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# How to Interpret a CSF—The Art and the Science

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## 1. Introduction

Cerebrospinal fluid (CSF) was described by Galen as early as the second century as a vaporous humor produced in the ventricles that provided energy to the rest of the body. Interestingly, such theories, although humorous, have not been universally replaced by scientific rationale (http://www.healtouch.com/csft/csf.html).

CSF is metabolically active and has many functions. By providing buoyancy, it reduces the effective weight of the brain from 1,500 to 50 g (Conly and Ronald, 1983) and provides a buffer against the effects of trauma. CSF is predominantly produced by the choroid plexuses of the lateral, third, and fourth ventricles and flows within the subarachnoid space, with approximately one-fifth lying in the ventricles (Davson et al., 1987; Blatter et al., 1995). Daily CSF production varies between 400 and 500 ml in adults and the entire CSF volume is replenished every 5–7 hr (Cutler et al., 1968; Wood, 1983). The CSF volume varies with age: from 170 ml in an adult (Blatter et al., 1995; Fujimaki et al., 2003); to between 65 and 140 ml from 4 to 13 years (Cutler et al., 1968); to 40 ml in a healthy full-term neonate; and to between 10 and 30 ml in a premature neonate (Otilia, 1948). CSF flow rate differs in the cervical, thoracic, and lumbar spinal canal (Freund et al., 2001), and CSF microscopy and biochemistry values may differ between lumbar and ventricular CSF (Freemont-Smith and Dailey, 1925; Goodwin and Shelley, 1925; Stewart, 1928; Marks, 1960; Fishman, 1980; Herndon and Brumback, 1989; Greenlee, 1990). Normal CSF comprises 99% water and contains various plasma components including glucose, proteins, electrolytes, minerals, and enzymes, as well as antibacterial components. The specific gravity ranges from 1.004 to 1.007. CSF is typically described as crystal or "gin" clear and colorless.

Lumbar puncture is frequently performed in the evaluation of the febrile infant or child to confirm or exclude a diagnosis of bacterial meningitis. A positive CSF culture ultimately provides the gold standard for diagnosing bacterial meningitis but is

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unavailable at the time of initial evaluation. Physicians therefore frequently make decisions based on initial CSF microscopy and biochemical analysis, including CSF pressure, white cell count, protein concentration, glucose concentration, and Gram stain. This requires knowledge of the normal ranges of these indices across different age groups and other factors that may influence them. Debate about the interpretation of CSF findings dates back nearly a century (Sidbury, 1920; Levinson, 1928; Munro, 1928; Stewart, 1928).

## 2. Variation in CSF Normal Values with Age

### 2.1. Pressure

In a series of 1,000 normotensive adults, CSF pressure ranged from 70 to 180 mm of water in 94% of cases (Meritt and Fremont-Smith, 1937). Although pressures up to 280 mm have been recorded in normal children (Fishman, 1980; Ellis, 1994), the generally accepted upper limit for the normal opening pressure during lumbar puncture with the patient in the lateral decubitus position is 150 mm of water in older children and lower (85–110 mm) in younger children (Bonadio et al., 1992; Meritt and Fremont-Smith, 1937). In newborns, a normal range between 0 and 60 mm of water has been reported (Sidbury, 1920; Levinson, 1928; Munro, 1928; Stewart, 1928). The CSF pressure is higher in the sitting position (up to 400 mm of water in adults) due to the hydrostatic effect of the column of CSF (Fishman, 1980). CSF pressure changes with respiration, typically increasing with expiration and decreasing with inspiration by 5–10 mm of water (Meritt and Fremont-Smith, 1937; Conly and Ronald, 1983; Seehusen et al., 2003). Hyperventilation is associated with a lower opening pressure, whereas obese and uncooperative patients may have higher opening pressures (Fishman, 1980; Ellis, 1994).

### 2.2. White Cell Count

The normal CSF white cell count in infants over 2 months of age is the same as for older children and adults, that is, less than $5 \times 10^6$ lymphocytes per liter (L). In contrast, as a consequence of increased permeability of the blood brain barrier (Adinolfi, 1985; Anagnostakis et al., 1992), it is quite common for CSF from normal neonates to contain more than $5 \times 10^6$/L white cells. This leads to difficulty in interpreting CSF white cell count in the newborn and early neonatal period. Normal ranges for CSF white cell count in non-infected neonates have been provided in several studies, but these differ in the age ranges evaluated as well as methodology (Stewart, 1928; Wolf, 1961; Sarff et al., 1976; Naidoo, 1982; Pappu et al., 1982; Portnoy and Olson, 1985; Rodriguez et al., 1990; Bonadio, 1992; Ahmed et al., 1996). In addition, viral CNS disease was not reliably excluded in most of these studies. Bonadio et al. compared normal CSF white cell counts in 75 infants in two age groups in the first 8 weeks of life (Bonadio et al., 1992). In 90% of cases, the total cell count was less than $22 \times 10^6$/L in infants in the first 4 weeks of life and less than $15 \times 10^6$/L in infants aged 4–8 weeks. In contrast, Ahmed et al. analyzed CSF from 108 normal infants from 0 to 30 days of age and found a lower normal CSF white

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cell count: 90% had a CSF white cell count of less than $11 \times 10^6$/L (Ahmed et al., 1996). This was attributed to tighter exclusion criteria including the use of PCR to exclude enteroviral meningitis. This study found that there was no significant difference in CSF white cell counts in each of the first 4 weeks although there was a trend towards increased number of cells in the first week.

The CSF white cell count does not differ remarkably between the term babies and premature or low birth weight infants. Statz reported mean CSF white cell counts in infants at different gestational ages (Statz and Felgenhauer, 1983). The mean numbers of CSF white cells were 7.6, 6.5, and $7.3 \times 10^6$/L at 27–32, 32–36, and 30–40 weeks, respectively, with a range from 0 to $20 \times 10^6$/L. Other studies have reported similar findings in premature and low birth weight infants (Otila, 1948; Gyllesward.A and Malmstrom, 1962; Rodriguez et al., 1990).

In summary, whilst there is wide variation in the reported 'normal' upper limit for CSF white cell count in neonates, the most robust studies suggest that CSF white cell counts over $11–22 \times 10^6$/L in the first four weeks of life are unusual in normal infants (Table 14.1).

## 2.3. Neutrophil Count

The presence of neutrophils in the CSF has been deemed as always abnormal (Conly and Ronald, 1983). Some authorities, however, accept that a single neutrophil may rarely be seen in normal CSF and is not necessarily abnormal if the CSF white cell count is $4 \times 10^6$/L or less and the protein and glucose are normal (Fishman, 1980; Bonadio, 1988b; Herndon and Brumback, 1989; Greenlee, 1990; Scheld et al., 1997).

In contrast, the presence of neutrophils in the CSF from neonates may not be so abnormal. There is disagreement in the literature about the differential white cell composition in normal neonatal CSF. Whilst Sarff et al. reported that up to 61% of the total CSF white cell count in healthy neonates may be neutrophils (Sarff et al., 1976), Bonadio et al. found substantially lower proportions of neutrophils (mean 2–3%) (Bonadio et al., 1992). In 90% of cases reported by Bonadio et al., the percentage of neutrophils was less than 6% in infants in the first 4 weeks of life and less than 9% in infants aged 4–8 weeks. This lower proportion was confirmed by Ahmed et al. who found a median CSF neutrophil count across all age ranges of $0 \times 10^6$/L with only 5% of infants having a neutrophil count greater than $1 \times 10^6$/L at any age (Ahmed et al., 1996).

There are fewer studies in low birth weight and premature infants but one study found the percentage of neutrophils to be as high as 11% in this group (Rodriguez et al., 1990).

In summary, neutrophils are absent in the CSF of the majority of normal neonates and their presence, particularly if more than 5% of the CSF white cell count should raise concern.

## 2.4. Protein

CSF protein concentration depends on serum protein concentration and the permeability of the blood brain barrier, which varies with age (Adinolfi, 1985). For this reason, CSF protein concentration is age dependent, being greatest at birth and decreasing

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**Table 14.1.** Normal Values for CSF White Cell Count ($\times 10^6$/L) from Selected Studies

| Study reference (n= number of patients) | | 1 to 7 days | 8 to 30 days | 1 to 2 mo | 2 to 3 mo | 3 to 4 mo | 4 to 6 mo | 6 mo to 10 y | 10 to 14 y | 14 to 16 y |
|---|---|---|---|---|---|---|---|---|---|---|
| (Ahmed et al., 1996) (n=108) | Median ($90^{th}$ centile) | 6 (18) | 4 (8–13) | | | | | | | |
| | | 4 (11) | | | | | | | | |
| (Bonadio et al., 1992) (n=75) | Median ($90^{th}$ centile) | 8.5 (22) | | 4.5 (15) | | | | | | |
| (Rodriguez et al., 1990) (n=71) | Mean ±SD | 3±3 | 4±4 | 4±3 | | For infants of birth weight ≤1,000 g | | | | |
| | Mean ±SD | 4±4 | 7±11 | 8±8 | | For infants of birth weight 1,001–1,500 g | | | | |

**Table 14.2.** Normal Values for CSF Protein Concentration (g/L) from Selected Studies

| Study reference (n= number of patients) | | 1 to 7 days | 8 to 30 days | 1 to 2 mo | 2 to 3 mo | 3 to 4 mo | 4 to 6 mo | 6 mo to 10 y | 10 to 14 y | 14 to 16 y |
|---|---|---|---|---|---|---|---|---|---|---|
| (Biou et al., 2000) (n=1074) | $95^{th}$ centile | 1.08* | 0.90 | 0.77 | 0.60 | 0.40 | | 0.32 | 0.41 | |
| (Wong et al., 2000) (n=225) | $90^{th}$ centile | 0.87 | | | 0.55 | 0.25 | | | 0.33 | |
| (Ahmed et al., 1996) (n=108) | Mean ±SD | 0.81±0.31 | 0.69±0.23 (8 to 14 days)<br>0.60±0.23 (15 to 21 days)<br>0.54±0.16 (22 to 30 days) | | | | | | | |
| | | 0.64±0.24 | | | | | | | | |
| (Bonadio et al., 1992) (n=75) | Mean ±SD | 0.84±0.45 | | 0.59±0.25 | | | | | | |
| (Rodriguez et al., 1990) (n=71) | Mean ±SD | 1.62±0.37 | 1.59±0.77 | 1.37±0.61 | | For infants of birth weight ≤1,000 g | | | | |
| | Mean ±SD | 1.36±0.35 | 1.37±0.46 | 1.22±0.47 | | For infants of birth weight 1,001–1,500 g | | | | |

*1 to 8 days

during the first few weeks of life, reaching a minimum value at 6 months of age (Tibbling et al., 1977; Statz and Felgenhauer, 1983; Lott and Warren, 1989; Rodriguez et al., 1990; Bonadio, 1992; Biou et al., 2000; Wong et al., 2000). Thereafter, the normal CSF protein range remains low, not increasing to adult values until at least after adolescence (Tibbling et al., 1977; Wong et al., 2000) (Table 14.2). Therefore, the use of adult reference ranges is inappropriate as values at the higher end of this range may

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be abnormal in preadolescent children. This was also illustrated in a study of 1,074 CSF protein concentrations by Biou et al. that showed CSF protein concentration rarely exceeds 0.35 g/L between 6 months and 10 years of age (Biou et al., 2000).

The study by Biou et al. also addressed the normal range for CSF protein in neonates. In the first week of life, the 95th centile for CSF protein in this study was 1.08 g/L, which is less than that documented in some previous studies for the early neonatal period, such as the often quoted upper value of 1.7 g/L reported by Sarff et al. (Sarff et al., 1976). Other authors have also suggested the upper limit for CSF protein in neonates is lower than previously suggested (Anagnostakis et al., 1992; Ahmed et al., 1996; Biou et al., 2000). In contrast, higher normal limits for CSF protein have been suggested for premature and low birth weight infants (Rodriguez et al., 1990).

In summary, CSF protein concentrations greater than around 1.0 g/L in neonates and greater than 0.35 g/L in children less than 10 years of age should be considered potentially abnormal.

### 2.5. Glucose

CSF glucose is derived from serum and as a general rule has a concentration approximately two-thirds of the serum level (Stewart, 1928; Powers, 1981; Donald et al., 1983; Greenlee, 1990). CSF glucose should therefore ideally always be interpreted in relation to the serum glucose concentration, taking into account that it takes approximately 4 hr for the CSF glucose to equilibrate with changes in the serum glucose (Powers, 1981). Like CSF protein, the CSF glucose normal range is age dependent. It is lower in neonates compared to older children reflecting their lower blood glucose levels, immature glucose exchange mechanisms, and the increased permeability of the blood brain barrier (Fishman, 1980; Remington and Klein, 2001). Bonadio et al. reported a mean CSF glucose of 2.55 $\pm$ 0.57 mmol/l in the first 8 weeks of life (Bonadio et al., 1992). There was no significant difference between values in the first 4 weeks of life and weeks 4–8. Ahmed et al.'s findings were similar though this study found a slightly higher mean value in the first 4 weeks (2.84 $\pm$ 0.71 mmol/l) (Ahmed et al., 1996).

## 3. Can CSF Abnormalities be Caused by Convulsions?

Whether convulsions cause changes in the CSF is frequently debated as there is inconsistent information about this in the literature (Aminoff and Simon, 1980; Schmidley and Simon, 1981; Edwards et al., 1983; Simon, 1985; Thompson and Salinsky, 1988; Woody et al., 1988). The reported frequency of seizure-induced CSF abnormalities has been estimated to be as high as 30% (Prokesch et al., 1983). The mechanism by which seizure activity might induce a CSF pleocytosis is unclear but a transient disruption of the blood brain barrier has been demonstrated (Meldrum and Breirley, 1973; Petito et al., 1977; Wenzel et al., 1980). Physiological responses, including the release of noradrenaline, have been proposed to be responsible for a transient rise in CSF glucose following an episode of status epilepticus.

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A number of studies have reported postictal CSF pleocytosis in patients with epilepsy following an episode of status epilepticus (Aminoff and Simon, 1980; Woody et al., 1988; Barry and Hauser, 1994; Rider et al., 1995) or prolonged seizure (Schmidley and Simon, 1981; Edwards et al., 1983; Prokesch et al., 1983; Devinsky et al., 1988; Rider et al., 1995). However, in most of these studies, observed changes were minimal. Moreover, it was difficult to exclude the possibility of undiagnosed infection or other cause for CSF changes in some of these studies.

Recently, there have been studies suggesting that it is inappropriate to attribute CSF changes to convulsions. Wong et al. retrospectively reviewed the results of CSF examinations on 62 patients who had had a convulsion within the previous 24 hr (in whom infection or other causes of CSF changes had been excluded) (Wong et al., 2001). Although CSF changes were found in a few patients (pleocytosis in 5%, neutrophilia in 6%, and increased protein in 10%), these were minimal; the maximum observed white cell count was $8 \times 10^6$/L and maximum protein 0.52 g/L. There was no significant difference between those with short or prolonged seizures. This and other studies (Portnoy and Olson, 1985) suggest that seizure-induced CSF abnormalities are rare in children.

## 4. CSF Eosinophilia

### 4.1. Eosinophilic Meningitis

Eosinophilic meningitis, defined by the presence of more than 10 eosinophils $\times 10^6$/L in the CSF, is rare (Bosch and Oehmichen, 1978). There are both infectious (most commonly parasitic) and non-infectious causes. The nematode infections angiostronglyliasis, gnathostomiasis, and baylisascaris are the commonest infections associated with eosinophilic meningitis (Lo Re and Gluckman, 2001; Lo Re and Gluckman, 2002; Lo Re and Gluckman, 2003). They are seen worldwide, but predominantly in the Pacific Basin including Hawaii, Indonesia, the Philippines, Japan, and Papua New Guinea. Clinical manifestations differ depending on the parasite but generally occur between 2 and 35 days following ingestion of larvae and can range from headaches and neck stiffness to delirium and seizures. Peripheral blood eosinophilia may also be present depending on the parasite (Schulte et al., 2002). The CSF is usually mildly turbid with a white cell count between 150 and 2,000 cells $\times 10^6$/L and eosinophils representing more than 10% of the total in the majority of patients (Kuberski et al., 1979). Patients with gnathostomiasis can have a CSF eosinophilia as high as 95% of the total CSF white cell count. Protein concentration is usually elevated with glucose being low or normal.

### 4.2. Shunt Pathology

CSF analysis is often used to help diagnose shunt pathology and to distinguish obstruction and infection. CSF eosinophilia has been reported to be a strong indicator of shunt pathology (Bosch and Oehmichen, 1978; Tzvetanova and Tzekoc, 1986; Vinchon et al., 1992; Wiersbitzky et al., 1998). Although specific, the finding of CSF eosinophilia has low sensitivity. In one study, hypereosinophilia

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(defined as greater than 5% of CSF white cells) was present in only 15 of 94 shunt infections (68 culture positive) (Vinchon et al., 1992). Recurrence of infection occurred earlier and more frequently in the group of patients with eosinophilia. Additionally, subsequent shunt complications, appeared to be associated with a higher level of eosinophilia at the end of treatment of the initial infection, a finding supported by Tung et al. (1991).

According to at least one study, the finding of CSF eosinophilia is less helpful in distinguishing between an infected and obstructed shunt. McClinton et al. reported CSF eosinophilia in 2 of 12 patients with infection and 11 of 13 patients with malfunction in a series of 81 patients concluding only that CSF eosinophilia greater than 5% is a good predictor of shunt pathology, rather than helpful in distinguishing between infection and obstruction (McClinton et al., 2001). However, this study did find that a combination of fever and greater than 10% ventricular CSF neutrophils had a 99% specificity, a 93% positive predictive value, a 95% negative predictive value, and a posttest probability of 92% for infection.

## 5. Interpretation of Blood-Contaminated CSF ("Traumatic Taps")

Traumatic lumbar punctures occur in up to 20% of cases undertaken in children and neonates (Yogev, 2002). It takes between 5,000 and 6,000 red cells $\times 10^6$/L for the CSF to appear bloody to the naked eye (Conly and Ronald, 1983). Interpreting the results of CSF analysis with a "bloody tap" is notoriously difficult.

Calculations to determine the corrected number of white cells in the CSF of blood-contaminated samples frequently underestimate the true CSF white cell count (Osborne and Pizer, 1981; Novak, 1984). Simple calculations to correct for blood contamination are based on the assumption that in a normal person the ratio of white to red cells in the CSF attributable to blood contamination is 1:500 to 750 (Solomon et al., 1934; Meritt and Fremont-Smith, 1937; Fishman, 1980; Feigin, 1981; Novak, 1984; Fuchs, 1997). These ratios are based predominantly on *in vitro* studies. Others have suggested calculations based on the peripheral blood white to red cell ratio. Rubenstein et al. used an equation to calculate the expected (predicted) CSF white cell count based on the ratio of red to white cells in the peripheral blood (CSF WBC (predicted) = CSF RBC $\times$ Blood WBC/Blood RBC) and concluded that CSF pleocytosis could go undetected using this calculation (Rubenstein and Yogev, 1985). This was highlighted by three patients with viral meningitis who had both a nontraumatic and traumatic lumbar puncture, in whom the calculation underestimated the number of CSF white cells in the traumatic sample, resulting in falsely normal corrected CSF results.

In contrast, the observed to predicted *ratio* of CSF white cells has been found to be helpful by some authors. Mayefesky et al. analyzed 720 traumatic lumbar puncture samples and confirmed a high proportion (55%) of false positive results by simply calculating the *adjusted* (observed—predicted) CSF white cell count to predict the presence of CSF pleocytosis (Mayefsky and Roghmann, 1987). In this study, an observed to predicted CSF white cell ratio greater than 10 was claimed to be both

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a sensitive (88%) and specific (90%) indicator of bacterial meningitis. Bonadio et al. reported an observed to predicted CSF white cell ratio greater than 1 as 100% sensitive but only 62% specific for predicting meningitis (Bonadio et al., 1990). In a study of 57 patients, 12 of whom had culture proven meningitis, the observed to predicted ratio was significantly higher in the meningitis group (Mazor et al., 2003). Mazor et al. reported that the observed to predicted CSF white cell ratio in a non-infected group was less than 1 in 98% of cases and concluded that an observed to predicted ratio less than or equal to 0.01, a CSF white to red cell ratio less than or equal to 1:100, and the absence of pleocytosis were each highly specific with a high positive predictive value for predicating the absence of meningitis (Mazor et al., 2003).

It has been suggested that contamination of the CSF by less than 10,000 red cells $\times 10^6$/L does not influence the CSF white cell count (Osborne and Pizer, 1981). Moreover, although the observed to predicted CSF white cell ratio appears to offer better sensitivity and specificity for the diagnosis of bacterial meningitis than using the CSF white to red cell ratio alone, many authorities still believe that it is safer to interpret blood-contaminated CSF using the same criteria as a non-contaminated CSF (Mehl, 1986; Bonadio, 1988a; Bonadio et al., 1990).

## 6. Distinguishing Viral and Bacterial Meningitis on the Basis of CSF Findings

The "typical" CSF findings in meningitis described in many textbooks make it seem deceptively easy to distinguish viral, bacterial, and tuberculous meningitis (Figure 14.1.). These indicate that in viral meningitis, the CSF is clear, contains up to a few hundred lymphocytes with a normal to slightly elevated protein concentration. In contrast, in bacterial meningitis the CSF is turbid, contains thousands of neutrophils, with substantially increased protein and decreased glucose concentrations, together with a positive Gram stain. In tuberculous meningitis, the CSF contains hundreds of lymphocytes, with substantially increased protein and markedly decreased glucose concentrations, together with a positive Ziehl–Neelsen stain. However, these CSF profiles relate to established meningitis in the absence of prior antibiotics. In reality, although many studies demonstrate a statistically significant higher CSF white cell count and protein concentration, and lower glucose concentration in bacterial compared with aseptic meningitis, there is considerable overlap in these values, particularly between the CSF findings in viral and early bacterial meningitis.

### 6.1. "Scary Facts" About CSF Findings in Meningitis

*The macroscopic appearance* of CSF does not appear cloudy until there are between 200 and 500 white cells $\times 10^6$/L, and turbid until there are greater than 500 white cells $\times 10^6$/L.

*Delays in the laboratory analysis* of CSF can alter the cell count as a result of lysis in CSF, which is hypotonic. There is a progressive reduction in both neutrophils

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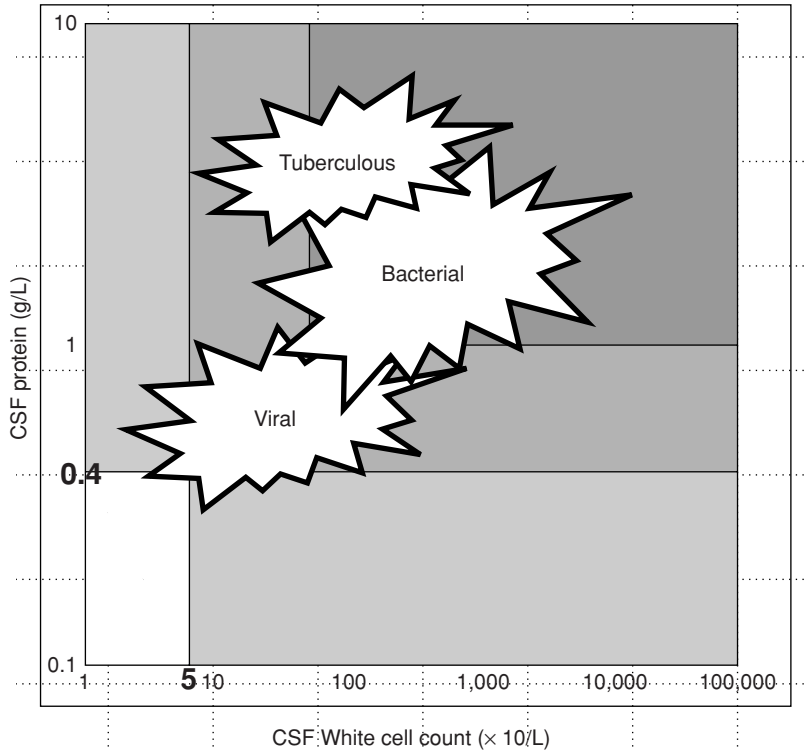



**Figure 14.1.** The "typical" CSF findings in viral, bacterial, and tuberculous meningitis.

and lymphocytes over a 4-hour period (Steele et al., 1986). The neutrophil count decreases by 33% at 1 hr and by 50% at 2 hr. For lymphocytes, the decrease is somewhat less with a 10% decrease at 2 hr.

*CSF lymphocyte predominance in viral meningitis and neutrophil predominance in bacterial meningitis is not a constant finding*. Whilst several studies have documented a predominance of neutrophils in early viral (particularly enteroviral) meningitis (Nye, 1983; Harrison and Risser, 1988; Greenlee, 1990), it is generally believed that there is a rapid shift from a neutrophil to a lymphocyte predominance over several hours (Feigin and Shackelford, 1973). A recent study of CSF findings during the enteroviral season over a 6-year period found that the majority of children with viral meningitis (57%) had a predominance of neutrophils in the CSF as expected (Negrini et al., 2000). However, in many cases a neutrophil predominance was still observed even when a lumbar puncture was performed up to 96 hr after the onset of symptoms, a finding supported by some earlier studies (Quick et al., 1965; Harrison and Risser, 1988). To add to the confusion, studies have demonstrated CSF lymphocytosis on initial evaluation in patients with bacterial meningitis (Powers, 1985; Bonadio, 1988a, b), although Bonadio reported this to be a rare event

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(Bonadio, 1988a). CSF lymphocytosis is also recognized to occur in bacterial meningitis after antibiotic treatment (Dalton and Allison, 1968; Converse et al., 1973; Blazer et al., 1983).

*An initial normal CSF does not exclude bacterial meningitis*. CSF culture may subsequently be positive even when CSF white cell count, protein, glucose, and Gram stain are negative, particularly in the early stages of bacterial meningitis (Scheld et al.). A repeat lumbar puncture may therefore be needed (Moore and Ross, 1973; Bonadio, 1989).

*Bacterial meningitis can occur in the absence of significant CSF pleocytosis* (Moore and Ross, 1973; Onorato et al., 1980; Fishbein et al., 1981; Michael et al., 1986; Polk and Steele, 1987; Wong et al., 1989; Coll et al., 1994; Freedman et al., 2001), particularly in patients with sickle cell disease (Seeler et al., 1972; Rao et al., 1983).

*The CSF glucose concentration is normal* in 9% of cases of bacterial meningitis (Greenlee, 1990).

*The CSF Gram stain is negative* in up to 40% of cases of bacterial meningitis even without prior antibiotics (Marton and Gean, 1986; Hristeva et al., 1993).

*Prior treatment with antibiotics* decreases the sensitivity of CSF Gram stain by 20% and of culture by 30% (Dalton and Allison, 1968; Converse et al., 1973; Blazer et al., 1983). CSF culture becomes sterile in 90–100% of patients within 24–36 hr of antibiotic treatment (Dalton and Allison, 1968; Converse et al., 1973; Blazer et al., 1983; Bonadio et al., 1992).

## 6.2. CSF Scores and Algorithms

Given the overlap in CSF findings in viral and bacterial meningitis, several authors have recently added to the many previous attempts to create meningitis scores (Nigrovic et al., 2002), diagnostic models, and algorithms to differentiate between viral and bacterial meningitis based on CSF white cell count, protein, and glucose. Some of these scoring systems also include features such as age, season, peripheral blood neutrophil count, and glucose (Spanos et al., 1989; Hoen et al., 1995; Leblebicioglu et al., 1996). These models are designed to identify a group of patients who are at low risk of bacterial meningitis who do not need admission and antibiotics. The most recent attempt at using a model to discriminate patients with bacterial meningitis illustrates the difficulties with this strategy (Bonsu and Harper, 2004a, b). Firstly, all such models are a trade off between sensitivity and specificity. Inevitably, any incremental increase in specificity (i.e., a reduction in the number of patients with viral meningitis who are allocated incorrectly to the high-risk group ("false positives")) is associated with a decrease in sensitivity (i.e., an increase in the number of patients with bacterial meningitis who are allocated incorrectly to the low-risk group ("false negatives")). These models are able to improve upon the specificity and sensitivity offered by the use of one parameter alone but ultimately suffer the same problem that there is overlap between cases of viral and (usually early) bacterial meningitis. Secondly, these models are sometimes complex and require calibration, if not revalidation, in each setting in which they are to be used (Bonsu and Harper, 2004a, b).

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### 6.3. Approach for Patients with Mild CSF Pleocytosis Only

The issue of bacterial meningitis in children with mild or no CSF pleocytosis has been addressed in a number of studies (Moore and Ross, 1973; Onorato et al., 1980; Fishbein et al., 1981; Michael et al., 1986; Polk and Steele, 1987; Wong et al., 1989; Coll et al., 1994; Freedman et al., 2001). Freedman et al. reported that 11% of 44 cases of bacterial meningitis had a CSF white cell count less than $3 \times 10^6$/L (Freedman et al., 2001). All of these children, however, had at least one other factor that indicated an increased risk of bacterial meningitis including age less than 1 year, increased FBE band count, increased CSF protein, or decreased CSF glucose. Freedman et al. offered an interesting and clear-thinking approach to the issue of CSF white cell count in influencing the probability of bacterial versus viral meningitis (Freedman et al., 2001). His study highlighted that, although bacterial meningitis can occur in patients with low CSF white cell counts, likelihood ratios can be determined that quantify the effect of CSF white cell magnitude on increasing or decreasing the post-test probability of bacterial meningitis. Of 1,469 patients (2 months–17 years) with a CSF white cell count less than or equal to $30 \times 10^6$/L, only 11 had bacterial meningitis. This was associated with a decrease in probability of bacterial meningitis from a pretest probability of 2.7% to a post-test probability of 0.7%. In contrast, bacterial meningitis was present in 33 out of the 148 patients with CSF white cell counts above 30, increasing the post-test probability to 22.2% (Frohna et al., 2001). The negative predictive value for a CSF white cell count of $30 \times 10^6$/L or less was 99.3%, and Freedman et al. concluded that children older than 6 months of age with CSF white cell counts in this range have a low risk of bacterial meningitis, provided other CSF parameters (protein, glucose, Gram stain) and peripheral blood band count are normal.

Interpretation of CSF results, whether evidence-based or statistically manipulated into algorithms, provides only one piece of information. Ultimately, distinguishing aseptic and bacterial meningitis depends on clinical evaluation in combination with CSF findings. The clinical picture should always remain foremost in the physician's decision process.

## 7. Alternative Methods for Distinguishing Bacterial and Viral Meningitis

### 7.1. Rapid Antigen Tests

Much has been reported in the literature about the detection of bacterial antigens by latex agglutination. This technique developed in an era when infection with *Haemophilus influenza* was common. Recent reports have highlighted the shortcomings of latex agglutination tests and many authorities believe that their low sensitivity and specificity preclude their use in clinical management decisions (Freedman et al., 2001; Tarafdar et al., 2001). More recently, it has been suggested that ultrasound-enhanced latex immunoagglutination has superior sensitivity and specificity, but this technique has yet to find widespread acceptance or use (Gray et al., 1999; Sobanski et al., 2002; Porritt et al., 2003).

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### 7.2. Inflammatory Cytokines and Other Marker

Most markers of inflammation in the peripheral blood or CSF have proved unhelpful in distinguishing bacterial from viral meningitis. Peripheral blood C-reactive protein (CRP) has been suggested to be useful in distinguishing bacterial from viral meningitis (Clarke and Cost, 1983; De Beer et al., 1984; Sabel and Hanson, 1974). In a recent study, CRP was shown to have high sensitivity and specificity in a group of 55 Finnish children with an initial negative Gram stain (Sormunen et al., 1999). Two children, however, with culture positive meningitis had a normal CRP level at presentation, a finding reported in other studies (Petola and Jaakola.M, 1988; Gendrel et al., 1997; Gendrel et al., 1998; Gendrel et al., 1999).

Procalcitonin (PCT), a glycopeptide that is normally undetectable in the blood of healthy children, has been shown to increase in a variety of bacterial infections with minimal elevation in viral disease (Schwarz et al., 2000; Marc et al., 2002). Gendrel reported that an initial blood PCT level greater than 5 μg/L had a sensitivity of 94% and specificity of 100% for the diagnosis of bacterial meningitis (Gendrel et al., 1997). False negative results (normal PCT in confirmed bacterial meningitis) limit the usefulness of this marker as with the other markers described above.

Although the mean value of a wide range of other peripheral blood and CSF markers (e.g., lactate, lactic dehydrogenase, creatine phosphokinase, glutamic oxaloacetic transaminase, elastase-α proteinase inhibitor, defensin, lactoferrin, TNF-α, IL-1β, IL-6, IL-8, S-100β) are generally higher in patients with bacterial when compared with viral meningitis, there is sufficient overlap in the values between the groups for these tests to be of limited value in clinical practice (Rutledge et al., 1981; Lorino et al., 2000; Paul et al., 2003; Sato et al., 2003).

### 7.3. The Future: Molecular Testing

Molecular tests hold much greater promise. The use of PCR for the diagnosis of enterovirus (Ramers et al., 2000; Stellrecht et al., 2002; Guney et al., 2003; Archimbaud et al., 2004; Mohamed et al., 2004; Mulford et al., 2004), meningococcus (Saunders et al., 1997; Kotilainen et al., 1998; Seward and Towner, 2000; Taha, 2000; Bryant et al., 2004), and pneumococcus (Cherian et al., 1998; Corless et al., 2001) are already routine in many hospitals (Hall et al., 1995; Backman et al., 1999; Dicuonzo et al., 1999; Lu et al., 2000; Rantakokko-Jalava et al., 2000; Saravolatz et al., 2003). More recently, the reported high sensitivity and specificity (regardless of prior antibiotics) offered by the use of broad range 16S ribosomal DNA PCR points to the future for CSF analysis (Schuurman et al., 2004).

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