Available online at www.sciencedirect.com

SciVerse ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 26–30

www.tjog-online.com

Original Article

Characteristics of early-onset neonatal sepsis caused by *Escherichia coli*

Chin-Han Tsai, Yi-Yung Chen, Kuo-Gon Wang, Chen-Yu Chen, Chie-Pein Chen*

Division of High Risk Pregnancy, Mackay Memorial Hospital, Taipei, Taiwan

Accepted 10 March 2011

Abstract

Objective: This study was conducted to document the perinatal risk factors associated with early-onset neonatal *Escherichia coli* sepsis and adverse neonatal outcomes.

Materials and Methods: A case-control study of early-onset *E coli* sepsis compared with that of non-*E coli* sepsis was conducted by a retrospective data review of all infants with a diagnosis of sepsis during the first 7 days of life from the pediatric unit of Mackay Memorial Hospital from January 2004 to October 2008. After adjustment for gestational age, each patient with *E coli* early-onset sepsis was further compared with two gestational age-matched uninfected controls.

Results: Compared with infants with non-*E coli* sepsis ($n = 27$), infants with *E coli* sepsis ($n = 19$) were more likely to have preterm birth, especially at less than 30 weeks of gestation (47% vs. 4%, $p < 0.01$), very low birth weights (<1500 g; 47% vs. 4%, $p < 0.01$), intrapartum fever (26% vs. 4%, $p = 0.036$), preterm premature rupture of membranes (PPROM; 74% vs. 11%, $p < 0.01$), prolonged rupture of membranes (>24 hours; 47% vs. 0%, $p < 0.01$), antibiotic use (63% vs. 15%, $p < 0.01$), and sepsis onset on the first day of life (63% vs. 15%, $p < 0.01$). After adjusting for gestational age, intrapartum fever (26% vs. 5%, $p = 0.035$) and PPROM (74% vs. 39%, $p = 0.015$) were more common in infants with *E coli* sepsis. Fifteen of the 19 *E coli* isolates (79%) were ampicillin-resistant, and three (16%) were gentamicin-resistant. Antepartum and intrapartum antibiotic exposure was associated with ampicillin-resistant *E coli* sepsis (100% vs. 43%, $p < 0.01$).

Conclusion: Early-onset *E coli* sepsis is more common in premature and very low birth weight infants and is more likely associated with intrapartum fever, PPROM, and sepsis onset on the first day of life than non-*E coli* sepsis. Broad-spectrum, multiple antibiotics or longer duration of antibiotic exposure may be associated with antibiotic-resistant pathogen infection.

Keywords: antibiotic resistance; early-onset neonatal sepsis; *Escherichia coli*; prematurity

Introduction

Early-onset neonatal sepsis is an uncommon but important cause of morbidity and mortality in infants, especially in those with very low birth weight (VLBW) [1,2]. Group B *streptococcus* (GBS) was the predominant cause of early-onset neonatal sepsis in the past. After the development of guidelines for intrapartum antibiotic prophylaxis for GBS infection [3,4], the incidence of early-onset neonatal sepsis caused by GBS decreased, but there was an increased incidence of non-GBS and antibiotic-resistant early-onset sepsis in preterm, low-birth-weight, or VLBW neonates [5]. *Escherichia coli* is a common pathogen in neonatal sepsis especially in preterm infants. The overall incidence of *E coli* sepsis remained stable after the introduction of intrapartum antibiotic prophylaxis, but the incidence increased in VLBW infants [1,6]. In premature infants, a growing problem of an increased trend in the incidence of early-onset sepsis caused by antibiotic-resistant *E coli* and other pathogens has been observed [6–8].

Several maternal factors and intrapartum events, including intrapartum fever, the presence or prolonged rupture of membranes, chorioamnionitis, maternal GBS colonization, urinary tract infection, prematurity, and low birth weight, were evaluated as neonatal sepsis risk factors in previous studies [9–12]. Intrapartum antibiotic administration is effective in preventing vertical GBS transmission and reducing maternal

* Corresponding author. Division of High Risk Pregnancy, Mackay Memorial Hospital, 92 Section 2, Zhong- Shan North Road, Taipei 104, Taiwan.
E-mail address: cpchen@ms2.mmh.org.tw (C.-P. Chen).

1028-4559/$ - see front matter
doi:10.1016/j.tjog.2012.01.006

and neonatal infection, but it may also result in apparent shifts of pathogens and their susceptibilities to antibiotics [5,13–17]. The objective of this study is to compare the maternal characteristics, risk factors, and neonatal outcomes associated with early-onset neonatal *E coli* sepsis with those of non-*E coli* sepsis. We also analyzed infants with *E coli* sepsis with gestational age-matched uninfected controls in an attempt to assess the particular potential risk factors, patient characteristics, and neonatal outcomes of early-onset *E coli* sepsis.

Materials and methods

This was a retrospective review of the data of all infants with a diagnosis of sepsis during the first 7 days of life from the pediatric unit at Mackay Memorial Hospital between January 2004 and October 2008. Approval from the Institutional Review Board of Mackay Memorial Hospital was obtained. Early-onset sepsis was defined as symptoms and signs of clinical sepsis in infants with pathogens isolated from a blood or cerebrospinal fluid culture between birth and the end of day 7 of life [18]. Onset of sepsis was defined as the time of the first positive culture. We divided the infants into two groups—those with *E coli* sepsis and those with non-*E coli* sepsis—and compared their maternal characteristics, risk factors, and neonatal outcomes. The patient characteristics and clinical data of all sepsis cases were collected. Maternal clinical data included age, parity, gestational age at delivery, intrapartum fever, chorioamnionitis, duration of membrane rupture, mode of delivery, and intrapartum antibiotic use. For women who received intrapartum antibiotic therapy, data were available on the total duration of therapy and the agents and number of doses administered. Antibiotic use was defined as receipt of at least one dose of antibiotics during the antepartum or intrapartum period for treatment of infection or prophylaxis. Neonatal clinical data included gestational age, birth weight, onset of sepsis, antibiotic susceptibility of the pathogens, Apgar score, ventilator use, intraventricular hemorrhage, respiratory distress, neonatal intensive care unit admission, length of hospital stay, and neonatal outcome.

A case-control study was also performed by comparing each infant with early-onset *E coli* sepsis with two gestational age-matched uninfected controls to identify the potential risk factors of adverse neonatal outcomes other than gestational age. The controls were matched with each case patient based on gestational age (same gestational week) and closest calendar month of birth (every control was born within 6 months of the birth of the respective case patient). Uninfected controls with maternal systemic diseases, obstetric emergency conditions, and maternal GBS colonization were excluded.

Univariable analysis was conducted to determine whether there were significant differences in each variable between the *E coli* sepsis group cases, non-*E coli* sepsis cases, and controls. Statistical significance was determined using the chi-square test or Fisher's exact test for dichotomous variables and by the independent *t*-test or Mann–Whitney *U*-test for continuous variables. A value of $p < 0.05$ was considered statistically significant. The statistical analyses were performed with SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA).

Results

Distribution of pathogens

Forty-six cases of early-onset sepsis were identified by clinical manifestations and positive neonatal blood cultures during the study period. *E coli* sepsis was identified in 19 infants, while non-*E coli* sepsis was found in 27 infants. GBS was the most common pathogen (50%, 12/24) in term infants, but *E coli* was the predominant pathogen in preterm infants (73%, 16/22). Twenty-two sepsis cases were caused by Gram-positive organisms, and the other 24 cases were caused by Gram-negative organisms, among which GBS (64%, 14/22) and *E coli* (79%, 19/24) were the most common pathogens, respectively (Table 1).

Cases of E coli sepsis and non-E coli sepsis

The characteristics of patients with *E coli* sepsis and non-*E coli* sepsis are shown in Table 2. Infants with *E coli* sepsis cases had lower gestational ages and lower birth weights than non-*E coli* sepsis infants, which was especially noted in those with gestational ages less than 30 weeks and birth weights less than 1500 gm (both 47% vs. 4%, $p < 0.01$). Intrapartum risk factors for early-onset sepsis, such as intrapartum fever (26% vs. 4%, $p = 0.036$), preterm premature rupture of membranes (PPROM; 74% vs. 11%, $p < 0.01$), and prolonged membrane rupture (>24 hours; 47% vs. 0%, $p < 0.01$) were also more common in the *E coli* sepsis group. Although there was no significant difference in chorioamnionitis (21% vs. 4%, $p = 0.085$) between groups, it was also more common in the *E coli* sepsis group. In addition, antibiotic use before delivery was more common in the *E coli* sepsis group (63% vs.15%, $p < 0.01$), and only two of the infants with non-*E coli* sepsis received antibiotics as intrapartum prophylaxis for maternal GBS colonization. Sixteen (84%) of the 19 early-onset *E coli* sepsis infants were premature. Twelve (63%) of them had

Table 1
Distribution of pathogens in 46 cases of early onset neonatal sepsis.

	Preterm ($n = 22$)	Term ($n = 24$)	Total ($n = 46$)
Gram-positive organisms ($n = 22$)			
β-Hemolytic *streptococcus* group B	2	12	14
Staphylococcus coagulase (−)	1	3	4
α-*Streptococcus* species	1	2	3
Enterococcus	1		1
Gram-negative organisms ($n = 24$)			
Escherichia coli	16	3	19
Klebsiella pneumonia		1	1
Acinetobacter baumannii		1	1
Serratia marcescens		1	1
Sphingomonas paucimobilis		1	1
Chryseobacterium meningosepticum	1		1

Table 2
Analysis of maternal and neonatal variables in infants with early onset *E coli* and non-*E coli* sepsis.

	E coli cases ($n = 19$)	Non-*E coli* cases ($n = 27$)	p
Maternal age (y)	33.1 (24–43)*	30 (24–36)*	0.027
Nulliparous	10 (53)	16 (59)	0.655
Gestational age (wk)	30.53 (24–39)*	37.67 (27–40)*	< 0.01
< 30	9 (47)	1 (4)	
30–36	7 (37)	5 (18)	
≧37	3 (16)	21 (78)	
Birth weight (g)	1861 (614–4450)*	2890 (1124–3900)*	<0.01
< 1500	9 (47)	1 (4)	
1501–2500	4 (21)	5 (18)	
≧2500	6 (32)	21 (78)	
Male gender	14 (74)	17 (63)	0.445
Vaginal delivery	10 (53)	15 (56)	0.845
Sepsis on d 1	12 (63)	4 (15)	<0.01
Intrapartum fever	5 (26)	1 (4)	0.036
Chorioamnionitis	4 (21)	1 (4)	0.085
PPROM	14 (74)	3 (11)	<0.01
≦24 h	5	3	
> 24 h	9	0	
Intrapartum antibiotic therapy	12 (63)	4 (15)	<0.01
≦7 d	4	4	
> 7 d	8	0	
1-min Apgar score < 7	10 (53)	2 (7)	<0.01
5-min Apgar score < 7	5 (26)	2 (7)	0.091
Intraventricular hemorrhage	3 (16)	0 (0)	0.064
Respiratory distress	17 (89)	18 (67)	0.073
Mechanical ventilation use	14 (74)	6 (22)	<0.01
Meningitis	4 (21)	5 (19)	0.559
NICU admission	16 (84)	16 (59)	0.07
Days in NICU (d)	18.63 (1–186)*	11.38 (1–62)*	0.057
Hospital stay of survivors (d)	46.0 (16–241)*	22.33 (8–73)*	0.079
Death	6 (32)	3 (11)	0.09

Data are presented as *n* (%) or *mean (range).
NICU = neonatal intensive-care unit; PPROM = preterm premature rupture of membranes.

sepsis onset on day 1, which was more common than in the non-*E coli* sepsis group (63% vs. 15%, $p < 0.01$). The proportions of 1-min Apgar score < 7 (53% vs. 7%, $p < 0.01$) and mechanical ventilation use (74% vs. 22%, $p < 0.01$) were higher in infants with *E coli* sepsis than those with non-*E coli* sepsis. There were no differences in intraventricular hemorrhage, respiratory distress syndrome, and neonatal intensive-care unit admission between groups. The overall mortality rate was 20% (9/46). Although the *E coli* sepsis group had a higher mortality rate than the non-*E coli* sepsis group, it did not reach statistical significance (32% vs. 11%, $p = 0.09$), possibly because of the small number of cases, and other conditions associated with the three deaths in the non-*E coli* sepsis group, including tension pneumothorax and necrotizing enterocolitis with bowel perforation. Nine neonates were born before 30 weeks of gestation, and six of them died. Five of these six infants died within 3 days.

Cases of E coli sepsis and uninfected controls

After adjusting for gestational age, the proportion of intrapartum fever and PPROM was more common in infants with *E coli* sepsis than in uninfected controls (Table 3). Other factors, including birth weight, chorioamnionitis, and antibiotic use before delivery, had no significant differences between these two groups. There were also no differences between these two groups in neonatal outcomes, including 1- or 5-min Apgar score < 7, mechanical ventilation use, respiratory distress, intraventricular hemorrhage, and mortality rate, but a higher proportion of infants were admitted to the neonatal intensive care unit in *E coli* sepsis compared with the uninfected controls (Table 3). All infants who died in the two groups were delivered at less than 30 gestational weeks.

Sensitivity of antibiotics

All isolates of *E coli* were further tested for antibiotic susceptibility. Fifteen of the 19 *E coli* isolates (79%) were ampicillin-resistant, and three (16%) were gentamicin-resistant. There were no cases of third-generation cephalosporin-resistant *E coli* in our study. Twelve mothers of infants with early-onset *E coli* sepsis (63%, 12/19) received ampicillin treatment before delivery, and three of them received multiple antibiotics. Eight of them had antibiotic courses longer than 7 days. Infants with early-onset *E coli* sepsis who had antibiotics

Table 3
Analysis of maternal and neonatal variables in infants with early onset *E coli* sepsis and gestational age-matched uninfected controls.

	E coli cases ($n = 19$)	Uninfected cases ($n = 38$)	p
Birth weight (g)	1861 (614–4450)*	1713 (540–3666)*	0.609
Nulliparous	10 (53)	18 (47)	0.708
Male gender	14 (74)	24 (63)	0.427
Vaginal delivery	10 (53)	22 (58)	0.706
Intrapartum fever	5 (26)	2 (5)	0.035
Chorioamnionitis	4 (21)	3 (8)	0.159
PPROM	14 (74)	15 (39)	0.015
≦24 h	5	5	
> 24 h	9	10	
Intrapartum antibiotic therapy	12 (63)	17 (45)	0.19
≦7 d	4	11	
> 7 d	8	6	
1-min Apgar score < 7	10 (53)	16 (42)	0.452
5-min Apgar score < 7	5 (26)	6 (16)	0.272
Intraventricular hemorrhage	3 (16)	3 (8)	0.313
Respiratory distress	17 (89)	34 (89)	0.661
Mechanical ventilation use	14 (74)	20 (53)	0.127
NICU admission	16 (84)	20 (53)	0.02
Days in NICU (d)	18.63 (1–186)*	51.4 (4–138)	0.033
Hospital stay of survivors (d)	46.0 (16–241)*	43.81 (4–155)*	0.83
Death	6 (32)	6 (16)	0.151

Data are presented as n (%) or * mean (range).
NICU = neonatal intensive-care unit; PPROM = preterm premature rupture of membranes.

Table 4
Analysis of variables in infants with early onset *E coli* sepsis with and without antibiotic use before delivery.

	With antibiotic use ($n = 12$)	Without antibiotic use ($n = 7$)	p
Antibiotic therapy > 7 d	8		
Multiple antibiotics	3		
Prematurity	12 (100)	4 (57)	0.036
PPROM	12 (100)	2 (29)	<0.01
Ampicillin-resistant *E coli*	12 (100)	3 (43)	<0.01
Gentamicin-resistant *E coli*	3 (25)	0 (0)	0.227

Data are presented as *n* (%).
PPROM = preterm premature rupture of membranes.

before delivery had higher proportions of prematurity (100% vs. 57%, $p = 0.036$) and PPROM (100% vs. 29%, $p < 0.01$) than those without antibiotic use (Table 4).

Discussion

E coli and GBS were the most common isolates of gram-negative and gram-positive pathogens in our study. Infants with *E coli* sepsis were more likely to have preterm births (84.2%), especially at less than 30 weeks of gestation, VLBWs, intrapartum fever, PPROM, prolonged rupture of membranes, antibiotic use, and sepsis onset on the first day. Most of the *E coli* isolates (79%) were ampicillin-resistant, which seemed to be associated with antepartum and intrapartum antibiotic exposure.

An increase in mortality rate was observed in *E coli* sepsis, although it did not reach statistical significance ($p = 0.09$) because of the small case number in our series. *E coli* sepsis is thought more likely to cause early fetal compromise in premature infants. In our series, nine neonates were born at less than 30 weeks of gestation, and six of them died. Thus, *E coli* sepsis may increase the odds of mortality, especially in infants born before 30 weeks of gestation. However, infants who survive early-onset *E coli* sepsis may also have neurodevelopmental impairment [19].

In addition to gestational age, prematurity, and VLBW, factors such as intrapartum fever, PPROM, and prolonged membrane rupture were more common in the *E coli* sepsis group than in the non-*E coli* group. A significant difference was still observed in PPROM and intrapartum fever between infants with *E coli* sepsis and gestational age-matched uninfected controls. These observations were similar to a report in which PPROM was associated with adverse perinatal outcomes and was an independent risk factor for chorioamnionitis [20]. Intrapartum fever and prolonged membrane rupture have been associated with increased odds of *E coli* infection in both term and preterm infants [9].

In recent years, there has been an increase in intrapartum antibiotic prophylaxis to prevent the vertical transmission of GBS. Antibiotic use may reduce maternal and neonatal illness if PPROM or chorioamnionitis occurs [21–23], and it has been effective against early-onset sepsis [9,16,24]. However, antibiotic resistance is a potential problem associated with intrapartum antibiotic therapy [13,16,17] and long duration of antibiotic use before delivery [25]. There are also trends of increasing incidence of sepsis related to antibiotic-resistant *E coli* and other pathogens [7,8,26]. In VLBW infants, the incidence of antibiotic-resistant *E coli* sepsis has also increased [1,6]. In our study, ampicillin-resistant strains were found in 15 (79%) infants with *E coli* sepsis, who were all VLBW infants, and there was an association between maternal antibiotic use and ampicillin-resistant *E coli* sepsis. Because of the increasing incidence of antibiotic-resistant *E coli* neonatal sepsis, current empiric management of neonatal sepsis may need reevaluation [27].

Ampicillin is commonly used for intrapartum prophylaxis for GBS infection, and to reduce PPROM infection, chorioamnionitis, urinary tract infection, and other infections associated with maternal and neonatal illnesses in Taiwan. The unnecessary, prolonged use of antibiotics may emerge as a problem in sepsis related to neonatal antibiotic-resistant *E coli* or other pathogens, and strategies in neonatal sepsis management may need to be changed. In our study, most of the florae causing *E coli* sepsis were resistant to ampicillin and were seen in patients who received antepartum antibiotics longer than 7 days. We further observed three infants with gentamicin-resistant *E coli* sepsis. All of them received antepartum antibiotics. There is no clear evidence concerning the use of gentamicin or other antibiotics to prevent neonatal sepsis caused by ampicillin-resistant *E coli* or other pathogens. Although the majority of pathogens causing neonatal sepsis have been found susceptible to commonly used empiric first-line antibiotic combinations which include gentamicin [28], the efficacy of gentamicin for preventing neonatal sepsis is not clear. When considering whether to add gentamicin or other antibiotics to prevent neonatal ampicillin-resistant pathogen infection, the possibility of selection of gentamicin-resistant or even multiple antibiotic-resistant pathogens should be of concern, especially in those given broad-spectrum or multiple antibiotics and longer courses of antibiotics.

References

[1] Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med 2002;347:240–7.
[2] Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, et al. Very low birth weight preterm infants with early onset neonatal sepsis. Pediatr Infect Dis J 2005;24:635–9.
[3] Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: a public health perspective. MMWR Recomm Rep 1996;45:1–24.
[4] Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. MMWR Recomm Rep 2002;51:1–22.
[5] Moore MR, Schrag SJ, Schuchat A. Effects of intrapartum antimicrobial prophylaxis for prevention of group-B streptococcal disease on the incidence and ecology of early-onset neonatal sepsis. Lancet Infect Dis 2003;3:201–13.
[6] Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. Pediatrics 2008;121:689–96.

[7] Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. Pediatrics 2002;110:690–5.
[8] Alarcon A, Peña P, Salas S, Sancha M, Omeñaca F. Neonatal early onset *Escherichia coli* sepsis: trends in incidence and antimicrobial resistance in the era of intrapartum antimicrobial prophylaxis. Pediatr Infect Dis J 2004;23:295–9.
[9] Schrag SJ, Hadler JL, Arnold KE, Martell-Cleary P, Reingold A, Schuchat A. Risk factors for invasive, early-onset *Escherichia coli* infection in the era of widespread intrapartum antibiotic use. Pediatrics 2006;118:570–6.
[10] Yancey MK, Duff P, Kubilis P, Clark P, Frentzen BH. Risk factors for neonatal sepsis. Obstet Gynecol 1996;87:188–94.
[11] Schuchat A, Zywicki SS, Dinsmoor MJ, Mercer B, Romaguera J, O'Sullivan MJ. Risk factors and opportunities for prevention of early-onset neonatal sepsis: a multicenter case control study. Pediatrics 2000; 105:21–6.
[12] Bevilacqua G, Braibanti S, Solari E, Anfuso S, Fragni G, Soncini E. Perinatal risk factors for infection in the newborn. Multicenter clinico-epidemiologic investigation. Pediatr Med Chir 2005;27:31–8.
[13] Towers CV, Briggs GG. Antepartum use of antibiotics and early-onset neonatal sepsis: the next 4 years. Am J Obstet Gynecol 2002;187: 495–500.
[14] Mercer BM, Carr TL, Beazley DD, Crouse DT, Sibai BM. Antibiotic use in pregnancy and drug-resistant infant sepsis. Am J Obstet Gynecol 1999; 181:816–21.
[15] Edwards RK, Clark P, Sistrom CL, Duff P. Intrapartum antibiotic prophylaxis 1: relative effects of recommended antibiotics on gram-negative pathogens. Obstet Gynecol 2002;100:534–9.
[16] Schuchat A. Impact of intrapartum chemoprophylaxis on neonatal sepsis. Pediatr Infect Dis J 2003;22:1087–8.
[17] Schrag SJ, Stoll BJ. Early-onset neonatal sepsis in the era of widespread intrapartum chemoprophylaxis. Pediatr Infect Dis J 2006;25: 939–40.
[18] Mehr SS, Sadowsky JL, Doyle LW, Carr J. Sepsis in neonatal intensive care in the late 1990s. J Paediatr Child Health 2002;38:246–51.
[19] Jones B, Peake K, Morris AJ, McCowan LM, Battin MR. *Escherichia coli*: a growing problem in early onset neonatal sepsis. Aust N Z J Obstet Gynaecol 2004;44:558–61.
[20] Newman DE, Paamoni-Keren O, Press F, Wiznitzer A, Mazor M, Sheiner E. Neonatal outcome in preterm deliveries between 23 and 27 weeks' gestation with and without preterm premature rupture of membranes. Arch Gynecol Obstet 2009;280:7–11.
[21] Gomez R, Romero R, Nien JK, Medina L, Carstens M, Kim YM, et al. Antibiotic administration to patients with preterm premature rupture of membranes does not eradicate intra-amniotic infection. J Matern Fetal Neonatal Med 2007;20:167–73.
[22] Ovalle A, Martínez MA, Kakarieka E, Gómez R, Rubio R, Valderrama O, et al. Antibiotic administration in patients with preterm premature rupture of membranes reduces the rate of histological chorioamnionitis: a prospective, randomized, controlled study. J Matern Fetal Neonatal Med 2002;12:35–41.
[23] Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of the membranes: a systematic review. Obstet Gynecol 2004;104:1051–7.
[24] Schrag S, Schuchat A. Prevention of neonatal sepsis. Clin Perinatol 2005; 32:601–15.
[25] Rentz AC, Samore MH, Stoddard GJ, Faix RG, Byington CL. Risk factors associated with ampicillin-resistant infection in newborns in the era of group B streptococcal prophylaxis. Arch Pediatr Adolesc Med 2004;158:556–60.
[26] Joseph TA, Pyati SP, Jacobs N. Neonatal early-onset *Escherichia coli* disease: the effect of intrapartum ampicillin. Arch Pediatr Adolesc Med 1998;152:35–40.
[27] Friedman S, Shah V, Ohlsson A, Matlow AG. Neonatal *Escherichia coli* infections: concerns regarding resistance to current therapy. Acta Paediatr 2000;89:686–9.
[28] Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed 2011;96:F9–14.