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*Original Article*

# A study of risk factors of gastroesophageal reflux complicated with pulmonary infections in neonates, characteristics of pathogenic bacteria and prevention strategies

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**Abstract:** Objective: This study aimed to analyze the risk factors of gastroesophageal reflux complicated with pulmonary infections and the characteristics of pathogenic bacteria, and to propose prevention strategies. Methods: A total of 40 patients admitted and definitely diagnosed with gastroesophageal reflux complicated with pulmonary infections in Gansu Provincial Maternity and Child-care Hospital from January 2017 to November 2017 were retrospectively analyzed. Univariate and multivariate logistic analyses were conducted for the evaluation of premature delivery, polyembryony, birth asphyxia and rescue history, birth weight, hyperglycemia, esophageal hiatal hernia and esophageal peristaltic dysfunction. The corresponding intervention measures were proposed, and the types of pathogenic bacteria of pulmonary infections were counted. Results: Premature delivery, birth asphyxia history, birth rescue history, postnatal hyperglycemia, definite esophageal hiatal hernia and esophageal peristaltic dysfunction were independent risk factors for neonatal gastroesophageal reflux complicated with pulmonary infections. Gram-negative ($G^-$) bacteria were sensitive to cefepime and ceftazidime, while Gram-positive ($G^+$) bacteria were sensitive to ampicillin and cefepime. Conclusion: Our data demonstrate that premature delivery, presence of birth asphyxia and rescue history, hyperglycemia after birth, definite esophageal hiatal hernia and peristaltic dysfunction are independent risk factors for neonatal gastroesophageal reflux complicated with pulmonary infections. $G^+$ bacteria are the dominant pathogens, suggesting the necessity of cefepime in empirical treatment.

**Keywords:** Neonate, gastroesophageal reflux, pulmonary infection, risk factor, anti-bacteria treatment

## Introduction

In clinical practice, gastroesophageal reflux mainly refers to the process in which the contents of the stomach and duodenum retrogradely flow towards the lower end of the human esophagus [1]. It is classified into physiological and pathological types, in which physiological gastroesophageal reflux often occurs in neonates and infants, generally with no obvious clinical manifestations [2]. In contrast, neonates with pathological gastroesophageal reflux often manifests as vomiting, breast milk rejection, no increase in body weight and recurrent respiratory infections [3], in which these neonates with clinical symptoms are clinically diagnosed with gastroesophageal reflux disease. This disease frequently occurs in infants and young children, especially in premature infants. A study has revealed that the incidence rate of the disease in premature infants is as high as over 80% within 7 d after birth [4]. At 3 months after birth, the gastroesophageal function gradually matures, and after the formation of anti-reflux barriers, its clinical symptoms can be gradually alleviated [5].

For patients with gastroesophageal reflux, especially premature infants, the rate of complications with pulmonary infections is more than

70% [6]. This disease not only easily leads to esophagitis, esophageal erosion and ulceration, but also causes aspiration by mistake, atelectasis, recurrent pulmonary infections and even suffocation, threatening the lives of children and bringing serious psychological burden and economic impact on the children and their families [7]. Gastroesophageal reflux disease is very common in infant populations and parents should be educated regarding symptoms, warning signs, and generally favorable prognosis. It is noted that infant gastroesophageal reflux revised questionnaires can be useful to the clinical screening and follow up for gastroesophageal reflux disease [8]. The most important antireflux mechanisms are lower oesophageal sphincters and adequate oesophageal clearance [9]. Also, extensive studies have been performed on anti-gastroesophageal reflux disease therapy, which include fundoplication as an effective and safe treatment in the neonates and infants with severe gastroesophageal reflux disease [10, 11]. To better treat pulmonary infections in these patients, the risk factors for neonatal gastroesophageal reflux complicated with pulmonary infections and the characteristics of the infected pathogenic bacteria were investigated, and the corresponding prevention strategies were proposed in this study. Results are reported as follows.

## Material and methods

### *General data*

A total of 40 neonates admitted and definitely diagnosed with gastroesophageal reflux complicated with pulmonary infections in our hospital from January 2017 to November 2017 were retrospectively analyzed. Inclusion criteria: All the patients had clinical manifestations, such as vomiting, breast milk rejection, no increase in body weight and recurrent respiratory infections, and 24-h gastroesophageal potential of hydrogen (pH) examination revealed that the pH in the esophagus was less than 4 for more than 5 min each time. This, together with the analysis of the case data as well as respiratory secretion culture and related test results, represented pulmonary infections. Exclusion criteria: Prophylactic fundoplication with neurologic deficit; accompanied with hiatal hernia; accompanied with congenital esophageal defects. This investigation was supported by the Medical Records Management Section and approved by the Medical Ethics Committee of the hospital. All the patients and their families voluntarily participated in the study and signed the informed consent.

### *Investigation methods*

Twenty-four hour gastroesophageal dynamic pH monitoring was carried out for the neonates with gastroesophageal reflux complicated with pulmonary infections, and a pH value of the esophagus less than 4 was taken as the diagnostic standard. Before inclusion, the children's guardians signed the voluntary inclusion agreement, and the study was approved by the Ethics Committee of the hospital. All the data were collected by newly trained investigators in the Neonatology Department through anonymous face-to-face interviews and data collection for the included children and their guardians. At the same time, during the investigation, the persons involved in the investigation were required to fully respect and care for the children and their guardians, answer the relevant questions posed by the respondents and meet their reasonable requirements. The information obtained from the investigation was not allowed to be let out to any organizations or individuals without the permission of the guardians. The reliability of relevant data in this study was measured using the reliability coefficient (a=0-1), which was 0.993 through calculation. In addition, the stability coefficient was evaluated at 30 d after the first investigation by the same investigators through the same questionnaire to collect the survey data. The obtained correlation coefficient for two consecutive times was the coefficient of stability. The data obtained after the implementation of the investigation were input into the EpiData software for analysis. The data input must be recorded after alternate inspection by two people, and then Statistical Product and Service Solutions (SPSS) 21.0 statistical software was applied for statistical analysis.

### *Culture and identification of pathogenic bacteria of pulmonary infections*

Culture and identification of Pathogenic bacteria for all the included children with pulmonary infections were carried out according to the detection methods and operation procedures of the *National Clinical Inspection and opera-*

*tion Procedure*. The drug sensitivity test was performed via the paper diffusion [Kirby-Bauer (K-B)] antibiotic method (fine bacteria) and the glucose peptone agar culture medium method (viruses and fungi), and respiratory secretions were inspected using the direct fluorescent antibody test (mycoplasma and chlamydia). All operation standards were in line with the regulation of Clinical & Laboratory Standards Institute (CLSI) (2008-2010), and the data analysis was carried out via WHONET5.3-5.4. The Columbia blood plate, the Mueller-Hinton (MH) plate, the agar medium and the drug sensitivity test paper were produced by Oxoid, UK. The tested strains included common pathogenic bacteria, viruses, fungi, mycoplasma and chlamydia. The detection operations were conducted strictly by the inspection technologist with over 5 years of clinical experience under the guidance of experimental guidelines.

*Observational indexes*

In the first place, univariate and multivariate Logistic analyses were performed for the related conditions of children included in the group, such as whether there were premature delivery, polyembryony, birth asphyxia and rescue history, hyperglycemia, esophageal hiatal hernia and esophageal peristaltic dysfunction as well as birth body weight. In addition, corresponding intervention measures were proposed for the risk factors. At the same time, the distribution of Gram-negative ($G^-$), Gram-positive ($G^+$), viruses, fungi, chlamydia and mycoplasma infections were detected for the patients with pulmonary infections. Sensitivities of $G^-$ and $G^+$ bacteria to the treatment with the commonly used antibiotics were evaluated.

*Statistical processing*

SPSS 21.0 (IBM Company) statistical software was adopted. Univariate and multivariate Logistic regression analyses were conducted, and measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). The intergroup comparison of percentage was conducted by $\chi^2$ test. $P<0.05$ represented that the difference was statistically significant.

## Results

*General data*

The 40 neonates with gastroesophageal reflux consisted of 25 males and 15 females, whose birth body weight was 1900-4300 g, with an average of (2650.0±25.0) g. In addition, their 1-min Apgar scores at birth were 1-10 points, with an average of (7.1±0.3) points. The time of definite diagnosis of gastroesophageal reflux in these children was within 24 h-21 d after birth, with an average of (6.1±0.1) d, and the pulmonary infection time was 7-21 d, with an average of (11.1±0.3) d. In addition, 16 patients (40%) were born prematurely, 3 patient (7.5%) had hypoxic brain injury, 23 (57.5%) had congenital heart disease, 8 (20%) had neurologic disease, 6 (15%) had respiratory disease, 7 (17.5%) had other gastrointestinal disease and 14 patients (35%) had multiple accompanying diseases.

*Univariate analyses of risk factors for gastroesophageal reflux complicated with pulmonary infections in neonates*

Univariate analyses revealed that premature delivery, birth asphyxia and rescue history, presence of hyperglycemia after birth, definite esophageal hiatal hernia and esophageal peristaltic dysfunction were related risk factors for neonatal gastroesophageal reflux complicated with pulmonary infections (**Table 1**).

*Multivariate logistic analyses of risk factors for gastroesophageal reflux complicated with pulmonary infections in neonates*

Multivariate Logistic analyses revealed that premature delivery, presence of birth asphyxia and rescue history, hyperglycemia after birth, definite esophageal hiatal hernia and esophageal peristaltic dysfunction were independent risk factors for neonatal gastroesophageal reflux complicated with pulmonary infections (**Table 2**).

*Distribution of pathogenic bacteria detected in pulmonary infections*

Pathogenic bacteria were detected in all 40 included cases, including bacterial infections, viral infections, fungal infections as well as mycoplasma and chlamydia infections. Among them, there were 20 cases with bacterial infections alone, 5 cases with virus infections alone, 2 cases with fungal infections alone, 2 cases with mycoplasma and chlamydia infections alone and 11 cases with infections of two or more above pathogenic bacteria (**Figure 1**).

**Table 1.** Univariate analyses of risk factors for gastroesophageal reflux complicated with pulmonary infections in neonates

| Related factor | Scale value | n | Incidence rate | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Premature delivery | Yes | 36 | 90.0% | 48.050 | 0.000 |
| | No | 4 | 10.0% | | |
| Polyembryony | Yes | 21 | 52.5% | 0.655 | 0.200 |
| | No | 19 | 47.5% | | |
| Birth asphyxia history | Yes | 37 | 92.5% | 54.450 | 0.000 |
| | No | 3 | 7.5% | | |
| Birth rescue history | Yes | 38 | 95.0% | 61.250 | 0.000 |
| | No | 2 | 5.0% | | |
| Birth weight | Over 2500 g | 20 | 50.0% | 0.000 | 1.000 |
| | Within 2500 g | 20 | 50.0% | | |
| Hyperglycemia | Yes | 39 | 97.5% | 68.450 | 0.000 |
| | No | 1 | 2.5% | | |
| Esophageal hiatal hernia | Yes | 38 | 95.0% | 61.250 | 0.000 |
| | No | 2 | 5.0% | | |
| Esophageal peristaltic dysfunction | Yes | 37 | 92.5% | 54.450 | 0.000 |
| | No | 3 | 7.5% | | |

**Table 2.** Multivariate Logistic analyses of risk factors for gastroesophageal reflux complicated with pulmonary infections in neonates

| | Partial regression coefficient | Standard error | *p* | Odds ratio (OR) value | 95% confidence interval (95% CI) |
|---|---|---|---|---|---|
| Premature delivery | 1.362 | 0.386 | 0.002 | 0.684 | 0.607~0.726 |
| Birth asphyxia history | 1.035 | 0.116 | 0.028 | 0.857 | 0.819~0.983 |
| Birth rescue history | 1.659 | 0.391 | 0.004 | 0.704 | 0.683~0.735 |
| Hyperglycemia | 1.058 | 0.165 | 0.012 | 1.169 | 1.041~1.836 |
| Esophageal hiatal hernia | 1.114 | 0.154 | 0.011 | 1.157 | 1.128~1.937 |
| Esophageal peristaltic dysfunction | 1.785 | 0.406 | 0.025 | 0.937 | 0.902~0.991 |

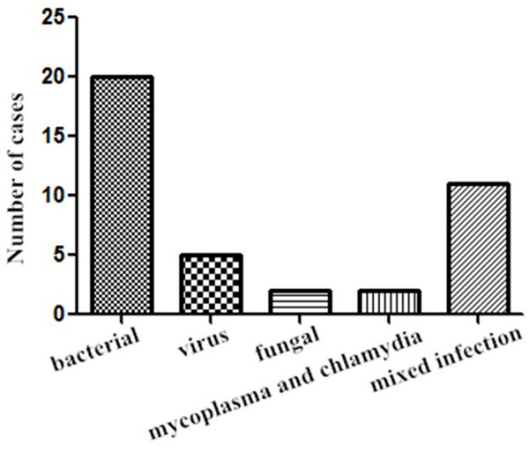


**Figure 1.** Distribution of pathogenic bacteria detected in pulmonary infections. There are 20 cases with bacterial infections alone, 5 cases with virus infections alone, 2 cases with fungal infections alone, 2 cases with mycoplasma and chlamydia infections alone and 11 cases with infections of mixed infections.

*Specific detected pathogen types of included patients*

Among the 40 included cases, $G^-$ bacteria were detected in 13 cases (32.5%), $G^+$ bacteria in 17 cases (42.5%), fungi in 7 cases (17.5%), and mycoplasma and chlamydia in 1 case for each (2.5%) (**Table 3**).

*Distribution of $G^-$ sensitive antibiotics*

There were 13 cases of $G^-$ bacteria in this group. Pseudomonas aeruginosa and Klebsiella pneumoniae were sensitive to cefepime and ceftazidime (**Table 4**).

*Distribution of $G^+$ sensitive antibiotics*

The 17 cases of $G^+$ bacteria in this group were sensitive to ampicillin and cefepime (**Table 5**).

**Table 3.** Distribution of the detected pathogenic bacteria

| Type of pathogenic bacteria | Bacterial strain (n) | Constituent ratio (%) |
|---|---|---|
| $G^-$ | 13 | 32.5% |
| Pseudomonas aeruginosa | 6 | 15.0% |
| Klebsiella pneumoniae | 4 | 10.0% |
| Acinetobacter baumannii | 1 | 2.5% |
| Escherichia coli | 1 | 2.5% |
| Enterobacter cloacae | 1 | 2.5% |
| $G^+$ | 17 | 42.5% |
| Staphylococcus aureus | 13 | 32.5% |
| Coagulase negative staphylococcus | 2 | 5.0% |
| Staphylococcus epidermidis | 2 | 5.0% |
| Fungi | 7 | 17.5% |
| Candida albicans | 6 | 15.0% |
| Candida tropicalis | 1 | 2.5% |
| Mycoplasma and chlamydia | 2 | 5.0% |
| Mycoplasma | 1 | 2.5% |
| Chlamydia | 1 | 2.5% |

**Table 4.** Distribution of $G^-$ sensitive antibiotics [n (%)]

| Antibacterial agent | Pseudomonas aeruginosa (n=6) | Klebsiella pneumoniae (n=4) |
|---|---|---|
| Ciprofloxacin | 1 (2.5%) | 1 (2.5%) |
| Ceftazidime | 6 (15.0%) | 4 (10.0%) |
| Sulfamethoxazole | 1 (2.5%) | 1 (2.5%) |
| Gentamicin | 1 (2.5%) | 1 (2.5%) |
| Cefotaxime | 1 (2.5%) | 1 (2.5%) |
| Cefepime | 6 (15.0%) | 4 (10.0%) |
| Levofloxacin | 2 (5.0%) | 1 (2.5%) |
| Amikacin | 1 (2.5%) | 1 (2.5%) |

**Table 5.** Distribution of drug resistance of main $G^+$ bacteria [n (%)]

| Antibacterial agent | Staphylococcus aureus (n=13) |
|---|---|
| Roxithromycin | 3 (7.5%) |
| Ampicillin | 13 (32.5%) |
| Gentamicin | 2 (5.0%) |
| Penicillin G | 3 (7.5%) |
| Sulfamethoxazole | 1 (2.5%) |
| Erythrocin | 2 (5.0%) |
| Ciprofloxacin | 2 (5.0%) |
| Cefepime | 13 (32.5%) |

## Discussion

Gastroesophageal reflux is a clinical disease mainly triggered by dysfunction of the esophageal sphincter, gastrointestinal dysfunction, and prolonged gastric emptying [7] resulting from systemic or local factors, thus leading to the reflow of gastric or duodenal contents to the esophagus and even the oral cavity [8]. The disease frequently occurs in the elderly and in neonates, especially in premature infants, with the incidence rate of more than 80% [9]. Its main clinical manifestations include vomiting, stagnant weight gain, anemia, malnutrition and esophagitis, in which pulmonary infections induced by reflux and accidental aspiration are regarded as one of the most serious complications of gastroesophageal reflux [10]. The disease may result in recurrent respiratory tract infections and even suffocation, threatening the life of the individual. A study has illustrated that reflux contents of neonates, especially premature infants, are easily aspirated into the airway by mistake, and the rate of complication with pulmonary infections is positively correlated with the degree of reflux. Recurrent inhalation pneumonia occurs in some children, which causes atelectasis or even asphyxia, thus resulting in sudden clinical death [11].

In this study, the risk factors for gastroesophageal reflux complicated with pulmonary infections in neonates admitted and treated in our hospital in recent years were retrospectively analyzed. The analysis of the pathogenesis risk factors revealed that premature delivery, presence of birth asphyxia and rescue history, hyperglycemia after birth, definite esophageal hiatus hernia and esophageal peristaltic dysfunction were related and independent risk factors for gastroesophageal reflux complicated with pulmonary infections in neonates. This suggests that premature infants, especially those with birth asphyxia and rescue history, should be watched in clinical practice to timely avoid the complications with gastroesophageal reflux, and actively preventing pulmonary infections is of great importance. In the clinic, these risk factors can be also applied in the early detection of the disease. Additionally, clinical attention paid to hyperglycemia after birth, definite esophageal hiatus hernia and esophageal peristaltic dysfunction should be improved, so as to detect gastroesophageal reflux in time and carry out targeted intervening measures, thus

preventing and reducing the incidence of pulmonary infections. Pathogenic bacteria of patients definitely complicated with pulmonary infections were studied, which manifested that the pathogenic bacteria of patients were mostly subjected to bacterial infections, especially $G^+$ bacteria, and patients were more sensitive to ampicillin and cefepime. Besides, patients whose pathogenic bacteria were $G^-$ bacteria were relatively sensitive to cefepime and ampicillin. The two groups of patients were sensitive to cefepime.

Moreover, in the aspect of prevention strategies of gastroesophageal reflux complicated with pulmonary infections in neonates, the placement of the body position of children in the daily life needs attention in the first place. It is recommended that the head height be placed 30° in the supine position, which is the ideal position [12]. Besides, children who were intermittently placed in the prone position with head high helps to enhance their oxygenation and pulmonary function, promote digestive function, improve the gastric emptying ability and reduce the risk of aspiration by mistake and the body energy consumption [13-15]. However, this position increased the risk of sudden death in children to a certain extent [16], so it should be selectively employed, and clinical observation should be strengthened in the placement of the prone position with head high to avoid accidental events. Meanwhile, in light of the feeding methods of children, nasal feeding is recommended, and attention should be paid to the total amount of breast milk and the feeding speed in the feeding process, with the interval of 3-4 hours is generally recommended [17-19]. Furthermore, the observation of children should be enhanced at the end of nasal feeding each time, and vacuum aspiration should be timely conducted once vomiting occurs. For patients who already have pulmonary infections, empirical administration is first recommended so as to carry out anti-infection treatments with drugs in real time [20-22], and the samples are reserved for examination, followed by the targeted anti-infection treatment after the identification of pathogenic bacteria [23, 24]. Another study [25] has demonstrated that it is important to implement gastric lavage intervention and retrograde enema for patients with the presence of vomiting after birth, thus providing a certain value for reducing reflux and aspiration by mistake as promoting gastrointestinal peristalsis [26-29]. The limitation in this study exists that our preliminary data is based on only 40 patients to reveal independent risk factors for neonatal gastroesophageal reflux complicated with pulmonary infections while further investigation may extend the study number which includes a larger number of samples in order to validate our current findings.

To sum up, premature delivery, birth asphyxia and rescue history, hyperglycemia after birth, definite esophageal hiatus hernia and esophageal peristaltic dysfunction are identified as independent risk factors for gastroesophageal reflux complicated with pulmonary infections in neonates. $G^+$ bacteria are the common pathogens, and it is recommended to apply cefepime in empirical treatments. Our data provide new leads for the further diagnosis and therapy against for gastroesophageal reflux complicated with pulmonary infections in clinical practice.

## Disclosure of conflict of interest

None.

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