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Retrospective Epidemiological Investigation on Nosocomial Neonatal Sepsis in Shaanxi Province (2008-2010)

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Abstract

Objective: This study assessed the incidence, mortality, and pathogens associated with nosocomial neonatal sepsis (NNS) in Shaanxi Province to improve the prevention and control of NNS. **Methods**: Nine large neonatal departments in Shaanxi Province participated in this retrospective epidemiological investigation of NNS during the period of 2008-2010, using standardized protocol. The incidence, mortality, pathogens, antibiotic sensitivity, clinical characteristics, prognosis, and costs were analyzed. **Results**: Of 16,642 neonates admitted to neonatal departments in the 9 hospitals during 2008-2010, there were 139 cases of NNS, with incidence of 8.3% and mortality of 20.8%. The predominant pathogens were Gram-negative bacteria, accounting for 67.6% of positive cultures. Gram-positive bacteria accounted for 24.5% and fungal infection accounted for 7.9%. The most common Gram-negative species were *Klebsiella pneumonia* (22.3%), *Escherichia coli* (15.1%), and *Enterobacter cloacae* (8.6%). The dominant Gram-positive species identified were coagulase negative staphylococcal species (CONS) (8.6%), followed by *Staphylococcus aureus* (7.9%). The recovered bacterial pathogens demonstrated varying antibiotic resis-

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tance, but no meropenem-or-vancomycin-resistant strains were detected. Preterm and full-term infants showed significant difference in clinical manifestations, laboratory findings, mortality, and cost. **Conclusion**: NNS in the hospitals of Shaanxi Province showed a decreasing trend from 2008 to 2010, but the mortality did not reduce significantly. The predominant bacteria were Gram negative, and pathogens were found to have varying antibiotic resistance. The preterm group had higher mortality and costs than the full-term infants. Therefore, effective measures should be taken to control NNS, especially in preterm infants.

Keywords

Incidence, Mortality, Pathogens, Nosocomial, Infection, Neonatal Sepsis

1. Introduction

About four million neonatal deaths occur worldwide annually, of which 900,000 are caused by sepsis and 450 newborns die every hour mainly from preventable causes [1]. Three major causes of neonatal deaths, including infections, complications of preterm birth, and intrapartum-related neonatal deaths, account for almost 90% of all neonatal deaths [2]. Almost all (99%) neonatal deaths occur in developing countries, and China is among the top 10 countries that contribute to the largest numbers of neonatal deaths [3]. Without addressing these concerns, the Millennium Development Goal for Child Survival cannot be achieved. Developed countries have a better grasp of epidemiological information. Although China has a large number of newborn babies, the research data in this field is very limited [4]. In October 2008, there were 8 neonatal deaths because of hospital-acquired infection in a tertiary hospital in Shaanxi Province, which triggered Chinese Ministry of Health to improve controlling of hospital-acquired infection among neonates by strengthening administrative management. To collect the clinical data of from 2008 to 2010, this study assessed the incidence, mortality, and pathogens associated with nosocomial neonatal sepsis (NNS) in Shaanxi Province to improve the prevention and control of NNS.

2. Methods

2.1. Study Design and Data Collection

The present research, conducted by the Neonatal Network Organization in Shaanxi Province, was a retrospective epidemiological survey that analyzed the overall data of NNS in 9 participant hospitals from Jan. 1, 2008, to Dec. 31, 2010. These 9 hospitals included 2 children's hospitals, 3 maternal and child health hospitals, and 5 general hospitals.

During the research period, the recruited patients' medical records were filled out by the neonatologists, Including perinatal risk factors, gestational age, birth weight, age of onset, clinical manifestation, laboratory examination, prognosis and disease burden, pathogen, antibiotic susceptibility test results. Bacterial culture was prepared using an automatic bacteria culture instrument and antibiotic sensitivity testing was performed by disc diffusion method [5]. The research was approved by the ethics committee of the Mother and Children's Healthcare Hospital of Shaanxi Province.

2.2. Definition

NNS is defined as follows , hospitalized neonates with clinical signs of sepsis and a positive culture were included in the study in the event of any of the following: sepsis-acquired infections during parturition and postpartum, which occurred 48h after birth; sepsis related with last hospitalization; or new pathogens different from original pathogen infection (excluding pollution and original mixed infection). Cases of neonatal trans-placental obtained sepsis were excluded (onset within 48h after birth [6] [7].

2.3. Statistical Analysis

The SPSS 17.0 Statistical Software Package (SPSS Inc, Chicago, IL) was used for data analysis. Continuous variables were summarized as median with inter-quartile range (IQR) or range and mean with SD. Categorical data were presented as absolute numbers and proportions. Comparisons of the categorical variables were performed with the Chi square test or Fisher's exact test.

3. Results

3.1. General Information

A total of 16,642 admitted newborns were surveyed, among which 139 were culture-proven NNS cases, including 97 male and 42 female infants, 84 preterm and 55 full-term, with gestational age of 27 to 42 weeks (**Figure 1**). Only 40% of the cases enjoyed the new type of rural cooperative medical care (NCMS) support which cover 30% - 50% of medical cost for family.

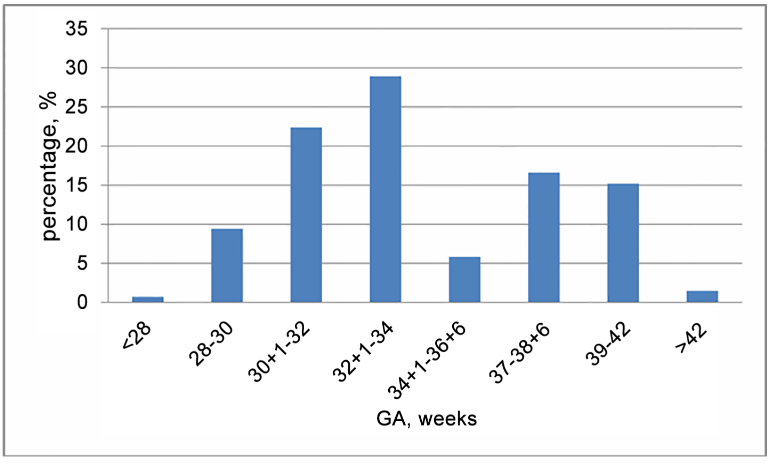

Figure 1. Gestational age distribution of NNS in Shaanxi Province: 2008-2010.

Among the 93 (low birth weight (LBW) infants, 2% (2/93) were extremly low birth weight (ELBW) and 27.9% (26/93) were very low birth weight (VLBW) In all NNS cases, the cesarean section rate was 61.8% (86/139), NICU treatment with incubators was performed in 71.9% (100/139), respiratory support including ventilation and oxygen therapy was provided in 20.1% (28/139), birth asphyxia developed in 8.6% (12/139), premature rupture of membranes was reported in 14.4% (20/139), and amniotic fluid contamination was reported in 10% (14/139). After admission, 88.4% (123/139) infants received antibiotic treatment, 50.4% (62/139) of whom were given prophylactic antibiotics. Third-generation cephalosporin or enzyme penicillin was used for therapeutic or prophylactic treatment in 69.1% (85/123) of infants, ampicillin in 9.8% (12/123) of infants, and none of them were treated with gentamicin. Up to 49.6% (69/139) received two antibiotic therapies. As many as 93.5% (130/139) of the infants were formula fed, and only 1.4% (2/139) were exclusively breast fed. The average time of starting enteral nutrition feeding was 2.5 days and the total enteral nutrition time was 19.7 days. Up to 88.4% (123/139) received intravenous nutrition therapies, 23% (32/139) used PICC, and 18.7% (6/32) developed catheter-related sepsis. Meanwhile, one nursing staff took care of 6 - 8 infants during daytime or 8-12 infants at night in these hospitals.

3.2. Incidence and Mortality

We identified 139 cases of culture-proven NNS among admitted neonates in the 9 hospitals during 2008-2010 (**Table 1**). The overall incidence of NNS was 0.83% and the mortality was 20.8% during the period. With comprehensive infection control measures, incidence and mortality of NNS decreased gradually but there were not statistically significant difference respectively in Shaanxi Province (P = 0.081, P = 0.817). The overall incidence of hospital infection among the admitted newborns to the total admissions in the neonatology departments was 38.9%. Although the proportion of NNS increased among overall hospital infections after strengthened prevention and control, there was no statistically significant difference (P = 0.618).

3.3. Clinical Manifestations, Laboratory Examinations and Outcomes

Despite atypical symptoms in NNS, the onset in full-term and preterm infants did not show the same initial clinical manifestations: Apnea, poor feeding, poor response, weight loss, and abdominal distension occurred in the preterm group, while the full-term group initially showed poor feeding, jaundice exacerbation, weight loss, and poor response. There was no significant difference between the two groups in terms of poor feeding, dyspnea stressed, no weight increase, or abnormal defecation. The mortality rate was high, abandoning treatment occurred quite frequently, and the mortality of the preterm infants was much higher than that of the full-term infants, resulting in a heavier disease burden (**Table 2**).

Laboratory examinations also showed different characteristics (**Table 3**). To some extent, the laboratory tests in NNS infants indicated of infection, with differentiated results between the full-term and premature groups, although both were very sensitive to changes in CRP. Premature infants showed a prominent decrease in white blood cells and a large proportion had neutropenia, while full-term infants showed an increase in

Table 1. Incidence and mortality of NNS in Shaanxi Province: 2008-2010.

Group	2008	2009	2010	Total
Admission in neonatal department, n	4972	5501	5501	16,642
HAI, n	139	113	105	357
HAI/Admission, %	2.8	2.3	1.7	2.1
NNS, n	52	42	45	139
NNS/HAI, %	37.4	37.1	42.8	38.9
Incidence of NNS, %	1	0.76	0.72	0.83
Death from NNS, n	12	9	8	29
Mortality of NNS, %	23	21.4	17.1	20.8

HAI: Hospital Acquired Infection, NNS: Nosocomial Neonatal Sepsis.

Table 2. Clinical manifestation and disease burden of NNS in Shaanxi Province: 2008-2010.

Group	Preterm	Full-term	P Value
N, %	84 (60.4)		55 (39.6)
Gestational age, weeks	32 ± 3.7	38 ± 1.9	0.007
Birth weight, g	1765 ± 789	3246 ± 881	0.043
Gender (Male/Female)	2.6:1	1.9:1	0.45
Average age of onset, days	16.5	6.7	0.002
Clinical manifestation, n (%)			
Apnea	72 (85.7)	4 (7.3)	0
Poor response	65 (77.3)	12 (21.8)	0
Poor feeding	44 (52.3)	35 (63.6)	0.222
Gastric retention	15 (17.8)	1 (1.8)	-
Hyperthermia	6 (7.1)	11 (20)	0.033
Hypothermia	21 (25)	5 (9)	0.025
Dyspnea stressed	19 (22.6)	6 (10.9)	0.113
No weight increase	69 (82.1)	41 (74.5)	0.294
Jaundice exacerbation	15 (17.8)	32 (58.1)	0
Abdominal distention	35 (41.6)	11 (20)	0.01
Abnormal defecation	11 (13.0)	8 (14.5)	0.806
Mortality, n (%)	25 (29.7)	25 (29.7)	0.001
Death due to quit treatment, n (%)	6 (24)	1 (25)	-
Average hospitalization, days	31	13	0.002
Average cost (RMB, Yuan)	19,350	6,843	0.007

Table 3. Laboratory examination of NNS in Shaanxi Province: 2008-2010.

Group	Preterm	Full-term	P Value
N, %	84(60.4)	55 (39.6)	-
WBC >20 × 109/L	36 (42.8)	38 (69.0)	0.003
WBC <5 × 109/L	38 (45.2)	10 (18.1)	0.001
Neutropenia	19 (22.6)	4 (7.3)	-
I/T of granulocyte >0.16	25 (29.7)	19 (34.5)	0.58
CRP >8 mg/L	75 (89.2)	46 (83.6)	0.439
PLT <100 × 109/L	43 (51)	15 (27)	0.064
Anemia	52 (61.9)	9 (16.3)	0
Acidosis	21 (25)	9 (16.3)	0.293
Hyperglycemia	23 (27.3)	11 (20)	0.42

WBC: white blood cell, CRP: C reaction protein, I/T: immature per total, PLT: platelets.

white blood cells. There was no statistically significant difference in terms of decreased platelets, metabolic acidosis, and hyperglycemia between the two groups ($P > 0.05$).

3.4. Pathogens

The predominant organism cultured was Gram-negative (67.6%) followed by Gram-positive (22.3%), and Candida albicans (7.9%). The most common Gram-negative organism identified in NNS was Klebsiella spp. (24.5%), followed by E. coli (15.1%) and E. cloacae (8.6%). The most common Gram-positive organism detected in NNS was Coagulase-negative staphylococci (CONS) (8.6%), followed by *Staphylococcus aureus* (7.9%) and *Enterococcus faecalis* (3.7%).

3.5. Antibiotic Sensitivity

The antibiotics resistant to *Klebsiella pneumonia* were ampicillin (91.3%), piperacillin (62%), and cefotaxime sodium (59.7%). The sensitive antibiotics were meropenem (100%), imipenem (100%), and cefepime (93.5%). The antibiotics resistant to E. coli were ampicillin (83.4%), cefotaxime sodium (53.2%), and cefuroxime sodium (47.5%). The antibiotics resistant to E. cloacae were ampicillin (84.1%), piperacillin (52.3%), and ceftriaxone (44%). The sensitive antibiotics of these two bacteria were meropenem (100%), imipenem (100%), and cefoperazone sulbactam (85.6% and 83.2%). The antibiotics resistant to CONS were penicillin (82%), erythromycin (74.1%), and cotrimoxazole (52.5%). The sensitive antibiotics of CONS were vancomycin (100%), rifampicin (96%), and minocycline (87.7%). The antibiotics resistant to S. aureus were penicillin (68.3%), erythromycin (65.2%), and rifampicin (59%). The antibiotics resistant to *Enterococcus faecium* were penicillin (86%), oxacillin (57%), and cotrimoxazole (42%). The susceptible antibiotics of these two were vancomy (100%), teicoplanin (100%), cin-levofloxacin levofloxacin (76.5%), and ciprofloxacin (72.3%) (Table 4).

Table 4. Pathogenic distribution of NNS in Shaanxi Province: 2008-2010.

Pathogen	Preterm	Full-term	P Value
N	84	55	139
Gram-positive bacteria	18 (21.4)	16 (29.1)	34 (24.5)
Coagulase-negative Staphylococci*	6 (7.0)	6 (11.0)	12 (8.6)
MRCNS	3 (3.6)	3 (5.5)	6 (4.3)
Staphylococcus aureus	4 (4.8)	7 (12.7)	11 (7.9)
MRSA	1 (1.2)	2 (3.6)	3 (2.1)
Enterococcus faecium	4 (4.8)	1 (1.8)	5 (3.7)
Enterococcus faecalis	2 (2.4)	0	2 (1.4)
Other Gram-positive bacteria	2 (2.4)	2 (3.6)	4 (2.9)
Gram-negative bacteria	57 (67.9)	37 (67.3)	94 (67.6)
Klebsiella pneumonia	20 (23.8)	11 (20)	31 (22.3)
ESBL positive	13 (15.5)	4 (7.3)	17 (12.2)
Klebsiella terrigena	4 (4.8)	4 (7.3)	8 (5.8)
Escherichia coli	14 (16.6)	7 (12.7)	21 (15.1)
Enterobacter cloacae	7 (8.3)	5 (9.2)	12 (8.6)
Pseudomonas spp.	4 (4.8)	2 (3.6)	6 (4.3)
Bauman acinetobacter spp.	3(3.6)	1 (1.8)	4 (2.9)
Serratia spp.	3 (3.6)	2 (3.6)	5 (3.6)
Other enterobacteriaceae	1 (1.2)	3 (5.5)	4 (2.9)
Other Gram-negative bacteria	1 (1.2)	2 (3.6)	3 (2.1)
Fungi	9 (10.7)	2 (3.6)	11 (7.9)

MRCNS: Methicillin Resistant Coagulase Negative Staphylococcus, MRSA: Methicillin Resistant Staphylococcus Aureus, ESBL: Extended Spectrum Beta Lactamases.

4. Conclusion

The overall incidence of NNS was 0.83% of the total 16,642 admitted neonates in the 9 hospitals, and the mortality rate was 20.8% in Shaanxi Province from 2008 to 2010. The pathogen was mainly Gram-negative (67.6%), Gram-positive (24.5%), or fungi (7.9%). Antibiotics had varying degrees of resistance, and the preterm group and full-term group showed significant differences in initial clinical manifestations and laboratory examinations. The preterm infants with NNS had higher mortality and heavier disease burden, which leads to abandoning of the treatment.

5. Discussion

5.1. Limitations of the Study

This was a retrospective study based on admitted patients but not birth population because of unavailability of an established nationwide medical information database in China. The positive rate of blood culture was not 100% [8], and if we take into account the cases of false-negative blood culture, the prevalence of NNS will be higher.

5.2. Incidence and Mortality

Huskins reported that rates of neonatal sepsis varied from 6.5 to 38 per 1000 live hospital-born babies. The bloodstream infection rates were 3 - 20 times higher in developing countries than the rates of 1 - 5 per 1000 live births reported in developed countries [9]. Stoll found that the incidence of LOS was 5.36-11.6% in hospitalized neonates [10]. Yi reported that sepsis in NICU was 19.8% and mortality was 10% - 50% in China [11].

Shaanxi is an underdeveloped province located in the northwestern China, with a population of 37 million. The birth rate was 8.88, 11.5 and 10.24 per one thousand people respectively, and the rate of institutional delivery was 97.1%, 98.8%, and 99.4% in 2008, 2009, and 2010, respectively. The increasing of neonatal in-patients was because of higher birth rate and improving infant care. From 2008 to 2010, neonatal mortality rate (NMR) was 13.99, 9.1, and 8.94 per one thousand live birth respectively, NNS mortality was accounted for 2.4, 1.63, and 1.3per one thousand admitted respectively, which showed the same declining trend but only by a small margin (0.11% vs. 0.5%) [12].

Both incidence and mortality of NNS obtained in our study were higher than those in developed countries. The incidence of sepsis was 4.06% among all NICU admissions in Taiwan. Mortality in LOS was 7% [13]. Isaacs reported an incidence of sepsis of 6.6 per 1000 live births in 7 Australian NICUs, of which 75% were LOS and overall mortality was 10% [14]. In 1998, in a cohort of 54 UK neonatal units that registered 3963 admissions, there was 204 (5%) cases of sepsis, of which 16 (8%) died [15]. The relatively low NNS incidence may be related to Chinese neonatal saving boundaries, which begin from gestational age of 28 weeks but not 23 weeks in developed countries. In our study, only one case was under 28 weeks and only two were ELBW infants. VLBW was reported in 27.9% of 93 LBW infants, who were the major contributors of NNS [16].

In our study, only 40% newborns had insurance (NCMS) support, which provided a reimbursement of 30% - 50%. In Shaanxi Province, the average disposable per capita income was 12,858, 14,129, and 15,695 Yuan for city residents, and 4390, 4980, and 5375 Yuan for rural residents in 2008, 2009, and 2010, respectively (6.7 Yuan = 1 $). Compared with the income, the disease burden was heavy, especially for rural residents with premature infants [17]. High giving-up rates resulted from economic difficulties and the refractory nature of the disease, which strongly suggested that not only treatment level but also insurance coverage should be improved to reduce NNS mortality in this region.

5.3. Clinical Manifestations, Laboratory Examinations, and Early Diagnosis

Early diagnosis of neonatal sepsis is important, but clinical signs are neither specific nor uniform [18]. Many markers have been developed for early detection, including cell-surface markers (CD11b, CD64, CD69), chemokines and cytokines (IL-6, IL-8, IL-10), and acute phase reactants (CRP, procalcitonin). However, no single infection marker is sensitive and specific enough to convince a doctor to use or withdraw antibiotic therapy in a sick infant. Developing diagnostic tools such as DNA arrays may be useful in the future [19].

Blood culture is the gold standard for the diagnosis of septicemia. However, it is not error-free because of the possibility of falsely sterile or insufficient sample, low-density bacteremia, or suppression of bacterial growth by earlier antibiotic administration [20]. Positive cultures reportedly ranged from 8% to 73% in the diagnosis of potential neonatal sepsis. The positive predictive value of blood routine test series was higher than the negative predictive value [21]. In underdeveloped regions, medical equipment and personnel are relatively insufficient for infants, and early recognition of atypical symptom experience is very important. We believe that it is more helpful to train medical staff and at the same time combine sepsis screening than to use biological markers or only monitoring.

5.4. Pathogens and Antibiotic Sensitivity

Jordan reported that 70% pathogens of LOS was Gram-positive bacteria, and fungi accounted for 15% [22]. NICHD Neonatal Research Network showed that Gram-positive organisms were most commonly associated with LOS among VLBW infants [17]. In UK, neonatal Network demonstrated that Gram-positive organisms comprised 70% of infections, Gram-negative organisms, 25%, and fungi, 5%, from 2006 to 2008. Of the Gram-positive pathogens, the top three were CONS (42%), *S. aureus* (10%), and *S. enterococci* (9%). Of the Gram-negative pathogens, E. coli contributed 8%, and Klebsiella spp. and *Enterobacter* spp., 5% each, and *Candida* spp. was responsible for all of the fungal infections [23]. In Japan, 58 NNS cases were diagnosed in 871 NICU-admitted neonates, 44.8% of which resulted from Staphylococcus species, including MRSA (25.9%), MSSA (3.4%), and CNS (15.5%) [24]. Kamath found that Gram-negative contributed to 71.8% of NNS, and the predominant pathogens were extended spectrum beta lactamase (ESBL)-producing Klebsiella species and MRSA [25]. In China, increasing Gram-negative bacilli dominance was reported, most of which was K. pneumoniae and *E. coli*. Nearly 6% of E. coli strains were reported as resistant to most cephalosporins and 83% of S. aureus strains were reported as resistant to oxacillin [26]. The differences in pathogens indicated that we cannot choose antibiotics based on the experience in developed countries. For example, doctors in developed countries use ampicillin and gentamicin as primary antibiotics, but it is not feasible in China because most pathogens of NNS are resistant to ampicillin; further, gentamicin is not permitted to be used for newborns in Chinese routine guidelines. The choice of antibiotics for an infant with suspected sepsis depends upon the predominant pathogens and antibiotic sensitivity pattern of a given region. However, routine use of these "high-level" antibiotics might increase the risk of infections with ESBL-positive organisms. We have also found that doctors use enzyme penicillin or cephalosporin as prophylactic antibiotics in our study, which may increase resistance to bacteria [27], for there is a challenge in management of extensive use of broad-spectrum antibiotics and long-term empirical use of antibiotics.

5.5. Therapy and Prevention

NNS needs comprehensive management, and the most effective method is hygiene of the hand. However, there are two primary factors that contribute to poor hygiene of the hand in underdeveloped regions: shortage of nursing staff and lack of investment to control hospital-induced infection [28]. Studies have shown that breastfeeding can reduce the incidence of LOS, but exclusive breast feeding rate is only 1.4% in our study compared with 50% - 90% in developed NICUs [29]. As indicated by our results, the infection control team of PICC catheter is insufficient. The success of the "One is Not Zero" philosophy requires strategies to prevent NNS, including improved hand hygiene, early breast milk feeding, limited use of invasive devices, rational use of antibiotics, and improved teamwork to contain infection [30].

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Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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