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ORIGINAL ARTICLE

Analysis of Differences in Neonatal Sepsis Caused by *Streptococcus Agalactiae* and *Escherichia Coli*

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SUMMARY

Background: ***Streptococcus agalactiae*** **(*GBS*) and *Escherichia coli* (*E. coli*) are the main pathogenic bacteria in neonatal sepsis. Therefore, the clinical characteristics, nonspecific indicators, and drug susceptibilities of these two bacteria were studied.**

Methods: **In total, 81 and 80 children with sepsis caused by *GBS* and *E. coli* infection, respectively, admitted to the neonatal department of our hospital between May 2012 and July 2023, were selected, and the clinical characteristics of the two groups were analyzed. Nonspecific indicators and drug sensitivity test results were analyzed retrospectively.**

Results: **Birth weight, tachypnea, groan, tachycardia or bradycardia, and the incidence of complications, such as pneumonia, respiratory failure, and purulent meningitis, were higher in the *GBS* group than in the *E. coli* group. The children were born prematurely, and the mother had a premature rupture of membranes. The incidence of jaundice, abdominal distension, atypical clinical manifestations, and complications of necrotizing enterocolitis was lower than of the *E. coli* group, and the differences were statistically significant ($p < 0.05$). The WBC, NE#, NE#/LY#, hs-CRP, and PCT of the *GBS* group were higher than those of the *E. coli* group, whereas the MPV, D-D, and FDP levels were lower than those in the *E. coli* group. The differences were all statistically significant ($p < 0.05$). The 81-bead *GBS* had high resistance rates against tetracycline (95%), erythromycin (48.8%), and clindamycin (40%), and no strains resistant to vancomycin, linezolid, penicillin, or ampicillin appeared, whereas 80 strains of *E. coli* were more resistant to penicillin and third-generation cephalosporins, with the higher resistance rates to ampicillin (68.30%), trimethoprim/sulfamethoxazole (53.6%), and ciprofloxacin (42.90%). Resistance rates to carbapenems and aminoglycosides were extremely low.**

Conclusions: **Both *GBS* and *E. coli* neonatal sepsis have specific clinical characteristics, especially in terms of clinical manifestations, complications, non-specific indicators, and drug resistance. Early identification is important for clinical diagnosis and treatment.**

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KEYWORDS

Neonatal sepsis, Streptococcus Agalactiae, Escherichia Coli

INTRODUCTION

Neonatal sepsis (NS) is a disease, in which pathogenic microorganisms invade the blood circulation system of newborns and continue to proliferate and secrete toxins, leading to a systemic infection [1]. The incidence of NS

among surviving newborns is approximately 0.45% to 0.97%, and the mortality rate can be as high as 11% to 19% [2], seriously endangering the life and health of newborns. Commonly associated with an insidious onset, NS, often accompanied by atypical clinical manifestations, a complex and diverse pathogen composition, a low sensitivity of routine examinations, and long blood culture times, makes clinical diagnosis and effective treatment the focus and difficulty of research on this disease [3]. Common pathogenic bacteria of NS include Gram-positive bacteria, Gram-negative bacteria, and fungi. There have been many studies analyzing the distribution and clinical characteristics of NS pathogens [4,5]; however, the research results are often divergent. In the 20th century, the United States Research from the National Institute of Child Health and the Human Development Neonatal Network shows that *GBS* and *E. coli* are the main pathogenic bacteria causing NS [6]. In recent years, due to the widespread implementation of intrapartum antibiotic prophylaxis and vaginal and rectal GBS screening, which have reduced the perinatal transmission of GBS, the epidemiology of NS is changing [7], and the antibiotic resistance rate of the two pathogenic bacteria may also change. Based on the reasons mentioned above, this article used a retrospective study method to focus on the clinical characteristics, complications, and nonspecific indicators of 81 cases of *GBS* and 80 cases of neonatal sepsis caused by *E. coli* infections, admitted to the neonatal department of our hospital from May 2012 to July 2023. Furthermore, the drug susceptibility test results of these two bacteria were analyzed to provide a basis for clinical diagnosis and treatment.

MATERIALS AND METHODS

Objectives

A retrospective analysis of the distribution of pathogenic bacteria was conducted in 483 children with NS, that were admitted to the Neonatology Department of the Fujian Maternal and Child Health Hospital between 05/2012 - 07/2023 and met the inclusion criteria. Finally, 81 children with GBS and 80 children with sepsis caused by E. coli infection were included in the study. General information on the two groups of children (gender, age of onset, gestation mode, birth weight, etc.), maternal factors, main clinical characteristics, complications, blood-related laboratory test results, distribution of pathogenic bacteria, and bacterial drug susceptibility test results were collected. This study was approved by the Ethics Committee of Fujian Maternal and Child Health hospital (approval number: 2023KY153).

Case definition

All included children met the diagnostic criteria for NS in the "Expert Consensus on Diagnosis and Treatment of Neonatal Sepsis (2019 Edition)" [8] and had complete hospitalization medical records. All patients were treated at the same hospital until they recovered, were discharged, discontinued treatment, or died. Children with developmental malformations or primary insufficiency of important organs, such as the heart, liver, and kidneys, with blood diseases and acquired immunodeficiency diseases, and those with suspected contamination of blood samples were excluded.

Identification and drug susceptibility testing

Blood cultures were performed by using a BCTA-ALERI3D fully automatic blood enrichment culture instrument (BioMérieux, France). The strains were identified and analyzed for drug susceptibility testing by using a VITEK-2 automatic microbial identification instrument. The supplementary drug sensitivity test used the disk diffusion method (K-B method), and the interpretation results were based on the latest versions of the American Clinical Laboratory Standards Institute (CLSI) standards for each year. Drug susceptibility disks were purchased from the British OXOID Company. The quality control strains used were *Escherichia coli* ATCC25922 and *Staphylococcus aureus* ATCC29 213 from the Provincial Clinical Laboratory Center.

Statistical analysis

Statistical analyses were performed by using GraphPad Prism 8.04 data editor. WHONET5.6 software was used for the drug sensitivity test result statistics. Count variables were analyzed by using Student´s *t*-test or Mann-Whitney U test. Categorical variables were analyzed by using the chi-squared test or Fisher's exact probability method. Normally distributed data results are expressed as mean ± standard deviation ($\bar{x}$ ± s), non-normally distributed results are expressed as interquartile range (IQR) results, and categorical variables are expressed as n (%); statistical significance was set at $p < 0.05$ for all analyses.

RESULTS

Distribution of pathogenic bacteria in children with sepsis

By retrieving hospital LIS system information data for statistics, after the inclusion and exclusion of cases, 483 children with confirmed sepsis were included in the study. The top two pathogenic gram-positive bacteria were *GBS* in 81 cases (16.77%) and coagulase-negative staphylococcus in 78 cases (16.15%), while the top two pathogenic bacteria among gram-negative bacteria were *E. coli* in 80 cases (16.56%) and Klebsiella pneumoniae in 76 cases (15.73%). *GBS* and *E. coli* were the main pathogens that caused NS in our hospital (Figure 1).

Comparison of the general conditions and maternal factors of children with sepsis between the *GBS* group and the *E. coli* group

The birth weight of the *GBS* group was higher than that of the *E. coli* group, and the incidence of premature

Table 1. Comparison of general circumstances and maternal factors between GBS and E. coli.

	General circumstances		GBS (n = 81)	E. coli (n = 80)	χ^2/t	p
General circumstances	gender (n)	male	50 (61.73%)	57 (71.25%)	1.637	0.2007
		female	31 (38.27%)	23 (28.75%)		
	birth weight (kg)		3.268 ± 0.570	2.969 ± 0.718	2.929	0.0039
	age of onset (days)		8.716 ± 9.168	10.230 ± 8.989	1.054	0.2933
	the apgar score at 5 minutes		9.483 ± 1.354 (58)	9.160 ± 1.361 (50)	1.232	0.2205
	preterm labor (n)		4 (4.94%)	19 (23.75%)	11.630	0.0006
Maternal factors	delivery mode (n)	spontaneous labor	66 (81.48%)	59 (73.75%)	1.386	0.2391
		caesarean birth	15 (18.52%)	21 (26.25%)		
	premature rupture of membranes (n)		4 (4.94%)	16 (20.00%)	8.393	0.0013
	amniotic fluid pollution (n)		17 (20.99%)	12 (15.00%)	0.977	0.3229
	pregnancy-induced hypertension		3 (3.7%)	2 (2.50%)	0.194	0.6598
	gestational diabetes (n)		13 (16.05%)	8 (10.00%)	1.299	0.2545

Table 2. Comparison of clinical characteristics between GBS and E. coli.

Clinical characteristics	GBS (n = 81)	E. coli (n = 80)	χ^2	p
Suffocation (n)	4 (4.94%)	3 (3.75%)	0.137	0.7116
Fever (n)	50 (61.73%)	51 (63.75%	0.070	0.7908
Poor response (n)	32 (39.51%)	31 (38.75%)	0.010	0.9217
Jaundice (n)	15 (18.52%)	30 (37.50%)	7.201	0.0073
Tachypnea (n)	52 (64.20%)	31 (38.75%)	10.440	0.0012
Groan (n)	48 (59.26%)	19 (23.75%)	20.890	< 0.0001
Cyanosis (n)	20 (24.69%)	11 (13.75%)	3.099	0.0783
Convulsions (n)	3 (3.7%)	1 (1.25%)	1.000	0.3173
Abdominal distension (n)	2 (2.47%)	13 (13.75%)	9.047	0.0026
Vomit (n)	7 (8.64%)	14 (17.50%)	2.784	0.0952
Poor appetite (n)	24 (29.63%)	18 (22.50%)	1.061	0.3031
Poor suckle (n)	29 (35.80%)	25 (31.25%)	0.374	0.5407
Tachycardia or bradycardia (n)	34 (41.98%)	21 (26.25%)	4.425	0.0354
Atypical clinical manifestations (n)	9 (11.11%)	20 (25.00%)	5.257	0.0219
Early-onset (n)	39 (48.15%)	29 (36.25%)	2.335	0.1265
Late-onset (n)	42 (51.85%)	51 (63.75%)	2.335	0.1265
Abandoning treatment or Death (n)	14 (17.28%)	14 (17.50%)	0.001	0.9712
Rehabilitation discharge (n)	67 (82.72%)	66 (82.50%)	0.001	0.9712

birth and premature membrane rupture was lower than of the *E. coli* group. These differences were statistically significant ($p < 0.05$). There were no statistically significant differences in age, mode of delivery, Apgar score at 5 minutes after birth, or maternal factors, such as amniotic fluid contamination, gestational hypertension, or gestational diabetes ($p > 0.05$) (Table 1).

Comparison of clinical characteristics between *GBS* group and *E. coli* group

The incidence rates of tachypnea, groaning, and tachycardia or bradycardia in the *GBS* group were higher than those in the *E. coli* group, while the incidence rates of jaundice, abdominal distension, and clinical atypical manifestations were lower than those in the *E. coli*

Table 3. Comparison of complication between GBS and E. coli.

Complication	GBS (n = 81)	E. coli (n = 80)	χ^2	p
Bleeding (n)	24 (29.63%)	18 (22.5%)	0.345	0.5571
Pneumonia (n)	48 (59.26%)	22 (27.50%)	16.520	< 0.0001
Necrotizing enterocolitis (n)	1 (1.23%)	7 (8.75%)	4.814	0.0282
Gazing dysfunction (n)	9 (11.11%)	10 (12.50%)	0.075	0.7848
Infectious shock (n)	9 (11.11%)	7 (8.75%)	0.251	0.6166
Respiratory failure (n)	28 (34.57%)	14 (17.50%)	6.081	0.0137
DIC (n)	3 (3.7%)	6 (7.50%)	1.099	0.2945
Hypoproteinemia (n)	17 (20.99%)	21 (26.25%)	0.618	0.4317
Brain injury (n)	24 (29.63%)	22 (27.50%)	0.089	0.7649
Hyperglycemia (n)	13 (16.05%)	7 (8.75%)	1.971	0.1603
Purulent meningitis (n)	35 (43.21%)	19 (23.75%)	6.838	0.0089

Table 4. Comparison of non-specific indicators between GBS and E. coli.

Non-specific indicators	GBS (n = 81)	E. coli (n = 80)	*t*	p
WBC (× 10^9/L)	22.74 ± 9.368	12.26 ± 6.338	8.303	< 0.0001
NE# (× 10^9/L)	16.44 ± 8.541	7.450 ± 5.051	8.116	< 0.0001
LY# (× 10^9/L)	3.758 ± 2.127	3.256 ± 1.941	1.565	0.1196
NE#/LY#	5.924 ± 4.427	3.065 ± 3.155	4.715	< 0.0001
RDW-CV (fL)	16.1 ± 1.710	15.59 ± 1.592	1.954	0.0525
PLT (× 10^9/L)	274.3 ± 121.8	257.4 ± 147.4	0.793	0.4288
MPV (fL)	10.24 ± 0.99	10.64 ± 1.119 (73)	2.371	0.0190
PDW (fL)	13.27 ± 2.223	12.38 ± 2.611 (73)	0.908	0.3653
hs-CRP (mg/L)	70.61 ± 56.7	43.44 ± 52.31	3.159	0.0019
PCT (ng/mL)	19.77 ± 15.94 (38)	8.941 ± 8.824 (44)	3.874	0.0002
D-D (mg/L)	2.416 ± 1.656 (43)	7.78 ± 9.491 (35)	3.644	0.0005
FDP (mg/L)	9.922 ± 6.037 (43)	35.36 ± 46.82(35)	3.532	0.0007

WBC - white blood cell count, NE# - neutrophil count, LY# - lymphocyte count, NE#/LY# - neutrophil-to-lymphocyte ratio, RDW-CV - red cell distribution width, PLT - platelet count, MPV - mean platelet volume, PDW - platelet volume distribution width, CRP - high sensitivity C-reactive protein, PCT – procalcitonin, D-D - D-dimer, FDP - fibrinogen degradation products.

group. The differences were statistically significant ($p < 0.05$), and there was no statistically significant difference in the incidence of other clinical characteristics between the two groups ($p > 0.05$) (Table 2).

Comparison of major complications between *GBS* group and *E. coli* group

The incidence rates of pneumonia, respiratory failure, and purulent meningitis were higher in the *GBS* group, whereas the incidence rates of necrotizing enterocolitis were lower in the *GBS* group. These differences were statistically significant ($p < 0.05$). The incidence of complications was not significantly different between the two groups ($p > 0.05$) (Table 3).

Comparison of non-specific indicators between GBS group and E. coli group

WBC, NE#, NE#/LY#, hs-CRP, and PCT of the GBS group were higher than of the E. coli group, whereas MPV, D-D, and FDP were lower than those of the E. coli group, and these differences were statistically significant ($p < 0.05$). There were no statistically significant differences in other non-specific indicators between the two groups ($p > 0.05$) (Table 4).

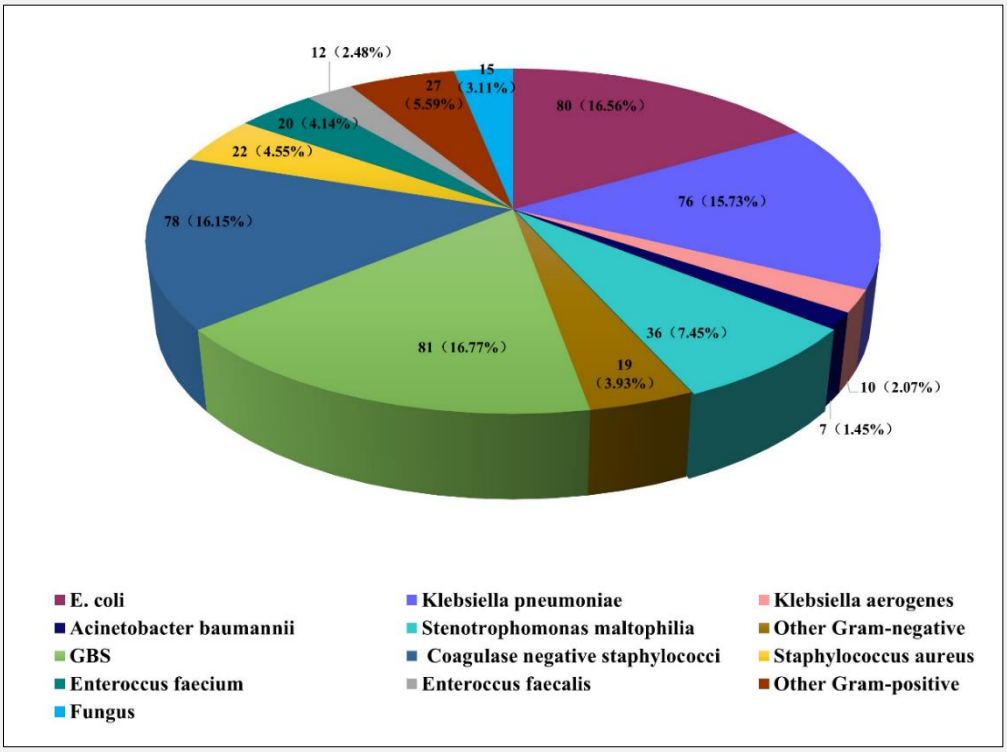

Figure 1. The distribution of pathogenic bacteria for neonatal septicemia from 2012 to 2023.

Drug resistance analysis of *GBS* and *E. coli*

The main rates of GBS resistance to tetracycline, erythromycin, clindamycin, and ciprofloxacin were 95%, 48.8%, 40%, and 30%, respectively. None of the strains were resistant to vancomycin, linezolid, penicillin, or ampicillin. Many E. coli strains were resistant to penicillin and third generation cephalosporins. The highest resistance rates were observed for ampicillin (68.30%), trimethoprim/sulfamethoxazole (53.6%), ciprofloxacin (42.9%), and cefazoline (40.2%), while the resistance rates to carbapenems and aminoglycosides were extremely low (Figures 2 and 3).

DISCUSSION

NS is a common and serious disease, encountered in neonatal wards. Because its symptoms are changeable and difficult to detect early on, they often lead to delays in the diagnosis and treatment. Therefore, NS is a major cause of neonatal death [9]. The incidence and clinical characteristics of NS caused by different pathogenic bacteria vary from country to country, region to region, and from medical institutions, even within the same region or the same medical institution at different times. Therefore, for clinical diagnosis and treatment, it is important to understand the distribution and drug resistance of common pathogenic bacteria of NS in our hospital, as well as the main clinical characteristics and complications of it.

This study showed that a total of 483 children with sepsis were admitted to the neonatal department of our hospital. From the distribution of pathogenic bacteria, *GBS* (81 cases, 16.77%) and *E. coli* (80 cases, 16.65%) were the two main pathogenic bacteria in neonatal sepsis. Foreign studies have shown that the top pathogenic bacteria causing sepsis in neonatal intensive care units are *GBS* and *E. coli* [10], which is consistent with the results of this study. However, there are many controversies in the research reports on the distribution of NS pathogens [11]. For example, there are other reports in the literature [12], that state that the main Gram-positive bacteria in NS in developed and in developing countries are coagulase-negative *staphylococci* (CNS). In the 20th century, maternal prenatal *GBS* infection and full-term and vaginal deliveries were high-risk factors for neonatal *GBS* sepsis [13,14]. Since 1992, the American Academy of Pediatrics has formulated guidelines for the use of antibiotics during delivery to prevent neonatal *GBS* infections in children. The 2002 guidelines recom-

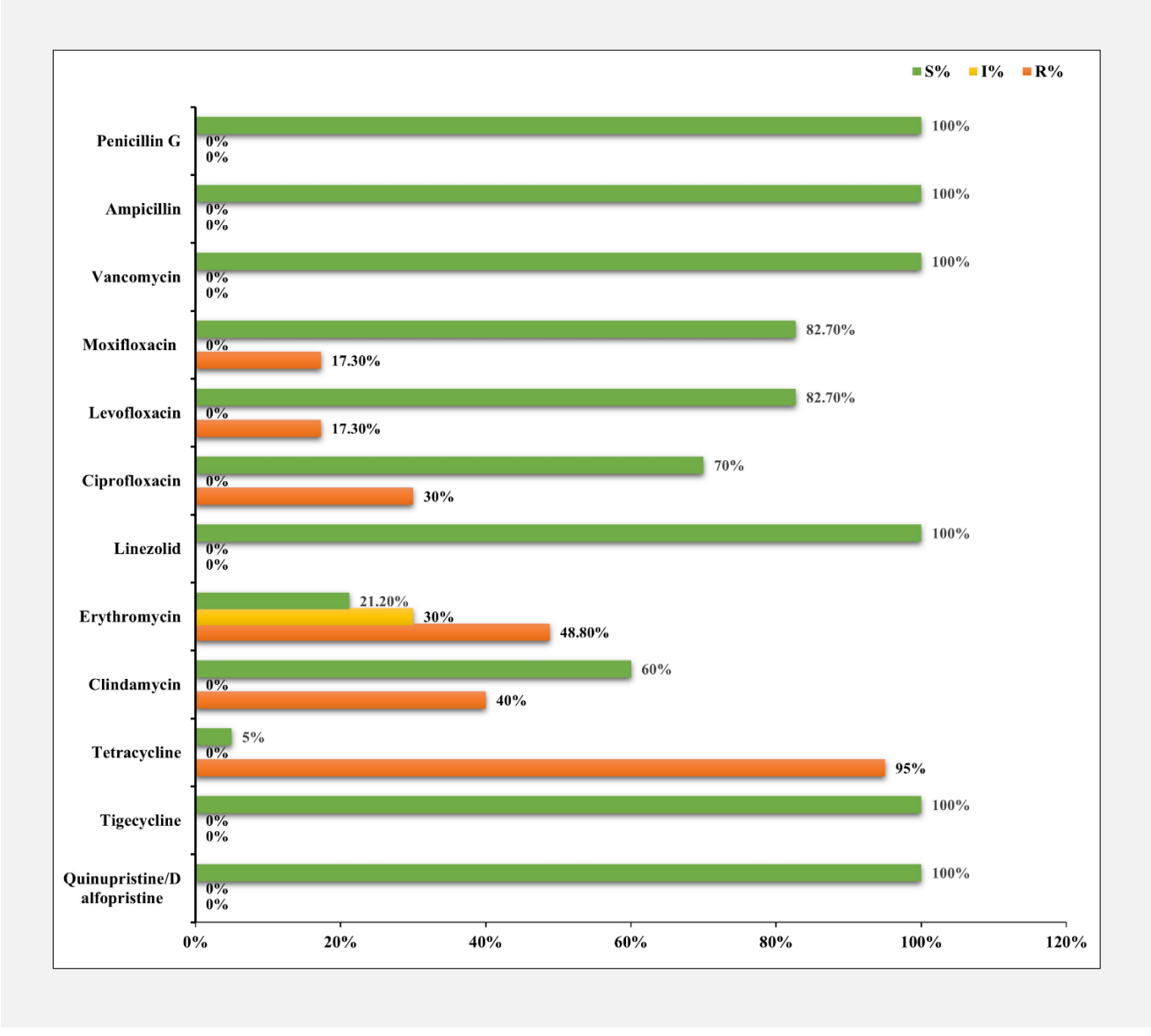

Figure 2. Antibiotic sensitivity test results for *GBS*.

mended screening for *GBS* infection in pregnant women between 35 and 37 weeks of gestation, and recommended penicillin as the first-line intrapartum antibiotic [15, 16]. Since then, the rate of *GBS* infection has greatly reduced, and Berardi et al. [17] found that *E. coli* is replacing *GBS* as the main pathogen causing NS. This is inconsistent with the results of this study, which may be related to the insufficient screening of maternal *GBS* in our hospital. Previous studies have shown that premature birth, a very low birth weight, and premature rupture of membranes are high-risk factors for an increased incidence of NS caused by *E. coli* [7,18]. In this study, there are also significant differences in these high-risk factors between the *E. coli* group and the *GBS* group.

Blood culture is the "gold standard" for the clinical diagnosis of NS [19]; however, it has shortcomings, such as a long-time consumption, a low positive rate, and the fact that it is easily contaminated. Therefore, understanding the differences in the clinical characteristics and the non-specific indicators between neonatal *GBS* and *E. coli* sepsis is crucial for an accurate diagnosis and treatment of this disease. The clinical characteristics of neonatal *GBS* sepsis are as follows: First, the children exhibit an abnormal body temperature, tachypnea, groaning, cyanosis, respiratory distress, and other respiratory system-based symptoms. The main manifestation is progressively aggravated breathing [20], and the children are prone to complications such as respiratory failure, pneumonia, and purulent meningitis. In addition, children may experience vomiting, diarrhea, and jaundice. The clinical characteristics of *E. coli* sepsis differ from those of *GBS*. First, children may have fe-

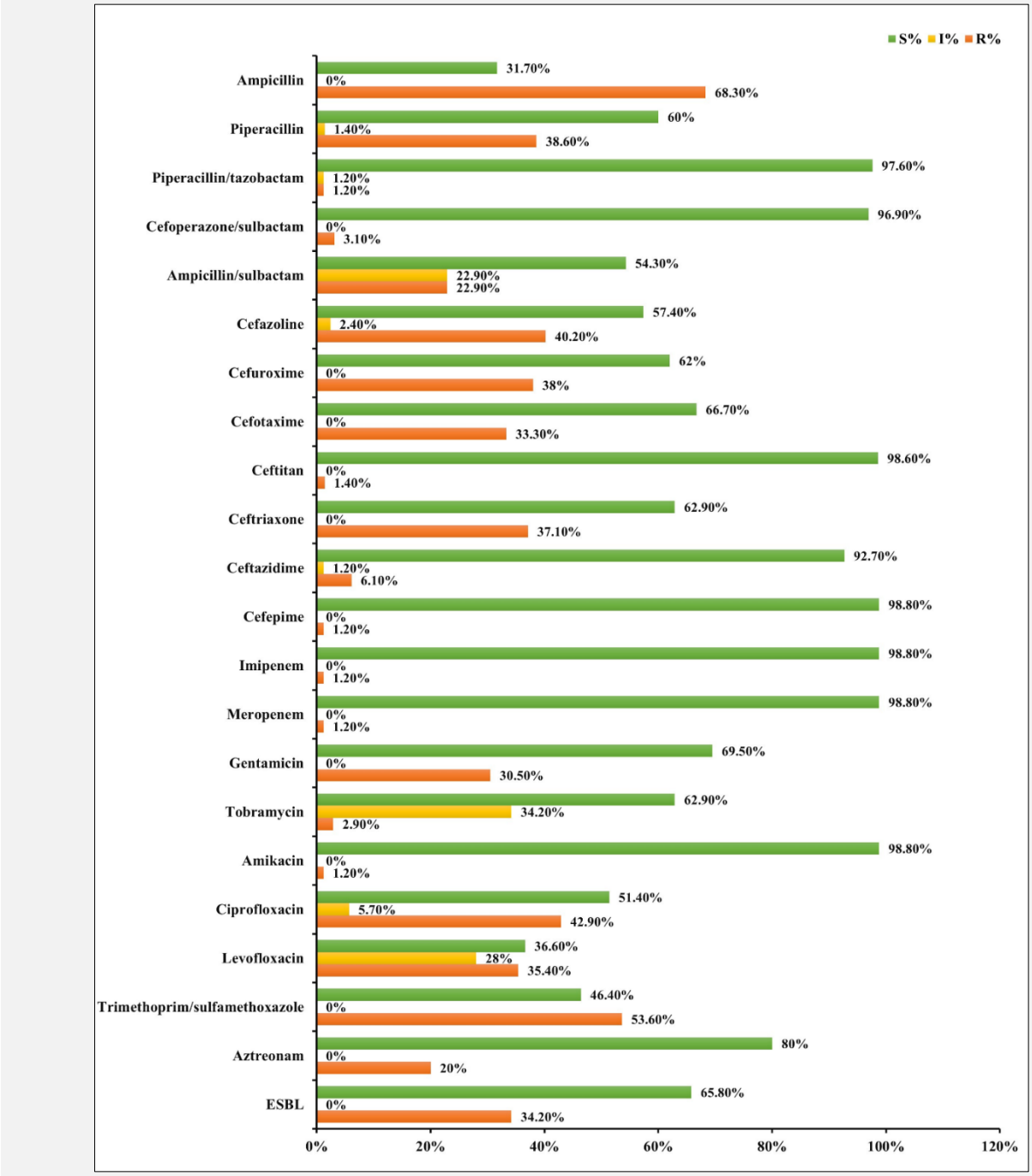

Figure 3. Antibiotic sensitivity test results for *E. coli*.

ver, abdominal distension, diarrhea, vomiting, and other digestive system symptoms, and they are prone to necrosis and complications such as enterocolitis. Second, the children may have symptoms such as tachypnea and jaundice. These clinical manifestations and complications are consistent with this study. In this study, most cases in the *GBS* and *E. coli* groups manifested fever, accounting for 61.73% and 63.75% of all cases, respectively. The *GBS* group had higher incidence rates of tachypnea, groaning, tachycardia or bradycardia, respiratory failure, pneumonia, and purulent meningitis than the *E. coli* group, while the incidence rates of abdomi-

nal distension, jaundice, atypical clinical manifestations, and necrotizing enterocolitis were lower. The differences between the two groups were statistically significant ($p < 0.05$). In addition to the clinical characteristics, nonspecific indicators are important for evaluating neonatal sepsis. Non-specific indicators such as WBC, NE#, NE#/LY#, hs-CRP, PCT, RDW, PLT, and MPV are commonly used in clinical practice for an auxiliary diagnosis and condition assessment of neonatal sepsis [21]. It is generally believed that WBC, NE#, NE#/LY#, PLT, and MPV have a low specificity and sensitivity, and are only suitable for NS screening. Memar et al. [22] pointed out that it is recommended to use PCT as a marker for early judgment of NS, which will help clinicians make an early and rapid diagnosis. Some foreign scholars [23] concluded that the combined detection of PCT and NE# has a better diagnostic value for sepsis than their respective individual determinations. Generally, hs-CRP is considered to exhibit a certain lag after infection [24], but it is a fast and economical predictive indicator. In addition, bacterial infection can trigger a series of inflammatory response syndromes by releasing toxins, in which inflammatory transmitters can cause coagulation disorders [25], resulting in abnormalities in coagulation function indicators such as D-D and FDP. The diagnostic significance of MPV for late-onset sepsis was lower than of PCT, hs-CRP, and other coagulation function indicators [26]. The results of this study showed that WBC, NE#, NE#/LY#, hs-CRP, and PCT were usually increased in both groups, but the increase in the *E. coli* group was lower than in the *GBS* group, while the MPV, D-D, and FDP of the *GBS* group were lower. In contrast, in the *E. coli* group, the differences in the above-mentioned indicators between the two groups were statistically significant ($p < 0.05$). Another important indicator in this study was RDW. RDW is an indicator of red blood cell dispersion. Martin et al. [27] found that the RDW was significantly increased in neonatal sepsis. In this study, the RDW increased in both groups, but the difference between the two groups was not statistically significant.

Selecting appropriate antibiotics based on blood culture and drug susceptibility test results is an ideal method for treating neonatal sepsis. However, bacterial cultures cannot produce results quickly. Clinicians usually choose antibiotics, based on their clinical experience; therefore, they must understand that the resistance of these two bacteria to different antibiotics is important. In this study, *GBS* showed a high rate of resistance to tetracycline and erythromycin, and no strains resistant to vancomycin, linezolid, penicillin, or ampicillin were found. These results were similar to the national average [28]. According to the Clinical Laboratory Standards Institute (CLSI) [29] recommendation, penicillin and ampicillin are the first choices for the treatment of GBS. If you are allergic to penicillin, you need to see the drug sensitivity test results of erythromycin and clindamycin. If the drug susceptibility test result is unknown or insensitive, it can be treated with vancomycin. Although *GBS* is sensitive to most antibiotics, following China, Portugal, and other countries, France has detected a subgroup of multi-drug resistant *GBS* that is not sensitive to lincosamides and aminoglycoside antibiotics [30-32]. However, many *E. coli* strains are resistant to penicillin and third generation cephalosporins, and the resistance rates to carbapenems and aminoglycosides are extremely low. These results were similar to the national averages [28]. Third-generation cephalosporins are available for E. coli, that do not produce extended-spectrum beta-lactamase (ESBL). For *E. coli* that produces ESBL, compound dosage forms of drugs with synergists can be used, such as cefoperazone/sulbactam, or other antibiotics that are stable against ESBL, such as imipenem; however, these drugs are not used as first-line drugs [33]. With the widespread use of antibiotics, the drug resistance of both *GBS* and *E. coli* has changed, and strains that are highly resistant to multiple antibiotics and multidrug-resistant strains have emerged, resulting in difficulties and new challenges in the clinical treatment of NS.

CONCLUSION

In summary, *GBS* and *E. coli* are the main pathogenic bacteria associated with neonatal sepsis. The clinical characteristics, complications, non-specific indicators, and drug resistance of NS, caused by these two bacteria, differ. This study provides an effective and practical guidance for the diagnosis and treatment of neonatal *GBS* and *E. coli* sepsis to reduce neonatal mortality.

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Declaration of Interest:
The authors state that there are no conflicts of interest regarding the contents of this article.

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