

# Cerebrospinal Fluid Analysis

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Cerebrospinal fluid (CSF) analysis is a diagnostic tool for many conditions affecting the central nervous system. Urgent indications for lumbar puncture include suspected central nervous system infection or subarachnoid hemorrhage. CSF analysis is not necessarily diagnostic but can be useful in the evaluation of other neurologic conditions, such as spontaneous intracranial hypotension, idiopathic intracranial hypertension, multiple sclerosis, Guillain-Barré syndrome, and malignancy. Bacterial meningitis has a high mortality rate and characteristic effects on CSF white blood cell counts, CSF protein levels, and the CSF:serum glucose ratio. CSF culture can identify causative organisms and antibiotic sensitivities. Viral meningitis can present similarly to bacterial meningitis but usually has a low mortality rate. Adjunctive tests such as CSF lactate measurement, latex agglutination, and polymerase chain reaction testing can help differentiate between bacterial and viral causes of meningitis. Immunocompromised patients may have meningitis caused by tuberculosis, neurosyphilis, or fungal or parasitic infections. Subarachnoid hemorrhage has a high mortality rate, and rapid diagnosis is key to improve outcomes. Computed tomography of the head is nearly 100% sensitive for subarachnoid hemorrhage in the first six hours after symptom onset, but CSF analysis may be required if there is a delay in presentation or if imaging findings are equivocal. Xanthochromia and an elevated red blood cell count are characteristic CSF findings in patients with subarachnoid hemorrhage. Leptomeningeal carcinomatosis can mimic central nervous system infection. It has a poor prognosis, and large-volume CSF cytology is diagnostic. (*Am Fam Physician*. 2021;103(7):422-428. Copyright © 2021 American Academy of Family Physicians.)

**Cerebrospinal fluid (CSF) analysis** is a diagnostic tool for many conditions affecting the central nervous system (CNS). The correct selection and interpretation of CSF tests can assist with diagnosing and treating a variety of conditions. *Table 1* lists the normal values of CSF components.<sup>1-4</sup>

## CNS Infections

Suspected CNS infection is a medical emergency and is the most common indication for lumbar puncture. Bacterial meningitis has a 14% to 25% mortality rate; therefore, rapid CSF evaluation and early empiric antibiotic treatment are critical.<sup>5,6</sup>

**Additional content** at <https://www.aafp.org/afp/2021/0401/p422.html>.

**CME** This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 401.

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CSF analysis is required to identify the causative organism and select appropriate antimicrobial coverage. An article on meningitis has been published previously in *American Family Physician*.<sup>7</sup>

When available, polymerase chain reaction (PCR) testing should be used to rapidly diagnose viral meningitis, which allows for early discontinuation of antibiotics.<sup>8-11</sup> It can also detect common viral and bacterial etiologies with more than 95% sensitivity and specificity,<sup>8,12</sup> whereas viral cultures require days to weeks and have lower accuracy.<sup>13</sup> However, PCR testing does not assess drug sensitivities, is not universally available, and does not detect every infectious organism. *Table 2* lists other suggested tests for various types of CNS infections.<sup>1,8,14-25</sup>

## BACTERIAL MENINGITIS

Opening pressure is the first CSF component assessed when performing a lumbar puncture. It is obtained before draining CSF fluid and should be measured with the patient in the lateral

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
To minimize unnecessary antibiotic use, polymerase chain reaction testing should be used to evaluate for viral infections in all patients with suspected meningitis. <sup>9-11,28</sup>	<b>B</b>	Consistent results from cohort studies showing reduced emergency department stays and no change in mortality
Gram stain testing of cerebrospinal fluid should be performed in all patients with suspected meningitis. <sup>28,29</sup>	<b>C</b>	Expert opinion and consensus guidelines in the absence of clinical trials
Patients with signs and symptoms of subarachnoid hemorrhage who present more than six to 12 hours after symptom onset should undergo cerebrospinal fluid analysis if computed tomography findings are equivocal. <sup>48</sup>	<b>C</b>	Expert opinion and consensus guideline in the absence of clinical trials

**A** = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <https://www.aafp.org/afpsort>.

decubitus position. Opening pressure is greater than 300 mm H<sub>2</sub>O in 39% of patients with bacterial meningitis.<sup>26</sup> The color of the CSF supernatant can be cloudy, green, or purulent.<sup>8</sup> The white blood cell (WBC) count is often greater than 1,000 per  $\mu$ L, and polymorphonuclear leukocytes are typically predominant.<sup>27</sup> However, 6% of patients with culture-diagnosed bacterial meningitis do not have an elevated WBC count, and lymphocytes are predominant in up to 10% of patients.<sup>28,29</sup> WBC elevations can be caused by traumatic lumbar punctures rather than infections. The classic method to correct for traumatic WBC elevations has been to subtract one WBC for every 500 to 1,500 red blood cells (RBCs)<sup>26</sup>; a more accurate method is to use the formula  $\text{WBCs (predicted)} = \text{CSF RBCs} \times (\text{blood WBCs/blood RBCs})$ .<sup>30</sup>

Nearly all patients with bacterial meningitis have an elevated CSF protein level.<sup>8</sup> The ratio of CSF glucose to serum glucose can be normal to significantly decreased depending on the type of pathogen, time since infection onset, and presence of dextrose in any intravenous fluids the patient has received.<sup>31</sup> Bacterial meningitis can be diagnosed with more than 99% certainty in patients with any of the following CSF measurements: glucose less than 34 mg per dL (1.89 mmol per L), protein greater than 220 mg per dL (2,200 mg per L), WBCs greater than 2,000 per  $\mu$ L, or neutrophils greater than 1,180 per  $\mu$ L.<sup>32</sup> Gram

stain testing is recommended for all patients with suspected CNS infection.<sup>28,29</sup> It has a specificity of 97% for bacterial meningitis and a sensitivity of 33% to 90%,<sup>8,27,33</sup> depending on the type of pathogen, cytocentrifugation, infection severity, laboratory personnel experience, the number of slides prepared, and the patient's exposure to antibiotics.<sup>27,31,34,35</sup> Therefore, a negative CSF

**TABLE 1**

### Normal Values of CSF Components

Component	Adults and children	Neonates
Color	Clear	Clear
CSF:serum glucose ratio	0.44 to 0.90	0.42 to 1.10
Differential	70% lymphocytes, 30% monocytes, rare PMNs or eosinophils	PMN count may be normal
Gram stain	Negative for organisms	Negative for organisms
Lactate level*	11.7 to 21.6 mg per dL (1.3 to 2.4 mmol per L)	8.1 to 22.5 mg per dL (0.9 to 2.5 mmol per L)
Opening pressure	Adults and children 8 years and older: 60 to 250 mm H <sub>2</sub> O Children younger than 8 years: 10 to 100 mm H <sub>2</sub> O	10 to 100 mm H <sub>2</sub> O
Protein level*	< 50 mg per dL (500 mg per L)	≤ 150 mg per dL (1,500 mg per L)
White blood cell count*	< 5 per $\mu$ L	< 20 per $\mu$ L

CSF = cerebrospinal fluid; PMN = polymorphonuclear leukocyte.

\*—Normal ranges may differ depending on laboratory calibration.

Information from references 1-4.

TABLE 2

**CSF Characteristics by Infection Type**

Infection type	Differential	Glucose level	Opening pressure
Bacterial (typical)*	Usually 80% to 90% PMNs; > 50% lymphocytes possible	< 40 mg per dL (2.22 mmol per L) in 50% to 60% of cases; CSF:serum glucose ratio < 0.4 is 80% sensitive and 98% specific	Adults and children 8 years and older: 200 to 500 mm H <sub>2</sub> O Children younger than 8 years can have lower pressures
Cryptococcal	Lymphocyte predominance	Usually > 40 mg per dL	> 250 mm H <sub>2</sub> O in severe cases; serial lumbar punctures or ventriculoperitoneal shunt required to drain CSF if pressure persistently > 250 mm H <sub>2</sub> O
Fungal (excluding cryptococcal)	Possible early PMNs progressing to lymphocyte predominance; eosinophils possible	Significant decrease possible	Variable
Neurosyphilis	Variable	Possibly decreased	Usually elevated in immunocompetent patients; may not be elevated in immunocompromised patients
Parasitic	Eosinophilia (> 10 eosinophils per $\mu$ L or > 10% of total cells)	Usually low normal or normal	Variable but can be persistently elevated, requiring CSF draining
Tuberculosis	Early lymphocyte and PMN predominance progressing to lymphocyte predominance	Median: 40 mg per dL; lower in advanced stages	Variable depending on stage
Viral	Lymphocyte predominance; possible PMN predominance in early infection	Usually normal; decreased in 25% of patients with mumps; mild decrease possible in patients with HIV infection	Usually normal

CSF = cerebrospinal fluid; PCR = polymerase chain reaction; PMN = polymorphonuclear leukocyte.

Information from references 1, 8, and 14-25.

Gram stain cannot exclude bacterial infection, particularly in patients who have already started antibiotic therapy.

Bacterial meningitis may still be present if results of the CSF analysis are normal or only mildly abnormal. Further testing can help clarify the diagnosis if results of the CSF analysis are equivocal. The Infectious Diseases Society of America does not recommend routine measurement of CSF lactate in patients with suspected bacterial meningitis, but two recent meta-analyses demonstrate its potential value.<sup>28,29,36</sup> A CSF lactate level greater than 35.1 mg per dL (3.9 mmol per L) is 93% to 95% sensitive and 94% to 99% specific for diagnosing bacterial meningitis if the CSF is obtained before antibiotic treatment begins.<sup>37,38</sup> The CSF lactate level is particularly helpful in neurosurgical patients because inflammation from surgery can lead to unreliable measurements of conventional markers.<sup>36</sup> Latex agglutination is another potentially useful adjunctive test for detecting bacterial antibodies or antigens in CSF. However, its sensitivity varies

depending on the organism, and false positives have been reported.<sup>26,39</sup> Latex agglutination is not recommended by the European Society of Clinical Microbiology and Infectious Diseases, which notes that this method is no more useful than Gram stain testing.<sup>29</sup>

CSF cultures can provide a definitive diagnosis and antimicrobial sensitivities. If antibiotic treatment is initiated before a CSF sample is obtained, the culture's yield will be decreased by 10% to 20%.<sup>29</sup>

**VIRAL MENINGITIS**

Viral meningitis is the most common type of CNS infection.<sup>40,41</sup> Opening pressure is typically normal; the WBC count is generally less than 250 per  $\mu$ L; and lymphocytes are typically predominant, although polymorphonuclear leukocytes may be predominant in the early phase.<sup>42</sup> The CSF protein level can be normal to mildly elevated (less than 150 mg per dL [1,500 mg per L]).<sup>31</sup> The CSF glucose level is usually normal but can be mildly decreased; mumps infection can lower

Protein level	White blood cell count	Other studies
Almost always elevated	Usually 1,000 to 5,000 per $\mu\text{L}$ 99% of children have > 100 per $\mu\text{L}$	Gram stain, CSF culture, CSF lactate (> 35.1 mg per dL [3.9 mmol per L]), PCR testing; latex agglutination if Gram stain is negative and antibiotics were given before lumbar puncture
Usually < 40 mg per dL (400 mg per L)	Usually mildly elevated; normal count possible, especially in patients with HIV infection	CSF culture, CSF cryptococcal antigen test, India ink capsule stain, latex agglutination, enzyme immunoassay, lateral flow assay, HIV test
50 to 250 mg per dL (500 to 2,500 mg per L)	Usually elevated, up to several hundred per $\mu\text{L}$	CSF (1-3)-beta-D-glucan (elevated level is 95% to 100% sensitive and 83% to 99% specific), CSF fungal culture, Gram stain (hyphae); PCR test is only 29% sensitive
> 45 mg per dL (450 mg per L)	Early stage: 10 to 400 per $\mu\text{L}$ Late stage: 5 to 100 per $\mu\text{L}$ Declines over decades	HIV test, CSF Venereal Disease Research Laboratory test (30% to 75% sensitive and 100% specific†), CSF fluorescent treponemal antibody absorption test (100% sensitive and 50% to 70% specific)
Usually elevated	150 to 2,000 per $\mu\text{L}$	PCR test; enzyme-linked immunosorbent assay for <i>Angiostrongylus cantonensis</i> , <i>Gnathostoma spinigerum</i> , and <i>Baylisascaris procyonis</i>
Usually 100 to 200 mg per dL (1,000 to 2,000 mg per L)	Usually 5 to 300 per $\mu\text{L}$ ; 500 to 1,000 per $\mu\text{L}$ in 20% of cases	Multiple cultures with acid-fast stain; PCR test (56% sensitive and 98% specific), CSF adenosine deaminase (> 10 U per L [166.67 nkat per L]); "pellicle" appearance of CSF‡
Normal or mildly elevated	Usually 100 to 1,000 per $\mu\text{L}$ ; higher in patients with enterovirus infection (elevated red blood cell count possible in patients with herpes infection)	PCR test preferred; other tests include CSF lactate (low), Gram stain, CSF or serum immunoglobulin M antibodies for arboviruses, electroencephalography or other neuroimaging for suspected encephalitis

\*—Most commonly *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Listeria monocytogenes*, and *Neisseria meningitidis*.

†—False-positive results can occur if blood is present in the CSF.

‡—Cobweb-like clot that forms after CSF is allowed to stand for a short time.

the CSF glucose level by 25%.<sup>8,31</sup> CSF and serum immunoglobulin M antibody testing are the preferred diagnostic tests for arboviruses such as West Nile virus.<sup>15</sup>

### IMMUNOCOMPROMISE

Immunocompromised patients are at increased risk of opportunistic infection. Adults older than 60 years and people with deficiencies in cell-mediated immunity have a higher incidence of *Listeria monocytogenes* meningitis.<sup>43</sup> Elevated CSF protein and WBC measurements are significantly less likely in these patients, and Gram stain is negative in 66% of cases.<sup>44</sup>

Patients with acute retroviral syndrome due to early or acute HIV infection can present with an aseptic CSF profile (mild lymphocyte elevation, normal to mild protein elevation, and a normal to slightly low glucose level).<sup>8</sup> Cryptococcal meningitis, toxoplasmosis, and neurosyphilis should be considered in patients with HIV and low CD4 cell counts.<sup>45</sup> Table 2 summarizes characteristics of CSF in patients with common infections.<sup>1,8,14-25</sup>

### Subarachnoid Hemorrhage

Subarachnoid hemorrhage has a mortality rate of 25% to 50% and requires urgent diagnosis.<sup>46</sup> Symptoms include sudden onset of severe headache, neck stiffness, photophobia, nausea and vomiting, seizure, and loss of consciousness. Most clinically significant subarachnoid hemorrhages are apparent on computed tomography of the head, which is nearly 100% sensitive in the first six hours of symptoms<sup>46,47</sup>; after six to 12 hours, the sensitivity wanes and CSF analysis may be required for diagnosis.<sup>48</sup>

CSF is usually colorless in patients with subarachnoid hemorrhage, but the presence of as few as 400 RBCs can change its appearance.<sup>47</sup> Enzymatic degradation of RBCs to produce bilirubin contributes to xanthochromia, a yellowish appearance of CSF. Xanthochromia begins to emerge after six hours in approximately 20% of subarachnoid hemorrhages and is present in 90% of patients after 12 hours.<sup>46</sup> At least 50% of patients who present with a subarachnoid hemorrhage had an initial subclinical sentinel bleed two to three

weeks earlier, which increases the likelihood of xanthochromia.<sup>46</sup> Xanthochromia can persist for up to two weeks after a bleeding event, and its presence significantly decreases the probability of blood being present due to traumatic lumbar puncture.<sup>46</sup> A CSF RBC count of less than 2,000 per  $\mu\text{L}$  in the absence of xanthochromia effectively rules out subarachnoid hemorrhage.<sup>42</sup> Other causes of xanthochromia include a serum bilirubin level greater than 10 to 15 mg per dL (171.04 to 256.56  $\mu\text{mol}$  per L), CSF protein level greater than 150 mg per dL, or a traumatic lumbar puncture with more than 100,000 RBCs per  $\mu\text{L}$ .<sup>1</sup> Decreasing RBC counts in successive CSF collection tubes strongly suggest a traumatic lumbar puncture.<sup>49</sup>

### Spontaneous Intracranial Hypotension

Intracranial hypotension, defined as an opening pressure lower than 60 mm  $\text{H}_2\text{O}$  in an adult, is an uncommon finding. It can be spontaneous or associated with a CSF leak, usually after a head injury.<sup>50</sup> Spontaneous intracranial hypotension has emerged as a significant cause of secondary headache syndrome, and its symptoms usually include a positional component.<sup>50</sup> Case studies suggest that it may contribute to reversible dementia.<sup>51</sup> Although evidence shows that many patients with spontaneous intracranial hypotension have low-normal opening pressures, less than 60 mm  $\text{H}_2\text{O}$  is considered diagnostic.<sup>50</sup>

### Idiopathic Intracranial Hypertension

Intracranial hypertension, defined as an opening pressure higher than 250 mm  $\text{H}_2\text{O}$  in an adult, can be idiopathic or associated with infectious meningitis or intracranial masses. Idiopathic intracranial hypertension, also called pseudotumor cerebri, should be considered in cisgender women of childbearing age who have obesity and chronic headaches; it is unclear whether this risk also pertains to trans men and nonbinary persons with XX chromosomes. It has an annual incidence of 19.3 cases per 100,000 women 20 to 44 years of age who have obesity and can result in permanent vision loss if untreated.<sup>52</sup> Diagnosis is based on the modified Dandy criteria (*eTable A*), which include an elevated opening pressure and normal CSF composition.<sup>53</sup> When performing a lumbar puncture in a patient with an elevated opening pressure, the manometer should be used throughout the procedure to continuously

monitor CSF pressure, and no fluid should be drained after the pressure decreases by 50%.<sup>54</sup>

### Demyelinating Disease

CSF analysis can assist in the diagnosis of neurologic conditions such as multiple sclerosis (MS) and Guillain-Barré syndrome. Patients with these conditions typically have an elevated CSF protein level but otherwise normal CSF composition. However, CSF analysis is only one component of these diagnoses; clinical and radiographic findings are also important considerations.<sup>55-58</sup>

CSF-restricted oligoclonal bands are the classic CSF finding in patients with MS. Their high sensitivity contributed to recent revisions in diagnostic criteria that allow the presence of CSF-restricted oligoclonal bands to substitute for the traditional dissemination-in-time criterion, particularly in patients younger than 50 years who have a clinical presentation otherwise typical of MS.<sup>55</sup> However, oligoclonal bands are not necessarily specific for MS and can occur in other inflammatory and infectious conditions. Elevations in CSF neurofilament light proteins correlate with relapsing MS.<sup>56</sup>

The classic CSF finding in patients with Guillain-Barré syndrome is an elevated protein level with a normal WBC count in the setting of acute ascending areflexic paralysis. It is present in 50% of patients in the first week after presentation, increasing to approximately 75% by three weeks.<sup>57</sup>

### Malignancy

Leptomeningeal carcinomatosis is a metastatic invasion of the leptomeninges that is difficult to treat and has a poor prognosis.<sup>59</sup> It can present with headache, confusion, and nuchal rigidity, mimicking a CNS infection. CSF findings may also suggest infection: a decreased glucose level and elevated opening pressure, WBC count, and protein level are common.<sup>59</sup> Magnetic resonance imaging has limited diagnostic specificity, and single-sample CSF cytology has poor sensitivity.<sup>60</sup> Obtaining three high-volume lumbar punctures (approximately 10 mL) improves the sensitivity to approximately 90%, and flow cytometry can improve specificity.<sup>59</sup> Recent evidence suggests that tumor cell-associated biomarkers in CSF (circulating tumor DNA, microRNA, and their respective metabolites) can assist in the diagnosis and treatment of

## leptomeningeal carcinomatosis; research into their potential use is ongoing.<sup>60</sup>

**This article** updates a previous article on this topic by Seehusen, et al.<sup>42</sup>

**Data Sources:** A literature search was performed in PubMed using the terms cerebrospinal fluid and meningitis. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. We also searched Essential Evidence Plus, the Cochrane database, and evidence reports from the Agency for Healthcare Research and Quality using the same terms. Search dates: August 2019 to July 2020.

**The opinions** or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, Department of Defense, or the U.S. government.

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## CSF ANALYSIS

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## eTABLE A

**Modified Dandy Criteria for the Diagnosis of Idiopathic Intracranial Hypertension**

CSF opening pressure > 250 mm H<sub>2</sub>O

Neuroimaging shows no etiology for intracranial hypertension

No impaired consciousness

No other cause of intracranial hypertension

No other neurologic abnormalities (except abducens nerve palsy)

Normal CSF composition

Signs and symptoms of increased intracranial pressure (e.g., headache, transient visual obscurations, pulsatile tinnitus, papilledema, vision loss)

CSF = cerebrospinal fluid.

*Information from Wall M, Corbett JJ. The modified Dandy criteria for idiopathic intracranial hypertension, no need to fix what is not broken. Neurology. January 10, 2014. Accessed May 10, 2020. <https://n.neurology.org/content/modified-dandy-criteria-idiopathic-intracranial-hypertension-no-need-fix-what-not-broken>*