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# Fellows Column: Case Report: Neonatal Intraventricular Hemorrhage in *E.coli* K1 Meningitis

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**Background:**

Neonatal meningitis is a rare yet devastating disease that can carry profound consequences. It results in acute inflammation of neonatal brain tissue during the first 28 days of life. (1) Compared to other ages, neonates are at the most significant risk for meningitis; therefore, rapid diagnosis and treatment are imperative.

Neonatal meningitis is categorized as being either early or late onset. Early-onset infections, generally occurring within the first 72 hours after birth (or within the first six days for Group B Streptococcus), typically result from vertical transmission from the maternal genital tract flora. Late-onset infections, occurring after six days of age, suggest maternal flora colonization or acquisition from nosocomial or community-acquired sources. (2, 3) Group B Streptococcus (GBS) is the most common cause of neonatal meningitis and sepsis, responsible for over 40% of early-onset infections. (4) *Escherichia coli*, the second most common pathogen, has accounted for a growing number of cases; as many as 30% of all cases of neonatal meningitis in contemporary reports ascribe this bacterium as the causative pathogen.

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Several risk factors can increase the likelihood of developing neonatal meningitis. (5) These include prematurity, maternal rectovaginal GBS colonization, chorioamnionitis or maternal fever, premature rupture of membranes, prolonged rupture of membranes (>18 hours), invasive fetal monitoring, VLBW (<1500 g), prolonged hospitalization, and presence of external devices (e.g., reservoirs, shunts, catheters). (5) Research has demonstrated that the invasiveness of the *E. coli* pathogen is best related to the K1 antigen rather than the O and H antigens. (6) While it is known that the K1 capsular antigen increases virulence, its expression is thermoregulated and interestingly turns off when the bacteria reach the brain. (7) Given the complexity and lethality of *E. coli* K1 meningitis, we present a case of this pathogen's virulence accompanied by a rapidly advancing intraventricular hemorrhage.

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***Perinatal Challenges: Maternal Health Profile***

A 40-year-old G4P4 woman was admitted due to early labor with membrane rupture three days prior to delivery. The mother's medical history revealed chronic hypertension, hypothyroidism, and type 2 diabetes. Her medications included aspirin, insulin, and levothyroxine. The mother's blood type was O positive, and the fetus's blood type was A positive, with a +1 Coombs test. As part of the preterm labor treatment protocol, the mother received ampicillin, magnesium hydralazine, and betamethasone.

***Neonatal Clinical Course:***

A 34-week-old male infant born at 1475 grams by cesarean section was admitted to the Neonatal Intensive Care Unit (NICU) due to respiratory distress and presumed sepsis. APGAR scores were 8 and 8 at 1 and 5 minutes, respectively. On admission, a blood culture was obtained due to prolonged rupture of membranes and

the baby started on Ampicillin and Gentamicin. The initial complete blood count (CBC) showed a white blood cell count (WBC) of 2.1 x $10^3$/µL (36% neutrophils with an absolute neutrophil count [ANC] of 882), hemoglobin (HgB) of 11.8 g/dL, hematocrit (Hct) of 34.7%, and a platelet count of 34,000/µL. CRP was 19.6. Due to the persistent thrombocytopenia, platelet transfusion was administered. The patient also received IVIG x3. The WBC differential initially showed 40% segmented neutrophils and 12% bands. After 12 hours, the segs and bands increased to 68% and 17%, respectively, indicating a notable left shift. A lumbar puncture obtained after admission revealed bloody, cloudy-appearing CSF with elevated WBC count of 250 cells/µL, RBC count of 375,000 cells/µL, total protein of 565 mg/dL, and a very low glucose level of less than 4.0 mg/dL. Cefepime was added at this time, and Ampicillin was increased to meningitic doses. CSF Gram stain showed Gram negative rods, and the culture grew *E. coli* K1 sensitive to gentamicin and cefepime. The patient remained on gentamicin and cefepime while ampicillin was discontinued. Of note, blood cultures remained negative throughout the hospital course.

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Head ultrasound (HUS) on day of life three (DOL #3) showed a small 5 x 1 x 3 mm echogenic focus within the left lateral ventricles, deemed to be of indeterminate clinical significance. Repeat HUS on DOL #4 showed a decreased 1 x 1 x 4 mm echogenic focus within the left lateral ventricle, indicating an improving grade 1 intraventricular hemorrhage (IVH). HUS on day of life six showed a grade 3 IVH with enlarged dilated bilateral ventricles. Electroencephalography (EEG) findings were abnormal, showing a generalized but asymmetric background slowing, consistent with diffuse but nonspecific cerebral dysfunction; however, no seizure activity was noted. Gentamicin was discontinued on DOL #6 but was promptly restarted the following day secondary to tachycardia and temperature instability.

On DOL #7, another HUS was performed and revealed a right-sided grade 4 germinal matrix hemorrhage (GMH) and a left-sided grade 2 or 3 GMH, along with bilateral dilation of the ventricles and the third ventricle. At this time, the parents were presented with the option of comfort care due to the likelihood of a poor prognosis. The parents, however, chose to proceed with full medical management. Many blood products and platelets were given due to thrombocytopenia from sepsis. On DOL #12, repeat HUS showed worsening moderate-to-severe ventriculomegaly with the left-sided GMH mildly increased in size (see Figure). The right-sided germinal matrix was not visualized at the time. Repeat EEG the following day showed burst suppression >100 bursts/hour.

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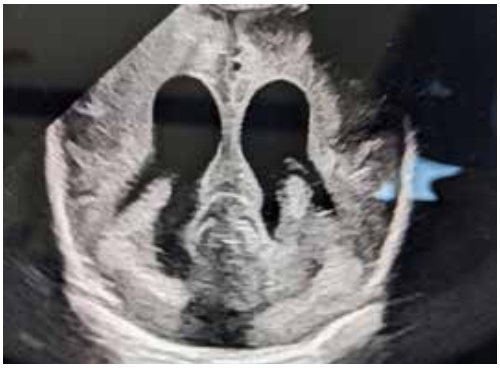
The patient's respiratory status was also a primary concern, leading to the implementation of non-invasive mechanical ventilation (NIMV) and high-frequency oscillatory ventilation (HFOV). The baby experienced respiratory challenges throughout his time in the NICU, necessitating constant adjustments in ventilator settings and fluid management. Caffeine was administered for additional apnea of prematurity. Ventilation support via HFOV was continued for five days before switching to Synchronized Intermittent Mandatory Ventilation-Volume Guaranteed (SIMV-VG).

After a lengthy and challenging hospital course, the patient was transferred to a higher-level care facility for further evaluation. Upon admission, a repeat HUS demonstrated an evolving grade 3/4 GMH with no new hemorrhage; however, increased areas of cystic change involving the periventricular leukomalacia became evident. An MRI of the head was also promptly performed and showed the presence of widespread leptomeningeal enhancement across both cerebral and cerebellar hemispheres coupled with sporadic enhancement in the bilateral frontal lobes and deep gray nuclei. These findings were likely associated with the previously diagnosed *E. coli* meningitis. As the patient's disease progressed, he also developed central diabetes insipidus, metabolic acidosis, bilateral renal hydronephrosis, and hypophosphatemia that required rapid treatment.

After multiple discussions involving the family, NICU team, Neurology, and Neurosurgery, a collaborative decision was made on DOL #29 to transition him into comfort care. A morphine drip was started for comfort prior to extubation. The patient underwent extubation and died while in the mother's arms with the father at the bedside.

**Figure.** Repeat HUS images on DOL #12 showing worsening moderate-to-severe ventriculomegaly with the left-sided GMH mildly increased in size. The right-sided germinal matrix was not visualized at the time.



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This patient's case illustrates the complexity of neonatal *E. coli* meningitis. Frequently, this pathology requires a multidisciplinary approach to care and continuous monitoring and adjustments in the care plan. Even then, as this case highlights, this diagnosis can have devastating consequences.

**Discussion:**

This patient's course highlights the complications and devastating effects of neonatal meningitis. Over 100 different *E. coli* capsular antigens have been recognized, with the K1 antigen strain responsible for 77% of neonatal *E. coli* meningitis cases. (6) As the most common cause of gram-negative neonatal meningitis, *E. coli* K1 has a reported mortality rate of 10–15%, with neurological sequelae in 30–50% of cases. (8) The most commonly reported clinical signs are temperature instability, irritability or lethargy, and poor feeding or vomiting.

The high morbidity and mortality associated with neonatal meningitis caused by the *E. coli* K1 antigen, in particular, highlights the limited efficacy of the current standard broad-spectrum antibiotic regimen. Researchers have successfully treated this pathogen in rat models by modifying the *E. coli* phenotype through bacteriophage-derived endolaseE, eliminating the K1 capsular antigen. (9) This alteration enables the host immune complement system to respond effectively. This research underscores new approaches to treating meningitis, as agents that address infections by modifying the bacterial phenotype could be more efficacious than relying on pathogen killing or growth inhibition. The evolving nature of bacterial infections has prompted the reevaluation of conventional antibiotic treatment modalities, emphasizing a growing need to diversify treatment approaches.

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An essential discussion regarding neonatal meningitis is the etiology of the disease and the routes of transmission. One manner in which neonates can acquire *E. coli* meningitis is through vertical transmission from their mothers during childbirth. This can happen when the baby comes into contact with the mother's infected genital or intestinal tract during delivery. In this case, our

patient may have been exposed to the mother's gut flora during the three days of the prolonged rupture of the membrane.

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In addressing the imperative issue of neonatal meningitis, a crucial focus lies in enhancing early diagnostic methods, identifying preventative measures, and understanding the ethical considerations surrounding a newborn facing a severe illness. It is also essential to recognize the limitations in treating advanced stages of meningitis; advocating for continued research and innovation is crucial. An important caveat to our case presentation is that it represents a singular occurrence of neonatal meningitis. It is important to note that this patient's disease course is unique, and the presentation of *E. coli* neonatal meningitis can vary significantly on a case-by-case basis.

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