Antibiotic Pharmacodynamics in Cerebrospinal Fluid

Irja Lutsar, George H. McCracken, Jr., and Ian R. Friedland

The term antibiotic pharmacodynamics encompasses the relation between drug concentrations at the site of infection and the antibacterial effect. Knowledge of the pharmacodynamic properties of a particular agent allows clinicians to determine a dosing regimen with the best therapeutic index. Antibiotic pharmacodynamics in various body sites have been studied in clinical and experimental settings. In general, on the basis of their pharmacodynamic characteristics, antibiotics can be divided into two major categories: concentration-dependent and concentration-independent. Aminoglycosides and fluoroquinolones are concentration-dependent, and β-lactam agents are concentration-independent [1]. Because of the absence of complement and antibody and the poor entry of drugs into CSF, the pharmacodynamic properties of antibiotics in CSF may differ from those in other body sites [2].

Our main focus is to review recent studies of antibiotic action in the CSF in meningitis. Pharmacodynamic studies are difficult to conduct in humans with meningitis; thus, most data in this review were obtained from experimental meningitis models. Although differences in pharmacokinetic indices (e.g., half-life, volume of distribution) exist between humans and animals, in general, the pharmacodynamic properties of antibiotics appear to be similar [1, 3, 4].

Physiology of CSF

CSF is an ultrafiltrate of plasma and functions to support brain cells, prevent mechanical damage, and to eliminate waste products. CSF also acts as an alternate circulation system within the brain, carrying peptides secreted in one brain region to another [5]. CSF is secreted mainly by the choroid plexuses of the lateral, third, and fourth ventricles, but small amounts are derived directly from brain extracellular fluid. CSF flows from the ventricular system through the foramina of Magendie and Luschka into the cisterna magna, and then into the subarachnoid space, where it circulates around the brain and spinal cord by pulsatile flow. The reabsorption of CSF into the bloodstream occurs not only through subarachnoid granulations, as originally proposed by Key, Retzius, and Weed [6], but also through the brain extracellular space, which is in open communication with the subarachnoid space [6]. The rate of CSF formation in adult humans is ~0.5 mL/minute, with complete exchange of CSF occurring four to five times a day. The percentage of turnover and the rate of CSF secretion per milligram of choroid plexus are constant in different animal species (approximately 0.5 mL/mg of choroid plexus), suggesting a common underlying secretory mechanism [5].

Alterations in CSF Physiology in Infections of the CSF

Several disease states and drugs may alter CSF dynamics. A marked reduction in the rate of CSF production has been demonstrated in an animal model of acute ventriculitis [7]. Data concerning CSF production in experimental meningitis are conflicting; investigators have reported both a significant decrease [8] and an unaltered CSF production rate [9]. Meningitis may result in communicating hydrocephalus because of reduced CSF outflow through the subarachnoid granulations [10]. Corticosteroids, often used as adjunctive therapy in bacterial meningitis, inhibit the secretion of CSF by 30% [5]. A decrease in CSF bulk flow might be expected to increase the half-lives of drugs in CSF, but experimental and clinical data suggest that antibiotic concentrations are often decreased or unaltered by concomitant steroid administration [11–14].

Blood-Brain Barrier

Physiology

The blood-brain barrier (BBB) refers to a functional barrier that excludes even very small serum components from neuronal tissue, thus maintaining homeostasis within the CNS. Water, most ions, and lipids pass freely from blood into cerebral extracellular fluids, whereas proteins and polar molecules are excluded. The major anatomical sites of the BBB are the cerebral microvascular endothelium of the arachnoid membrane and the choroid plexus epithelium. Three important histologic differences have been observed between general capillaries and those in the CNS. Capillaries throughout the body are fenestrated, permitting movement of large molecules between endothelial...
cells. Cerebral capillary endothelial cells, however, are fused along the luminal edge by belt-like tight junctions, which are composed of 6–8 parallel strands with complex anastomoses; these junctions restrict the passage of all substances with a diameter $>10–15$ Å. Another characteristic of cerebral endothelial cells is the very low content of intracytoplasmic pinocytic vesicles, which allows only a low rate of transcellular transport of various substances. The role, if any, of pinocytosis in antibiotic movement across capillaries is not known. Lastly, brain endothelium contains many mitochondria; the significance of this is unclear [15]. To transport important nutrients (e.g., glucose and amino acids) from the blood to the brain, cerebral endothelial cells express on their surface a number of enzymes and transport molecules that are present in much larger quantities than in other endothelia.

**Alterations of the BBB in Bacterial Meningitis**

The pathogenic mechanisms responsible for the increased BBB permeability that occurs in various neuroinflammatory diseases are reviewed in detail by De Vries et al. [16]. Bacterial meningitis increases the permeability of the BBB to various substances. After intracisternal inoculation of meningeal pathogens, a significant increase in pinocytic vesicle formation and a complete separation of $15%–17%$ of intercellular tight junctions was observed in a rat meningitis model [17]. Such morphologic changes are not directly caused by microorganisms but are a result of the host inflammatory response mediated by cytokines, eicosanoids (arachidonic acid metabolites), and free radicals (e.g., nitric oxide). The components of the bacterial cell that are predominantly responsible for the induction of inflammation include lipopolysaccharide (gram negative), lipo-teichoic acid (gram positive), and peptidoglycan (both gram-positive and gram-negative organisms) [17–20]. The influence of inflammation on antibiotic concentrations in CSF is discussed below.

**Pharmacokinetics of Antibiotics in CSF**

Antibiotics are not known to be metabolized in CSF and thus their concentrations and half-lives in CSF depend on the balance between drug penetration and elimination through the blood-brain barrier.

**Transport of Antibiotics Through the BBB**

A number of factors influence the entry of antibiotics into CSF (table 1). Antibiotics enter the CSF predominantly via passive diffusion down a concentration gradient; the major determinant of CSF penetration is lipid solubility [21, 23]. Quinolones and rifampin are lipophilic agents and diffuse via transcellular pathways; peak concentrations in CSF occur relatively rapidly, and entry into CSF is affected minimally by the presence of inflammation [21, 22, 30]. In contrast, hydrophilic agents, such as $\beta$-lactam antibiotics and vancomycin, enter CSF through paracellular pathways; their transport depends on the opening of tight junctions, and peak concentrations are relatively delayed. Although entry of hydrophilic agents in healthy individuals is more restricted than that of lipophilic antibiotics, the median CSF concentrations of hydrophilic agents are still higher than the MBCs for most microorganisms; these agents have been used effectively as prophylaxis in patients undergoing ventriculostomies or after traumatic brain injury [33–36]. An active system that transports penicillin and ceftriaxone from blood to CSF is present in cerebral capillaries [37]. This system, however, has a low affinity and capacity and is responsible for the passage of limited amounts of drug into the CSF.

Concentration-time curves in CSF lag behind those in serum [33, 38, 39]. Therefore, calculations of penetration based on single simultaneous measurements of CSF and serum antibiotic concentrations can be misleading. For example, in a pediatric meningitis trial, the penetration of meropenem (as determined by CSF/serum concentration) was 7.8% when measured within 2 hours of antibiotic administration but was 23.9% when determined after 2 hours [40].

CSF penetration is probably better assessed by measurement of the ratio of the area under the concentration curve (AUC) in CSF to that in serum or by measurement of the ratio of antibiotic concentrations in the steady state [41, 42]. In studies where both AUC and peak concentration were measured in

**Table 1. Factors influencing antibiotic concentrations in CSF.**

<table>
<thead>
<tr>
<th>Factor(s) [reference]</th>
<th>Example</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug lipophilicity</td>
<td>Fluoroquinolones, Rifampin</td>
<td>Rapid entry into CSF, Relatively good CSF concentrations, $T_{1/2}$ similar to serum</td>
</tr>
<tr>
<td>High degree of ionization</td>
<td>$\beta$-Lactam antibiotics</td>
<td>Low lipid solubility, poor penetration through BBB</td>
</tr>
<tr>
<td>High serum protein binding</td>
<td>Ceftriaxone</td>
<td>Delayed entry into CSF, long CSF and serum $T_{1/2}$</td>
</tr>
<tr>
<td>Active transport system</td>
<td>Penicillin</td>
<td>Relatively rapid entry into CSF, short duration of effective CSF levels</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Meningitis</td>
<td>Increased penetration of hydrophilic agents (minimal effect on lipophilic agents)</td>
</tr>
</tbody>
</table>

**NOTE.** BBB = blood-brain barrier; $T_{1/2} = half-life.
CSF and blood, the penetration values were greater when expressed as the AUC ratio [33, 43–45]. For example, in children with bacterial meningitis, the penetration of ampicillin, expressed as a ratio of peak concentrations in CSF and blood, was 13.4% but was 25.1% when calculated as the ratio of AUC values [28]. Estimation of AUCs requires multiple CSF sampling and is not feasible in humans. This problem can be overcome by performing lumbar punctures at different times in different patients [28, 29, 46] or by repeated sampling from patients with external ventriculostomies or Ommaya reservoirs [33, 47], although in patients with CSF obstruction the dynamics of CSF production and flow could be altered.

Table 2 summarizes the available data concerning CSF penetration by selected antibiotics that are commonly used as therapy for meningitis. This table includes only concentration ratios because AUC ratios have not been reported for most antibiotics.

To increase the permeability of the BBB to drugs, various methods such as administration of neurotransmitters, inflammatory mediators, hyperosmotic solutions, or conjugation of drug to receptor-specific antibodies have been used [21]. However, the influence of such techniques on antibiotic penetration into CSF in bacterial meningitis has received little attention.

Elimination of Antibiotics from the CSF

Low antibiotic concentrations in CSF are often presumed to be the result of poor BBB penetration. However, Fishman [62] first suggested the possibility of a saturable, probenecid-sensitive system that transported penicillin from the CSF. Spector and Lorenzo [63] demonstrated that this active efflux pump is located in the choroid plexus and is saturable at high penicillin concentrations. Results of further studies confirmed that the low concentrations of benzylpenicillin in CSF are due in part to active transport from the CSF [25, 26]. It has been demonstrated that active transport across the choroid plexus accounts for approximately two-thirds of the elimination of benzylpenicillin from CSF; CSF turnover and diffusion across ependymal surfaces into brain parenchyma accounts for the remaining 12% and 24% of elimination, respectively [64].

Meningeal inflammation not only increases the permeability of the BBB but also has an inhibitory effect on the elimination pump. With antibiotic treatment, inflammation subsides and the functioning of the BBB slowly normalizes [37, 63, 65]. When compared with the initial values, by the fifth day of treatment in humans with bacterial meningitis, penicillin concentrations and elimination half-lives in CSF are significantly reduced [29]. Unlike benzylpenicillin, other β-lactam antibiotics (e.g., ceftriaxone, imipenem, and ampicillin) have a low affinity for active transport systems; they are eliminated from the CSF less efficiently, and their elimination is minimally influenced by the presence of inflammation; thus clinically useful CSF levels are attained for longer periods [25, 28, 37]. Active transport systems play only a small role in the elimination of quinolones and aminoglycosides from the CSF; these agents exit the CSF predominantly by passive diffusion [66–68].

Table 2. CSF to blood concentration ratios (penetration) of commonly used antibiotics in the treatment of human and experimental meningitis.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Humans (%)</th>
<th>Animals (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Lactams</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>5–10 [48, 49]</td>
<td>5–6 [31, 50, 51]</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>13–14 [28]</td>
<td>8–12 [52, 53]</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>10.1 [54]</td>
<td>3–9 [38, 55]</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1.5–9 [13, 41, 48]</td>
<td>6–12 [12, 33, 38, 50, 51]</td>
</tr>
<tr>
<td>Cefepime</td>
<td>10 [46]</td>
<td>16–22 [55]</td>
</tr>
<tr>
<td>Imipenem</td>
<td>8.5 [48]</td>
<td>3–13 [25, 51]</td>
</tr>
<tr>
<td>Meropenem</td>
<td>21 [48]</td>
<td>6.4 [56]</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0–30 [49]</td>
<td>21–25 [57]</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>21–26 [49]</td>
<td>21–26 [53]</td>
</tr>
<tr>
<td><strong>Quinolones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>42–72 [49]</td>
<td>40–60 [58]</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>26 [59]</td>
<td>21–25 [58]</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>7–14 [13, 49]</td>
<td>5–13 [12, 60]</td>
</tr>
<tr>
<td>Rifampin</td>
<td>7–56 [48]</td>
<td>18–22 [61]</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>&lt;41 [48]</td>
<td>35–39 [52]</td>
</tr>
</tbody>
</table>

NOTE. C<sub>CSF</sub> = CSF concentration; C<sub>serum</sub> = serum concentration.
Antibiotic Half-Lives in CSF

Antibiotic half-lives in the CSF of humans are largely unknown because of the difficulties in obtaining serial CSF samples. Table 3 summarizes data that are available in both humans and animals with experimental meningitis. For most antibiotics, half-lives in CSF are longer than those in serum and half-lives in humans are longer than those in small animals. Quinolones are the exception, in that their half-lives in CSF are similar to those in serum.

Pharmacokinetics of Intrathecally and Intraventricularly Administered Antibiotics

Potentially toxic antibiotics, such as aminoglycosides and vancomycin, are sometimes administered directly into the CSF, especially in patients with CSF shunt infections [73, 74]. The pharmacokinetics of directly administered antibiotics have not been well studied, and most published data are based on case reports or small series [75, 76]. Antibiotics can be delivered directly into CSF either by lumbar intrathecal administration or by intraventricular injection [76, 77]. Drugs administered intrathecally are unevenly distributed in CSF and may not reach adequate ventricular concentrations, whereas intraventricularly administered antibiotics achieve high concentrations throughout the CSF [78, 79]. For example, after administration of 5 mg of gentamicin or tobramycin into a lateral ventricle, high concentrations are achieved in both ventricular and lumbar CSF, 12.8–40 μg/mL and 5–27 μg/mL, respectively, during the first 6 hours [80]. In contrast, the same antibiotics given intrathecally resulted in concentrations in lumbar CSF of 27–81 μg/mL, but the ventricular CSF concentrations were low (0–2.1 μg/mL).

When compared to intravenously administered antibiotic therapy, intraventricular administration results in higher peak CSF concentrations and maintenance of therapeutic CSF concentrations for >24 hours [79–81]. For example, 1 hour after intraventricular administration of 10 mg of vancomycin in three patients with staphylococcal shunt infections, drug concentrations in the CSF ranged from 72.2–812.6 μg/mL [82]. However, such concentrations are not necessary to cure infection. After intraventricular administration, vancomycin is slowly eliminated from CSF; half-life values in humans vary from patient to patient and range from 7.6–77.7 hours [82, 83]. The currently recommended dosages for intraventricular therapy are empiric and are provided by Kaufman [75].

Clinical success after intrathecal or intraventricular administration of antibiotic therapy has been reported in a small number of individuals who failed conventional therapy [80, 83]. Although antibiotics are frequently administered through intrathecal catheters, a randomized comparison with intravenous therapy has not been reported. Despite the potential for achieving greater intraventricular concentrations, intraventricular therapy with certain antibiotics (gentamicin, penicillin, and cephalosporins) could be harmful rather than beneficial [75, 79]. On the other hand, there is no evidence that intraventricular administration of vancomycin is associated with untoward toxicity [83].

Pharmacodynamics of Antibiotics in CSF

Logical decisions in dosing of antibiotic therapy for meningitis depend not only on knowledge of drug penetration and elimination, but also on knowledge of the pharmacodynamic properties of the antibiotic in the CSF. Because the immune response in CSF is ineffective, optimal therapy for bacterial meningitis is dependent on achieving bactericidal antibiotic concentrations at the site of infection. Antibiotic penetration into CSF should be considered in the context that the principal determinant of antibiotic effectiveness is the relation between antibiotic concentrations in CSF and the MBC for the infecting microorganism. For example, although the penetration of aminoglycosides through the BBB is relatively high, ranging from 20%–25% [53, 57], the concentrations achieved in CSF with standard dosing regimens only approximate the MBC for most gram-negative bacteria that cause meningitis [79, 80]. This explains the relative ineffectiveness of gentamicin therapy for meningitis [79]. In contrast, the penetration of β-lactams through the BBB is seldom >10% but, because larger doses can be used without increasing toxicity, therapeutic concentrations can be readily achieved in the CSF. Table 4 shows the expected ratios of CSF antibiotic concentrations to bacterial MICs (MICs rather than MBCs are presented because the latter are not frequently published).

Antibiotics can be roughly divided into two major groups based on their pattern of bactericidal activity in body fluids [1]. Aminoglycosides and fluoroquinolones are concentration-dependent drugs; their efficacy depends on high peak concentrations and their prolonged postantibiotic effect (PAE) [84]. In contrast, the bactericidal activity of β-lactam antibiotics is

---

Table 3. Half-lives of commonly used antibiotics in the CSF and in blood in rabbits and humans.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Half-life (hours)</th>
<th>Rabbit CSF</th>
<th>Rabbit Blood</th>
<th>Human CSF</th>
<th>Human Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin [28, 69]</td>
<td>0.8</td>
<td>0.5</td>
<td>2.1–3.6</td>
<td>0.7–1.4</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime [33, 38]</td>
<td>1.0</td>
<td>1.0</td>
<td>9.3*</td>
<td>0.9–1.7</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone [33, 70]</td>
<td>7–8</td>
<td>3–3.5</td>
<td>16.8*</td>
<td>5.4–10.9</td>
<td></td>
</tr>
<tr>
<td>Meropenem [71]</td>
<td>ND</td>
<td>ND</td>
<td>0.83–1.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin [38, 49]</td>
<td>2.3</td>
<td>0.9</td>
<td>ND</td>
<td>2–3</td>
<td></td>
</tr>
<tr>
<td>Vancomycin [60, 72]</td>
<td>7–8</td>
<td>2–2.5</td>
<td>ND</td>
<td>6–8</td>
<td></td>
</tr>
<tr>
<td>Trovafoxacin [30, 43]</td>
<td>2.4–3.8</td>
<td>1.8–2.7</td>
<td>10.7</td>
<td>14.4</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. ND = not determined.
* Half-life determined in patients with external ventriculostomies [33].
Table 4. Ratio of peak CSF antibiotic concentration to MIC<sub>90</sub> for selected meningeal pathogens.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg/kg)</th>
<th>HI</th>
<th>Neisseria meningitidis</th>
<th>PSSP</th>
<th>PRSP</th>
<th>CoNS</th>
<th>Escherichia coli</th>
<th>Pseudomonas aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>50–70</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>80</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>300</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+/-</td>
<td>–</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>100–150</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Meropenem</td>
<td>40</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

NOTE. CoNS = coagulase-negative Staphylococcus species; HI = Haemophilus influenzae; PRSP = penicillin-resistant <i>S. pneumoniae</i>; PSSP = penicillin-susceptible <i>S. pneumoniae</i>; – = Concentration/MIC<sub>90</sub> ratio <1; + = Concentration/MIC<sub>90</sub> ratio 1–10; ++ = Concentration/MIC<sub>90</sub> ratio >10.

* Non-β-lactamase producing strains.

† Intermediately/highly penicillin-resistant strains.

dependent on the time their concentrations exceed the MIC (T > MIC) for the infecting organism [1]. Further study is required to determine whether these pharmacodynamic properties apply in CSF because most studies concerning meningitis are not specifically designed to compare the concentration-dependency vs. time-dependency of the agent being investigated.

**β-Lactam Antibiotics**

Experts have suggested that, unlike infections in other body sites, the activity of β-lactam antibiotics in meningitis is concentration-dependent. This conclusion is based on the results of experimental meningitis studies, where bacterial killing increased as peak CSF concentrations increased; the maximal bactericidal rate was attained only once peak CSF antibiotic concentrations exceeded the MBC for the pathogen by 10- to 30-fold [50, 85–87]. However, peak concentrations and T > MBC values are interrelated. Because T > MBC was not specifically determined, those studies did not clarify which of the two pharmacodynamic measures correlated best with bacterial killing rates. It is likely in those studies that T > MBC values increased in parallel with peak concentrations; when peak concentrations were ~10-fold greater than the MBC, drug concentrations remained above the MBC for the entire study period. This would explain why the bacterial effect did not improve with larger doses and suggests that the activity of β-lactam antibiotics in CSF is actually time-dependent rather than concentration-dependent. The fact that the administration of ampicillin in more frequent smaller doses increased the bacterial killing rate in CSF [87] is consistent with this supposition. Earlier studies that failed to demonstrate the superiority of continuous administration of various β-lactams over bolus administration [31, 51, 88] should be interpreted with caution because the antibiotic concentrations in CSF achieved in these studies exceeded the MBC for the infecting organism for the entire study period, even when the antibiotic was given as a bolus; again indicating that the activity of β-lactams is time-dependent.

A recent study was specifically designed to examine the interrelation of various pharmacokinetic indices of ceftriaxone in CSF including T > MBC, peak concentration over the MBC (C<sub>peak</sub>/MBC), and AUC over the MBC (AUC/MBC) in an animal model of highly β-lactam-resistant pneumococcal meningitis [70]. This study confirmed the co-dependency of these three pharmacokinetic measures but found that T > MBC was the only index which correlated independently with the bacterial killing rate (BKR) (figure 1). Furthermore, bacterial killing dependent on the concentration reached the MBC. However, the study did not determine which of the two pharmacodynamic measures correlated best with bacterial killing rates. It is likely that those studies that T > MBC values increased in parallel with peak concentrations; when peak concentrations were ~10-fold greater than the MBC, drug concentrations remained above the MBC for the entire study period. This would explain why the bacterial effect did not improve with larger doses and suggests that the activity of β-lactam antibiotics in CSF is actually time-dependent rather than concentration-dependent. The fact that the administration of ampicillin in more frequent smaller doses increased the bacterial killing rate in CSF [87] is consistent with this supposition. Earlier studies that failed to demonstrate the superiority of continuous administration of various β-lactams over bolus administration [31, 51, 88] should be interpreted with caution because the antibiotic concentrations in CSF achieved in these studies exceeded the MBC for the infecting organism for the entire study period, even when the antibiotic was given as a bolus; again indicating that the activity of β-lactams is time-dependent.

A recent study was specifically designed to examine the interrelation of various pharmacokinetic indices of ceftriaxone in CSF including T > MBC, peak concentration over the MBC (C<sub>peak</sub>/MBC), and AUC over the MBC (AUC/MBC) in an animal model of highly β-lactam-resistant pneumococcal meningitis [70]. This study confirmed the co-dependency of these three pharmacokinetic measures but found that T > MBC was the only index which correlated independently with the bacterial killing rate (BKR) (figure 1). Furthermore, bacterial killing dependent on the time their concentrations exceed the MIC (T > MIC) for the infecting organism [1]. Further study is required to determine whether these pharmacodynamic properties apply in CSF because most studies concerning meningitis are not specifically designed to compare the concentration-dependency vs. time-dependency of the agent being investigated.

**β-Lactam Antibiotics**

Experts have suggested that, unlike infections in other body sites, the activity of β-lactam antibiotics in meningitis is concentration-dependent. This conclusion is based on the results of experimental meningitis studies, where bacterial killing increased as peak CSF concentrations increased; the maximal bactericidal rate was attained only once peak CSF antibiotic concentrations exceeded the MBC for the pathogen by 10- to 30-fold [50, 85–87]. However, peak concentrations and T > MBC values are interrelated. Because T > MBC was not specifically determined, those studies did not clarify which of the two pharmacodynamic measures correlated best with bacterial killing rates. It is likely in those studies that T > MBC values increased in parallel with peak concentrations; when peak concentrations were ~10-fold greater than the MBC, drug concentrations remained above the MBC for the entire study period. This would explain why the bacterial effect did not improve with larger doses and suggests that the activity of β-lactam antibiotics in CSF is actually time-dependent rather than concentration-dependent. The fact that the administration of ampicillin in more frequent smaller doses increased the bacterial killing rate in CSF [87] is consistent with this supposition. Earlier studies that failed to demonstrate the superiority of continuous administration of various β-lactams over bolus administration [31, 51, 88] should be interpreted with caution because the antibiotic concentrations in CSF achieved in these studies exceeded the MBC for the infecting organism for the entire study period, even when the antibiotic was given as a bolus; again indicating that the activity of β-lactams is time-dependent.

A recent study was specifically designed to examine the interrelation of various pharmacokinetic indices of ceftriaxone in CSF including T > MBC, peak concentration over the MBC (C<sub>peak</sub>/MBC), and AUC over the MBC (AUC/MBC) in an animal model of highly β-lactam-resistant pneumococcal meningitis [70]. This study confirmed the co-dependency of these three pharmacokinetic measures but found that T > MBC was the only index which correlated independently with the bacterial killing rate (BKR) (figure 1). Furthermore, bacterial killing dependent on the concentration reached the MBC. However, the study did not determine which of the two pharmacodynamic measures correlated best with bacterial killing rates. It is likely that those studies that T > MBC values increased in parallel with peak concentrations; when peak concentrations were ~10-fold greater than the MBC, drug concentrations remained above the MBC for the entire study period. This would explain why the bacterial effect did not improve with larger doses and suggests that the activity of β-lactam antibiotics in CSF is actually time-dependent rather than concentration-dependent. The fact that the administration of ampicillin in more frequent smaller doses increased the bacterial killing rate in CSF [87] is consistent with this supposition. Earlier studies that failed to demonstrate the superiority of continuous administration of various β-lactams over bolus administration [31, 51, 88] should be interpreted with caution because the antibiotic concentrations in CSF achieved in these studies exceeded the MBC for the infecting organism for the entire study period, even when the antibiotic was given as a bolus; again indicating that the activity of β-lactams is time-dependent.

A recent study was specifically designed to examine the interrelation of various pharmacokinetic indices of ceftriaxone in CSF including T > MBC, peak concentration over the MBC (C<sub>peak</sub>/MBC), and AUC over the MBC (AUC/MBC) in an animal model of highly β-lactam-resistant pneumococcal meningitis [70]. This study confirmed the co-dependency of these three pharmacokinetic measures but found that T > MBC was the only index which correlated independently with the bacterial killing rate (BKR) (figure 1). Furthermore, bacterial killing dependent on the time their concentrations exceed the MIC (T > MIC) for the infecting organism [1]. Further study is required to determine whether these pharmacodynamic properties apply in CSF because most studies concerning meningitis are not specifically designed to compare the concentration-dependency vs. time-dependency of the agent being investigated.
(r = 0.94) between the pharmacodynamic indices, T > MBC, C\text{peak}/MBC, and AUC/MBC, with gatifloxacin and trovafloxacin therapy in pneumococcal meningitis. A significant correlation between AUC/MBC and BKR was found (figure 3); it was not surprising, however, that T > MBC and C\text{peak}/MBC, being components of AUC/MBC, also correlated with the BKR [43, 44].

The pharmacodynamics of quinolones in meningitis differ from those described in other infections; in meningitis, features of both time-dependency and concentration-dependency can be demonstrated. To achieve maximal bactericidal effectiveness in pneumococcal meningitis, the concentrations of fluoroquinolones in CSF need to exceed the MBC for the entire dosing interval [44, 90]. Also, divided-dose regimens appear superior to single-dose regimens (figure 3) [44]. These findings are probably the result of the short sub-MIC effect of quinolones against pneumococci in CSF. Similar short sub-MIC effects have been demonstrated with ciprofloxacin in experimental E. coli meningitis [91]. The relative importance of T > MBC with quinolone therapy was demonstrated recently in an in vitro pharmacodynamic model of gram-negative infection [92].

Vancomycin and Rifampin

Whether the bactericidal activity of vancomycin in CSF is time-dependent, as it is in serum [93, 94], is yet to be confirmed. The pharmacodynamic properties of vancomycin in CSF have been characterized in an experimental pneumococcal meningitis model [60]. In that study, the maximal bacterial killing rate was achieved with C\text{peak}/MBC ratios of 5:1 to 10:1; further increases in vancomycin concentration in CSF did not result in a greater BKR. A similar effect occurs with \textit{\beta}-lactam antibiotics.

Aminoglycosides and Quinolones

Aminoglycosides exhibit concentration-dependent bacterial killing, both in vitro and in vivo [1]. This appears to hold true in meningitis as well. A direct correlation between gentamicin concentrations and bacterial killing rates in CSF was demonstrated in experimental \textit{Escherichia coli} meningitis [57]. Furthermore, single-dose gentamicin therapy was as effective as divided dosing regimens, despite different T > MBC values (figure 2). The applicability of these results to treatment of meningitis in humans needs to be established.

The pharmacodynamic variables that correlate best with the bactericidal activity of quinolones in experimental infections and in clinical trials are C\text{peak}/MIC and AUC/MIC, whereas T > MIC is thought to be less important [84, 89]. The positive correlation between bactericidal activity and concentrations of various quinolones in CSF has been demonstrated in an experimental pneumococcal meningitis model [58]. Recent experiments in our laboratory demonstrated a significant interrelation
of ampicillin in the CSF was inactivated [97] or eliminated. The CSF half-lives of lipophilic agents, such as quinolones, in contrast, no PAE was found when the residual concentration in vitro (2.5±18 hours vs. 1±4.3 hours, respectively) [88, 97]. A sub-MIC effect was shown to be much longer than the PAE [58x389] 10-fold greater than the MIC [11, 60, 101]. The penetration of lipophilic antibiotics such as rifampin and the quinolones, which traverse transcellular routes, are affected minimally by concomitant steroid administration [11, 12, 102]. Whether the detrimental effect of steroid therapy on antibiotic penetration, as demonstrated experimentally, is of clinical significance is unknown because there are no published controlled studies in humans. In clinical meningitis trials, delayed sterilization of CSF occurred with similar frequency in steroid-treated and control patients (6.1% vs. 5.7%, respectively) [103]. However, almost all infections were caused by susceptible strains and the ratios of antibiotic concentration to MBC were one-half the MIC; at a concentration of 100 times the MIC the PAE lasted 4.3 hours. The PAE was the same whether bacteria were cultured in broth or in CSF. In contrast, other investigators demonstrated significant increases in the PAEs of cefotaxime, ciprofloxacin, and gentamicin in vitro for E. coli in pooled human CSF compared with the PAE in Mueller-Hinton broth, despite similar bactericidal activity in both fluids [98, 99]. It is not clear, however, which component of CSF is responsible for this effect and whether this has clinical significance.

In contrast to in vitro studies, in which antibiotics can be easily removed from the culture medium, it is difficult to eliminate antibiotics from the site of infection in vivo. As a result, different methodologies have been used to study the PAE in animal models of meningitis. Most investigations have focused on the continued suppression of bacterial regrowth once antibiotic concentrations fall below the MIC (post sub-MIC effect). With ampicillin therapy in pneumococcal meningitis, the post sub-MIC effect was shown to be much longer than the PAE in vitro (2.5–18 hours vs. 1–4.3 hours, respectively) [88, 97]. In contrast, no PAE was found when the residual concentration of ampicillin in the CSF was inactivated [97] or eliminated [91]. These findings suggest that slowly declining sub-MIC antibiotic concentrations are important and result in delayed bacterial regrowth but that a true PAE is minimal in CSF.

Although the clinical relevance of the above studies has not been demonstrated, the longer half-lives of many antibiotics in CSF compared with those in serum, coupled with a prolonged sub-MIC effect, suggest that dosing intervals longer than those traditionally recommended would be effective in therapy for meningitis. Quinolones are notable exceptions, however, because their CSF half-lives are similar to those in serum and their sub-MIC effects are short lived [43, 44, 91].

### Influence of Corticosteroids on Antibiotic Penetration and Effectiveness

Corticosteroids may reduce the permeability of the BBB in meningitis and, thereby, decrease the penetration of hydrophilic antibiotics into CSF [11, 12, 100, 101]. An associated reduction in bacterial clearance has been described with some therapeutic regimens but not with others (table 5). A reduction in antibiotic effectiveness is particularly noticeable when the peak CSF antibiotic concentrations are <10-fold greater than the MIC [11, 60, 101]. The penetration of lipophilic antibiotics such as rifampin and the quinolones, which traverse transcellular routes, are affected minimally by concomitant steroid administration [11, 12, 102].

Whether the detrimental effect of steroid therapy on antibiotic penetration, as demonstrated experimentally, is of clinical significance is unknown because there are no published controlled studies in humans. In clinical meningitis trials, delayed sterilization of CSF occurred with similar frequency in steroid-treated and control patients (6.1% vs. 5.7%, respectively) [103]. However, almost all infections were caused by susceptible strains and the ratios of antibiotic concentration to MBC were presumably high, even for subjects who were receiving steroid therapy. The negative effect of dexamethasone therapy on vancomycin penetration has been proposed to have contributed to clinical failures [104], but definitive proof is lacking in that study. Klugman et al. [13] reported that adequate CSF vancomycin concentrations (3.3 ± 1.1 µg/mL) could be achieved reliably with 60 mg/(kg · d) regimens in children with meningitis who were receiving concomitant dexamethasone therapy. Two recent studies using high doses of cefotaxime (300 mg/(kg · d) for the treatment of bacterial meningitis either with [14] or without dexamethasone [105] reported similar median values of cefotaxime (4.7 µg/mL and 4.4 µg/mL, respectively) in the CSF. Thus, there are no clinical data to support experimental findings of a detrimental influence of steroid therapy on antibiotic penetration into CSF. This issue will, however, be resolved only by randomized controlled clinical studies.

### Summary

The CSF half-lives of lipophilic agents, such as quinolones, are similar to those in serum and peak concentrations in CSF
Table 5. Effect of corticosteroid therapy on antibiotic concentration and bacterial clearance in CSF.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antibiotic therapy</th>
<th>Cpeak/MBC (with no concomitant DXM)</th>
<th>Decreased antibiotic concentration</th>
<th>Decreased bacterial clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>Gentamicin 2.5 mg/(kg·h) [100]</td>
<td>5 or &lt;5</td>
<td>Yes</td>
<td>No*</td>
</tr>
<tr>
<td>hCRSP</td>
<td>Ceftriaxone 75 mg/kg [12]</td>
<td>5</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>hPRSP</td>
<td>Vancomycin 20 mg/kg [60]</td>
<td>5–10</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>hPRSP</td>
<td>Trovafloxacin 25 mg/kg [11]</td>
<td>&gt;10</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>hPRSP</td>
<td>Rifampin 10 mg/kg [12]</td>
<td>&gt;10</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>hPRSP</td>
<td>Vancomycin 40 mg/kg [60]</td>
<td>&gt;10</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PSSP</td>
<td>Ampicillin 30 mg/(kg·h) [100]</td>
<td>&gt;50</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PSSP</td>
<td>Ceftriaxone 50 mg/kg [101]</td>
<td>&gt;100</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

NOTE. Cpeak = peak concentration; hCRSP = highly cephalosporin-resistant Streptococcus pneumoniae; hPRSP = highly penicillin-resistant S. pneumoniae; PSSP = penicillin-susceptible S. pneumoniae.
* Because gentamicin therapy was poorly bactericidal, demonstration of a further decrease in efficacy was not possible.
† CSF samples were collected at 1 hour; therefore, the peak concentrations might have been missed.

References


Downloaded from http://cid.oxfordjournals.org/ by guest on September 23, 2016

The “Conflict-of-Interest Policy” of the Office of Continuing Medical Education, UCLA School of Medicine, requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company which might pose a potential, apparent, or real conflict of interest with regard to their contribution to the program. The authors report no conflict of interest.
This test affords you the opportunity to assess your knowledge and understanding of the material presented in the preceding clinical article, "Antibiotic Pharmacodynamics in Cerebrospinal Fluid," by Irja Lutsar, George H. McCracken Jr., and Ian R. Friedland, and to earn continuing medical education (CME) credit.

CME Sponsor
The Office of Continuing Medical Education, UCLA School of Medicine, is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Accreditation
The Office of Continuing Medical Education, UCLA School of Medicine, designates this educational activity for up to 1 hour in category I credit toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

To earn credit, read the State-of-the-Art Clinical Article carefully and answer the following questions. Mark your answers, only one answer per question, by circling the correct responses on the answer card (usually found toward the front of the issue), and mail this card after affixing first-class postage. To earn credit, a minimum score of 80% must be obtained.

Certificates of CME credit will be awarded on a per-volume (biannual) basis. Each answer card must be submitted within 3 months of the date of the issue.

1. The degree of penetration of antibiotics through the blood-brain barrier depends on all of the following factors except
   A. drug lipophilicity
   B. protein binding of the drug
   C. oral vs. intravenous administration
   D. the infecting organism
   E. the degree of inflammation

2. The ratio of CSF to blood concentration (penetration) of ceftriaxone is low because the agent
   A. is highly protein bound.
   B. is highly lipophilic.
   C. has a high affinity for the CSF elimination transport mechanism.
   D. is highly ionized at normal pH.

3. Which of the following is the most critical for effective treatment of meningitis?
   A. the ratio of CSF drug concentration to the MBC for the infecting organism

4. Concomitant administration of corticosteroids and antibiotics has which of the following effects?
   A. reduction in CSF concentrations of both lipophilic and hydrophilic antibiotics
   B. reduction in CSF concentrations of hydrophilic but not lipophilic antibiotics
   C. delay in CSF sterilization in clinical trials
   D. increase in CSF antibiotic half-life

5. Characteristics of quinolones include
   A. inflammation-independent penetration into CSF
   B. long postantibiotic effect against pneumococci in CSF
   C. limited activity against meningal pathogens
   D. elimination from CSF predominantly by active transport mechanisms

6. β-Lactam antibiotics are most commonly used as prophylaxis in penetrating brain injury because
   A. they penetrate better than other antibiotics through uninflamed meninges.
   B. they have long half-lives and can be administered daily.
   C. they achieve bactericidal CSF concentrations against the most likely infecting organisms.
   D. they have no seizure-inducing potential.

7. CSF is formed predominantly by
   A. astroglial cells.
   B. arachnoid granulations.
   C. diffusion from cerebral interstitial fluid.
   D. choroid plexus.

8. Antibiotics that are predominantly concentration-dependent include
   A. aminoglycosides
   B. vancomycin
   C. cephalosporins
   D. carbapenems

9. Which of the following statements regarding the blood-brain barrier is correct?
   A. Tight junctions are located between neuronal cells.
   B. The blood-brain barrier exists between cerebral capillaries and neurons.
   C. Pneumococci produce enzymes that dissolve tight junctions.
D. The blood-brain barrier allows most proteins into the CNS.
E. β-Lactams traverse the blood-brain barrier mainly by transcellular routes.

10. The advantages of the third-generation cephalosporins over penicillin include
   A. greater penetration into CSF
   B. longer serum and CSF half-lives necessitating less frequent administration
   C. longer postantibiotic effects
   D. significantly higher concentration/MBC ratios for penicillin-sensitive pneumococci