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Original Article

Escherichia coli Meningitis in Neonatal Intensive Care Units: A Five Years Study

KK ***Chik***, WK ***To***, K ***Luk***, B ***Lam***, CC ***Shek***, C ***Tse***, D ***Ng***

Abstract ***Introduction:*** Neonatal meningitis causes severe morbidity. The incidence of ampicillin-resistant *Escherichia coli* (*E. coli)* meningitis was reported to be increasing in overseas neonatal intensive care units (NICUs) recently. This is the first local study to investigate *E. coli* neonatal meningitis. Choice of empirical antibiotics for intrapartum period and neonates will be discussed. ***Methods:*** Retrospective study was performed in 2 NICUs between 1st January 2011 and 31st May 2016. Neonates with *E. coli* meningitis were included. Demographic data, laboratory results, antibiotics use and antimicrobial susceptibilities were reviewed. ***Results:*** Eleven neonates were identified and 55% had early-onset (EO) meningitis. Ninety-one percent of *E. coli* isolates were ampicillin-resistant. Twenty-seven percent were extended-spectrum-beta-lactamase (ESBL) producing and all were isolated in EO meningitis group. Use of intrapartum ampicillin and ESBL-*E. coli* infection in neonates showed no statistical significance. ***Conclusions:*** The risk of ampicillin-resistant *E. coli* meningitis in neonates continues despite of using intrapartum antibiotics in high risk group. Choice of intrapartum antibiotic and empirical treatment of neonatal sepsis has an urgent need to be reviewed.

Key words Antibiotic resistance; *Escherichia coli*; Neonatal meningitis

Department of Pathology, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong, China

KK **Chik** (戚嘉琪) *FHKAM(Path), HKCPath, FHKAM(Paed)*
WK **To** (杜榮健) *FHKAM(Path), FHKCPath*
K **Luk** (陸奭) *FHKAM (Path), FHKCPath*
B **Lam** (林愷韶) *FHKAM (Path), FHKCPath*

Department of Paediatrics, Princess Margaret Hospital, 2-10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong, China

CC **Shek** (石志超) *FHKAM(Paed), FHKCPaed*

Department of Pathology, Kwong Wah Hospital, 25 Waterloo Road, Yaumatei, Kowloon, Hong Kong, China

C **Tse** (謝詠詩) *FHKAM(Path), FHKCPath*

Department of Paediatrics, Kwong Wah Hospital, 25 Waterloo Road, Yaumatei, Kowloon, Hong Kong, China

D **Ng** (吳國強) *FHKAM(Paed), FHKCPaed*

Correspondence to: Dr KK **Chik**
Email: chikkk@ha.org.hk

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Introduction

Neonatal meningitis is a serious infection causing high mortality and morbidity including neurological disability. The major pathogens causing neonatal meningitis are *Streptococcus agalactiae* (GBS) and *Escherichia coli* (*E. coli*). The United States started the national screening programme for GBS in pregnancy in 1996, since then the incidence of early onset group B streptococcus disease decreased from 1.7 per 1000 live births to 0.6 per 1000.[1,2] However, the incidence of neonatal *E. coli* sepsis and meningitis showed an increasing trend.[3,4] There were also case reports of ampicillin-resistant *E. coli* neonatal infection after implementing the universal intrapartum antibiotic prophylaxis to maternal Group B Streptococcus carriers.[3,5] Not just ampicillin-resistance, infection caused by extended spectrum β-lactamases (ESBL) producers are also spreading rapidly. ESBL enzyme results in resistance to many commonly used beta-lactam antibiotics, including ampicillin, first, second and third generation cephalosporin. This may affect the choice of empirical antibiotic in neonatal sepsis. Hong Kong started the antenatal screening and treatment

programme for maternal GBS in 2012. There was no local study on neonatal *E. coli* meningitis all along. To address this issue, we carried out the first local retrospective study to describe the demographic data of *E. coli* neonatal meningitis and the antibiotic susceptibility pattern of the isolates between 2011 and 2016. We investigate and analyse the association between demographic data, laboratory findings, use of intrapartum ampicillin and drug resistance *E. coli* neonatal infection, also review the choice of empirical intrapartum antibiotic and empirical neonatal antibiotics.

Methods

Study Design

A retrospective study performed in two Hong Kong neonatal intensive care units (NICU). The demographic data were reviewed including the gestational age, days of symptoms onset, gender, birth weight, maternal and neonates' laboratory results, intrapartum antibiotic and empirical antibiotic use in neonates. Their neurological outcomes were also reviewed. In addition, the antimicrobial susceptibilities of the isolates were analysed. Data were collected between 1st January 2011 and 31st May 2016 via Clinical Data Analysis and Reporting System of Hong Kong Hospital Authority.

Patients

Neonates </=28 days of age and microbiological confirmed *E. coli* meningitis were included. The diagnosis of meningitis was based on positive culture of *E. coli* from cerebrospinal fluid (CSF) and/or from blood culture associated with pleocytosis (>/=10 cells/mm^3) in CSF. The included patients were categorised into early onset neonatal meningitis and late onset neonatal meningitis according to their gestational age and the time of symptoms onset. Early onset neonatal meningitis was defined as onset of bacterial meningitis at ≤72 hours in preterm infants and ≤7 days in term infants. Late onset meningitis was defined as the onset occurred after 72 hours of life in preterm babies and >7 days up to 90 days in term infants.

Statistical Analysis

Excel spreadsheets were used for tabulation of data. Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 17; SPSS Inc, Chicago [IL], US) Fisher's exact test and Mann-Whitney U test were used for categorical variables and continuous variables respectively to analyse the association between study factors and ESBL *E. coli* infection among neonates. P values of <0.05 were considered statistically significant.

Ethics Review

This proposal was reviewed and approved by the Research Ethics Committee of the Kowloon West Cluster (Kowloon West; REC [KWC REC No.: 107-07]).

Results

Demographics and Maternal Peripartum Risk Factors for Neonatal Sepsis

Between 2011 and 2016, the total number of live born in Hong Kong public hospitals was around 227, 300 and 58, 113 babies were born in the two study hospitals. It accounted for 25% of all living newborns in all Hong Kong public hospitals. With eleven cases of neonatal *E. coli* meningitis were identified in this study, the prevalence rate of *E. coli* meningitis infection in neonates of the study hospitals was estimated to be 0.02% (11/58113). This was based on the assumption that all cases delivered in these 2 hospitals would be admitted to the same hospital's NICU while babies with *E. coli* meningitis delivered in other hospitals were not admitted to these 2 NICUs. Demographic data were shown in Table 1a, 1b and Table 2. Six of them were male (male to female ratio 1.2:1). Mean gestational age was 34 weeks (range 29-40 weeks). Fifty-five percent were preterm babies. The mean age of onset was 10.7 days (range 0-28 days). Six had early onset infection and 5 had late onset. Mean birth weight was 2.31 kg (range 1.36-3.61 kg). Among those with early onset disease, 83% had maternal risk factors for neonatal sepsis, including prematurity, premature rupture of membranes, maternal intrapartum fever and acute chorioamnionitis confirmed by placental histology. Although intrapartum intravenous ampicillin was given as per protocol, their babies still had early onset meningitis with ampicillin-resistant *E. coli.*

Clinical Presentation and Laboratory Results

Eight neonates presented with fever, 2 had recurrent apnoea and 1 had malaise and feeding intolerance. Majority did not have congenital abnormalities except one had Hirschsprung's disease presented with abdominal distension and intestinal obstruction. For the laboratory results, all had elevated C-reactive protein level (range 48.3-173 mg/L). For the cerebrospinal fluid (CSF) study, 72.7% had

polymorph predominant pleocytosis, CSF glucose level was ranged from 0.6 to 6.3 mmol/L and 54.5% had low CSF glucose level which was defined as </=1.1 mmol in preterm and </=2.5 mmol/L in term infant.[6-8] CSF protein level was ranged from 1.02 to 6.47 g/L and seven of them had abnormal result which was defined as >1.50 g/L in preterm and >1 g/L in term infants.[6-8] (Table 2) Among those six with abnormal CSF glucose level, they also had elevated CSF protein (Figure 1). Five neonates had Gram-negative bacilli detected on the Gram stain of the CSF and all of them had low CSF glucose level and elevated CSF protein level. Among these five babies, 80% had positive result on *E. coli* K1 latex agglutination test. None had positive agglutination result while the CSF Gram stain was negative. Three babies had *E. coli* isolated in the urine specimens with same susceptibility pattern as the CSF culture isolate. Ninety-one percent had coexisting *E. coli* bacteraemia.

Antibiotic Susceptibility

Antibiotic susceptibility patterns of the isolates were determined according to the Clinical & Laboratory Standards Institute guideline. Ninety-one percent of the isolates were resistant to ampicillin. One isolate (9.1%) was resistant to gentamicin. Three isolates (27.3%) were ESBL producing and resistant to third generation cephalosporins. Otherwise, all tested isolates were susceptible to amoxicillin-clavulanate; meropenem, and amikacin (Table3).

ESBL E. coli Isolate and Intrapartum Antibiotic Prophylaxis (IAP)

The demographic data, laboratory results and antibiotics use among neonates with and without ESBL - *E. coli* infection were analysed. It was identified that all cases infected with neonatal ESBL *E. coli* were presented with early onset meningitis and were given intrapartum ampicillin. There was

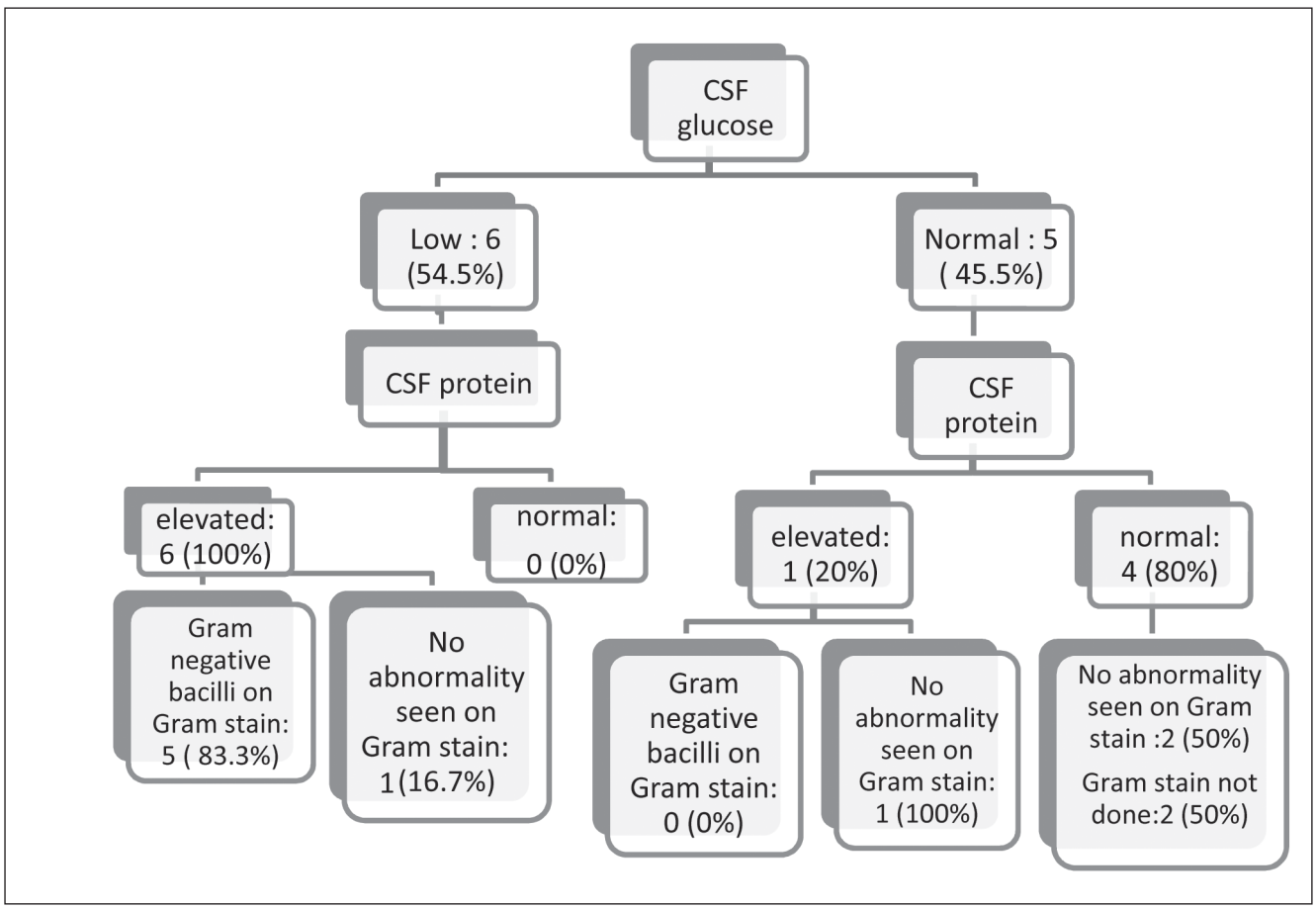

Figure 1 Cerebrospinal fluid results among neonates with *E. coli* meningitis. Normal CSF protein: <1 g/L in preterm and <1 g/L in term infants; Normal CSF glucose concentration: </=1.1 mmol/L in preterm and </= 2.5 mmol/L in term infants.

no ESBL *E. coli* infection among the group without intrapartum ampicillin given. After analysis with Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables, there was no statistical significance identified between intrapartum ampicillin use and neonatal ESBL *E. coli* infection (p value: 0.061). There was also no significance association between ESBL *E. coli* infection and other demographic data and laboratory results (Table 4).

Neurological Outcome

Three babies had developmental delay, one of them had hydrocephalus and seven had normal development on follow-up. One baby defaulted follow-up (Table 2). There was no statistical association between neonatal ESBL *E. coli* infection and delay in neurological development (Table 4).

Discussion

Hong Kong does not have a registry on the incidence of neonatal *E. coli* infection. To our knowledge; this is the first local study of neonatal *E. coli* meningitis in NICUs. The study hospitals accounted for more than 25% of total live births in Hong Kong public hospitals; therefore the result is representative to Hong Kong situation. The estimated prevalence of neonatal *E. coli* meningitis was 0.02%, with the significant mortality and morbidity, it is a problem worthy of further investigations. There is no doubt that use of IAP, i.e. ampicillin in pregnant women with GBS colonisation can reduce early-onset neonatal GBS infection. The reported odd ratio was 0.17.[1,2] However, some overseas studies reported that the incidence of neonatal *E. coli* sepsis and meningitis had increased after this practice, together with the emergence of ampicillin-resistant *E. coli* infection in neonates.[3-5] A Taiwanese study also described an increase in the percentage of early onset neonatal *E. coli* sepsis from 40.9% to 70% since the implementation of the guideline on prevention of perinatal group B streptococcal disease by Center for Disease Control and Prevention.[4] Hong Kong has started the GBS screening in 2012 but we lack of data on this.

Concerning the microbiological aspect and the pathogenesis, *E. coli* is a normal flora of the human gastrointestinal tract. It has diverse and complex antigenic structures. Some strains carry a specific virulence factor K1 capsular antigen, a polysialic acid, which impairs host's opsonophagocytic killing. The amount and persistence of K1 antigen in the CSF is closely linked to neonatal meningitis and the disease severity. Infants infected with K1 antigenic strains have increased morbidity and mortality compared to those infected with other strains. Unfortunately, up to 50% of *E. coli* colonised in maternal vagina can express K1 antigen which poses risk for vertical transmission of this virulence strain.[9] In the past, researchers suggested the *E. coli* strains with K1 capsular antigen, i.e. virulent strain, were able to cause invasive infection but they were more susceptible to antimicrobial drugs, as they could not possess resistant genes. While the more antimicrobials resistant organisms, the more difficult for them to reconcile bacterial virulence and thus could only cause noninvasive infection.[9] Later on, this postulation was being challenged by the case reports of ESBL *E. coli* neonatal meningitis.[10] Our findings also opposed the

Table 1a Demographic data of neonates with early onset and late onset sepsis

	Total cases	**Early onset**	**Late onset**
	11	**6**	**5**
Mean age of symptoms onset in days (range)	Day 10.7 (0-28)	Day 3.17 (0-6)	Day 19.4 (11-28)
Sex M:F	1.2:1	2:1	1:1
Mean birth weight (range)	2.31 kg (1.36-3.61)	2.29 kg (1.13-3.61)	2.86 kg (1.49-3.39)
Mean gestation (range)	34 weeks (29-40)	32.8 weeks (29-37)	37.2 week (30-40)
Full term	5	1	4
Preterm	6	5	1

Table 1b Demographic data of preterm and term neonates

	Preterm		**Full term**	
	Early onset	**Late onset**	**Early onset**	**Late onset**
Number of cases	5	1	1	4
Mean gestation (range)	32 (29-36)	30	37	39 (38-40)
Sex M:F	3:2	1:0	1:0	1:1
Mean birth weight (range)	2.0 (1.36-3.55)	1.49	3.61	3.2 (2.82-3.35)
Mean age of symptoms onset in days (range)	Day 3.2 (0-6)	Day 11	Day 3	Day 24 (17-29)

Table 2 Demographic data, investigation results, treatment and outcome

	Gestation	Sex	IPAB	Maternal risk factors for peripartum infection	Placenta histology	Birth weight (kg)	• Symptoms onset • EO vs LO/ • Presenting symptoms	Max CRP (mg/L)	Blood culture/ CSF culture	• CSF WBC/ polymorph (%) • RBC • Protein (g/L) • Glucose (mmol/L)	• Gram stain • Latex agglutination	Susceptibility pattern	ESBL	Initial antibiotic	Subsequent antibiotic	Other investigations results	Neurological outcome
1	29 week	F	Amp	PPROM	Acute chorio-amnionitis	1.36	• D6 • EO • Fever	79	*E. coli*/ *E. coli*	• 140/99% • 780 • 6.47 • <0.7	• GNB • Positive	Amp R; Aug S; CTX R; Gen S; Mem S; Levo S	Positive	Aug & Gen	Mem	Ear swab & G/L: ESBL *E. coli*; Urine: no growth; Urine WBC 10/mm^3	Delay
2	30 week 6d	M	Amp + Gen	PPROM maternal fever	Acute chorio-amnionitis	1.45	• DO • EO • Fever	173	*E. coli*/ *E. coli*	• 1640/90% • 790 • 4.32 • 1.1	• GNB • Positive	Amp R; Aug S; CTX S; Gen S; Levo S	Negative	Aug & Gen	CTX	*G/L: E. coli & K. pnumoniae*	Delay
3	38 week	M	Nil	Nil	ND	3.39	• D19 • LO • Fever	65	*E. coli*/ *E. coli*	• >10000/97% • 640 • 2.11 • 2.3	• GNB • Positive	Amp R; Aug S; CTX: S; Gen S; Levo R	Negative	Aug & CTX	CTX	Urine: *E. coli, S. bovis* Urine WBC 10-100/mm^3	Normal
4	38 week	F	Nil	Nil	ND	2.82	• D28 • LO • Fever	57	*E. coli*/ *E. coli*	• 4280/95% • 396 • 4.2 • 0.6	• NAS • Negative	Amp R; Aug S; CTX S; Gen S; Levo S	Negative	Aug & CTX	CTX	Urine: no growth Urine WBC <10/mm^3	Normal
5	36 week	M	Amp	PPROM	Acute chorio-amnionitis	2.66	• D5 • EO • Poor feeding	51	*E. coli*/ *E. coli*	• 2930/75% • 105 • 13.4 • 1.1	• GNB • Positive	Amp R; Aug S; CTX S; Gen S; Levo S; Mem S	Negative	Amp & Gen	CTX	Urine: *E. coli* Urine WBC <10/mm^3	*Normal*

Amp: ampicillin, Aug: augmentin, CRP: C reactive protein, CSF: cerebrospinal fluid, CSU: catheter saved urine, CTX: cefotaxime; EO: early onset, ESBL: extended spectrum beta lactamase, F: female, FEP: cefepime, GBS: group B streptococcus carrier, Gen: gentamicin, G/L: Gastric Lavage, IPAB: intrapartum antibiotic, Levo: levofloxacin ; LO: late onset, GNB: Gram negative bacilli, M: male, Mem: meropenem, Met: metronidazole, NAS: no abnormality seen, ND: not done, Pen: penicillin, PPROM: preterm prelabour rupture of membrane, R: resistant, S: sensitive; WBC: white blood cell

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Table 2 Demographic data, investigation results, treatment and outcome (cont'd)

	Gestation	Sex	IPAB	Maternal risk factors for peripartum infection	Placenta histology	Birth weight (kg)	• Symptoms onset • EO vs LO/ • Presenting symptoms	Max CRP (mg/L)	Blood culture/ CSF culture	• CSF WBC/ polymorph (%) • RBC • Protein (g/L) • Glucose (mmol/L)	• Gram stain • Latex agglutination	Susceptibility pattern	ESBL	Initial antibiotic	Subsequent antibiotic	Other investigations results	Neurological outcome
6	29 week	M	Amp	PPROM maternal fever	Acute chorio-amnionitis	1.13	• DO • EO • Apnoea	115	*E. coli*/ *E. coli*	• Blood stained (WBC and RBC count not performed) • 1.43 • 3	• ND • Negative	Amp R; Aug S; CTX R; Gen S; Levo R; Mem S	Positive	Aug & Gen	Mem	Eye swab & G/L & ear swab: ESBL *E. coli*	Normal
7	35 week	F	Nil	Nil	ND	3.55	• D5 • EO • Fever	148	*E. coli*/ *E. coli*	• 0/0% • 171 • 1.02 • 2.8	• ND • ND	Amp R; Aug S; CTX S; Gen S	Negative	Aug & Gen	Mem	Urine: no growth Urine WBC nil	Defaulted follow up
8	Full term	F	Nil	Nil	No	3.26	• D17 • LO • Fever	56.1	*E. coli*/ *E. coli*	• 5760/57% • 640 • 2.65 • 1	• GNB • Negative	Amp R; Aug S; CTX S; Gen S	Negative	Amp & CTX	CTX+Gen	Urine: *E coli* & *enterococcus*	Normal
9	Full term	M	Amp	Maternal fever	ND	3.61	• D3 • EO • Fever	56	*E. coli*/ *E. coli*	• 0/0% • 425 • 0.86 • 6.3	• ND • ND	Amp R; Aug S; CTX R; Gen S; Levo R; Mem S	Positive	Amp & CTX & Met	Mem+Gen	Peritoneal swab: *ESBL E coli* (Hirschrung's disease)	Delay
10	30 week	M	Nil	Nil	No	1.49	• D11 • LO • Apnoea	154	*E. coli*/ *E. coli*	• 2/ND • 535 • 1.24 • 4.2	• NAS • Negative	Amp R; Aug S; CTX S; Gen R	Negative	Pen & Gen	CTX	Urine & central line tip: no growth	Normal
11	Full term	F	Nil	Nil	No	3.35	• D22 • LO • Fever	48.3	No growth/ *E. coli*	• 320/94% • 2480 • 1.37 • 2.9	• NAS • Negative	Amp S; Aug S; CTX S; Gen S; Mem S	Negative	Amp & CTX	Amp	Urine: no growth	*Normal*

Amp: ampicillin, Aug: augmentin, CRP: C reactive protein, CSF: cerebrospinal fluid, CSU: catheter saved urine, CTX: cefotaxime; EO: early onset, ESBL: extended spectrum beta lactamase, F: female, FEP: cefepime, GBS: group B streptococcus carrier, Gen: gentamicin, G/L: Gastric Lavage, IPAB: intrapartum antibiotic, Levo: levofloxacin ; LO: late onset, GNB: Gram negative bacilli, M: male, Mem: meropenem, Met: metronidazole, NAS: no abnormality seen, ND: not done, Pen: penicillin, PPROM: preterm prelabour rupture of membrane, R: resistant, S: sensitive; WBC: white blood cell

Table 3 Antibiotic susceptibility

	Ampicillin	Amoxcillin-Clavulanic acid	Cefotaxime	Meropenem	Gentamicin	Amikacin	ESBL+
E. coli (susceptible / total isolate)	1/11	11/11	8/11	11/11	10/11	11/11	3/11
EO (susceptible / total isolate)	0/6	6/6	3/6	6/6	6/6	6/6	3/6
LO (susceptible / total isolate)	1/5	5/5	5/5	5/5	4/5	5/5	0/5

ESBL: Extended spectrum beta lactamase; EO: Early onset meningitis; LO: Late onset meningitis

postulation, as among four *E. coli* strain with positive K1 antigen detected in CSF, one of them was ESBL producing.

The global burden of neonatal ESBL producing Enterobacteriaceae infection is high. An overseas study reported 17% of organisms causing neonatal sepsis were ESBL producing Enterobacteriaceae among all culture positive cases.[11] While our study showed 27.3% of *E. coli* meningitis were ESBL producing. This was much higher than the overseas study which probably due to small sample size and different in the denominator. The known risk factors of neonatal ESBL producing pathogens infection were prematurity, and extremely low birth weight.[4] There is a controversy about the association between the use of intrapartum ampicillin and neonatal ESBL- Gram negative organism infection. Cordero et al[12] reported there was no increase in neonatal sepsis caused by drug-resistant Gram-negative pathogen after national maternal GBS screening and prophylaxis, while other study suggested IAP might play a role in neonatal ESBL Gram negative organisms' infection.[5] Though our study did not show a statistical significant relationship between IAP and neonatal ESBL *E. coli* meningitis, further study and monitoring deemed necessary on this issue. Meanwhile, conclusion is difficult to draw.

Table 4 Statistical analysis of demographic data, laboratory results, intrapartum antibiotic (IAP) use, neurological outcome in associate with neonatal ESBL *E. coli* infection

	ESBL negative (n=8)	ESBL positive (n=3)	P value*
Male	4	2	1.00
Ampicillin use (IAP)	2	3	0.061
Maternal HVS/blood grew ESBL-*E. coli*	0	0	ND
Placental swab grew ESBL-*E. coli*	0	2	ND
Acute chorioamnionitis	2	2	0.491
Gestation (week)	36±3.8	32.7±6.4	0.376
Birth weight (kg)	2.7±0 .8	2±1.4	0.497
Symptoms onset (days of life)	13.4±9.7	3.0±3.0	0.133
Maximum CRP (mg/L)	94.1±53.9	83.3±29.7	1.00
Delay in neurological development	1	2	0.183

*Fisher exact test for categorical variables, Mann-Witney U test for continuous variables

Besides the above identifiable risk factors for neonatal infection by ESBL producing organism, the global increase in the prevalence of ESBL producers infection among general population also played a part. In United States, 36% of all community-acquired *E. coli* infections were ESBL producing,[13] while our local data in 2015 was 26%.[14] The high rate of ESBL *E. coli* infection in our community has been postulated to the overuse of antibiotics in livestock farming. One study identified 53.6% of the local live pigs had faecal carriage of ESBL-producing *E. coli*.[15] This emergence of ESBL-producing organisms in the community poses a major challenge to the choice of empirical antibiotic in newborns. According to the international guideline, intrapartum intravenous benzylpenicillin to mother or combination of ampicillin and gentamicin to the neonates should be used to prevent early-onset neonatal infection in those mothers had risk factors of neonatal sepsis. If there is microbiological evidence of neonatal Gram-negative bacterial sepsis or meningitis; the guideline suggests benzylpenicillin/ampicillin, gentamicin and cefotaxime until further results are available. This is a widely adapted regime with good coverage for GBS and *E. coli*, and even *L. monocytogenes* infection.[16-18] However, this empirical antibiotic regime cannot treat meningitis caused by ESBL producing Enterobacteriaceae as it is intrinsically resistant to third generation cephalosporin and benzylpenicillin/ ampicillin. Even adding gentamicin is inadequate as *E. coli* can also be resistant to gentamicin as shown in one of our patient. Furthermore aminoglycoside (gentamicin and amikacin) is not a good agent to penetrate the blood brain

barrier. Nevertheless, empirical use of broad-spectrum antibiotics such as carbapenem is not a way of solving this problem. Broad-spectrum antibiotic would alter the neonatal intestinal flora colonisation patterns and thus increase the risk of necrotising enterocolitis and candidaemia. The dilemma thus comes up. However, at the time of writing, there are no well-powered randomised trials on empirical antibiotic therapy for neonatal sepsis. Further studies are deemed necessary to determine the most appropriate choice of empirical intrapartum antibiotic and empirical antibiotic for neonatal sepsis in the era of increasing drug resistance organisms especially when Gram negative organism meningitis is suspected.

The limitation of our study is the small sample size despite of taking five-year data in 2 large neonatal intensive care units. We suggest continuous monitoring of the incidence of Gram negative bacterial infection in neonates and a cross centre study on the issue of intrapartum antibiotic use and empirical antibiotic use in neonatal sepsis is urgently needed.

Conclusion

The risk of *E. coli* sepsis among neonates continues despite of improvement in perinatal care and empirical use of intrapartum antibiotic. Though this study did not identify any statistical significance between intrapartum ampicillin use and ESBL infection, with the widespread drug resistance, choice of intrapartum antibiotic and empirical treatment of neonatal sepsis has an urgent need to be reviewed.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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