Submitted: 21 January, 2022 Accepted: 14 April, 2022 Published: 08 May, 2023 DOI:10.22514/sv.2022.050

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ORIGINAL RESEARCH

Risk factors for multidrug resistant bacterial infection in infants with bronchopulmonary dysplasia re-hospitalized due to lower respiratory tract infection: a case-control study

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Abstract

To evaluate the epidemiological characteristics and risk factors for multidrug-resistant bacterial infection (MDRI) in infants with bronchopulmonary dysplasia (BPD) readmitted to the hospital due to lower respiratory tract infection (LRTI), providing a basis for the clinical prevention and treatment of MDRI.A retrospective analysis of readmission due to LRTI in infants with BPD within 1 year corrected age from October 2012 to December 2020 was performed. Twenty-nine children with MDRI were selected as the case group, and 80 children without MDRI during the same period served as the control group. We reviewed and collected relevant infants' neonatal hospitalization experience, broad-spectrum antibiotic (BSA) selection, and microbiological data. BSA included carbapenem antibiotics, third-generation cephalosporins and cephalosporin/β-lactamase inhibitor combinations, and penicillin/β-lactamase inhibitor (P/BLI) combinations.The length of stay in hospitalized patients with MDRI was significantly prolonged ($p < 0.05$), and the BSA use rate was high (>94.1%). Single-level factor analyses showed that nosocomial infection and the P/BLI usage rate in the Neonatal Intensive Care Unit (NICU) were related to MDRIs (all $p < 0.05$). NICU-MDRI, BSA, dual antibiotics, and mechanical ventilation were not significantly associated with MDRIs on readmission (all $p > 0.05$). Binary logistic regression analysis indicated nosocomial infection as an independent risk factor related to MDRIs (Odds ratio (OR) 5.3, 95% confidence interval (CI) 1.7–16.4).Nosocomial infection remains the most important risk factor for MDRI in BPD infants. For infants with BPD, more cautions should be taken on whether to choose BSA directly based on the bacterial species infected during the NICU or the long-term hospitalization history.

Keywords

Broad-spectrum antibiotics; Nosocomial infection; Multidrug resistant bacteria infections; Bronchopulmonary dysplasia

1. Background

Over the past decade, microbial drug resistance has become one of the most dangerous public health hazards and will have a greater impact in the future [1]. In the latest antibiotic resistance list released by the US Centers for Disease Control and Prevention (US CDC) in November 2019, extended-spectrum beta-lactamase (ESBL)-producing Enterobacter, Panresistant Acinetobacter baumannii (PDR-AB), and Methicillin-resistant Staphylococcus aureus (MRSA) remain a "serious threat", whereas carbapenem-resistant Enterobacter and Acinetobacter represent an "urgent threat" [2, 3]. Long-term hospitalization and broad-spectrum antibiotic (BSA) exposure are believed as leading causes of multidrug-resistant bacterial infection (MDRI) [4, 5]. Infants with bronchopulmonary dysplasia (BPD) are a high-risk group for MDRI. As a special group, these infants experiencing long-term hospitalization and BSA exposure during the neonatal period are prone to multiple hospitalizations for respiratory infections after discharge [5]. The damage induced by of MDRI, such as BPD, maybe fatal invulnerable population. Furthermore, the harm caused by MDRIs to such immunocompromised infants with BPD may be fatal [5]. Therefore, this article aimed at exploring the risk factors for MDRI in infants with BPD who were readmitted to the hospital due to lower respiratory tract infections (LRTIs). In particular, whether BSA treatment and hospitalization experience in the neonatal period are related to MDRIs should be considered to optimize medical care and procedures.

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2. Materials and methods

2.1 General information

We conducted a retrospective case-control study at the West China Second Hospital of Sichuan University. From October 2012 to December 2020, 916 children with BPD were readmitted at the West China Second Hospital of Sichuan University for various reasons, including 624 diagnosed in the West China Second Hospital of Sichuan University, and 292 in other hospitals. 86 of the 624 cases were re-hospitalized for LRTIs within 1 year of postmenstrual age (PMA) correction, and 141 of the 292 cases had complete data in the neonatal period. Finally, eligible subjects included 227 children with complete data who were diagnosed with BPD in the hospital and were readmitted to the hospital for LRTIs within 1 year corrected age. We excluded 109 children who were hospitalized for LRTIs, but complicated with other disease, such as improper feeding, genetic metabolic disease, heart disease, digestive system disease, neurological disease, kidney disease, immune disease, blood system disease or abnormal airway structure development. A total of 109 cases were included in the final analysis (Fig. 1), of whom 29 with MDRI were served as the case group, and 80 without MDRI during the same period as the control group.

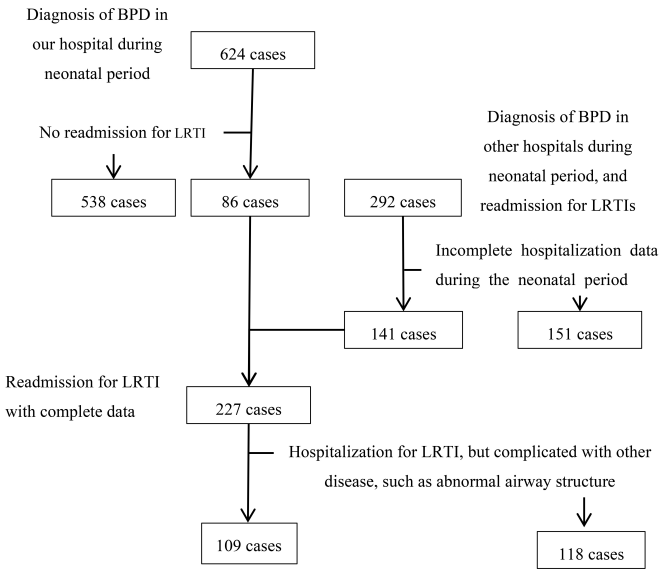

FIGURE 1. Flow Chart. BPD, Bronchopulmonary dysplasia; LRTI, Lower respiratory tract infection.

The BPD defined by National Institute of Child Health and Human Development (NICHD) in 2019 is based on the pattern of respiratory support at 36 weeks of PMA and is graded according to the severity of the respiratory support pattern: mild, nasal cannula flow of <2 L/min; moderate, nasal cannula flow of >2 L/min or noninvasive positive pressure ventilation (nasal continuous positive airway pressure, nCPAP or nasal intermittent positive pressure ventilation, NIPPV); or severe, invasive positive pressure ventilation (PPV) [6]. Multidrug-resistant bacterials (MDRs) are defined as bacteria that are simultaneously resistant to three or more antimicrobial drug classes [7]. Nosocomial infection refers to an infection that occurs 48 hours after admission (more than the average time of the clear incubation period) or an infection that is directly related to the last hospitalization [8]. The BSA in the study included carbapenem antibiotics, third-generation cephalosporins and cephalosporin/β-lactamase inhibitor (C/BLI) combinations and penicillin/β-lactamase inhibitor (P/BLI) combinations [9]. Malnutrition is diagnosed only by anthropometric indicators associated with height and weight (weight-for-height z-score (WHZ) below -2 Standard Deviation (SDs) [10].

2.2 Outcome measurement

A Vitek 2-Com-pact automatic bacterial identification drug susceptibility instrument (France BioMérieux) was used to identify the strains isolated from the specimens and supplemented by the K-B method. The drug susceptibility test and result determination standards were based on the interpretation standards and quality control of the 2002 edition of the Clinical and Laboratory Standard Institute (CLSI) drug selection rules.

2.3 Intervention methods

Clinical information of children, including sex, gestational age, birth weight, BPD, number of hospitalizations and length of stay, days of antibiotic treatment (DOT), BSA exposure, MDRI, and nosocomial infection, was collected from the electronic medical record system.

2.4 Statistical methods

The chi-square test or Fisher test was used for the comparison of count data, and the Mann-Whitney rank sum test for the comparison between continuous and non-normally distributed variables. The case group was used as the dependent variable, and variables with differences in the single-level factor analyses were included ($p < 0.10$). Binary logistic regression analyses were applied to screen for risk factors. Statistical analysis was performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). All significance tests were two-tailed, and $p < 0.05$ indicated a significant difference.

3. Results

3.1 Epidemiological characteristics of MDRI

Of the 29 confirmed cases of MDRI, there were 8 cases of ESBL producing Klebsiella pneumoniae (ESBL-KP) infection, 5 cases of carbapene-resistant KP (CR-KP) infection; 6 cases of ESBL-Escherichia coli (E. coli) infection, 2 cases of CR-E. coli, MDR-Haemophilus influenzae, and MRSA infection each, and 1 case of CR-Enterobacter hosei, Methicillin-resistant Staphylococcus aureus (MRSE), PDR-AB and PDR-Pseudomonas aeruginosa (PDR-PA) infection each (Table 1).

Among the 29 confirmed MDRI specimens, 26 were detected in sputum, 2 detected in whole blood, and 1 detected at the tip of the tracheal tube (Table 2).

MDR-KP and MDR-E. coli are the main MDRIs with a 100% resistance rate to ampicillin/sulbactam and no resistance to amikacin. MDR-KP cells showed higher resistance to most third-generation C/BLI inhibitor combinations and carbapen-

ems than MDR-E. coli cells. The resistance of MDR-E. coli to quinolone antibiotics was higher than that of MDR-KP (7.7% *vs.* 50.0%) (Table 4).

TABLE 1. Bacterial distribution of MDRIs.

MDR	Number of cases (n = 29)	Composition ratio (%)
CRE	8	27.6
ESBL-KP	8	27.6
ESBL-E. coli	6	20.7
MRSA	2	6.9
MDR-Haemophilus influenzae	2	6.9
PDR-AB	1	3.4
PDR-PA	1	3.4
MRSE	1	3.4

MDRI,multidrug-resistant bacterial infection; MDR, multidrug-resistant bacterial; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; KP, Klebsiella pneumoniae; E. coli, Escherichia coli; MRSA, Methicillin-resistant Staphylococcus aureus; PDR-AB, Panresistant Acinetobacter baumannii; PDR-PA, Panresistant Pseudomonas aeruginosa; MRSE, Methicillin-resistant Staphylococcus epidermidis.

TABLE 2. Source of MDRI from clinical specimens.

MDR	Sputum	Whole blood	Tracheal tube tip
CRE (n = 8)	7	0	1
ESBL-KP (n = 8)	8	0	0
ESBL- E. coli (n = 6)	6	0	0
MRSA (n = 2)	1	1	0
MDR-Haemophilus influenza (n = 2)	2	0	0
PDR-AB (n = 1)	1	0	0
PDR-PA (n = 1)	1	0	0
MRSE (n = 1)	0	1	0
ALL	26	2	1

MDRI, multidrug-resistant bacterial infection; MDR, multidrug-resistant bacterial; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; KP, Klebsiella pneumoniae; E. coli, Escherichia coli; MRSA, Methicillin-resistant Staphylococcus aureus; PDR-AB, Panresistant Acinetobacter baumannii; PDR-PA, Panresistant Pseudomonas aeruginosa; MRSE, Methicillin-resistant Staphylococcus epidermidis.

3.2 Single-level factor analyses of risk factors for MDRI.

Seventeen out of 109 children had nosocomial infection, including 13 who were identified more than 48 hours after admission, and 4 colonizations (3 nonmultidrug-resistant bacteria were the same as that noted in the neonatal period). Nosocomial infection and the use of P/BLI combinations in the NICU were significantly associated with MDRIs (all $p < 0.05$). However, the association between gestational age, birth weight, Pediatric Intensive Care Unit (PICU) hospitalization history, severe BPD, malnutrition, hospitalization stay, DOT, BSA exposure, mechanical ventilation, MDRI in the NICU and MDRIs were not significant (all $p > 0.05$) (Table 3).

3.3 Binary logistic regression analysis of risk factors for MDRI

The occurrence of MDRI served as the dependent variable. To avoid the omission of items, the following items with p value less than 0.1 in the above mentioned single-level factor analyses served as independent variables: PICU hospitalization history (yes 1, no 0), nosocomial infection (yes 1, no 0), P/BLI combinations exposure in the NICU (yes 1, no 0), P/BLI combinations exposure for more than 7 days in the NICU (yes 1, no 0), carbapenems exposure in the NICU (yes 1, No 0), and carbapenems exposure for more than 7 days in the NICU (yes 1, no 0). Binary logistic regression analysis suggested that nosocomial infection was an independent risk factor for MDRI in BPD infants readmitted due to lower LRTI (Table 5).

3.4 Differences in hospital stay and BSA exposure between MDRI and non-MDRI children within PMA-1 year old

The length of stay (total length of stay, length of stay in PICU, length of single stay over 14 days) and DOT of BSA (total DOT, DOT except for NICU) were significantly prolonged in children with MDRI within PMA-1 year old compared with children without MDRI. Besides, those with MDRI had longer intensive care unit (ICU) stay with greater usage rates of dual antibiotics, quinolone antibiotics and long-term (DOT >7 days) carbapenem (all $p < 0.05$). The rate of BSA exposure in children with BPD during readmission was very high (>96%), and no difference existed between MDRI and non-MDRI children (all $p > 0.05$). (Table 6)

4. Discussion

Children with BPD are often admitted to hospital a few times and are susceptible to MDRIs, but there are few related studies analyzing the risk factors for MDRI in infants with BPD. Our data showed that more than a quarter (26.7%, 26/109) of infants with BPD readmitted for LRTI developed MDRIs or even pan-resistant bacterial infections, causing increases in hospitalizations, medical health care costs and a rising demand for care [5]. Some studies have reported that risk factors for MDRI include BSA exposure, nosocomial infection, prolonged hospitalization before MDRI, ICU admission, mechanical ventilation, and two or more antibiotic exposures

TABLE 3. Single-level factor analysis of MDRI in infants with BPD readmitted for LRTIs.

Variable	MDRI n = 29	no-MDRI n = 80	*p*
Gestational age, median (IQR), wk	29.4 (28.1–31.5)	29.4 (28.3–31.2)	0.676
Birth weight, median (IQR), g	1250.0 (1085.0–1515.0)	1270.0 (1133.0–1508.0)	0.776
Length of stay in the NICU, median (IQR), d	52.0 (36.5–72.5)	46.0 (33.0–60.0)	0.351
DOT in the NICU, median (IQR), d	52.0 (36.5–72.5)	46.0 (33.0–60.0)	0.297
Male, n (%)	19 (65.5)	49 (61.3)	0.684
PICU hospitalization history, n (%)	26 (89.7)	60 (75.0)	0.098
Nosocomial infection, n (%)	10 (34.5)	7 (8.8)	0.001
Severe BPD, n (%)	11 (37.9)	42 (52.5)	0.179
Malnutrition, n (%)	11 (37.9)	40 (50.0)	0.264
BSA exposure in the NICU, n (%)	9 (31.0)	36 (45.0)	0.191
BSA exposure for more than 7 days in the NICU, n (%)	9 (31.0)	36 (45.0)	0.191
Carbapenems exposure in the NICU, n (%)	5 (17.2)	29 (36.3)	0.058
Carbapenems exposure for more than 7 days in the NICU, n (%)	5 (17.2)	29 (36.3)	0.058
Third-generation cephalosporins and C/BLI combinations exposure in the NICU, n (%)	7 (24.1)	25 (31.3)	0.471
Third-generation cephalosporins and C/BLI combinations exposure for more than 7 days in the NICU, n (%)	7 (24.1)	25 (31.3)	0.471
P/BLI combinations exposure in the NICU, n (%)	3 (10.3)	24 (30.0)	0.044
P/BLI combinations exposure for more than 7 days in the NICU, n (%)	3 (10.3)	21 (26.6)	0.072
Dual antibiotic exposure in the NICU, n (%)	4 (13.8)	16 (20.0)	0.459
Mechanical ventilation in the NICU, n (%)	16 (55.2)	37 (46.3)	0.410
Mechanical ventilation for more than 7 days in the NICU, n (%)	7 (24.1)	20 (25.0)	0.927
MDRI in the NICU, n (%)	3 (10.3)	7 (8.8)	0.724

MDRI, multidrug-resistant bacterial infection; LRTI, Lower respiratory tract infection; IQR, Interquartile Range; DOT, days of antibiotic treatment; PICU, pediatric intensive care unit; BPD, bronchopulmonary dysplasia; BSA, broad-spectrum antibiotics; NICU, newborn intensive care unit; C/BLI, cephalosporin/β-lactamase inhibitor; P/BLI, penicillin/β-lactamase inhibitor.

[4, 10–13]. Malnutrition increases the susceptibility to respiratory infections in children [14]. Although infants with BPD have many of the risk factors mentioned above, it is difficult to determine the actual causes of MDRIs in these children. Our study showed that the incidence of malnutrition was high (51/109), but the difference between MDRIs and non-MDRIs was not statistically significant ($p > 0.05$). This may be related to the fact that our diagnosis of malnutrition did not include mid-arm hip circumference and edema [10], and that we did not analyze the type of parenteral nutrition. We cannot yet consider malnutrition as a risk factor for MDRI. The effect of malnutrition and the type of the parenteral nutrition on the immune status of the studied cases could not be ignored and further RCT studies are still needed regarding this issue. Children with MDRI are less likely to develop infection from colonization (4/29), and their incidence of nosocomial infection was high (10/29). Nosocomial infections were associated with MDRIs ($p < 0.05$). PICU admission, BSA exposure to NICU, and hospitalization experience (NICU-hospital length, NICU-mechanical ventilation, NICU-MDRIs) were not significantly associated with MDRIs (all $p > 0.05$). Of note, nosocomial infection increased the risk of MDRI by 5.3 fold (OR 5.3, 95% CI 1.7–16.4) and thus it remains the leading cause of MDRI in infants with BPD on readmission for LRTI.

Colonization of the infants in the NICU developed into a nosocomial infection on readmission without causing MDRI, and the MDRI strains confirmed during NICU admission and readmission were not the same. However, we cannot assume that bacterial colonization and the occurrence of MDRI during the NICU are directly causally related to MDRI during readmission. Therefore, it is not yet believed that the BSA exposure and hospitalization experience of BPD infants during the neonatal period affect the subsequent MDRI on admission. When infants with BPD develop LRTIs, it may be

TABLE 4. The distribution of drug resistance of MDR-KP and MDR-E. coli in 13 of 29 confirmed MDRI cases.

	MDR-KP (n = 13)		MDR-E. coli (n = 8)	
Antibacterial drugs	Number of strains	Resistance rate (%)	Number of strains	Resistance rate (%)
Aztreonam	9	69.2	4	50.0
Ampicillin	13	100.0	8	100.0
Ceftazidime	10	76.9	3	37.5
Ceftriaxone	11	84.6	8	100.0
Ciprofloxacin	4	30.8	4	50.0
Cefoperazone/sulbactam	7	53.8	2	25.0
Gentamicin	4	30.8	5	62.5
Ampicillin/sulbactam	13	100.0	8	100.0
Levofloxacin	1	7.7	4	50.0
Amikacin	0	0.0	0	0.0
Piperacillin/tazobactam	9	69.2	3	37.5
Imipenem	5	38.5	1	12.5
Meropenem	5	38.5	1	12.5
Cotrimoxazole	5	38.5	5	87.5

MDR-KP, multidrug-resistant bacterial- Klebsiella pneumonia; MDR-E. coli, multidrug-resistant bacterial- Escherichia coli; MDRI, multidrug-resistant bacterial infection.

TABLE 5. Binary logistic regression analysis of MDRI.

Exposure variable	B	S.E.	Wald	Sig	OR (95% CI)
Nosocomial infection	1.673	0.573	8.529	0.003	5.327 (1.733–6.367)
P/BLI combinations exposure in the NICU	−1.309	0.68	3.703	0.054	0.270 (0.071–1.025)

P/BLI, penicillin/β-lactamase inhibitor; NICU, newborn intensive care unit; B, beta; S.E., standard error; OR, Odds ratio; CI, confidence interval.

inappropriate for clinicians to directly select BSA based on their intuition that the patient is likely to be infected by drug-resistant strains. A more cautious attitude should be taken. Specifically, selection of BSA should hinge on the bacterial species involved in the infection during the NICU stay or its high risk factors for MDRI in cases of community-acquired pneumonia in infants with BPD. Although no direct causal relationship is noted between MDRIs in the NICU and those on readmission, physicians still need to be highly vigilant about the risk of colonization developing into infection in case that subsequent reinfection takes place in infants with MDRIs in the NICU. It is suggested that we should continue to strengthen the surveillance of colonization infection. In the future, it may even be necessary to conduct further comprehensive research on the removal of colonization infection.

To prevent MDRIs, in addition to strengthening the surveillance and averting colonization infection and nosocomial infection by multimodality [15], good antibiotic stewardship is essential as a core key factor [4]. Infants with BPD are a vulnerable group in ICUs and emergency departments where empiric antibiotic therapy is necessary for life-threatening infections before identification of pathogens, which should be narrowed to pathogens specific to medical institutions when covering common related pathogens [16]. MDRIs in BPD infants readmitted for respiratory infection in the West China Second Hospital of Sichuan University were similar to the pathogens responsible for MDRIs of other ages and nosocomial respiratory infections [6, 12, 17]. In total, 26 of the 29 confirmed MDRIs were Gram-negative bacteria, including 22 Gram-negative bacilli (8 cases of ESBL-KP, 5 cases of CR-KP, 6 cases of ESBL-E. coli, 2 cases of CR-E. coli and 1 case of CR-Enterobacter hosei). The incidence of resistance to quinolones in children was higher than expected, which may be due to the increased use of quinolones in children [18]. In addition, care should be taken when administering quinolones to children. All isolates were sensitive to tigecycline [6], which may be related to the low rate of tigecycline use in children. With rising application of tigecycline in the future, we need to be alert to the possibility of tigecycline resistance.

This study had several limitations. Our study was a single-center study with a small sample size. Our study excluded children with genetic metabolic diseases, heart disease, airway dysplasia, and other diseases, so the risk factors for MDRIs in these children remain unknown. Therefore, multicenter studies with larger sample sizes, and stratified analyses of multiple underlying diseases are required in the future to support and analyze the risk factors for MDRIs to optimize the monitoring, prevention and reduction of MDRI occurrence.

TABLE 6. Characteristics of hospitalization time and antibiotics in children with MDRI and MDRI within PMA-1 year old.

Variable	MDR n = 29	no-MDR n = 80	*p*
Total length of hospital stay, median (IQR), d	93.0 (59.0–105.0)	73.0 (56.3–87.8)	0.024
Length of stay in PICU, median (IQR), d	18.0 (10.5–38.0)	12.0 (0.5–23.8)	0.014
Total DOT, median (IQR), d	89.0 (52.5–103.5)	64.0 (50.0–82.5)	0.002
DOT (except for NICU), median (IQR), d	28.0 (17.0–42.0)	18.0 (11.0–27.0)	0.002
Number of hospitalizations, median (IQR)	3.0 (3.0–4.0)	3.0 (2.0–4.0)	0.083
Number of ICU hospitalizations, median(IQR)	3.0 (2.0–3.0)	2.0 (1.0–3.0)	0.022
Length of single stay over 14 days, n (%)	20 (69.0)	36 (45.0)	0.027
Length of single stay in PICU stay for more than 7 days, n (%)	26 (89.7)	64 (80.0)	0.240
Mechanical Ventilation, n (%)	11 (37.9)	19 (23.8)	0.143
Ventilation-associated Pneumonia, n (%)	5 (17.2)	6 (7.5)	0.158
Dual antibiotics, n (%)	9 (31.0)	10 (12.5)	0.024
Quinolone antibiotics, n (%)	6 (20.7)	4 (5.0)	0.021
BSA exposure, n (%)	28 (96.6)	79 (98.2)	0.463
Carbapenems exposure, n (%)	19 (65.5)	39 (48.8)	0.121
Carbapenems exposure for more than 7 days, n (%)	18 (62.1)	27 (33.8)	0.008
Third-generation cephalosporins and C/BLI combinations exposure, n (%)	2 (69.0)	56 (69.7)	0.917
Third-generation cephalosporins and C/BLI combinations exposure for more than 7 days, n (%)	15 (51.7)	41 (51.2)	0.965
P/BLI combinations exposure, n (%)	10 (34.5)	36 (45.0)	0.326
P/BLI combinations exposure for more than 7 days, n (%)	6 (20.7)	15 (18.8)	0.821

MDRI, multidrug-resistant bacterial infection; PMA, postmenstrual age; IQR, Interquartile Range; DOT, days of antibiotic treatment; NICU, newborn intensive care unit; ICU, intensive care unit; BSA, broad-spectrum antibiotics; C/BLI, cephalosporin/β-lactamase inhibitor; P/BLI, penicillin/β-lactamase inhibitor.

5. Conclusions

Therefore, it is necessary to evaluate the risk factors for MDRI in these 109 children to provide a basis for the clinical prevention and treatment of MDRI. BPD infants readmitted due to LRTIs may be more susceptible to MRDIs than normal infants. This finding suggested that antibiotics should be utilized in accordance with the clinical condition, and considerable attention should be given to the prevention and control of nosocomial infection. At the same time, the monitoring of MDRI colonization infection in the NICU should be emphasized, and future clearance work should be conducted. Once MDRI occurs in these special groups of children, the infectious agents are possibly classified as a "serious threat" and "urgent threat". We should also pay more attention and strengthen the monitoring and drug resistance analysis of MDRIs to further guide the choice of empirical antibiotic therapy for these children. Antimicrobial stewardship plans and measures to prevent or avoid nosocomial infection will need to be analyzed in detail in future studies with increased case numbers. Unfortunately, current research on respiratory pathogens in children with BPD mainly focus on respiratory syncytial virus. This study is a single-center study with small sample size MDRIs, but it also reminded us the risk of MDRI due to LRTI in children with underlying diseases such as BPD, which is different from what we previously recognized.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YM and LNQ—designed the research study. YM—performed the research. LNQ—provided help and advice on the ELISA experiments. YM and LNQ—analyzed the data. YM—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final

manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Medical Ethics Committee of West China Second University Hospital of Sichuan University (Approval No. Keji (2017) No. 46-4). No consent to participate is required in this study given that data from patients have been presented in a general manner, and no patient can be identified by the third parties.

ACKNOWLEDGMENT

The authors thank the pediatric intensive care unit team for help with the preparation of this manuscript. Thank numerous individuals participated in this study. Thanks to all the peer reviewers for their opinions and suggestions.

FUNDING

This work was supported by Central Government Funds of Guiding Local Scientific and Technological Development for Sichuan Province (No. 2021ZYD0105).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Yang Min, Li-Na Qiao. Risk factors for multidrug resistant bacterial infection in infants with bronchopulmonary dysplasia re-hospitalized due to lower respiratory tract infection: a case-control study. Signa Vitae. 2023; 19(3): 84-90. doi: 10.22514/sv.2022.050.