidelines every decade.

Strengths and Limitations

A notable strength of this study was the large number of respondents, representing varied geographic regions and differing health systems throughout the US. Several limitations should be noted, however. While the EIN represents about 18% of IDSA physician members and about 20% of subspecialty board-certified physicians, members "self-select" to join the EIN and thus are not randomly selected and may not represent the broader community of ID physicians. Moreover, the relatively low 33% response rate, which may partially be due to deployment in the summer months only, raises the possibility of response bias. Finally, this survey only addresses ID physicians' opinions on encephalitis management, and further study on other specialists' management for encephalitis would provide a more comprehensive understanding of the challenges and opportunities in the field.

CONCLUSIONS

ID physicians report substantial involvement with patients with encephalitis. This survey highlights the need for (1) multidisciplinary training of ID physicians on diagnosis and management of encephalitis, utilizing in part newer online or mobile formats for broader access; (2) additional research to clarify the role of advanced NGS and other novel diagnostic tools in encephalitis; and (3) a formal update to the 2008 IDSA guidelines for the management of encephalitis, with discussion of topics such as the interpretation and stewardship of newer diagnostic tools for patients with suspected encephalitis and the causes, mechanisms, and management of autoimmune etiologies of encephalitis.

Supplementary Data

Supplementary materials are available at *Open Forum 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

Disclaimer. The findings and conclusions presented in this manuscript are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention (CDC) or the Department of Health and Human Services.

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