1-1-2022

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Recommended Citation

Morrison AR, Jones MC, Makowski CT, Samuel LP, Ramadan AR, Alangaden GJ, Davis SL, and Kenney RM. Evaluation of the selection of cerebrospinal fluid testing in suspected meningitis and encephalitis. Diagn Microbiol Infect Dis 2022; 102(1):115571.

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Diagnostic Microbiology and Infectious Disease 102 (2022) 115571

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Evaluation of the selection of cerebrospinal fluid testing in suspected meningitis and encephalitis

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ARTICLE INFO

Article history:
Received 17 May 2021
Revised in revised form 24 September 2021
Accepted 4 October 2021
Available online 11 October 2021

Keywords:
Diagnostic stewardship
Cerebrospinal fluid (CSF) testing
Meningitis
Encephalitis
Antimicrobial stewardship

ABSTRACT

Diagnostic stewardship interventions can decrease unnecessary antimicrobial therapy and microbiology laboratory resources and costs. This retrospective cross-sectional study evaluated factors associated with inappropriate initial cerebrospinal fluid (CSF) testing in patients with suspected community-acquired meningitis or encephalitis. In 250 patients, 202 (80.8%) and 48 (19.2%) were suspected meningitis and encephalitis, respectively. 207 (82.8%) patients had inappropriate and 43 (17.2%) appropriate testing. Any inappropriate CSF test was greatest in the immunocompromised (IC) group (n = 54, 91.5%), followed by non-IC (n = 109, 80.1%) and HIV (n = 44, 80%). Ordering performed on the general ward was associated with inappropriate CSF test orders (adjOR 2.81, 95% CI [1.08−7.34]). Laboratory fee costs associated with excessive testing was close to $300,000 per year. A stepwise algorithm defining empiric and add on tests according to CSF parameters and patient characteristics could improve CSF test ordering in patients with suspected meningitis or encephalitis.

1. Introduction

Molecular tests provide clinicians with a sensitive, specific, and rapid result for a multitude of pathogens. However, there is a tendency to perform syndromic testing or request multiple tests in an effort to obtain at least 1 positive result (Morgan et al., 2017). In patients with a low pretest probability, unnecessary therapy is a potential consequence of indiscriminate testing because of the difficulty in distinguishing a false-positive from a true positive infection (McGlynn et al., 2015; Morgan et al., 2017; Patel and Fang, 2018). Diagnostic stewardship is a concept designed to optimize the process associated with the analytic phases of test ordering, performance, and reporting (Morgan et al., 2017; Patel and Fang, 2018). Interventions aim to reduce unnecessary testing, which prevents potential downstream effects of false-positives and inappropriate antimicrobial use. This synergistically works with antimicrobial stewardship efforts to curb unnecessary antimicrobial therapy and prevent adverse drug effects and antimicrobial resistance (Morgan et al., 2016). Furthermore, reduction of inappropriate testing can impact microbiology laboratory resources and costs (Hauser et al., 2017).

In central nervous system (CNS) infections, empiric therapy with multiple intravenous antimicrobials is required until the cause is established. Rapid precision diagnostics have become widely available and are an integral component of practice to provide prompt identification and clinical decisions (He et al., 2016; Steiner et al., 2012). To optimize the diagnostic practice in suspected CNS infections, previous studies have suggested algorithms based on cerebrospinal fluid (CSF) analysis (Hanson et al., 2007; Hauser et al., 2017; Mamoojee and Chadwick, 2011; McCreery et al., 2019; Roa et al., 2013; Wilen et al., 2015).

Lumbar puncture is routinely performed for patients who present with mental status changes, and rapid diagnostic tests for multiple etiologies may be ordered prior to knowing the results of chemistry and cell counts. This approach can lead to over testing and false positives among patients who have no CSF parameter abnormalities. Therefore, our institution advocates a sequential approach with selective up-front testing, followed by add on testing if CSF parameters warrant additional work up. The purpose of this study was to assess the appropriateness of CSF polymerase chain reaction (PCR) ordering in the diagnostic management of patients with suspected meningitis or encephalitis using an algorithm-based decision tool.

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https://doi.org/10.1016/j.diagmicrobio.2021.115571
0732-8893/

2. Methods

2.1. Study design and setting

The present study was an IRB-approved, retrospective cross-sectional study conducted at a 5-hospital health system in Michigan. Data was abstracted from the health system's electronic medical record and recorded in a standardized electronic case report form.

2.2. Patient groups and characteristics

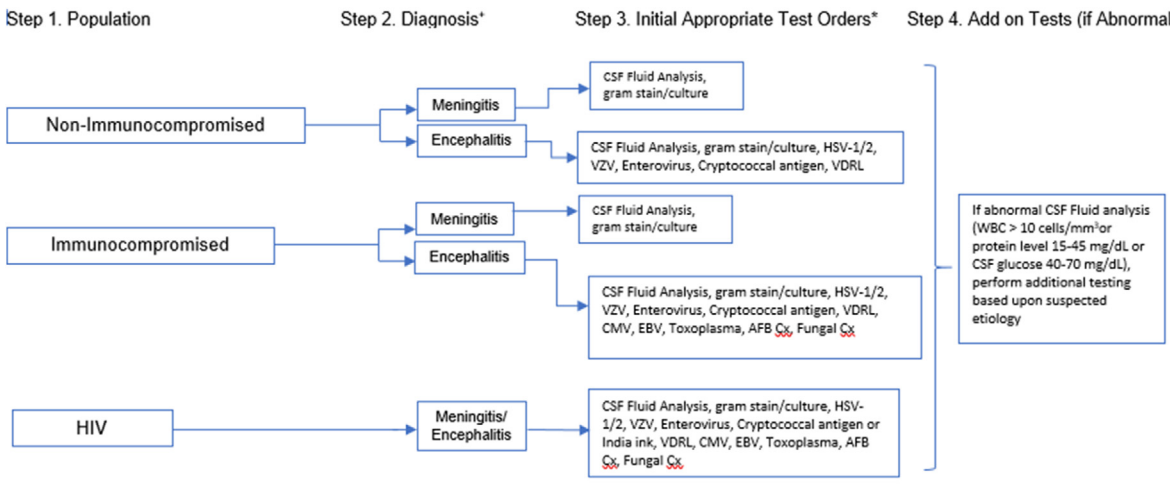
Patients eligible for study inclusion presented between January 1, 2017 and December 31, 2019 and had suspected community-acquired meningitis or encephalitis with a lumbar puncture (LP) performed. Community-acquired was defined as neurological and/or constitutional symptom onset prior to hospital admission. Patients meeting the following criteria were included: age ≥18 years old, orders for any CSF diagnostic test, and CSF test qualified with a positive or negative result. Exclusion criteria included: history of neurosurgery, CNS devices (e.g., CNS shunts, drains, intrathecal pumps, deep brain stimulators), outside hospital system transfers, focal brain lesion on CNS imaging prior to LP, previously known dementia related condition, or penetrating head trauma. The suspected diagnosis of meningitis or encephalitis was defined by the admitting or primary team medical record documentation. No institutional guidance or limitations was in place for the thirteen individual CSF tests. Multiplex PCR CSF panel testing was not available for in-house testing. Patients were compared based on immune status at admission according to medical record documentation (non-immunocompromised (non-IC), immunocompromised (IC), or HIV. Immunocompromised was defined as hematological malignancies, solid malignancies on chemotherapy or immune-modulating agents, bone marrow or solid organ transplant, or systemic steroid equivalent of 20 mg prednisone ≥ 2 weeks.

2.3. Outcomes

In the absence of an established algorithm defining appropriate initial CSF testing for adults, a stepwise algorithm was developed in collaboration with a licensed neurointensivist and infectious disease specialist and in concordance with national guidelines. The algorithm was developed for specific populations including immunocompetent, immunocompromised, and HIV to retrospectively assess the appropriateness of initial CSF laboratory testing (Fig. 1) (Venkatesan et al., 2013). The algorithm emphasizes a sequential approach with CSF fluid analysis and limited up-front testing, followed by add on testing if CSF fluid parameters warrant additional work up. Inappropriate CSF laboratory testing was defined as any initial CSF test ordered outside of algorithm criteria prior to results of CSF fluid analysis. Normal CSF parameters were defined as: white blood cell (WBC) 0-10 cells/mm^3, protein level 15 to 45 mg/dL, CSF glucose 40 to 70 mg/dL (McCreery et al., 2019; Roa et al., 2013; Wilen et al., 2015). If red blood cells (RBCs) were present in the CSF sample a correction was made using a ratio of 500 RBCs:1 WBC. The primary objective was to evaluate associations between patient and provider characteristics and inappropriate CSF testing. Secondary end points included duration of antimicrobial therapy (days), and safety outcomes including 30-day inpatient all-cause mortality, hospital length of stay, development of *Clostridioides difficile* infection within 30 days, subsequent infection with a multidrug resistant organism within 90 days, treatment-related adverse drug events, acute kidney injury (defined as serum creatinine greater than >1.5x baseline or > 0.5 increase from the start of antimicrobials), and complications of outpatient parenteral antibiotic therapy. Additionally, a cost analysis, defined as: median default fee schedule price x median number of excessive tests, was performed to determine default laboratory fee costs associated with excessive inappropriate testing.

2.4. Statistical analysis

Results were reported as median and interquartile range (IQR) for continuous data and compared using the Mann-Whitney test or *t* test, as appropriate. Categorical data was reported as number and percentage (no., %) and compared using the chi-squared test or Fisher's exact test, as appropriate. Data extrapolated from previous pediatric literature looking at the appropriateness of management pathways in CSF infections was used for modeling the expected frequency of appropriate and inappropriate management (Kelly et al.,



+Diagnosis of meningitis or encephalitis was defined according to medical record documentation. Appropriate initial test orders are defined as those specified in algorithm step 3.
*Additional criteria-based testing:
Seasonal (e.g., summer/fall: West Nile Virus and other arboviruses, tick-borne disease)
Location (e.g., arboviruses, tick-borne disease)
Exposure (e.g., rabies, listeria)
Host Factor's (e.g., HHV 6, JC Virus)

Fig. 1. Stepwise CSF Testing Algorithm.

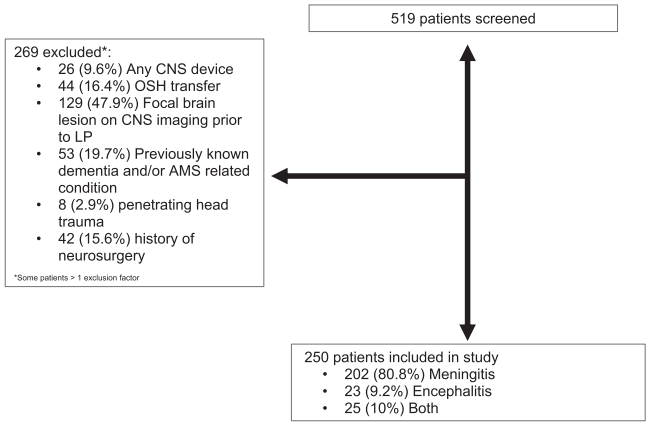


Fig. 2. Number of Patient Screened and Included in the Study.

2012). Assuming an α of 0.05 and β of 0.2, a sample size of 250 patients was selected with an expected 190 inappropriate and 60 appropriate in each group, respectively. All tests with *P* values <0.05 were considered statistically significant. *A priori*, we planned multivariable regression analyses to assess for independent variables associated with inappropriate testing and treatment adverse related effects. Variables with $P < 0.2$ in bivariate analysis and clinical rationale were considered for model inclusion, restricted to a subject-to-variable ratio of 10:1, and reported as odds ratios (OR) and 95% confidence intervals (95% CIs). Statistical analysis was performed using IBM SPSS version 25 (Chicago, IL).

3. Results

After assessment for eligibility, patients were screened until a random selection of 250 patients were included in this study (Fig. 2). Suspected meningitis and encephalitis comprised 80.8% and 19.2% of the population, respectively. Two hundred seven (82.8%) patients were defined as inappropriate, and 43 (17.2%) appropriate testing. Table 1 provides information about patient characteristics, lumbar puncture indication, and location of CSF test ordering. The demographics between appropriate and inappropriate CSF groups were similar regarding sex, 144 (57.6%; *P* value = 0.168) male, and median age of 48 years (33–62; *P* value =0.197). There were differences in immune status with IC (11.6% vs 26.1%, *P* value = 0.048) and meningitis indication for lumbar puncture (95.4% vs 77.8%, *P* value = 0.005), respectively.

The proportion of any inappropriate CSF test was greatest in the IC group (*n* = 54, 91.5%), followed by non-IC (*n* = 109, 80.1%) and HIV (*n* = 44, 80%). In both non-IC and IC groups with suspected meningitis, excessive testing was observed with a median of 3 (2,5) and 5 (3,7) CSF tests per patient, respectively. The most common CSF PCR order was herpes simplex virus (HSV) (Non- IC *n* = 88, 97.8%; IC *n* = 36, 94.7%), followed by varicella zoster virus (VZV) (Non-IC *n* = 43, 47.8%; IC *n* = 24, 63.2%). Among patients with suspected encephalitis, inadequate testing occurred more frequently than excessive testing 57.8% and 86.3% in non-IC and IC groups, respectively. The most common inadequate test was enterovirus, ordered twice in the non-IC group (10.5%) and once in the IC group (6.3%). Similarly, the HIV group experienced a high frequency of insufficient testing (94.6%). Among the subgroup of patients with ≤ 10 CSF WBC/ mm^3, 6 (4.4%) patients had a positive result. Underlying conditions and concurrent infections provided an explanation of the positive results. Table 2 provides a comprehensive summary of the initial inappropriate CSF tests requested between the 3 patient groups.

The single independent factor associated with an increased odds of inappropriate CSF test orders was test ordering performed on the general ward (adjOR 2.81, 95% CI [1.08–7.34]). ID consult prior to lumbar puncture and meningitis indication for lumbar puncture were independently associated with a reduction in inappropriate CSF test orders: adjOR 0.28, 95% CI (0.10–0.79) and adjOR 0.18, 95% CI (0.04–0.74).

Initial antibiotics were prescribed in 76.4% of the cohort with vancomycin (*n* = 168, 87.9%) and ceftriaxone (*n* = 130, 68.1%) being the most common. Additionally, over 50% of patients received acyclovir empirically. The median duration of antimicrobial therapy for patients with non-infectious or aseptic meningitis was 2 (1.75–4) and 3 days (McGlynn et al., 2015; Morgan et al., 2016; Patel and Fang, 2018), respectively. Among the subgroup of patients with ≤ 10 CSF WBC/ mm^3 median antimicrobial duration was 2 (McGlynn et al., 2015; Morgan et al., 2016, 2017; Patel and Fang, 2018) days. Fifty-eight total treatment-related adverse events occurred within 48 (19.2%) patients. The most common treatment related adverse event was acute kidney injury (*n* = 34; 13.6%). After controlling for other factors, recipient of vancomycin or acyclovir were independently associated with an increase in the odds of a

Table 1
Patient and CSF test ordering characteristics.

Variable N (%) or median [IQR]	Total (*n* = 250)	Inappropriate group (*n* = 207)	Appropriate group (*n* = 43)	*P* value
Demographics				
Age, years	48 [33–62]	49 [33–62]	43 [31–60]	0.197
Male gender	144 (57.6)	116 (67.4)	29 (67.4)	0.168
Reason for lumbar Puncture				0.005
Meningitis	202 (80.8)	161 (77.8)	41 (95.4)	
Encephalitis	48 (19.2)	46 (22.2)	2 (4.6)	
Immune status				
Non-IC	136 (54.4)	109 (52.7)	27 (62.8)	0.224
IC+	59 (23.6)	54 (26.1)	5 (11.6)	0.048
HIV	55 (22)	44 (21.2)	11 (25.6)	0.533
Length of hospitalization	4 [3–9]	4 [3–9]	3 [2–7]	0.083
Unit location of order(s)				
ED	153 (61.2)	124 (59.9)	29 (67.4)	0.356
General ward unit	74 (29.6)	65 (31.4)	9 (20.9)	0.171
Intensive care unit	23 (9.2)	18 (8.7)	5 (11.7)	0.562
Consultation service prior to lumbar puncture				
Neurology	48 (19.2)	39 (18.8)	9 (20.9)	0.716
Infectious disease	33 (13.2)	24 (11.6)	9 (20.9)	0.099

HIV = human immunodeficiency virus; IC = immunocompromised.
+ Immunocompromised was defined as hematological malignancies, solid malignancies on chemotherapy or immune-modulating agents, bone marrow or solid organ transplant, or systemic steroids of 20 mg prednisone > 2 weeks

Table 2
Description of inappropriate testing.

	Population tested				
	Meningitis		*Encephalitis*		*Meningitis/ encephalitis*
Test n, %	Non-IC (*n* = 90)	IC (*n* = 38)	Non-IC (*n* = 19)	IC (*n* = 16)	HIV (*n* = 44)
HSV	88 (97.8)	36 (94.7)	19 (100)	16 (100)	39 (88.6)
VZV	43 (47.8)	24 (63.2)	14 (73.7)	11 (68.8)	24 (54.5)
Enterovirus	10 (11.1)	5 (13.2)	2 (10.5)	1 (6.3)	3 (6.8)
Cryptococcus	13 (14.4)	20 (52.6)	7 (36.8)	9 (56.3)	41 (93.2)
VDRL	32 (35.6)	11 (28.9)	13 (68.4)	5 (31.3)	27 (61.4)
CMV	34 (37.8)	18 (46.2)	8 (42.1)	5 (31.3)	22 (50)
EBV	36 (40)	24 (63.2)	10 (52.6)	6 (37.5)	20 (45.5)
Toxoplasma	4 (4.4)	4 (10.5)	2 (10.5)	3 (18.8)	13 (29.5)
AFB culture	8 (8.9)	12 (31.6)	5 (26.3)	2 (12.5)	13 (29.5)
Fungal culture	13 (14.4)	20 (52.6)	5 (26.3)	8 (50)	26 (59.1)
Lyme serology	10 (11.1)	5 (13.2)	5 (26.3)	2 (12.5)	3 (6.8)
West Nile serology	33 (36.7)	19 (50)	5 (26.3)	7 (43.8)	8 (18.2)
JC virus	0 (0)	2 (5.3)	0 (0)	1 (6.3)	2 (4.5)
Total number of CSF tests	324	200	95	73	241
Number of excessive tests	324 (100)	200 (100)	40 (42.1)	10 (13.7)	13 (5.4)
Number of inadequate tests	0 (0)	0 (0)	55 (57.8)	63 (86.3)	228 (94.6)

AFB = acid fast bacilli; CMV = cytomegalovirus; EBV = Epstein Barr virus; HSV = human simplex virus; JC = John Cunningham; VDRL = venereal disease research laboratory; VZV = varicella zoster virus.

Table 3
Multivariate logistic regression for effect on treatment related adverse effects.

Covariate	End point absent (*n*, %)	End point present (*n*, %)	Unadjusted odds ratio	Adjusted odds ratio	*P* value
Vancomycin	41 (85.4)	7 (14.6)	3.28 (1.17–9.21)	3.39 (1.21–9.51)	0.020
Acyclovir	36 (75)	12 (25)	2.37 (0.96–5.85)	2.58 (1.08–6.17)	0.033
Ceftriaxone	23 (47.9)	25 (52.1)	0.38 (0.17–0.827)	0.39 (0.18–0.85)	0.018
Any immunocompromised	28 (58.3)	20 (41.7)	1.71 (0.79–3.68)	1.76 (0.88–3.51)	0.110
ID consult prior to LP	10 (20.8)	38 (79.2)	1.87 (0.77-4.55)	1.91 (0.79-4.61)	0.148
Inappropriate testing	40 (83.3)	8 (16.7)	0.89 (0.35–2.28)	Did not fit	
Cases with $\leq$ 10 CSF WBC/mm^3	24 (50)	24 (50)	0.68 (0.33–1.39)	Not included in final model	

Hosmer and Lemeshow Goodness of Fit = 0.72.

treatment-related adverse event: adjOR 3.39, 95% CI (1.21–9.51) and adjOR 2.58, 95% CI (1.08–6.17), respectively. Receipt of ceftriaxone was independently associated with a reduction in the odds of a treatment-related adverse event adjOR 0.39, CI 95% (0.18–0.85) (Table 3). Outpatient parenteral antimicrobial therapy (OPAT) was required more frequently in the appropriate group (11.6% vs 8.7%; *P* value 0.001). However, OPAT related complications occurred more in the inappropriate group (88.9% vs 40%; *P* value 0.048). Sixteen patients (6.4%) had an infection with an MDR organism within 90 days. Fourteen patients (5.6%) experienced 30-day all-cause mortality.

Cost analysis for excessive meningitis testing per patient was $229.50 (153–382.50) and $382.50 (229.50–535.50), and excessive encephalitis testing per patient was $154.00 (76.50–308) and $114.75 (76.50–153) in non-IC and IC, respectively. When this is applied to the estimated total of patients with suspected community acquired meningitis or encephalitis and CSF testing at this health system in 2019 (~1100; assuming 900 [80%] inappropriate) it amounts to close to $300,000 per year alone of potential default laboratory fee costs associated with excessive inappropriate testing.

4. Discussion

We identified widespread empiric CSF test ordering, prior to knowledge of CSF chemistry and counts, resulting in a high proportion of inappropriate tests. Additionally, provider specialty was a predictor of appropriateness of CSF testing. Orders placed by a general medicine ward prescriber were less likely to be appropriate. Infectious Diseases consultation prior to lumbar puncture improved appropriateness. Suspected encephalitis was associated with undertesting; only 3 out of 35 encephalitis patients had samples tested with an enterovirus PCR, which is recommended as routine by current national guidelines (Venkatesan et al., 2013). Overall, we estimated that inappropriate testing costs our health system at least $300,000 in US dollars annually. Implementation of diagnostic stewardship in the form of a clinical algorithm could improve proper initial CSF test orders and laboratory expenditures, while also decreasing the risk of treatment-related adverse events through discontinuation of unnecessary antimicrobial therapy. Future directions at our institution include education of providers and optimizing the electronic medical record CSF testing order set.

In our present study, we used an initial CSF test ordering algorithm approach from a licensed neurointensivist and infectious disease specialist in concordance with national guidelines based on host characteristics. Additionally, we used CSF WBC cut off value of > 10 cells/mm^3 for further add on testing for immunocompetent and immunocompromised (divided into non-HIV and HIV) patients. This approach minimizes excess up-front testing for patients who are ultimately found to have normal CSF analysis. The majority of previous studies used CSF WBC cut off of >5 cells/mm^3 and/or CSF protein level > 50 mg/dL with some including age and/or immune status for CSF HSV PCR criteria. Others have used acceptance criteria of CSF WBC >10 cells/mm^3 only for immunocompetent patients (McCreery et al., 2019; Roa et al., 2013; Wilen et al., 2015). Additional criteria for immunocompromised have not been evaluated because of their immunosuppressed state and reduced CSF inflammatory markers compared to immunocompetent patients (Hauser et al., 2017). Our algorithm is relatively novel because it incorporates host immune status, multiple CSF markers including WBC, glucose, and protein, and is not limited to HSV.

In previously reported studies, rates of positive viral CNS infections were found in 1% to 5% of patients (Bhaskaran et al., 2013; Davies et al., 2005; Roa et al., 2013; Wilen et al., 2015). Using our algorithm, we detected a positivity rate of 3.1%. The majority of CSF specimens that yielded positive results met our appropriate CSF test ordering criteria and CSF WBC cut off value of > 10 cells/mm^3. Of the 132 patients with ≤ 10 CSF WBC/mm^3, 7 patient's CSF specimens had positive results, and were suspected false positives. Three were positive for VZV and all had facial zoster. Similar to our study, other researchers have reported false-positive CSF VZV PCR tests and suggested viral shedding in patients with facial zoster (Bhaskaran et al., 2013; Cinque et al., 1997). The other 3 patients with ≤ 10 CSF WBC/mm^3 had a reactive VDRL and all had a prior history of neurosyphilis. Two could not be attributed to other ongoing illness processes and required re-treatment for possible neurosyphilis based on risk-benefit assessment. One was attributed to other ongoing illness processes and not treated. Electronic medical record decision support to cancel molecular tests for patients with ≤10 WBCs in CSF analysis may be a helpful strategy to mitigate unnecessary test ordering and false positive tests in this population.

Several limitations are inherent to the design of the study such as selection bias and information bias. Selection bias is a risk because the study population is not guaranteed to be representative of the general population. However, patient selection was done by random sampling during the time period to control for this. To ensure proper algorithm development, algorithm validation was confirmed by an infectious diseases specialist and neurointensivist in concordance with national guidelines. However, some data results were limited to documentation in the electronic medical record. Though our rates of positive results reflect previous studies, institutional practices may affect our prevalence of test ordering and positive results. Distinction between meningitis and encephalitis can be difficult to assess in certain situations. Patients with documentation of suspected mixed diagnosis were classified as encephalitis for the purposes of assessing test ordering appropriateness. The results of this study are not generalizable to pediatrics. Logistical barriers exist for add-on testing as there is potential for incomplete testing or exclusion. Criteria implemented within an institution's electronic medical record and microbiology laboratory for reflex testing assists in overcoming some of these barriers by reporting the rejected sample to the ordering physician for potential re-assessment. Also, all cost calculations are based on default laboratory cost, which likely underestimate the true cost of this complex patient population.

In conclusion, for patients with suspected meningitis or encephalitis, the ordering provider specialty was associated with appropriateness of CSF test ordering. An algorithm that utilizes a sequential approach with CSF fluid analysis and defined up-front testing, followed by add on testing according to CSF fluid parameters and host characteristics could improve patient care and safety by optimizing the usage of CSF test ordering and reducing exposure to antimicrobials in clinical practice. In an era of high-reliability, value-based healthcare, systems must scrutinize and eliminate laboratory testing that is unlikely to impact patient care. Additionally, unnecessary testing in a low-prevalence setting is associated with false positive results (Hanson et al., 2016; McGlynn et al., 2015; Morgan et al., 2017; Patel and Fang, 2018; Zanella et al., 2021) More research is needed to assess the impact of diagnostic stewardship strategies and optimize utilization of CSF tests for suspected meningitis or encephalitis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

A.M., S.D., R.M conceived of the presented idea, contributed to the design and implementation of the research, and to the analysis of the results. M.J., C.M., L.S., A.R., G.A. contributed to the design and implementation of the research. All authors discussed the results and contributed to the final manuscript.

Declaration of competing interest

The authors report no conflicts of interest relevant to this article.

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