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The Clinical Characteristics of Neonatal Sepsis Infection in Southwest China

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Abstract

Objective To identify the pathogens responsible for neonatal sepsis in a high-volume women and children's hospital in Southwest China.

Methods We retrospectively studied 133 neonates who were admitted to the West China Women and Children's Hospital between 2008 and 2012 for sepsis. The clinical characteristics of the patients were recorded, and the antibiotic sensitivities of the isolated bacteria were determined.

Results All of the included patients had clinical symptoms of sepsis, and subsequent blood cultures confirmed the infection. Almost 80% of patients were infected with coagulase-negative staphylococci (52.8%), *Escherichia coli* (23.6%), *Klebsiella pneumoniae* (16.0%) or *Staphylococcus aureus* (7.5%). Neonates who were infected with gram-negative bacteria, particularly *K. pneumoniae*, had lower birth weights and were admitted to hospital within 24 hours of birth. Additionally, 87.5% of the isolated *K. pneumoniae* strains were resistant to third generation cephalosporins.

Conclusion Coagulase-negative staphylococci were the most common pathogens found in neonatal sepsis. Moreover, neonatal sepsis caused by gram-negative bacteria was more often observed in newborns of low birth weight. The isolated strains of gram-negative bacteria were highly resistant to cephalosporins. This observation highlights the issue of antibiotic-resistant pathogens in the clinical setting, which poses an added risk to infants presenting with sepsis.

Key words: neonatal sepsis, drug resistance, coagulase-negative staphylococci, *E. coli*, *K. pneumonia*

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Introduction

Due to immunological insufficiency, newborn infants are particularly susceptible to infection and sepsis, which results in a higher mortality risk (1, 2). Annually, approximately 4 million neonatal infants die within the first four weeks of life (1). The vast majority of neonatal deaths occur in low- and middle-income countries, and severe infections account for approximately 28% of these deaths. The lack of appropriate hygiene during labor and delivery, postnatal care, and feeding are major contributors to the development of systemic infections and death in vulnerable newborns (3-5), and neonatal infections remain prevalent despite the use of potent antibacterial agents and supportive care (1, 6-8).

The antibiotic sensitivity of these pathogens is continuously changing, and resistance patterns are poorly characterized due to the lack of appropriate laboratory facilities in community settings (2, 9, 10). Therefore, the present study was designed to investigate the pathogens responsible for neonatal sepsis in Chengdu, China. Additionally, we sought to determine the antibiotic susceptibility of the most common pathogens. The proper identification of the most common pathogens encountered in a community setting and the characterization of their antibiotic resistance patterns could lead to improvements in the care provided to infants presenting with sepsis. The results of the present study will help clinicians to make a more accurate empirical judgment

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and to prescribe more appropriate antibiotics.

Materials and Methods

Study subjects

This was a retrospective study conducted in newborns treated in the neonatal wards of the pediatric intensive care unit (PICU) between January 2008 and December 2012 at the West China Women and Children's Hospital, Sichuan University, which is the largest women and children's hospital in Southwest China.

The inclusion criteria were as follows: 1) infants younger than 28 days post-partum; 2) hospitalized in the neonatal ward; and 3) diagnosed with sepsis. In cases where sepsis was suspected due to symptoms including fever, cyanosis, tachypnea, wheezing, vomiting, anorexia, jaundiced pallor, hypotonia or hypertonia, apnea, dyspnea, poor peripheral perfusion, C-reactive protein levels, and/or white blood cell count, a blood culture was performed. Sepsis was diagnosed upon detection and confirmation of a blood pathogen in the specimen taken on admission to the PICU using a routine laboratory blood culture. Patients with a positive blood culture for coagulase-negative staphylococcus who did not present any clinical symptoms and those whose routine blood examinations showed normal results were excluded due to the possibility of contamination during sample handling.

The ethics committee of the West China Women and Children's Hospital, Sichuan University approved this study.

Data collection

The clinical characteristics of the neonates that were collected from their medical records included: gender, age at admission to the PICU, length of gestation, birth weight, mode of delivery, clinical diagnosis, length of stay, coexisting conditions or diseases, and antibiotic susceptibility/allergy. The mother's age and any perinatal complications that she might have experienced were also recorded. An independent observer assessed the reliability of the data entry.

Specimen collection

On admission, 1-3 mL of venous blood was directly drawn into a BACT/ALERT specimen collection tube (BioMérieux, Lyons, France) before patients received any antibiotic treatment. The procedure followed the CLSI M47-A Principles and Procedures for Blood Cultures-Approved guidelines (11).

Bacterial culture

Blood cultures were performed using the fully automated BACT/ALERT 3D-120 microbial detection system (BioMérieux) to detect common aerobic bacteria and fungi.

Bacterial identification and antimicrobial susceptibility testing

Between January 2008 and May 2010, bacterial species were identified using the BBL Crystal™ Identification Systems (BD Diagnostics, Sparks, USA) and API® strips (BioMérieux). The susceptibility of bacteria to antibiotics was performed using ATB™ test strips (BioMérieux). After June 2010, bacterial identification and anti-microbial susceptibility testing were performed using the VITEK 2 Compact System (BioMérieux), a fully automated microbial analysis system. Quality controls were performed according to the manufacturer's instructions and the CISI criteria. The diagnosis of coagulase-negative staphylococcal sepsis required at least two positive bloodcultures, as previously described (12).

Statistical analysis

Statistical analyses were performed using SPSS 17.0 for Windows (IBM, Armonk, USA). Continuous variables were tested for normality, and are presented as the means ± standard deviation or medians, as appropriate. Normally distributed data were analyzed by one-way analysis of variance (ANOVA), while the non-parametric Rank Sum Test was used for non-normally distributed data. Two-sided p values of <0.05 were considered to be statistically significant.

Results

The epidemiology of neonatal sepsis

Between January 2008 and December 2012, 12,037 neonates were hospitalized, including 2,765 (22.97%) with suspected sepsis. Positive blood cultures confirmed the diagnosis of sepsis in 133 (4.81%) neonates.

The most commonly identified pathogens were (in order of frequency): coagulase-negative staphylococci (56/133), *Escherichia coli* (25/133), *Klebsiella pneumoniae* (17/133) and *Staphylococcus aureus* (8/133) (Table 1). These four pathogens accounted for 79.7% of all confirmed cases of sepsis.

The less commonly detected pathogens included *Enterobacter cloacae*, *Enterococcus feces*, *Monocytogenes listeria* and *Candida albicans* (Table 1). The rates of coagulase-negative staphylococci detection in 2008, 2009 and 2010 were 43.5%, 59.5%, and 52.9% respectively. These values were significantly higher than those detected in 2011 and 2012 (21.1%, and 25.0%, respectively) (Table 1, $p<0.001$). The prevalence of infection with gram-negative bacteria *E. coli* and *K. pneumoniae* did not differ significantly over the four-year period. Additionally, 106 neonates were infected with coagulase-negative staphylococci, *E. coli*, *K. pneumoniae* or *S. aureus* between 2008 and 2012. The clinical characteristics of these patients are described in Table 2. Fifty-six (52.8%) neonates were infected with coagulase-negative staphylococci, 25 (23.6%) with *E. coli*, 17 (16.0%) with *K. pneumoniae*, and 8 (7.5%) with *S. aureus*. No neonates were infected with multiple pathogens.

Table 1. Pathogens Detected in 133 Cases of Neonatal Sepsis.

	2008 (n = 23)	2009 (n = 42)	2010 (n = 17)	2011 (n = 19)	2012 (n = 32)	Total [n (%)] (n = 133)
Coagulase-negative staphylococci	10	25	9	4	8	56 (42.1)
E.coli	5	4	3	8	5	25 (18.8)
K. pneumoniae	6	4		1	6	17 (12.8)
S. aureus		1	1	2	4	8 (6.0)
Enterobacter cloacae	1	2	1	1	2	7 (5.3)
Enterococcus feces		6		1		7 (5.3)
Monocytogenes Listeria				1	3	4 (3.0)
Candida albicans			1			1 (0.8)
Bowman Acinetobacter			1			1 (0.8)
Chryseobacterium meningosepticum			1			1 (0.8)
Enterobacter aerogenes				1		1 (0.8)
Streptococcus mitis					1	1 (0.8)
Candida parapsilosis					1	1 (0.8)
Streptococcus agalactiae					1	1 (0.8)
Onion Burkholderia					1	1 (0.8)
Acinetobacter Lu's (Loffi)	1					1 (0.8)

Table 2. Neonates Infected with the Four Most Common Pathogens [n (%)].

	Coagulase-negative staphylococci (n = 56)	***E. coli* (n = 25)**	***K. pneumoniae* (n = 17)**	***S. aureus* (n = 8)**	**Total (n = 106)**
Gender					
Male	39 (69.6)	18 (72.0)	11 (64.7)	5 (62.5)	73 (68.9)
Female	17 (30.4)	7 (28.0)	6 (35.3)	3 (37.5)	33 (31.1)
Admission age (d)					
<1	39 (69.6)	12 (48.0)	7 (41.2)	4 (50.0)	62 (58.5)
1-7	4 (7.1)	5 (20.0)	7 (41.2)	3 (37.5)	19 (17.9)
>7	13 (23.2)	8 (32.0)	3 (17.6)	1 (12.5)	25 (23.6)
Birth weight (g)	3,031±681	2,666±861	1,814±769	2,955±616	
<1,500	1 (1.8)	2 (8.0)	7 (41.2)	0 (0)	10 (9.4)
1,500-2,500	9 (16.1)	6 (24.0)	7(41.2)	1 (12.5)	23 (21.7)
2,500-4,000	38 (67.9)	15 (60.0)	3 (17.6)	7 (87.5)	63 (59.4)
≥4,000	5 (8.9)	1 (4.0)	0 (0.0)	0 (0)	6 (5.7)
No Data	3 (5.4)	1 (4.0)	0 (0.0)	0 (0)	4 (3.8)
Gestational age (wk)	37.8±2.5	36.4±4.2	36.4±4.2	37.5±2.7	
<37 (preterm)	9 (16.1)	8 (32.0)	15 (88.2)	1 (12.5)	33 (31.1)
37-42	40 (71.4)	17 (68.0)	2 (11.8)	7 (87.5)	66 (62.3)
>42 (postterm)	7 (12.5)	0 (0.0)	0 (0.0)	0 (0)	7 (6.6)
Delivery mode					
Cesarean section	32 (57.1)	8 (32.0)	8 (47.1)	5 (62.5)	53 (50.0)
Vaginal delivery	24 (42.9)	17 (68.0)	9 (52.9)	3 (37.5)	53 (50.0)
Multiple birth					
Singleton	54 (96.4)	23 (92.0)	8 (47.1)	7 (87.5)	92 (86.8)
Twin	2 (3.6)	2 (8.0)	9 (52.9)	1 (12.5)	14 (13.2)
Outcome					
Cure	52 (92.9)	19 (76.0)	12 (70.6)	8 (100)	91 (85.8)
Abandoned (discharged without treatment)	3 (5.4)	3 (12.0)	3 (17.6)	0 (0)	9 (8.5)
Death	0 (0)	3 (12.0)	2 (11.8)	0 (0)	5 (4.7)
No Data	1 (1.8)	0 (0.0)	0 (0)	0 (0)	1 (0.9)
Maternal age (y)					
≤35	48 (85.7)	21 (84.0)	16 (94.1)	7 (87.5)	92 (86.8)
>35	6 (10.7)	2 (8.0)	1 (5.9)	1 (12.5)	10 (9.4)
No Data	2 (3.6)	2 (8.0)	0 (0.0)	0 (0)	4 (3.8)
PPROM	9 (16.1)	9 (36.0)	8 (47.1)	1 (12.5)	27 (25.5)
Mechanical ventilation	7 (12.5)	13 (52.0)	12 (70.6)	2 (25.0)	34 (32.1)
Hospital stay of survivors (d)	13.98 (11.87, 16.09)	14.33 (9.89, 18.78)	26.69 (18.31, 35.07)	15.88 (9.63, 22.12)	17.34 (15.37, 19.31)

Table 3. **Coexisting Conditions [n (%)].**

Coexisting diseases	Coagulase-negative staphylococci (n = 56)	*E.coli* (n = 25)	*K. pneumoniae* (n = 17)	*S. aureus* (n = 8)	Total (n = 106)
Intraventricular hemorrhage	1 (1.8)	1 (4.0)	0 (0)	1 (12.5)	3 (2.8)
Respiratory disease	35 (62.5)	24 (96.0)	15 (88.2)	7 (87.5)	81 (76.4)
Meningitis	2 (3.6)	8 (32.0)	3 (17.6)	1 (12.5)	14 (13.2)
Electrolyte disturbance	9 (16.1)	6 (24.0)	7 (41.2)	1 (12.5)	23 (21.7)
Metabolic acidosis	4 (7.1)	3 (12.0)	0 (0)	0 (0)	7 (6.6)
Physiological jaundice	14 (25.0)	4 (16.0)	0 (0)	2 (25.0)	20 (18.9)
Neonatal asphyxia	3 (5.4)	4 (16.0)	10 (58.8)	1 (12.5)	18 (17.0)
Neonatal anemia	1 (1.8)	0 (0)	0 (0)	0 (0)	1 (0.9)
Neonatal pneumonia	17 (30.4)	6 (24.0)	5 (29.4)	3 (37.5)	31 (29.2)
Hypoxic-ischemic encephalopathy	0 (0)	1 (4.0)	0 (0)	0 (0)	0 (0)

The risk factors for neonatal sepsis

The majority (68.9%) of neonates infected with coagulase-negative staphylococci, *E. coli*, *K. pneumoniae* or *S. aureus* were male. Upon enrollment, neonates were grouped according to the infecting pathogen, and male infants were over-represented in each of the four most populous groups. However, the gender distribution did not vary significantly between pathogen groups (p=0.936) (Table 2). Coagulase-negative staphylococci infection was more common in early-onset sepsis than in late-onset sepsis (76.8% vs. 23.2%, p<0.05).

Of the 106 neonates infected with the four most common pathogens, 81 (76.4%) were admitted to the neonatal ward within seven days of delivery. When the enrolled neonates were grouped according to the infecting pathogen, the differences in the age at the onset of each pathogenic infection were not significant (p=0.334); however, there was a significant difference between the groups in mean birth weight (Table 2, p<0.001). The neonates who were infected with coagulase-negative staphylococci had the highest birth weight (3,031±681 g), and those infected with *K. pneumoniae* had the lowest birth weight (1,814±769 g). There was a significant difference between the birth weights of the neonates diagnosed with sepsis and the mean normal birth weight (3,304±380 g) observed at our center (coagulase-negative staphylococci: p=0.005; *E. coli*: p=0.001; *K. pneumoniae*: p=0.001; and *S. aureus*: p<0.001) (13).

In addition, of the 106 neonates infected with the four most common pathogens, 53 (50%) were delivered by caesarean section, and 53 (50%) were delivered by vaginal delivery (Table 2). When neonates were grouped according to pathogens, the mode of delivery did not differ significantly between the four groups (Table 2). Thirty three (31.1%) neonates had a gestational age of less than 37 weeks, 66 (62.3%) had a gestational age of between 37 and 42 weeks, and 7 (6.6%) had a gestational age of more than 42 weeks (Table 2). The gestational age of infants infected with coagulase-negative staphylococci was significantly higher than the gestational age of infants infected with either *K. pneumoniae* or *E. coli* (p<0.05), but did not differ significantly from the gestational age of infants infected with *S. aureus*. The mean gestational age of the *S. aureus* group was significantly higher than the mean gestational age of the *K. pneumoniae* group (p<0.05), but did not differ from the mean gestational age of the *E. coli* group.

Of the mothers of the 106 neonates infected with the four most common pathogens, 92 (86.8%) were aged over 35 years at the time of birth (Table 2). When the enrolled neonates were grouped according to the infecting pathogen, no differences were found in the average ages of the mothers in the four groups.

Twenty-seven (25.5%) mothers had a pre-term premature rupture of membranes (PPROM). However, when the enrolled neonates were grouped according to pathogens, there were no differences in the rates of maternal PPROM.

Outcome of neonatal sepsis

Of the 106 neonates infected with the four most common pathogens, 34 (32.1%) received mechanical ventilation, of which 7 (20.6%) were infected with coagulase-negative staphylococci, 13 (38.2%) with *K. pneumoniae*, 12 (35.3%) with *E. coli*, and only 2 (5.9%) with *S. aureus*. The rate of mechanical ventilation usage did not differ significantly between these groups (p=0.27, Table 2).

Most neonates tested positive for multiple simultaneous diseases (Table 3). The most common were as follows: respiratory disease (n=81, 76.4%), mostly associated with coagulase-negative staphylococci (n=35/81, 43.2%); neonatal pneumonia (n=31, 29.2%), mostly associated with coagulase-negative staphylococci (n=17/31, 54.8%); and electrolyte disturbance (n=23, 21.7%), mostly associated with coagulase-negative staphylococci (n=9/23, 39.1%) (Table 3). The mean duration of hospital stay for the neonates infected with *K. pneumoniae* (26.7±15.7 days) was significantly longer than that in the neonates infected with coagulase-negative staphylococci (14.0±7.9 days), *E. coli* (14.3±10.5 days) or *S. aureus* (15.9±7.5 days) (Table 2). This extended hospitalization of neonates infected by *K. pneumoniae* could be the result of ineffective treatments, as we later determined that the majority of the isolated *K. pneumoniae* strains were resistant to third generation cephalosporins and/or amoxicillin.

Of the 106 neonates infected with the four most common pathogens, five died in hospital, treatment was abandoned in nine who were lost in follow-up and one was transferred to

Table 4. **Drug Resistance of Gram-negative Bacteria.**

	Drug resistance rate (%)	
	Escherichia coli (n=25)	*Klebsiella pneumoniae* (n=17)
Amikacin	33.3	0.0
Amoxicillin	62.5	100.0
Amoxicillin/clavulanic acid	16.7	50.0
Aztreonam	21.4	66.7
Ertapenem	0.0	16.7
Macrodantin	0.0	0.0
Trimethoprim-sulfoxazole	50.0	43.8
Ciprofloxacin	16.7	12.5
Meropenem	0.0	0.0
Netilmicin	30.0	0.0
Piperacillin	82.4	100.0
Piperacillin/ tazobactam	5.9	33.3
Gentamicin	33.3	25.0
Tetracycline	75.0	0.0
Ticarcillin	100.0	100.0
Ticarcillin/clavulanic acid	60.0	100.0
Cefepime	37.5	81.3
Cefuroxime	61.1	88.9
Ceftriaxone	33.3	100.0
Cefalotin	90.0	100.0
Cefotaxime	70.0	100.0
Ceftazidime	29.2	87.5
Cefotetan	0.0	20.0
Cefoxitin	20.0	80.0
Cefazolin	28.6	100.0
Tobramycin	25.0	6.7
Imipenem	0.0	0.0
Levofloxacin	14.3	16.7

Table 5. **Drug Resistance of Gram-positive Bacteria.**

	Drug resistance rate (%)	
	Coagulase-negative staphylococcus (n=56)	*Staphylococcus aureus* (n=8)
Oxacillin	87.5	12.5
Macrodantin	0.0	0.0
Fusidic acid	4.5	0.0
Trimethoprim-Sulfoxazole	65.5	37.5
Erythrocin	85.5	62.5
Ciprofloxacin	50.0	0.0
Clindamycin	48.1	62.5
Quinupristin/ Dalfopristin	3.4	0.0
Rifampicin	12.5	0.0
Linezolid	0.0	0.0
Minocycline	0.0	0.0
Moxifloxacin	0.0	0.0
Norfloxacin	53.5	0.0
Penicillin	96.4	100.0
Gentamicin	66.1	37.5
Tetracycline	45.3	25.0
Tigecycline	0.0	0.0
Teicoplanin	2.6	0.0
Vancomycin	0.0	0.0
Levofloxacin	44.4	0.0

another hospital (Table 1). Three of the five neonates were diagnosed with *E. coli* and two were diagnosed with *K. pneumoniae*. Ninety-one (85.8%) neonates recovered from sepsis, and the rate of recovery of neonates infected with gram-positive bacteria was significantly higher than in neonates infected by gram-negative bacteria ($p<0.05$). The mortality rate of neonates infected with gram-negative bacteria was >10%.

The antimicrobial susceptibility of isolated pathogens

The patterns of drug resistance are presented in Tables 4 and 5. Of the eight isolated *S. aureus* strains, we found that all were methicillin-resistant. One isolate was resistant to oxacillin. All isolates were sensitive to fusidic acid, quinolones, teicoplanin, vancomycin, linezolid and quinupristin. The drug resistance of *E. coli* to ceftazidime was relatively low (29.2%), while the drug resistance of *K.*

pneumoniae to ceftazidime was relatively high (87.5%); however, the drug resistance of these two Gram-negative bacteria to cefotaxime was relatively high (*E. coli*: 70.0%; *K. pneumoniae*: 100%). While β-lactamase inhibitors reduced *E. coli* resistance rates, the drug resistance of *E. coli* to amoxicillin/clavulanic acid was 50%. However, >50% of the *K. pneumonia strains* were resistant to amoxicillin and clavulanate potassium. All of the isolated *E. coli* and *K. pneumonia* strains were sensitive to imipenem.

Discussion

In this retrospective study, we investigated the pathogens isolated from neonatal patients with sepsis. We found that the four most commonly isolated pathogens were coagulase-negative staphylococci, *E. coli*, *K. pneumoniae* and *S. aureus,* and that these strains were responsible for nearly 80% of the cases of sepsis. Moreover, we found that gram-positive bacteria, including *S. aureus*, were responsible for 56.4% of sepsis cases. This finding is consistent with the literature (12, 14, 15); however, it should be interpreted with caution since some studies did not include patients with coagulase-negative staphylococci bacteremia. A meta-analyses reviewing 19 studies found that three of the four organisms that we highlighted (*S. aureus*, *E. coli*, and *Klebsiella* species) caused nearly half (44%) of all infections in neonates (16). However, in that same study, coagulase-negative staphylococci were detected with less frequency (only 18%) in comparison to the present study (as high as 42.1%) (16). Coagulase-negative staphylococci are commonly found on the skin, and can contaminate patient samples during handling. In the present study, patients with positive cultures for coagulase-negative staphylococci but without clinical symptoms of sepsis were excluded. The results of the present study will help the clinicians to make a more accurate empirical judgment and to prescribe more appropriate antibiotics.

It was previously found that coagulase-negative staphylococci are predominantly responsible for early-onset neonatal sepsis (17, 18). In the present study, coagulase-negative staphylococci were most frequently detected in late-onset neonatal sepsis in pre-term infants. However, as outlined above, the blood cultures from several of these patients may have been contaminated during sample handling, and may be false-positives. Sample contamination cannot be ruled out even in the presence of symptoms of sepsis, since some of the symptoms are not exclusive to sepsis. We found that infants born prematurely were more likely to be infected with *K. pneumoniae*, and that infants infected with *K. pneumoniae* exhibited lower than average birth weights. This may be due to the fact that neonates with a low birth weight have an impaired immune system, making them more susceptible to infections (19). However, the present study did not examine the immune function of the included neonates.

Infection with gram-negative bacteria was predominantly responsible for early-onset sepsis, and was more frequently detected in neonates of low birth weight. In contrast, *S. aureus* predominated in late-onset neonatal sepsis, as has been previously reported (20). We conclude that premature infants, and those with low birth weights, are more susceptible to symptomatic systemic infections with these pathogens, and that they more frequently develop nosocomial infections.

Neonatal sepsis was found to frequently coexist with other conditions including respiratory diseases, electrolyte disturbance, meningitis, physiological jaundice, neonatal asphyxia and neonatal pneumonia. The neonates infected with *E. coli* were more likely to suffer from respiratory diseases and meningitis, while neonates infected with *K. pneumoniae* were more likely to suffer from electrolyte disturbance and neonatal asphyxia. Intraventricular hemorrhage, neonatal anemia and hypoxic-ischemic encephalopathy were only rarely observed in the present study.

The antibiotic resistance demonstrated by the neonatal pathogens in this study is increasing globally. In order to develop appropriate management strategies, anti-microbial resistance must be monitored very carefully and accurately. In the present study, 100% (8/8) of the *S. aureus* strains were methicillin-resistant, but only 12.5% (1/8) of these same isolates were resistant to oxacillin (ORSA), representing a lower prevalence of resistance than previously reported, i.e. that 23% of isolated strains were ORSA (21). The lower rate of resistance that we detected could be attributed to our study including patients in whom the infection was exclusively systemic, rather than superficial and systemic (22). However, as our sample included only eight patients with *S. aureus*, we cannot draw any firm conclusions. Although all the *S. aureus* isolates were resistant to penicillin, each isolate was found to be sensitive to fusidic acid, quinolones, teicoplanin, vancomycin, linezolid and quinupristin.

The antimicrobial susceptibility of three common Gram-negative bacteria was quite concerning. All of the isolated strains of *K. pneumoniae* were resistant to amoxicillin and piperacillin, and more than 60% of the isolated *E. coli* strains were resistant to amoxicillin and piperacillin, although we found that both piperacillin and β-lactamase inhibitors were effective when used in combination. Surprisingly, 87.5% of the isolated *K. pneumoniae* strains were resistant to third-generation cephalosporins, while *E. coli* strains were far less frequently resistant to third-generation cephalosporins (29.2%), which is consistent with the rates observed in South Asia (23). In addition, resistance to third-generation cephalosporins was more common in isolated *K. pneumoniae* (66%), and less common in *E. coli* (19%) (23). Resistance to third-generation cephalosporins among *K. pneumoniae* and *E. coli* was almost consistent with the rates that have been previously reported in South Asia (2). All isolates were sensitive to imipenem. We found that 33.3% of *E. coli* isolates were resistant to gentamicin, a higher rate than that reported by Thaver et al. (23). However, we also observed a lower rate of gentamicin resistance in *K. pneu-*

moniae, possibly due to the small study population in our single center analysis.

Overall, we found evidence of antibiotic resistance in most of the tested pathogens. Particularly concerning was the observed resistance of gram-negative bacteria to cephalosporins. Although these pathogens mostly retained sensitivity to the aminoglycosides, these drugs often cause severe adverse reactions in neonates, particularly ototoxicity and nephrotoxicity, and are thus rarely administered to neonates at our hospital.

The present study is associated with some limitations. First, even if we are the largest mother and child hospital in southwest China, the sample size was small due to the relative rarity of neonatal sepsis, even in a developing country. In addition, the retrospective nature of the study prevented us from perform any more assays that could have yielded some clues about the mechanisms of drug resistance. Finally, we had no means of determining the sources of infection, and we may only suppose that it was through mother-infant transmission.

Conclusion

We found that 23% of hospitalized neonates were admitted with sepsis. Coagulase-negative staphylococci, *E. coli*, *K. pneumoniae* and *S. aureus* were the most common bacterial pathogens responsible for neonatal sepsis. Gram-negative bacterial infection predominated in the first week and in neonates of low birth weight. We detected an alarming rate of antibiotic resistance in the isolated strains of pathogenic bacteria. Gram-negative bacteria were frequently resistant to cephalosporins, highlighting the transmission of antibiotic resistant pathogens in a clinical setting, posing a particular problem for the clinical therapy and management of these infants. Further analysis of the resistance patterns seen in nosocomial infections is therefore required to improve clinical practice in the future.

The authors state that they have no Conflict of Interest (COI).

Yongmei Jiang and Linghan Kuang contributed equally to this work.

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