Objectives: To investigate the epidemiology and outcomes of community-acquired meningitis in older adults.

Design: Retrospective study.

Setting: Participants adults in Houston, Texas, with community-acquired meningitis hospitalized between January 1, 2005, and January 1, 2010 (N = 619; n = 54, 8.7%, aged ≥65; n = 565 aged <65).

Methods: An adverse clinical outcome was defined as a Glasgow Outcome Scale score of 4 or less.

Results: Older adults had higher rates of comorbidities, abnormal neurological and laboratory (serum white blood cell count >12,000/µL, and cerebrospinal fluid protein >100 mg/dL) findings (P < .001), abnormalities on computed tomography and magnetic resonance imaging of the head (P = .002), and adverse clinical outcomes (ACOs) (P < .001). The majority of participants (65.8%) had meningitis of unknown etiology. Bacterial meningitis was an infrequent cause of community-acquired meningitis (7.4%). Of the known causes, bacterial meningitis and West Nile virus were more common in older than younger adults; younger participants more frequently had cryptococcal and viral meningitis. On logistic regression, female sex was predictive of a poor outcome in the older participants (P = .002), whereas abnormal neurological examination (P < .001), fever (P = .01), and a cerebrospinal fluid glucose level less than 45 mg/dL (P = .002) were significant poor prognostic factors in younger participants.

Conclusion: Most cases of community-acquired meningitis are of unknown origin. Older adults are more likely than younger adults to have bacterial meningitis and West Nile virus infection when a cause can be identified. They also have more neurological abnormalities, laboratory and imaging abnormalities, and adverse clinical outcomes. J Am Geriatr Soc 2014.

Key words: meningitis; older adults; community-acquired

Community-acquired meningitis encompasses a broad range of infectious and noninfectious causes, but existing studies in older adults have predominately focused on bacterial meningitis. 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. Changes in host factors also play an important role, as the population shifts toward a larger aging cohort and conditions emerge that compromise the immune system. As a result, older adults have become an increasingly more vulnerable group, with high rates of adverse outcomes.

Diagnosing meningitis in older adults presents a unique challenge because there is greater variability of disease presentation. The absence of consistent characteristic features can be misleading for diagnosticians, prompting the search for other causes and potentially delaying treatment. Bacterial meningitis is associated with high morbidity and mortality in older adults, but bacteria remain an uncommon cause of community-acquired meningitis, and few studies have described the characteristics of community-acquired meningitis in this older group. The purpose of this study was to expand the focus beyond bacterial meningitis to describe the etiologies and differences in clinical features, laboratory findings, and outcomes between older and younger individuals with community-acquired meningitis.

Methods

Study Design and Case Definition

This was a retrospective descriptive study of 619 adults with community-acquired meningitis. A case was defined as an adult (aged >16) with symptoms of meningitis (fever, headache, stiff neck, altered mental status or focal
neurological symptoms) and a cerebrospinal fluid (CSF) white cell count greater than 5 cells/mm³ who presented to an emergency department (ED) between January 1, 2005, and January 1, 2010, at one of eight Memorial Hermann hospitals in Houston and surrounding areas. The University of Texas Health in Houston Committee for the Protection of Human Subjects and the Memorial Hermann Hospital Research Review Committee approved the study.

Data Collection, Laboratory Testing, and Definition of Diagnostic Outcomes

Baseline participant characteristics were recorded at a specified “zero time,” defined as the time when the participant was in the ED. Sociodemographic data, comorbid conditions (measured using the Charlson Comorbidity Index), immunocompetence, exposures, clinical features (including neurological examination and Glasgow Coma Scale), laboratory results, and management decisions were recorded. CSF Gram stains were performed on cytospin samples. Board-certified neuroradiology faculty at the hospitals read the computed tomography (CT) and magnetic resonance imaging (MRI) scans of the brain and classified them as abnormal if any intracranial parenchymal abnormality was noted. Cerebral atrophy or concomitant sinusitis was not considered abnormal.

Etiologies of the meningitis were divided into four categories: unknown, untreatable, treatable but not urgent, and urgent treatable. Etiologies predetermined to represent urgent treatable causes included bacterial, fungal, and mycobacterial meningitis; Herpes simplex virus (HSV), varicella-zoster virus, and cytomegalovirus meningoencephalitis; rickettsial meningoencephalitis; bacteremia; meningeval carcinomatosis; central nervous system vasculitis; parameningeval or intracranial mass lesions (e.g., tumor, abscess); and intracranial hemorrhage. The primary study endpoint was an adverse clinical outcome. Participant outcomes were assessed at time of discharge from the hospital using the Glasgow Outcome Scale; a score of 1 indicates death; a score of 2, 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, 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 Scale score of 1 to 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 were entered into a logistic regression model to verify independent associations with an adverse clinical outcome. Fisher exact, chi-square, and Student t tests were used in the bivariate analyses. To avoid overfitting in the regression modeling, no more than one variable was entered per six outcome events.

RESULTS

Cohort Assembly

After 727 individuals with meningitis were screened, 108 were excluded for the following reasons: presence of a ventricular peritoneal shunt (n = 24) or postcraniotomy 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, 619 participants were enrolled and divided into younger (17–64; n = 565) and older (≥65; n = 54) cohorts.

Baseline Features and Clinical Findings

Baseline sociodemographic characteristics, comorbidities, clinical and laboratory findings, and follow-up data are shown in Tables 1 and 2. Older adults accounted for 8.7% (54/619) of total cases and differed significantly from the younger cohort with respect to sex, race, insurance status, comorbidities, presenting history, and examination findings. Older participants 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 human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). Comorbidity (Charlson score ≥1) was present in 59.3% of older and 23.9% of younger participants. Similarly, older participants had higher rates of predisposing conditions, such as sinusitis, otitis, and history of central nervous system lesions. Younger participants 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 immunosuppression

Older adults were sicker on presentation, with fewer symptoms but more abnormalities on neurological examination (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 (>38.4°C), and 24.4% had an abnormal neurological examination. In contrast, older participants presented less frequently with headache (P < .001), nausea (P < .001), stiff neck (P = .02), and photophobia (P < .001). Abnormal neurological findings—seizure, abnormal mental status (disorientation, lethargy, or Glasgow Coma Scale score <15), focal motor deficit, cranial nerve abnormality, or aphasia—were more common in older participants (P < .001).

Laboratory Results and Physician Management

All participants underwent lumbar puncture. Serum and CSF findings demonstrated marked differences between the two age groups (Table 2). Older participants had higher median serum leukocyte counts (P < .001), CSF leukocyte counts (P < .001), and CSF protein (P < .001). Indicating the degree of disease severity, they were more likely to have a serum leukocyte count of 12,000 cells/µL or higher (P < .001), CSF protein of 100 mg/dL or higher
Clinical outcome, with the older cohort having significantly higher rates of adverse outcomes (51.9% vs 7.4%, \( P < .001 \)).

### Etiologies and Clinical Outcomes

The etiological agent for the episode of meningitis was identified for 212 participants (34.2%). Meningitis had an unknown cause in 407 (65.8%) participants. An urgent treatable cause, which included bacterial meningitis, Cryptococcus neoformans meningitis, varicella-zoster virus, HSV encephalitis, toxoplasmosis, tuberculosis, brain tumors, and other miscellaneous conditions, was identified in 127 participants (20.5%). Untreatable causes, such as enterovirus, Epstein-Barr virus, West Nile Virus (WNV), and St. Louis encephalitis, were identified in 44 (7.1%) participants. Forty-one participants (6.6%) had a nonurgent treatable etiology, which included HSV meningitis, neurophilitis, multiple sclerosis, HIV seroconversion, influenza type A, and cytomegalovirus (Table 3).

Older participants were more likely to have meningitis of an urgent treatable or untreatable cause, whereas younger participants tended to have more nonurgent or unknown causes of meningitis (all \( P < .05 \)). Bacterial meningitis was an infrequent cause overall (n = 46, 7.4%) but occurred more often in older (n = 16, 29.6%) than younger (n = 30, 5.3%) participants (\( P < .001 \)). *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. Of urgent treatable causes, bacterial meningitis was most likely to cause an adverse clinical outcome in older participants (8/13, 61.5%). 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%, \( P < .001 \)). In contrast, younger participants were more likely to have cryptococcal and enteroviral meningitis (\( P < .001 \)). Causes of adverse outcomes in this group were more diverse, consisting of bacterial, viral, fungal, and unknown causes, but the risk of an adverse outcome was lower across all etiology categories (\( P < .05 \)) except nonurgent treatable causes, in which no adverse clinical outcomes occurred.

Factors Associated with Adverse Clinical Outcomes

Bivariate analysis was used to identify potential predictors of adverse clinical outcomes and found female sex to be significant in the older cohort (Table 4). Sex remained significant after logistic regression modeling with validation by bootstrapping (odds ratio (OR) = 5.81, 95% confidence interval (CI)=1.63–20.70, \( P = .004 \)) (Table 5). No association was detected between female sex and any other variables in the bivariate analysis (data not shown).

In the younger group, comorbidities, abnormal neurological examination (including abnormal mental status, GCS score <15, seizures, and focal neurological deficits), fever (>38.4°C), and abnormal laboratory findings (serum leukocyte ≥12,000 cells/μL, CSF protein ≥100 mg/dL, CSF glucose <45 mg/dL) were all significantly associated with adverse clinical outcomes in bivariate analysis (Table 4). Clinical variables remaining significant after logistic regression analysis that were validated by bootstrapping included abnormal neurological examination (OR=12.84, 95% CI=4.98–33.15), fever (OR=2.72, 95% CI=1.20–6.13), and CSF glucose less than 45 mg/dL (OR=5.24, 95% CI=2.19–12.58) (Table 5).

**DISCUSSION**

This study is the largest to analyze clinical features of and prognostic factors for community-acquired meningitis of bacterial and nonbacterial causes in older adults. Existing studies have focused exclusively on confirmed cases of bacterial meningitis\(^8\)–\(^10\),\(^14\) or have had limited sample size.\(^2\)
The study demonstrated that community-acquired meningitis in older adults differs significantly from in younger adults with respect to clinical features, etiology, and outcomes. Older participants have more comorbidities and neurological abnormalities on examination but 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 older adults.\(^\text{2,9,10}\) Neurological compromise can interfere with an individual’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 older adults.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.1,4,10 Empirical antibiotics were also given at similar rates. Older participants more often had abnormalities on CT scanning, prompting further imaging with MRI, which was also more likely to be abnormal. Laboratory results more often showed serum leukocytosis, high CSF protein, and hypoglycorrhachia. The greater frequency of bacterial meningitis in this population can explain this trend in part. Younger participants 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, laboratory test results, and imaging showed that older participants were sicker at initial presentation.

Meningitis of unknown cause accounted for 65.8% cases (Table 3). Unknown etiologies present a clinical dilemma for diagnosticians because the main benefit of determining 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 tends to have a better prognosis, although 36.4% of older participants with meningitis of unknown etiology and 3.1% of younger participants had adverse clinical outcomes. When the Gram stain or bacterial culture is negative, CSF results alone are insufficient to differentiate bacterial from nonbacterial causes, although CSF lactate and serum procalcitonin levels have shown diagnostic promise.16–18 Microbiological testing was underused as a diagnostic tool in this study. Although almost every participant had a Gram stain and bacterial culture, fewer than half had a PCR result, and PCR testing was infrequently ordered in participants with unknown etiologies. PCR has higher diagnostic yield than viral culture or intrathecal antibody testing for viruses but may still fail to identify an etiology in more than 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. A higher prevalence of HIV/AIDS leading to immune system suppression can explain the number of cryptococcal meningitis cases.

Appropriately risk stratifying older adults presenting with suspected community-acquired meningitis will continue to remain a challenge because of variable clinical presentation and few prognostic factors. This study identified female sex to be independently associated with a poor outcome. The reason for this is not readily apparent. Confounding is unlikely because of the lack of association with other variables of interest (comorbidities, immunocompetence, HIV/AIDS, abnormal neurological examination, urgent treatable causes, serum leukocytosis, CSF protein ≥100 mg/dL, CSF glucose <45 mg/dL) (P = .39) (data not shown). In contrast, abnormal neurological examination, fever, and hypoglycorrhachia were significant prognostic factors in younger adults. Neurological compromise appeared to be a robust indicator of disease severity for both cohorts, and a finding that research on bacterial meningitis in adults has supported.3,20

This study had several limitations. With a retrospective study design, it was not possible to standardize the diagnostic examination for each participant, so missing data were inevitable. To avoid potentially misclassifying participants with urgent treatable causes as unknown because of pretreatment with antibiotics, 32 individuals who received oral antibiotics before lumbar puncture, were treated with intravenous antibiotics for longer than 48 hours, or and had no identifiable etiology were excluded. 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, several cases were discovered that were misdiagnosed as meningitis (e.g., vasculitis, lymphoma, bleed, abscess) because of similar presentations. This illustrates the challenge in differentiating meningitis from other conditions, although physicians should continue to maintain a high index of suspicion for meningitis because rapid treatment of urgent treatable causes can be lifesaving. Finally, the large percentage of individuals with an unknown etiology (65.8%) means there is much that is not understood about this syndrome.

Risk scores exist to predict outcomes for individuals with bacterial meningitis,21 but this study showed that a significant number of adverse clinical outcomes are not attributable to bacterial meningitis. Risk stratification models have recently been developed for individuals with a negative Gram stain.22,23 Better understanding of the clinical spectrum and prognostic factors for community-acquired meningitis will help guide diagnostic and management decisions to improve outcomes.
CONCLUSION

Community-acquired meningitis in older adults differs significantly from in younger adults with regard to clinical presentation, etiology, and disease severity. Older adults present with more neurological 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. Older women have poor outcomes, whereas an abnormal neurological examination, fever, and hypoglycorrhachia were poor prognostic factors for younger individuals. 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.

ACKNOWLEDGMENTS

We would like to thank Mr. and Mrs. Starr from the Grant A. Starr Foundation for their support of the study. This study was also supported by a grant from the National Center for Research Resources (NIH-1K23 RR018929–01A2) (PI, Hasbun).

Conflict of Interest: No competing interests for all the authors.

Author Contributions: Wang: data analyses and preparation of manuscript. Machicado: Manuscript preparation. Khoury, Salazar: data abstraction. Wootton: manuscript revision and obtaining grant support. Hasbun: study concept and design, data analyses, revision of manuscript and tables, obtaining grant support.

Sponsor’s Role: The funding agencies had no influence on any aspects of the study.

REFERENCES


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