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Title:

Monitoring intraventricular vancomycin for ventriculostomy access device infection in preterm infants

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Abstract

Purpose: Ventriculitis is a known complication during external CSF drainage in preterm infants with posthaemorrhagic ventricular dilatation. *Staphylococci* are most frequently isolated in device-associated ventriculitis and hence intraventricular vancomycin is a commonly used therapy. Our aim was to study the CSF vancomycin level pattern and drug safety in ventriculostomy access device infection in preterm infants less than 28 weeks gestation.

Methods: This single centre, retrospective case series included 7 infants with a median gestational age of 25+4 weeks (range 23+6 to 27+5 weeks). Ventriculitis was defined as elevated CSF white cell count of $>20/\text{mm}^3$ or positive CSF culture. The CSF vancomycin concentrations following intraventricular vancomycin administration were studied.

Results: Forty treatment episodes of intraventricular vancomycin administration were studied in 7 preterm infants. Maximum CSF vancomycin concentrations were 24.9mg/L (3mg, n= 8, Observed concentration time(OCT), hours(h)=19), 96.3mg/L (5mg, n=17, OCT(h)=14), 94mg/L (10mg, n= 14, OCT(h)=24), 230.7mg/L (15mg, n=1, OCT(h)=24). The threshold for re-dosage is set at CSF vancomycin level of $<10\text{mg/L}$. In all patients ventriculitis resolution (defined as sterile CSF and CSF WCC of $<20/\text{mm}^3$) was achieved in a median of 5.5 days (range 2-31 days). Individual microbiology data is provided in online resource.

Conclusion: Intraventricular vancomycin is an effective treatment for ventriculostomy access device infection in preterm infants. In doses ranging from 3mg to 15 mg, sufficient CSF vancomycin level is generated to achieve microbiological cure without any reported adverse effects. Daily CSF drug monitoring is recommended to define dosage interval to maintain drug concentration above breakpoint of minimum inhibitory concentration.

Keywords: Ventriculitis - Intraventricular vancomycin -Therapeutic drug monitoring-
Posthaemorrhagic ventricular dilatation

Introduction:

Ventriculitis is a known device-associated complication during external cerebrospinal fluid (CSF) management of posthaemorrhagic ventricular dilatation (PHVD) in preterm infants.

Staphylococci are the most common causative organisms of ventriculitis in preterm infants undergoing external CSF drainage with ventriculostomy access device. Approximately 6% of preterm infants undergoing daily CSF drainage with ventriculostomy access device develop ventriculitis [1]. The incidence of ventriculitis has been associated with prematurity, diminished skin integrity and the frequency of ventricular access device taps, despite full aseptic technique practiced throughout the procedure.

Intravenous (IV) vancomycin is the drug of choice in severe Gram positive infections in the neonatal period. Intravenous vancomycin therapy is known to have variable CSF penetration, ranging from 0.77-18% [2]. Therefore, intraventricular vancomycin (IVV) therapy is used in this specific group of infants with ventriculitis and suspected reservoir infections, often with concomitant IV vancomycin therapy. However, data on IVV dosing, pharmacokinetics and drug safety are still limited in preterm infants.

We aimed to explore vancomycin pharmacokinetics in the CSF following IVV administration in infants born at less than 28 weeks gestation, diagnosed with ventriculitis during treatment of PHVD using a ventriculostomy access device (Ommaya reservoir). Four local established vancomycin dosage models, guided clinically according to the extent of ventricular dilatation (VD) present on ultrasound examination were studied. Table on local dosage regimen guidelines is provided in online resource 1 (Table 1). In addition, as part of the IVV treatment safety review, we also examined any associated hearing defects in this cohort of preterm infants. Routine monitoring of serum creatinine in the 7 infants did not reveal any abnormalities.

Methods:

This was a retrospective clinical case review of 7 preterm infants born at less than 28 weeks gestation, admitted to Southmead Hospital Neonatal Intensive Care Unit (NICU), in Bristol, United Kingdom. The study period covered was 7 years, from 2009 to 2015. The 7 infants represent all the cases of ventriculitis treated in our unit in the defined time period. Four infants were inborn and three infants were transferred to the unit for the management of PHVD and ventriculitis. Patients were included in the study after the diagnosis of ventriculitis, defined as elevated CSF white cell count (WCC) $>20/\text{mm}^3$ or positive microbiological CSF culture, during daily CSF drainage via ventriculostomy access device (Ommaya reservoir), for management of PHVD (n=6) or post infectious hydrocephalus (n=1). Clinical characteristics, pharmacokinetics data on IV vancomycin and IVV of the study population were collected from patient electronic and written medical records. For each patient, data on the following parameters were recorded: CSF WCC, microbiological CSF culture results, CSF protein levels, IV vancomycin and IVV doses administered, all available CSF vancomycin levels and serum vancomycin levels. Date and time of IV vancomycin doses, IVV doses, serum and CSF vancomycin levels were recorded.

The CSF vancomycin measurement was performed by an immuno-assay in the local microbiology laboratory, which is a national referral centre for antibiotic assays (INDIKO, Thermo Fisher, UK) [3]

Our laboratory uses Quantitative Microsphere System (QMS®Thermo Scientific) based immunoassay for measurement of vancomycin levels. The details of the test performance are provided in Table 1 below [4]:

Table 1 CSF vancomycin assay test performance

Analyte	Accuracy (%)	Inter and Intra Assay Precision (%)	Specificity	Analytical Range (mg/L)	Lab bias (%)	Lower limit of Quantification (mg/L)
Vancomycin	Low = <15.0 Med/High = <10.0	Low = <15.0 Med/High = <10.0	No known interferences	2.0 - 100	Mean/median negative bias 2-3	2.0

IVV was given as part of the regular reservoir tap. A sterile vancomycin preparation for intraventricular use, was administered at a concentration of 10mg/ml at the end of the tap, as a slow bolus over 2 minutes, followed by a 1ml sterile NaCl 0.9% flush of the ventriculostomy reservoir and catheter.

Our practice is to obtain CSF vancomycin levels routinely on regular basis, as and when dictated by the clinical need to access the reservoir. Therefore, the levels are random concentrations and the repeat dose was administered if the levels were below the set threshold of 10mg/L. Although this random sampling method was utilised, in this patient cohort, we observed that CSF vancomycin levels in 13 out of 40 treatment episodes were taken immediately prior to the next dose administration. Hence, pre-dose CSF levels were available for these 13 treatment episodes. 1 treatment episode is defined as administration of a single IVV dose. We didn't measure the supposed peak CSF vancomycin levels routinely, as this (taken one hour after the administered dose) would have required, a separate sample thereby increasing the risk of infection, and vancomycin peak levels would not have added value to the dosage and interval decisions. We aimed to achieve a target CSF vancomycin concentration of at least 10 times above the breakpoint of minimum inhibitory concentration (MIC) for *coagulase negative staphylococci*, a predominant organism in our neonatal ventriculitis patients, during all the dosing intervals. We do not routinely measure MIC of isolates from the individual neonate's CSF culture. We instead use our trust level MIC breakpoint for specific isolates, with EUCAST MIC breakpoint as a guide[5]. Our trust level MIC breakpoint for *coagulase negative staphylococci* is 1mg/L (EUCAST MIC breakpoint: 4mg/L) [5]. This is based on MIC₉₀ of *coagulase negative staphylococci* isolates from our centre. In this context, MIC₉₀ is the lowest concentration of vancomycin at which point 90% of the *coagulase negative staphylococci* isolates are inhibited [6].

The infants who were treated with concomitant IV vancomycin therapy received a standardised initial dose protocol for IV vancomycin, at 15mg/kg. The interval varies with gestation, with infants <29

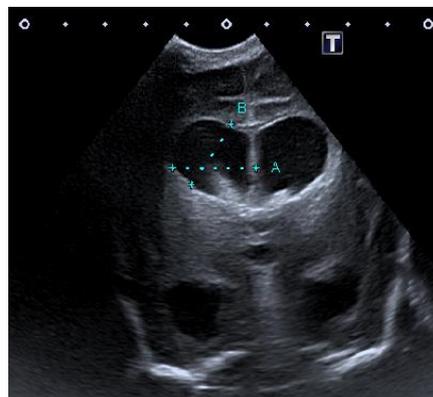
weeks postmenstrual age receiving it at a 24 hourly interval and infants 29-35 weeks postmenstrual age, at 12 hourly intervals [7].

Cranial ultrasound studies (CUSS) were performed with a Philips HD5 USS machine using an 8.5 MHz sector transducer. Intraventricular haemorrhage (IVH) was classified according to Volpe at 7 days of postnatal age [8]. During treatment of PHVD, CUSS was performed 2-3 times in a week, which included measurement of ventricular index (VI) and anterior horn width (AHW) (defined as the diagonal width of the anterior horn measured at its widest point in the coronal plane) [9].

The measurement of the ventricular size was based on assessment of the VI, defined as the distance between the falx and the lateral wall of the anterior horn in the coronal plane [9]. The VI is then plotted on a Levene's centile chart and the degree of VD assigned as the following; no VD (up to 97th centile), mild VD (>97th centile and up to 97th centile + 2mm), moderate VD (>97th centile + 2mm and up to 97th centile + 4mm) and severe VD (>97th centile+ 4mm) [10]. Figure 1 below demonstrates an example of VI and AHW measurements.

All 7 infants underwent regular CSF drainage through the Ommaya reservoirs. This clinical decision is based on the parameters of degree of ventriculomegaly on the CUSS, rate of increase of head circumference measurements and clinical signs such as irritability and bulging anterior fontanelle. The CSF volume drained ranged from 5-10ml/kg/day.

Figure 1 Measurement of VD. Trans-fontanel CUSS; Coronal plane at term corrected age of a preterm infant with PHVD following bilateral grade 3 IVH, undergoing external CSF drainage via ventriculostomy access device (right lateral ventricle). Right lateral ventricle: VI (A) and AHW (B).



Clinical outcomes of ventriculitis resolution (defined as sterile CSF and CSF WCC of < 20/mm³), mortality, need for permanent ventricular shunt insertion and hearing outcomes were studied. Hearing outcomes were documented following newborn hearing screening with otoacoustic emissions (OAEs), automated auditory brainstem response (AABR) or on further audiology assessment if needed. All babies had newborn hearing screen, and the period of observation for hearing outcome is 12 months to 2 years.

Data analysis

Data management and analysis were carried out using Microsoft Excel. Simple descriptive statistics were used to represent the results in the form of median (range).

Ethics

The study protocol was approved by NHS England Health Research Authority (HRA). As the study is of a retrospective and quality audit design; and given anonymised data, the committee requested no parental informed consent.

Results

Demographic data of study infants, trans-fontanel CUSS results and details on reservoir insertion and time point of diagnosis of ventriculitis are given in Table 2. First episode of ventriculitis was diagnosed at a median of 22 days (range 4-43 days) after the reservoir insertion.

Table 2 Patient Demographics

	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 5	Pat. 6	Pat. 7
Mean GA (weeks)	25	26	27	25	23	27	24
Birth weight (g)	860	1000	883	655	517	1130	700
Gender	Male	Male	Female	Female	Female	Female	Male
IVH (max. grade)	Grade 4* + PI	Grade 4# + PI	Grade 3#	Grade 2+	Grade 3*	Grade 3*	3 */ 4+ + PI
Diagnosis	PHVD	PHVD	PHVD	Meningitis [§]	PHVD	PHVD	PHVD
Age at VAD insertion (days)	29	16	17	162	45	25	20
Age at diagnosis (days)	32	27	59	165	66	63	54

GA gestational age, Pat patient, IVH intraventricular haemorrhage, VAD ventricular access device, #bilateral, *left side, +right side, PI parenchymal involvement [§]Diagnosis of late onset GBS meningitis with development of ventricular dilatation.

Laboratory and CUSS imaging results

Eight ventriculitis events, covering 40 treatment episodes, were studied in 7 premature infants. The highest CSF WCC per episode has a median value of 112/mm³ (range 0-510/mm³). The highest CSF protein per episode has a median value of 7.03g/L (range 0.97-24.34g/L). *Coagulase negative staphylococci* was a frequently associated causative organism. In all patients ventriculitis resolution was achieved in a median of 5.5 days (range 2-31days). Individual microbiology data is provided in online resource 2 (Table 2).

Ventricular size was assessed in all patients prior to the administration of the initial dose. Four patients received an initial IVV dose of 3mg, with median weight 2.05kg (range 1.055-3.919kg), median VI of 25.95mm (range 17-34.6mm) and degree of ventriculomegaly classified as severe. Three patients

received an initial IVV dose of 10mg, with median weight of 1.94 kg (range 0.84-2.19 kg), median VI of 15.1mm (range 14.1-18.1mm) and degree of ventriculomegaly classified as mild (n=2) to severe (n=1). Only 1 patient received an initial intraventricular vancomycin dose of 15mg (weight 1.225kg), with VI of 17.6mm that was in the severe category of ventriculomegaly.

IV vancomycin was used concomitantly in 5/8 ventriculitis events, according to the standard protocol described in the methods section. The median pre-dose (trough) serum vancomycin level was 6.1mg/L (range <2 - >100mg/L). The serum vancomycin concentration of >100mg/L appears very high. This level most probably reflects either a sampling or an analytical error, however we are unable to clarify this due to the retrospective nature of our data. When the serum vancomycin level was retested 14 hours later, it was 7.2mg/L.

IVV dose and CSF vancomycin levels

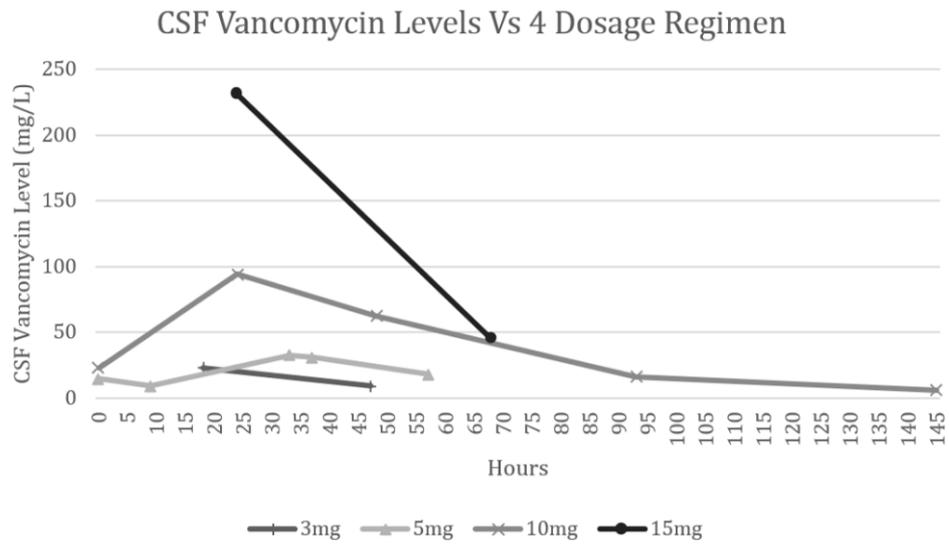
Data was collected on all the CSF vancomycin levels available for a given dose, prior to the administration of the next dose. A total of 40 doses (treatment episodes) were administered in the 8 ventriculitis events. The doses used were 3mg, 5mg, 10mg and 15mg. These dose models are demonstrated below: 8 datasets were available for the 3mg model. The highest CSF vancomycin level recorded was 24.9mg/L, at 19 hours post administration of the 3mg dose. The lowest level recorded was 3.5mg/L at 59 hours post administration. The data demonstrated that the CSF Vancomycin levels were maintained at 18-24 hours, at >20mg/L. These levels declined to <10mg/L as they approached the 48 hours mark. The longest interval where the CSF vancomycin level was held > 10mg/L was 45 hours, at 12.8 mg/L.

17 datasets were available for the 5mg model. The highest CSF vancomycin level recorded was 96.3mg/L, at 14 hours post administration of the 5mg dose. The lowest level recorded was 2.5mg/L at 43 hours post administration. The CSF levels declined to < 10mg/L in two treatment episodes by 25 hours. The longest interval where the CSF vancomycin level was held > 10mg/L was 97 hours, at 21.4 mg/L.

14 datasets were available for the 10mg model. The highest CSF vancomycin level recorded was 94 mg/L, at 24 hours post administration of the 10mg dose. The lowest level recorded was 4.2 mg/L at 62 hours post administration. All available CSF vancomycin levels measured between 20-48 hours were maintained at >10mg/L. The longest interval where the CSF vancomycin level was held > 10mg/L was 114 hours, at 19.5mg/L.

1 dataset was available for the 15mg model. The highest CSF vancomycin level recorded was 230.7 mg/L, at 24 hours post administration of the 15mg dose. The lowest level recorded was 44.9mg/L at 68 hours post administration. Only 2 levels were available for the 15mg model. Figure 2 illustrates CSF vancomycin concentrations for the 4 dosage regimen used, over 4 treatment episodes. Figure 3a and 3b in online resource 3 illustrate two examples of individual patient's IVV dosage and CSF drug concentration during the treatment course.

Figure 2: CSF vancomycin concentrations for the 4 dosage regimen



Permanent ventricular shunt and IVV treatment safety profile

5/6 infants required ventriculoperitoneal (VP) shunt and 1 had insertion of ventriculoatrial (VA) shunt. 1 infant died following redirection of care unrelated to ventriculitis, hence did not reach the stage for consideration of a shunt.

There were no confirmed adverse effects due to the IVV treatment in our patient cohort. 5/6 infants had satisfactory hearing outcome using OAE, AABR or on further audiology assessment if initial tests were unsuccessful. The infant who died did not have a hearing assessment. One infant treated with IVV starting dose of 3mg and subsequent maximum vancomycin peak concentration of 24.9mg/L was diagnosed with bilateral reduced hearing requiring hearing aids at present.

Discussion:

Limited data is available on the pharmacokinetics of IVV in preterm infants [11]. Our study aims to describe a structured approach to IVV dosing, through assessment of VI and associated degree of ventriculomegaly. We have explored different dose models in a case series of preterm infants diagnosed with ventriculitis.

It has been demonstrated that IV vancomycin in the treatment of *staphylococcal* associated ventriculitis often does not achieve sufficient CSF concentration to eradicate the pathogenic organism. Reiter et al examined the CSF vancomycin concentration after intravenous administration in 3 premature infants[12]. The study reported CSF vancomycin concentration between 2.2 mg/L to 5.6mg/L, with CSF penetration reported to be between 26-68% [12]. The recommended trough level of CSF against *Staphylococcus aureus* and *S.epidermidis*, the organisms implicated in shunt infection, is 5-10mg/L[13].

IVV treatment has been proposed in the treatment of device associated *staphylococcal* ventriculitis in preterm infants. Pau et al had demonstrated trough CSF levels between 12.7 mg/L to 25 mg/L in an infant of 29 weeks gestation, with highest peak level reported as 144mg/L [14]. IVV doses ranging from 5mg-10mg were used in this case report[14]. The variability of CSF vancomycin levels even in a single preterm baby calls for further robust data in the neonatal population.

We have studied the CSF vancomycin level pattern in 7 preterm neonates of < 28 weeks gestational age, covering 8 ventriculitis events and 40 IVV doses. Initial dosing was clinically guided by extent of ventricular dilatation, giving rise to 4 dose models which is an approach not described previously in the neonatal population. On review of our patient cohort, patients had mild to severe ventriculomegaly, as defined by the Levene's chart, at the point where treatment was initiated for ventriculitis[10]. In practice, the starting dose in our cohort varied from 3mg, 10mg and 15mg.

Overall, the CSF vancomycin levels were sufficiently maintained at the 24 interval of >10mg/L. This is in accordance to at least 10 times above the breakpoint of MIC for *coagulase negative staphylococci*, of 1mg/L, for the different dose models described. However, there were exceptions at the 5mg model where 2 doses declined to 9.2mg/L (pre-dose 14.4mg/L) at 9 hours and 3.2mg/L (pre-dose 19.2 mg/L) at 25 hours respectively. This emphasizes the clinical variability observed between different preterm babies. Our data demonstrated that the larger the dose, the higher the CSF vancomycin level for a given interval. Additionally, the CSF vancomycin levels were maintained at sufficient levels (10 times above MIC for *coagulase negative staphylococci*) for longer at the higher doses. Our data demonstrated that it is important to individualize the dosage regimen in a patient as the drug concentration declines faster than expected in some patients as observed with the 5mg model. CSF disposal rate is an important factor to consider, as this was constant in our cohort at 5-10ml/kg/day. We hypothesize that the higher disposal rate may lower the CSF vancomycin level at a faster rate.

A recent study suggested that lower IVV dose of 5mg may be sufficient as a starting dose in the newborn population, as they found that the CSF vancomycin concentration was adequate at 72 hours post administration, at 16.5 mg/L [15]. Moreover, Nagl et al demonstrated that the microbicidal effect of vancomycin in human CSF samples against *Staphylococcus aureus* and *S.epidermidis*, with MIC of

2mg/L, is noted to be at the maximum at 5-10mg/L[13]. This effect cannot be improved at higher levels [13]. Our data however showed that the lower starting dose at 3 mg may lead to a decline below target concentration of 10mg/L faster than the larger doses, hence necessitating frequent re-dosages. The higher starting doses, although produces a high initial CSF vancomycin level lead to a longer duration at target concentration, with lower subsequent doses. These findings are exemplified by figure 3a and 3b in online resource 3.

It has been suggested that initial IVV dosing could be stratified according to ventricular size and volume. Our data supports the idea that an appropriate starting dose might be estimated from the degree of ventriculomegaly, represented by VI measurements on routine CUSS. However, in our patient cohort with severe ventriculomegaly, initial starting doses ranging between 3mg to 15mg achieved the target CSF vancomycin concentration, of >10mg/L.

CSF vancomycin levels taken every 24 hours adequately indicated the time course of CSF vancomycin concentrations guiding the timing for re-dosage. Assessment of CSF vancomycin concentrations over a shorter interval might be further re-assuring, however, taking into account the increased infection risk of multiply accessing the ventricular access device, this seems not necessary.

It may be appropriate to consider lower dose regimen of 3mg-5mg for the remainder of the treatment course to maintain steady concentration of CSF vancomycin, in accordance with the MIC. It would also avoid prolonged high CSF vancomycin levels. The clinician should also take into account the CSF disposal rate, which typically tends to be higher in the severe ventriculomegaly and other comorbidities when adjusting doses.

It is important to be mindful of the potential adverse effects of IVV therapy, especially from high CSF vancomycin levels. Klibanov et al proposed an association between intrathecal vancomycin and permanent sensorineural hearing loss[16]. This is based on the acute onset, bilateral sensorineural hearing loss in one adult patient who had received two 5mg doses of intrathecal vancomycin, although the CSF vancomycin levels were not measured in this case [16]. Preliminary adult data has also suggested neurological sequelae following the administration of intraventricular vancomycin [17]. A potential adverse effect from high CSF vancomycin levels in preterm infants has not been reported. The etiology of sensori-neuronal hearing loss in preterm infants is multifactorial including genetic, infectious (CMV infection) and drug related toxicity (Aminoglycosides) [18,19]. Our study did not reveal specific neuronal hearing loss in 6/7 of the infants studied, despite CSF vancomycin concentration > 40mg/L. One patient in our cohort was diagnosed with bilateral reduced hearing. In this patient, CSF vancomycin levels measured were between 3.5-24.9 mg/L. Therefore, we would not consider excessive CSF vancomycin concentration as a causative factor.

This study has several limitations. As this was a retrospective clinical case review, CSF vancomycin levels were not obtained at set intervals in the patients examined, therefore it is difficult to study exact pharmacokinetics parameters such as true CSF vancomycin peak levels and half-life of the antibiotic. The number of patients is limited due to the rare occurrence of the complication. Nevertheless, the presented study represents the largest cohort of preterm infants of < 28 weeks gestation and birth weight of < 1500g, with IVV treatment for device associated ventriculitis in the literature. The most

recent and relevant study by Matsunaga et al examined the CSF vancomycin concentrations following IVV therapy in the newborn population, however this study only included 2 preterm infants of < 28 weeks gestation, post IVH[15]. The presented cumulative CSF vancomycin level pattern observed with the different dose models provides useful information for the clinicians to optimize the dosage, taking into account the ventricular size of the preterm infant. It is worth noting that in the adult population, a study by Popa et al has demonstrated no significant relationship between CSF vancomycin concentration and ventricular size, in patients who had received IVV therapy [20]. To our knowledge, there is no published data that examined such relationship in the neonatal population.

In our study, we did not examine the effect of CSF protein on the bioavailability of intraventricular vancomycin. The presented free drug concentration might not accurately reflect the total vancomycin availability and longevity as it has been demonstrated that 50-55% of vancomycin is protein bound [21]. As the CSF protein levels in a preterm baby is higher than that of a term infant, this is an important factor that might influence the CSF vancomycin levels [22].

Future prospective studies should apply pharmacokinetics modelling to explore the effects of clinical covariates of CSF and plasma parameters, with the aim of optimizing the current IVV dosage regimen. Such pharmacokinetics models have been successfully used to optimize IV vancomycin therapy in the neonatal population and hence is an area worth exploring [23,24].

Conclusion

IVV therapy, with doses ranging from 3mg to 15 mg, is a safe and effective treatment for neonatal ventriculitis. IVV doses of 3mg-5mg are capable of producing sufficient CSF vancomycin levels in accordance with the minimum inhibitory concentration (MIC) of common pathogenic Gram-positive bacteria. However, daily monitoring of CSF vancomycin level is recommended to individualize treatment interval.

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data Availability: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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