Challenges in treating *Staphylococcus epidermidis* ventriculitis: The role of biofilm formation and antimicrobial resistance

Esteban Perez Montoya DO, Amritpal Dhot DO, Anish Saikumar DO, Andres Guardado MD

Abstract

Ventriculitis caused by Staphylococcus epidermidis *presents significant management challenges due to biofilm formation and antimicrobial resistance, particularly in patients with external ventricular drains (EVDs). This case report highlights the complexities of treating* S. epidermidis*-associated ventriculitis and the role of combination antibiotic therapy in overcoming persistent infection.*

A 54-year-old male with diabetes mellitus and hypertension presented with altered mental status and was diagnosed with a spontaneous hemorrhage in the left basal ganglia (Figure 1). An EVD was placed for intracranial pressure management, but the patient subsequently developed ventriculitis, confirmed by cerebrospinal fluid (CSF) cultures positive for S. epidermidis*. Initial treatment with IV Vancomycin failed to eradicate the infection, prompting the addition of Rifampin, a strategy supported by literature on biofilm-associated infections. The patient's clinical course was further complicated by a non-occlusive pulmonary embolism.*

This case underscores the limitations of vancomycin monotherapy against biofilm-associated S. epidermidis *infections and highlights the efficacy of Rifampin in achieving bacterial clearance. Notably, CSF cultures remained persistently positive until rifampin was introduced, leading to the first negative culture and eventual placement of a ventriculoperitoneal shunt. Coagulase-negative staphylococci, including* S. epidermidis, *account for 50–75% of central nervous system (CNS) shunt infections and typically elicit a less robust inflammatory response, complicating early diagnosis. Our findings emphasize the need for early recognition of biofilm formation and prompt initiation of targeted antimicrobial therapy to improve outcomes in CNS device-related infections. This case supports the use of combination antibiotic therapy and device management as critical components in treating biofilm-associated ventriculitis.*

Keywords: *Staphylococcus epidermidis*, ventriculitis, biofilm, rifampin, antimicrobial resistance

Introduction

A substantial proportion of shunt infections are caused by staphylococcal species, with *Staphylococcus epidermidis* responsible for at least 50% of infections involving cerebrospinal fluid (CSF) shunts and external ventricular drains (EVDs), while *Staphylococcus aureus* accounts for up to 25% of cases.[1,2] Although part of the normal skin flora, *S. epidermidis* poses significant clinical risks due to its ability to form biofilms on medical device surfaces. Biofilms shield bacteria from immune responses and antibiotic therapies, complicating both infection detection and treatment. Biofilm formation on EVDs is particularly facilitated by the continuous nutrient supply from CSF, which fosters bacterial colonization and biofilm resilience.[3] Risk factors influencing infection severity and mortality include advanced age, underlying comorbidities such as diabetes or immunosuppression, prolonged or delayed diagnosis, and the presence of indwelling

Corresponding author: **Esteban Perez**
Contact Information: Esperezmontoya@gmail.com
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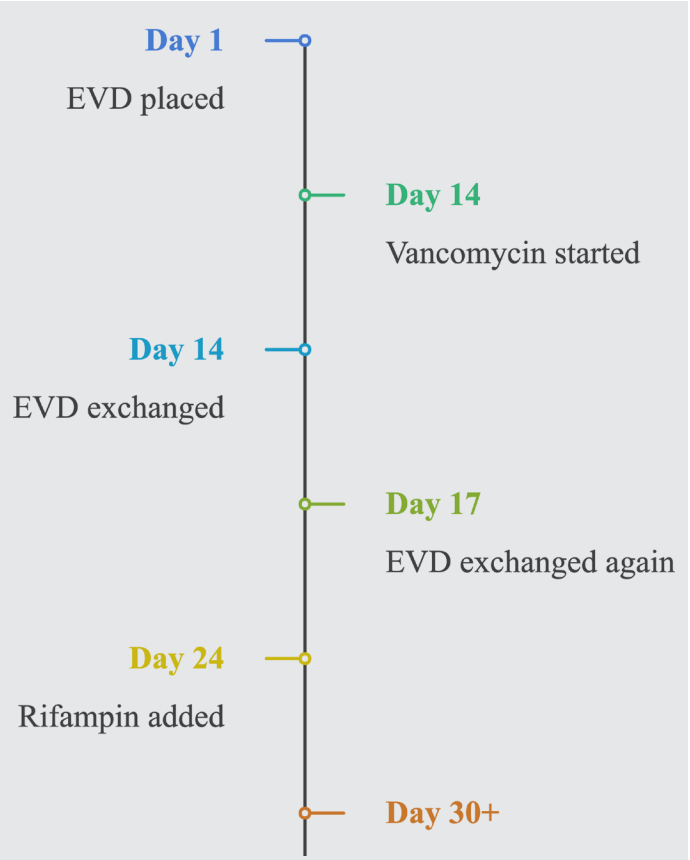

Figure 1. Coronal CT scan of the brain demonstrating ventricular enlargement with evidence of intraventricular debris, consistent with ventriculitis. This imaging was performed prior to external ventricular drain placement in a patient with *Staphylococcus epidermidis*-related ventriculitis.

medical devices.[4] Additionally, biofilm infections tend to induce a lower inflammatory response in the central nervous system (CNS), characterized by decreased CSF glucose and white blood cell (WBC) counts, which can complicate early detection. Due to the protective nature of biofilms, these infections rarely disseminate systemically, often necessitating device removal for successful eradication and recovery.[3]

This case report describes a 54-year-old male with diabetes and hypertension who developed *S. epidermidis*-related ventriculitis following EVD placement. Standard vancomycin therapy proved ineffective, necessitating the addition of rifampin to combat biofilm-associated resistance. This case highlights the complexity of managing biofilm-related infections and underscores the importance of combination antibiotic therapy alongside device removal to prevent recurrence. Consent was obtained from the patient in accordance with manuscript submission requirements. To further contextualize the management of *S. epidermidis* ventriculitis, we have compiled a comprehensive review of key studies evaluating diagnostic approaches, treatment strategies, and infection outcomes in patients with CSF shunts and EVDs (summarized in Table 1). These studies offer critical insights into the effectiveness of antibiotic regimens, the role of device removal, and the challenges posed by biofilm formation in treatment resistance. As *S. epidermidis* is increasingly recognized as a leading cause of biofilm-associated infections in neurosurgical devices, understanding these findings is essential for optimizing treatment strategies, improving patient outcomes, and preventing recurrent infections in individuals with indwelling CNS devices.

Case

The patient is a 54-year-old male with a significant past medical history of diabetes mellitus and hypertension. He presented to the hospital with altered mental status. On initial evaluation, a computed tomography (CT) scan revealed a spontaneous hemorrhage in the left basal ganglia (Figure 1). His clinical presentation raised concerns for CNS involvement, and he had a Glasgow Coma Scale (GCS) score of 8, indicating severe neurological impairment. Laboratory investigations upon admission showed mildly elevated WBC counts, but the patient's blood and urine cultures were negative. Initial chest and abdominal imaging were unremarkable. The patient underwent emergency EVD placement to manage increased intracranial pressure (ICP) and was briefly intubated for the procedure. His initial CSF analysis was unremarkable. However, his mental status continued to decline on post-admission day 6, necessitating re-intubation and raising suspicion for infection. Given the lack of

Table 1. Key Studies on CSF Shunt and EVD-Related Ventriculitis

Studies on Ventriculitis in EVD and Shunt-Related Infections				
Authors and Publication Year	**Study Type**	**Study Participants**	**Key Findings**	**Relevance to Ventriculitis in EVD Patients**
Archer et al., 1978		20 patients with prosthetic valves, 7 with CSF shunts	63% of *S. epidermidis* isolates resistant to nafcillin; none resistant to vancomycin.	Highlights the role of antibiotic resistance in *S. epidermidis* infections, emphasizing vancomycin and gentamicin as effective options while cautioning against rifampin monotherapy due to rapid resistance emergence.
Trump et al., 1982	Retrospective observational study	31 patients with neoplastic meningitis who were treated with thiotepa and methotrexate via subcutaneous reservoir and ventricular catheter (SRVC)	CSF infections in patients with subcutaneous reservoirs and SRVCs were mainly caused by *S. epidermidis* and required device removal for successful treatment. Targeted IV antibiotics, leading to a revised prophylactic regimen favoring nafcillin or vancomycin, proved most effective.	The study found that cephalothin and cephalexin prophylaxis failed to prevent SRVC-related CSF infections, which required device removal and treatment with IV antibiotics like vancomycin, methicillin, gentamicin, and chloramphenicol. Due to frequent *S. epidermidis* infections, prophylaxis was switched to nafcillin or vancomycin for better coverage.
Bayston et al., 1987	Retrospective cohort	Laboratory study on *Staphylococcus epidermidis* antimicrobial resistance in infected indwelling devices.	Intraventricular vancomycin (20 mg/day) combined with shunt removal achieved a 92% cure rate in gram-positive ventriculitis.	Demonstrates the efficacy of intraventricular vancomycin for ventriculitis, especially with adjunctive systemic antibiotics and device removal.
Williamson et al., 2001	Review article	NA	Describes pathogenesis of biofilm-associated infections in ventriculoperitoneal shunts.	Highlights biofilm formation as a key factor in *S. epidermidis* ventriculitis and explains why ventriculitis often requires combination antibiotic therapy and device removal for effective treatment.
Martinez et al., 2002	Prospective cohort	25 patients	Procalcitonin levels were not significantly elevated in ventriculitis but were higher in bacterial meningitis.	Suggests PCT is not a reliable biomarker for ventriculitis, highlighting the diagnostic challenges in distinguishing bacterial ventriculitis from other CNS infections.
Beer et al., 2009	Prospective observational	20 patients with EVD-related ventriculitis	Intraventricular vancomycin (10–20 mg daily) combined with systemic antibiotics and EVD replacement led to successful treatment in 85% of cases.	Supports the use of intraventricular vancomycin in combination with systemic therapy and device management for treating EVD-related ventriculitis.

Table 1. Key Studies on CSF Shunt and EVD-Related Ventriculitis (*Continued*)

Studies on Ventriculitis in EVD and Shunt-Related Infections				
Authors and Publication Year	**Study Type**	**Study Participants**	**Key Findings**	**Relevance to Ventriculitis in EVD Patients**
Stoodley et al., 2010	Experimental study	NA	Demonstrated biofilm resistance mechanisms, showing that *S. epidermidis* biofilms significantly reduce immune response activation and antibiotic penetration.	Supports intraventricular antibiotic administration, particularly for biofilm-associated ventriculitis cases.
Ng et al., 2012	Systematic review	NA	Compared intraventricular versus systemic antibiotic therapy, concluding that direct CSF antibiotic administration leads to better bacterial clearance in ventriculitis.	Supports adjunctive intraventricular therapy for improved outcomes.
Stevens et al., 2012	Review article	NA	Examines the pathogenesis, treatment, and implications of *S. epidermidis* ventriculoperitoneal shunt-related infections.	Discusses biofilm-associated infections and highlights treatment challenges for ventriculitis cases related to VP shunts.
Flint et al., 2013	Retrospective cohort	262 EVD placements analyzed over 6 years	Implementation of a standardized infection control protocol reduced the incidence of CSF culture positivity from 9.8% to 0.8%.	Demonstrates the effectiveness of infection control measures, highlighting that strict protocols reduce ventriculitis risk.
Gordon et al., 2014	Case-control study	200+ patients	Identified prolonged catheter duration, multiple catheter exchanges, and repeated CSF sampling as major risk factors for ventriculitis.	Supports the need for limited EVD manipulation and early catheter removal to reduce infection risk.
Jamjoom et al., 2017	Prospective multicenter	495 patients with EVDs across the UK and Ireland	Identified risk factors for EVD-related infections, including prolonged catheterization and frequent manipulations; recommended strategies to mitigate these risks.	Provides insights into risk factors and preventive strategies for EVD-related ventriculitis.
Rao et al., 2018	Prospective observational study	55 patients with suspected bacterial infections	Proposed sTREM-1 as a novel biomarker with high specificity for detecting bacterial CNS infections, distinguishing them from non-infectious causes.	Introduces sTREM-1 as a potential rapid diagnostic tool for ventriculitis, which may improve early detection and guide timely treatment
Rodríguez-Lucas., 2018	Case study	1 patient with meticillin- and linezolid-resistant *S. epidermidis* strain	Multidrug-resistant S. epidermidis ventriculitis was treated successfully with daptomycin combined with meticulous EVD management.	Highlights the role of alternative therapies and device management for treating MDR *S. epidermidis* ventriculitis.

Table Description: Summary of major studies highlighting diagnostic challenges, treatment approaches (including intraventricular antibiotics and device removal), and the role of *S. epidermidis* biofilms in ventriculitis.

Figure 2. Timeline of Management and Antibiotic Initiation. This table summarizes the patient's antibiotic regimen by day, highlighting the timing of rifampin addition in the context of persistent CSF infection and its impact on culture results.

an identifiable source, vancomycin was empirically initiated due to concern for an EVD-related infection.

Clinical Course

Following EVD placement, the patient developed progressively worsening symptoms, including fluctuating fevers and an increased WBC count, suggestive of a developing infection. CSF cultures obtained on post-admission day 6 revealed gram-positive cocci, later identified as *S. epidermidis*. While often considered a contaminant, it is also a significant pathogen in patients with indwelling medical devices. Despite treatment with IV Vancomycin 1250 mg Q24hrs, the patient's condition worsened. He experienced persistent febrile episodes and leukocytosis, and his clinical status further deteriorated with evidence of a non-occlusive pulmonary embolism, a common complication in ICU patients with prolonged immobilization. Repeated CSF cultures continued to grow *S. epidermidis*, suggesting a biofilm-related infection resistant to standard antibiotic treatment. Due to the persistent infection, the planned ventriculoperitoneal (VP) shunt placement was delayed. However, ongoing positive cerebrospinal fluid (CSF) cultures suggested biofilm-associated resistance, prompting the addition of rifampin 600 mg Q24hrs via NGT to the antimicrobial regimen. Rifampin's ability to penetrate biofilms and cross the blood-brain barrier made it a critical adjunctive therapy. Its lipophilic properties enable it to reach bacteria embedded within biofilms, initiating activity within hours, although prolonged exposure over 24–48 hours is typically required to disrupt the biofilm matrix. Notably, within 24 hours of initiating rifampin, CSF cultures converted to negative, marking a pivotal turning point in infection control. A summary of antibiotic changes and the timing of rifampin initiation is outlined in Figure 2.

Discussion

Ventriculitis is a serious and often challenging infection following EVD or shunt placement. Despite ongoing research, standardized treatment guidelines remain lacking, and management strategies vary across institutions. The presence of bacterial biofilms, particularly with *S. epidermidis*, contributes significantly to persistent infection and antibiotic resistance, complicating eradication efforts. Given these complexities, a multimodal approach that includes intraventricular antibiotic therapy, risk factor mitigation, optimized antimicrobial selection, and infection control strategies are essential for effective treatment.

Risk Factors for Infection and Mortality

The development of ventriculitis following EVD placement is influenced by multiple risk factors, ranging from device-related variables to patient-specific conditions. Identifying these risks early is crucial to preventing infections and improving patient outcomes.[5] Studies have identified prolonged catheter duration and multiple exchanges as major contributors to ventriculitis incidence.[6] Similarly, research has demonstrated that frequent CSF sampling increases bacterial contamination risk.[6] These findings underscore the importance of minimizing unnecessary interventions and adhering to strict sterile protocols.[6]

Optimizing Antibiotic Therapy for Biofilm-Associated Ventriculitis

Studies have demonstrated higher success rates with direct antibiotic administration into the CSF, particularly in biofilm-associated ventriculitis.[7] A systematic review found that intraventricular vancomycin led to faster bacterial clearance and improved outcomes compared to systemic antibiotics alone.[7] Similarly, intraventricular or intrathecal antibiotic administration has been shown to significantly reduce mortality rates in ventriculitis patients.[8] Although vancomycin remains the first-line agent, its biofilm penetration is limited.[9] Combination regimens, such as vancomycin and rifampin, have been proposed to enhance efficacy.[7,10] Rifampin, known for its ability to penetrate biofilms, has been shown to improve bacterial eradication when used alongside vancomycin.[4] Additionally, ceftaroline has emerged as a potential alternative for treating multidrug-resistant (*MDR S. epidermidis*) infections when standard therapies fail.[11] These findings underscore the importance of selecting optimized antimicrobial regimens to overcome biofilm-associated resistance and improve patient outcomes.

Foreign Device Removal and Infection Control Strategies

In cases where antibiotic therapy alone fails, device removal becomes necessary to eliminate biofilm-associated infections.[4] Studies have consistently shown that prolonged device retention is associated with higher treatment failure rates.[12] Research has demonstrated that biofilms contribute to recurrent infections despite appropriate antibiotic therapy, supporting early catheter removal in refractory cases.[12] Strict infection control protocols have been shown to significantly reduce ventriculitis rates, reinforcing the importance of minimizing catheter duration and manipulation.[6] While antibiotic impregnated catheters (AICs) have been introduced as a preventive measure, recent findings suggest that AICs do not significantly reduce biofilm formation, challenging their routine use in infection prevention.[11] These studies support a comprehensive infection control approach, including: minimizing catheter duration, reducing unnecessary CSF sampling, prioritizing device removal in cases of persistent infection.

Novel Biomarkers for Infection Detection

Accurate early detection of ventriculitis remains a clinical challenge, as standard CSF parameters such as WBC, and protein levels often lack specificity.[13] Recent studies have explored biomarker-based diagnostics as a potential tool to improve infection detection and differentiation from other CNS conditions.[9] Procalcitonin (*PCT*) has been investigated as a biomarker, but results showed that PCT levels were not significantly elevated in ventriculitis cases, making

it an unreliable marker for this condition.[9] However, *sTREM-1* has emerged as a promising biomarker, demonstrating a strong correlation with bacterial ventriculitis and offering higher specificity than traditional CSF parameters.[9] These findings suggest that biomarker-based diagnostics, particularly *sTREM-1*, may allow for earlier identification and treatment of ventriculitis. Future research should aim to validate these markers in larger patient populations and determine cutoff values for clinical application.

Conclusion

This case illustrates the complexity of managing *S. epidermidis* ventriculitis, particularly in patients with indwelling CNS devices like EVDs. Biofilm-associated infections often require prolonged antimicrobial treatments due to their resilience.[3] In this case, adding rifampin to vancomycin was pivotal for overcoming biofilm defenses and achieving infection resolution. [7] Rifampin's mechanism targets bacterial RNA polymerase, inhibiting protein synthesis and reducing bacterial viability within the biofilm matrix.[9] Specifically, rifampin binds to the RNA polymerase's beta subunit, blocking RNA transcription and impacting bacterial survival even in dormant cells.[3] Its lipophilic nature further enhances biofilm penetration, allowing rifampin to access both active and dormant bacteria, unlike many other antibiotics.[4] The combination of rifampin with vancomycin, which disrupts biofilm structure, highlights the value of synergy in biofilm-associated infections where monotherapy may be ineffective.[9] Vancomycin's disruption of the biofilm matrix enhances rifampin's reach into biofilm depths, allowing it to target bacteria in lower metabolic states a challenge in biofilm treatments.[9] Given the higher morbidity and mortality associated with biofilm-related infections in CNS devices, there is a need for improved treatment protocols and innovative management strategies.[15] Future studies should optimize antibiotic regimens for biofilm-related infections and explore alternative strategies like novel anti-biofilm agents or device coatings that prevent bacterial colonization. An expanded understanding of biofilm pathophysiology and rifampin's specific actions can enable more effective management of these challenging infections.

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From: University of Incarnate Word, San Antonio, Texas
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