Successful Salvage of Ventriculoperitoneal Shunt Using Rifampicin in *Staphylococcus epidermidis* Infection

Yotam D. Eshel MD[1], Emily H. Kestenbaum MD[2], Keren B. Rochwerger MD[2], Mickey Gideon MD MBA[3], Aya Khalaila MD[1], and Lior Carmon MD[2]

[1]Department of Pediatrics Hematology and Oncology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel
[2]Department of Pediatrics, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel
[3]Department of Neurosurgery, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

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Ventriculoperitoneal shunt (VPS) placement is a standard treatment for pediatric hydrocephalus. However, infection remains a significant complication, occurring in 5–27% of cases, with coagulase-negative staphylococci (CONS) and *Staphylococcus aureus* being the most common pathogens [1]. Current guidelines recommend empirical antibiotic treatment and surgical removal of the infected shunt [2]. While shunt removal and replacement are recommended for managing shunt infections, these procedures subject the child to the risks associated with multiple surgeries. However, recent approaches have suggested that in certain cases antibiotics alone may suffice, thus avoiding the risks of surgery [3].

We describe two children with VPS infections caused by CONS who were successfully treated with vancomycin and rifampicin alone, without the need for shunt removal.

PATIENT DESCRIPTION

PATIENT 1

An 11-month-old baby of Bedouin origin was admitted to the hospital with 2 days of fever and irritability. His past medical history included a premature birth at 26 weeks. During his admission to the neonatal intensive care unit (NICU), he presented with respiratory distress syndrome, bronchopulmonary dysplasia, periventricular leukomalacia, and sepsis due to *Staphylococcus aureus* and *Candida*. At 8 months, he developed meningitis and ventriculitis due to *Candida albicans*, which was complicated by hydrocephalus. He completed a long course of treatment with amphotericin B and underwent VPS insertion.

At his most recent admission, notable findings at physical examination included a high temperature of 38.5°C, irritability, and a wound on the scalp above the shunt trajectory. Diagnostic workup revealed a normal white blood cell (WBC) count, moderate elevation of C-reactive protein (CRP) (6 mg/dl), and a head computed tomography (CT) scan showing no changes in the size of the ventricles or the position of the VPS. Neurosurgeons were consulted for a shunt tap, and 15 ml of clear CSF was aspirated under low pressure and sent for analysis, culture, and pan-bacterial/pan-fungal polymerase chain reaction (PCR). Fluid analysis showed nucleated cells at 148 × 10^6 cells/L (normal < 5 × 10^6 cells/L), with 42% neutrophils, 47% lymphocytes, 53 red blood cells (RBCs), glucose of 40 mg/dl (normal > 50 mg/dl), and protein of 261 mg/dl (normal < 40 mg/dl). Empiric antibiotic treatment was initiated with vancomycin, ceftazidime, and fluconazole. The Gram stain revealed Gram-positive cocci. A final culture and pan-bacterial PCR were significant for *Staphylococcus epidermidis*, sensitive to rifampicin

Due to his relatively good clinical condition, we decided to continue antibiotic treatment without removing the VPS, reserving shunt removal only if the antibiotic treatment failed. After the bacteria were isolated, rifampicin was added and ceftazidime was discontinued. After 72 hours of treatment, the patient was afebrile, less irritable, and had an improved appetite, with CRP decreasing to 4 mg/dl. After 7 days of treatment, another shunt tap was

performed, revealing clear CSF with nucleated cells at 115 × 10^6, 25% neutrophils, 65% lymphocytes, protein at 146 mg/dl, and glucose at 33 mg/dl. Gram stains and cultures were negative. Ten days later, another shunt tap revealed 40 cells mm^3, 20% neutrophils, 22% mononuclear cells, 57% lymphocytes, glucose at 40 mg/dl, and protein at 64 mg/dl. Gram stains and cultures were again negative.

The patient completed 23 days of intravenous vancomycin and oral fluconazole in addition to 21 days of intravenous rifampicin without any adverse reaction to the treatment. He remained well for the next 45 months without any recurrence of VPS infection.

PATIENT 2

A 2.5-year-old male of Bedouin origin was admitted to the hospital with fever, weakness, and irritability. His past medical history was significant for congenital hydrocephalus, seizures, severe hypotonia, severe cognitive delay, and failure to thrive. The underlying cause of his overall condition remains unknown. One month prior to admission, he underwent VPS replacement due to shunt malfunction.

Diagnostic workup revealed a WBC count of 19 × 10/mm^3 with 90% neutrophils and an initial CRP level of 19 mg/dl. Chest X-ray showed no local consolidation. A head CT showed no acute changes compared to an image taken one month prior, right after the VPS replacement. Neurosurgeons were consulted for a shunt tap, and 5 ml of clear CSF fluid was aspirated under low pressure and sent for analysis and culture. Fluid analysis revealed 62 cells/mm^3, 60% lymphocytes, 22% segments, glucose of 22 mg/dl, and protein of 61 mg/dl. CSF Gram stain revealed Gram-positive cocci, and final culture was significant for *Staphylococcus epidermidis*, sensitive to rifampicin.

Initially, the patient started vancomycin (20 mg/kg every 6 hours) and intravenous ceftriaxone (100 mg every 24 hours). Due to the patient's overall good condition, it was decided to continue with antibiotics and consider shunt removal only if the antibiotic treatment failed. After 72 hours of treatment, the patient still had a fever but no signs of discomfort or irritability, and his WBC count normalized with a CRP level declining to 7 mg/dl. Another shunt tap was performed, yielding clear CSF with similar parameters. CSF Gram stain again showed Gram-positive cocci, and final culture was significant for *Staphylococcus epidermidis*.

At this point, rifampicin was added and ceftriaxone was discontinued. It was decided to give another trial for shunt salvage. Two days after the initiation of rifampicin, the patient became afebrile, and the CRP declined to 3.3 mg/dl. According to his parents, the patient returned to his baseline condition. Ten days after the second shunt tap, a third tap revealed no cells, normal protein and glucose levels, and sterile CSF culture.

The patient completed a total of 25 days of treatment with vancomycin and 21 days with rifampicin, without any adverse reaction to the treatment. Over the past 3 years the patient has been followed at our institute, with no evidence of VPS infection during this period.

COMMENT

We report on the clinical features and treatment outcomes of two patients with *Staphylococcus epidermidis* VPS infections who were successfully treated with vancomycin and rifampicin, thus avoiding the need for shunt removal. In the second case, the addition of rifampicin was notably associated with improvement in the clinical condition followed by sterilization of the CSF.

The Infectious Diseases Society of America (IDSA) guidelines for VPS infections recommend the complete removal of the infected VPS and its replacement with an external ventricular drain [2]. While this strategy boasts a success rate of up to 96%, it subjects patients to 1–2 additional surgeries, with both predictable and unpredictable perioperative complications.

A less common strategy involves initially treating the infection with antibiotics alone and reserving shunt removal for cases where antibiotic treatment fails [3]. There are no recent prospective studies comparing the outcomes of antibiotic treatment followed by shunt removal versus antibiotic treatment with attempted shunt salvage, with shunt removal only in the case of treatment failure. Reported success rates for this approach vary widely, ranging from 15% to 100% [3].

Rifampicin belongs to the ansamycin family of antibiotics. Its antibacterial activity results from high-affinity binding to the DNA-dependent RNA polymerase of prokaryotic cells leading to the inhibition of RNA synthesis. It is a potent broad-spectrum antibiotic with high CSF penetration and antibiofilm activity. It is a key component of anti-tuberculosis therapy and is known for its anti-biofilm activity, which is beneficial in orthopedic device-related infections [4]. In addition, several clinical trials have investigated the

efficacy of rifampicin-coated VPS in preventing shunt infections.

We identified two case reports in the English literature of VPS infections managed without shunt removal by adding rifampicin to the antibiotic regimen [5]. In both cases, however, the pathogen was *Streptococcus.*

Our decision to add rifampicin to the regimen was based on its high CSF penetration, its antibiofilm activity, and the fact that it has no drug interaction with vancomycin. According to the IDSA guidelines for the treatment of ventriculitis, the recommended duration of antibiotic therapy is 14 days from the time of obtaining a sterile culture. In our cases, at least 14 days of treatment were completed after achieving sterile CSF cultures [2]. In addition, due to the decision to retain the shunt and the absence of adverse effects in the first patient, an extra 3 days of antibiotic therapy were administered. Prolonged treatment with rifampicin can lead to the development of resistance, particularly when used as monotherapy. To reduce the risk of resistance, our patients were treated with a combination of rifampicin and vancomycin. Considering the potential for pharmacokinetic interactions between rifampicin and vancomycin, serum vancomycin levels were monitored regularly to maintain therapeutic efficacy and to avoid potential toxicity.

Although shunt removal is generally considered the default treatment for VPS infections and is also the approach recommended by current guidelines, it is possible that with appropriate antibiotic regimens and close monitoring, some carefully selected patients might benefit from the strategy of treating VPS infection with antibiotics alone, reserving shunt removal for cases of antibiotic failure.

Further carefully designed studies are needed to identify which patients might be effectively managed with antibiotics alone, potentially sparing them from the risks associated with shunt removal.

Correspondence

Dr. Y. Eshel
Dept. of Pediatrics Hematology and Oncology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva 84101, Israel
Phone: (972-8) 640-3839
Email: eshely77@gmail.com

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Capsule

Determinants of successful AAV-vectored delivery of HIV-1 bNAbs in early life

Ardeshir and co-authors hypothesized that neonatal delivery of bNAbs using adeno-associated virus (AAV) could provide durable HIV-1 immunity during infancy. Here, using infant rhesus macaques (*Macaca mulatta*) as a model, they show that a one-time administration of an AAV vector encoding bNAb 3BNC117 at birth led to sustained bNAb expression for more than three years without redosing. This approach significantly protected both infant and pre-adolescent rhesus macaques from infection with simian–human immunodeficiency virus in mucosal challenge models that mimic HIV-1 transmission through breastfeeding and sexual intercourse. Age at the time of AAV-3BNC117 administration was a main determinant of success and was inversely correlated with the incidence of host anti-drug antibodies that restricted bNAb expression. Consistent with principles of neonatal tolerance, newborn rhesus macaques exhibited higher levels of bNAb expression than older infants and juveniles following AAV-3BNC117 dosing. Furthermore, in utero exposure to recombinant 3BNC117 suppressed anti-drug antibodies and improved AAV-vectored delivery of this bNAb in older infants. Thus, our results suggest that neonatal and fetal immunological tolerance can be leveraged to improve postnatal AAV delivery of HIV-1 bNAbs in primates. Since years-long HIV-1 immunity can be generated in rhesus macaques from a one-time AAV vector administration at birth, future studies should evaluate the ability of this strategy to prevent perinatal and adolescent HIV-1 infections in humans.

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Eitan Israeli