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Community-Acquired Meningitis in Older Adults: Clinical Features, Etiology, and Prognostic Factors

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Abstract

Background—Bacterial meningitis in older adults is a well-studied and serious disease, but few studies have investigated the epidemiology and outcomes of community-acquired meningitis in older adults.

Methods—We conducted a retrospective study of 619 adults in Houston, Texas, with community-acquired meningitis hospitalized between January 1, 2005, and January 1, 2010. Patients were categorized as older if age ≥65 (N=54) and younger if age 18–64 (N=565). An adverse clinical outcome was defined as a Glasgow Outcome Scale score of 4 or less.

Results—Older patients consisted of 8.7% (54/619) of the total cohort and had higher rates of comorbidities, abnormal neurological and laboratory findings, abnormalities on computed tomography and magnetic resonance imaging of the head and adverse clinical outcomes (ACO) ($p<0.05$). The majority of patients (65.8%) had meningitis of unknown etiology. Bacterial meningitis was an infrequent cause (7.4%). Of the known causes, bacterial meningitis and West Nile virus were more common in older patients. In contrast, younger patients more frequently had cryptococcal and viral meningitis. On logistic regression, female gender was predictive of a poor outcome in the older patients, whereas abnormal neurologic exam, fever, and CSF glucose <45mg/dLwere significant poor prognostic factors in younger patients ($p<0.05$).

Conclusion—Most cases of community-acquired meningitis are of unknown origin. Older patients are more likely to have bacterial meningitis and West Nile virus infection when a cause can be identified. They also have more neurologic abnormalities, laboratory and imaging abnormalities, as well as adverse clinical outcomes.

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Keywords

meningitis; older adults; community-acquired

INTRODUCTION

Community-acquired meningitis encompasses a broad range of infectious and noninfectious causes, but existing studies in the older population have predominately focused on bacterial meningitis[1,2]. In recent decades, the epidemiology of meningitis has changed with the introduction of vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, the development of new diagnostic tools, and the discovery of new infectious etiologies, such as the West Nile virus[3–5]. Changes in host factors also play an important role, as the population shifts towards a larger aging cohort and conditions emerge that compromise the immune system[6]. As a result, older adults have become an increasingly more vulnerable group with high rates of adverse outcomes[3,7].

Diagnosing meningitis in older patients presents a unique challenge due to greater variability of disease presentation[7,8]. The absence of consistent characteristic features can be misleading for the diagnostician, prompting the search for others causes and potentially delaying treatment [7–9]. It is well known that bacterial meningitis is associated with a high morbidity and mortality in the older population [9,10]. However, bacteria remain an uncommon cause of community-acquired meningitis[1], and few studies have described the characteristics of community-acquired meningitis in this older age group. The purpose of this study is to expand the focus beyond bacterial meningitis in order to describe the etiologies and differences in clinical features, laboratory findings, and outcomes between older and younger patients with community-acquired meningitis.

METHODS

Study Design and Case Definition

This is a retrospective descriptive study of 619 adults with community-acquired meningitis. A case was defined as an adult patient (age >16 yrs) with community-acquired symptoms of meningitis (fever, headache, stiff neck, altered mental status or focal neurological symptoms) and cerebrospinal fluid (CSF) white cell count > 5 cells/mm^3, who presented to an emergency department (ED) between January 1, 2005 and January 1, 2010 at 8 Memorial Hermann hospitals in Houston and surrounding areas. The study was approved by the University of Texas Health in Houston Committee for the Protection of Human Subjects and by the Memorial Hermann Hospital Research Review Committee.

Data collection, Laboratory testing and definition of diagnostic outcomes

Baseline patient characteristics were recorded at a specified “zero time”, defined as the time when the patient was in the emergency department. Sociodemographic data, comorbid conditions (measured by the Charlson comorbidity scale)[11], immunocompetence, exposures, clinical features (including neurological exam and Glasgow coma scale[12], laboratory results and management decisions were recorded. The CSF Gram stains were performed on

cytospin samples. Head computerized tomography (CT) scans and magnetic resonance imaging (MRI) of the brain were read by board-certified neuroradiology faculty at the different Memorial Hermann hospitals and classified as abnormal if any intracranial parenchymal abnormality was noted. Cerebral atrophy or concomitant sinusitis was not considered abnormal.

Etiologies of the patients were divided into four categories: a) unknown cause; b) untreatable cause; c) treatable but not urgent cause; d) urgent treatable cause[6]. Etiologies predetermined to represent urgent treatable causes included: bacterial, fungal or mycobacterial meningitis; *Herpes simplex virus* (HSV) encephalitis, *Varicella-Zoster virus* (VZV), or *Cytomegalo virus* (CMV) meningoencephalitis, rickettsial meningoencephalitis; bacteremia; meningeal carcinomatosis; central nervous system vasculitis; parameningeal or intracranial mass lesions (e.g., tumor, abscess); or intracranial hemorrhages[6]. The primary study endpoint was the presence of an adverse clinical outcome. Patient's outcomes were assessed at time of discharge from the hospital by using the Glasgow outcome scale[3]. In this scale, a score of 1 indicates death; a score of 2 indicates a vegetative state (inability to interact with the environment); a score of 3, severe disability (unable to live independently but follows commands); a score of 4, moderate disability (able to live independently but unable to resume some previous activities, either at work or in social life); and a score of 5, mild or no disability (able to resume normal activities with minimal to no physical or mental deficits). An adverse clinical outcome was defined as a Glasgow outcome score of 1–4.

Statistical analysis

Baseline characteristics having a clinically plausible association with an adverse clinical outcome were examined in bivariate analysis. As a variable reduction strategy, only clinically relevant baseline variables showing a bivariate association ($p<0.05$) were entered into a logistic regression model to verify independent associations with an adverse clinical outcome. Fisher-exact test, Chi square, and Student t-test were used in the bivariate analyses. To avoid over fitting in the regression modeling, no more than one variable was entered per 6 outcome events[13].

RESULTS

Cohort Assembly

After screening 727 patients with meningitis, we excluded 108 patients for the following reasons: presence of a ventricular peritoneal shunt (n=24) or post-craniotomy meningitis (n=17); received oral antibiotics before lumbar puncture, were treated with intravenous antibiotics for more than 48 hours, and had no identifiable etiology (n=32); and incomplete medical records (n=35). Therefore, a total of 619 patients were enrolled and divided into younger (age 17–64) (n=565) and older (age ≥65) cohorts (n=54).

Baseline Features and Clinical Findings

Baseline sociodemographic characteristics, comorbidities, clinical and laboratory findings and follow up data are shown in Table 1 and 2. Older adults consisted of 8.7% (54/619) of total cases and differed significantly from the younger cohort with respect to sex, race,

insurance status, comorbidities, and presenting history and exam findings. Older patients were more likely to be female (63.0%), Caucasian (68.5%), and insured (92.6%). Coexisting medical conditions were more common in the older group, with the exception of HIV/AIDS. Comorbidity as defined by a Charlson score ≥1 was present in 59.3% of older vs. 23.9% of younger patients. Similarly, older patients had higher rates of predisposing conditions, such as sinusitis, otitis, and history of central nervous system (CNS) lesions. Younger patients had significantly higher rates of HIV infection and AIDS (11.5% vs.0%), but no difference in immunosuppression status was found after accounting for all causes of immune suppression ($p=0.35$).

Compared to younger adults, the older adults were sicker on presentation with fewer symptoms but more abnormalities on neurologic exam (Table 1). Overall, the most common symptoms included headache (91.3%), nausea (68.0%), subjective fever (63.2%), and stiff neck (45.1%). On clinical examination, 31.2% had nuchal rigidity, 31.0% were febrile (T >38.4°C), and 24.4% had an abnormal neurologic exam. In contrast, older patients presented less frequently with headache, nausea, stiff neck, and photophobia compared to younger patients ($p<0.05$). Abnormal neurologic findings – defined as presence of seizure, abnormal mental status (i.e., disorientation, lethargy, or GCS <15), focal motor deficit, cranial nerve abnormality, or aphasia –were present in the majority of older patients ($p<0.05$).

Laboratory Results and Physician Management

All patients received a lumbar puncture. Serum and CSF findings demonstrated marked differences between the two age groups (Table 2). Older patients had higher median elevations in serum leukocyte counts, CSF leukocyte counts, and CSF protein ($p<0.01$). Indicating the degree of disease severity, they were more likely to have a serum leukocyte ≥12,000 cells/μL, CSF protein ≥100 mg/dL, and CSF glucose <45 mg/dL ($p<0.05$). In addition, older patients more often had positive gram stains and blood cultures ($p<0.01$).

Diagnostic testing beyond the lumbar puncture and gram stain were inconsistently performed as a regular part of the meningitis work-up. Polymerase chain reaction (PCR) testing was done in 47.3% (293/619) of all patients. Even when performed, the rate of positive test results was low: 27.0% in older adults and 10.8% in younger adults. Older patients were more likely to have a positive bacterial culture ($p<0.05$). CSF cultures for other etiologies were infrequently performed.

No significant differences in admission rates and initiation of empiric antibiotic and antiviral therapy between both groups were noted ($p>0.05$). Most patients were admitted to the hospital (97.1%); 74.0% received empiric antibiotic therapy, and 25.5% received empiric antiviral therapy. A head CT scan was performed in 553 (89.3%) patients as part of their initial evaluation in the ED with only 41 (7.4%) scans being abnormal. Additionally, 290 (46.8%) also underwent an MRI of the brain, with 109 (37.6%) of them being abnormal. Older patients were more likely to have an abnormal result on CT and MRI ($p<0.01$). Follow up information at discharge was available on all patients. The majority of patients (88.7%) had no residual neurological morbidity; but 70 patients (11.3%) had an adverse clinical outcome, in which the older cohort had significantly higher rates of adverse outcomes (51.9% vs. 7.4%) ($p<0.01$).

Diagnostic Causes and Clinical Outcomes

Diagnostic causes for the episode of meningitis were identified for 212 patients (34.2%). The majority of patients with meningitis had an unknown etiology (407 patients, 65.8%). An urgent treatable cause was identified in 127 patients (20.5%), which included bacterial meningitis, *Cryptococcus neoformans* meningitis, VZV, HSV encephalitis, toxoplasmosis, tuberculosis, brain tumors, and other miscellaneous conditions. Untreatable causes, such as Enterovirus, EBV, *West Nile Virus* (WNV), or St. Louis encephalitis, were identified in 44 (7.1%) patients. Forty-one patients (6.6%) had a non-urgent treatable etiology, which included HSV meningitis, neurosyphilis, multiple sclerosis, HIV seroconversion, influenza type A, and CMV. (Table 3)

Older patients were more likely to have meningitis of an urgent treatable or untreatable cause, whereas younger patients tended to have more non-urgent or unknown causes of meningitis (all $p<0.05$). Bacterial meningitis was an infrequent cause overall (46/619 = 7.4%) but did occur more often in older patients ($p<0.05$), affecting 16/54 patients (29.6%), as compared to 30/565 (5.3%) of the younger patients. *Streptococcus pneumoniae* remained the leading cause of bacterial meningitis for both groups. More organism diversity was represented in the younger cohort, and group B Streptococcus was found exclusively in the older group. Among urgent treatable causes, bacterial meningitis was most likely to cause an adverse clinical outcome in older patients (8/13). WNV encephalitis was another common etiology and was responsible for all adverse outcomes due to untreatable causes for both cohorts. In situations of an unknown etiology, the older group had more adverse clinical outcomes (36.4% vs. 3.1%, $p<0.05$). In contrast, younger patients were more likely to have cryptococcal and enteroviral meningitis ($p<0.05$). Causes of adverse outcomes in this group were more diverse, consisting of bacterial, viral, fungal, and unknown causes, but the risk for an adverse outcome was lower across all etiology categories ($p<0.05$), except non-urgent treatable causes where no adverse clinical outcomes occurred.

Factors Associated with Adverse Clinical Outcomes

We used bivariate analysis to identify potential predictors of adverse clinical outcomes and found female gender to significant in the older adult cohort. (Table 4) This variable remained significant after logistic regression modeling with validation by bootstrapping, where female gender had an odds ratio (OR) of 5.81 (95% CI: 1.63 – 20.70, $p<0.01$). (Table 5) Interestingly, no association was detected between female gender and any other variable in the bivariate analysis. (Data not shown)

In the younger adult group, presence of comorbidity, abnormal neurologic exam (including abnormal mental status, GCS score <15, seizures, and focal neurologic deficits), fever ($T>38.4°C$) and abnormal laboratory findings (serum leukocyte ≥12,000 cells/μL, elevated CSF protein ≥100 mg/dL, decreased CSF glucose <45 mg/dL) were all significantly associated with an adverse clinical outcome in the bivariate analysis. (Table 4) Clinical variables remaining significant after logistic regression analysis with bootstrapping included abnormal neurologic exam (OR=12.84, 95% CI: 4.98 – 33.15), fever (OR=2.72, 95% CI: 1.20 – 6.13), and CSF glucose <45 mg/dL (OR=5.24, 95% CI: 2.19 – 12.58). (Table 5)

DISCUSSION

This study is the largest to date analyzing clinical features and prognostic factors for community-acquired meningitis of bacterial and non-bacterial causes in older adults. Existing studies have focused exclusively on confirmed cases of bacterial meningitis [8–10,14] or have limited sample size[2]. We demonstrated that community-acquired meningitis in older adults differs significantly from younger adults with respect to clinical features, etiology, and outcomes. Older patients have more co-morbidities and neurologic abnormalities on exam, yet have fewer symptoms of headache, nausea, stiff neck, and photophobia. (Table 1) These results are consistent with the current literature on acute bacterial meningitis in the older population [2,9,10]. It is noteworthy that the presence of neurologic compromise can interfere with a patient's ability to relay important historical details, such as having a headache or stiff neck. This suggests that neurologic abnormalities are not only responsible for fewer meningitis symptoms, but may, in part, explain the variability of disease presentation described in the older population[7,8].

Both cohorts received similar triage management, including no differences in the rate of head CT imaging (Table 2), which has been identified as a major reason for delaying antibiotic therapy [8,10]. Empiric antibiotics were also given at similar rates. Older patients more often had abnormalities on CT scanning, prompting further imaging with MRI, which were also more likely to be abnormal. Laboratory results more often showed serum leukocytosis, elevated CSF protein, and hypoglycorrhachia. This trend can be explained in part by the greater frequency of bacterial meningitis in this population. Younger patients with similar laboratory findings were also more likely to have a bacterial cause, but this may also be indicative of disease severity. Abnormalities on presentation, labs, and imaging showed that older patients were indeed sicker at initial presentation.

Meningitis of unknown cause accounted for a significant portion of cases (65.8%). (Table 3) Unknown etiologies present a clinical dilemma for the diagnostician because the main benefit to pursuing an etiology is early identification of an urgent treatable cause and initiation of appropriate treatment[6,15]. Many of the unknown cases were presumed to be viral meningitis, which tend to have a better prognosis. However, in the older cohort, 36.4% of patients with meningitis due to unknown etiology had an adverse clinical outcome. This is compared with 3.1% in the younger cohort. When the gram stain or bacterial culture is negative, CSF results alone are insufficient for differentiating between bacterial and non-bacterial causes, although CSF lactate and serum procalcitonin levels have shown diagnostic promise[16–18]. Unfortunately, microbiology testing was underutilized as a diagnostic tool in this study. While almost every patient had a gram stain and bacterial culture, less than half of the patients had a PCR result, and PCR testing was infrequently ordered on patients with unknown etiologies. PCR has higher diagnostic yield than both viral cultures and intrathecal antibody testing for viruses but may still fail to identify an etiology in over half of aseptic meningitis cases[19].

Of known causes, bacterial meningitis and WNV were more common in older adults, and both had higher rates of adverse clinical outcomes. *Streptococcus pneumoniae* was the most common cause of bacterial meningitis in both groups. Cryptococcal meningitis and viral

meningitis, such as enterovirus and HSV, were more likely to affect younger adults, and they experienced fewer adverse outcomes overall. The number of cryptococcal meningitis cases can be explained by a higher prevalence of HIV/AIDS leading to immune system suppression.

Appropriately risk stratifying an older patient presenting with suspected community-acquired meningitis will continue to remain a challenge due to variable clinical presentation and relatively few prognostic factors. This study identified female gender to be independently associated with a poor outcome. The reason for this is not readily apparent. Confounding is unlikely due to the lack of association with other variables of interest (ie. comorbidities, immunocompetency, HIV/AIDS, abnormal neurologic exam, urgent treatable causes, serum leukocytosis, CSF protein ≥100 mg/dL, CSF glucose <45 mg/dL) ($p>0.05$). (Data not shown) In contrast, abnormal neurologic exam, fever, and hypoglycorrhachia were significant prognostic factors in younger adults. Neurologic compromise appears to be a robust indicator of disease severity for both cohorts, and this finding has been well supported by research on bacterial meningitis in adults [3,20].

While this is the first study to describe the complete spectrum of community-acquired meningitis, including the unknown and non-bacterial causes, several limitations exist. With a retrospective study design, it was not possible to standardize the diagnostic work-up for each patient, so missing data were inevitable. To avoid potentially misclassifying patients with “urgent treatable” causes as “unknown” due to pre-treatment with antibiotics, we excluded 32 patients who either received oral antibiotics before lumbar puncture, were treated with intravenous antibiotics for >48 hours, and had no identifiable etiology. This study population was drawn from the Houston area only, so the results should not be generalized to other geographical areas without further confirmatory studies. After the diagnostic evaluation, we discovered several cases that were misdiagnosed as meningitis (e.g., vasculitis, lymphoma, bleed, abscess), due to similar presentations. This illustrates the challenge in recognizing meningitis from other conditions, though physicians should continue to maintain a high index of suspicion for meningitis as rapid treatment of urgent treatable causes can be life-saving. Finally, the large percentage of patients with an unknown etiology (65.8%) means there is much we do not yet understand about this syndrome.

Risk scores exist to predict outcomes for patients with bacterial meningitis [21], but we have shown that there are a significant number of adverse clinical outcomes not attributable to bacterial meningitis. More recently, risk stratification models were developed for patients with a negative Gram stain [22,23]. Better understanding of the clinical spectrum and prognostic factors for community-acquired meningitis will help guide our diagnostic and management decisions to improve patient outcomes.

Conclusion

Community-acquired meningitis in older adults differs significantly from younger adults with regards to clinical presentation, etiology, and disease severity. Older patients present with more neurologic compromise and abnormalities on laboratory and imaging results. Bacterial meningitis and WNV are common causes of disease, and they have higher rates of adverse clinical outcomes. Among older adults, females have poor outcomes, whereas an

abnormal neurologic exam, fever, and hypoglycorrhachia were poor prognostic factors for younger patients. Meningitis of unknown etiology is a significant cause of adverse clinical outcomes, and better diagnostic tools and guidelines are needed to identify treatable causes and standardize disease management.

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TABLE 1

Baseline Characteristics of 619 Adults with Community-Acquired Meningitis[a,b]

Clinical Features	< 65 (n = 565)	≥ 65 (n = 54)	P-value[c]
Age (years)	35 (18–64)	71 (65–92)	<0.01
Female	293 (51.9)	34 (63.0)	0.12
Race			
Caucasian	250 (44.2)	37 (68.5)	<0.01
African American	159 (28.1)	9 (16.7)	0.07
Hispanic	140 (24.8)	6 (11.1)	0.02
Other	16 (2.8)	2 (3.7)	0.72
Uninsured	186/562 (33.1)	4 (7.4)	<0.01
Coexisting medical conditions			
Charlson Comorbidity Index score ≥1	135 (23.9)	32 (59.3)	<0.01
Immunosuppressed[d]	78 (13.8)	5 (9.3)	0.35
HIV/AIDS	65/564 (11.5)	0 (0)	<0.01
History of injection drug use	12/558 (2.2)	0 (0)	0.39
Sinusitis or otitis	30 (5.3)	11 (20.4)	<0.01
History of CNS lesion	12/559 (2.1)	6 (11.1)	<0.01
Presenting symptoms			
Headache	518/551 (94.0)	29/48 (60.4)	<0.01
Nausea	385/543 (70.9)	18/50 (36.0)	<0.01
Subjective fever	355/558 (63.6)	31/53 (58.5)	0.71
Stiff neck	250/539 (46.4)	15/48 (31.3)	0.02
Photophobia	214/497 (43.1)	4/44 (9.1)	<0.01
Malaise	204/537 (38.0)	19/50 (38.0)	0.74
Respiratory symptoms	70/545 (12.8)	2/50 (4.0)	0.07
Presenting signs			
Nuchal rigidity	165/528 (31.3)	14/46 (30.4)	0.08
Temperature > 38.4°C	164/559 (29.3)	26 (48.1)	0.01
Abnormal neurologic exam[e]	134 (23.7)	38 (70.4)	<0.01
Vesicular or petechial rash	9/556 (1.6)	2/53 (3.8)	0.53

[a] HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome; CNS = central nervous system; GCS = Glasgow Coma Scale

[b] Data are presented as number (percentage) or median (range).

[c] P value comparing the <65 and ≥65 cohorts.

[d] Include patients with HIV, AIDS, organ transplants, steroid use, congenital diseases, and other conditions affecting immune status.

[e] Defined as presence of seizure, abnormal mental status (ie. Disorientation or GCS <15), focal motor deficit, cranial nerve abnormality, or aphasia.

TABLE 2

Laboratory Results and Follow-up of 619 Adults with Community-Acquired Meningitis[a,b,c]

Clinical Features	< 65 (n = 565)	≥ 65 (n = 54)	P-value[d]
Blood and CSF Analysis			
Serum leukocyte count (cells/μL)	8,500 (900–43,500)	11,500 (4,700–30,000)	<0.01
CSF leukocyte count (cells/μL)	150 (6–53,600)	229 (7–44,040)	<0.01
CSF protein (mg/dL)	77 (18–706)	131 (37–598)	<0.01
CSF glucose (mg/dL)	56 (1–421)	58 (2–320)	0.58
Serum leukocyte ≥12,000 cells/μL	126 (22.3)	26 (48.1)	<0.01
CSF protein ≥100 mg/dL	202 (35.8)	35 (64.8)	<0.01
CSF glucose <45 mg/dL	100 (17.7)	16 (29.6)	0.03
Microbiology analysis			
Positive Gram Stain	34/564 (6.0)	8 (14.8)	<0.05
Positive Blood Culture	16/356 (4.5)	5/44 (11.4)	<0.01
Positive PCR Test[e]	70/267 (26.2)	3/26 (11.5)	0.25
Positive CSF Culture			
Bacterial	25/551 (4.5)	9 (16.6)	<0.01
Viral	2/120 (1.7)	0 (0)	0.69
Cryptococcus neoformans[f]	40/195 (20.5)	0 (0)	0.11
Acid fast bacillus	5/155 (3.2)	0 (0)	0.21
Management decision			
Admission to Hospital	547 (96.8)	54 (100.0)	0.18
Empirical antibiotic therapy	408/558 (73.1)	44/53 (83.0)	0.27
Duration of antibiotic therapy (day)	2 (0–45)	5 (0–21)	<0.01
Empirical acyclovir therapy	143/563 (25.4)	14/53 (26.4)	0.31
Head CT taken	501 (88.7)	52 (92.3)	0.08
Abnormal[g]	31/501 (6.2)	10/52 (19.2)	<0.01
Brain MRI taken	255 (45.1)	35 (64.8)	<0.01
Abnormal[h]	91/255 (25.6)	18/35 (51.4)	<0.01
Clinical status at discharge			
Adverse clinical outcome[i]	42 (7.4)	28 (51.9)	<0.01

[a] CSF = cerebrospinal fluid; PCR = polymerase chain reaction; CT = computed tomography; MRI = magnetic resonance imaging; GCS = Glasgow Coma Scale

[b] Data are presented as number (percentage) or median (range).

[c] SI conversion factors: To convert CSF protein to mg/L, multiply by 10; to convert serum leukocyte count to 10^9/L, multiply by 0.001; to convert CSF glucose to mmol/L, multiply by 0.05551.

[d] P value comparing the <65 and ≥65 cohorts.

[e] Includes herpes simplex virus, varicella zoster virus, and enterovirus.

[f] Positive fungal culture or cryptococcal antigen

[g] Findings include focal (i.e., mass lesions, strokes, or bleeds) or nonfocal (i.e., hydrocephalus, white matter changes) intracranial abnormalities.

[h] Findings include mass lesions, strokes, hypoattenuations, meningeal enhancement, bleeds, white matter abnormalities

[i] Glasgow Outcome Scale score of 1–4.

TABLE 3

Etiologies and Adverse Clinical Outcomes (ACO) in 619 Patients with Community-Acquired Meningitis[a]

Etiology[b]	< 65 (n = 565)		≥ 65 (n = 54)	
	No. (%) of patients	No. (%) of ACOs	No. (%) of patients	No. (%) of ACOs
Unknown*†	385 (68.1)	12 (3.1)	22 (40.7)	8 (36.4)
Urgent treatable*†	104 (18.4)	23 (22.1)	23 (42.6)	13 (56.5)
Bacterial meningitis*[c]	30	7	16	8
Cryptococcus neoformans	44	5	0	0
Herpes simplex encephalitis	11	6	2	2
Mycobacterium tuberculosis	5	2	0	0
Varicella zoster virus	5	0	2	2
CNS lymphoma/carcinomatosis	2	2	1	1
Other[d]	7	1	2	0
Untreatable*†	35 (6.2)	7 (20.0)	9 (16.7)	7 (77.8)
West Nile Virus	20	7	9	7
Enterovirus	11	0	0	0
St Louis encephalitis virus	3	0	0	0
Epstein-Barr virus	1	0	0	0
Non-urgent treatable*	41 (7.3)	0 (0)	0 (0)	0 (0)
Herpes simplex meningitis	34	0	0	0
Acute HIV	3	0	0	0
Other[e]	4	0	0	0
Total	**565 (100.0)**	**42 (7.4)**	**54 (100.0)**	**28 (51.9)**

[a] CNS = central nervous system; HIV = human immunodeficiency virus

[b] Significant p values ($p < 0.05$) comparing the etiologies (*) and ACOs (†) between <65 and ≥65 cohorts.

[c] Organisms identified are expressed as a ratio of (<65) to (≥65) and include *Streptococcus pneumoniae* (11:17), *Enterobacter cloacae* (1:0), Enterococcus (1:1), *Haemophilus influenzae* (1:1), *Listeria monocytogenes* (1:0), Methicillin-sensitive *Staphylococcus aureus* (1:0), *Neisseria meningitidis* (2:0), *Staphylococcus aureus* (1:1), Coagulase-negative Staphylococcus (1:0), Group A Streptococcus (2:0), Group B Streptococcus (0:3), *Streptococcus anginosusmilleri* (1:0).

[d] Other urgent treatable etiologies include Systemic lupus erythematosus flare, *Toxoplasma gondii*, infective endocarditis, histoplasmosis, cerebral aneurysm, epidural empyema, Brucella, and *Escherichia coli* urinary tract infection.

[e] Other nonurgent treatable etiologies include neurosyphilis, multiple sclerosis, influenza virus type A, and cytomegalovirus.

TABLE 4

Bivariate Analysis of Factors Associated with an Adverse Clinical Outcome in 619 Adults with Community-Acquired Meningitis[a]

Characteristics	< 65 (n = 565)		≥ 65 (n = 54)	
	Odds Ratios (95% CI)	P-value	Odds Ratios (95% CI)	P-value
Gender (female)	0.68 (0.36 – 1.28)	0.23	6.27 (1.81 – 21.70)	<0.01
Historical features				
Charlson Comorbidity Index score ≥1	2.90 (1.53 – 5.51)	<0.01	1.13 (0.38 – 3.36)	0.82
Immunosuppressed	1.52 (0.68 – 3.42)	0.31	1.44 (0.22 – 9.39)	0.70
Sinusitis or Otitis	2.01 (0.67 – 6.06)	0.21	0.73 (0.19 – 2.74)	0.63
History of CNS Lesion	2.54 (0.54 – 11.97)	0.22	2.00 (0.33 – 11.97)	0.44
Presenting features				
Abnormal Neurologic Exam[b]	21.41 (9.24 – 49.63)	<0.01	3.37 (0.98 – 11.67)	0.05
Temperature > 38.4°C	3.81 (1.99 – 7.31)	<0.01	1.17 (0.40 – 3.40)	0.78
Nuchal rigidity	1.11 (0.54 – 2.27)	0.11	1.18 (0.33 – 4.17)	0.66
Laboratory findings				
Serum WBC ≥12,000 cells/μL	2.88 (1.51 – 5.50)	<0.01	1.17 (0.40 – 3.40)	0.78
CSF protein ≥100 mg/dL	4.51 (2.29 – 8.90)	<0.01	0.95 (0.31 – 2.92)	0.93
CSF glucose <45 mg/dL	4.03 (2.10 – 7.77)	<0.01	0.63 (0.19 – 2.04)	0.44

[a] CI = confidence interval

[b] Defined as presence of seizure, abnormal mental status (ie. Disorientation or GCS <15), focal motor deficit, cranial nerve abnormality, or aphasia.

TABLE 5

Logistic Regression Analysis of Factors Independently Associated with an Adverse Clinical Outcome in 619 Adults with Community-Acquired Meningitis[a, b]

Characteristics	< 65 (n = 565) OR (95% CI)	≥ 65 (n = 54) OR (95% CI)
Gender (female)	-----	5.81 (1. 36 – 20.70)*
Charlson Comorbidity Index score ≥1	1.20 (0.53 – 2.75)	-----
Presenting features		
Abnormal Neurologic Exam[c]	12.84 (4.98 – 33.15)*	2.95 (0.77 – 11.26)
Temperature > 38.4°C	2.72 (1.20 – 6.13)*	-----
Laboratory findings		
Serum WBC ≥12,000 cells/μL	1.68 (0.72 – 3.92)	-----
CSF protein ≥100 mg/dL	1.42 (0.61 – 3.32)	-----
CSF glucose <45 mg/dL	5.24 (2.19 – 12.58)*	-----

[a] CI = confidence interval

[b] All variables are validated with bootstrap analysis, and those with a $p < 0.05$ are indicated by (*)

[c] Defined as presence of seizure, abnormal mental status (ie. Disorientation or GCS <15), focal motor deficit, cranial nerve abnormality, or aphasia.