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REVIEW ARTICLE

Vancomycin for Treating Cerebrospinal Fluid Shunt Infections in Pediatric Patients

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Infection is a major cause of CSF shunt failure that places the patient at risk of intellectual impairment, development of loculated CSF compartments, and death. The purpose of this article is to review the published literature related to vancomycin for treatment of pediatric CSF shunt infections. Fifty percent of shunt infections appear within 2 months of shunt placement or revision; 90% occur within 6 months. Ninety percent of organisms infecting CSF shunting devices are *Staphylococcus* and *Streptococcus* species. The emergence of methicillin-resistant strains of staphylococci has made vancomycin the antibiotic of choice for these infections. The usual intravenous regimen is 60 mg/kg/day divided every 6 hours. Intraventricular vancomycin should be considered for most patients, starting with 10 mg daily. CSF vancomycin concentrations should be monitored and dosing adjustments made as needed to maintain CSF trough vancomycin concentrations between 5 and 20 mg/L.

KEYWORDS: cerebrospinal fluid, pediatric, shunt infections, vancomycin, ventriculoperitoneal

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INTRODUCTION

Hydrocephalus is the abnormal accumulation of cerebrospinal fluid (CSF) in the ventricles of the brain and can result in enlargement of the ventricles, atrophy of brain tissue, seizures, and other complications.[1] Correcting hydrocephalus may require removing the excess CSF from the brain using a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt. These devices divert CSF through a synthetic tube from the ventricles through the skull and subcutaneous tissue of the neck and chest, and into either the peritoneal cavity or the right atrium. These shunts may also contain a subcutaneous reservoir that can be accessed with a small needle, and some have a valve that controls intraventricular pressure.[2]

ABBREVIATIONS: BBB, blood-brain barrier; CSF, cerebrospinal fluid; IV, intravenous; IVT, intraventricular; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; VA, ventriculoatrial; Vd, volume of distribution; VP, ventriculoperitoneal

Infection is a major cause of CSF shunt failure, placing the patient at risk of intellectual impairment, development of loculated CSF compartments, and death.[1] The incidence of postoperative CSF shunt infections varies considerably among centers and ranges from 1% to 39%[3]; however, most centers report infection rates of about 5%.[1]

A shunt infection is defined as unequivocal evidence of infection of the shunt equipment,

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the overlying wound, the CSF, or distal drainage site related to the shunt. Unequivocal evidence requires demonstration of the organism on Gram stain or culture from material in, on, or around the shunt or from fluid withdrawn from the shunt. Fifty percent of shunt infections appear within 2 months of shunt placement or revision, while 90% occur within 6 months. Confirmation that a shunt infection has been eradicated requires long-term follow-up (i.e., 6 months to 1 year). Shunt infections may present clinically in a variety of ways. Ventriculitis manifests as fever, irritability, headache, and possibly neck stiffness. Shunt infections may present as a wound infection with fever, redness over the wound or shunt tract, and purulent drainage from the wound. Infections may also present with predominantly distal end symptoms: signs of peritonitis with VP shunts, and septicemia, shunt nephritis, or cor pulmonale with VA shunts.[1]

Ninety percent of organisms infecting CSF shunting devices are *Staphylococcus* and *Streptococcus* species. *Staphylococcus epidermidis* and *Staphylococcus aureus* together account for 50% to 75% of shunt infections, while the remainder are caused by *Streptococcus* species, *Corynebacterium* species, gram-negative bacilli, diptheroids, and *Micrococcus* species.[4–5] The emergence of methicillin-resistant strains of staphylococci has made vancomycin the antibiotic of choice for most shunt infections caused by gram-positive organisms. Vancomycin is active against *Staphylococcal* species in a time-dependent (amount of time the concentration is above the minimum inhibitory concentration (MIC) of the infecting organism) manner. Its activity is due to its inhibition of cell wall synthesis and its alteration of cell membrane permeability and RNA synthesis. Vancomycin has antimicrobial activity against methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* as well as *Streptococcus* species, *Listeria monocytogenes, Lactobacillus* species, *Actinomyces* species, *Clostridium* species, and *Bacillus* species.[6] Because of vancomycin's limited penetration, CSF vancomycin concentrations following systemic administration vary widely. This lack of penetration may potentially result in subtherapeutic ventricular vancomycin concentrations and subsequent failure to eradicate bacterial pathogens.

Several authors have suggested that shunt removal plus intravenous (IV) antibiotics is necessary for cure,[5,7–9] while others have suggested that complete removal is not always necessary, especially when intraventricular antibiotics are used in conjunction with IV antibiotics.[10] Everett et al. favors complete shunt replacement 48–72 hours after IV plus intraventricular antibiotics have begun.[11] Treating a shunt infection without removing the shunt avoids surgical intervention, but may prolong morbidity and duration of hospitalization.[5] Despite decades of experience treating shunt infections, there is no consensus regarding proper management. The purpose of this article is to review the published literature related to vancomycin for treatment of pediatric CSF shunt infections.

PHARMACOKINETIC AND PHARMACODYNAMIC ISSUES

Penetration into CSF

Drug entry from the blood into the brain and CSF is regulated by the blood-brain barrier (BBB) and the blood-CSF barrier. The BBB consists of tightly joined brain capillary endothelial cells and glial cells. If a medication has ideal characteristics, it can pass through these capillary cells to enter the extracellular fluid of the brain and ultimately brain tissue. Ependymal cells of the choroid plexus serve as an active transport barrier to drug entry into the CSF. Inflammation of this barrier influences both drug penetration through the choroid epithelial cells and distribution into the CSF. A patient with uninflamed barriers experiences poor drug penetration when compared to a patient with inflamed barriers (i.e., meningitis).[12–14] Certain medications can also influence drug penetration into the CNS. The addition of dexamethasone significantly decreased vancomycin CSF concentrations and bactericidal titers in a rabbit model of meningitis.[15] In children with acute bacterial meningitis, however, CSF vancomycin concentrations were approximately 20% of serum concentrations, despite the fact that all were receiving dexamethasone.[16]

Medication characteristics also influence a drug's entry into the CSF. Drug penetration

into the CNS is more likely to occur if a medication has a low affinity for protein, is highly lipid soluble, and has a low molecular weight. Unfortunately, even in the presence of impaired CNS barriers and use of a medication with ideal characteristics for penetration, adequate distribution to the desired CNS tissues may still not be obtained. Administering the agent intraventricularly bypasses these barriers.

Vancomycin is a tricyclic glycopeptide antibiotic that has a moderate affinity for plasma proteins (55%) and a high molecular weight of 1,485.73. It is estimated that CSF vancomycin concentrations are 10% of those found in serum in patients with inflamed meninges.[17–21] Because the CNS behaves like a 'deep' pharmacokinetic compartment, changes in vancomycin CSF concentrations occur more slowly than in the blood.[22] Young et al. noted that the CSF vancomycin peak concentration was < 6 mg/L at 30 min postdose and then remained constant, while the serum vancomycin concentration fell sharply from a postinfusion peak of 92 mg/L.[20] Since the drug concentration-time relationship in the serum may not parallel that in CSF, serum concentrations may not be a reliable indicator of CSF concentrations throughout the dosing interval.

Vancomycin clearance from CSF

Several conditions may alter the CNS volume of distribution (Vd) and clearance of vancomycin in patients with shunt infections. In hydrocephalic infants, CSF formation rate averaged 0.29 mL/min,[23] which extrapolates to 417.6 mL/day. Therefore, CSF is completely exchanged several times per day. This rapid turnover influences CSF drug clearance. Diseases may also alter CSF dynamics and potentially affect therapy. Because most drug clearance occurs by bulk flow of CSF across the arachnoid villi,[24] patients with ventriculitis may have decreased vancomycin clearance due to the decrease in CSF production. A marked reduction in the rate of CSF production has been demonstrated in an animal model of acute ventriculitis.[25] In rabbits, CSF production decreased 48%–53% (culture-proven infection) and 56%–66% (clinical signs of infection) when compared to controls without CNS infection.[25] In another study, ventriculitis did not significantly alter the clearance of a 30 mcg intraventricular dose of vancomycin in rabbits compared to controls.[26] However, rabbits that received 120 mcg had slower elimination rates, suggesting that vancomycin clearance in the CSF might be saturable.[26]

Ventriculitis itself seems to be an elusive diagnosis. Inflammation or infection of the lining of the ventricles of the brain is usually not measured directly. Ventriculitis has been established or defined by researchers in different ways. Haworth et al. established experimental ventriculitis by intraventricular inoculation of $10^{7.13}$ colony-forming units of *S. aureus* in rabbits.[26] Swayne et al. defined ventriculitis as fever and clinical signs of meningitis in addition to pus and bacteria in the ventricular CSF,[27] whereas Schaad et al. defined it as a positive culture result plus > 50 white cells/mm^3 in ventricular fluid.[19] It remains unclear to what extent ventriculitis affects vancomycin clearance from the CSF in patients.

Reference Range

The reference range for CSF vancomycin concentrations has not been prospectively determined. Studies reporting vancomycin concentrations in serum or CSF are outlined in the Table 1. The goal is to maintain trough concentrations above the MIC of the infecting organism.[9] Several authors have identified "desired concentrations" based on individual experiences. McLaurin and Frame tried to achieve 24-hour CSF vancomycin trough concentrations of 10–20 mg/L, which is approximately 10–20 times the MIC for most staphylococci.[2] Pau et al. adjusted vancomycin dosages to maintain CSF trough concentrations below 20 mg/L in order to reduce the potential for toxicity.[28]

Nagl et al. prospectively studied the bactericidal activity of vancomycin in CSF.[29] The authors examined the *in vitro* activity of vancomycin at high concentrations against *Staphylococcus aureus* and *Staphylococcus epidermidis* in human CSF samples and found equal efficacies for concentrations of 10, 100, and 300 mg/L. A concentration of 5 mg/L showed slightly lower activity (not statistically significant) while a concentration of 2 mg/L was significantly less bactericidal ($P < 0.01$). These results suggest that a reasonable reference range for vancomycin in CSF is 5–20 mg/L.

When evaluating literature to determine an upper limit for a reference range, one finds

Table 1. Studies reporting vancomycin concentrations in serum or CSF of pediatric patients with CNS or shunt infections

Age (n)	Infx	Shunt (n)	Vancomycin Dose IV [IVT]†	Vancomycin Concentration mg/L		Comments	Outcome	Ref
				CSF [postdose time]	Serum [postdose time]			
5m–17y (19)	M	No	60 mg/kg	1.6 ± 0.8 [0.3–5h]	NR	CSF concentrations after ≥ 5th dose	No relapse or recurrence at 6–12m follow up (n = 9); no follow up (n = 10)	44
7–67m (31)	M	No	60 mg/kg + 0.6 mg/kg DM	3.3 ± 1.1 (2–5.9) [2–3h]	17.3 ± 6.7 (7.1–30.7) [2–3h]	Also received ceftriaxone 80–100 mg/kg/day	"All responded to therapy."	16
2m–16y (7), 19–56y (7)	M	No	10 mg/kg on days of LP	0.7* (0.1–2.6) day ≤ 3 [1–3h] 0.3* (< 0.1–8.5) day ≥ 7 [1–3h]	NR	*Median (range). LP on days 1,2,3,7,10, 14,18 or 21	1 child died; all others survived	45
1m–63y (46); 17 < 10y	V	Yes (45)	[5–20 mg]; IV in 7 patients, dose NR	26.8* (5–236) [24h, n = 25] (26 – 280) [0–4h, n = 7]	NR	*Median (range)	62% "cured"	3
1m–12y (13); 12 < 3m	V	Yes (12)	30–80 mg/kg	5.5 ± 5.2 (< 1–17.3) [1–10h]	NR	No difference in conc at different sampling times	CSF sterilized by 7 days (median) in 10/12 children	31
		No (1)	45–94 mg/kg + [1–25 mg]	23.5 (4.5–58.6) [1–10h]				
8m, 29 WGA (1)	V	Yes	50 mg/kg + [10 mg]	29 (dose 3) [1h], 82 (day 11) [1h]	NR		Died	28
			50 mg/kg + [5 mg]	92.1 (day 14) [1h]				
			50 mg/kg + [5 mg IVT q 48h]	144 (day 26) [1h], 12.7 [trough]				
4m, 31 WGA (1)	V (n = 4)	Yes	60 mg/kg + [45 mg IVT X 1 (inadvertent dose)]	119.5 [random] 21 [10 days after 45–mg IVT dose]	NR		Shunt removed (malfunction) 4 weeks after completion of treatment; *S epidermidis* recovered from CSF at that time	28
			60 mg/kg + [4 mg]	9.5–23 [Troughs]				
Neo (10) Inf (11) C (12)	V	Yes	10–15 mg/kg/dose q 6–12h	3.9 ± 0.6* (1.0–12.3) [NR]	33.2 ± 9.2 [Peak] 9.2 ± 4.2 [Trough]	*Mean ± SE. CSF conc 18% (mean) of simultaneous serum conc	All responded clinically; pathogen eradicated in 7/7 assessable patients	19
< 5m (1)	V	Yes	[20 mg]	810 [Peak]	NR		NR	17
< 5m (1)	V	Yes	[5 mg]	54 [Peak], 5 [Trough]	0 [2h]		NR	17
< 5m (2)	V	Yes	10–15 mg/kg/dose, frequency NR	2.0–4.2 [2h]			NR	17
Inf (1)	SI	Yes	40 mg/kg	4.3 [48h of treatment]	NR	Conc in brain cyst 7.6 mg/L after 96h of treatment	NR	40
Neo (21) Inf (16) C (18)	SI (n = 3)	Yes	10–15 mg/kg/dose, frequency NR	3.1 (1.2–4.8) [NR]	NR	CSF conc 3rd–11th day. CSF conc 14% (7–21%) of simultaneous serum conc	All 3 with shunt infection were clinically & bacteriologically cured	18

**See comments section. Data are mean ± SD, mean (range) or (range) unless otherwise specified in comments section.*
†Total dose per day unless otherwise specified.
C = children; conc = concentration; CSF = cerebrospinal fluid; DM = dexamethasone; Inf = infants; Infx = infection; IV = intravenous; IVT = intraventricular; LP = lumbar puncture; M = meningitis; n = number of patients; NR = not reported; NS = not specified; Neo = neonates; Ref = reference; SI = shunt infection; V = ventriculitis; WGA = weeks gestational age.

various reports of extremely elevated vancomycin concentrations that are not associated with any apparent toxicity. A 4-month-old infant born at 31 weeks gestational age with VP shunt ventriculitis received an inadvertent dose of 45 mg intraventricularly. Forty-four hours after the dose, the CSF concentration was 119.5 mg/L. There were no changes in the CSF white blood cell count and no apparent side effects.[28] A patient (age not reported) with methicillin-resistant *Staphylococcus aureus* (MRSA) ventriculitis who had received intraventricular vancomycin (10 mg) daily for 7 days had a peak CSF vancomycin concentration of 812.6 mg/L 1 hour after a dose. Trough concentrations were always < 20 mg/L. No adverse effects were reported.[30] An infant receiving 20 mg intraventricular vancomycin daily had a peak concentration of 810 mg/L with no reported toxicity.[17] Each of these case reports demonstrates elevated vancomycin concentrations without any reported toxicities; however, there should be an upper limit to the reference range due to the possibility of adverse events (see Complications section).

INTRAVENOUS VANCOMYCIN

McGee and colleagues reviewed the charts of 13 pediatric patients (ages 1 month to 12 years) diagnosed with ventriculitis.[31] Twelve patients received only IV vancomycin (30 to 80 mg/kg/day); CSF vancomycin concentrations at 0.5–10 hours after a dose were between 1 and 17.3 mg/L. In patients who received IV vancomycin alone, the ventricular fluid cultures became sterile by a median of 7 days (range, 3 to 14 days). Those children whose ventricular fluid cultures were sterile by the 7th day had a mean CSF vancomycin concentration of 9.7 ± 4.5 mg/L, while those whose ventricular fluid cultures were not sterile until after the 7th day had a mean CSF concentration of 1.7 ± 1.2 mg/L ($P < 0.001$).

Congeni et al. reported CSF vancomycin concentrations of 2.1–4.2 mg/L 2 hours after 10–15 mg/kg of IV vancomycin was administered to 2 infants with shunt infections.[17] In another study, 12 CSF specimens (collected from the 3rd to 11th days of therapy) from 3 infants treated with vancomycin 10–15 mg/kg/dose for shunt infections had a mean CSF vancomycin concentration of 3.1 mg/L (range, 1.2–4.8 mg/L) and a mean CSF penetration of 14% (range, 7–21%).[18] Schaad et al. also reported penetration of vancomycin into the ventricular fluid of 10 pediatric patients with shunt infections who received 15 mg/kg IV every 6 hours. Sterilization of the CSF was achieved with a mean CSF vancomycin concentration of 3.9 mg/L (range, 1–12.3 mg/L) and a mean penetration of 18% (range, 7%–37%). Fan-Havard et al. noted that CSF vancomycin concentrations did not exceed the vancomycin MIC of MRSA following three IV doses of 15 mg/kg every 6 hours administered as prophylaxis at the time of shunt placement. CSF concentrations were obtained at 0.8 to 3 hours after infusion of vancomycin; 5 of 6 patients had undetectable values while one patient had a CSF concentration of 0.8 mg/L.[32] Additionally, LeRoux et al. found no correlation between adequate serum concentrations and corresponding CSF concentrations in 25 adult patients receiving vancomycin at the time of shunt insertion for hydrocephalus.[33]

On the other hand, some investigators have reported higher CSF vancomycin concentrations. Three very low birth weight infants born at 26–31 weeks gestational age with suspected or proven sepsis or meningitis received vancomycin 20 mg/kg IV every 18–24 hours. CSF vancomycin concentrations were 2.2–5.6 mg/L while serum vancomycin concentrations were 8.2–13.1 mg/L. The percent penetration was 26%–68%.[34] Klugman et al. studied children < 5 years of age with bacterial meningitis receiving dexamethasone 0.6 mg/kg/day for four days in addition to IV vancomycin 60 mg/kg/day divided every 6 hours. CSF vancomycin concentrations were 3.3 ± 1.1 (2–5.9) mg/L while serum vancomycin concentrations were 17.3 ± 6.7 (7.1–30.7) mg/L. The percent penetration was 21% ± 6%.[16]

INTRAVENTRICULAR VANCOMYCIN

Although empiric intraventricular vancomycin doses of 5, 10, or 20 mg are recommended, very little is known about the pharmacokinetics of intraventricular vancomycin when used for shunt infections. Reesor et al. reported that the CSF vancomycin volume of distribution (Vd) was stable and reflected the physiologic CSF volume (0.25 L) in an 82-year-old male

who received 50 mg of vancomycin intraventricularly.[35] The authors also noted that drug accumulation may occur since the elimination half-life doubled after 24 hours of therapy (9.3 hours vs. 20.5 hours). Others have also reported accumulation of vancomycin following intraventricular administration.[2,28,36] Conversely, Pfausler et al. noted no drug accumulation in two patients given intraventricular vancomycin for staphylococcal ventriculitis.[30] In these patients, vancomycin trough concentrations always were < 20 mg/L, even in the presence of peaks greater than 800 mg/L.[30] Bayston suggested that the dose of intraventricular vancomycin should not be based on body weight or age but on ventricular volume.[3] Quantification of ventricular volume is possible using cranial magnetic resonance imaging[37] and computed tomography.[33] However, some authors have suggested that ventricular volume is not related to CSF concentrations. In two infants with infected ventricular shunts receiving antibiotics through the shunt or an external ventricular drain, ventricular size had no predictable influence on CSF antibiotic concentration.[38] The method and amount of CSF drainage in these infants was not reported; CSF output could factor heavily in the removal of drug from the ventricles. LeRoux et al. also found no correlation between ventricular volume, calculated as ventricular-brain ratio, and CSF vancomycin concentrations in adult patients.[33] The patients in this study had little variability in their ventricular-brain ratios (mean 12.9%, standard deviation 1.7%) and had much smaller ventricular-brain ratios than would be expected in children with hydrocephalus; thus, it is difficult to apply these data to a pediatric population. Overall, it is unclear if ventricular volume is related to CSF vancomycin concentrations.

Hirsch et al. described the pharmacokinetics of vancomycin following a single 7.5 mg dose that was administered into an Ommaya reservoir for a 25-year-old patient with lymphomatous meningitis. CSF vancomycin concentrations measured at 2.25, 17.67, and 25.92 hours later were 80.6, 3.9, and 0.6 mg/L, respectively. The calculated half-life was 3.52 hours. The extrapolated CSF peak concentration was 126 mg/L; therefore, the apparent volume of distribution in CSF was 60 mL. The authors concluded that these pharmacokinetic parameters were consistent with a first-order, one-compartment model. A dosing regimen of 2.6 mg twice a day into the reservoir was begun based on the calculated parameters. CSF trough concentrations ranged from 0.3-15.0 mg/L. Pharmacokinetic parameters calculated again on the last day of therapy (10 days total) were consistent with the original data; the half-life was 3.54 hours.[39]

Pfausler et al. conducted a prospective study to determine the efficacy and pharmacokinetics of intraventricular vancomycin in three patients (ages not reported) with shunt-associated ventriculitis.[30] Vancomycin 10 mg was instilled via an external ventricular drainage catheter, which was then flushed with 2 mL of normal saline and clamped for 1 hour. Vancomycin CSF concentrations were measured 1 hour after instillation and then every 2 hours. Peak vancomycin concentrations reached a mean of 292.9 mg/L (standard deviation or range was not reported). The mean CSF trough concentration measured 24 hours after a dose and immediately before readministration of vancomycin was 7.6 mg/L. All three patients were cured clinically and bacteriologically, and no side effects occurred. The authors concluded that 10 mg intraventricular vancomycin per day appeared to be safe and effective and achieved mean trough CSF concentrations between 5 and 10 mg/L.

Other investigators have differing views. Gump supports intraventricular vancomycin doses that do not exceed 5 mg/day unless CSF concentrations are inadequate.[40] Other authors have indicated that vancomycin 20 mg/day is the appropriate intraventricular dose but only after initial IV antimicrobials have failed to eradicate the infection.[21,41] McLaurin and Frame recommend 20 mg/day intraventricular vancomycin for children and 10 mg/day for newborns with expected trough CSF concentrations of 10 mg/L.[2] Some authors support calculation of the pharmacokinetic parameters (i.e., CSF Vd, drug elimination half-life) after initial dosing, with follow-up dosing based on those parameters.[35]

INTRAVENTRICULAR PLUS IV VANCOMYCIN

When inadequate CSF vancomycin penetration occurs (i.e., IV alone fails), the combination

of IV plus direct instillation into the CSF has been reported to be highly successful.[3,17,20,27] In a study of 20 patients receiving various medications via the intraventricular route (i.e., vancomycin, methicillin, gentamicin, cephalothin) in addition to IV administration, CSF concentrations for all antibiotics were well above the MIC at 24 hours.[10]

In a retrospective review, 15 patients (9 children) were studied who had shunt-associated ventriculitis caused by staphylococci or streptococci.[27] Patients were treated with intraventricular vancomycin (20 mg/day in adults, 10 mg/day in children) with or without IV vancomycin. Courses ranged from 5 to 19 days and all patients' CSF was sterilized. However, no CSF vancomycin concentrations were obtained. In another retrospective study, 46 patients received intraventricular vancomycin in 50 separate episodes.[3] Ages ranged from 1 month to 63 years (17 patients were < 10 years, 11 of whom were < 1 year of age). Thirty-eight patients received 20 mg of vancomycin daily, 1 patient received 15 mg, 5 patients received 10 mg, and 6 patients received 5 mg. The drug was given for a period ranging from 3 to 38 days. Concurrent IV vancomycin was given in seven cases. CSF vancomycin trough concentrations measured 24 hours after at least two doses and not more than five doses in 25 patients ranged from 5 to 236 mg/L. CSF vancomycin peak concentrations were measured in seven cases within 4 hours of administration and ranged from 26 to 280 mg/L. Sixty-six percent of patients had long-term eradication of infection at 4 months-3 years follow-up. No toxicity was reported despite elevated CSF trough concentrations in some patients (actual number not reported).

McGee et al. described five children who received both IV (45 to 94 mg/kg/day) and intraventricular (1 mg to 25 mg daily) vancomycin.[31] In these patients, the mean ventricular vancomycin concentration was 23.5 mg/L (range, 4.5 to 58.6 mg/L). The wide variation in the CSF vancomycin concentrations between the two groups (mean 5.5 ± 5.2 mg/L in patients receiving IV alone vs. mean 23.5 mg/L, range 4.5–58.6 mg/L, in patients receiving IV plus intraventricular vancomycin) indicates that after IV vancomycin administration, it may be difficult to achieve and maintain elevated vancomycin concentrations within the ventricular fluid. The authors found no correlation between the IV dose and the CSF vancomycin concentration. However, a direct correlation was found between the ventricular vancomycin concentrations and indices of ventricular inflammation (i.e., CSF protein, white blood cell count, and glucose concentrations).

Al-Jeraisy et al. conducted a retrospective chart review of 17 children with shunt infections in whom CSF vancomycin concentrations were measured.[42] Sixteen patients received 10 mg/day and 1 patient received 5 mg/day of intraventricular vancomycin. The duration of intraventricular therapy ranged from 3 to 23 days. All patients except one received concomitant IV vancomycin. Trough CSF vancomycin concentrations were obtained in 17 patients across the duration of therapy and ranged from 0.4 to 187.3 mg/L. The mean maximum trough CSF vancomycin concentration noted for the 16 patients who received 10 mg/day of intraventricular vancomycin was 18.4 ± 21.8 mg/L. All 4 patients ≥ 25 kg had CSF vancomycin concentrations ≤ 5 mg/L (mean 2.6 ± 1.8; range, 0.4–5 mg/L), three of four infants/children between 10 and 25 kg had trough CSF vancomycin concentrations between 10 and 20 mg/L (mean 13.4 ± 7.7; range, 2–18.5 mg/L), and five of nine infants ≤ 10 kg had CSF vancomycin concentrations > 20 mg/L (mean 29.1 ± 26.3; range, 4.8–187.3 mg/L).[42] All organisms were eradicated; CSF cultures became sterile by a median of 5 days (range, 2–10 days). CSF drainage outputs ranged from 50 to 950 mL/day in patients with externalized shunts, but this output did not correlate with CSF vancomycin concentrations. Interestingly, the patient with the highest CSF output also had the highest CSF vancomycin concentration. A similar case has been previously reported. Of 2 hydrocephalic infants receiving the same dose of ampicillin, the infant with massive hydrocephalus had CSF ampicillin concentrations 10–100 times those of the infant with only moderate ventricular enlargement.[38] In the Al-Jeraisy study, although CSF trough vancomycin concentrations were highly variable, they appeared to be lower in older children (< 5 mg/L) and elevated in infants (> 20 mg/L). The authors concluded that infants < 5 kg may require a daily dose of intraventricular vancomycin less than 10 mg

(i.e., 5 mg), while children > 25 kg may require 20 mg/day.[42]

DURATION OF THERAPY

The duration of vancomycin therapy, whether IV, intraventricular, or both, is variable in the published literature. Schaad et al. reported a mean duration of 13.2 days (IV only) with successful eradication in all assessable patients (n = 11).[19] Swayne et al. reported sterilization of CSF in all 20 episodes of shunt infection when intraventricular ± IV vancomycin was administered for 5–19 days.[27] In another study, the overall median duration of antibiotics for shunt infections in a seven-year review at one center was 15 days; no relapses or reinfections occurred in patients treated with vancomycin, though the route of administration was not reported.[5] In the retrospective review of 17 children with shunt infections treated with intraventricular and IV vancomycin by Al-Jeraisy and colleagues, the duration of therapy was 3–23 days; all achieved CSF sterilization.[42]

Many authors have published recommendations on duration of therapy for shunt infections. Bayston et al. suggested intraventricular therapy until CSF cultures have no growth for 3–4 days, then replacing the shunt.[3] Everett et al. recommended 10–14 days of intraventricular therapy along with 2–5 weeks of IV therapy.[11] McLaurin and Frame preferred externalizing the distal portion of the shunt and treating with intraventricular therapy until the shunt was reinternalized, and continuing IV therapy as long as 4 weeks if certain criteria were present (wound infection along the course of the catheter, need for additional shunt revisions, intraventricular therapy could not be given for 2 weeks, CSF bactericidal titers were < 1:8, or presence of highly resistant organisms).[2] Barrett recommended IV and intraventricular therapy until 5 consecutive CSF cultures had no growth for 48 hours (duration usually 14–21 days) if the shunt was not replaced. For patients that had the shunt removed initially and an external ventricular drain placed, Barrett recommended IV and intraventricular therapy until the CSF culture had no growth for 48 hours, then replacing the shunt and continuing therapy for several days postoperatively.[9]

A survey of practicing pediatric neurosurgeons published in 2001 illustrated the variability in management and duration of therapy for shunt infections. Sixty-five percent of the members of the American Society of Pediatric Neurosurgeons responded to the survey. For shunts infected with *S. aureus* or *S. epidermidis,* responders indicated that the usual duration of antimicrobial therapy was 2–21 days; 80% of practitioners based the actual duration of therapy on achieving a set number or length of sterile CSF cultures.[43] This survey along with the various recommendations found in the literature illustrate that the optimal duration of therapy is uncertain.

OUTCOMES

Most of the studies in this review were retrospective or case reports; none were randomized controlled trials. Nonetheless, patient outcomes were reported in many cases (see Table 1). In studies of pediatric patients with meningitis, CSF vancomycin concentrations ranged from 0.3–3.3 mg/L at 0.3 to 5 h postdose; all of those studies reported successful patient outcomes.[16,44–5] Outcomes in ventriculitis or shunt infection were more variable. Only 62% success was attained in one study (n = 46) when CSF peak concentrations were 26–280 mg/L and trough concentrations were 5–236 mg/L (median 26.8 mg/L).[3] Two studies reported successful outcomes with random CSF vancomycin concentrations averaging 3.9 mg/L[19] and 5.5 mg/L.[31] Another study reported apparent treatment failure in two cases where random CSF vancomycin concentrations ranged from 9.5–144 mg/L.[28] It appears from these data that low CSF vancomycin concentrations were efficacious in meningitis, but not always in ventriculitis. Definite correlations between CSF concentrations and outcomes cannot be drawn from these types of data; randomized clinical trials are needed.

COMPLICATIONS

Most studies have not reported any complications following the administration of vancomycin intraventricularly. A few isolated cases of chronic eosinophilia in the CSF have been reported.[46] A 3-month-old female received one

20 mg intraventricular vancomycin dose in the operating room then 10 mg intraventricularly twice daily. After 48 hours of therapy, she developed CSF eosinophilia; the percent eosinophils reached the highest point at 87%. A 15-month-old female received two 20 mg intraventricular doses in the operating room (one dose in each of two drains) then 10 mg intraventricularly twice daily. After 3 days of therapy she developed CSF eosinophilia, with the highest percent eosinophils reached during therapy being 82%. Vancomycin concentrations were not reported in either patient.[46] In the Al-Jeraisy review, one patient whose CSF vancomycin concentration was 187 mg/L developed chronic eosinophilia that was presumed to be related to intraventricular vancomycin.[42]

Grabb and colleagues' proposed mechanism of vancomycin-induced CSF eosinophilia is that a vancomycin concentration-dependent stimulation of mast cell degranulation occurs. This causes release of eosinophil chemotactic factor, which stimulates release of eosinophils from bone marrow to CSF. The possible problems caused by this increased percentage of eosinophils are, first, a direct effect on the CNS. The authors report that 30% of patients with increased eosinophils have neurologic symptoms; experimentally, rabbits show clinical ataxia and motor weakness with white matter degeneration. Second, eosinophils could be misinterpreted as neutrophils on gram stain, leading to confusion regarding efficacy of therapy. Third, eosinophils themselves may be detrimental because they may selectively ingest and destroy antigen-antibody complexes but they do not ingest bacteria; thus, eosinophils may not be helpful in fighting bacterial infection.[46] These are hypothetical concerns at this time, since there are no human data to support these statements, and the clinical impact in humans is unknown.

SUMMARY AND RECOMMENDATIONS

Differences in study designs and definitions complicate the interpretation of the literature regarding vancomycin CSF concentrations. Flushing all of the valves after instilling vancomycin may not be a standard of practice at all institutions. Falsely elevated vancomycin concentrations may result if valves are not flushed. The time at which peak concentrations are drawn is also variable. Not all reports include the timing of concentrations in relation to doses; some clamp the shunt for one hour after instilling the drug and then draw CSF for the peak concentration at the end of this clamp time, resulting in very elevated peak concentrations.[30] Some authors report values simply as "peak" and "trough."[17] Most reports do not include information about length of time a shunt is clamped or flushing of valves.

Clearly, more study is needed to determine the most rational approach to treating pediatric CSF shunt infections. Factors that influence vancomycin CSF concentrations need to be more clearly defined. A practical manner to determine CSF volume and output when considering dosing strategies and monitoring plans may be helpful. The ability to determine the concentration of the drug at the site of infection (i.e., the shunt tubing vs. the ventricle) would be valuable. Most importantly, a randomized, controlled trial comparing intraventricular therapy to the combination of intraventricular plus intravenous and to intravenous therapy alone would answer ultimate questions as to which is the most effective and tolerable treatment regimen. It is imperative that future studies address questions relating to clamp time, flushing of valves, and other technical issues that may affect the interpretation of CSF concentrations. Possible complications of intraventricular therapy should also be identified and reported.

A review of extant literature does not suggest that any consensus exists regarding the ideal vancomycin regimen for treating pediatric CSF shunt infections. Nonetheless, some general recommendations can still be made. Goals of therapy should include maintaining the vancomycin concentration in the CSF above the MIC of the infecting organism (or above the usual MIC of suspected organisms for the institution), maximizing efficacy and minimizing toxicity. To meet these goals, it is necessary to monitor CSF vancomycin concentrations. Because complications appear to be infrequent, intraventricular therapy should be considered for most patients. A rational starting regimen is vancomycin 60 mg/kg/day IV divided every 6 hours with or without intraventricular vancomycin 10 mg daily. CSF vancomycin concen-

trations should be monitored at least every few days. If intraventricular therapy is not started initially, then it should be considered in patients that have suboptimal clinical or microbiological responses to IV therapy alone. If initial CSF vancomycin concentrations are subtherapeutic (i.e., < 5 mg/L or < MIC of the organism if it is known), the intraventricular dose should be increased up to a maximum of 20 mg daily (unless a larger dose is required based on a patient's individual pharmacokinetic parameters). If initial CSF vancomycin trough concentrations are greater than 20 mg/L, the next intraventricular dose should be held and the daily dose decreased. Measuring serum concentrations of vancomycin as a marker of CSF penetration is controversial. The literature does not support a correlation between serum and CSF concentrations. If a patient is receiving adequate doses of IV vancomycin (e.g., 60 mg/kg/day), renal function is normal, and signs of infection are resolving, serum vancomycin concentrations are probably not indicated.

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