103. An Association Between Abnormal CSF Analysis and Inpatient Mortality in Cryptococcal Meningitis, a Tertiary Care Center Experience

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Session: O-22. Neurologic Infections

Background. Cryptococcal meningitis (CM) is a life-threatening condition that requires prompt recognition and management. With high morbidity in mind, we elected to compare the key CSF analysis, blood culture and serum cryptococcal antigen (CrAg) to prognosticate the probability of mortality in this population.

Table 1. Comparison of demographics, serum and CSF analysis

	The non-survivor group (N=19)		The survivor group (n=41)		P value
	N	%	N	%	
Median age (years)	57.47		50.90		0.11
Male	14	73.7%	32	78.0%	0.47
HIV-infection	4	21.1%	10	24.4%	0.52
Transplant patients	3	15.8%	4	9.8%	0.38
Non-HIV, non-transplant	12	63.2%	24	58.5%	0.48
Positive blood culture	9/18	50.0%	12/39	30.8%	0.16
Median serum cryptococcal antigen (IQR)	≥1:512	(1:76-1:640)	≥1:512	(1:128-1:2048)	0.76
Median opening pressure (cm H2O) (IQR)	35	(20.5 – 41.5)	30	(24-41.75)	0.96
Median CSF nucleated cell counts, cells/μL (IQR)	39	(16.5 – 100.5)	72	18 - 152	**<0.001**
Median CSF lymphocyte percentage (IQR)	59.5	(43-76)	76	(38.25 – 87.5)	**0.04**
Median CSF protein (IQR)	93	(60-140.75)	88	(66/172)	0.14
Median CSF glucose, mg/ml (IQR)	27	(16-66.5)	35	(25-46)	**0.02**
Positive India ink finding	9/17	52.9%	25/41	61.0%	0.39
Median CSF cryptococcal antigen (IQR)	≥1:1024	(1:256-1:3072)	≥1:256	(1:32-1:1024)	**<0.001**
Positive CSF culture finding	14/19	73.7%	29/41	70.7%	0.53
Positive Cytopathology finding	10/17	58.8%	18/30	60.0%	0.59

Methods. We retrospectively reviewed all charts of patients admitted to our tertiary care center from 10/2005 to 10/2017. Inclusion criteria encompassed patients with positive CSF CrAg, positive CSF cultures, India ink, cytopathology, or CSF cell count >5 with CNS symptoms, positive serum CrAg titer or blood cultures.

Results. Sixty patients who met the inclusion criteria were divided into the survivor (n=41) and the non-survivor (n=19) groups based on the inpatient mortality. There was no difference in age, sex, and immune status between the two groups. The median CSF nucleated cell counts in the non-survivor group was 39 cells/μL with median lymphocyte 59.5% whereas in the survivor group was 72 cells/μL with median lymphocyte 76% (P< 0.001 and 0.04 respectively). The median CSF glucose was 27 mg/ml in the non-survivor compared to 35 mg/ml in the survivor group (P=0.02). Median CSF CrAg was higher at 1:1024 in the non-survivor group whereas the survivor group was 1:256 (P < 0.01). CSF opening pressure (cm H_2O), blood culture, and serum CrAg level were not statistically significant between the two groups.

Conclusion. Low CSF cell count, low glucose, and high CSF CrAg were independently associated with inpatient mortality in CM. This is in line with the prior findings. A novel finding in this study is significantly decreased median CSF lymphocyte % in the non-survivor group. Serum CrAg titer, positive blood cultures, and median CSF protein were not statistically significant between the two groups. However, a study with a larger sample size may be needed to confirm these findings.

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104. Plague Meningitis - A Systematic Review of Published Cases, Antimicrobial Treatment, and Outcomes

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Session: O-22. Neurologic Infections

Background. Plague meningitis is a rare but serious manifestation of infection with the bacterium *Yersinia pestis.* The risk factors, clinical evolution, and optimal treatment strategies of plague meningitis are not well understood, and data is limited to sporadic case reports. To advance knowledge of this condition and support clinical practice recommendations, we conducted a systematic review of published cases of plague meningitis.

Methods. We reviewed PubMed Central, Medline, Embase, and other databases for publications on plague meningitis in any language. Articles that contained reports of patients with plague meningitis plus information on patient outcome were included.

Results. Among 1,090 articles identified in our search, we found 54 articles describing 83 cases eligible for inclusion. Cases occurred between 1898 and 2015; mean age of patients was 20.5 years (range 6 wks - 64 yrs) and 65% were male. Most patients lived in the United States (23%), Argentina (18%), Vietnam (12%), or China (12%). Four patients (5%) had primary plague meningitis. More than half (59%) of patients developed meningitis secondary to primary bubonic plague; the remainder developed meningitis secondary to other or unknown forms of plague. Of patients with a bubo, 51% had an axillary bubo. The most common symptoms were fever (66%), nuchal rigidity (43%), and headache (35%); 23 patients had focal neurologic deficits such as cranial nerve abnormality. Case fatality rate was 96% (n=23/24) for patients who did not receive antimicrobial treatment and 42% (n=25/59) for patients treated with antimicrobials. Case fatality rate by antimicrobial received, including patients who received multiple antimicrobial classes, was 50% for sulfonamides (n= 38), 50% for fluoroquinolones (n=2), 19% for aminoglycosides (n=21), 11% for chloramphenicol (n=19), and 0% for tetracyclines (n=14).

Conclusion. Plague meningitis has a high fatality rate, but antimicrobial treatment can improve patient outcomes. Having an axillary bubo may be a risk factor for developing plague meningitis – in contrast to our findings, a recent analysis found that only 24% of patients with bubonic plague had buboes in the axillary region. Additional research would be helpful to investigate this association further.

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105. Impact of a Multiplex Polymerase Chain Reaction Panel on Duration of Empiric Antibiotic Therapy in Suspected Bacterial Meningitis

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Session: O-22. Neurologic Infections

Background. Multiplex polymerase chain reaction (PCR) panels allow for rapid detection or exclusion of pathogens causing community-acquired meningitis and encephalitis (ME). However, the clinical impact of rapid multiplex PCR ME panel results on the duration of empiric antibiotic therapy is not well characterized.

Methods. We performed a retrospective pre-post study to evaluate the implementation of the FilmArray ME panel (BioFire Diagnostics, LLC) for diagnosis of bacterial meningitis at our institution. We included adults who presented with suspected bacterial meningitis, received empiric antibiotic therapy, and underwent cerebrospinal fluid microbiological testing in the emergency department. The primary outcome was duration of empiric antibiotic therapy. A bivariable analysis that compared baseline demographics, clinical characteristics, and study outcomes between the pre-ME panel and post-ME panel periods was performed using Mann-Whitney tests, chi-squared tests, or Fisher's exact tests. Time-to-event analysis used the Kaplan-Meier method and log-rank statistics.

Results. In the pre-ME panel period, the positive detection rate of bacterial pathogens was 2.2% (3/137) by cerebrospinal fluid culture and 4.3% (3/69) in the post-ME panel period. Table 1 shows baseline characteristics of patients. Compared to the pre-ME panel period, there were significant reductions in the post-ME panel period for the duration of empiric antibiotic therapy (median 34.7 h, IQR 8.5–61.7, vs. 12.3 h, IQR 3.3–40.0, *P*=0.01), time to targeted therapy (59.3 h, IQR 36.5–74.6, vs 7.02 h, IQR 0.9–12.4, *P*< 0.001), and hospital length of stay (4 d, IQR 2–7, vs. 3 d, IQR 1–5, *P*=0.03), as shown in Table 2. There was also significant reduction in time to discontinuation or de-escalation of empiric antibiotic therapy (*P*=0.049) as shown in Figure 1.

Table 1. Baseline characteristics for patients with suspected bacterial meningitis

Characteristic	n (%) Pre-ME panel (n=137)	Post-ME panel (n=69)	*P* value
Age, median (IQR), years	42 (32–62)	41 (32–57)	0.80
Female	87 (63.5)	35 (50.7)	0.07
Race			0.31
White	62 (45.3)	39 (56.5)	
Black	19 (13.9)	9 (13.0)	
Asian	8 (5.8)	4 (5.8)	
Other	18 (13.1)	4 (5.8)	
Not specified	30 (21.9)	10 (14.5)	
Comorbidities			
Cancer[a]	11 (8.0)	8 (11.6)	0.40
Coronary artery disease	14 (10.2)	4 (5.8)	0.43
Diabetes mellitus	19 (13.9)	7 (10.1)	0.43
Hypertension	34 (24.8)	15 (21.7)	0.62
Use of immunosuppressive drugs[b]	13 (9.5)	12 (17.4)	0.10
Clinical presentation			
Fever	75 (54.7)	37 (53.6)	0.88
Headache	84 (61.3)	49 (71.0)	0.17
Neck stiffness	46 (33.6)	16 (23.2)	0.13
Altered mental status	46 (33.6)	24 (34.8)	0.86
Seizure	10 (7.3)	2 (2.9)	0.34
Focal neurologic deficit	9 (6.6)	6 (8.7)	0.58

Abbreviations: ME, meningitis and encephalitis.

[a] Active cancer, defined by any of the following: diagnosed or receiving therapy within 6 months of presentation; recurrent or metastatic cancer.

[b] Within 30 days prior to presentation. Most common immunosuppressive drugs were systemic corticosteroids (n=14), TNF-alpha inhibitors (n=4), monoclonal antibodies (n=4), and tacrolimus (n=4).

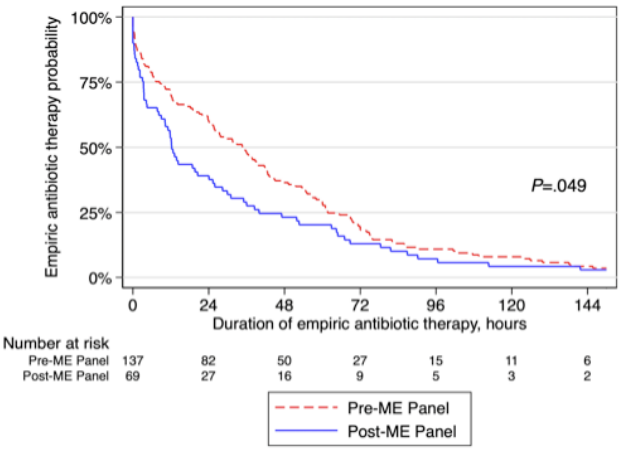
Table 2. Antimicrobial use and hospitalization outcomes

Clinical outcome	Pre-ME Panel (n=137)	Post-ME Panel (n=69)	*P* value
Duration of empiric antimicrobial therapy, hours, median (IQR)	34.7 (8.5–61.7)	12.3 (3.3–40.0)	0.01
Duration of total antimicrobial therapy in hospital, hours, median (IQR)	39.6 (10.3–86.0)	14.3 (4.3–64.9)	0.02
Time to targeted therapy, hours, median (IQR)	59.3 (36.5–74.6)[a]	7.02 (0.9–12.4)[b]	<0.001
Patients hospitalized, n (%)	126 (92.0)	63 (91.3)	0.87
Hospital length of stay, days, median (IQR)	4 (2–7)	3 (1–5)	0.03
In-hospital mortality, n (%)	3 (2.2)	2 (2.9)	1.00

Abbreviations: IQR, interquartile range; ME, meningitis and encephalitis
[a] In the pre-ME panel period, 24 of 137 (17.5%) patients had de-escalation of antibiotics to targeted therapy.
[b] In the post-ME panel period, 14 of 69 (20.3%) patients had de-escalation of antibiotics to targeted therapy.

Compared to the pre-ME panel period, there were significant reductions in the post-ME panel period for the duration of empiric antibiotic therapy (P=0.01), time to targeted therapy (P<0.001), and hospital length of stay (P=0.03).

Figure 1. Probability of Empiric Antibiotic Therapy Between Pre- and Post-ME Panel Periods



Kaplan-Meier analysis of the time from initiation of empiric antibiotic therapy to discontinuation or de-escalation of empiric antibiotic therapy between the pre- and post-ME panel periods. P value from log-rank test=0.049 (n=206). There was a significant difference in the time to discontinuation or de-escalation of empiric antibiotic therapy between the groups (sex- and immunosuppressant use-adjusted hazard ratio, 1.46 [95% confidence interval, 1.08–1.97]; P=0.01).

Conclusion. The implementation of the FilmArray ME panel for suspected bacterial meningitis appears to reduce the duration of empiric antibiotic therapy, time to targeted therapy, and hospital length of stay compared to traditional culture-based microbiological testing methods.

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106. Risk Classification to Differentiate Autoimmune from Viral Encephalitis

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Session: O-22. Neurologic Infections

Background. Autoimmune encephalitis is an urgent treatable etiology that needs to be differentiated from viral encephalitis. Prompt recognition and therapy is of utmost importance.

Methods. We performed a retrospective cohort of encephalitis cases in 16 hospitals in Houston, Texas, between January 2005 and December 2019.

Results. A total of 1,310 adult (age ≥18 years) inpatient hospital admissions were identified by the presence of an encephalitis-related discharge diagnosis per the International Classification of Disease 9th edition codes. Of these, only 279 cases met the 2013 International Encephalitis Consortium criteria for probable encephalitis. A laboratory confirmed diagnosis of autoimmune encephalitis or viral encephalitis was identified in 36 (12.9%) and 88 (31.5%) cases, respectively. There were 155 cases (55.5%) that had no identifiable cause and were considered idiopathic.

As compared to viral encephalitis, patients with autoimmune encephalitis were more likely to be younger (< 60 years old), have a subacute (6-30 days) or chronic (>30 days) presentation, have seizures, and have psychiatric and/or memory complaints (P< 0.001). Furthermore, patients with autoimmune encephalitis were less likely to be febrile and to lack inflammatory cerebrospinal fluid (CSF) (defined as white blood cells < 50 per microliter or protein < 50 milligrams per deciliter) [See Table 1]. In the multivariable logistic regression model, subacute/chronic presentation, psychiatric and/or memory complaints, and lack of inflammatory CSF were significantly associated with autoimmune encephalitis. Using these 3 variables, patients were classified into 3 risk categories for autoimmune encephalitis: low risk (0-1 variables); 0%; intermediate risk (2 variables); 16%; and high risk (3 variables); 83% (P value < 0.001).

Table 1. Baseline and presenting clinical characteristics

		Autoimmune N=36 (%)	Viral N=88 (%)	OR (95% CI)	P value
Age less than 60 y.		33 (91%)	54 (61%)	6.926 (1.97-24-35)	0.001*
Gender					
	Female, n/N (%)	21 (58%)	37 (42%)	0.51 (0.23-1.13)	0.09
Race					
	White	7	42		
	Black	16	18		
	Hispanic	9	20		
	Asian	3	4		
	Unspecified	1	4		
Coexisting medical conditions					
	Immunosuppressed	6 (16%)	23 (26%)	0.56 (0.20-1.53)	0.25
	HIV/AIDS	3 (8%)	16 (18%)	0.38 (0.10-1.42)	0.14
Timing to presentation					
	Subacute (6-30 days) to chronic (>30 days)	31 (86%)	38 (43%)	8.15 (2.89-22.95)	0.000*
Clinical Features					
	Absence of Fever	27 (75%)	27 (30%)	6.77 (2.81-16.34)	0.000*
	Psychiatric, memory complaints	35 (97%)	33 (37%)	58.33 (7.6-445.9)	0.000*
	Seizures	24 (66%)	27 (30%)	4.51 (1.9-10.34)	0.000*
	Absence of Inflammatory CSF (WBC <50/ul or Protein <50 mg/dl)	36 (100%)	42 (47%)	1.85 (1.51-2.28)	0.000*

Conclusion. Adults with encephalitis can be accurately stratified for the risk of having autoimmune encephalitis using clinical variables available upon presentation.

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107. A Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Oteseconazole (VT-1161) Oral Capsules versus Fluconazole and Placebo in the Treatment of Acute Vulvovaginal Candidiasis Episodes in Subjects with Recurrent Vulvovaginal Candidiasis (ultraVioleT)

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Session: O-23. New Developments in Antibiotic Efficacy

Background. Recurrent vulvovaginal candidiasis (RVVC) affects nearly 138 million women globally each year. Currently there are no FDA approved treatments. The study was conducted to evaluate the efficacy of oral oteseconazole (VT-1161) in the prevention of culture-verified acute VVC episodes through Week 50 and compare the efficacy of oteseconazole and fluconazole in treatment of an acute VVC episode in RVVC subjects.

Methods. 219 subjects with history of RVVC (≥ 3 acute episodes within prior 12 months) were enrolled at 51 US sites. The study consisted of two phases.

Induction Phase: Subjects who presented with a vulvovaginal signs and symptoms score of ≥ 3 and positive KOH test identifying *Candida* were randomized to either:

- 600 mg oteseconazole on Day 1, 450 mg oteseconazole on Day 2 and matching placebo capsules; OR
- 3 sequential 150 mg doses (every 72 hours) of over-encapsulated fluconazole together with matching placebo capsules

Maintenance Phase: 185 subjects with resolved acute VVC infections (clinical signs and symptoms score of < 3) on Day 14 received:

- 150 mg oteseconazole or placebo weekly for 11 weeks
- then 37-week Follow-up period

Results. Study achieved primary and secondary efficacy endpoints. Oteseconazole was superior to fluconazole/placebo in the proportion of subjects with ≥ 1 culture-verified acute VVC episode through Week 50 in the intent-to-treat (P < 0.001).

The average percentage of subjects with ≥ 1 culture-verified acute VVC episode through Week 50 was lower in the oteseconazole group (5.1%) compared to the fluconazole/placebo group (42.2%). Oteseconazole was noninferior to fluconazole in the proportion of subjects with resolved acute VVC infections at Day 14; 93.2% oteseconazole group, 95.8% fluconazole/placebo group.

The percentage of subjects who had ≥ 1 treatment-emergent adverse event (TEAE) was similar; oteseconazole (54%), fluconazole/placebo (64%). Most TEAEs experienced were mild or moderate severity in both groups and no drug-related SAEs or adverse effects on liver function or QT intervals.