ANALYSIS OF DRUG RESISTANCE OF CARBAPENEM-RESISTANT ACINETOBACTER BAUMANNII IN CHILDREN AND ITS RISK FACTORS

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ABSTRACT

Objective: *This study aimed to provide a theoretical basis for improving the clinician's awareness of carbapenem-sensitive A. baumannii, thus preventing and controlling its infections.*

Methods: *In this retrospective study, 110 cases of Acinetobacter baumannii infection were analyzed, including 46 and 64 cases of carbapenem-resistant and -sensitive infections, respectively to investigate its drug resistance in children and its risk factors for infection.*

Results: *The infection resistance analysis and risk factors investigation showed that carbapenem-resistant A. baumannii infection occurred more in ICU.*

Conclusion: *Greater the varieties of antibiotics used, higher the risk of infection. Moreover, children had worse prognosis in the case of carbapenem-sensitive A. baumannii infection.*

Keywords: *Carbapenem-resistant Acinetobacter baumannii, children, antibiotic.*

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Introduction

Acinetobacter baumannii (Ab) is a common conditioned pathogen. In recent years, the National Children's Antimicrobial Resistance Surveillance Organization (ISPED) has shown that the infection rate of Ab in children was among the top 10 clinical bacterial infections[1-2]. The Ab-resistant patients often have combined severe infections with high mortality[3]. Carbapenem antibiotics are widely used as the most important therapeutic in the treatment of serious bacterial infections. However, owing to an increase in its unreasonable application, the carbapenem-resistance has gradually increased worldwide. The emergence of carbapenem-resistant A. baumannii (CR-aba) has posed severe challenges to the clinicians in selection of antibiotics, leading to adverse effects such as prolonged hospitalization and increased costs[4]. At present, there is insufficient clinical research on CR-aba and its infection in children. Therefore, this paper retrospectively analyzed 12 cases of Ab infection in our hospital from January 2016 to February 2018 and investigated the drug resistance of CR-aba and the risk factors for infection.

This study found that CR-aba infection occurred more in intensive care units (ICU), and CR-aba group had a worse prognosis than the carbapenem-sensitive A. *baumannii* infection (CS-aba) group. Previous use of carbapenem antibiotics and ventilator-associated pneumonia are independent risk factors for CR-aba infection ($p<0.05$). This study provides data for national surveillance of antimicrobial resistance in children, improves clinicians' awareness of CR-aba, thus helping in prevention and control of infection.

Data and methods

General data

A. *baumannii* positive samples were collected and cultured in our children's hospital from January 2016 to December 2018 (excluding duplicate isolated strains from the same patient at the same site).

Patients' clinical data were collected from the in-hospital medical record enquiry system, including gender, age, antibiotic use, ventilator-associated pneumonia, mechanical ventilation time, hospital stay, department, invasive procedure, clinical diagnosis and prognosis.

Strain isolation culture method

The strains were isolated and cultured according to the National Clinical Laboratory procedures and were identified using French BioMerieux VITEK-2 microbiological analysis and identification system. The carbapenem phenotype screening was done by the Clinical and Laboratory Standards Institute (CLSI) 2017 recommended modified carbapenem inactivation method (mCIM) test.

Grouping

According to the results of drug resistance screening, the cases were divided into CR-aba and CS-aba groups, for follow-up analysis and risk factors for CR-aba infections.

Data analysis

The WHONET 5.6 software was used to analyze the department source distribution, specimen source distribution and carbapenem resistance of A. baumannii strain. Statistical analysis was performed using SPSS19.0 software. Chi-square test was used to compare the rates among different groups. Univariate analysis and logistic regression were used to screen the related and independent risk factors for CR-aba infection. $p<0.05$ suggests statistical difference.

Results

Department distribution of Ab infection

A total of 110 cases of Ab-positive infections in bacterial culture of children were collected (for repeatedly isolated strains in the same site of the same patient, only the first strain was recorded). Of which, 33 cases were collected in 2016, with an isolation rate of 3.2%; 42 cases in 2017 with an isolation rate of 4.9%; and 35 cases in 2018, with an isolation rate of 5.9%. This indicated that the detection rate of Ab infection in children in our hospital had increased every year. The departmental distribution data showed that Ab infection was mainly prevalent in Pediatric Intensive Care Unit (PICU) and the Neonatal Intensive Care Unit (NICU), and the infection rate of PICU increased every year. The specific data was as shown in Table 1.

Department	Year 2016 N (%)	Year 2017 N (%)	Year 2018 N (%)
PICU	13(39.4%)	26(61.9%)	24(68.6%)
NICU	12(36.3%)	9(21.4%)	6(17.1%)
Hematology	2(6.1%)	2(4.7%)	2(5.7%)
Respiratory	3(9.1%)	2(4.8%)	2(5.7%)
Outpatient		1(2.4%)	1(2.9%)
Surgery	2(6.1%)		
Endocrinology	1(3.0%)		
Digestive		1(2.4%)	
Nephrology		1(2.4%)	
	33	42	35

Table. 1: Number of Ab isolates and departmental distribution in year 2016-2018.

Specimen source and department distribution of CR-aba infection

In this study, CR-aba reflects resistance to either imipenem or meropenem. As shown in Table 2, there were 46 CR-aba specimens. Of these 35 (76.2%) were observed in sputum, and 4 (8.7%) in blood. The departmental distribution of 46 cases of CR-aba infection was as shown in Table 3. About 38 cases (82.7%) were observed. in PICU.

Specimen source	Strain number (n)	Composition ratio (%)
Sputum	35	76.2
Blood	4	8.7
Urine	2	4.4
Secretion	2	4.4
Catheter	1	2.1
Bronchoalveolar lavage fluid	1	2.1
Pus	1	2.1
Total	46	100

Table. 2: Source and composition ratio of CR-aba specimens.

Department	Strain number (n)	Composition ratio (%)
PICU	38	82.7
NICU	4	8.7
Hematology	2	4.3
Respiratory	2	4.3
Total	46	100

Table. 3: The CR-aba distribution as per departments and its composition ratio.

Analysis of resistance to different antibiotics in the treatment of CR-aba and CS-aba infections

According to the results of drug resistance screening test, of the 110 Ab infection patients, 46 had CR-aba infection, and 64 had CS-aba infection.

As shown in Table 4, patients with CR-aba infection had higher overall resistance rate to common antibiotics than those of CS-aba group. The incidences of multi-drug resistance in CR-aba infection group was 95.7%; while that in CS-aba group was 17.2%. In total 4 (8.7%) CR-aba patients were resistant to all the antibiotics listed in the table.

Antibiotics	Ab infection	CR-aba infection	CS-aba infection
Ceftazidime	51(46.4%)	39(84.4%)	12(18.8%)
Ceftriaxone	51(46.4%)	37(80.4%)	14(21.9%)
Cefepime	43(39.1%)	33(71.7%)	10(15.6%)
Ampicillin and Sulbactam	56(50.9%)	42(91.3%)	14(21.9%)
Ciprofloxacin	51(46.4%)	39(84.4%)	12(18.8%)
Imipenem	46(41.8%)	46(100%)	0
Gentamicin	51(46.4%)	41(89.1%)	10(15.6%)
Amikacin	11(10%)	10(21.7%)	1(0.9%)
Levofloxacin	29(26.4%)	18(39.1%)	11(17.2%)
Multi-drug resistance	52(47.3%)	46(95.7%)	11(17.2%)
Resistant to all the above stated antibiotics	4(3.6%)	4(8.7%)	0
Total	110	46	64

Table. 4: Resistance analysis of different antibiotics in the treatment of CR-aba or CS-aba infection.

Comparison of antibiotics used in CR-aba and CS-aba groups.

Table 5 provides the comparison of types of antibiotics used in CR-aba and CS-aba-infected children. It can be seen that overall more types of antibiotics were used in CR-aba group than CS-aba group.

Number of antibiotic types used	CR-aba	CS-aba	X^2	P
1 type	8(47.1%)	14(73.7%)	4.647	0.031*
2 types	5(29.4%)	5(26.3%)		
3 types	4(23.5%)	0(0.0%)		

Table. 5: Comparison of antibiotics used in children with CR-aba and CS-aba.
**Trend chi-square test.*

Comparison of prognosis between CR-aba group and CS-aba group

As seen in Table 6, as compared to 64 children with CS-aba infection, 46 children with CR-aba infection had worse prognosis. A total of 32 (69.6%) children with CR-aba infection showed improvement, while 55 (85.9%) children with CS-aba infection showed improvement after the treatment. The difference is statistically significant ($p<0.05$).

Prognosis	CR-aba (N=46)	CS-aba (N=64)	Z/X^2	P
Improvement	32(69.6%)	55(85.9%)	4.338	0.037
Not improved or died	14(30.4%)	9(14.1%)		

Table. 6: Comparison of prognosis between children with CR-aba and CS-aba infection.

Univariate analysis of risk factors associated with CR-aba infection

Univariate analysis revealed that (Table 7), non-neonatal, ventilator-associated pneumonia, myocarditis, respiratory failure, treatment with more than three antibiotics, empirical use of carbapenem antibiotics and diagnosis of ventilator-associated pneumonia were significantly associated with CR-aba infection, thus accounting as risk factors for CR-aba infection ($p<0.05$). Whereas, factors like gender, age, treatment with one or two antibiotics and tracheotomy were less correlated with CR-aba infection ($p>0.05$).

		CS-aba (N=64)	CR-aba (N=46)	Z/X^2	*P*
Gender	Male	38(59.4%)	26(56.5%)	0.090	0.765
	Female	26(40.6%)	20(43.5%)		
Age	Newborn	15(23.4%)	2(4.3%)	7.464	0.006
	Non-neonatal	49(76.6%)	44(95.7%)		
Combined ventilator-associated pneumonia	No	41(64.1%)	12(26.1%)	15.459	<0.001
	Yes	23(35.9%)	34(73.9%)		
Combined myocarditis	No	39(60.9)	11(23.9)	14.797	<0.001
	Yes	25(39.1)	35(76.1)		
Combined respiratory failure	No	39(60.9)	13(28.3)	11.465	<0.001
	Yes	18(28.1)	1(2.2)		
Treatment with more than one antibiotic	No	45(70.3%)	29(63.0%)	0.642	0.537
	Yes	19(29.7%)	17(37.0%)		
Treatment with more than 2 antibiotics	No	59(92.2%)	37(80.4%)	3.328	0.068
	Yes	5(7.8%)	9(19.6%)		
Treatment with more than 3 antibiotics	No	64(100.0%	42(91.3%)	-	0.028*
	Yes	0(0.0%)	4(8.7%)		
Use of carbapenem antibiotics before bacterial culture returns	No	55(85.9%)	30(65.2%)	6.543	0.011
	Yes	9(14.1%)	16(34.8%)		
Definite diagnosis of ventilator-associated pneumonia	No	41(64.1%)	12(26.1%)	15.459	<0.001
	Yes	23(35.9%)	34(73.9%)		
Fiberoptic bronchoscopy	No	62(96.9%)	43(93.5%)	0.712	0.399
	Yes	2(3.1%)	3(6.5%)		
Hospital stay (days)		24(14-44)	19(13-36)	-1.079	0.280
Mechanical ventilation time (days)		11(2-20)	10(6-19)	-0.133	0.895

Table. 7: Analysis of risk factors for CR-aba infection resistance.
**Fisher's Exact Test.*

Multivariate analysis of risk factors for CR-aba infection

As seen in Table 8, logistic regression analysis

showed that use of carbapenem antibiotics before bacterial culture return and ventilator-associated pneumonia were independent risk factors for CR-aba infection (p<0.05).

		OR	95% CI	*p*
Use of carbapenem antibiotics before bacterial culture return	No	1	-	
	Yes	3.506	1.240-9.908	0.018
Combined ventilator-associated pneumonia	No	1	-	
	Yes	6.267	2.497-15.728	<0.001

Table. 8: Multivariate analysis of CR-aba infection.

Discussion

A. baumannii is an important conditioned pathogen causing nosocomial infections. According to the recent data of bacterial infections and drug resistance in children, the detection rate of Ab has been increasing every year. The increasing rate of CR-aba has made the treatment to Ab infection a global problem and its outbreak has seriously threatened the healthcare of children[5-6].

Epidemiological studies

In this study, the Ab samples were mainly procured from PICU department of our hospital. The results showed that Ab infection rate in PICU was increasing every year. These findings were consistent with the 2016-17 ISPED data, however, it differed from the reports of Wang Si, et al.[7], which stated that Ab infection rate was higher in NICU than in PICU from year 2008-12. It indicated that Ab infection rate showed a NICU decrease, which may be related to the increased control of infection in NICU, higher standardization of invasive mechanical ventilation and the increased use of non-invasive mechanical ventilation in recent years. The CR-aba is defined as resistance to any of imipenem, meropenem or ertapenem. At present, the detection rate of CR-aba is quite different at home and abroad. Latania et al. reported that the detection rate of CR-aba in children aged 1-17 years in the United States generally decreased from 1999 to 2012, reaching a peak of 12.7% in 2008 and dropping to 6.1% in 2012, however, it was on the rise in ICU[4]. Ngai et al. reported that the detection rate of CR-aba in children from hospital ICU was 67% as per a multi-center study from Vietnam in 2016[8]. As per the 2017 ISPED data of China, the Ab drug resistance in non-neonatal patients was 54.6% against meropenem, while that in neonatal patients was 34.9%.

The detection rate of CR-aba in this study was 41.8%, which was roughly consistent with the 2017 ISPED data of China.

Drug resistance analysis

Multidrug resistance (MDR) refers to bacterial resistance to 3 or more commonly used types of sensitive antibiotics, and it also includes pan-drug resistance (XDR)[9]. Pan-drug resistance implies that bacteria are almost fully resistant to commonly used antibiotics, in addition to being sensitive to colistin and tigecycline. It poses enormous challenges to global public health and clinical medicine. A. baumannii is usually phenotyped as XDR, and one of the main representative of XDR is CR-aba[10]. In this study, we saw that Ab was resistant to a variety of antibiotics The resistance rate of CR-aba group was over 80% against ceftazidime, ceftriaxone and ciprofloxacin, and close to 90% against gentamicin. Its MDR rate was over 95%. In the CR-aba group, 4 cases were observed to resistant to all the antibiotics in the study. We therefore speculated that these 4 cases were XDRs. At present, except incase of scientific research, hospitals are unable to conduct environmental XDR monitoring. Therefore, strengthening the monitoring of CR-aba could be of great significance for the prevention and control of XDR.

Risk factors for CR-aba infection

Tala et al. reported that CR-aba infection occurred primarily in ICU, and the infection group had a worse prognosis and higher mortality than the control group[11]. These findings were consistent with the results of our study. Patients in ICU are critically ill, often with multiple organ involvement, and needing ventilator-assisted ventilation. Moreover, most ICU patients have a complicated history of medication and have been treated with multiple antibiotics. Using a univariate analysis, this study found that, CR-aba infection was associated with patient age, combined ventilator-associated pneumonia, myocarditis, respiratory failure, number of antibiotics used, and application of carbapenems antibiotics (see Table 5 for details). However, there was no correlation with gender, fiberoptic bronchoscopy, length of hospital stay and mechanical ventilation time. Multivariate analysis showed that use of carbapenems antibiotics and ventilator-associated pneumonia were independent risk factors for CR-aba infection (p<0.05). Zhang Tongqiang et al. conducted a clinical and drug resistance analysis in 32 children with CR-aba infection and showed that, surgery, tracheal

intubation mechanical ventilation for >10 days, and use of carbapenem antibiotics for 2 weeks before CR-aba detection were independent risk factors for its onset. Whereas, Routsi et al. found that ventilator-associated pneumonia was an independent risk factor for CR-aba bacteremia in ICU[12]. This study expanded the sample size to further confirm that use of carbapenems antibiotics and ventilator-associated pneumonia are independent risk factors for CR-aba infection. Thus, strengthening the usage management of carbapenem antibiotics, standardizing the aseptic procedures of medical staff, and reducing the incidence of ventilator-associated pneumonia are the key to reducing and preventing CR-aba infection.

Treatment

The CR-aba has the tropism of MDR and XDR[10], and the treatment options for CR-aba infection are limited. Chang et al. reported that ampicillin and sulbactam are effective in the treatment of hematogenous MDR Ab infection and skin soft tissue CR-aba infection[13]. Hsu et al. recommended ampicillin and sulbactam or tigecycline for the treatment of CR-aba infection in children, with ampicillin 400 mg/kg/d for intravenous injection every 4-6 hours, not more than 2g each time. Tigecycline was used in the same way as ampicillin sodium and sulbactam [14]. As one of the few treatment options for current MDR infection, polymyxin faces a large difference in awareness in pediatric, especially neonatal application. There are very few reports on it, and thus more pharmacokinetic and safety studies are needed for guidance on its drug usage and dosage[15-16]. At present, for the treatment of CR-aba in the central nervous system, some studies advocate the usage of combination with antibiotics. However, our study found that CR-aba group had used more varieties of antibiotics than CS-aba group. We therefore speculated a greater likelihood of carbapenem antibiotic resistance if more varieties of antibiotics are used in Ab-infected children. The impact of combination therapy in the treatment of CR-aba infection and the incidence of CR-aba infection needs to be further elucidated.

Conclusion

The CR-aba infection occurs primarily in ICU patients, and CR-aba group had a worse prognosis than CS-aba group. The complexity of treating CR-aba infection poses serious challenges to clinicians. In the case of non-neonatal, ventilator-associated pneumonia, myocarditis, respiratory failure and use of multiple antibiotics, especially carbapenem antibiotics, patients should be warned about to the CR-aba infections. Pan-drug resistant or even full-resistant Ab should be isolated and disinfected in time, once discovered, to prevent infection diffusion. Strengthening the rational application of carbapenem antibiotics, standardizing the aseptic operation of medical staff and reducing the incidence of ventilator-associated pneumonia are the key to prevention and control of CR-aba infections.

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