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Neonatal sepsis within and beyond China

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Abstract

Sepsis remains a significant cause of neonatal morbidity and mortality in China. A better understanding of neonatal sepsis in China as compared with other industrialized and non-industrialized countries may help optimize neonatal health care both regionally and globally. Literature cited in this review was retrieved from PubMed using the keywords "neonatal sepsis," "early-onset (EOS)" and "late-onset (LOS)" in English, with the focus set on population-based studies. This review provides an updated summary regarding the epidemiology, pathogen profile, infectious work-up, and empirical treatment of neonatal sepsis within and beyond China. The incidence of neonatal EOS and the proportion of Group B *Streptococcus* (GBS) within pathogens causing EOS in China seem to differ from those in developed countries, possibly due to different population characteristics and intrapartum/postnatal health care strategies. Whether to adopt GBS screening and intrapartum antibiotic prophylaxis in China remains highly debatable. The pathogen profile of LOS in China was shown to be similar to other countries. However, viruses as potential pathogens of neonatal LOS have been underappreciated. Growing antimicrobial resistance in China reflects limitations in adapting antibiotic regimen to local microbial profile and timely cessation of treatment in non-proven bacterial infections. This review stresses that the local epidemiology of neonatal sepsis should be closely monitored in each institution. A prompt and adequate infectious work-up is critically important in diagnosing neonatal sepsis. Adequate and appropriate antibiotic strategies must be overemphasized to prevent the emergence of multi-resistant bacteria in China.

Keywords: Antibiotic resistance; Blood culture; Early-onset sepsis; Late-onset sepsis; Neonatal sepsis; Nosocomial neonatal sepsis

Introduction

Neonatal sepsis is a cause of significant morbidity and mortality. Based on population-level studies during the last two decades, the global estimate of the incidence of neonatal sepsis was 2202 (95% confidence interval [CI] 1099–4360) per 100,000 live births (LBs), with mortality between 11% and 19%.[1,2] In China, birth population-based surveys from one region that have approximated national average levels estimated the incidence of neonatal sepsis to be 25.6 per 1000 LBs.[3] Between 1996 and 2015, the cause-specific mortality of neonatal sepsis in China decreased from 0.4 to 0.1 per 1000 LBs, which was significantly lower than the global estimate of 2.8 per 1000 LBs in 2015.[4] Notably, great inequity exists in mortality rate of neonatal sepsis across regions in China.[4]

Clinical signs of neonatal sepsis range from sub-clinical infection to severe manifestations of focal or systemic disease.[5] The pathogens responsible for sepsis might be acquired through *in utero* infection,[6] maternal microbiota during delivery, or postnatal hospital or community environment.[7] The timing of the exposure, inoculum size, immune status of the infant, and virulence of the causative micro-organism may greatly influence the clinical manifestations of neonatal sepsis. Based on different definitions across regions, early-onset sepsis (EOS) occurs within the first 3 to 6 days of life, whereas late-onset sepsis (LOS) occurs after 4 to 7 days within the first 1 to 3 months of life.[5] Apart from the onset of time, there are marked differences in terms of pathogen profile and antimicrobial susceptibility among EOS, community-acquired LOS, and hospital-acquired LOS.[7,8] In light of the above, great challenges exist to manage and reduce neonatal sepsis.

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China is one of the most populous countries in the world with some regions closely approaching industrialized countries in terms of socioeconomic development and health care, while some relatively lagging behind. The second-child policy since 2015 may further complicate the clinical picture of neonatal sepsis. Therefore, this review will provide an updated summary regarding important aspects of neonatal sepsis, such as epidemiology, pathogen profile, infectious work-up, and empirical treatment, both within and beyond China, in the hope of optimizing neonatal health care both regionally and globally.

Early-Onset Neonatal Sepsis

Incidences and pathogen profiles

Industrialized countries

In developed countries like USA, although the overall incidence of EOS has remained relatively stable at around 0.8 cases per 1000 LBs over the last two decades,[9] there have been marked changes in the pathogen-specific incidence of EOS. Group B *Streptococcus* (GBS) and *Escherichia coli* are predominant pathogens of neonatal EOS, accounting for 36% and 25% of EOS cases identified in four US States from 2005 to 2014.[9] Particularly, in the National Institute of Child Health and Human Development birth cohort of very low birth weight (VLBW) infants, there was a marked reduction in EOS caused by GBS (from 5.9 to 2.08 per 1000 LBs, $P < 0.001$), but an increase in *E. coli* sepsis (from 3.2 to 5.09 per 1000 LBs, $P = 0.004$) between 1991–1993 and 2006–2009.[10,11] In contrast, the incidence of GBS EOS plateaued or even slightly increased in some other developed countries [Table 1].[12,13] It has been speculated that different population structure, emergence of new GBS clones, increased recognition of EOS symptoms, and modified criteria for diagnosing neonatal sepsis might have contributed to higher incidence of GBS EOS over time in some regions.[13]

Non-industrialized countries

In contrast, the incidence of neonatal GBS EOS is less clear in developing countries, mainly due to limitations in

Table 1: Population-based studies reporting on temporal changes in the incidence of neonatal early-onset sepsis.

Network	Birth year	Population of cohort	No. of neonates	Onset of EOS (days)	Incidence of EOS (per 1000 LBs)	Case fatality *n/N*, %
USA						
NICHD[10]	1991–1993	VLBW	7606	≤3	All pathogens: 19.3 GBS: 5.9 *E. coli*: 3.2	NA
	1998–2000	VLBW	5447	≤3	All pathogens: 15.4 GBS: 1.7 *E. coli*: 6.8	31/84, 37%
NICHD[11]	2006–2009	All LBs	396,586	≤3	All pathogens: 0.98 GBS: 0.41 *E. coli*: 0.28	61/389, 16% 15/160, 9% 35/107, 33%
		VLBW	12,956	≤3	All pathogens: 10.96 GBS: 2.08 *E. coli*: 5.09	NA
UK						
CoSurv[12]	2000–2001	All LBs	794,037	≤6	GBS: 0.48	38/377, 10.6%
NeonIN[13]	2006–2008	All LBs	130,763	≤2	All pathogens: 0.9 GBS: 0.5 *E. coli*: 0.2	NA
BPSU[20]	2014–2015	All LBs	914,132	≤6	GBS: 0.57	27/517, 5.2%
		VLBWs	7569	≤6	GBS: 2.24	
The Netherlands						
AMC-RVIM[19]	1987–1999	All LBs	NA	<7	GBS: 0.11	NA
	2000–2011	All LBs	NA	<7	GBS: 0.19	
Asia						
Five NICUs[15] in China, Kuwait, Malaysia, Thailand	2005	All LBs	35,294	≤2	All pathogens: 0.72 GBS: 0.51 GNB: 0.15	6/47, 12.8% 4/18, 22% 2/17, 12.5%
Three NICUs[16] in China, Malaysia, Thailand	2006–2009	All LBs	76,141	<3	All pathogens: 0.62 GBS 0.24 GNB: 0.11	13/181, 7.2%
China[17]	2015–2018	All LBs < 34 weeks	19,084	<3	All pathogens: 9.7	42/186, 22.6%

EOS: Early-onset sepsis; LBs: Live births; NICHD: National Institute of Child Health and Human Development; BPSU: British Paediatric Surveillance Unit; AMC-RVIM: Netherlands Reference Laboratory for Bacterial Meningitis of the Amsterdam Medical Center and the National Institute of Public Health and the Environment; NICU: Neonatal intensive care unit; VLBW: Very low birth weight; NA: Not available; GBS: Group B *Streptococcus*; GNB: Gram-negative bacilli.

detection methodology as well as difficulties in defining population denominator.[14] Although not based on nationwide surveillance system, two consecutive prospective multi-center studies in Asia have shed some light on the trend of neonatal EOS in this region, showing a steady decline in overall as well as pathogen-specific incidence of EOS from 2005 to 2009 [Table 1].[15,16] Meanwhile, the overall case fatality of EOS decreased by nearly 40% [Table 1].[15,16] Moreover, EOS in developing countries may have different pathogen profiles. Based on a recent multicenter study including preterm infants <34 weeks' gestation admitted to 25 tertiary neonatal units in China (2015–2018), the incidence of EOS was 11.7 cases per 1000 admissions (321/27,532) or 9.7 cases per 1000 LBs if only inborn infants in 18 perinatal centers were considered (186/19,084).[17] The leading pathogen was Gram-negative bacteria (GNB) like *E. coli* (20.3%), followed by coagulase-negative staphylococci (CoNS) (16.5%), whereas EOS caused by GBS was relatively rare (2.5%).[17] The case fatality rate of EOS in China was 19% (61/321).[17]

Intrapartum antibiotic prophylaxis (IAP) for EOS

The US

As the primary risk factor for neonatal GBS EOS is maternal colonization of the genitourinary and gastrointestinal tracts, the American College of Obstetricians and Gynecologists (ACOG) recommends universal maternal screening by vaginal-rectal culture between 36 and 38 weeks of gestation to effectively prevent GBS EOS [Supplementary Figure 1A–1C, http://links.lww.com/CM9/A244, http://links.lww.com/CM9/A245, http://links.lww.com/CM9/A246].[18] Approximately 50% of women who are colonized with GBS will transmit the bacteria to their newborns.[18] Vertical transmission usually occurs during labor or after preterm premature rupture of membranes.[6] In the absence of IAP, 1% to 2% of these newborns will develop GBS EOS.[18] All women whose vaginal-rectal cultures are positive for GBS should receive appropriate IAP, mostly penicillin or amoxicillin, unless a pre-labor caesarian section is performed in the setting of intact membranes.[18] Although a shorter duration of recommended intrapartum antibiotics less than 4 h may not be as effective as that of more than 4 h, 2 h of antibiotic exposure has been shown to reduce GBS vaginal colony counts and decrease the frequency of a clinical neonatal sepsis diagnosis. Obstetrical interventions, whenever necessary, should not be delayed in order to provide the 4-h antibiotic administration before birth.[18]

Europe

In contrast to universal maternal screening, risk-based stratification has been adopted in other industrialized countries.[12,13,19] Based on a prospective national surveillance of invasive GBS in infants younger than 90 days from 2014 to 2015 in the UK and Ireland, the incidence of all GBS infection was 0.94 (95% CI 0.88–1.00) per 1000 LBs, with GBS EOS being 0.57 (95% CI 0.52–0.62) per 1000 LBs.[20] The case fatality rate of GBS EOS was 5.2%, lower than that in the US [Table 1].[10,11,20] Notably, both the incidence and case fatality rate were about five-fold higher in VLBW infants than in those with a BW >1500 g. In the Netherlands, despite IAP guidelines to prevent GBS EOS on the basis of culture-based screening at 35 to 37 week's gestation, the incidence of GBS EOS increased slightly over the last two decades, demonstrating a similar secular trend as in the UK [Table 1].[19] In the UK, five serotypes (Ia, Ib, II, III, V) accounted for 377 (94%) of all isolates GBS strains, with the predominant serotypes being III (60%) and Ia (17%).[20] A particular concern is the large number of isolates identified as sequence type (ST)17, a clone associated with a high risk of invasive neonatal sepsis and meningitis.[21] Thus, much hope lies on a vaccine against GBS which is still under development.[22]

China

Currently, no standard guidelines exist for maternal GBS screening and neonatal GBS disease prevention in China. While some hospitals perform IAP following a risk-based strategy, others apply universal screening recommended by ACOG. A recent systematic review of published data from Chinese literature revealed that the maternal GBS colonization rate in the mainland of China may range from 5.7% to 14.5% among institutions.[23] Based on so far the largest population-based surveillance study for GBS disease burden from 18 urban tertiary hospitals across 16 Chinese provinces (2015–2017), the overall incidence of invasive GBS disease in infants ≤3 months of life was estimated to be 0.31 (95% CI 0.27–0.36) cases per 1000 LBs, ranging from 0 to 76 cases per 1000 LBs across participating hospitals.[24] The incidence of early- and late-onset GBS disease was 0.18 (95% CI 0.15–0.22) and 0.13 (95% 0.11–0.16) per 1000 LBs, respectively.[24] The majority (76.6%) of invasive GBS disease occurred in term infants, and only 13.2% of GBS-case mothers received GBS screening during pregnancy.[24] Similar to the UK, five serotypes (Ia, Ib, II, III, and V) accounted for the majority of GBS invasive cases in the mainland of China, and isolated GBS strains were most commonly III serotype and ST 17.[23,24] Due to population characteristics and sociocultural background, the actual rate of maternal GBS colonization and neonatal GBS diseases in China may differ greatly from those reported in industrialized countries, and are probably much lower based on current knowledge. Unresolved issues remain as to whether GBS screening and prevention protocols should be incorporated in China, and if so, what kind of strategies. As such, immunizing pregnant women against GBS, despite being an emerging approach to protect neonates from GBS disease in some countries, could not yet be introduced in China.

So far, chorioamnionitis as a significant risk factor of neonatal EOS has not been fully appreciated in China. It has been suggested that pathological and microbiological examination of the placenta should be routinely performed, especially in preterm deliveries, in order to better assess EOS and combined perinatal co-morbidities.[25] Notably, the predominance of nosocomial and opportunistic pathogens (eg, GNB and CoNS) among neonatal EOS cases in China raised the concern of possible unhygienic practices or inappropriate perinatal exposure to antibiotics favoring intestinal translocation of GNB.[17]

Late-Onset Neonatal Sepsis

Maternal post-partum transmission of GBS is underestimated

LOS still accounts for about one-third of neonatal GBS sepsis, and the case fatality rate of GBS LOS was higher than that of GBS EOS (7.7% *vs.* 5.2%).[20] Mother-to-infant transmission may constitute an important source of GBS LOS. A longitudinal study was carried out in 160 mother-baby pairs from Italy to assess postnatal colonization with GBS and the impact of IAP.[26] Specimens from the rectum, vagina, and milk of mothers were collected from the time of delivery to 8 weeks post-partum. Women were grouped into culture-positive carriers ($n = 83$), culture-negative carriers ($n = 26$), and non-carriers ($n = 51$) at discharge from hospital. A total of 35 (22%) neonates were colonized by GBS from at least one body site, and the majority of them (30/35) were born to culture-positive carriers. Infants of culture-positive carriers exposed to IAP were less likely to be colonized (15/57 *vs.* 15/26, $P = 0.01$), or heavily colonized (7/57 *vs.* 1/26, $P = 0.04$). However, neonates exposed to IAP and discharged GBS-free from hospital often became subsequently colonized (12/57 *vs.* 1/26, $P = 0.09$), and six out of 83 culture-positive carrier mothers showed positive milk cultures with heavy colonization of GBS in their babies. Molecular typing analysis confirmed identical GBS strains in all mother-baby pairs. These data call the attention of physicians to maternal transmission after delivery as an underestimated source of neonatal LOS.

GNB are associated with severe neonatal LOS

Despite being less common than Gram-positive bacteria to cause neonatal LOS, GNB are associated with more severe clinical manifestations such as meningitis, and have a higher mortality, especially in VLBW infants.[27]*E. coli* is the most common cause of bacterial meningitis in preterm infants and the second most common after GBS in term neonates in the UK.[28] In France, the average number of LBs each year was around 800,000 between 2001 and 2013, of whom 6.6% were born preterm.[29] In 2001, the Pediatric Infectious Group of the French Pediatric Society (GPIP/ACTIV) established an active bacterial pediatric meningitis surveillance network including 233 pediatric wards and 168 microbiology laboratories. From 2001 to 2013, 325 infants were prospectively diagnosed with *E. coli* meningitis, which was seven-fold more frequent in preterm than in term infants.[30] The median age at diagnosis was 14 days, with two peaks of infection onset at 0 to 3 days of age (EOS in mostly preterm neonates), and 11 to 15 days of age (LOS in mostly term infants). Severe clinical manifestation was reported in 51.9% of patients, and 9.2% died. Death was associated with very preterm birth (odds ratio [OR]: 7.3, 95% CI 2.7–20.9; $P < 0.001$), cerebrospinal fluid (CSF) to blood glucose ratio <0.1 (OR: 15.3, 95% CI 1.8–128.3; $P = 0.012$), uncommon strains like O7 serogroup ($P = 0.034$), and PapGII adhesin (OR: 2.3, 95% CI 1.2–4.5; $P = 0.015$). Translocation of GNB into the systemic circulation via an interrupted gastrointestinal barrier has been speculated to be a key mechanism of GNB LOS.[27,31]

Pathogen profiles of community- and hospital-acquired neonatal LOS

An emerging body of evidence has demonstrated completely different microbiological findings between various types of sepsis. This is of critical importance to guide empirical antibiotic therapy strategy, which should not only be adapted to the timing (early *vs.* late), but also to circumstances (hospital- *vs.* community-acquired).

Industrialized countries

To assess the epidemiology and types of neonatal sepsis, all newborn infants with blood culture-proven sepsis admitted to neonatal intensive care units (NICUs) in Switzerland between 2011 and 2015 were included.[7] Infants with LOS were classified as community- or hospital-acquired LOS if onset of infection was ≤48 or >48 h following admission. In 429 infants there were 444 episodes of blood culture-proven sepsis, with 20%, 62%, and 18% being EOS, hospital-acquired LOS, and community-acquired LOS, respectively. Correspondingly, the estimated incidence was 0.28, 0.86, and 0.28 per 1000 LBs, and case fatality 18%, 12%, and 0%, respectively. Major pathogens were GBS, other Gram-positive bacteria, and *E. coli* for EOS; GBS and *E. coli* for community-acquired LOS. In contrast, CoNS, *Staphylococcus aureus*, and other GNB were mostly isolated in hospital-acquired LOS [Supplementary Figure 2A, http://links.lww.com/CM9/A247 and 2B, http://links.lww.com/CM9/A248].[7]

Non-industrialized countries

The burden of neonatal infections in developing countries is highly variable, maybe because of the lack of vital registries and surveillance systems.[32] Information about community-acquired bacteremia in South Asia and Southeast Asia was approached through a review of 17 eligible studies enrolling 40,644 patients.[33] Pathogenic organisms were isolated in 1722 (7%) of 26,258 children. *Salmonella enterica* serotype Typhi was the most common bacterial pathogen. Other commonly isolated organisms in children were *Streptococcus pneumoniae* and *Haemophilus influenzae*, probably reflecting the lack of large-sale vaccination. Severe bacterial infections are a leading cause of death among neonates in low-income countries with poor hygiene and frequent exposure to antibiotics without documentation of bacterial infection, resulting in the emergence and spread of multi-resistant bacteria.[34] With advancing pediatric healthcare, the use of central venous catheters (CVC) has become a fundamental part of neonatal and pediatric intensive care.[35] Maximal sterile barrier precautions have been shown to independently contribute to decreased CVC-associated bloodstream infection in VLBW infants.[36] Currently, there is a lack of population-based data on the pathogen profile of neonatal LOS in China. Gram-positive bacteria, mainly CoNS and *S. aureus*, were indicated as being responsible for the majority of neonatal LOS, while *E. coli* and *Klebsiella* spp. may account for most GNB LOS.[16,37-41]. Most hospital-acquired LOS occurred in very preterm infants who were very likely to receive some kind of ventilatory support and parenteral nutrition through a CVC.[42]

Neonatal Viral Sepsis

The incidence of overall viral sepsis

Viruses are common but largely underappreciated pathogens of neonatal sepsis. In a population-based pregnancy surveillance at five sites in Bangladesh, India, and Pakistan from 2011 to 2014, babies with illnesses meeting the World Health Organization definition of possible serious bacterial infections (pSBI) were referred to study physicians for culture and molecular assays of blood and respiratory samples.[8] Among 63,114 babies, 6022 pSBI episodes were identified (95.4 per 1000 LBs), with causes specified in 28% of episodes (16% bacterial and 12% viral). The mean incidence of bacterial and viral infections was 13.2 (95% credible interval 11.2–15.6) and 10.1 (95% credible interval 9.4–11.6) per 1000 LBs, respectively. The leading viral pathogen was respiratory syncytial virus (5.4 per 1000 LBs). This study was among the first to provide valuable population-based data on neonatal viral sepsis with universal detection of pathogen species. So far, species-specific data on neonatal viral sepsis are limited.

Herpes simplex virus (HSV)

HSV may cause potentially devastating infection in neonates. However, large-scale assessment of its frequency in potentially infected infants has not been performed, apart from one retrospective cross-sectional study in 23 North American pediatric emergency departments enrolling infants ≤60 days old with CSF samples for HSV polymerase chain reaction (PCR) or culture.[43] Of 26,533 eligible encounters, 112 infants had HSV identified (0.4%), corresponding to 1.2% of all infants tested for HSV. Among them, 90 (80.4%) occurred in weeks 1 to 4, with the median age of HSV-infected infants being 14 days (interquartile range 9–24 days). Notably, 68 of 112 test-positive infants had central nervous system (CNS) or disseminated HSV disease. The proportion of infants subjected to an HSV test (35%, range 14%–72%) and to whom acyclovir was administered (23%, range 4%–53%) varied widely across centers. Thus, both pediatric emergency physicians and neonatologists should keep in mind this rare but deadly cause of neonatal sepsis, which requires urgent acyclovir administration. A careful review of the maternal history and close communication with obstetricians are critical for a timely diagnosis and treatment of neonatal HSV disease.

Enteroviruses

Enteroviruses have been increasingly recognized to be causes of meningitis, sepsis-like disease, and fever without source in neonates and older children. A prospective multicenter study performed at 35 French pediatric and emergency departments has shown that positive blood PCR results for enterovirus was common.[44] Between 2015 and 2016, a total of 71 newborns were subjected to enterovirus testing, the detection of enterovirus was more frequent in blood than in CSF (70/71 *vs.* 62/71, $P = 0.011$). As such, PCR for enterovirus should be part of the sepsis workup in neonatal sepsis, and empiric antibiotic therapy should be promptly discontinued in confirmed cases of viral infection. So far, there is a lack of population-based data on neonatal infection due to enterovirus in China. In a hospital-based prospective study in a level-3 NICU in East China, enterovirus infection among febrile neonates with an admission temperature >38°C was diagnosed by PCR testing of stool and/or CSF samples.[45] One-hundred thirty one (39.2%) of 334 febrile neonates had PCR-confirmed enterovirus infection, with PCR results being positive in 130 (99.2%) of stool and in 58 (44.3%) of CSF samples, respectively. Among 131 infected neonates, mostly term infants in their 2 to 3 postnatal weeks, 69 (52.7%) had diarrhoea, 48 (36.6%) respiratory symptoms, 22 (16.8%) poor feeding, 34 (26.0%) rash, and 18 (13.7%) lower platelet counts $<150 \times 10^9$/L.[45] These data indicate that enterovirus infection may be common in febrile neonates and stool samples should be included in diagnostic work-up. Although all infected patients received supportive treatment with none developing fulminant disease course, the long-term outcome of neonates infected with enterovirus may be worrying. Another case series of 12 Chinese neonates with a GA of 35 to 39 weeks showed that enterovirus can cause severe encephalitis associated with white matter damage in the neonatal period, and the severity of the imaging abnormalities might correlate with later neurodevelopmental outcome.[46]

Infectious Work-up of Neonatal Sepsis

Initial signs and symptoms of neonatal sepsis are often mild and not specific. Infected infants are likely to appear generally ill, without fever or system-related symptoms. However, the disease course may also be fulminant with development of septic shock, respiratory distress, neurological dysfunction, and even death. As such, a prompt and adequate infectious work-up is essential for timely diagnosis of neonatal sepsis and the prevention of adverse outcomes.

Culture-dependent and independent tests

Sufficient amount (1–2 mL) of blood should be taken to optimize the yield of blood culture,[47] besides the volume needed for a full blood cell count, venous pH, and lactate, and other parameters to assess the disease status [Table 2]. Urine sample obtained via aseptic bladder catheterization and CSF via lumbar puncture (LP) should be considered in a respiratory- and hemodynamically-stable infant.[48-50] A positive bacterial culture after 24 to 36 h confirm the type of bacterial pathogen, and allows antimicrobial susceptibility testing.[42] Biological markers, such as procalcitonin (PCT), C-reactive protein (CRP), white blood cell, and absolute neutrophil count (ANC), are not specific of bacterial infection. However, the Lab-score based on PCT levels (<0.5, ≥0.5, and ≥2 ng/mL), CRP levels (<40, 40–99, and ≥100 mg/L), and urine dipstick (negative or positive) has been shown to be highly predictive of a urinary tract infection (UTI).[51] Nonetheless, UTI should be defined by bacterial counts of uropathogen (mostly *E. coli*), with the minimum concentration ranging between 10^5 and 10^6 colony-forming units/mL.[52] Recently, two prediction rules to identify young febrile infants at risk of SBI in the pediatric emergency department have been validated. The "*Step-by-Step*" approach developed in

Table 2: Neonatal sepsis workup.

Parameter	Test	Optimal conditions for specimen collection	Value in diagnosing neonatal sepsis
Infectious markers			
Blood	Culture	1–2 mL of blood	Standard for bacteremia
Urine	Culture	Bladder catheterization	Gold standard for UTI
CSF	Culture	Non-traumatic lumbar puncture	Standard for meningitis
Nasopharyngeal	PCR	Winter epidemics, contact with a sick case; Nasal aspirates for RSV, nasal swab for influenza virus	Discuss plausibility and PCR positivity: possible respiratory tract infection
Biological markers			
pH, ABG, lactate	Blood	Arterial or venous sampling	Lactate >2 mol/L (indicate shock)
ANC	Blood count	Take into account the potential normal range for postnatal age	Neutropenia <1500/mm^3 (Not specific of bacterial infection)
Platelets	Blood count	No clotting sampling	Thrombocytopenia <50,000/mm^3
PCT	Blood	2–6 h after onset of infection	>2 ng/mL (not specific)
CRP	Blood	8–24 h after onset of infection	>20 mg/L (not specific)
Sepsis scores[53,54]	Multiple test	24 h after onset of sepsis	Useful for low-risk SBI

CSF: Cerebrospinal fluid; ABG: Arterial blood gases; ANC: Absolute neutrophil count; PCT: Procalcitonin; CRP: C-reactive protein; PCR: Polymerase chain reaction; RSV: Respiratory syncytial virus; UTI: Urinary tract infection; SBI: serious bacterial infection; IF: Immunofluorescence.

Europe assesses abnormal clinical appearance at first, followed by young age (<3 weeks), significant leukocyturia and bacteruria confirmed by high-power field microscope, PCT >0.5 ng/mL, CRP >20 mg/L, or ANC >10,000/mm^3 to define low-risk and high-risk of SBI.[53] The prediction rule of the PECARN group in USA identifies febrile infants 60 days or younger at low risk of SBI using the urinalysis, ANC, and PCT levels.[54]

Particularities of LP

LP is mandated in young febrile infants if sepsis is highly suspected and the patient's condition allows.[53-55] The previously recommended practice of performing brain imaging before a LP has been shown to significantly delay antibiotic treatment and increase the likelihood of a poor neurologic outcome, both in adults and children with proven bacterial meningitis.[56,57] As a traumatic LP can complicate the interpretation of CSF, it is helpful to evaluate the mean spinal canal depth (MSCD) using either the following rule MSCD (mm) = 0.4 × weight (kg) + 20 or direct ultrasound imaging.[58] Direct examination of CSF sample under microscope is mandatory to determine the bacterial type and number per high-power field, providing valuable guidance for empirical antibiotic therapy. The presence of Gram-positive cocci in long chains under microscope may suggest GBS meningitis, and Gram-negative bacilli meningitis caused by *E. coli* or even extended-spectrum beta-lactamase (ESBL) *Enterobacteriaceae*, depending on microbial surveillance results at the local institutions. In a multicenter study in Asia which included 453 documented episodes of neonatal sepsis, the most common pathogens for neonatal meningitis were *Klebsiella* spp. (27/76), followed by CoNS (11/76) and *E. coli* (10/76), with GBS identified only in one case.[15] One recent province-level multicenter study in South China including 838 cases of neonatal meningitis from 12 hospitals (2011–2016) showed that the first three causes were GBS (88/249), *E. coli* (55/249), and CoNS (32/249).[59]

Empirical Treatment of Neonatal Sepsis

Timing and regimen of antibiotics

Empirical antibiotic treatment should be initiated as soon as neonatal sepsis is suspected, in fear of negative outcomes associated with missed septic cases. As streptococci are often sensitive to penicillin/ampicillin and about 50% of *E. coli*, noticeably K1, are resistant to ampicillin/amoxicillin, most recommendations of treating neonatal EOS are now to combine amoxicillin/ampicillin with gentamicin.[5,60] If culture confirms GBS, amoxicillin/ampicillin is recommended, and gentamicin should be discontinued after 48 h to prevent cumulative nephro- and oto-toxicity.[61,62] In case of ampicillin-resistant *E. coli* infection, a third-generation cephalosporin like cefotaxime should be used (100 mg/kg per day), and at a higher dosage (200 mg/kg per day) when meningitis is suspected. In case of hospital-acquired LOS which is often caused by CoNS like *Staphylococcus epidermidis*,[42] vancomycin by intravenous injection (or continuous infusion through a CVC if it is infected) is recommended at first,[63,64] as many of CoNS are indeed methicillin-resistant. When culture results are positive for GNB, aminoglycoside is preferred given its narrow spectrum and reduced risk of resistance.[5] However, escalation to third-generation cephalosporin and even carbapenem should be considered, depending on local epidemiology, clinical presentation especially with CNS involvement, and whether there is evidence of ESBL *Enterobacteriaceae*.[5] As community-acquired LOS is

often related to respiratory viral infections,[65] antibiotic treatment must be rapidly discontinued when viral infections is confirmed by multiplex PCR of nasopharyngeal aspirates.

The duration of antibiotic treatment

Recently, two statements regarding the management of neonates born at <35 and >35 weeks' gestation with suspected or proven early-onset bacterial sepsis have been released in the US.[66,67] Suspected EOS should always be confirmed by cultures of blood, urine or CSF, and antibiotic therapy should be discontinued if cultures are sterile.[66,67] This rule also applies to the management of LOS. Furthermore, non-specific biological markers (eg, blood cell count, PCT, CRP) alone do not justify prolonged use of antibiotics.[66,67] A fruitful dialogue should be maintained between neonatologists and microbiologists to optimize the duration of antibiotic treatment, which relies often upon empirical rules: 7 to 10 days for bacteremia, 14 days for Gram-positive meningitis, and 21 days for Gram-negative meningitis,[3,68] Given the general trend to shorten antibiotic therapy and minimize the selection of multi-resistant bacteria,[69] PCT as a highly sensitive biomarker of sepsis has been investigated to guide the cessation of antibiotic therapy.[70]

Overuse and misuse of antibiotics contribute to microbial resistance

Both the inappropriate overuse of broad-spectrum antibiotics, such as third-generation cephalosporins and carbapenem, and inadequacy of antibiotic stewardship have led to the emergence of multi-resistant bacteria, mostly ESBL *Enterobacteriaceae*, in neonatal sepsis in China.[71] In a retrospective study reporting the temporal trend of antimicrobial resistance over a period of 25 years in the largest neonatal unit in Southwest China, a dramatic six- and two-fold increase was found in the resistance rate of ceftazidime and imipenem respectively, in *Klebsiella* spp. isolated from neonates with sepsis.[38] A recent meta-analysis of Chinese literature (2009–2014) on neonatal sepsis revealed that more than 50% of *E. coli* and *Klebsiella* spp. were resistant to third-generation cephalosporin, and ampicillin resistance of *E. coli* was almost 80%,[37] similar to that in the US (85%).[11] Unsurprisingly, the resistance rate of amikacin was relatively low (around 10%–15%) in *E. coli* and *Klebsiella* spp.,[37] probably due to the fact that aminoglycoside is not routinely used to treat neonatal sepsis in China. Carbapenem-resistance was found in 9% of *E. coli* and 6% of *Klebsiella* spp., respectively.[37] Similar antibiotic susceptibility results of GNB were corroborated by other systematic reviews and web-based surveys.[72,73] As for Gram-positive bacteria, although resistance to glycopeptide including vancomycin and linezolid seem to be rare in China, methicillin resistance was reported for 60% to 70% of *Staphylococcus* spp.[37,38,40]

Antimicrobial resistance in developing countries, such as India[74] and Egypt,[75] is alarming. A very recent report from a multinational, multicenter online database showed that third-generation cephalosporin resistance rates among Gram-negative isolates ranged from 26% to 84%, and carbapenem resistance rates ranged from 0% to 81% in 12 low- and middle-income countries.[73] Glycopeptide resistance rates among Gram-positive bacteria ranged from 0% to 45%.[73] Staff to patient ratio and antibiotic availability were considered to be key factors affecting antimicrobial resistance rate in these settings.[73] The rising antibiotic resistance very much complicates both the choice of initial empirical antibiotic treatment and secondary antibiotic strategy, as last-resource antibiotics are not readily accessible in many settings.[76]

To minimize the selection of multi-resistant bacteria, there is an urgent need to restrict antibiotic therapy to proven neonatal bacterial infection and shorten antibiotic course. Furthermore, surveillance and assessment of antibiotic consumption has been demonstrated to positively influence antibiotic stewardship strategy and reduce antibiotic use.[77] Screening for GNB on neonatal body sites may have a predictive value in neonatal LOS,[78] and decolonization has been investigated as an approach to prevent sepsis and the spread of multi-resistant GNB.[79] However, the prognostic value of routine screening of neonatal microbial colonization remains controversial, due to a lack of high-quality evidence, especially in VLBW infants.[31,78]

Supportive treatment of neonatal sepsis: uncertainties and certainties?

Neonatal sepsis can progress to septic shock, which may requires volume loading and vasopressors in order to maintain organ function. However, after the publication of the paradoxical results of the fluid expansion as supportive treatment (FEAST) trial comparing repeated boluses of 20 mL/kg of either saline or 5% albumin with no bolus in 3141 African children with severe infection,[80] there is now a trend to restrict unnecessary volume loading in order to stabilize hemodynamics while preventing the occurrence of brain and lung edema, especially in resource-limited settings.[81]

For years, intravenous immunoglobulins (IVIG) have been used in severe neonatal sepsis, because newborns are relatively deficient in endogenous immunoglobulins. However, a large phase III clinical trial of 3493 infants at 113 hospitals comparing two iv infusions of 500 mg (10mL) per kg body weight 48 h apart with placebo failed to demonstrate a significant difference in the incidence of subsequent sepsis episodes and the rates of major or non-major disability at 2 years of follow-up.[82] Since the large clinical trial included neonates from both developing and developed countries, the negative results should be interpreted as high-level evidence to abandon IVIG administration among septic neonates in China.

Conclusions

To sum up, the epidemiology and pathogen profile of neonatal sepsis may differ substantially between countries and regions, and data from elsewhere should always be interpreted with caution before being extrapolated to any local institution in China. The alarmingly high

antimicrobial resistance rate of pathogens causing neonatal sepsis in China poses a substantial challenge, given its very large annual birth population.[83] Emphasis is laid on continuous monitoring of *a priori* antibiotic susceptibility of the causative micro-organisms. Notably, viral infection may mimic clinical signs of bacterial sepsis but require antiviral therapy (or no therapy) instead of antibiotics. There is an urgent need for the early diagnosis of neonatal sepsis followed by adequate and appropriate empirical therapy. Equally important is the early cessation of antimicrobial treatment as soon as negative microbial evidence has been yielded, despite the presence of isolated abnormal inflammatory markers. Last but not the least, efficient communication with both obstetricians for reliable maternal history and microbiologists for culture results is strongly recommended, especially in resource-limited settings in China, to optimize the regimen and duration of antibiotic treatment.

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Conflicts of interest

None.

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