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Clinical analysis of 14 cases of community-acquired *Pseudomonas aeruginosa* bacteraemia in children.

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Abstract

This aims to study the clinical features and outcomes of Community-Acquired *Pseudomonas aeruginosa* Bacteraemia (CAPAB) in children. Retrospectively analysed the conditions of patients diagnosed with sepsis over nearly 6 years and screened out 14 cases of CAPAB in children to statistically analyse the related clinical features, biochemical tests, susceptibility results, and treatment outcomes. There were 7 boys and 7 girls among the 14 Community-Acquired *Pseudomonas aeruginosa* Bacteraemia (CAPAB) children with an average age of 21.8 months. Community-Acquired *Pseudomonas aeruginosa* Bacteraemia (CAPAB) occurred mainly in spring and winter, and all participants exhibited fever symptoms with an average course of 6.1 days. Most cases were associated with digestive symptoms, and 4 exhibited necrotic abscess-like rash changes. No child received effective antibiotic treatment before admittance, 9 progressed to septic shocks, and 7 died; the mortality rate was 50%. Community-Acquired *Pseudomonas aeruginosa* Bacteraemia (CAPAB) incidence in children was low and was more associated with fever and digestive symptoms. Necrotic abscess-like rash was the specific change, and shock might have progressed rapidly and resulted in high mortality.

Keywords: *Pseudomonas aeruginosa*, Community acquired, Septic shock, Children.

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Introduction

In developing countries and rural areas, septic shock remains one of the major causes of child mortality [1]. Knowing how to identify septic shock early and perform appropriate anti-shock treatment is essential for the prognosis of affected children [2,3]. However, due to the sporadic features of septic shock and the fact that children with septic shock more commonly exhibit "warm shock," which differs substantially from that in adults [4], it is difficult for clinicians to identify in its early stage, thus missing the best treatment timing. We summarized the data of children diagnosed with sepsis over nearly 6 years and combined the final blood culture results, screening out certain bacterial infections caused by septic shock. The hope was to retrospectively analyse the disease characteristics and biochemical tests and help clinicians to recognize septic shock and perform targeted antibiotic therapy in the early stage. As a rare community-acquired pathogen, *Pseudomonas aeruginosa* might exhibit specific clinical manifestations and high mortality rate after infection, so it attracted our attention.

Pseudomonas aeruginosa is also known as *Bacillus aeruginosus* and widely exists in soil, water, air, normal skin, and respiratory and intestinal tracts as one of the most common clinical conditional pathogens. Patients with lower body resistance, congenital immune deficiencies, blood diseases, and malignant cancers as well as postoperative or long-term administrated antibiotics might be susceptible to these bacteria [5]. Foreign studies have shown that the incidence rate of *Pseudomonas aeruginosa* sepsis in populations was 3.16/100,000 to 4.70/100,000 per year, about 1/5th of which was community-acquired *Pseudomonas aeruginosa* sepsis [6]. This disease occurs mainly in adults over the age of 60, and the proportion in children is very low. Community-acquired *Pseudomonas aeruginosa* bacteraemia (Community-Acquired *Pseudomonas Aeruginosa* Bacteraemia (CAPAB)) in healthy children is even less common, so the current clinical reports in China and abroad are rare [7-9]. This study collected 14 cases of Community-Acquired *Pseudomonas Aeruginosa* Bacteraemia (CAPAB) in children admitted into the Paediatric Intensive Care Unit (PICU), Shengjing Hospital of China Medical University, from April 2009 to May 2015, and summarized and analysed their clinical characteristics and treatment outcomes.

Materials and Methods

Subject source and diagnostic criteria

The 14 cases enrolled were selected from the children treated in the Shengjing Hospital of China Medical University PICU from April 2009 to May 2015 and met the following 3 criteria. 1. Clinical manifestations and laboratory tests were in line with

the sepsis diagnostic criteria. The diagnostic criteria of sepsis and septic shock referred to the Guidelines of International Sepsis Treatment in 2012 [10] and the criteria developed in the 2006 International Paediatric Sepsis meeting [11] (sepsis pus cardiovascular dysfunction: exhibited blood pressure reduction after intravenously infused isotonic liquid for more than 40 ml/kg within 1 h and less than 5% of that in this age group, or the systolic blood pressure was less than 2 standard deviations from the normal value in this age group, or vasoactive drugs were needed to maintain the blood pressure within normal dopamine range >5 μg/(kg•min) or any dose of dobutamine, epinephrine, or norepinephrine. Met 2 of the 5 following items: (1) unexplainable metabolic acidosis, base deficit>5 mmol/L; (2) arterial blood lactate level was increase more than 2 times the normal upper limit; (3) without urine: urine output<0.5 ml/(kg•h); (4) capillary refilling was prolonged (>5s); (5) center-to-surrounding temperature difference was>3˚C). 2. Within 48 h of admission, blood bacterial culture exhibited positive results of *Pseudomonas aeruginosa* at least once, with or without positive results of humoral *Pseudomonas aeruginosa* culture from the lesion sites. 3. The following high-risk situations were excluded: admitted within nearly 1 month and had surgical history; required dialysis or needed long-term stay in nursing unit; had long-term catheter indwelling, intravenous, or other percutaneous devices. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of China Medical University. Written informed consent was obtained from all participants' guardians.

General information

The 14 cases included 7 male and 7 female patients with a mean age of 21.8 months. The youngest was 2 months old, and the eldest was 11 years old; 12 patients were aged<3 years old. Seven cases lived in urban areas, and the rest lived in rural areas. Thirteen cases were physically healthy previously without history of major diseases; 1 case had once been hospitalized in our hospital's department of paediatric general surgery for 2 months for "perineal anoplasty and fistula closing surgery." The operations and healing went well. Season of onset: There were 10 cases in winter and 4 in summer. Eleven had a history of outpatient medication, 7 of which were applied penicillin or cephalosporins (first or second generation), and the longest treatment duration was a 6-day outpatient intravenous infusion of second-generation cephalosporins (Ceftezole). The remaining 4 cases had once received antiviral drugs or macrolides as shown in Table 1.

Table 1. *General information of the 14 patients (N=14).*

No	Gender	Age	Blood type	Fever duration (days)	Symptoms in digestive system	Symptoms in nerve system	Rash	Previous history	Outpatient medication
1	F	1 year	B-RH (-)	15	N/A	N/A	N/A	Healthy	Azithromycin for 5 days
2	M	1 year	O-RH (+)	4	Abdominal distension, diarrhoea	Irritable	N/A	Healthy	Penicillin for 1 day
3	M	2 months	B-RH (+)	4	Diarrhoea	Convulsion	N/A	Healthy	Ceftezole, Xiyanping for 1 day
4	F	4 months	B-RH (+)	3	Diarrhoea, vomiting	N/A	N/A	Performed surgery 2 months age	No
5	F	1 year	B-RH (+)	5	Diarrhoea, abdominal distension	Lethargy	yes	Healthy	Ceftezole, Xiyanping for 6 days
6	M	3 months	A-RH (+)	7	N/A	Convulsion	N/A	Healthy	Erythromycin, Shaduolika for 3 days
7	M	5 months	O-RH (+)	7	Diarrhoea	N/A	Yes	Healthy	N/A
8	F	4 months	B-RH (+)	4	N/A	Convulsion	N/A	Healthy	Xiyanping, complex coenzymes for 2 days
9	M	6 months	AB-RH (+)	6	N/A	N/A	Yes	Healthy	Second-generation cephalosporins for 3 days
10	F	7 years	B-RH (+)	3	N/A	N/A	Yes	Healthy	Erythromycin, second-generation cephalosporins for once
11	M	6 months	B-RH (+)	5	Abdominal distension	N/A	N/A	Healthy	N/A
12	F	11 years	B-RH (+)	13	N/A	N/A	Yes	Healthy	Second-generation cephalosporins, Xiyanping for 6 days

13	M	5 months	O-RH (+)	5	N/A	Drowsiness	N/A	Healthy	Erythromycin, Xiyanping for 3 days
14	M	19 months	O-RH (+)	5	N/A	N/A	N/A	Healthy	Second-generation cephalosporins, Xiyanping for 3 days

Results

Clinical manifestations

All patients exhibited fever before admission with durations ranging from 3 to 15 days (average 6.1 days). Six cases were associated with gastrointestinal symptoms (diarrhoea, abdominal distension, or vomiting), 4 had idiopathic rash appearance, and 6 exhibited nervous system involvement (drowsiness and convulsion). In 4 cases, soft tissue purulence-like changes were found in physical examination when admitted (2 cases of facial cellulitis, 1 case of perianal abscess, and bi-lower limb abscess in all). Nine patients were diagnosed with "septic shock" when admitted.

Blood routine, CRP, and primary biochemical tests

Twelve cases exhibited White blood cell (WBC)<4.0 × 10^9/L, 1 case was normal, and 1 case was>10.0 × 10^9/L. Among WBC proportions, only 4 cases exhibited neutrophils as the main proportion (>50%); the remaining 10 cases exhibited lymphocytes as the main proportion (>50%). Seven cases had varying degrees of anaemia (Hb<90 g/L), 6 exhibited significantly decreased platelets with the lowest at 20 × 10^9/L, and 4 exhibited reduction in all 3 lines. The C-Reactive Protein (CRP) levels were significantly increased; 5 cases were within 8 ~ 100 mg/l, and 9 cases were>100 mg/l. 9 patients received Procalcitonin (PCT) assay with the results>5 ηg/ml, and 9 were associated with albumin reduction (ALB<30 g/L) as shown in Table 2.

Immunologic tests

Eleven patients received immunoglobulin assay, 9 of which exhibited IgG<2.5 g/L with or without IgM and IgA reduction and could be diagnosed with "temporary hypogammaglobulinemia". 7 patients received lymphocyte subsets assay, and 4 exhibited significantly reduced NK% (<5%) (Normal range: 7 ~ 36%).

Bacterial culture and sensitivity results

France bioMerieux API system and VITEK 2-COM-PACT system were used for strain identification. The agar disc diffusion method (K-B method) was used for *in vitro* sensitivity assay, strictly following the method recommended by the Clinical and Laboratory Standards Institute (CLSI). Quality control strain was PAATCC27853. The sensitivity criteria were divided into 3 levels: sensitive, intermediary sensitive, and resistant. A total of 16 *Pseudomonas aeruginosa* positive strains were tested (14 in blood culture and 2 in pus culture). Fourteen patients received drug sensitivity assay as shown in Table 2, the results of which indicated the strains were generally resistant to second-generation cephalosporins, ceftriaxone, and cefotaxime. While highly sensitive to aztreonam, amikacin, ceftazidime, cefoperazone, cefepime, carbapenems, and quinolones, all strains showed no ESBLs (Extended-Spectrum β-Lactamase Strains) and multi-drug resistance.

Treatment and outcomes

Twelve patients received a "high-strength, wide-coverage, combined antibiotic treatment strategy" based on clinical experience after admittance, which included sodium cefoperazone/sodium sulbactam, cefepime, or carbapenems plus vancomycin or linezolid for the anti-inflammatory treatment. The remaining 2 patients were admitted into the general ward for "pneumonia, diarrheal disease" because of their atypical clinical symptoms, and, after receiving second-generation cephalosporins for 2-day anti-inflammatory treatment, they were quickly transferred to our department for the associated occurrence of septic shock. Although they were given aggressive anti-shock treatment, they both died within 24 hours.

Nine patients received ventilator-assisted therapy, 2 received blood purification, 2 received bowel resection and anastomosis after intestinal perforation, and 3 received necrotic tissue debridement and skin eschar grafting after eschar removal.

Among the total 14 patients, 7 died, 1 was discharged from hospital, and 6 survived. The reason for the deaths was refractory septic shock, which was eventually merged with DIC, pulmonary haemorrhage, and refractory hypotension, and the patients died within 72 hours of admission. Among the 6 patients who survived, 5 underwent surgery, with an average length of hospital stay of 42.7 days as shown in Table 3.

Table 2. *Results of sensitivity assay (N=14).*

No	Amikacin	Aztreonam	Ceftriaxone	Ceftazidime	Cefotaxime	Cefuroxime	Cefaclor	Cefoperazone	Cefepime	Cefoperazone/ sulbactam	Piperacillin	Gentamicin	Imipenem	Levofloxacin	Ciprofloxacin

1	R	S	I	S	I	R	R	S	S	S	S	R	S	S	S
2	S	S	R	S	R	R	R	S	S	S	S	S	S	S	S
3	S	S	I	S	I	R	R	S	S	S	S	S	S	S	S
4	S	S	I	I	I	R	R	S	S	S	I	R	S	S	S
5	S	S	I	S	I	R	R	S	S	S	S	S	S	S	S
6	S	S	S	S	S	R	R	S	S	S	S	S	S	S	S
7	S	S	I	S	I	R	R	S	S	S	S	S	S	S	S
8	S	S	I	S	I	R	R	S	S	S	S	S	S	S	S
9	S	S	S	S	I	R	R	S	S	S	S	S	S	S	S
10	R	S	R	S	I	R	R	S	S	S	I	I	S	S	S
11	S	S	I	S	R	R	R	S	S	S	S	I	S	S	S
12	S	S	S	S	S	R	R	S	S	S	S	S	S	S	S
13	S	S	I	S	R	R	R	S	S	S	R	R	S	R	R
14	S	S	S	S	I	R	R	S	S	S	S	R	S	S	S
Sensitivity rate (%)	85.7	100	28.6	92.9	14.3	0	0	100	100	100	78.6	57.1	100	92.9	92.9

Note: S: Sensitive; I: Intermediary; R: Resistance.

Table 3. *Biochemical markers and clinical outcomes of the patients (N=14).*

No.	WBC ($^{*}10^{9}$/L)	Hb (g/L)	PLT ($^{*}10^{9}$/L)	CRP (mg/L)	PCT (ng/ml)	Septic shock	Mechanical ventilation (day)	Surgery	Hospital stay (day)	Outcome
1	1.9	66	32	36.8	N/A	Yes	1	N/A	2	Died
2	1.3	82	158	163	N/A	Yes	1	N/A	1	Died
3	9.6	113	280	337	N/A	N/A	N/A	N/A	16	improved
4	1.6	67	227	171	N/A	Yes	1	N/A	2	Died
5	3.5	89	20	171.59	9.7	N/A	N/A	Bowel resection, anastomosis	64	cured
6	3	92	186	31.3	N/A	N/A	N/A	Bowel resection, anastomosis	42	improved
7	1.1	62	25	53.4	6.32	yes	6	skin eschar grafting	56	Improved
8	0.6	95	66	314	21.96	Yes	6	Facial debridement	53	Improved
9	3.7	83	69	183	7.7	N/A	N/A	Necrotic tissue debridement	25	Improved
10	3	92	313	96.2	8.91	Yes	1	N/A	1	Died
11	17	115	22	202	>100	N/A	N/A	N/A	6	Discharged
12	0.2	111	281	330	26.1	Yes	1	N/A	1	Died
13	1.5	73	151	10.2	57.53	Yes	1	N/A	2	Died
14	3.4	130	212	112	88.42	Yes	1	N/A	1	Died

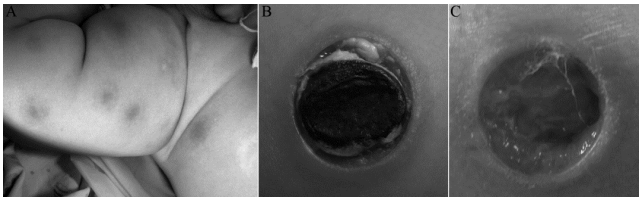

Figure 1. *Early rash changes (A). Painless red maculopapular rash; (B). Late rash changes; necrotic abscess-like changes; (C). Wound reached as deep as muscle layer after scab fell off.*

Discussion

Sepsis is a serious state of infection, which often leads to higher mortality and enormous health care costs. In many hospitals, especially in ICU, *Pseudomonas aeruginosa* has become a very important hospital-acquired pathogen. Many studies [12-16] have shown *Pseudomonas aeruginosa* bacteremia mortality to be more than 20%, and that of the patients infected with Multidrug-Resistant *Pseudomonas aeruginosa* (MDRPA, at least resistant to 3 kinds of β-lactamase, carbapenems, aminoglycosides, and quinolones) was even higher [17,18]. The early application of antibiotics as well as the occurrence of respiratory failure and septic shock was significantly correlated with mortality [12,16,19-21].

Obritsch et al. monitored an American ICU ward and found that MDRPA incidence rose from 4% in 1993 to 14% in 2002 and the antibiotics with the highest resistance rates were β-lactams and ciprofloxacins, while aminoglycosides, fluoroquinolones, and piperacillin/tazobactam exhibited the lowest resistance rates [22]. With the rapid developments of paediatric intensive medicine, the increased infection status of *Pseudomonas aeruginosa* in PICU wards has attracted more and more attention. Yang et al. collected information from 62 cases of hospital-acquired PAB in children over nearly 10 years and studied their clinical characteristics and treatment outcomes, finding that 59 patients had basic diseases. Long-term PICU stay (>1 month) was a significant risk factor for *Pseudomonas aeruginosa* infection, and respiratory failure was one risk factor of death [23]. Long-term PICU stay and respiratory failure often predicted MDRPA infection and higher mortality, and, in this study, the incidence of MDRPA was 11.3% with a mortality of 14.5%. The PICU department of Shengjing Hospital of China Medical University performed statistical analysis towards antibiotic-resistance cases of *Pseudomonas aeruginosa* over nearly 5 years [24] and found that MDRPA incidence did not fluctuate much with an average of 7.3%, exhibiting high sensitivity to cefoperazone/sulbactam, meropenem, and ceftazidime with a mortality rate of 24%.

Differing from those with hospital-acquired *Pseudomonas aeruginosa* infections, patients with CAPA infections had no long history of hospitalization and long-term applications of antibiotics; thus, MDRPA incidence would be low. However, because of the infections' delitescence as well as the application delay of sensitive antibiotics, its mortality rate is often high. Some studies have shown [13,25] that CAPA infections in adults occurred more in patients with cancers with the mortality as high as 39%. Currently, there are few articles about large-sample CAPA infections in children. Only some small-sample studies have been reported [10,26], most occurring in previously healthy children with fulminant septic shock as the main cause of death and mortality rates from 30% to 62%.

Among the 14 Community-Acquired *Pseudomonas aeruginosa* Bacteraemia (CAPAB) cases in this study, most patients were previously healthy, and infants accounted for the majority (85.7%), suggesting that it might be related with infants' immature immune systems and low intestinal barrier functions. 11 patients received immunoglobulin detection, and 9 (81.8%) exhibited varying degrees of immunocompromised status, consistent with those in foreign studies finding that the occurrence of Community-Acquired *Pseudomonas aeruginosa* Bacteraemia (CAPAB) in previously healthy infants had a certain relationship with potential immunodeficiency [27].

Clinical manifestation of CAPAB infections in children varied, while fever and digestive system-involved performance might occur in most cases, appearing as abdominal distension, diarrhoea, vomiting, and other symptoms, and could progress to toxic intestinal paralysis and intestinal obstruction, even intestinal perforation. It was considered to be related with retrograde infection of certain bacteria. Among the 6 surviving infants in this study, 2 received bowel resection and anastomosis and showed multiple intestinal perforation and ulcer-like changes during surgery. Because the positions of early hyperaemia, oedema, multiple ulcer, and possible perforation in lots of intestinal canals in toxic intestinal paralysis were difficult to determine, the surgical timing was often difficult to choose, which was not mentioned in literature. Based on the experience of paediatric surgery in our hospital, we recommended that early dynamic observation be carried out with daily abdominal plain film examination. Once intestinal perforation was discovered, emergency surgical treatment should be performed.

Necrotic abscess-like rash was the specific change of Community-Acquired *Pseudomonas aeruginosa* Bacteraemia (CAPAB) and an important basis for judging *Pseudomonas aeruginosa* infections early [8,28], but its incidence rate was low. The initial appearance of rash was painless red rash or pimples, which then became nodules, blisters, or pustules and eventually evolved into center-depressed black or gray necrotic tissues with red projections around, similar to the changes of crater, and the survivors would need elective necrotic tissue removal surgery shown in Figure 1. When such changes are found during physical examination, it should be highly suspected as caused by this disease, and clinicians must pay a close attention as early antibiotic treatment, bacterial culture, and related assay of infection indexes is critical [29,30].

Twelve patients in this study exhibited decreased leukocyte levels when admitted (85.7%), and most were associated with the reduction of haemoglobin and platelets, which was considered to be related with bone marrow suppression after severe infections. Simultaneously, the levels of CRP and procalcitonin were significantly increased, supporting the

diagnosis of severe sepsis. The above infection indicators could be obtained more rapidly than blood bacterial culture; in particular, procalcitonin could much more accurately reflect sepsis severity. Therefore, once infants exhibited such symptoms as fever and diarrhoea and infection indexes appeared the above changes, it should attract our vigilance for early empirical applications of antibiotic treatment that could cover *Pseudomonas aeruginosa*. If early antibiotic application does not cover these bacteria, this disease will progress rapidly, and most patients will soon develop into septic shock. In this paper, 9 patients (64.2%) appeared to experience septic shock, and because of early delitescence of shock performance, clinicians could not easily find these symptoms. Among these patients, 7 died of refractory hypotension, DIC, and pulmonary haemorrhage.

Obritsch et al. summarized the literature in 1966-2005 and published a review about epidemiology and antibiotic treatment strategy of hospital-acquired MDRPA infections [7]. The paper emphasized the importance of joint antibiotic applications towards critically ill patients with MDRPA infections. It recommended the selection of β-lactams joint with aminoglycosides or quinolones; even if the sensitivity assay indicated resistance, a certain study still found synergistic effects of joint application, which could still achieve better therapeutic effects. If wide-range resistance caused the limited selection of antibiotics, polymyxin could be considered for the treatment, but it is still necessary to inform the patients of the possible side effects. Within the current limited reports [9,26,31,32], MDRPA stain was rarely found in CAPA infections in children, but the patients with suspected infection of this bacteria should be recommended the initial antibiotic treatment that could cover *Pseudomonas aeruginosa*, such as β-lactams or aminoglycosides. While ceftriaxone and cefotaxime were not included, the sensitivity results of blood culture in this study also supported the above conclusions. Quinolones also exhibited high sensitivity against *Pseudomonas aeruginosa*, but due to the impacts on children's safety, they were currently not used as first-line therapy.

Recent studies have shown that the ABO blood type has certain relevance with *Pseudomonas aeruginosa* infections in children; children with B-type blood are more vulnerable to the infection, and its principle might be related with humoral immunity and clinical susceptibility [33]. In this study, 8 patients had B-type blood (57.1%), but the case number was too small to effectively prove the above assertion. Further large-sample studies are still needed.

CAPA infections in children were clinically rare, and mostly occurred in small infants and previously healthy children with such symptoms as fever and diarrhoea. The initial general state was acceptable with atypical clinical manifestations, and the laboratory blood routine assay might exhibit low leukocytes in most cases, so it is easily misdiagnosed by clinicians as common viral or bacterial infection. If in-time effective antibiotics and other supportive care are not performed, this disease might progress rapidly and develop quickly into septic shock, so its mortality rate is high and should attract extensive attention by clinical front-line physicians. Empirical early effective antibiotic treatment and early shock judgment was key towards successful rescue.

Conflicts of Interest

Tao Zhang, Jiujun Li, Xiaoshi Zheng, Lijie Wang and Zhijie Zhang declare that they have no conflicts of interest regarding this paper.

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