Acute versus subacute community-acquired meningitis
Analysis of 611 patients

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Abstract
Community-acquired meningitis can be classified into acute and subacute presentations by the duration of illness of ≤ or ≥ 5 days, respectively. There are currently no studies comparing the clinical features, management decisions, etiologies, and outcomes between acute and subacute presentations.

It is a retrospective study of adults with community-acquired meningitis hospitalized in Houston, TX between January 2005 and January 2010. An adverse clinical outcome was defined as a Glasgow Outcome Scale score of ≤4.

A total of 611 patients were identified, of which 458 (75%) were acute and 153 subacute (25%). The most common etiologies were unknown in 418 (68.4%), viral in 94 (15.4%), bacterial in 47 (7.7%), fungal in 42 patients (6.9%), and other noninfectious etiologies in 6 (1%). Patients with subacute meningitis were more likely to be immunosuppressed or have comorbidities, had fungal etiologies, and had higher rates of hypoglycorrachia and abnormal neurological findings (P < .05). Patients with an acute presentation were more likely to be treated empirically with intravenous antibiotics and had higher cerebrospinal fluid pleocytosis and serum white blood cell counts (P < .05). On logistic regression, age ≥ 65 years and abnormal neurological findings were predictive of an adverse clinical outcome in both acute and subacute meningitis, whereas fever was also a significant prognostic factor in acute meningitis. (P < .05).

Acute and subacute meningitis differ in regards to clinical presentations, etiologies, laboratory findings, and management decisions, but did not differ in rates of adverse clinical outcomes. Future studies including thoroughly investigated patients with new diagnostic molecular methods may show different results and outcomes.

Abbreviations: ABM = acute bacterial meningitis, AFB = acid fast bacilli, AIDS = acquired immunodeficiency syndrome, CAM = community-acquired meningitis, CMV = cytomegalovirus, CSF = cerebrospinal fluid, CT = computerized tomography, EBV = Epstein-Barr virus, GOS = Glasgow Outcome Scale, HIV = human immunodeficiency virus, HSV = herpes simplex virus, IVDU = intravenous drug use, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, TBM = tuberculous meningitis, VZV = varicella zoster virus, WNV = West Nile virus.

Keywords: acute, community-acquired, meningitis, subacute

1. Introduction
Community-acquired meningitis (CAM) can be classified as acute or subacute based on the duration of symptoms of ≤ or ≥ 5 days.[1] When approaching a patient with CAM, it is important to consider the duration of symptoms as subacute and chronic presentations are usually seen more often in tuberculous and fungal meningitis, whereas bacterial and viral are most likely considered in those with acute presentations. Acute bacterial meningitis (ABM) should always be considered in the differential diagnosis as it is associated with high mortality and neurologic sequelae requiring urgent antibiotic therapy and adjuvant corticosteroid therapy especially in those with pneumococcal meningitis.[2] Unfortunately, the majority of patients with CAM have unknown etiologies most likely due in part to the underutilization of currently available diagnostic techniques such as arboviral testing or polymerase chain reaction (PCR) for the most common viral etiologies and for the lack of sensitivity of cerebrospinal fluid (CSF) cultures for bacteria, mycobacteria, and fungal etiologies (i.e., *Histoplasma capsulatum* and *Coccidioides immitis*).[3–6] Tuberculous meningitis (TBM) represents a diagnostic and management challenge to clinicians as acid fast bacilli (AFB) cultures are insensitive and can take up several weeks to grow but patients require early antimycobacterial therapy and adjunctive steroids to improve clinical outcomes.[7] The Thwaites and the Lancet scoring systems have been developed to help distinguish TBM from bacterial meningitis but may not be
as helpful in other subacute etiologies such as Brucella meningiti.

The main purpose of this study was to compare the etiologies, clinical presentation, laboratory findings, imaging studies, management decisions, and prognostic outcomes between acute and subacute CAM. Furthermore, we analyzed prognostic factors in both acute and subacute meningitis.

2. Materials and methods

2.1. Case definition

A total of 611 adult patients (>16 years) with CAM were enrolled between January 1, 2005 to January 1, 2010 at 8 Memorial Hermann Hospitals in Houston, Texas. All patients presented with symptoms of meningitis (fever, headache, stiff neck, altered mental status, or focal neurological symptoms) and had CSF white cell count >5 cells/mm³. 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.

2.2. Data collection and definition of outcomes

Baseline patient characteristics were recorded when the patient was in the emergency department. Comorbid conditions were measured by the Charlson comorbidity scale.[9] Head computerized tomography (CT) scans and magnetic resonance imaging (MRI) of the brain reports were classified as abnormal if any intracranial parenchymal abnormality was noted. Cerebral atrophy or concomitant sinusitis was not considered abnormal.

Patients were classified into acute and subacute presentations by the duration of illness of ≤ or >5 days, respectively. Inpatient electronic medical records were retrospectively reviewed to extract the following data: demographic information, comorbidities, immune status, clinical presentation, laboratory findings, imaging studies, and management decisions in both groups. The primary study endpoint was the presence of an adverse clinical outcome. Patient’s outcomes were assessed at the time of discharge from the hospital by using the Glasgow outcome scale (GOS).[9] The GOS categories were as follows: 1 = death, 2 = persistent vegetative state, 3 = severe disability (defined as partially or totally dependent on assistance from others in daily living), 4 = moderate disability (defined as independent and can resume almost all activities in daily living, but disabled to the extent that they cannot participate in a variety of social and work activities), and 5 = good recovery. An adverse clinical outcome was defined as a GOS score of ≤4.

2.3. Statistical analysis

Data analysis was performed with χ² and analysis of variance test using IBM SPSS program version 21. Baseline characteristics having clinical association with an adverse clinical outcome were examined in bivariate analysis. Only variables showing a bivariate association (P <.05) were entered into a logistic regression model. Bootstrapping was performed to validate the regression model.

3. Results

3.1. Cohort assembly

We screened 638 patients with meningitis, 27 patients were excluded due to incomplete medical records. A total of 611 patients were classified into acute and subacute meningitis based on the duration of symptoms ≤5 days (n = 458) and >5 days (n = 153), respectively.

3.2. Baseline features and clinical findings

Baseline sociodemographic characteristics, comorbidities, clinical and laboratory findings, and follow-up data are shown in Tables 1 and 2. Acute meningitis patients consisted of 75% (458/611) of total cases, with a median age of 36 years, whereas subacute meningitis patients consisted of 25% (153/611), with a median age of 38 years. Both groups did not statistically differ in regards of age >65 years, female gender, race, symptoms, signs, and coexisting medical conditions. Overall, the most common symptoms and signs included headache (90.7% vs 91.9%), nausea (67.7% vs 68.5%), fever (63.8% vs 63.8%), stiff neck (45.4% vs 44.5%), photophobia (40.9% vs 38.1%), seizures (3.7% vs 5.9%), malaise (36.7% vs 40.1%), respiratory findings (11.6% vs 14.2%), temperature >38.4°C (30.5% vs 30.9%), nuchal rigidity (33.3% vs 24.5%), vesicular or petechial rash (1.9% vs 2%), sinusitis (3.7% vs 6.8%), otitis (2.7% vs 2.1%), and intravenous drug use (IVDU) 2.6% vs 3.4% for acute and subacute cases, respectively.

Subacute meningitis patients had significantly higher rates of comorbidities (defined by a Charlson comorbidity scale ≥1), (P = .020); immunosuppression, (P = .001); human immunodeficiency virus (HIV), (P = .003); and abnormal neurological findings (altered mental status: disorientation, lethargy, or Glasgow Coma Scale score <15; and focal motor deficit, or cranial nerve palsy or aphasia), (P = .037).

3.3. Laboratory results, imaging studies, and physician management

Acute meningitis patients had higher median elevations in serum leukocyte counts (P = .033) and CSF leukocyte counts (P = .023) (Table 2). Whereas, subacute meningitis cases had more positive CSF gram stain (P = .017); positive fungal CSF cultures and cryptococcal antigen (P <.001); lower mean values of CSF glucose (P = .008), and more CSF glucose levels <45 mg/dL (P = .003). No significant differences in regards of serum leukocyte counts ≥12,000 cells/µL (P = .606), mean values of CSF protein (P = .323), CSF protein ≥100 mg/dL (P = .464); positive CSF bacterial cultures (P = .073), positive CSF herpes simplex virus (HSV) PCR (P = .084), positive CSF enterovirus PCR (P = .159), positive CSF varicella zoster virus (VZV) PCR (P = .778), positive West Nile virus (WNV) serology (P = .166), and positive tuberculosis CSF cultures (P = .050) for acute and subacute cases were noted.

No statistically significant differences in regards of abnormal CT findings of the head (P = .187); abnormal MRI findings of the brain (P = .323); admission to hospital (P = .063); empirical acyclovir therapy (P = .840) for acute and subacute cases were found. Empiric antibiotic therapy was more often administered in acute meningitis cases (P <.001), whereas empiric antifungal therapy was more often in subacute meningitis cases (P <.001).

3.4. Etiologies and clinical outcomes

The majority of patients with meningitis in both groups presented with unknown etiology (418 patients, 68.4%). We were able to identify the etiologies in 31.6% (193/611). Etiologies were divided into acute and subacute presentations based on the duration of symptoms ≤5 days (n = 458) and >5 days (n = 153), respectively.
noninfectious (Table 3). There were no significant differences in unknown etiologies ($P=.374$), bacterial ($P=.083$), tuberculosis ($P=.050$), viral ($P=.210$), and noninfectious ($P=.643$). Bacterial etiologies consisted of 7.7% of meningitis cases in both groups; 8.73% and 4.58% of acute and subacute cases, respectively. Bacterial etiologies in acute meningitis comprised of Streptococcus pneumoniae (6.33%), 2 cases of Neisseria meningitides, Enterococcus sp, and Group B streptococcus; 1 case of alpha streptococcus, Listeria monocytogenes, Streptococcus milleri, methicillin-sensitive Staphylococcus aureus, Escherichia coli, Haemophilus influenzae, Brucella sp, Mycoplasma pneumoniae, and syphils. Bacterial etiologies in subacute meningitis consisted of 2 cases of S. pneumoniae (1.3%), 1 case of H. influenzae, methicillin-sensitive S. aureus, coagulase-negative staphylococcus, and Group A streptococcus. Viral etiologies included 15.4% of all patients; 16.4% and 12.4% of acute and subacute meningitis, respectively. The most common viral etiologies in acute meningitis included HSV (8.3%), WNV (4.6%), enterovirus (2%); Saint Louis virus (0.4%), 1 case of VZV, cytomegalovirus (CMV), HIV, influenza virus, and Epstein–Barr virus (EBV). Viral etiologies in the subacute group consisted of HSV (5.88%), WNV (3.3%), HIV (1.3%), 1 case of Saint Louis virus, VZV, and enterovirus.

Fungal etiologies consisted of 6.9% of all patients, 4.4% and 14.4% of acute and subacute meningitis, respectively. The majority of fungal causes were due to Cryptococcus neoformans in both groups; 1 case of H. capsulatum meningitis in the subacute group. TBm consisted of 0.7% of both groups, 1 case in acute and 3 cases in subacute meningitis. Noninfectious etiologies were seen in 4 cases of acute meningitis (0.9%); 1 case of cerebral arteries aneurysm, central nervous system lymphoma, meningeal carcinoma, and lupus cerebritis; noninfectious etiologies were seen in 2 cases of subacute meningitis, 1 case of each paraneoplastic syndrome due to breast cancer and neurosarcoidosis.

### 3.5. Factors associated with adverse clinical outcomes

We used bivariate analysis to identify potential predictors of adverse clinical outcomes (Table 4). In acute meningitis, age >65 years, presence of comorbidity, abnormal neurologic findings, fever ($T>38.4\degree C$), and abnormal laboratory findings (serum leukocyte ≥12,000 cells/µL, elevated serum 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 age >65 years (OR = 5.340, 95% CI: 2.303–12.381; $P<.001$); fever >38.4°C (OR = 2.350, 95% CI: 1.072–5.154; $P=.033$); and abnormal neurologic findings (OR = 9.132, 95% CI: 3.540–25.000).

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**Table 1**

Baseline characteristics of 611 adults with acute and subacute meningitis.

| Clinical Features | Acute (n=458) | Subacute (n=153) | $P$-value |
|-------------------|---------------|------------------|-----------|
| Age (>65 years)   | 60/458 (13.1) | 15/153 (9.8)     | .282      |
| Median            | 36            | 38               | .439      |
| Range             | 18–92         | 18–78            | .064      |
| Female gender     | 256/458 (55.8)| 74/153 (48.3)    | .497      |
| Race              |               |                  |           |
| Caucasian         | 220/458 (48.1)| 65/153 (42.4)    | .374      |
| African American  | 117/457 (25.6)| 49/153 (32.0)    | .210      |
| Hispanic          | 104/457 (22.7)| 36/153 (23.9)    | .209      |
| Other             | 16/457 (3.5)  | 3/153 (2.0)      | .374      |
| Uninsured         | 136/457 (29.7)| 50/153 (32.6)    | .643      |
| Coexisting medical conditions | | | |
| Charlson comorbidity index score ≥1 | 48/458 (10.5) | 27/153 (17.6) | .020 |
| Immunosuppressed† | 49/458 (10.6) | 32/153 (20.9) | .001 |
| HIV               | 32/153 (21.7) | 28/153 (18.1)   | .003      |
| History of injection drug use | 12/458 (2.6)  | 5/148 (3.4)     | .788      |
| Sinusitis         | 16/458 (3.7)  | 10/148 (6.8)    | .107      |
| Otis              | 12/440 (2.7)  | 3/146 (2.1)     | .656      |
| Presenting symptoms |             |                  |           |
| Headache          | 402/443 (90.7)| 137/149 (91.9)  | .657      |
| Nausea            | 295/436 (67.7)| 102/149 (68.5)  | .657      |
| Subjective fever  | 287/450 (63.8)| 97/152 (63.8)   | .993      |
| Stiff neck         | 197/434 (45.4)| 65/146 (44.8)   | .855      |
| Photophobia        | 164/401 (40.9)| 51/134 (38.1)   | .562      |
| Seizures           | 17/455 (3.7)  | 9/152 (5.9)     | .249      |
| Malaise            | 159/433 (36.7)| 59/147 (40.1)   | .460      |
| Respiratory symptoms | 51/440 (11.6)| 21/148 (14.2)  | .404      |
| Presenting signs   |               |                  |           |
| Temperature >38.4°C| 138/452 (30.9)| 47/152 (30.9)   | .928      |
| Nuchal rigidity    | 142/427 (33.3)| 34/139 (24.5)   | .052      |
| Vesicular or petechial rash | 9/453 (1.9) | 3/147 (2.0) | .968 |
| Abnormal neurological findings‡ | 26/451 (5.8) | 16/151 (10.6) | .037 |

Data are presented as number (percentage) or median (range). 
* $P$ value comparing the acute and subacute meningitis. Bolded values are significant. 
† Include patients with human immunodeficiency virus, acquired immunodeficiency syndrome, organ transplants, steroid use, congenital diseases, and other conditions affecting immune status. 
‡ Defined as the presence of abnormal mental status (i.e., disorientation, lethargy, or GCS value <15) in addition to focal motor deficit, cranial nerve abnormality, or aphasia.
### Table 2

**Laboratory results and follow-up of 611 adults with acute and subacute meningitis.**

| Clinical features | Acute (n=458) | Subacute (n=153) | P-value |
|-------------------|--------------|-----------------|---------|
| Blood and CSF analysis | | | |
| Serum leukocyte count, cells/µL | 8950 (900–43,500) | 7400 (1000–34,800) | .033 |
| Serum leukocyte count, cells/µL | 110/457 (24.07) | 40/153 (26.14) | .606 |
| CSF leukocyte count, cells/µL | 173.5 (5–44,040) | 82 (5–3405) | .023 |
| CSF protein, mg/dL | 62 (18–706) | 80 (22–460) | .323 |
| CSF glucose, mg/dL | 57 (1–421) | 53 (4–160) | .008 |
| CSF protein >100 mg/dL | 16/458 (37.1) | 61/151 (40.4) | .464 |
| CSF glucose <45 mg/dL | 82/456 (17.9) | 44/151 (29.1) | .003 |

**Microbiology analysis**

- Positive CSF cultures
  - Bacterial: 38/458 (8.4) vs 6/153 (3.9) | P = .073
  - Fungal culture + Cryptococcus neoformans: 22/175 (12.6) vs 22/91 (24.2) | P = .001
  - Tuberculosis: 1/458 (0.2) vs 3/153 (2.0) | P = .050

- Positive PCR tests CSF
  - HSV: 39/188 (20.2) vs 9/79 (11.4) | P = .084
  - Enterovirus: 9/130 (7.7) vs 1/50 (2.0) | P = .195
  - VZV: 1/5 (20.0) vs 1/5 (20.0) | P = .778

- West Nile virus serology
  - 21/126 (16.7) vs 5/55 (9.1) | P = .166

**Management decision**

- Admission to hospital: 439/455 (96.5) vs 152/153 (99.3) | P = .063
- Empirical antibiotic therapy: 350/452 (77.4) vs 95/151 (62.9) | P = .001
- Empirical antifungal therapy: 12/458 (2.6) vs 17/153 (11.1) | P = .001
- Empirical acyclovir therapy: 118/455 (25.9) vs 39/153 (25.5) | P = .840

- Abnormal CT head
  - 53/406 (13.1) vs 23/130 (17.7) | P = .187

**Adverse clinical outcome**

- Clinical status at discharge
  - 46/449 (10.2) vs 20/145 (13.8) | P = .237

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**P-value comparing the acute and subacute meningitis. Bolded values are significant.**

1. Positive fungal culture or cryptococcal antigen.
2. †Includes herpes simplex virus, varicella zoster virus, and enterovirus.
3. ‡Antibiotics: Ceftriaxone 2 g IV q 12 hours: acute (333, 73.7%) subacute (89, 58.9%); vancomycin loading dose: 25 mg/kg IV then 15 mg/kg IV q 8 hours: acute (144, 31.6%) subacute (45, 29.8%); cefepime 2 g IV q 8 hours: acute (12, 2.7%) subacute (2, 1.3%); ampicillin 2 g IV q 4 hours: acute (12, 2.7%) subacute (2, 1.3%); imipenem 6 g IV q 8 hours: acute (5, 1.1%) subacute (4, 2.6%). Vancomycin, cefepime, ampicillin, and imipenem doses modified according to kidney functions in acute kidney injury patients.
4. ‡‡Antifungal: Amphotericin B (liposomal) 5 mg/kg IV q 24 hours: acute (10, 2.2%) subacute (11, 7.2%); fluconazole 400 mg IV q 24 hours: acute (8, 1.8%) subacute (5, 3.9%); amphotericin B (liposomal) + fluconazole was administered empirically in 8 acute meningitis patients.
5. ††Acyclovir 10 mg/kg IV q 8 hours, dose, modified according to kidney functions in acute kidney injury patients.
6. ‡‡‡Findings include focal (i.e., mass lesions, strokes, or bleeds) and nonfocal (i.e., hydrocephalus and white matter changes) intracranial abnormalities.
7. ‡‡‡‡Findings include mass lesions, strokes, hypotension, meningeal enhancement, bleeds, and white matter abnormalities.
8. †††Glasgow Outcome Scale score of 1–4.
9. ††††4.316–19.323, P < .001 (Table 5). In subacute meningitis, age >65 years, abnormal neurologic findings, and abnormal laboratory findings (CSF protein ≥100 mg/dL) were all significantly associated with an adverse clinical outcome in the bivariate analysis. Clinical variables remaining significant after logistic regression analysis with bootstrapping included age >65 years (OR = 5.305, 95% CI: 1.241–22.682; P < .001) and abnormal neurological examination (OR = 13.119, 95% CI: 4.023–42.780; P < .001).

### 4. Discussion

This is the first study describing the clinical, laboratory features, management decisions, and prognostic factors for acute and subacute CAM in adults. Even though patients with subacute meningitis were more likely to have significant comorbidities or to be immunosuppressed, there was no significant differences in their clinical presentation except for a higher likelihood of having an abnormal neurological finding in those with subacute disease (P = .037) (Table 1). The only studies to our knowledge that has compared patients with meningitis based on duration of symptoms have been done in cryptococcal meningitis and TBM.[6,10–12] A recent study of HIV negative cryptococcal meningitis showed that patients with acute/subacute presentation had more altered consciousness and hypoglycorrachia than patients with a chronic presentation (as defined by a duration of >30 days).[10] A subacute duration of symptoms has been incorporated into 2 clinical models that help differentiate tuberculous from bacterial meningitis,[6,11] which recently been applied in Brucella meningitis that typically also has a subacute presentation.[7] In our study, there was a trend towards more bacterial meningitis cases in those with an acute presentation (8.4% vs 4.6%, P = .085) with more patients with subacute disease having fungal meningitis (24.2% vs 11.4%, P < .001). Additionally, as expected, empiric antibiotic therapy was administered more frequently in acute and empiric antifungal therapy in those with subacute presentations, respectively (P < .001). A positive Gram...
**Table 3**

| Etiologies of acute and subacute meningitis. |
|---------------------------------------------|
| **Etiology** | **Acute (n=458)** | **Subacute (n=153)** |
|--------------|------------------|---------------------|
| Unknown¹⁷| 318/458 (69.4) | 100/153 (65.4) |
| Bacterial etiologies (P = .065) | 40/458 (8.8) | 7/153 (4.5) |
| Streptococcus species⁴ | 29/458 (6.3) | 3/153 (2.0) |
| Neisseria meningitides | 2/458 (0.4) | 0 |
| Enterococcus species | 2/458 (0.4) | 0 |
| Haemophilus influenzae | 1/458 (0.2) | 1/153 (0.7) |
| Listeria monocytogenes | 1/458 (0.2) | 0 |
| MSSA | 1/458 (0.2) | 1/153 (0.7) |
| Escherichia coli | 1/458 (0.2) | 0 |
| Syphilis | 1/458 (0.2) | 0 |
| Mycoplasma pneumoniae | 1/458 (0.2) | 1/153 (0.7) |
| Bocceelia species | 1/458 (0.2) | 0 |
| Coagulase-negative staphylococcus | 0 | 1/153 (0.7) |
| Mycobacterium tuberculosis (P = .050) | 1/458 (0.22) | 3/153 (2.0) |
| Viral etiologies (P = .210) | 75/458 (16.4) | 19/153 (12.4) |
| HSV | 3/458 (20.0) | 9/137 (16.1) |
| Enterovirus | 9/458 (13.0) | 1/39 (2.6) |
| West Nile virus | 21/105 (20.0) | 5/50 (10.0) |
| HIV | 1/180 (0.5) | 2/82 (2.4) |
| VZV | 1/5 (0.2) | 1/5 (0.2) |
| CMV | 1/5 (0.2) | 0 (0.0) |
| Saint Louis virus | 2/155 (1.3) | 1/50 (2.0) |
| EBV | 1/13 (0.7) | 0 (0.0) |
| Influenza | 1/5 (0.2) | 0 |
| Fungal etiologies (P < .001) | 20/458 (4.4) | 22/153 (14.4) |
| Cryptococcus neoformans | 20/458 (4.4) | 22/153 (14.4) |
| Histoplasma capsulatum | 0 | 1/4 (25.0) |
| Other noninfectious etiologies | 1/458 (0.2) | 0 |

CMV = cytomegalovirus, EBV = Epstein–Barr virus, HSV = human immunodeficiency virus, H3V = herpes simplex virus, MSSA = methicillin-sensitive Staphylococcus aureus, VZV = varicella zoster virus.

¹⁷ Significant P Values (P < .05) comparing the etiologies between acute and subacute cohorts. Bolded values are significant.

¹ Unknown: meningitis without microbiological diagnosis or identified noninfectious etiology.

⁴ Organisms identified are expressed as a ratio of acute to subacute meningitis and include S pneumoniae (25:2), Group B streptococcus (2:0), Streptococcus anginosus milleri (1:0), alpha hemolytic Streptococcus (1:8), S pneumoniae or Enterococcus (1:0), Group A streptococcus (0:1).

² Other noninfectious etiologies: meningitis due to noninfectious etiologies: malignancy, autoimmune, and vascular diseases.

Stain was more common in the subacute cohort due to the presence of yeast (Cryptococcus) in the majority of cases (P = .017). The clinical presentation, laboratory findings, and prognostic outcomes of our acute meningitis group were similar to other studies on acute bacterial meningitis.⁸,¹⁴

There was no significant difference regarding viral etiologies between both groups, (P = .210). The most common viral etiology in both groups was HSV. Even though the median duration of symptoms in HSV meningitis or encephalitis is 2 days, patients can present with a range up to 21 days.⁶ The second most common viral etiology was WNV, a widespread pathogen in Texas during summer season. The median duration of symptoms in patients with WNV neuroinvasive disease is 4 days with a wide range from 1 to 21 days similar to HSV.⁴ Other viral etiologies included 3 cases of HIV seroconversion syndrome causing meningitis: 2 patients with subacute and 1 patient with acute presentation. There was no evidence of an opportunistic central nervous system infection. TBM was diagnosed with positive cultures in only 4 patients; 1 and 3 patients with acute and subacute presentation, respectively. Meningitis of unknown cause accounted for the majority of cases in both acute and subacute groups (69.4%, 65.4%, respectively, P = .374). This could in part be due to underutilization of current available diagnostic serological and molecular diagnostic techniques.¹³,¹⁴

Subacute meningitis presented with lower serum and CSF leukocyte and more hypoglycorrhachia than patients with acute presentations (P < .05). This could be due to the higher proportion of immunosuppressed patients and cryptococcal meningitis in the subacute cohort. Patients with acquired immunodeficiency syndrome (AIDS) that presents with cryptococcal meningitis can have low serum leukocyte counts with lymphopenia, low or absent CSF pleocytosis, and have significant hypoglycorrhachia.¹⁵ Even though hypoglycorrhachia is an important predictor of adverse clinical outcomes,¹⁷ there was no difference in outcomes between those with acute and subacute presentation. On logistic regression, age > 65 years, abnormal neurological findings were predictive of an adverse clinical outcome in both acute and subacute meningitis, whereas fever was also significant prognostic factor in acute meningitis (P < .05). Older age and abnormal neurological findings have also been shown to be associated with adverse clinical outcome in other studies.¹⁷,¹⁸

**Table 4**

| Bivariate analysis of factors associated with an adverse clinical outcome in 611 adults with acute and subacute meningitis. |
|---------------------------------------------------------------|
| **Characteristics** | **Odds ratios (95% CI)** | **P-value** | **Odds ratios (95% CI)** | **P-value** |
|---------------------|--------------------------|------------|--------------------------|------------|
| Age (>65 years) | 10.514 (5.359–20.629) | <.001 | 7.188 (2.135–24.201) | .001 |
| Female gender | 1.147 (1.068–2.130) | .558 | 1.650 (1.000–4.537) | .328 |
| Insurance | 1.060 (0.772–3.338) | .201 | 0.580 (0.213–1.584) | .284 |
| Historical features | | | | |
| Charlson comorbidity index score ≥ 1 | 4.879 (2.397–10.043) | <.001 | 1.564 (0.464–5.260) | .496 |
| Immunosuppressed | 0.864 (0.295–2.536) | 1.000 | 1.981 (0.635–6.176) | .317 |
| Fever | 3.991 (2.113–7.536) | <.001 | 1.600 (0.574–4.461) | .366 |
| Seizures | 2.842 (0.887–9.113) | .086 | 3.961 (0.882–17.244) | .090 |
| Abnormal neurological findings” | 13.357 (6.768–26.360) | <.001 | 9.004 (3.071–26.374) | .001 |
| Laboratory findings | | | | |
| Serum leukocyte ≥12,000 cells/µL | 2.511 (1.334–4.727) | .003 | 1.889 (0.673–5.297) | .222 |
| CSF protein ≥100 mg/dL | 4.087 (2.133–7.832) | <.001 | 2.724 (0.986–7.529) | .047 |
| CSF glucose <45 mg/dL | 2.604 (1.329–5.101) | .004 | 1.973 (0.702–5.434) | .192 |

² Defined as the presence of abnormal mental status (i.e., disorientation or GCS < 15) in addition to focal motor deficit, cranial nerve abnormality, or aphasia. Bolded values are significant.
Our study had several advantages. First, this is the only study of CAM to our knowledge comparing clinical, laboratory, etiologies, and prognostic factors in acute and subacute meningitis. Second, the large number of patients in our study enabled us to perform valid multivariable analysis to identify independent predictors for an adverse clinical outcome using a well-validated scale in both acute and subacute groups. Despite these advantages, we had some limitations. First, due to the retrospective design of the study, diagnostic testing was not comprehensive and the majority of patients had unknown etiologies. Unfortunately, this high proportion of unknown causes has been seen in other studies with CAM and could in part be due to underutilization of currently available diagnostic techniques.1,5,13,15,17,18 Second, missing data and nonstandardized evaluations of the patients was inevitable. Lastly, as this study was done only in the Houston area, the results may not be generalizable to other cities in the USA or to other parts of the world.

**5. Conclusion**

The majority of patients with CAM have unknown etiologies. Even though acute and subacute meningitis differ in their clinical presentation, etiologies, laboratory findings, and management decisions, they have similar rates and prognostic factors of adverse clinical outcomes. Findings could be different if patients had been thoroughly investigated with new diagnostic molecular methods. Further studies should be done to validate these results in different areas of the world.

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**References**

[1] Zunt JR, Baldwin KJ. Chronic and subacute meningitis. Continuum (Minneapolis, Minn) 2012;18:1290–318.

[2] Koster-Rasmussen R, Korchin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. J Infect 2008;57:449–54.

[3] Vanichanan J, Salazar L, Wootton SH, et al. Use of testing for West Nile virus and other arboviruses. Emerg Infect Dis 2016;22:1387–93.

[4] Bahr NC, Marais S, Caws M, et al. GeneXpert MTB/Rif to diagnose tuberculous meningitis: perhaps the first test but not the last. Clin Infect Dis 2016;62:1133–5.

[5] Hasbun R. Cerebrospinal fluid in central nervous system infections. Chapter 2 In: Infections of the Central Nervous System. 4th ed. Edited by Scheld, Whitley & Marra. 2014; 4–23.

[6] Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis 2010;10:803–12.

[7] Erdem H, Senbayrak S, Gencer S, et al. Tuberculous and brucellosis meningitis differential diagnosis. Travel Med Infect Dis 2015;13:185.

[8] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.

[9] Plum F, Levy DE. Predicting prognosis in coma. Can one improve medical decisions? Am J Med 1978;65:224–6.

[10] Zheng H, Chen Q, Xie Z, et al. A retrospective research of HIV-negative cryptococcal meningocardiitis patients with acute/subacute onset. Eur J Clin Microbiol Infect Dis 2016;35:299–303.

[11] Thwaites GE, Chau TT, Stepniewska K, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. Lancet (London, England) 2002;360:1287–92.

[12] Bijlsma MW, Brouwer MC, Bossuyt PM, et al. Risk scores for outcome in bacterial meningitis: Systematic review and external validation study. J Infect 2016;73:393–401.

[13] Kaurpoowat Q, Salazar L, Aguiera E, et al. Herpes simplex and varicella zoster CNS infections: clinical presentations, treatments and outcomes. Infection 2016;44:337–45.

[14] Jiajakul S, Arias CA, Hossain M, et al. Toscana meningoencephalitis: a comparison to other viral central nervous system infections. J Clin Virol 2012;55:204–8.

[15] Neshet I, Hadi CM, Salazar L, et al. Epidemiology of meningitis with a negative CSF Gram stain: under-utilization of available diagnostic tests. Epidemiol Infect 2016;144:189–97.

[16] Williamson PR, Jarvis JN, Panackal AA, et al. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol 2017;13:13–24.

[17] Shrikant V, Salazar L, Khoury N, Wootton S, Hasbun R. Hypoglycorrhachia in adults with community-acquired meningitis: etiologies and prognostic significance. Int J Infect Dis 2015;39:39–43.

[18] Wang AY, Machicado JD, Khoury NT, et al. Community-acquired meningitis in older adults: clinical features, etiology, and prognostic factors. J Am Geriatr Soc 2014;62:2064–70.