



**Case Report**

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# Early Onset *Escherichia coli* Sepsis and Severe Intraventricular Hemorrhage in Extremely Premature Infants: Cases Series and Literature Review



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## Abstract

**Background:** Widespread use of intrapartum antibiotics for Group B streptococcal prophylaxis has effectively reduced early onset gram-positive sepsis, possibly at the cost of increasing risk of *Escherichia coli* sepsis and its complications in very low birth weight infants. Chorioamnionitis and early onset sepsis are among the predisposing factors for germinal matrix hemorrhage, however there is a lack of reports on the emerging role of *E.coli* sepsis as a risk factor for intraventricular hemorrhage (IVH) compared to other organisms. **Case presentation:** We report a possible association between early onset resistant *E. coli* sepsis and severe IVH in a series of 5 preterm infants born in our regional NICU in Alberta between January and August 2015. All five infants had a history of premature rupture of membrane >24 hours before delivery, histological chorioamnionitis and maternal intrapartum prophylaxis with Ampicillin and Erythromycin. *E.coli* strains isolated from blood and CSF were resistant to empiric antibiotics commonly used in our NICU. All infants developed severe IVH (grade III/IV) with considerable sequelae. **Conclusion:** Early onset *E.coli* sepsis in extremely premature infants may be associated with increased risk of severe IVH and subsequent white matter injury. The temporal relationship between *E.coli* sepsis and IVH should be further evaluated in a large prospective cohort study.

**Keywords:** Neonatal Sepsis; Intraventricular haemorrhage; *Escherichia coli*

**Abbreviations:** VLBWI : Very Low Birth Weight Infants; IVH: Intraventricular Hemorrhage; *E.coli*: *Escherichia coli*; GBS: Group B Streptococcal prophylaxis; EOS: Early onset sepsis; CSF: Cerebrospinal fluid

## Background

Premature infants are prone to develop early sepsis because of immature immunity or may be born premature secondary to maternal intra-amniotic infection. Early onset sepsis (EOS) is defined as infection caused by bacterial pathogens, transmitted vertically from mother to infant before or during delivery, thus isolated from blood or cerebrospinal fluid (CSF) within 72 hours of birth [1]. In 2002, CDC recommended screening recto-vaginal cultures of pregnant women at 35-37wks gestation and chemoprophylaxis to women positive for Group B Streptococcus (GBS) to reduce the risk of neonatal infection [2].

When delivery is imminent before a screening test is done, it has been recommended to provide GBS prophylaxis until cultures rule out GBS colonization or the infant is born. With the advent of these guidelines, the rate of EOS GBS sepsis has been effectively

reduced to 0.98 per 1000 live-births while non-GBS EOS has gained predominance among the causes of mortality and morbidity, especially in premature infants. [2,3] More premature the infant is, the greater is the risk and severity of the disease. *Escherichia coli* has emerged as the most common cause of preterm EOS and gram-negative sepsis in neonates while GBS continues to be the commonest pathogen affecting term infants [3].

A narrow spectrum antibiotic such as Penicillin is the agent of choice for GBS prophylaxis but often in settings of preterm premature rupture of membrane (pPROM) a broad-spectrum agent such as Ampicillin is used at doses that would prolong latency with adequate GBS coverage [2]. In our center, irrespective of GBS colonization status, mothers who have threatened preterm labour before 32wks with pPROM are given

parenteral ampicillin and erythromycin for 48 hours followed by amoxicillin and erythromycin orally for 5 days [4]. Although effective in reducing overall incidence of EOS, administration of intrapartum broad-spectrum antibiotics has raised concerns about selective colonization by antibiotic resistant organisms [5]. In premature infants, prevention of *E coli* EOS continues to be a challenging. *E coli* is associated with more fulminant disease than non-*E coli* gram-negative organisms [6]. Early onset *E coli* sepsis in premature infants may result in systemic involvement as evidenced by thrombocytopenia and hypotension requiring aggressive interventions such as fluid boluses and inotropes, increasing the risk of germinal matrix hemorrhage in these infants. We report a possible association between early onset *E coli* sepsis in 5 extremely preterm infants and severe intraventricular hemorrhage (IVH).

**Case Presentation**

We report a series of 5 very low birth weight infants (VLBWI) with early onset *E coli* sepsis in our regional NICU between

January and August 2015. In all cases there was history of pPROM more than 24 hours prior to delivery and mothers had received intrapartum antibiotics as per unit policy and complete courses of antenatal corticosteroids. All infants had positive blood cultures growing *E. coli* within 12-16 hours after birth. Two cases had culture proven *E Coli* meningitis and one had positive eye swab culture for *E coli* as well as positive sputum cultures for the same organism. Maternal and perinatal characteristics of the infants are enumerated in Table 1. Isolated strains in cases 1-3 were resistant to Ampicillin and Ciprofloxacin but sensitive to Gentamicin and 3<sup>rd</sup> generation cephalosporin. Twins (Case 4 & 5) were infected with multidrug resistant extended spectrum beta lactamase (ESBL) producing *E.coli* sensitive only to Carbapenem. *E coli* strains isolated from CSF were Ampicillin resistant but sensitive to cephalosporin and Carbapenem. Of three surviving infants, two were successfully treated with monotherapy of Cefotaxime and Meropenem for 10 days respectively, one was initially treated with Meropenem and later switched to Cefotaxime for 3 weeks to treat meningitis.

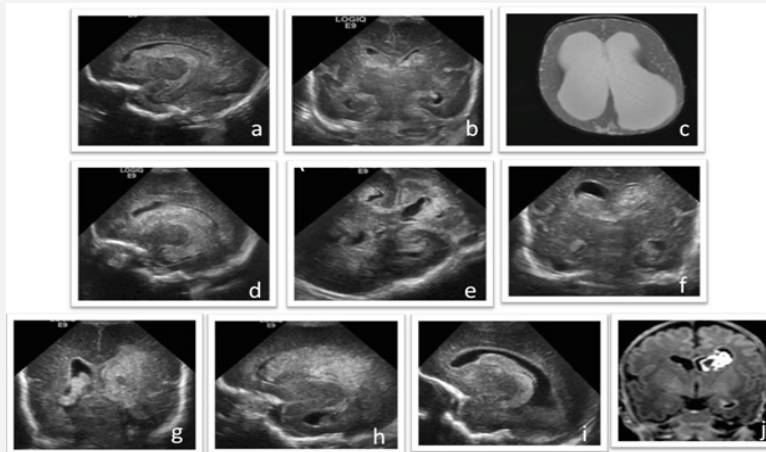
**Table 1:** Demographic Characteristics of the Cases with Clinical course and Outcome.

	Case 1	Case 2	Case 3	Case 4	Case 5
Gestation age, weeks	26 <sup>+1</sup>	25 <sup>+5</sup>	27 <sup>+1</sup>	24 <sup>+0</sup>	24 <sup>+0</sup>
Birth weight, g	785	750	1120	580	760
(centile)	(50 <sup>th</sup> )	(50-90 <sup>th</sup> )	(50-90 <sup>th</sup> )	(10-50 <sup>th</sup> )	(50 <sup>th</sup> )
Birth order	Singleton	Singleton	Singleton	Twin 1	Twin 2
Maternal age (years)	24	35	39	38	38
Gender	Female	Female	Female	Male	Male
Maternal infection	Asymptomatic bacteruria <i>E. coli</i> UTI	None	<i>Group B streptococcal</i> colonization	Asymptomatic bacteruria	Asymptomatic bacteruria
Mode of delivery	Vaginal	Caesarean	Caesarean	Vaginal	Vaginal
PPROM, days	4	12	9	2	2
Intrapartum antibiotics, days	<7	>7	>7	< 7	< 7
Apgar at 5min	6	7	5	8	7
Chorioamnionitis	Yes	Yes	Yes	Yes	Yes
Duration of ventilation, days	7	10	-	-	21
Parenteral Nutrition, days	9	13	-	-	15
Hypotension requiring ionotropes	No	No	Yes	Yes	Yes
Significant PDA	No	Yes, Ibuprofen	Yes, not treated	Yes, not treated	Yes, Ligation
Lowest platelet count	122	45	49	22	58
Mortality	No	No	Yes (day 6)	Yes (day 12)	No
Meningitis	No	Yes	Yes	No	No
Antibiotics	Cefotaxime	Meropenem	Meropenem	Meropenem	Meropenem
Intracranial Hemorrhage	Bilateral Grade II, PHH	Bilateral Grade II	Bilateral Grade III & cerebellar	Grade II (Rt) & Grade IV (Lt)	Grade II (Rt) & Grade IV (Lt)
Periventricular Leukomalacia	Rt frontal lobe cyst	No	Non-cystic echogenicity	No	Bilateral cystic

**Abbreviations:** IVH: Intraventricular Hemorrhage; PDA: Patent Ductus Arteriosus; UTI: Urinary Tract Infection; PPROM: Prolonged Premature Rupture of Membrane; Rt: Right; Lt: Left; PHH: Post Hemorrhagic Hydrocephalus.

All the infants developed IVH in the first week of life. Case 3 & 4 had severe septic shock syndrome along with Grade III/IV IVH and cerebellar hemorrhages, thus care was withdrawn with parental consent. Case 1 had bilateral Grade II IVH complicated with post-hemorrhagic hydrocephalus. Of note, this infant had a relatively uneventful stay with invasive ventilation for 7 days, was on full enteral feeds by 10 days, neither had meningitis,

thrombocytopenia nor medical management of patent ductus arteriosus (PDA). The post-hemorrhagic hydrocephalus was initially managed with a reservoir and serial CSF tapping and later required choroid plexus coagulation and 3<sup>rd</sup> ventriculostomy followed by ventriculo-peritoneal shunt placement. Case 5 had progressive ventricular dilatation during NICU stay that stabilised at corrected term gestational age, thus did not require invasive management. Case 1&5 had white matter injury manifested as porencephalic cysts while Case 3 had no noted complications of IVH (Figure 1).



**Figure 1:** (a,b) Case 1 Bilateral grade II IVH on US, (c) Case 1 post-hemorrhagic hydrocephalus on MRI, (d,e,f) Case 3 Bilateral grade III IVH with cerebellar hemorrhage. (g,h,i) Case 5 right sided grade IV IVH and left sided grade II IVH and left sided Grade II IVH, (j) Case 5 Porencephalic cyst on MRI.

## Discussion

Our findings suggest that antibiotic resistant *E coli* vertically transmitted from mothers can particularly affect the immature brain and may associated with an increased risk of severe IVH. A cluster of 5 cases within a span of 6 months raises concern about changing trends in microbiological pattern of EOS and antibiotic sensitivity pattern. There is an emerging trend towards organisms resistant to empirical antibiotics used in NICU. Severe systemic infection and resulting cytokine response may lead to germinal matrix bleeds especially in the first 48hrs of life when the culture sensitivity of the infecting organism is pending. With the initiation of antibiotics specific to the particular organism, the systemic infection can be promptly treated and controlled but severe intraventricular hemorrhages that have occurred within first 48hrs may have major effect on future neurological outcome among survivors.

Overall incidence of EOS in infants <1500g is 10 per 1000 live births. *E coli* is the pathogen in 5 per 1000, significantly more than GBS (2 per 1000) [3]. Use of intrapartum antibiotics for prevention of GBS sepsis has led to reduction in EOS but *E coli* still accounts for 30% of the disease burden [3]. Broad-spectrum antibiotics given to mothers with pPROM reduces neonatal morbidities [7] but there is a potential problem of significant increase in Ampicillin

resistant *E coli* causing more fulminant disease especially in mothers with an intrapartum fever [8]. We report a series of five infants born before 28wks to mothers who had pPROM and developed EOS with *E coli* resistant to the empirical antibiotics used in NICU. Certain clinical signs like intrapartum fever and pPROM > 2 days may help identify the mothers who need to be screened for *E coli* so that culture sensitivity is available for the suspected organism even before the infant is born.

All *E coli* isolates in our case series were resistant to Ampicillin and Ciprofloxacin and two strains were ESBL producing organism resistant to all antibiotics except Carbapenem. Mothers of infants did not visit known countries where there is an increased risk of ESBL producing organisms. Whether use of broad-spectrum antibiotic prophylaxis has increased the risk of resistant *E coli* infection is still controversial [5,6,8-10]. Alarmingly, all isolates in our case series were Ampicillin resistant while the empirical antibiotic used in our NICU was Ampicillin with an aminoglycoside. Fortunately, most of the isolates were Gentamicin sensitive but due to the severity of illness clinicians opted to treat with Carbapenem in 3/5 cases. Choice of empirical antibiotics that provides adequate *E coli* coverage may be vital in this scenario as the culture sensitivity takes at-least 48 hours after birth, a time period very critical for the immature brain.

The majority of IVH occurs within first 72 hours of life and all infants in our series developed moderate to severe IVH. Association between *E coli* sepsis and IVH is unclear. Tsai et al. found no difference in the incidence of IVH in neonates with *E. Coli* sepsis compared to uninfected controls of same gestational age.

[6] A retrospective study identified all *E coli* EOS cases and found 27% had IVH while 33% of the survivors assessed at infancy had impaired motor development, abnormal cognitive outcome and seizure disorders. [11] Clinical outcome of infants with *E coli* EOS from previously published studies are summarized in Table 2.

**Table 2:** Review of reported cases.

Study	Type of Study	Number	Study Population	Maternal Characteristics	Neonatal Characteristics	Antibiotic Resistance	Clinical Outcome
Stoll et al. 1996	Database research 1991-93	24	VLBW <1500g: 7606 EOS 19/1000LB GBS 31% <i>E. coli</i> 16%	31% mothers had IA 36% of infants with EOS had ROM <6hr	GA <28wks twice the risk of EOS Odds of severe IVH in EOS 2.65 (1.76-3.98)	Variability in antibiotic administration	Mortality 18% Death <72 hours 12%
Stoll et al. 2002	Database research 1998-2000	37	VLBW <1500g: 5447 EOS 15/1000LB GBS 10% <i>E. coli</i> 44%	65% of mothers had IA, 81% of mothers were infants had <i>E. coli</i> sepsis had IA 41% of infants with EOS had ROM <6 hr	GA <28wks twice the risk of EOS Odds of severe IVH or PVL in EOS 3.2(1.9-5.5)	Ampicillin resistant <i>E. coli</i> 85% Gentamicin resistant 3%	Mortality 37% Death <72 hours 20%
Tsai et al. 2012	Retrospective chart review, single center, 2004-2008, Case-control	19	All infants with sepsis within 7 days of life, 46	74% of <i>E. coli</i> sepsis had PROM, 47% for >24hr, 53% had vaginal delivery, 63% had sepsis on day 1, 20% had intrapartum fever and chorioamnionitis,	47% of <i>E. coli</i> sepsis was in infants <30wks and <1500g	79% Ampicillin and 16% Gentamicin resistant <i>E. coli</i> , none resistant to 3 <sup>rd</sup> generation cephalosporin	16% of <i>E. coli</i> sepsis had IVH, 21% had meningitis, 32% died
Bergin et al. 2015	Database search, 2012	109	All cases of <i>E. coli</i> positive blood cultures, 267, EOS 42% of cases,	56% of mothers received IA, higher proportion of mothers received IA in ampicillin resistant than sensitive group	60% of cases of <i>E. coli</i> sepsis in infants <1500g and 68% in <32 wks infant	9 ESBL organism, 49% Ampicillin resistant <i>E. coli</i> in EOS	Mortality 21%
Jones et al. 2004	Laboratory database	20	All positive <i>E. coli</i> blood and CSF cultures <7 days	50% had PPROM, 25% had intrapartum fever, Of the infants with amoxicillin resistant <i>E. coli</i> , 91% of mothers received IA	Median GA 29 wks and BW 1045g, 72% were born <32wks	55% amoxicillin, and 5% were gentamicin resistant.	Meningitis 40% Mortality 40%, IVH 27% Abnormal neurological exam at 6months 33%
JFriedman et al. 2000	Laboratory data base search, 1994-98	4	All infants with <i>E. coli</i> positive culture within 28d, Total 23, EOS 17%	47% of total cases had PROM, 26% mothers received IA	Median GA 29 (24-40) wks and BW 1045 (610-3945) g, 72% were born <32wks,	75% Ampicillin and 50% Gentamicin resistant in EOS group	Mortality 34%

Shrag et al. 2006	Retrospective case-control study, 1997-2001	132	Cases infants < 7 Cases infants <7d with positive blood/ CSF <i>E. coli</i> culture Cases 132 Control 1212	53% cases exposed to IA, 20% of cases had intrapartum fever, 45% had ROM>18 hrs.	48% of cases <33wks, 47% <1500g	59% of cases had Ampicillin resistant strain,	Mortality 16%, Meningitis 9%
Bizarro et al. 2008	Retrospective chart review Period 1(1979-92): Before GBS prophylaxis guideline, 2(1993-96): risk factor based treatment 3(1997-2006): screening based treatment	53	All infants with sepsis, Total 1385 EOS 17% LOS 83% <i>E. coli</i> sepsis 13%	Proportion of infants delivered after preterm labor (period 1: 50%, period 2: 75%, period 3: 82%), PROM (period 1: 50%, period 2: 50%, period 3: 44%), and chorioamnionitis (period 1: 0%, period 2::	50% of EOS <i>E. coli</i> sepsis in VLBWI	In period 1, 20% of cases were ampicillin-resistant, IN period 2 44% and Period 3 54%	Meningitis 10% Mortality 26%

**Abbreviations:** GA: Gestational Age; BW: Birth Weight; pPROM: Preterm Premature Rupture of Membrane; IVH: Intraventricular Hemorrhage; EOS, Early Onset Sepsis; LOS: Late Onset Sepsis; IA: Intrapartum Antibiotics.

Among the studies that have reported the clinical characteristics of *E. coli* sepsis, only two studies mention the incidence of IVH ranging from 15-30% and only one reports long-term outcome. Systemic inflammation either intrauterine or within the first week of life increases the likelihood of IVH in extreme premature infants [12,13]. The other organism, associated with higher risk IVH is *Ureaplasma Urealyticum* colonizing maternal genital tract [14]. Given the fact that *E. coli* is a more virulent organism, we speculate that the virulence of the pathogen is an important trigger for severe inflammatory response and possibly causing severe intraventricular haemorrhage [15].

*E. coli* EOS may lead to increased risk of IVH directly as well as secondary to associated thrombocytopenia and coagulopathy, which increases the propensity to bleed. Lower platelet count during first 3 days of life increases the risk of IVH in VLBWI with gram negative EOS [16]. The effect of neonatal sepsis on platelet count is believed to be organism specific, the platelet nadir being significantly of lower in gram-negative sepsis [15]. Four cases in our case series had significant thrombocytopenia in the first week of life requiring transfusions. Affected infants are more likely to receive volume expanders due to hypotension and have a hemodynamically significant PDA contributing to the fluctuations in cerebral blood flow. Premature infants with their limited capacity of cerebral autoregulation, further impaired by systemic illness, are unable to buffer the effect of fluctuations leading to germinal matrix hemorrhage [17].

### Conclusion

We report a possible association between early onset Ampicillin resistant *E. coli* infection and IVH in VLBWI. There is need of continued surveillance to monitor changes in sensitivity pattern of pathogens causing EOS in NICU and emergence of strains resistant to the antibiotics used for antepartum prophylaxis.

Clinicians need to be aware of the risk factors that precede *E. coli* sepsis and its implications on VLBWI. Timely interventions like aggressive antimicrobial therapy, platelet transfusions and early PDA closure may reduce the risk of severe IVH. Further prospective studies would be needed to establish temporal relationship.

### Author's Contributions

IG performed literature search and started writing the manuscript. KM conceived the idea, obtained results, manuscript revision, and pictures. AL contributed to manuscript, finalized the manuscript. SD did critical analysis of the manuscript and obtaining consent for publication. All the authors read and approved the final manuscript.

### Consent

Written consent was obtained from parents in institutional forms for publication of data.

### Competing Interests

The authors declare that they have no competing interests. We acknowledge advice from Stephen L Wood, MD, Associate Professor, Department of Obstetrics & Gynaecology, during the preparation of the manuscript.

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