








# Challenges in Diagnosis and Treatment of Neonatal Ventriculitis: A Case Report and Systematic Review of Difficult-to-Treat Central Nervous System Infection Resistant to Conventional Therapy

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## Abstract

**Objective** Ventriculitis is an example of the increasing global trend in difficult-to-treat infections in neonates caused by pathogens resistant to conventional therapies. This article describes the first use of intravenous and intraventricular tigecycline to treat ventriculitis caused by vancomycin-resistant enterococci in a preterm neonate and systematically review the literature on challenges posed by the definitions, diagnosis, and treatment of neonatal ventriculitis

**Methods** The authors searched PubMed and Internet search engines for “ventriculitis” in the period from 2003 to 2023 restricting the research to “Newborn,” “Human,” “English language,” and “full-text availability.”

**Results** Thirty-seven publications (20 case reports, 6 case series, and 11 research articles) were extracted upon research. Preterm birth, posthemorrhagic ventricular dilatation requiring placement of ventricular access devices, and sepsis preceded neonatal ventriculitis. Infections caused by rare microorganisms, in particular gram-negative bacteria resistant to conventional therapies, predominated in the publications describing the need for a combination of intravenous (IV) and intraventricular (IVT) therapies. Survivors of neonatal ventriculitis developed neurodevelopmental impairments such as hydrocephalus, seizures, motor function, hearing, and vision impairment.

**Conclusion** Clinical suspicion of ventriculitis indicated by subtle signs is key for prompt diagnosis. Effective IV and IVT antibiotics are essential to prevent serious sequelae and mortality. The drug delivery method should be changed if there is no clinical response. This study emphasizes the urgent need for pediatric trials of antibiotics against organisms resistant to other drugs.

## Keywords

- ▶ central nervous system infection
- ▶ preterm neonate
- ▶ tigecycline
- ▶ intraventricular treatment

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## Introduction

Neonates are more likely to develop central nervous system (CNS) infections than older persons given their immature immune system and more permeable blood–brain barrier.<sup>1</sup> The incidence of neonatal CNS infections depends on the quality of health care, ranging from 0.3/1,000 live births in high-income countries to 6.1/1,000 in resource-limited settings.<sup>2</sup> The risk is 10-fold greater in preterm neonates.<sup>3</sup>

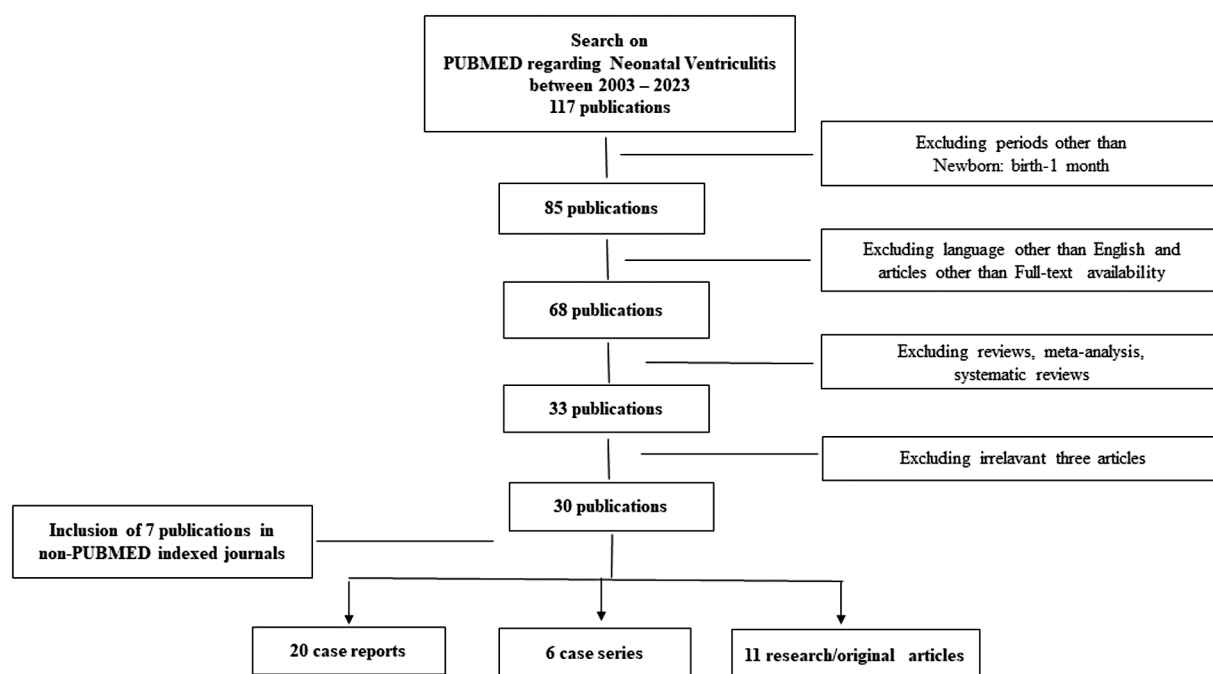
Ventriculitis, which refers to inflammation of the ventricles, ventricular fluid, and surrounding tissue, frequently develops secondary to meningitis associated with obstruction of cerebrospinal fluid (CSF) flow.<sup>4</sup> Infectious pathogens reach the ventricles and surrounding tissue via the bloodstream after sepsis/meningitis, or directly through a CNS device used to drain CSF or as a postneurosurgical complication. In a Canadian neonatal CNS infection cohort, the ventriculitis rate was 6.3% in neonates with proven bacterial meningitis.<sup>5</sup> Over 20% of neonates with meningitis eventually develop ventriculitis.<sup>3,6</sup> Approximately 6% of preterm neonates with germinal matrix hemorrhage (GMH)/intraventricular hemorrhage (IVH) and posthemorrhagic hydrocephalus develop ventriculitis as a device-associated complication of CSF drainage.<sup>7</sup> The ventriculitis rate can reach 52 to 94% in those with gram-negative bacterial (GNB) meningitis.<sup>8,9</sup>

Given the advances in neonatal care, mortality from CNS infections has fallen, but survivors must deal with neurological sequelae and lifelong impairment.<sup>2,10</sup> Early recognition and prompt treatment are crucial to minimize potential risks; however, diagnosis and treatment are challenging. The clinical signs of infection and fever may be subtle, and variations in disease definitions have made diagnosis controversial.<sup>11,12</sup> The current recommendations are mainly based on expert opinion.<sup>13</sup> A low CSF glucose level and/or

pleocytosis do not reliably differentiate an infection from ventricular hemorrhage. CSF cultures may be normal if antimicrobials have been prescribed. Another challenge is encountered during treatment. The impaired immune responses of neonates (particularly those who are preterm) give rise to difficult-to-treat infections caused by rare microorganisms resistant to conventional therapies. However, newer preventative techniques, diagnostic methods, and treatment strategies continue to improve neonatal outcomes. Herein, we describe the first use of intravenous (IV) and intraventricular (IVT) tigecycline to treat ventriculitis caused by vancomycin-resistant enterococci (VRE) in a preterm neonate and systematically review the literature on challenges posed by the definitions, diagnosis, and treatment of neonatal ventriculitis.

## Materials and Methods

In line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we searched PubMed for “ventriculitis” and “newborn” from 2003 to 2023. We retrieved case reports, case series, clinical trials, retrospective analyses excluding reviews, systematic reviews, and meta-analyses. A search using “neonatal ventriculitis” identified 117 publications (►Fig. 1), which were then refined using the terms “newborn,” “birth to 1 month,” “human,” “English language only,” and “full-text availability.” The full texts of two case reports and one original article were unavailable; we excluded these articles and three irrelevant articles. Titles and abstracts of the remaining 30 publications were screened. Another search on Google Scholar was performed to identify articles published in non-PubMed indexed journals. Seven publications were found, so we finally reviewed 37 texts (20 case reports, 6 case



**Fig. 1** Schematic diagram of literature review.

series,<sup>6,7,14–37</sup> and 11 original articles<sup>2,3,9,38–45</sup> [5 retrospective and 3 epidemiological surveillance studies, 1 prospective observational study, 1 pilot population pharmacokinetic modeling study, and 1 research article]).

Signed parental consent was obtained to retrieve and publish patient data in scientific journals.

Case

A 2,700-g neonate was born at 36 weeks of gestational age to a 31-year-old mother. The pregnancy had been complicated by placenta previa and heavy hemorrhage. The baby was hypoxic at delivery, with Apgar scores of 3, 5, and 7 at 1, 5, and 10 minutes, respectively. He was transferred to a neonatal intensive care unit (NICU), underwent high-frequency oscillatory mechanical ventilation, and was treated for hypothermia given the clinical and laboratory signs of perinatal asphyxia and persistent pulmonary hypertension. He developed fever, persistent seizures, and feeding intolerance on day 16. Late-onset sepsis and neonatal meningitis were suspected given the clinical deterioration and laboratory findings of CSF protein 790 mg/dL (normal range: 15–45 mg/dL), CSF glucose 2 mg/dL (blood glucose: 64 mg/dL), and white blood cell (WBC) count of 100/mm<sup>3</sup> in CSF obtained by

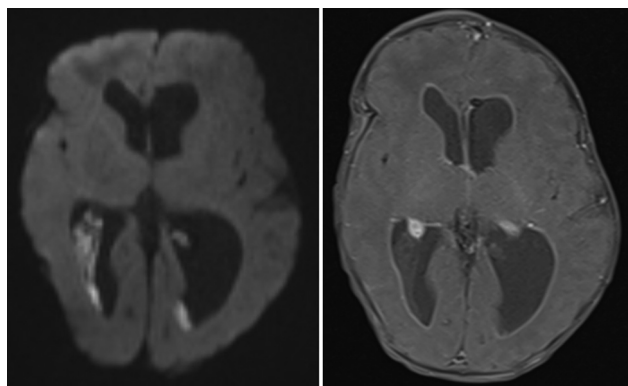
lumbar puncture (LP; ►Table 1). *Enterococcus faecium* was detected on CSF culture (minimal inhibitory concentrations [mg/L]: ampicillin > 256, imipenem > 32, vancomycin > 256, teicoplanin > 192, linezolid = 1.5, ciprofloxacin > 32, and tigecycline = 0.047). Using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria,<sup>46</sup> the isolate was resistant to vancomycin but sensitive to linezolid and tigecycline.

Meropenem IV (40 mg/kg every 8 hours) and vancomycin IV (15 mg/kg every 6 hours) were initiated, but there was no clinical response and repeated vancomycin-resistant (VR) culture positivity during follow-up raised a suspicion for ventriculitis. Neuroimaging (transfontanelle ultrasound and contrast-enhanced magnetic resonance imaging [MRI]) revealed hydrocephalus, enhancement of the lateral ventricles, and debris in the posterior horn and fourth ventricle (►Fig. 2). An extraventricular drain (EVD) was inserted. The patient received tigecycline IV (1.2 mg/kg every 12 hours) and IVT (initial dose of 2 × 1 mg, followed by 2 × 2 mg in 2–3 mL saline with closure of the EVD over the next 2 hours), and contemporaneous IV linezolid (10 mg/kg every 8 hours for 5 weeks). CSF culture became normal on day 17. Complete resolution (at least three consecutive sterile CSF cultures and CSF glucose, protein, and white blood cell [WBC] levels within the normal

Table 1 Laboratory findings of the preterm neonate

CSF protein (mg/dL)	CSF glucose (mg/dL)	Blood glucose (mg/dL)	CSF WBC (mm <sup>3</sup> )	CSF culture	Antibiotics
Clinical deterioration (postnatal day 16) Diagnosis: neonatal meningitis					
790	2	74	100	VRE. faecium	IV meropenem + vancomycin
538	11	81	92	VRE. faecium	IV meropenem + vancomycin
437	1	87	70	VRE. faecium	IV meropenem + vancomycin
Neuroimaging Diagnosis: neonatal ventriculitis IV meropenem replaced by IV linezolid Extraventricular drain insertion IV + IVT tigecycline					
308	19	87	44	Sterile (day 17)	IV linezolid IV + IVT tigecycline
335	18	90	56	Sterile	IV linezolid IV + IVT tigecycline
220	36	155	44	Sterile	IV linezolid IV + IVT tigecycline
139	57	101	40	Sterile	IV linezolid IV + IVT tigecycline
151	43	87	22	Sterile	IV linezolid IV + IVT tigecycline
93	50	90	7	Sterile (day 24)	IV linezolid IV tigecycline
39	36	77	5	Sterile	IV linezolid
IV tigecycline discontinued by day 24 IV tigecycline discontinued by day 29 IV linezolid discontinued by day 49 Ventriculoperitoneal shunt insertion					

Abbreviations: CSF, cerebrospinal fluid; IV, intravenous; IVT, intraventricular therapy; VRE, vancomycin-resistant enterococci; WBC, white blood cell.



**Fig. 2** Contrast-enhanced magnetic resonance imaging of the brain.

ranges) was achieved on day 24. The baby had thus received 7 weeks of IV and 25 days of IVT antibiotics. No adverse effects were detected. The immunological profile at 2 months postnatally revealed low immunoglobulin G (IgG), CD19, and CD56 + CD16 levels, creating a need for IgG (0.5 g/kg) administration every 3 weeks (initial values: IgG 204 mg/dL [reference range: 375–483 mg/dL]; CD19  $0.455 \times 10^9/L$  [reference range:  $0.64\text{--}1.96 \times 10^9/L$ ]; CD56 + CD16  $0.098 \times 10^9/L$  [reference range:  $0.15\text{--}1.33 \times 10^9/L$ ]; *all reference ranges were corrected for age*).<sup>47,48</sup> A ventriculoperitoneal shunt (VPS) was inserted to treat obstructive hydrocephalus. Before discharge, neurological assessment revealed lower extremity spasticity but no hearing or visual impairment. Follow-up involved monthly pediatric neurology, immunology, and physical therapy consultations.

## Results

Sixty affected neonates were identified in 20 case reports and 6 case series. The 37 publications reviewed are listed in ►Tables 2 and 3. Preterm birth, posthemorrhagic ventricular dilatation (PVHD) requiring placement of ventricular access devices (Ommaya/Rickham reservoirs or VPS), and sepsis preceded neonatal ventriculitis. GNB that exhibited increasing resistance to antimicrobials predominated in reports describing a need for a combination of IV and IVT therapies. Despite effective treatment, neonates were at risk of hydrocephalus requiring permanent CSF diversion and poor outcomes including seizures, delayed neurological development, impaired vision/hearing, and cerebral palsy.

## Discussion

We are the first to use IV and IVT tigecycline to treat a preterm neonate with VRE ventriculitis. This represents an example of the increasing global trend in difficult-to-treat infections in neonates caused by rare microorganisms resistant to conventional therapies and emphasizes the need to administer newer antimicrobials in an unconventional manner.

The newborn brain serves as a reservoir for bacterial growth and facilitates the development of antibiotic resistance given the glycogen-rich choroid plexus and the mor-

phological structures of the ependyma and subependymal tissue.<sup>49</sup> This histomorphology, combined with immature immunity, makes neonates vulnerable to severe CNS infections. Approximately 25% of neonates with bacteremia develop meningitis<sup>8</sup> caused by either early- or late-onset sepsis or a late-onset focal infection. This is more common in preterm neonates with IVH attributable to the immature vasculature of the germinal matrix. Depending on the IVH grade, 33% of preterm neonates with GMH-IVH develop PHVD<sup>50</sup>; the spontaneous regression rate is 33%. Other patients often require temporary CSF drainage such as serial LP, EVD, ventriculosubgaleal shunting (VSGS), use of an Ommaya reservoir, endoscopic coagulation of the choroid plexus, endoscopic third ventriculostomy, or more definitive measures including permanent VPS. Approximately 34% of all PVHDs eventually require permanent shunting.<sup>50</sup> Any intervention that accesses the CNS to treat congenital or acquired hydrocephalus raises the risk of ventricular infection; the rate after EVD insertion can reach 10.7%.<sup>50</sup> A study by the Hydrocephalus Clinical Research Network reported infection rates of 14 and 17% after VSGS and placement of ventricular reservoirs, respectively.<sup>51</sup> The postsurgical infection rate is higher in neonates born with neural tube defects.<sup>39</sup> In the studies reviewed here, the major preexisting conditions were preterm birth and PVHD/congenital hydrocephalus requiring temporary or permanent CSF drainage.

Diagnosis of neonatal ventriculitis is challenging. Suspicion is essential when evaluating subtle clinical signs.<sup>18</sup> Fever is present in only 40 to 57% of affected neonates.<sup>12,34</sup> A poor clinical and laboratory response or secondary deterioration during follow-up should trigger investigation of ventriculitis; cytological, biochemical, and microbiological CSF analyses are warranted.<sup>13</sup> However, a definitive diagnosis remains difficult because the definition of ventriculitis varies, ranging from the use of microbiological criteria to broader definitions based on inflammatory features.<sup>11,52</sup> According to the 2017 guideline of the Infectious Diseases Society, an elevated protein count ( $>50$  mg/dL), low glucose level ( $<25$  mg/dL), pleocytosis ( $>10$  cells/ $\mu$ L with  $\geq 50\%$  neutrophils), and gram-positive culture or stain suggest ventriculitis.<sup>13</sup> Notably, the blood–brain barrier in neonates differs from that at all other ages; the “normal” CSF values are influenced by both gestational and chronological age.<sup>53</sup> The reference values are 20 to 22 CSF WBCs/ $\mu$ L (neutrophils  $<2\text{--}8$  cells/ $\mu$ L), CSF protein  $<150$  mg/dL (preterm neonates) and  $<100$  mg/dL (term neonates), and CSF glucose  $>30$  mg/dL (preterm neonates) and  $>36$  mg/dL (term neonates).<sup>54</sup> However, these recommendations are based on studies that included neonates who had received antibiotics prior to LP or had not reliably excluded viral meningitis. Also, biochemical and/or cytological CSF evaluation or negative cultures may not exclude infection. CSF cultures may be negative if LP yields only small amounts of CSF or after antibiotic pretreatment.<sup>55</sup> The international guideline suggests that CSF cultures be incubated for at least 10 days to detect low-virulence microorganisms such as *Propionibacterium acnes*.<sup>13</sup> Novel methods of pathogen detection are required. Nucleic acid amplification by polymerase chain reaction (PCR) multiplex or panel-based testing is

**Table 2** Neonatal ventriculitis: case reports/case series

Publications (no. of cases)	Term/preterm (n)	Gender (F/M)	Age at diagnosis	Preexisting condition	Microorganism (n)	Interventions	Complications Neurological outcome/mortality
Helgason et al <sup>14</sup> (n = 1)	Preterm GA: 28 wk	M	11 d after NICU discharge	PHVD requiring Ommaya reservoir + VPS	MRSA	IVT vancomycin Removal of Ommaya reservoir + VPS Second VPS insertion	Bacterial growth in second VPS Normal development
Hussain et al <sup>6</sup> Case series (n = 7)	Preterm GA: 30.7 wk (26–34 wk) BW: 1.38 kg (1.02–1.5 kg)	M (5) F (2)	26.9 (18–44) d	IVH (5), HIE (1), pneumonia (2), VPS (4)	MDR-GNB <i>Acinetobacter baumannii</i> (5), <i>Klebsiella pneumoniae</i> + <i>A. baumannii</i> (1), <i>K. pneumoniae</i> + <i>E. coli</i> (1)	IV meropenem + IVT Colistin in addition to IV colistin in five neonates	Exitus (1), seizure (3), hydrocephaly requiring VPS (2), CP + impaired hearing/vision (1)
Honavar et al <sup>15</sup> (n = 1)	Preterm GA: 36 wk BW: 2,500 g	M	Day 12	PPROM (36 h) sepsis	Multidrug-resistant <i>Elizabethkingia anophelis</i>	IV therapy	Hydrocephalus requiring VPS Delayed development at 6 mo
Kara et al <sup>16</sup> (n = 1)	Preterm GA: 34 wk BW: 2,400 g	M	2 mo	Congenital hydrocephalus requiring VPS at day 36	Panresistant <sup>a</sup> <i>A. baumannii</i> except tigecycline	IVT colistin + tigecycline	Hydrocephalus + septations
Bhat et al <sup>17</sup> Case series (n = 5)	Full term (4) Preterm (1)	M (3) F (2)	Range: 6–26 d	Postresuscitation care (2), MAS (1), ruptured meningo- myelocele (1), prematurity (1)	<i>A. baumannii</i> (1) <i>C. albicans</i> + <i>A. baumannii</i> (1) <i>Non-Candida albicans</i> (1), unidentified (2)	EVD insertion + IVT colistin (3) (Persistent infection in 2 neonates)	Mortality (2), VPS (3), neurological sequelae (2), left-against-advice (1)
Honda et al <sup>18</sup> (n = 1)	Term GA: 39 wk BW: 2,970 g	M	Day 22	Hydrocephalus	Group B streptococcus	Insertion of Ommaya reservoir IV antibiotherapy No IVT treatment	VPS Normal development at 10 mo
Furudate et al <sup>19</sup> (n = 1)	Preterm GA: 23 wk BW: 547 g	M	Day 89	PVHD Ommaya reservoir	<i>Aspergillus fumigatus</i>	IV voriconazole, endo- scopic IVT lavage, septum pellucidum fenestration	VPS, neurologic sequelae (no head control, no eye tracking)
Pratheep et al <sup>20</sup> (n = 1)	Preterm GA: 27 wk BW: 1,028 g	–	Day 17	PPROM (12 d) Late-onset sepsis	Extensively drug-resis- tant <i>A. baumannii</i>	IVT colistin + tigecycline Ventricular tap	VPS insertion, neurologic sequelae (axial hypotonia)
Huang et al <sup>21</sup> (n = 1)	Preterm GA: 24 wk BW: 720 g	M	5.5 wk	PPROM + cho- rioamnionitis PHVD requiring VAD + daily reservoir taps	<i>Mycoplasma hominis</i>	IV doxycycline	VPS, cystic encephaloma- lia, tracheostomy + gastro- stomy

(Continued)

**Table 2** (Continued)

Publications (no. of cases)	Term/preterm (n)	Gender (F/M)	Age at diagnosis	Preexisting condition	Microorganism (n)	Interventions	Complications Neurological outcome/mortality
Joshi et al <sup>22</sup> (n = 1)	Term BW: 3.5 kg	M	Day 6	–	<i>Elizabethkingia meningoseptica</i>	EVD, IVT vancomycin IV ciprofloxacin + tigecycline + vancomycin + oral rifampin	Hydrocephalus VPS Normal development at 9 mo
Parasuraman et al <sup>7</sup> Case series (n = 7)	Preterms Median (range) 25 <sup>+4</sup> wk (23 <sup>+6</sup> –27 <sup>+5</sup> wk)	M (3) F (4)	Range: 27–165 d	PHVD (6), infection-related hydrocephalus (1)	CNS	Insertion of Ommaya reservoir IVT vancomycin	VPS (6), VA shunt (1), neurologic sequelae (impaired hearing; 1), outcome unknown (1), exitus (1)
Yamamura et al <sup>23</sup> (n = 1)	Term BW: 3,680 g	M	Day 28	–	<i>Streptococcus gallolyticus</i> subsp. <i>pasteurianus</i>	–	Normal development
Mahabeer et al <sup>24</sup> (n = 1)	Preterm GA: 28 wk BW: 1,020 g	M	Day 44	Prematurity PVHD	Multidrug-resistant <i>A. baumannii</i>	IVT colistin (via ventricular puncture) + IV meropenem	Colistin-induced ventriculitis Neurologic outcome unknown
Lubián-López et al <sup>25</sup> (n = 1)	Preterm GA: 29 wk BW: 1,350 g	M	Day 41	PVH serial lumbar punctures NEC	Intraventricular empyema with <i>Veillonella parvula</i>	EVD Metronidazole + meropenem	Neurologic outcome unknown
Preuß et al <sup>26</sup> (n = 1)	Preterm GA: 29 wk BW: 1,682 g	M	Day 62	PHVD Rickham reservoir	<i>Staphylococcus epidermidis</i>	–	Retroclival arachnoid cyst, VPS Achieved milestones at 9 mo
Sadarangani et al <sup>27</sup> (n = 1)	Preterm GA: 34 wk	M	Day 40	Prematurity, PPROM NEC + sepsis	<i>Clostridium septicum</i>	VPS + endoscopic 3rd ventriculostomy, cyst fenestration	Dilated cystic loculations, neurologic sequelae (delayed development at 6 mo, right gaze preference, nystagmus)
Özlü et al <sup>28</sup> Case series (n = 16)	Preterm (11) Term (5) GA: 33 ± 5 wk Mean ± SD	M (13) F (3)	Range: 13–90 d	PHVD (11) Congenital hydrocephalus (5) Ventricular tap (13)	GNB predominant <i>K. pneumonia</i> , <i>P. Aeruginosa</i>	IVT antibiotics VPS insertion (7) VPS reinfection (6)	Mortality (7), VPS (1), left-against-advice (8)
Piparsania et al <sup>29</sup> (n = 1)	Preterm GA: 32 wk BW: 1,500 g	M	Day 22	Prematurity Late-onset sepsis	Pan-drug-resistant <sup>a</sup> <i>A. baumannii</i>	Polymyxin B	VPS, Bayley's motor development index 80, pervasive development index 65
Mehar et al <sup>30</sup> (n = 1)	Preterm GA: 34 wk BW: 1.5 kg	M	Day 22	Late-onset sepsis	Multidrug-resistant <i>A. baumannii</i>	IVT polymyxin B by alternate day ventricular punctures	Hydrocephalus: VPS Normal development
Hartmann et al <sup>31</sup> (n = 1)	Term	F	Day 53	Sacrocoxygeal teratoma + hydrocephalus Rickham reservoir	Vancomycin-resistant <i>Enterococcus faecium</i>	IVT gentamicin IV + IVT chloramphenicol	VPS, neurologic sequelae (motor deficit at 18 mo)



**Table 2** (Continued)

Publications (no. of cases)	Term/preterm (n)	Gender (F/M)	Age at diagnosis	Preexisting condition	Microorganism (n)	Interventions	Complications Neurological outcome/mortality
Kumar et al <sup>32</sup> (n = 1)	Preterm GA: 35 wk	F	6 wk	PHVD requiring VPS	Vancomycin-resistant <i>E. faecium</i>	VPS removal IV linezolid	Neurologic outcome unknown
Chen et al <sup>33</sup> Case series (n = 2)	Preterm (2) BW: 1,558 and 1,180 g	M (2)	–	PPROM (1), cho- rioamnionitis (1)	<i>Listeria monocytogenes</i>	IV ampicillin + gentamicin	Hydrocephalus, VPS (1), exitus (1)
Miyairi et al <sup>34</sup> Case series (n = 3)	Term (2), SGA baby (1)	–	Day 66 Day 19 Day 20	–	<i>Group B streptococcus</i> <i>serotype III</i>	VPS (2), VAD	Hydrocephalus (1) VPS (1), neurologic sequelae (1)
Nava-Ocampo et al <sup>35</sup> (n = 1)	Term BW: 3,300 g	M	Day 2	Congenital hydrocephalus requiring VPS	<i>Enterococcus faecalis</i>	VPS removal, EVD inser- tion IVT vancomycin	IVT vancomycin toxicity Exitus (1)
Wong et al <sup>36</sup> (n = 1)	Preterm GA: 24 wk BW: 680 g	M	Day 9	Prematurity	<i>Candida albicans</i>	IV therapy	Neurologic outcome unknown
Laborada et al <sup>37</sup> (n = 1)	Preterm GA: 29 wk BW: 1,550 g	F	Day 26	PVHD + VPS	MRSA	VPS removal Serial ventricular taps IVT vancomycin	VPS Normal hearing test Discharged home Long-term follow-up unknown

Abbreviations: BW, birthweight; CNS, coagulase-negative staphylococci; *E. coli*, *Escherichia coli*; EVD, extraventricular drainage; GA, gestational age; IV, intravenous; IVH, intraventricular hemorrhage; IVT, intraventricular treatment; MAS, meconium aspiration syndrome; MDR-GNB, multidrug-resistant gram-negative bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; NEC, necrotizing enterocolitis; PHVD, posthemorrhagic ventricular dilatation; VA, ventriculoatrial shunt; VAD, ventricular access device; VPS, ventriculoperitoneal shunt; PPRM, preterm premature rupture of the membranes.

\*Pan-drug-resistant *Acinetobacter* is defined as isolates resistant to all five classes of antimicrobial agents considered first-line therapy for *Acinetobacter* infections. These include (1) antipseudomonal cephalosporins (ceftazidime or ceftipime), (2) antipseudomonal carbapenems (imipenem or meropenem), (3) ampicillin–sulbactam, (4) fluoroquinolones (ciprofloxacin or levofloxacin), and (5) aminoglycosides (gentamicin, tobramycin, or amikacin).

**Table 3** Original/research articles

Original/research articles	
Çay et al <sup>38</sup> Retrospective study	<ul style="list-style-type: none"> <li>● Retrospective evaluation of 25 enterococci isolates in children with meningitis/ventriculitis (VRE isolates: 20%)</li> <li>● Common preexisting condition: hydrocephalus requiring VPS and preterm birth</li> <li>● Fourteen (66%) patients received IVT treatment</li> <li>● Mortality of 8.3%</li> <li>● Neonatal ventriculitis observed in three preterm neonates of GA 26, 28, and 29 weeks. Preexisting condition of three preterm infants: PVHD requiring VPS (1), sepsis (1), and NEC (1). Age at ventriculitis: 1 mo after hospital discharge, at days 39 and 29. Prognosis of preterm neonates: unknown</li> </ul>
Singh et al <sup>39</sup> Retrospective study	<ul style="list-style-type: none"> <li>● Retrospective study evaluating clinicoepidemiological profile of 25 neonates with neural tube defects</li> <li>● Defect repair was performed to 13 neonates in the form of primary repair ± VPS ± EVD</li> <li>● Neonatal ventriculitis occurred in 5 of 13 (38%) patients as postsurgical complication</li> <li>● Outcome: NICU discharge (12), left against advice (11), and mortality of 8%</li> <li>● Neurologic outcome of neonates presented with ventriculitis are unknown</li> </ul>
Ray et al <sup>9</sup> Prospective observational study	<ul style="list-style-type: none"> <li>● Prospective observational study on neurodevelopment outcome at 2–5 y in 87 neonatal <i>Acinetobacter baumannii</i> meningitis/ventriculitis (ventriculitis, <math>n = 12</math>, 13.7%) out of 162 culture-positive cases</li> <li>● Mean (SD) GA and birthweight: 30 (2.9) wk and 1,207 (426) g</li> <li>● Preexisting condition: late onset sepsis</li> <li>● Extensively drug resistant <i>A. baumannii</i> (sensitive to colistin only): 61.3% of isolates in blood and CSF cultures</li> <li>● Prognosis in 55 of 60 (92%) infants: death within 2 y (53), developmental delay (2), lost to follow-up (12)</li> <li>● During the follow-up of 7 children, 2 infants had spastic CP + hearing deficit + significant developmental delay, 4 children had average delay, 1 infant with severe hearing deficit + delay in communication skill. Eye problems: squint (2), amblyopia (1), and myopia (1)</li> </ul>
Parasuraman et al <sup>40</sup> Pilot population pharmacokinetic modelling	<ul style="list-style-type: none"> <li>● A pilot population pharmacokinetic modeling study examining intraventricular vancomycin in 8 preterm infants of &lt;28 wk (median: 25.3 wk; range: 23.9–27.7 wk) with neonatal ventriculitis</li> <li>● Four starting doses of 3, 5, 10, and 15 mg were used</li> <li>● The study demonstrated (1) no appreciable drug transfer between plasma and CSF and (2) ventricular index and CSF protein had no influence on CSF vancomycin. The authors reported intraventricular vancomycin to be an effective route for treating ventriculitis</li> <li>● Neonatal outcome: unknown</li> </ul>
Guillén-Pinto et al <sup>2</sup> Epidemiological surveillance	<ul style="list-style-type: none"> <li>● Epidemiological surveillance for neonatal meningitis in a multicenter study in Peru</li> <li>● Cumulative hospital incidence: 1.4/1000 livebirths</li> <li>● Preterm neonates constitute 54.7% of the study population</li> <li>● Preexisting neonatal condition: sepsis</li> <li>● Common isolates: <i>E. coli</i> and <i>Listeria monocytogenes</i></li> <li>● Ventriculitis and hydrocephalus were common acute and chronic neurological complications</li> <li>● Neonatal outcome: neurologic complications occur in 25% of the population; death in 2 neonates</li> </ul>
Peros et al <sup>3</sup> Retrospective cohort	<ul style="list-style-type: none"> <li>● Retrospective cohort in neonates with 45 culture-proven CNS infections (36 meningitis and 9 neonatal ventriculitis)</li> <li>● No. of neonatal ventriculitis = 9</li> <li>● Demographics of neonatal ventriculitis: <ul style="list-style-type: none"> <li>- Median GA: 27.4 wk (range: 25.4–30 wk) and birthweight 895 g (range: 725–1,570 g)</li> <li>- Age at diagnosis was <math>34.7 \pm 32.1</math> d</li> <li>- Preexisting condition: prematurity and PHVD (4). Two neonates of four PHVD patients had CSF drainage devices in situ (Ommaya drain)</li> <li>- Pathogens in CSF culture: GNB in six neonates, gram-positive bacteria in three neonates</li> </ul> </li> <li>● Outcome: hydrocephalus (5), seizure (4), cerebral abscess (2), and mortality (3). Neurologic outcome unknown (1)</li> </ul>
Ochi et al <sup>41</sup> Research article	<ul style="list-style-type: none"> <li>● Evaluation of six children with health care–associated meningitis or ventriculitis caused by gram-positive cocci</li> <li>● Median age of 17 mo, ranging from 22 d to 13 y</li> <li>● Common infectious pathogen: methicillin-resistant CNS (2), <i>Enterococcus faecalis</i> (1), <i>Streptococcus mitis</i> (1), <i>S. oralis</i> (1), <i>Staphylococcus lugdunensis</i> (1)</li> <li>● Preexisting conditions: IVH in 22-day-old newborn (1), brain tumor (2), Wiskott–Aldrich syndrome (1), leukemia (1), Dandy–Walker syndrome (1)</li> </ul>



**Table 3** (Continued)

Original/research articles	
	<ul style="list-style-type: none"> <li>● Interventions: Five patients necessitated EVD (4) in addition to VPS (2) and/or Ommaya reservoir (2)</li> <li>● IV therapy were shifted from vancomycin to linezolid in four children due to persistent CSF culture (2)</li> <li>● Prognosis: cure (5), exitus (1). Neurologic outcome: unknown</li> </ul>
Vallejo et al <sup>42</sup> Prospective surveillance	<ul style="list-style-type: none"> <li>● Prospective surveillance in 68 children with <i>S. aureus</i> CNS infection</li> <li>● Median age of diagnosis: 2.6 y (range: 0.03–18.1 y)</li> <li>● Preexisting conditions: congenital CNS malformation (32%), IVH (25%), prematurity (39%), intracranial tumor or cyst removal (25%), NTD (12.5%)</li> </ul>
Akturk et al <sup>43</sup> Retrospective case-control study	<ul style="list-style-type: none"> <li>● Retrospective case-control study on carbapenem-resistant <i>Klebsiella pneumoniae</i> colonization in pediatric intensive (41) and NICU admissions (44)</li> <li>● Population age ranged from 1 to 205 mo</li> <li>● Overall infection rate: 28.2%; infection rate in NICU: 18.1%</li> <li>● Neonatal ventriculitis developed in two preterm neonates with hydrocephalus. Both babies necessitated EVD insertion</li> <li>● Overall mortality: 16.6%. Neonatal outcome is unknown</li> </ul>
Chu et al <sup>44</sup> Retrospective cohort	<ul style="list-style-type: none"> <li>● Retrospective cohort on neonates with bacteremia-related neurologic complications</li> <li>● Fifty-seven neonates with bacteremia eventually developed meningitis, 8 neonates proceeded to ventriculitis</li> <li>● Group B streptococcus meningitis was independently associated with neurological complications (aOR: 8.90; 95% CI: 2.20–36.08)</li> <li>● Prognosis: exitus (8), left against advice (6), survivors (22), and neurologic sequelae (8)</li> </ul>
Bentlin et al <sup>45</sup> Epidemiological study	<ul style="list-style-type: none"> <li>● Epidemiological study of 3,910 NICU admissions within 10 y</li> <li>● Confirmed meningitis (22), ventriculitis (15)</li> <li>● Culture positivity in neonates with ventriculitis: GNB (10), gram-positive bacteria (5)</li> <li>● Infections with GNB are more likely to develop ventriculitis, brain abscesses, and hydrocephaly</li> <li>● Mortality 27%</li> </ul>

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CNS, coagulase-negative staphylococci; CSF, cerebrospinal fluid; *E. coli*, *Escherichia coli*; *E. cloacae*, *Enterobacter cloacae*; EVD, extraventricular drainage; GA, gestational age; GNB, gram-negative bacteria; IVT, intraventricular therapy; NICU, neonatal intensive care unit; NTD, neural tube defects; PHVD, posthemorrhagic ventricular dilatation; *S. aureus*, *Staphylococcus aureus*; VPS, ventriculoperitoneal shunting; VRE, vancomycin-resistant enterococci.

very sensitive and specific. Small amounts of pathogen deoxyribonucleic acid (DNA) may be detected in CSF.<sup>56,57</sup> Multiplex panel assays are more sensitive than bacterial culture if an infant has received antibiotics prior to CSF analysis. A recently developed 16S rRNA gene PCR/next-generation sequencing (NGS) platform (the noncommercial MYcrobiota platform) provides highly accurate and comprehensive overviews of microbes in clinical samples. The lower limit of detection is far below those of conventional 16S rRNA gene sequencing methods; very low levels of bacteria can be detected.<sup>55</sup> Other methods not yet validated for neonatal populations include the use of Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry to rapidly detect GNBs; observation of oligoclonal immunoglobulin G or M bands; measures of CSF procalcitonin, lactate, interleukin-1 (IL-6), and phosphatidyl choline levels to detect bacterial infections; and nucleic acid amplification tests of genes involved in CSF  $\beta$ -D-glucan and galactomannan synthesis to detect fungal infections.<sup>4</sup>

Neuroimaging aids ventriculitis diagnosis. Ultrasound is essential, particularly for preterm babies, to detect hydrocephalus and ventriculitis. Radiologists generally agree that increased ventricular thickness, irregularity, and ependymal echogenicity; debris in the ventricular cavities; septal formation by exudates; and IVT cysts late in infection all

suggest ventriculitis.<sup>3,58</sup> However, IVT blood, which is common in preterm neonates, may complicate a diagnosis of ventriculitis because the ultrasonographic findings overlap. Contrast-enhanced computed tomography and MRI are the second-line neurodiagnostic tools.<sup>59</sup> Ventricular debris is common, and it is hyperintense (compared with CSF) on CSF T1-weighted images but hypointense on T2-weighted images.

Infection caused by multidrug-resistant (MDR) pathogen is another concern in the topic of ventriculitis. In general, the bacteria that cause neonatal CNS infections are similar to those associated with early- or late-onset sepsis and include group B streptococci (GBS), GNBs (*Escherichia coli*, followed by *Klebsiella* species), and *Listeria monocytogenes*.<sup>8</sup> Staphylococci are more common in preterm infants undergoing external CSF drainage via ventriculostomic access.<sup>7</sup> The pathogens are highly variable and depend on the gestational/postnatal age and the resource setting of facility.<sup>6</sup> Unfortunately, the incidence of CNS infections caused by MDR pathogens dramatically rose from 41 (1991–2002) to 58% (2003–2014).<sup>60</sup> Moreover, the pathogen distribution has shifted from GBS to MDR GNBs,<sup>3,6,9,16,17,20,24,28–30</sup> Enterobacteriaceae.<sup>31,32,35,38</sup> GNB pathogens, in particular *E. coli*, *Klebsiella*, and *Pseudomonas* species, are detected in 20 to 25% of early-onset bacteremia and 14% of infant meningitis worldwide.<sup>61</sup> *Acinetobacter*

*baumannii* is another concern in NICUs and isolated in 3.6 to 11.2% of cases who developed bacterial meningitis after VPS.<sup>20</sup> Carbapenem resistance of the pathogen were 43.4 and 62.4% in Mediterranean countries and Southeast Asia, respectively; the colistin-resistance rates exceed 10%.<sup>20,62</sup> The challenge in eradicating MDR-GNB infection using conventional IV antibiotics results in significant mortality that can be as high as 71.3 to 72.6%, particularly in neonatal ventriculitis after neurosurgical procedures.<sup>6</sup> Recently, uncommon nosocomial infections caused by *Veillonella parvula*,<sup>25</sup> *Elizabethkingia anophelis*,<sup>15</sup> *E. meningoseptica*,<sup>22</sup> *Streptococcus gallolyticus* subspecies *pasteurianus*,<sup>23</sup> *Candida albicans*,<sup>36</sup> *Aspergillus fumigatus*,<sup>19</sup> and *Mycoplasma hominis*<sup>21</sup> have been reported in patients with neonatal ventriculitis.

The enterococci are gram-positive ovoid bacteria of the normal bowel flora with 14 typical and 3 atypical isolates. *E. faecalis* and *E. faecium* account for 50 to 90% and 5 to 37% of all isolates, respectively,<sup>63</sup> but an uncommon cause of meningitis, *E. gallinarum*, was recently reported in an immunocompromised neonate with hemolytic disease.<sup>64</sup> Most enterococci exhibit rapidly developing intrinsic resistance to multiple antibiotics including ampicillin, penicillin, and vancomycin. In 2017, the World Health Organization declared an urgent need for new antibiotics against carbapenemase and extended-spectrum  $\beta$ -lactamase (ESBL) producing Enterobacteriaceae by classifying the microorganism as one of the “Priority-1: Critical” pathogens.<sup>65</sup> The U.S. National Healthcare Safety Network reported that enterococci were the second-most common cause of nosocomial infections and that the VR rate was 35.5%.<sup>66</sup> In 2022, Williams et al reviewed the major MDR pathogens (including VR *E. faecium*) responsible for neonatal mortality.<sup>1</sup> The pathogens that we identified were similar; anatomical CNS defects or CSF drainage devices was the underlying cause of disease.<sup>29,30,33,34</sup> Çay et al reported their experience with enterococcal meningitis/ventriculitis in 24 children, including neonates (median age, 23 months), finding that EVD and VPS insertion were the major predisposing factors.<sup>38</sup> CNS infections were postoperative (28%), posttraumatic (8%), and spontaneous (8%).

The conventional ventriculitis treatment is IV antibiotics for 4 to 6 weeks after removal of the CNS device.<sup>13</sup> The primary challenge is achieving effective therapeutic antimicrobial concentrations in the ventricle. Drugs weakly penetrate the blood-brain barrier, and CSF flow may be obstructed by cellular debris and proteins.<sup>8</sup> Persistently poor clinical and laboratory findings suggest an unsatisfactory response and that a second delivery method is required to increase drug concentrations in the ventricles. IVT therapy refers to direct instillation of the drug into the ventricular system via an EVD or a reservoir. No guideline on IVT antibiotic administration in neonates has appeared since that of the 2012 Cochrane database,<sup>8</sup> but several publications reported successful IVT therapy for infections caused by MDR bacteria.<sup>6,14,16,17,20,22,24,28,30,31,35,37,39,40</sup> The drug of choice depends on the nature and antibiotic susceptibility of the pathogen. Aminoglycosides (amikacin, gentamycin, tobramycin, netilmicin, and streptomycin), polymyxins (colistin, polymyxin B, and daptomycin), glycopeptides

(vancomycin and teicoplanin), quinupristin-dalfopristin, tigecycline, and antifungals including amphotericin-B and caspofungin can be delivered IVT.<sup>65</sup>

Tigecycline, a semisynthetic tetracycline, can be used to treat serious MDR infections when there are few or no other options.<sup>67</sup> The drug exhibits broad activity, targeting MDR/extensively drug-resistant (XDR) gram-positive and GNBs with the exceptions of *Pseudomonas* spp. and anaerobic and atypical bacteria.<sup>67–69</sup> The U.S. Food and Drug Administration (FDA) has approved tigecycline for adults with complicated intra-abdominal and skin/skin structure infections or community-acquired bacterial pneumonia. However, pediatric use has been very limited, and there have been no phase 3 clinical trials of children.<sup>2</sup> The first use of IV tigecycline to treat a toddler with MDR *E. faecium* occurred in 2010.<sup>70</sup> In 2019, tigecycline safety and efficacy were studied at 1.2 mg/kg (maximum 50 mg) every 12 hours in children aged 8 to 11 years and at 50 mg every 12 hours in children older than 12 years.<sup>69</sup> Although not FDA approved to treat VRE, use of the drug via the IV and IVT routes should be considered when a child is diagnosed with MDR ventriculitis.<sup>66</sup> Tissue drug distribution is rapid, but the CSF concentrations are low when the IV route is used. Therefore, IVT administration is suggested in combination with IV carbapenems.<sup>67</sup> The guideline of the Infectious Diseases Society of America suggests that therapy should continue for 10 to 14 days after the last positive culture.<sup>13</sup> In 2018, the first pediatric IVT delivery of tigecycline was reported; the patient was an 8-month-old infant infected with XDR *Klebsiella* spp.<sup>67</sup> In 2019, a 5-month old infant with VR *E. faecium* was similarly treated,<sup>66</sup> followed in 2020 by a 2-month-old infant with MDR *A. baumannii*.<sup>16</sup> All three infants exhibited congenital hydrocephalus that required VPS insertion. The first use of pediatric IVT tigecycline occurred in 2019 to treat a preterm neonate (born at 27 weeks of gestation) with late-onset sepsis and ventriculitis caused by MDR *A. baumannii*.<sup>20</sup> The case that we report here is the first to use IV + IVT tigecycline to treat VR *E. faecium* ventriculitis in a preterm neonate. No drug-related adverse effect was observed during follow-up.

The durations of EVD and/or IVT therapy are subjects open to debate. Kumar et al published a case series of patients with meningitis-related ventriculitis treated in northern India; the IVT therapy duration averaged 9.1 days (range: 3–19 days).<sup>12</sup> It was suggested that EVD should be prolonged when the infection does not resolve or the increased intracranial pressure (ICP) persists after temporary EVD occlusion. Bhat et al suggested insertion of a second EVD at a different site when IVT therapy continued for greater than 5 days,<sup>17</sup> but the Neurocritical Care Society does not recommend routine changing of the EVD catheter.<sup>71</sup> To maintain aseptic conditions, most experts choose antimicrobial-impregnated catheters, limit manipulation, routinely apply aseptic dressings, ensure appropriate daily care, and favor early catheter removal.<sup>72</sup> An infected EVD or shunt should be removed and antimicrobial therapy commenced if a catheter-related infection develops. Any reimplantation decision must consider the microorganism, the CSF findings, and the patient.

Neonatal ventriculitis remains associated with significant morbidity, especially in preterm infants and those with MDR-GNB ventriculitis.<sup>11</sup> Mortality rate is 33%.<sup>3</sup> Of all survivors, 20 to 50% may develop long-term neurological sequelae including developmental delay (25–50%), cerebral palsy (15–20%), hydrocephalus (15–20%), seizures (10–20%), hearing loss (5–10%), and vision impairment (<10%).<sup>73,74</sup> Postinfectious hydrocephalus requiring permanent CSF drainage remains problematic. Ray et al prospectively evaluated the long-term outcomes of patients with neonatal meningitis/ventriculitis aged 2 to 5 years<sup>9</sup>; 28% of patients exhibited moderate to severe disabilities and 19% had cerebral palsy.

This study had several limitations. Publications in languages other than English and articles without full-text availability were excluded from the review. This has led to the question of whether pathogen distribution might affect the predominating etiology in different populations depending on gestational age or level of neonatal care given. Second, local epidemiology and patterns of resistance in variable hospital settings were not investigated because they were beyond the scope of this review. Our aim was to describe the first use of IVT tigecycline in a preterm neonate with VRE ventriculitis and the challenges in diagnosis and treatment in many NICUs.

## Conclusion

Clinical suspicion of ventriculitis indicated by subtle signs is key for prompt diagnosis. Effective IV and IVT antibiotics are essential to prevent serious sequelae and mortality. The drug delivery method should be changed if there is no clinical response. We describe the first use of IVT tigecycline to treat VR ventriculitis in a preterm neonate; this study emphasizes the urgent need for pediatric trials of antibiotics against organisms resistant to other drugs.

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### Conflict of Interest

None declared.

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