Clinical Characteristics Of Carbapenem Resistant Enterobacteriaceae Bloodstream Infection: A Retrospective Study Among Children

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Abstract

Purpose: The clinical features and treatment of Carbapenem resistant Enterobacteriaceae (CRE) bacteremia among children were different from the adults. Clinical studies about CRE infection among children was still lack of enough samples. The aim of this study was to share our experience of diagnosis and treatment of CRE bacteremia and to improve the prognosis of children infected with CRE.

Methods: Clinical records were systematically reviewed to extract the detailed information and treatment results. Potential risk factors for infection mortality were examined by a case-control study. Case-patients were those who died from the BSI and control-patients those who survived. Data were analyzed to explore the difference of clinical characteristics resulted from CRE infection between neonate and non-neonate group and more appropriate treatment strategy by using SPSS 23.0.

Results: A total of 36 CRE BSI were collected from January 2016 to December 2019, including 21 neonates and 15 non-neonates. The mortality due to CRE infection was 25%. *K.pneumoniae* (22, 61.1%) was the main pathogen. Patients suffered from different clinical manifestations, including fever(24, 66.7%), Breath holding spell(13, 36.1%), Sepsis(11, 30.6%), MODS(6, 16.7%), digestive tract symptom(15, 41.6%). The incidence of breath holding spell was higher among newborn group($P<0.05$) while the incidence of sepsis was higher among non-neonate group($P<0.05$). There was no difference of percentage of underlying diseases between survival group and non-survial group. Combination therapy shown a significant reduction of mortality ($P<0.05$).

Conclusion: *Klebsiella.Pneumoniae* was the most common isolates among children CRE BSI .Monotherapy maybe appropriate for neonates for those with slightly clinical manifestation resulted from CRE BSI while combination therapy are more effective and could give rise to significant reduction of mortality among children.

What Is Known

Klebsiella.Pneumoniae was the most common isolates among children CRE BSI .

Combination therapy are more effective and could give rise to significant reduction of mortality among children.

What is new

CRE infection gradually occurred in neonatal department in recent years.

Monotherapy maybe appropriate for neonates without sepsis resulted from CRE BSI,even those with central nervous system infections.

Introduction

Multi-Drug Resistant Organism (MDRO) is one kind of dreadful organism which being a worldwide threat and of global concern these days[1, 2]. Among the MDRO, Carbapenem-resistant Enterobacteriaceae (CRE) is one of the highest priority for the development of new antibiotics[3–5]. During the last decades, CRE infections are becoming more and more prevalence and being known to be associated with significant morbidity and mortality[4, 6, 7]. These pathogens have made their way to the vulnerable populations now, including children[8–10]. A national report which analyzed data from CHINET (a Chinese antimicrobial resistance surveillance network) has shown that carbapenem resistance among children also has been increasing these years in China[11].

Most of the previous studies focused on CRE infection were involved in adult patients[7, 12–15]. What's more, a large proportion among those studies have explored risk factors of CRE infection and molecular mechanisms of drug resistant.[16–18] However, data of clinical treatment and outcomes are still remain insufficient. Although some studies have investigated benefits of various combinations of antimicrobial agents for the treatment of CRE infection, most of those are discussed about adult patient rather than children[19]. Treatment strategy especially antibiotic regimen of CRE infected pediatric patients usually was adopted and adjusted based on data of adult CRE infection studies. Currently, antibiotic options for the treatment of carbapenem-resistant Enterobacteriaceae (CRE) are still very limited, especially for pediatric patients[20, 21]. Polymyxins, tigecycline, fosfomycin, quinolones, carbapenem and aminoglycosides were considered as the mainstays of antibiotics. However, most of these drugs are limited in children because of their side effects[22, 23]. The prevention and treatment of CRE infection is still a huge challenge for children, especially newborns. A Systematic review[11] have shown that only 9 of 491 studies about CRE infection focused on neonate and reported clinical data including patient demographics, underlying conditions, antibiotic treatment and clinical outcomes.

The aim of this study was to investigate clinical characteristics, antibiotic treatment and clinical outcomes in pediatric patients with CRE bloodstream infection (BSI), especially neonates. We are hoping to provide evidence and experience about pediatric CRE infection by demonstrating the detail information and explore the possible factors which will maybe useful to improve the treatment outcomes in children.

Materials And Methods

This retrospective observational single-centre study was conducted in a specialized children's hospital in China, which had been approved by the ethics committee of Shanghai children's hospital. Children younger than 17 years old with CRE bloodstream infection (BSI) between 1 January 2015 and 31 December 2019 were identified from laboratory records of our hospital. CRE was defined according to Centers for Disease Control and Prevention criteria. Bacterial Pathogens were defined as resistant/intermediate/susceptible to antimicrobial therapy based on CLSI interpretative breakpoints. Only the first positive blood culture isolate was included for each child so that each child was included only once irrespective of the number of positive blood cultures or episodes of CRE BSI that they experienced. Screening process was shown as Fig. 1.0.

Clinical data and general information were collected by specialized infectious department pediatrician, which including age, gender, department (the one that patient was admitted when the first CRE was isolated, underlying disease, hospitalization, clinical manifestation, laboratory tests including acute reactive protein(CRP), procalcitonin(PCT), white blood cell(WBC), blood culture and drug sensitivity test results) when the CRE BSI occurred, invasive procedures 90 days before CRE isolation, antibiotic treatment measures and clinical outcomes.

Data were analyzed using SPSS (version 23.0, IBM company). Categorical variables were presented with frequencies and percentages, while continuous variables were presented with mean with standard deviation or median with inter quartile range. T- test was used for categorical variables. P value < 0.05 was considered as statistical significant.

Results

Clinical And Epidemiological Characteristics

A total of thirty-six patients hospitalized between 1 January 2016 and 31 December 2019 met the inclusion criteria. Among which twenty-one (53.8%) cases were newborns. As to gender, 22 patients (61.1%) were males. Almost all of the patients stay in hospital for more than 1 month, the average hospitalization days was as long as 66.25 ± 44.23 .

Most of the cases in our cohort were hospital-acquired infections (n=31) and only five cases (n=5) were community-acquired infections. Fever was the most common symptom. The second clinical manifestation was digestive tract symptom n=15, 41.6%, which including: diarrhea n=7, 19.4%, vomiting(n=3, 8.3%), gastric retention n=6, 16.7%, abdominal distension n=6, 16.7%, gastrointestinal hemorrhage (n=3, 8.3%). 13 patients (36.1%) suffered from breath holding spell. As the most severe complications, septic shock and multiple organ dysfunction syndrome (MODS) were confirmed in 11 (30.6%) and 6 (16.7%) patients respectively (Table 1). Furthermore, septic shock show higher incidence rate among non-neonatal group, while digestive tract symptom and apnea was found more common among neonatal group (p<0.05). (Table 2)

We also analyzed the laboratory test results of all the CRE BSI patients, including WBC, CRP and PCT, which usually been thought as indicator for infectious disease. The average level of leukocyte, CRP and PCT were 14.04 ± 19.23 , 58.83 ± 47.24 and 9.00 ± 10.11 respectively. All the three items were significantly increase and the samples were collected at the same time of bacteraemia. (Table 1)

As to department, most of the cases n=21, 60% occurred in neonatal ICU 16.6% (n=6) patients in department of hematology, 11.1% (n=4) patients in pediatric ICU, 5.5% (n=2) patients in surgical ward, others in general pediatric ward.

In our cohort, all of the children suffered from underlying diseases and had received invasive operation before the isolate of CRE organism. Premature with low birth weight was the most common condition

which was occurred in up to 16 patients (44.4%). The following is congenital heart disease and digestive tract disease including necrotizing enterocolitis (NEC) and short bowel disease (SBS). 7 patients (19.4%) suffered from hematologic diseases (5 patients with Lymphoblastic leukemia (ALL) and 2 patients with solid tumor. (Table 1)

Microbiological And Drug Sensitivity Results

Klebsiella pneumoniae (*K. pneumoniae*) was the most common bacterial isolate, account for as high as 61.1% (n=22). The others included *Klebsiella aerogenes* (n=7, 19.4%), *K. pneumoniae subspecies* (n=4, 11.1%), *Escherichia coli* (*E. coli*) (n=2, 5.5%) and *Enterobacter cloacae* (*E. cloacae*) (n=1, 2.7%) (Table 1). According to the laboratory records, we calculated the susceptibility rate of antibiotic drugs, which were shown as follows: fosfomycin (75%), amikacin (64%), imipenem (25%), meropenem (2%), ertapenem (2%), aztreonam (70%) and tegacycline (95%).

Treatment And Outcomes

The mortality rate due to CRE BSI was 25% in our cohort. Generally, all the patients accepted monotherapy or combined therapy, results show that eighteen children (50%) received monotherapy while eighteen patients (50%) received combined therapy. It is interesting that 82.3% (n=14) patients of the monotherapy group were neonatal while 61.1% (n=11) of the combined therapy group were non-neonatal. Statistical analyse confirmed the significant of this phenomenon. However, There was no difference between non-neonate and neonata in terms of survival rate ($P < 0.05$). (Table 2)

We analysed the data and explore possible factors associated with mortality, and found the survival group was mainly treated with combination therapy ($P < 0.05$). (Table 3) It seems that combination antibiotic therapy (specific scheme shown in Table 4.0) could result to reduction of mortality of CRE BSI versus monotherapy. There was no significant difference of underlying diseases between the survival and non-survival group ($P > 0.05$). (Table 3)

Discussion

With the increasing prevalence of CRE infection, lots of previous studies had done interesting work of the drug-resistant molecular mechanisms [16, 24, 25]. However, the development of new antibiotic drugs is still relatively slow [15]. Thus, for the clinical treatment, more clinical researches based on this conditions about CRE infection are desired, especially for children. In the last decades, CRE were not considered the common causes of bacteremia in children [26]. More recently, changes in the epidemiology of bacteriaemia have been reported that carbapenem resistance is increasing both in China and worldwide, and data show that *S. aureus* and enterobacteriaceas are considered as more common pathogens now. [27–31] A national report using data from CHINET (a Chinese antimicrobial resistance surveillance network) has shown that the overall prevalence of meropenem-resistance increased from 2.9–28.0% during 2005 to 2020.

Generally, based on published data, the CRE infection rate is still lower in children than adults[10]. In our children hospital, the first CRE strain from blood was isolated from a patient of NICU in 2016. This study was conducted in a specialized children's hospital in China rather than in pediatric department of comprehensive hospital, which would be less likely influenced by hospital acquired CRE organisms resulted from adult patients.

We totally included 36 cases of CRE bacteraemia in the paediatric population, in which 58.3% (n = 21) were neonates. Male was the predominant gender in our cohort which accounted for 61.1% (n = 22), but no correlation was found between gender and treatment outcomes. The mean hospitalized day was 66.25 ± 44.23 , range from 13 to 173 days, prominently longer than other common infectious disease. The main kind of CRE specie was *K. pneumoniae* (n = 22, 61.1%), which is consistent with the previous data both of adult and pediatric population[3–5]. However, clinical manifestation was various among the cohort though infected with the same organism. In general, severe complications such as septic shock and MODS were more common among the non-neonate patients, while the neonate more usually suffered from relatively mild symptoms, for example, breath holding spell or some digestive tract symptom. We wonder that whether it correlated with the inflammatory response level as the neonate group do show a lower increasing level of laboratory test results (WBC, CRP and PCT) which were considered as indicators of inflammation, but no significant difference was found between neonate and non-neonate group in our cohort.

There is a study[13] show that most of the infected children had at least one underlying comorbidity such as pulmonary disease, premature, received surgery and others. A more recently retrospective study[32] among hematologic oncologists children from Spanish analysed the underlying disease of 38 CRE infected patients, in which 52.6% (n = 20) patients had received transplant surgery, 36.8% (n = 14) patients were born prematurely. These indicated that low immunity conditions maybe risk factors for drug-resistant organism infection. Our data also certified this phenomenon for each of our patient suffered from underlying comorbidity. In our cohort, neonates accounted for a slightly higher proportion (58.3%, n = 21) and 44.4% (n = 16) were born prematurely, ALL and solid tumors accounted for 19.3%. As we all known, apart from the susceptibility due to low immune status because of premature, hematologic oncologists and premature are at high risk in receiving invasive procedures due to parenteral nutrition and chemotherapy requirements. Furthermore, these patients are more likely treated with long exposure to antibiotics. Both of these are risk factors for CRE infection, which had been reported by many studies along with other possible factors including recent surgical procedure, mechanical ventilation and invasive device[33–35].

Similar as previous studies[36], nosocomial infection is the main infected way which up to more than 90%. There have been studies which reported that intestinal tract was found to be the most common origin of CRE BSI[32], followed by central venous catheter-related bacteraemia. In our study, most cases occurred in severely ill children, with serious premorbid conditions and chronic underlying illnesses. Digestive tract symptom was more common among neonate, which indicated intestinal tract maybe the most common origin causing CRE BSI among neonates.

Beside the increasing prevalence, the terrible mortality for CRE infection was up to 52.0% according to published data, ranging from 18.4–52.0%[17, 37], which is another important reason to attract attention of infectious disease physician. The mortality rate of CRE BSI in our study was 25% which is below the average level of published mortality. Compared with the more recently published study in Spanish,[32] no patient received organ transplant surgery and more neonate included in our cohort. Thus we hypothesised that could be related to a better immune status and the relatively low rate of severe bacteraemia in our study, for example, 30% presented as septic shock and 16.7% suffered from MODS. Data analysis between neonates and non-neonates show the incidence of septic shock and MODS was higher among non-neonates while the relatively slightly symptom (such as breath holding spell, abdominal distension and gastric retention) was more common among neonates, and this was the reason that monotherapy was more adopted in neonates (Table 4). To our knowledge, no relevant studies have been reported this so far. However, no difference was found between clinical outcomes. We explored the possible factors of mortality then. No difference was found about the underlying disease and age between the survival and non-survival group. Based on this, we analysed the impact of treatment measures. Results show that combined therapy was more effective versus monotherapy and gave rise to significant reduction of mortality (Table 3). There were two fundamental principle should be took into consideration to establishing precision and personalized antibiotic treatment strategy among children: first are the infected site and in vitro drug susceptibility testing results, second are the unique metabolism characteristics and organ function of children, especially children in severe ill conditions. According to previous studies, combined therapy was associated with reduction of the mortality while monotherapy has the potential of inducing drug-resistance[38–40]. Guidelines usually also recommend combined therapy including two or three drugs (at least two drugs combination) based on tigecycline or polymyxin for adult CRE infection. However, the most appropriate combined antibiotic regimens for adult was not always suitable for children. The tigecycline and polymyxin were not always chosen as the first-line treatment for CRE infections among children.

Among neonate, the antibiotics with high concentration in CSF tissue always should be taken into consideration for the CRE BSI because of the high incidence rate of complication of central nervous system infection. In our study, all the neonate patients received lumbar puncture examination, 4 out of 21 cases was diagnosed as central nervous infection. This is a relatively high morbidity, but only 1 patient was found with positive CSF culture. As to outcomes, 3 cases with negative cultures got better outcomes treated with large dosage meropenem. The one with positive cultures died at last though who was treated with meropenem and fosfomycin based on susceptibility testing results (only sensitive to fosfomycin, tigacycline, imipenem and tigecycline), but the therapeutic effect was unsatisfactory. The guardian refused further treatment due to the poor prognosis, the baby died at last. According to susceptibility testing results, although imipenem can penetrate well into the cerebrospinal fluid, pediatric patient rarely treated with it for its reported side effect of epilepsy[41]. Among our neonate patients—none of the infants received imipenem treatment. However, seven non-neonate patients treated with imipenem in our study, there was no adverse effects of epilepsy have been found among our cases. Whether should we completely reject imipenem because of its adverse reactions needs to be considered among CRE

infection of children. As one of the antibiotic drugs in adult, aztreonam has a better capacity penetrating the blood brain barrier [BBB]. In our study, Four neonate patients accepted aztreonam combined therapy. Though aztreonam is not recommended in the treatment of neonates, aztreonam could be an alternative regimen if no sensitive drugs supplied. Meropenem monotherapy could be used in combination with the above drugs when the efficacy of meropenem monotherapy is poor in CRE BSI children with complication of central nervous infection. Tigecycline has limited effect on meningitis caused by CRE, which has a poor capacity penetrating BBB. Although there have reports of successful cases of adults treated with increased doses of tigecycline[42], there have a few similar reports in newborn. Intrathecal injection of polymyxin was used to treat meningitis in adults, however there have few similar reports in neonates[43]. In addition—in our cohort, 2 cases among the 21 neonates suffered from severe complication of septic shock. Both of the two case were empirically treated with meropenem combined with fosfomycin. The condition (included inflammatory factor) did not turn better and antibiotic regimens was adjusted then based on susceptibility testing results. Amikacin was added in one case. The other was treated with four drug combined therapy measures: meropenem and fosfomycin accompanied with amikacin and tigecycline. No severe side effect was found and both of them were cured at last. The choice of medication was consistent with that of children in the non-neonatal group with septic shock.

Unlike newborns, combination therapy was mainly used in the non-neonatal group. Combined therapy including meropenem was the main therapy among non-neonatal group. There are some studies reported that meropenem was still recommended when the MIC < 8ug/ml for the treatment of CRE infection[19, 44]. However, in our hospital, drug susceptibility was tested by paper diffusion, which is unable give rise to the MIC data. Among survival group, combined therapy was the main treatment measure—which indicated that combined therapy could lead to lower mortality. The treatment of CRE infection among children should be more individualized. From our clinical data, most of combined therapy was based on meropenem, and tigecycline and polymyxine would be considered when meropenem combined regimens invalid. Tigecycline was more usually used in patients with complication of abdominal and respiratory infection for its high concentration in these tissues. Polymyxine is rarely used in children in our hospital for its side effect and expensive price. In this cohort, only 1 myelosuppression patient was treated with polymyxine, who had received chemotherapy due to hemopathy but died at last.

Clinical trial of new drugs usually was done with adult population, though the effect and side effect may be similar among pediatric patients apart from the difference of dosage, it is still hard to choose appropriate drugs for pediatrician, especially among neonates. In our cohort, combined therapy was not the first choice among neonates because of their mild clinical symptoms. Based on the sensibility test results, monotherapy was usually reserved but adjusted to improve the effectiveness, which was got by empirical increasing the infusion dose and prolonging the infusion time to increase MIC. According to our experience, this was certified to have low chance resulting to complications due to the side effect of more drug usage.

We did not get further laboratory detection information about the subtype carbapenemase, which limited the analysis of the molecular mechanism and drug selection. But our data would supply more suitable

experience about CRE infection over a more widely region for not all the medical center has the facility to detect CRE types. Though our data have shown combined therapy would reduce the mortality while monotherapy maybe more appropriate for neonates with slightly clinical manifestation. However, considering of the relatively small sample and the limitation of design of our study, more detailed and ensured antibiotic strategy still can not be proposed. The most promising way maybe development of new effective drugs in the future, but more prospective studies to exploit the best function of exist drugs seems more practicable to date.

Abbreviations

acute respiratory distress syndrome (ARDS)

acute lymphoblastic leukemia (ALL)

blood brain barrier(BBB)

bloodstream infection(BSI)

Carbapenem-resistant Enterobacteriaceae(CRE)

acute reactive protein(CRP)

Chinese antimicrobial resistance surveillance network(CHINET)

congenital heart disease(CHD)

Escherichia coli (*E.coli*)

Enterobacter cloacae (*E.cloacae*)

Klebsiella.Pneumoniae (*K.pneumoniae*)

infection time(IT)

Multi-Drug Resistant Organism (MDRO)

multiple organ failure syndrome (MODS)

neonatal necrotizing enterocolitis(NEC)

procalcitonin(PCT)

short bowel syndrome(SBS)

upper gastrointestinal hemorrhage(UGIH)

white blood cell(WBC)

Declarations

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Conflicts of interest :The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

Availability of date and material: All data, models, and code generated or used during the study appear in the submitted article

Code availability: Data was analyzed using SPSS Version 23.0 IBM

Contributors'Statement:

Dr Song and Prof Zhang Ting conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Song designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Pan fen,Jiang Bingxin ,Liu Honghong and Zhang Hong coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Ethics approval: Research program of this study was approved by Ethic committee of Shang Hai Jiao Tong University.

Consent to participate All authors approved to participate in this research.

Consent for publication: All authors approved the final submitted manuscript and agree to be accountable for all aspects of the work.

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Tables

Table 1. Characteristics of BSI caused by CRE infection among children

Characteristics	Percentage (n=36)
Age	
Neonate	21 (58.3)
Non-neonate	15 (41.7)
Gender	
Female	14 (38.9)
Male	22 (61.1)
Hospital day (d)	66.25±44.23
CRE species	
K.pneumoniae	22 (61.1)
Klebsiella.aerogenes	7 (19.4)
K.pneumoniae subspecies	4 (11.1)
E.coli	2 (5.5)
E.cloacae	1 (2.7)
Clinical manifestation	
Fever	24 (66.7)
Breath holding spell	13 (36.1)
Sepsis	11 (30.6)
MODS	6 (16.7)
Digestive tract symptom	15 (41.6)
Diarrhea	7 (19.4)
Vomiting	3 (8.3)
Gastric Retention	6 (16.7)
Abdominal distension	6 (16.7)
Gastrointestinal hemorrhage	3 (8.3)
Laboratory tests	
WBCs (*109 /L)	14.04±19.23
CRP (mg/L)	58.83±47.24
Pct (ug/L)	9.00±10.11
Underlying disease status	
Premature	16 (44.4)
Low birth weight	17 (47.2)
Congenital heart disease	13 (36.1)
Necrotizing enterocolitis	8 (22.2)
Short bowel syndrome	7 (19.4)
Lymphoblastic leukemia	5 (13.8)
Solid tumors	2 (5.5)
Outcome	
Cure	27 (75)
Death	9 (25)

Table 2. The difference of clinical characteristics of CRE BSI between neonate group and non-neonate group

Item		Neonate	Non-neonate	Statistical quantity	P value
Sex					
Boy	22	12	10	0.334	0.563
Girl	14	9	5		
Infection time (d)		29.33±20.37	25.20±24.71	0.549	0.587
Clinical manifestation					
Fever	Yes	14	10	0.000	1
	No	7	5		
Breath holding Spell	Yes	13	0	14.534	0.000
	No	8	15		
Sepsis	Yes	2	9	5.600	0.018
	No	19	6		
MODS	Yes	0	6		0.003
	No	21	9		
Diarrhea	Yes	2	5		0.103
	No	19	10		
Vomiting	Yes	0	3		0.064
	No	21	12		
Gastric Retention	Yes	6	0		0.030
	No	15	15		
Abdominal distension	Yes	6	0		0.030
	No	15	15		
Gastrointestinal hemorrhage	Yes	1	2		0.559
	No	20	13		
Laboratory tests					
WBCs(10^9 /L)		13.23±7.08	15.18±29.16	0.353	0.726
CRP (mg/L)		52.42±43.12	67.80±52.69	0.961	0.343
Pct (ug/L)		6.99±6.52	11.83±13.41	1.291	0.212
Therapy					
Monotherapy		14	4		0.040
Combined therapy		7	11		
Outcom					
Cure		18	9		0.122
Death		3	6		

Table 3. Univariate analysis of factors associated with infection mortality for 36 patients with CRE BSI

Item	Classification	Survival	Nonsurvival	Statistical quantity	P value
Age					
Neonate		18	3		0.122
Non-neonate		9	6		
Sex					
Boy		16	6		1.000
Girl		11	3		
HD (d)		72.00±46.69	33.00±15.88	3.751	0.001
IT (d)		30.00±24.23	20.44±11.84	1.131	0.266
Underlying disease					
Premature	Yes	13	3		0.700
	No	14	6		
Low birth weight	Yes	14	3		0.451
	No	13	6		
ARDS	Yes	6	2		1.000
	No	21	7		
NEC	Yes	5	3		0.384
	No	22	6		
CHD	Yes	12	1		0.114
	No	15	8		
SBS	Yes	6	1		0.652
	No	21	8		
UGIH	Yes	3	2		0.581
	No	24	7		
ALL	Yes	3	2		0.581
	No	24	7		
Hodgkin's lymphoma	Yes	0	1		0.250
	No	27	8		
Hepatoblastoma	Yes	1	0		1.000
	No	26	9		
Therapy					
Monotherapy		17	1		0.018
Combined therapy		10	8		

NOTE*: **ARDS:**acute respiratory distress syndrome, **NEC:**neonatal necrotizing enterocolitis

CHD:congenital heart disease, **SBS:**short bowel syndrome, **IT:**infection time

ALL:acute lymphoblastic leukemia **UGIH:** upper gastrointestinal hemorrhage

Table 4. Antibiotic therapy for 36 patients with CRE BSI

Age	Antibiotic Therapy	N(36)
Neonate 21	meropenem	14
	meropenem and fosfomycin	1
	meropenem .fosfomycin and amikacin	1
	meropenem and aztreonam	4
	meropenem.fosfomycin.amikacin and tigecycline	1
Non-neonate 15	meropenem	4
	Imipenem. amikacin and tigecycline	1
	Imipenem .fosfomycin and tigecycline	1
	meropenem and sepamycin	3
	Imipenem .isepamicin. and polyxin	1
	meropenem .fosfomycin and tigecycline	1
	Imipenem.fosfomycin.amikacin and tigecycline	2
	meropenem .fosfomycin .amikacin and tigecycline	1
	meropenem .isepamicin and tigecycline	1

Figures

Figure 1

Diagram of CRE isolates identification process