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Original Article

The drug resistance of multidrug-resistant bacterial organisms in pediatric pneumonia patients

Xianbo Chen[1], Danfeng Pan[2], Yongzheng Chen[1]

[1]*Department of Pediatrics, Wenling Maternal and Child Health Hospital, Wenling City, Zhejiang Province, China;* [2]*Department of Pediatrics, The First People's Hospital of Wenling, Wenling City, Zhejiang Province, China*

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Abstract: Objective: This study aimed to investigate the distribution of multidrug-resistant organisms in pediatric patients with infectious pneumonia and to analyze their resistance and risk factors. Methods: Pediatric patients infected with five MDROs (MRSA, MDR-PA, MDRAB, ESBL KP, and ESBL *E. coli*) and five sensitive bacteria (MSSA, PA, AB, KP, and *E. coli*) were recruited as the study cohort. The distribution of the MDROs and the risk factors for MDRO-infected pneumonia were investigated. The two groups' treatment costs, hospitalization times, and prognoses were compared. Results: A total of 219 children were included, including 3 cases of mixed infections with MDRO and sensitive bacteria (1.37%), 110 cases of MDRO infections (50.23%), and 106 cases of sensitive bacterial infections (48.40%). Imipramine was sensitive to MDR-PA, MDRAB, ESBL KP, and ESBL *E. coli*, and vancomycin was sensitive to MRSA. A logistic regression model and a multifactorial analysis showed that ICU treatment, mechanical ventilation, arterial and venous intubation, fiberoptic bronchoscopy, concomitant chronic lung disease, and chronic cardiovascular disease were the independent risk factors for MDRO ($P < 0.05$). The hospitalization times, the treatment costs, and the 30-day mortality rate of the children in the MDRO group were significantly higher than they were in the children infected with sensitive bacteria ($P < 0.05$). Conclusion: Vancomycin or imipenem may result in good clinical outcomes in children treated in the ICU subject to mechanical ventilation, arterial and venous intubation, fiberoptic bronchoscopy, the overuse of antimicrobial drugs, and children with concomitant chronic lung disease or chronic cardiovascular disease.

Keywords: MDROs, pediatric patients, infectious pneumonia, drug resistance

Introduction

Multi-drug resistant organisms (MDROs), also known as multidrug resistant microorganisms, are primarily bacteria that are resistant to three or more classes of clinically used antimicrobial agents [1]. In recent years, with the widespread use of antimicrobials in clinical practice, the abuse of antibiotics has become more and more prominent. The incidence of MDROs has increased every year since methicillin-resistant *Staphylococcus aureus* (MRSA) was reported in the 1960s, making many severe infections and refractory infections increasingly difficult to treat [2, 3].

MDRO infections have spread over almost all the world, posing a threat to global health. Keiji Fukuda, director-general of the World Trade Organization, said that "superbugs" are challenging modern medicine, and mankind is stepping into the "post-antibiotic era" [4]. Children have an immature immune system. Statistics show that infectious diseases account for about 60% of deaths among children. However, the use of antibiotics in children is also a "double-edged sword" [5, 6]. Evidence has shown that children have a high risk of MDRO infections, in which gram-negative bacterial infections make up 67.98%, with ESBL-producing *Escherichia coli* (ESBL *E. coli*) and ESBL-producing *Klebsiella pneumoniae* (ESBL KP) the most-often detected [7]. MRSA is a potentially serious bacterial infection in children, and it is of great significance to define the characteristics of MDRO infection and standardize the use of antimicrobial drugs in children.

The purpose of this study was to investigate the distribution characteristics of MDRO in children

with infectious pneumonia and to explore and analyze the risk factors that lead to MDRO infections in children, thereby providing clinical guidance for controlling the spread of MDRO and guiding the rational use of antibiotics in children.

Materials and methods

General information

A total of 219 children with infectious pneumonia caused by five types of MDRO (MRSA, MDR-PA, MDRAB, ESBL KP, and ESBL *E. coli*) and five types of sensitive bacteria (MSSA, PA, AB, KP, and *E. coli*) from February 2012 to January 2020 were recruited as the study cohort, among which 3 children with mixed infections of MDRO and sensitive bacteria were excluded. The remaining 216 children were divided into the MDRO group (n=110) and the sensitive bacteria group (n=106) according to the type of bacteria they were infected with.

Inclusion criteria: (1) children who met the diagnostic criteria for infectious pneumonia [8] and who had typical symptoms, (2) children with complete medical records, and (3) children who were 14 years or younger. This study was approved by the Ethics Committee of Wenling Maternal and Child Health Hospital. All the children's guardians signed the informed consent forms.

Exclusion criteria: (1) children suffering from mental illnesses, (2) children with severe liver and kidney dysfunction, (3) children with congenital heart disease and congenital immune system diseases, (4) children with tuberculosis, pulmonary insufficiency, pulmonary embolisms, pulmonary edema, or other diseases, and (5) children with malignant tumors.

Intervention methods

The baseline data, including the gender, age, weight, height, and some other details that may influence the clinical outcomes of the children were collected using a questionnaire designed by the hospital. Meanwhile, sputum samples were collected from each child's artificial trachea or tracheal tube using a disposable sterile sputum suction tube. The samples were placed in a closed sterile container and cultured by the laboratory. The isolation, cultivation, and drug susceptibility testing of the pathogenic bacteria were completed in the laboratory.

Outcome measurement

The dominant bacteria identified twice in succession in the samples collected from children's sputum were the pathogens determined using the HW-138 semi-automatic bacterial analysis system. The drug susceptibility test was implemented using the K-B method with a reference to the standards issued by the American Laboratory Standards Committee in 2002. The hospitalization times, the treatment costs, and the 30-day mortality rates of the two groups were reviewed.

Statistical methods

SPSS 20.0 was used to carry out the statistical analysis. The continuous variables expressed as the mean ± standard deviation were compared using analyses of variance. The continuous variables that did not conform to a normal distribution were examined using non-parametric tests. The count data were indicated as a percentage and compared using *Chi*-square tests. Logistic multifactorial regression analyses were applied to screen for the risk factors and calculate the OR values of the risk factors as well as the 95% confidence intervals. $P < 0.05$ indicated a significant difference [9].

Results

Comparison of the baseline data

The baseline data, such as gender, age, and weight, were not significantly different between the two groups of patients (P>0.05), so they were comparable (**Table 1**).

Distribution of the pathogenic bacteria

The distribution of the pathogenic bacteria in the 216 children (excluding the 3 children with mixed infections) enrolled was analyzed, and the results showed that among the 110 children in the MDRO group, there were 21 (19.09%) MRSA infection cases, 20 (18.18%) MDR-PA infection cases, 19 (17.27%) MDRAB infection cases, 23 (20.91%) ESBL KP infection cases, and 27 (24.55%) ESBL *E. coli* infections. Among the 106 children with sensitive bacterial infections, there were 20 (18.87%) MSSA infec-

Table 1. Comparison of the baseline data ($\bar{x} \pm s$)/[n (%)]

Baseline data		MDRO group (n=110)	Sensitive bacteria group (n=106)	t/X^2	P
Gender	Male	60	56	0.064	0.8
	Female	50	50		
Average age (years)		5.18±2.11	5.21±1.98	0.108	0.914
Average weight (kg)		20.19±2.33	19.98±2.41	0.651	0.516
Average height (cm)		100.28±10.22	102.28±9.87	1.462	0.145

Table 2. Distribution of the MDRO pathogens

	Pathogen	Proportion of infection	Strains (%)
G+	MDR-PA	20	18.18
	MDRAB	19	17.27
	ESBL KP	23	20.91
	ESBL *E. coli*	27	24.55
G-	MRSA	21	19.09

tion cases, 19 (17.92%) PA infection cases, 17 (16.04%) AB infection cases, 10 (9.43%) KP infection cases, and 40 (37.74%) *E. coli* infection cases. Each of the above bacteria's proportion of the total infections is detailed in **Table 2**; and **Figure 1**.

Sensitivity analysis of the MDROs

G+ resistance was more significant in MDRO, among which ESBL *E. coli* was resistant to sulprosan, fudaxin, butyricetin, ampicillin, cefazolin, ciprofloxacin and Bactrim, while MDRAB was resistant to sulprosan, fudaxin, ampicillin, cefazolin, ciprofloxacin and Bactrim (**Table 3**). G- resistance was also more pronounced in MDRO, and MRSA was resistant to imipenem, tezetocin, ampicillin, benzylpenicillin, and erythromycin (**Table 4**).

The risk factors for MDRO-related infectious pneumonia

A single factor analysis was conducted to compare the MDRO group with the sensitive bacteria group, and the results showed that patients with a history of ICU treatment, surgery, urinary catheter retention, undergoing mechanical ventilation, arterial placement, fiberoptic bronchoscopy, with concomitant chronic lung disease and chronic cardiovascular disease were more likely to develop infectious pneumonia associated with MDRO infections (**Table 5**). A logistic regression model and a multifactorial analysis revealed that a history of ICU treatment, mechanical ventilation, arterial and venous intubation, bronchoscopy, and concomitant chronic lung disease and cardiovascular disease were all independent risk factors for MDRO-related infectious pneumonia ($P < 0.05$) (**Table 6**).

Comparison of the treatment parameters between the MDRO group and the sensitive bacteria groups

The hospitalization times, the treatment costs, and the 30-day mortality rate of the children in the MDRO group were significantly higher than they were in the sensitive bacteria group ($P < 0.05$) (**Figures 2** and **3**).

Discussion

The overuse of antibiotics, especially broad-spectrum antimicrobial drugs has made resistant bacteria more common, so antibiotic overuse has become one of the most concerning issues in the worldwide pharmaceutical community [10, 11]. MDRO infections are more common in hospitals, and are associated with improper operations by doctors and nurses, equipment, ineffective contact precautions, etc. MDRO infections pose a serious threat not only to patients' own health, but also to hospital capacity [12, 13]. Although the incidence rate of MDRO-related infectious pneumonia has decreased steadily, its mortality rate has shown an increasing trend. Data from 2010 show that the mortality rate of MDRO infectious pneumonia was 20.11%, a rate that increased to 22.19% in 2015 [14, 15]. Experts believe that the evolution of pathogenic bacteria may contribute the rise in the number of diagnosed cases and called for the rational use of antibiotics to improve the effectiveness of medical intervention.

This study was conducted to investigate the distribution of pathogenic bacteria, the results of drug susceptibility tests, and the associated risk factors in patients with infectious pneumo-

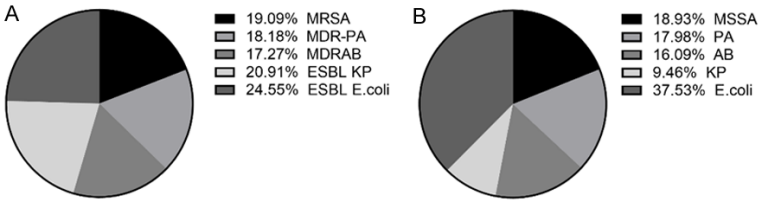

Figure 1. Distribution of the pathogenic bacteria detected in the two groups of children. Our analysis showed that the proportions of MRSA, MDR-PA, MSRAB, ESBL KP, and ESBL *E. coli* in the MDRO group (A) were 19.09%, 18.18%, 17.27%, 20.91%, and 24.55%, respectively. The proportions of MSSA, PA, AB, KP, and *E. coli* in the sensitive bacteria group (B) were 18.93%, 17.98%, 16.09%, 9.46%, and 37.53%, respectively.

Table 3. Susceptibility test results of the G+ MDROs

Pathogen	n	A	B	C	D	E	F	G	H
ESBL KP	23	12	16	0	0	23	23	16	11
MDR-PA	20	0	0	0	0	20	20	20	0
ESBL *E. coli*	27	27	27	27	0	27	27	27	27
MDRAB	19	19	19	0	0	19	19	19	19

Note: A: Sulphasan, B: Fodaxin, C: Butylcana, D: Imipenem, E: Ampicillin, F: Cefazolin, G: Ciprofloxacin, H: Bactrim.

Table 4. G- sensitivity test results of the MDROs

Pathogen	n	A	B	C	D	E	F	G	H
MRSA	21	0	0	21	21	14	21	21	21

Note: A: Vancomycin, B: Ticloplanin, C: Imipenem, D: Tergisin, E: Bactrim, F: Ampicillin, G: Benzylpenicillin, H: Erythromycin.

nia, and we found that G+ accounted for the vast majority of MDROs in terms of pathogen distribution, and 80% of the five drug-resistant bacteria were G+, with MDR-PA infections accounting for 18.18%, MDRAB infections for 17.27%, ESBL KP infections for 20.91%, and ESBL *E. coli* infections for 24.55%. A national bacterial drug resistance report compiled by the China Ministry of Health in 2010 showed that there were 83,195 G+ out of 10,289 strains, dominated by *Enterococcus* spp. and *Streptococcus* spp., which is similar to the results of this study [16, 17]. The susceptibility tests showed that all five strains are highly resistant to ESBL *E. coli*, and ESBL *E. coli* is resistant to sulforaphane, fudasin, bupivacaine, ampicillin, cefazolin, ciprofloxacin and Co-trimoxazole, MDRAB was resistant to sulforaphane, fudasin, ampicillin, cefazolin, ciprofloxacin, and cotrimoxazole, and MRSA was resistant to imipenem, tergisin, ampicillin, benzathine penicillin, and erythromycin. Some scholars conducted studies on the drug sensitivity of MDROs in 12 hospitals in China, and the results showed that 9 out of 10 MDROs showed resistance to ampicillin, while 7 MDROs showed resistance to erythromycin, which is similar to the results of this study [18, 19]. We believe that the drug sensitivity of MDROs can provide a theoretical reference for subsequent treatment.

A single-factor and multifactor logistic analysis of the risk factors for MDRO infectious pneumonia was conducted, indicating that a history of ICU treatment, mechanical ventilation, arterial and venous intubation, bronchoscopy, concomitant chronic lung disease, and concomitant cardiovascular disease were the independent risk factors for MDRO infectious pneumonia. Evidence has shown that tracheal intubation and mechanical ventilation can increase the risk of bacterial colonization of the airways, and these treatment options are not recommended unless they are necessary to improve patient outcomes [20, 21]. We speculated that the history of ICU treatment confirmed that the patient's condition was critically ill, his immune system was mostly destroyed, and there was a significant decline in organ function, which could provide opportunities for MDRO infection, while tracheal intubation, mechanical ventilation, arterial and venous intubation, and bronchoscopy are invasive or traumatic procedures, and they can increase the risk of bacterial infection [22-24]. A history of chronic lung disease and cardiovascular disease indicates that the integrity of the patient's respiratory epithelial cells has been impaired, and their protective and barrier functions have been significantly minimized, leading to a reduced clearance rate of respiratory sputum and increasing the likelihood of bacterial colonization of the respiratory tract [25, 26]. A comparison of the general therapeutic indicators between the two groups showed that MDRO infections signifi-

Table 5. Single factor analysis of the risk factors for MDRO infectious pneumonia

Risk factor	Risk factor	MDRO group (n=110)	Sensitive bacteria group (n=106)	X^2	*P*
Gender	Male	60	56	0.064	0.8
	Female	50	50		
History of ICU treatment	Yes	80	36	32.627	< 0.001
	No	30	70		
Surgical history	Yes	76	40	21.346	< 0.001
	No	34	66		
Indwelling catheter	Yes	89	26	68.928	< 0.001
	No	21	80		
Mechanical ventilator	Yes	90	20	85.595	< 0.001
	No	20	86		
Arterial and venous intubation	Yes	100	50	48.67	0.001
	No	10	56		
Fibroscopy	Yes	60	20	29.465	< 0.001
	No	50	86		
Gastroscopy	Yes	70	26	33.437	< 0.001
	No	40	80		
Comorbid chronic lung disease	Yes	88	30	58.209	< 0.001
	No	22	76		
Comorbid cardiovascular disease	Yes	80	30	42.63	< 0.001
	No	30	76		
Diabetes	Yes	60	55	0.153	0.695
	No	50	51		

Table 6. A multifactorial logistic analysis of the risk factors for MDRO infectious pneumonia

Risk factor	β	SE	Exp (β)	95% CI	*P*
History of ICU treatment	1.221	0.341	3.481	2.112-4.328	< 0.001
History of mechanical ventilation	0.981	0.321	2.989	1.827-2.321	< 0.001
Arterial and venous intubation	0.781	0.298	2.554	1.782-2.289	< 0.001
Fibroscopy	1.298	0.443	3.671	2.234-5.301	< 0.001
Comorbid chronic lung disease	1.344	0.541	3.871	2.781-5.574	< 0.001
Comorbid cardiovascular disease	1.431	0.617	3.981	2.981-5.598	< 0.001

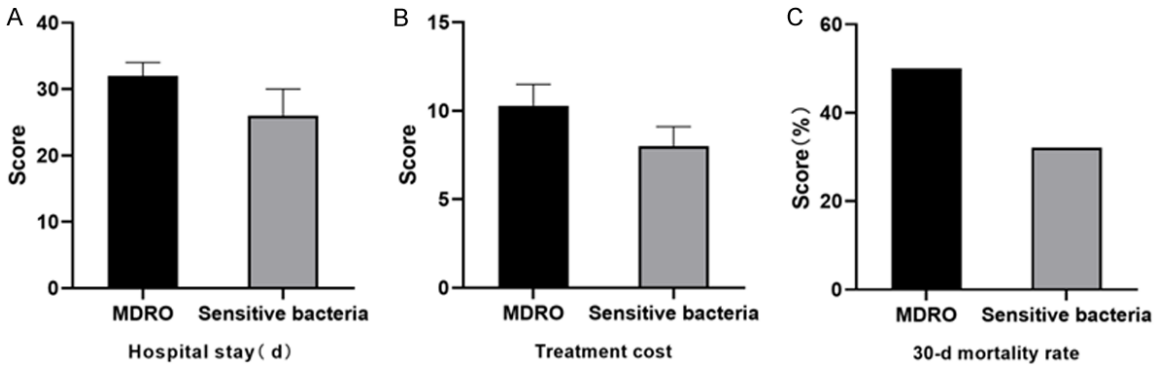

Figure 2. Comparison of the differences in the outcomes between the MDRO group and the sensitive bacteria group. The hospitalization times (A), treatment costs (B), and 30-day mortality rate (C) of the children in the sensitive bacteria group were significantly lower than the 30-day mortality rate of the children in the MDRO group ($P < 0.05$) # $P < 0.05$ compared with the sensitive bacteria group.

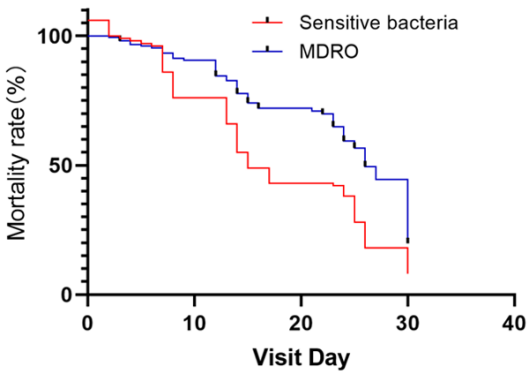

Figure 3. Comparison of the 30 day case fatality rate between the two groups. The 30 day mortality rate of the sensitive bacteria group was significantly lower than it was in the MDRO group.

cantly increased the severity of the disease, suggesting that health workers should focus on preventing MDRO infections.

In summary, children treated in the ICU, children receiving mechanical ventilation, arterial and venous intubation, children undergoing fiberoptic bronchoscopy, children who misuse antimicrobial drugs, and children with concomitant chronic lung disease as well as chronic cardiovascular disease should be protected against drug-resistant bacterial infections, and the use of vancomycin or imipenem may have a better clinical efficacy.

The limitation of this study is that the types of primary diseases in the enrolled children were not investigated, which may lead to the possibility that the analysis of the risk factors and the prognoses of children with MDRO infectious pneumonia may be influenced by the severity of the primary disease. This needs to be improved in future studies.

Disclosure of conflict of interest

None.

Address correspondence to: Yongzheng Chen, Department of Pediatrics, Wenling Maternal and Child Health Hospital, No. 102, Xiabao Road, Chengdong Street, Wenling 317500, Zhejiang Province, China. Tel: +86-13666867090; E-mail: chenyongzheng7090@126.com

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