

# Cerebrospinal Fluid Analysis

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Lumbar puncture is frequently performed in primary care. Properly interpreted tests can make cerebrospinal fluid (CSF) a key tool in the diagnosis of a variety of diseases. Proper evaluation of CSF depends on knowing which tests to order, normal ranges for the patient's age, and the test's limitations. Protein level, opening pressure, and CSF-to-serum glucose ratio vary with age. Xanthochromia is most often caused by the presence of blood, but several other conditions should be considered. The presence of blood can be a reliable predictor of subarachnoid hemorrhage but takes several hours to develop. The three-tube method, commonly used to rule out a central nervous system hemorrhage after a "traumatic tap," is not completely reliable. Red blood cells in CSF caused by a traumatic tap or a subarachnoid hemorrhage artificially increase the white blood cell count and protein level, thereby confounding the diagnosis. Diagnostic uncertainty can be decreased by using accepted corrective formulas. White blood cell differential may be misleading early in the course of meningitis, because more than 10 percent of cases with bacterial infection will have an initial lymphocytic predominance and viral meningitis may initially be dominated by neutrophils. Culture is the gold standard for determining the causative organism in meningitis. However, polymerase chain reaction is much faster and more sensitive in some circumstances. Latex agglutination, with high sensitivity but low specificity, may have a role in managing partially treated meningitis. To prove herpetic, cryptococcal, or tubercular infection, special staining techniques or collection methods may be required. (Am Fam Physician 2003;68:1103-8. Copyright© 2003 American Academy of Family Physicians.)

Primary care physicians frequently perform lumbar puncture, because cerebrospinal fluid (CSF) is an invaluable diagnostic window to the central nervous system (CNS). Commonly performed tests on CSF include protein and glucose levels, cell counts and differential, microscopic examination, and culture. Additional tests such as opening pressure, supernatant color, latex agglutination, and polymerase chain reaction also may be performed. Knowing which tests to order and how to interpret them allows physicians to use CSF as a key diagnostic tool in a variety of diseases.

## Opening Pressure

To measure CSF opening pressure, the patient must be in the lateral decubitus position with the legs and neck in a neutral position. The meniscus will fluctuate between 2 and 5 mm with the patient's pulse and between 4 and 10 mm with respirations.<sup>1</sup> The patient should be advised not to strain, because straining can increase the opening

pressure, and cautioned not to hyperventilate, because hyperventilating will lower the opening pressure.

Normal opening pressure ranges from 10 to 100 mm H<sub>2</sub>O in young children, 60 to 200 mm H<sub>2</sub>O after eight years of age, and up to 250 mm H<sub>2</sub>O in obese patients.<sup>2</sup> Intracranial hypotension is defined as an opening pressure of less than 60 mm H<sub>2</sub>O. This finding is rare except in patients with a history of trauma causing a CSF leak, or whenever the patient has had a previous lumbar puncture.<sup>3</sup>

Opening pressures above 250 mm H<sub>2</sub>O are diagnostic of intracranial hypertension. Elevated intracranial pressure is present in many pathologic states, including meningitis, intracranial hemorrhage, and tumors. Idiopathic intracranial hypertension is a condition most commonly seen in obese women during their childbearing years. When an elevated opening pressure is discovered, CSF should be removed slowly and the pressure monitored during the procedure. No additional CSF should be removed once the pressure reaches 50 percent of the opening pressure.<sup>4</sup>

See page 1039 for definitions of strength-of-evidence levels.

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### Supernatant Color

Normal CSF is crystal clear. However, as few as 200 white blood cells (WBCs) per mm<sup>3</sup> or 400 red blood cells (RBCs) per mm<sup>3</sup> will cause CSF to appear turbid. Xanthochromia is a yellow, orange, or pink discoloration of the CSF, most often caused by the lysis of RBCs resulting in hemoglobin breakdown to oxyhemoglobin, methemoglobin, and bilirubin. Discoloration begins after RBCs have been in spinal fluid for about two hours, and remains for two to four weeks.<sup>5</sup> Xanthochromia is present in more than 90 percent of patients within 12 hours of subarachnoid hemorrhage onset<sup>2</sup> and in patients with serum bilirubin levels between 10 to 15 mg per dL (171 to 256.5 μmol per L). CSF protein levels of at least 150 mg per dL (1.5 g per L)—as seen in many infectious and inflammatory conditions, or as a result of a traumatic tap that contains more than 100,000 RBCs per mm<sup>3</sup>—also will result in xanthochromia.<sup>2</sup> Newborn CSF is often

**TABLE 1**  
**Cerebrospinal Fluid Supernatant Colors and Associated Conditions or Causes**

<i>Color of CSF supernatant</i>	<i>Conditions or causes</i>
Yellow	Blood breakdown products Hyperbilirubinemia CSF protein ≥150 mg per dL (1.5 g per L) >100,000 red blood cells per mm <sup>3</sup>
Orange	Blood breakdown products High carotenoid ingestion
Pink	Blood breakdown products
Green	Hyperbilirubinemia Purulent CSF
Brown	Meningeal melanomatosis

*CSF = cerebrospinal fluid.*

*Information from references 2, 4, and 5.*

xanthochromic because of the frequent elevation of bilirubin and protein levels in this age group. *Table 1* lists CSF colors associated with various conditions.

### Cell Count

Normal CSF may contain up to 5 WBCs per mm<sup>3</sup> in adults and 20 WBCs per mm<sup>3</sup> in newborns.<sup>6</sup> Eighty-seven percent of patients with bacterial meningitis will have a WBC count higher than 1,000 per mm<sup>3</sup>, while 99 percent will have more than 100 per mm<sup>3</sup>. Having less than 100 WBCs per mm<sup>3</sup> is more common in patients with viral meningitis.<sup>2</sup>

Elevated WBC counts also may occur after a seizure,<sup>7</sup> in intracerebral hemorrhage, with malignancy, and in a variety of inflammatory conditions. *Table 2* lists common CSF findings in various types of meningitis.

Peripheral blood in the CSF after a “traumatic tap” will result in an artificial increase in WBCs by one WBC for every 500 to 1,000 RBCs in the CSF. This correction factor is accurate as long as the peripheral WBC count is not extremely high or low.

A traumatic tap occurs in approximately 20 percent of lumbar punctures. Common practice is to measure cell counts in three consecutive tubes of CSF. If the number of RBCs is relatively constant, then it is assumed that the blood is caused by an intracranial

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hemorrhage. A falling count is attributed to a traumatic tap. The three-tube method, however, is not always reliable.<sup>8</sup>

Xanthochromia is a more reliable predictor of hemorrhage. If a traumatic tap occurs within 12 hours of a suspected subarachnoid hemorrhage, it is reasonable to repeat the lumbar puncture one interspace up to try and obtain clear CSF.<sup>9</sup>

### Cell Differential

The WBC count seen in normal adult CSF is comprised of approximately 70 percent lymphocytes and 30 percent monocytes. Occasionally, a solitary eosinophil or polymorphonucleocyte (PMN) will be seen in normal CSF.<sup>2</sup> Several PMNs in a neonatal patient's CSF is not unusual.<sup>6</sup>

The majority of patients with Guillain-Barré syndrome will have 10 or fewer monocytes per mm<sup>3</sup> and a minority of patients will have 11 to 50 monocytes per mm<sup>3</sup>. Up to 50 monocytes per mm<sup>3</sup> are seen in about 25 percent of patients with multiple sclerosis.<sup>2</sup> The cell differential alone cannot differentiate between bacterial and nonbacterial meningi-

tis. Lymphocytosis is seen in viral, fungal, and tuberculous infections of the CNS, although a predominance of PMNs may be present in the early stages of these infections. CSF in bacterial meningitis is typically dominated by the presence of PMNs. However, more than 10 percent of bacterial meningitis cases will show a lymphocytic predominance, especially early in the clinical course and when there are fewer than 1,000 WBCs per mm<sup>3</sup> (*Table 2*).<sup>10</sup>

Eosinophilic meningitis is defined as more than 10 eosinophils per mm<sup>3</sup> or a total CSF cell count made up of more than 10 percent eosinophils. Parasitic infection should be suspected in this situation. Other possible causes may include viral, fungal, or rickettsial meningitis; having ventriculoperitoneal shunts with or without coexisting infection; malignancy; and adverse drug reactions.<sup>11</sup>

### Microscopic Examination

Gram stain is positive in 60 to 80 percent of untreated cases of bacterial meningitis and in 40 to 60 percent of partially treated cases. The sensitivity according to the causative organism ranges from 90 percent in pneumococcal or

TABLE 2  
Typical Cerebrospinal Fluid Findings in Various Types of Meningitis

Test	Bacterial	Viral	Fungal	Tubercular
Opening pressure	Elevated	Usually normal	Variable	Variable
White blood cell count	≥1,000 per mm <sup>3</sup>	<100 per mm <sup>3</sup>	Variable	Variable
Cell differential	Predominance of PMNs*	Predominance of lymphocytes†	Predominance of lymphocytes	Predominance of lymphocytes
Protein	Mild to marked elevation	Normal to elevated	Elevated	Elevated
CSF-to-serum glucose ratio	Normal to marked decrease	Usually normal	Low	Low

CSF = cerebrospinal fluid; PMNs = polymorphonucleocytes.

\*—Lymphocytosis present 10 percent of the time.

†—PMNs may predominate early in the course.

Information from references 2, 10, 17, and 20.

staphylococcal meningitis to less than 50 percent in *Listeria meningitis*. Hyphae can occasionally be seen in *Candida* or other fungal meningitis cases.

Several factors influence the sensitivity of Gram stain. Laboratory techniques used to concentrate and stain CSF can greatly influence reliability. Cytocentrifugation increases the ability to detect bacteria.<sup>12</sup> Greater numbers of colony-forming units (CFU) per mm<sup>3</sup> of CSF increase the likelihood of a positive result. Staining will be positive in 25 percent of cases if fewer than 1,000 CFU per mm<sup>3</sup> are present, and in 75 percent of cases if more than 100,000 CFU per mm<sup>3</sup> are present.<sup>1</sup> Lastly, the experience of laboratory personnel is very important. Up to 10 percent of initial Gram stains are misread.<sup>13</sup>

Acid-fast staining should be done if tuberculosis is clinically suspected. Only 37 percent of initial smears will be positive for acid-fast bacilli. This result can be increased to 87 percent if four smears are done.<sup>14</sup> Sensitivity also can be increased by examining the CSF sediment.<sup>15</sup>

Other stains should be performed if indicated by the situation. *Cryptococcus* may be

identified up to 50 percent of the time on an India ink preparation. A tap-water control should always be done to ensure that the India ink is not contaminated.<sup>16</sup>

Toxoplasmosis can be diagnosed with Wright or Giemsa stain. A simple wet preparation of CSF under a cover slip can yield positive results in a variety of protozoan and helminthic infections.<sup>14</sup>

### Protein Level

CSF protein concentration is one of the most sensitive indicators of pathology within the CNS. Newborn patients have up to 150 mg per dL (1.5 g per L) of protein.<sup>2</sup> The adult range of 18 to 58 mg per dL (0.18 to 0.58 g per L) is reached between six and 12 months of age.<sup>4</sup> The physician should know what the normal reference range is for his or her laboratory, because the measurement is somewhat technique-dependent.

Elevated CSF protein is seen in infections, intracranial hemorrhages, multiple sclerosis, Guillain Barré syndrome, malignancies, some endocrine abnormalities, certain medication use, and a variety of inflammatory conditions (*Table 3*). Protein concentration is falsely elevated by the presence of RBCs in a traumatic tap situation. This can be corrected by subtracting 1 mg per dL (0.01 g per L) of protein for every 1,000 RBCs per mm<sup>3</sup>.<sup>5</sup> [Evidence level B: observational study] This correction is only accurate if the same tube is used for the protein and cell counts.

Low CSF protein levels can occur in conditions such as repeated lumbar puncture or a chronic leak, in which CSF is lost at a higher than normal rate.<sup>5</sup> Low CSF protein levels also are seen in some children between the ages of six months and two years, in acute water intoxication, and in a minority of patients with idiopathic intracranial hypertension. CSF protein levels do not fall in hypoproteinemia.<sup>2</sup>

### Glucose Level

A true normal range cannot be given for CSF glucose. As a general rule, CSF glucose is

**TABLE 3**  
**Average and Range of Cerebrospinal Fluid Protein**

Condition	Average: mg per dL (g per L)	Range: mg per dL (g per L)
Bacterial meningitis	418 (4.18)	21 to 2220 (0.21 to 22.2)
Brain tumor	115 (1.15)	15 to 1920 (0.15 to 19.2)
Brain abscess	69 (0.69)	16 to 288 (0.16 to 2.88)
Aseptic meningitis	77 (0.77)	11 to 400 (0.11 to 4.0)
Multiple sclerosis	43 (0.43)	13 to 133 (0.13 to 1.33)
Cerebral hemorrhage	270 (2.7)	19 to 2110 (0.19 to 21.1)
Epilepsy	31 (0.31)	7 to 200 (0.07 to 2.0)
Acute alcoholism	32 (0.32)	13 to 88 (0.13 to 0.88)
Neurosyphilis	68 (0.68)	15 to 4200 (0.15 to 42.0)

*Adapted with permission from Fishman RA. Cerebrospinal fluid in diseases of the nervous system. 2d ed. Philadelphia: Saunders, 1992.*

about two thirds of the serum glucose measured during the preceding two to four hours in a normal adult. This ratio decreases with increasing serum glucose levels. CSF glucose levels generally do not go above 300 mg per dL (16.7 mmol per L) regardless of serum levels.<sup>5</sup> Glucose in the CSF of neonates varies much more than in adults, and the CSF-to-serum ratio is generally higher than in adults.<sup>4</sup>

CNS infections can cause lowered CSF glucose levels, although glucose levels are usually normal in viral infections (*Table 2*).<sup>14</sup> Normal glucose levels do not rule out infection, because up to 50 percent of patients who have bacterial meningitis will have normal CSF glucose levels.<sup>5</sup>

Chemical meningitis, inflammatory conditions, subarachnoid hemorrhage, and hypoglycemia also cause hypoglycorrhachia (low glucose level in CSF). Elevated levels of glucose in the blood is the only cause of having an elevated CSF glucose level. There is no pathologic process that causes CSF glucose levels to be elevated.

### Culture

Cultures done on 5 percent sheep blood agar and enriched chocolate agar remain the gold standards for diagnosing bacterial meningitis.<sup>12</sup> Antibiotic treatment prior to lumbar puncture can decrease the sensitivity of culture, especially when given intravenously or intramuscularly.<sup>17</sup>

Enterovirus, the leading cause of viral meningitis, can be recovered in 40 to 80 percent of cases. Culture for herpes simplex virus is 80 to 90 percent sensitive but can take five to seven days to become positive.<sup>18</sup> Results of viral cultures rarely change the initial management of meningitis.<sup>19</sup>

*Mycobacterium tuberculosis* is best grown using multiple large volume samples of CSF. At least 15 mL and preferably 40 to 50 mL of CSF are recommended. Culture is positive 56 percent of the time on the first sample, and improved to 83 percent of the time if four separate samples are cultured. These

*Cultures of cerebrospinal fluid are still the gold standard for confirming the diagnosis of bacterial meningitis.*

cultures often take up to six weeks for positive identification.<sup>20</sup>

Fungal cultures are positive in more than 95 percent of *Cryptococcus neoformans* cases and in 66 percent of candidal meningitis cases. Other fungi are less likely to be culture positive.<sup>9</sup> Similar to tuberculous meningitis, culture yield in fungal meningitis can be increased by obtaining large volumes of CSF via repeated lumbar punctures.<sup>15</sup>

### Latex Agglutination

Latex agglutination (LA) allows rapid detection of bacterial antigens in CSF. Sensitivity varies greatly between bacteria. LA for *Haemophilus influenzae* has a sensitivity of 60 to 100 percent, but is much lower for other bacteria. The specificity for LA is very low.<sup>5</sup> However, LA can be useful in partially treated meningitis cases where cultures may not yield an organism.<sup>13</sup> Because false positives lead to unnecessary treatment, LA is not routinely used today. Some experts suggest using LA in cases of suspected bacterial meningitis if the initial Gram stain and bacterial culture are negative after 48 hours.<sup>12</sup>

### Polymerase Chain Reaction

Polymerase chain reaction (PCR) has been a great advance in the diagnosis of meningitis. PCR has high sensitivity and specificity for many infections of the CNS, is fast, and can be done with small volumes of CSF. Although testing is expensive, there is a potential for cost savings by decreasing overall diagnostic testing and intervention.<sup>21</sup>

PCR has been especially useful in the diagnosis of viral meningitis. PCR of the CSF has a sensitivity of 95 to 100 percent, and a sensitivity of 100 percent for herpes simplex virus type 1, Epstein-Barr virus, and enterovirus.<sup>14</sup>

*Polymerase chain reaction testing has proved to be especially useful in the diagnosis of viral meningitis.*

PCR is faster and more sensitive than culture for enterovirus meningitis.<sup>22</sup> When PCR is positive for enterovirus, it allows earlier hospital discharge and less intervention.<sup>23</sup> [Evidence level B: retrospective chart review]

PCR is the most sensitive means of diagnosing CMV infections of the CNS,<sup>21</sup> and it has been suggested that PCR should replace brain biopsy as the gold standard for herpes encephalitis.<sup>24</sup>

PCR has a sensitivity of 54 to 100 percent and a specificity of 94 to 100 percent for tuberculous meningitis, and could replace acid-fast bacillus smear and culture as the test of choice.<sup>25</sup> PCR is sensitive for acute neurosyphilis but not for more chronic forms.<sup>21</sup> PCR also is being studied as a diagnostic tool for bacterial meningitis and other infections of the CNS.<sup>12</sup>

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