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Carbapenem-Resistant Enterobacteriaceae Infection in Immunocompromised Children with CRE Colonization: Incidence and Outcomes in an Antibiotic-Limited Setting

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Abstract

Objective: To determine the incidence of carbapenem-resistant Enterobacteriaceae (CRE) infection in patients with CRE colonization and compare the treatment outcomes between febrile patients with non-septic presentation who received empirical treatment with meropenem and those who did not.

Material and Methods: The medical records of febrile patients with CRE colonization aged <15 years who were hospitalized at Songklanagarind Hospital between January 2018 and December 2020 were reviewed.

Results: Among the 61 patients with CRE colonization, CRE infection was identified during eight febrile episodes in six patients (9.8%). Hematologic malignancies, solid tumors, and other diseases were diagnosed in 21 (34.4%), 25 (41.0%), and 15 (24.6%) patients, respectively. The median (interquartile range [IQR]) duration from CRE colonization to the first episode of fever was 22 (1.8–60.8) days.

Among the 82 febrile episodes without initial sepsis or central nervous system infection, 19 and 63 episodes, respectively, were initially treated with meropenem and non-carbapenems. Treatment outcomes—including the proportion of patients needing step-up antibiotics (21.1% vs. 36.5%), development of sepsis (5.3% vs. 15.9%), and death within 30 days (6.6% vs. 9.8%) - were not significantly different between the two groups.

Patients who developed sepsis had significantly higher resistance to empirical antibiotics (75% vs. 26.3%) as well as a significantly higher incidence of severe neutropenia lasting more than one week (85.7% vs. 21.9%) than those without sepsis.

Conclusion: Patients with CRE colonization who exhibit fever without clinical sepsis and have an absolute neutrophil count >100 cells/mm^3 can be empirically treated with non-carbapenems.

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Introduction

The incidence of carbapenem-resistant Enterobacteriaceae (CRE) has recently been increasing worldwide. In the USA, the incidence of CRE infections increased from 0% in 2000 to 5.0% in 2012[1]; this was consistent with the findings of previous studies indicating a prevalence of CRE colonization ranging from 2.7% to 15.5% in a province hospital and a university hospital in Thailand, respectively[2,3].

With the limited availability of new antibiotics for CRE such as ceftazidime/avibactam, meropenem/vaborbactam, and cefiderocol in Thailand, currently, the treatment of CRE infection requires high doses of meropenem with extended infusion (EI) (40 mg/kg/dose over 3 hour at 8 hour intervals) in combination with other antibiotics, such as colistin, aminoglycosides, or ciprofloxacin[4-8].

In Thailand, 65.0–71.0% of CRE produce New Delhi metallo-β-lactamase (NDM),[9,10] for which new antibiotics-such as cefiderocol and eravacycline are indicated; however, these antibiotics are not approved for children aged <18 years[11].

One of the most important risk factors for CRE colonization is prior antibiotic exposure, especially to carbapenems[12,13]. In patients with CRE colonization, the CRE infection rates among critically ill adult patients and pediatric liver transplant recipients were reported to be 47.2% and 27.3%, respectively[14,15]; overall mortality rates among patients with CRE colonization have been reported at 8.3-10.0%[16,17].

CRE prevention and control, including contact precautions, patient cohorting, and antimicrobial stewardship-especially the restriction of carbapenem antibiotic prescriptions-is crucial for the prevention of CRE colonization.

To date, few studies have compared outcomes between febrile children with CRE colonization who were empirically treated with meropenem and with other antibiotic groups. The objectives of this study were to determine the incidence of CRE infection in children with CRE colonization, as well as compare treatment outcomes between febrile children with non-septic presentations who underwent empirical therapy with or without meropenem.

Material and Methods

Study design and population

The medical records of febrile children with CRE colonization aged <15 years and hospitalized at Songklanagarind Hospital, a medical teaching hospital and the major tertiary care facility in Southern Thailand, between January 2018 and December 2020 were reviewed. CRE infection referred to febrile children with CRE isolated from sterile sites such as blood, cerebrospinal fluid, pus, or urine.

We compared the outcomes and risk factors for treatment failure in patients who were initially treated with meropenem and non-carbapenems. We excluded septic patients and/or those exhibiting evidence of intracranial device infection because meropenem would be used as an empirical treatment for most of them.

Demographic data including age, sex, underlying disease(s), complete blood counts (CBCs) on the first day of fever, lowest absolute neutrophil counts (ANCs), duration of neutropenia, type of infection, treatment failure, and complications were reviewed. Treatment failure was defined as the need for stepped-up antibiotic treatment after the initial treatment due to sepsis or the presence of microbiologically documented infection (MDI); this was defined by resistance to initial antibiotics, the development of a new infection, or progressive clinically documented infection (CDI).

Complications were defined as the occurrence of sepsis, organ failure, or death within 30 days after the febrile episode. Sepsis was assessed based on the age-

based systemic inflammatory response syndrome, defined as follows: meeting >2 of the diagnostic criteria; having confirmed or suspected invasive infection; and having cardiovascular dysfunction, acute respiratory distress syndrome, or >2 non-cardiovascular organ system dysfunctions. Septic shock was defined by cardiovascular dysfunction or impaired perfusion[18]. Acute respiratory failure was defined by severe hypoxemia requiring mechanical ventilation. Acute liver failure was defined by the rapid development of severe acute liver injury with impaired synthetic function (international normalized ratio (INR) ≥1.5) and encephalopathy in patients with no history of liver disease or an INR >2.0 in patients without encephalopathy. Hematologic failure was defined by active bleeding requiring transfusion with packed red cells and/or other blood components. Acute kidney injury was defined by a sudden increase in serum creatinine levels to >2 mg/dL or a serum creatinine concentration more than double the previous or subsequent value and also higher than the upper limit of normal values for the patient's age[19].

A febrile episode was defined as a body temperature (BT) ≥38.3 °C on one or ≥38 °C on two or more occasions at least one hour apart within a 12-hour period. Neutropenia was defined as an ANC ≤1,000 cells/mm^3. During antibiotic treatment, the ANCs in all CBCs were recorded to identify the lowest ANC and duration of neutropenia. Profound neutropenia was defined as a duration of neutropenia >1 week, with an ANC ≤100 cells/mm^3.

CRE was defined as carbapenem-nonsusceptible and extended-spectrum cephalosporin-resistant *Escherichia coli*, *Enterobacter aerogenes, Enterobacter cloacae* complex, *Klebsiella pneumoniae*, or *Klebsiella oxytoca.*

Identification of CRE colonization

Patients who were admitted to the immunocompromised ward or pediatric intensive care unit (PICU) had regular rectal swabs, and if CRE colonization was present, they were moved to the cohort ward. The rectal swabs were taken every three months until CRE was undetected.

Statistical analysis

Categorical variables were described using frequencies and percentiles and analyzed using Pearson's chi-squared and Fisher's exact tests. Nonparametric continuous data were analyzed using the Mann–Whitney U test and presented as medians and interquartile ranges (IQR). All results were considered significant at p-value <0.05.

Ethical approval

The study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC. 63-460-1-4).

Results

Incidence of CRE infection in patients with CRE colonization

During the 3-year study period, 61 patients were found to have CRE colonization, of whom 51 (83.6%) were male and the median age was 5.9 (range: 2.4–10.7) years. Hematologic malignancies, solid tumors, and other diseases were diagnosed in 21 (34.4%), 25 (41.0%), and 15 (24.6%) patients, respectively. The other diseases were aplastic anemia in eight patients, congenital gastrointestinal tract anomalies in two patients, and lupus erythematosus, thalassemia, nephrotic syndrome, Down syndrome, and hyper IgM syndrome in one patient each.

The median (IQR) duration between CRE colonization and the first episode of fever was 22 (1.8–60.8) days, with a median (IQR) duration from the first episode of fever to the last follow-up date of 21.9 (11.8–26.7) months. Ninety-two fever episodes occurred among 61 patients, with sixteen patients having two episodes, three patients having three episodes, and three patients having four episodes of fever.

CRE infections developed in six patients (9.8%) with eight total episodes of fever. One, three, and four CRE infection cases were identified from the skin, blood, and urine samples, respectively. *E. coli* and *K. pneumoniae* were identified in four episodes each. All CREs were resistant to cephalosporins, carbapenems, and cotrimoxazole, but susceptible to ciprofloxacin, amikacin, gentamicin, and colistin in two (25.0%), four (50.0%), five (62.5%), and eight (100%) specimens, respectively (Table 1).

Comparison of clinical characteristics and laboratory findings between patients empirically treated with and without meropenem

There were 92 episodes of fever, of which 10 episodes were excluded due to sepsis (n=8) or CNS infection (n=2). Of the 82 remaining episodes, 19 and 63 were initially treated with meropenem and non-carbapenems, respectively.

History of exposure to third-generation cephalosporins and carbapenems, underlying diseases, initial median (IQR) CBCs (including total white blood counts, percentages of neutrophils, ANCs, and platelet counts), durations of neutropenia, and lowest ANCs were not significantly different between the febrile patients treated with meropenem and non-carbapenems (Table 2).

Causes of fever among the 82 episodes

Fevers without source (FWS), CDI, and MDI were found in 43, 16, and 23 episodes of infections, respectively.

The 16 episodes of CDI included pneumonia (4 episodes), diarrhea (4 episodes), skin infection (2 episodes), phlebitis (2 episodes), and 1 episode each of mucositis, cholangitis, otitis externa, and parotitis.

During the 23 episodes of MDI, bacteria were isolated from blood (nine episodes), urine (seven episodes), pus from the skin (two episodes), pus from the trachea of a patient with bacterial tracheitis (two episodes), stool from two patients with bloody diarrhea, and from one patient with infected continuous ambulatory peritoneal dialysate. Gram-negative and gram-positive organisms were identified in 16 and 7 episodes, respectively. Among the 16 gram-negative organisms, *E. coli*, *K. pneumoniae*, *Pseudomonas aeruginosa*, non-typhoid *Salmonella, Burkholderia cepacia,* and *Ralstonia mannitolilytica* were identified in five, four, three, two, one, and one episodes of fever, respectively. Among the seven gram-positive organisms, methicillin-susceptible *Staphylococcus aureus* was identified in five episodes of fever, and *Enterococcus faecalis* and *Streptococcus oralis* were identified in one each.

Treatment outcomes between patients empirically treated with and without meropenem

The median (IQR) duration of antibiotics (11 [8.0–16.0] vs. 7 [5.0–12.0] days, p-value=0.03) and length of stay (19 [14.0–30.0] vs. 14 [8.0–23.0] days, p-value=0.03) were significantly longer in the meropenem than the non-carbapenems groups (Table 3).

The proportions of patients who needed stepped-up antibiotics and were treated with antifungals were not significantly different between the two groups. Nonetheless, the proportion of patients who developed sepsis was higher in the non-carbapenems than in the meropenem groups, although the difference was not significant (15.9% vs 5.3%, p-value=0.44). The proportions of deaths and patients who further developed organ failure were not significantly different between the two groups (Table 3). When comparing patients with and without sepsis, the rates of underlying diseases, sources of infections, total white blood counts, ANCs, and lowest ANCs were not significantly different between the two groups. Among the 11 episodes with sepsis, microorganisms were identified in four, including three cases of CRE and one episode of *B. cepacia*. Resistance to empirical therapy and severe neutropenia (ANC ≤100 cells/mm^3) for over one week were significant risk factors for sepsis (p-value<0.01) (Table 4).

Table 1 Carbapenem-resistant Enterobacteriaceae in eight episodes of fever among six study patients: management and outcomes

Patient	Disease	Organism and Sites	Susceptibility	Management	Outcome
1	3-month-old with colonic obstruction from post-necrotizing enterocolitis (post-surgery)	*E. coli* blood	amikacin, gentamicin, colistin	ET: cefotaxime + metronidazole Step-up: EI meropenem + colistin	Septic shock: 2 days after ET Death: 7 days after step-up therapy
2	13-year-old with acute myeloid leukemia during chemotherapy	*E. coli* blood	colistin	ET: EI meropenem + colistin	AKI after ET for 3 days with full recovery within 30 days
3	7-month-old with imperforate anus who underwent rectourethral fistula (post-surgery); 1st UTI episode	*E. coli* urine	amikacin, gentamicin, ciprofloxacin colistin	ET: ceftriaxone Step-up: add amikacin	No complications
	2nd UTI episode, 7 months after 1st episode	*E. coli* urine	amikacin, gentamicin, ciprofloxacin, colistin	ET: ceftriaxone Step-up: amikin	No complications
4	3-year-old with Burkitt lymphoma during induction therapy	*K. pneumoniae* blood	colistin	ET: EI meropenem + amikin Step-up: add colistin	Septic shock: 2 days after ET Death: 13 days after step-up therapy
5	12-year-old with diffuse large B-cell lymphoma	*K. pneumoniae* urine	colistin	ET: ceftriaxone Step-up: EI meropenem + amikacin and then add colistin	Septic shock: 2 days after ET Death: 30 days after step-up therapy
6	14-year-old with Ewing sarcoma of the left femur with cord compression and neurogenic bladder, 1st UTI episode with septic shock	*K. pneumoniae* urine	colistin	ET: EI meropenem + colistin Step-up: no	No complications
	2nd episode UTI, 4 months after 1st episode	*K. pneumoniae* urine	gentamicin, colistin	ET: ceftazidime Step-up: add colistin	No complications

[erratic capitalization of drug names]
AKI=acute kidney injury, ALF=acute liver failure, ARF=acute respiratory failure, CRBSI=catheter-related blood stream infection, DIC=disseminated intravascular coagulation; ET= empiric therapy, EI=extended infusion, NEC=necrotizing enterocolitis, UTI=urinary tract infection

Table 2 Characteristics, initial complete blood counts, durations of neutropenia, and lowest ANCs in febrile study patients treated with carbapenem and non-carbapenem antibiotics

	Meropenem N=19	Non-carbapenems N=63	p-value
Prior exposure to cephalosporin within 2 months, n (%)	15 (78.9)	45 (71.4)	0.72
Prior exposure to carbapenem within 2 months, n (%)	8 (42.1)	30 (47.6)	0.87
Underlying diseases, n (%)			
Hematologic malignancy	5 (26.3)	28 (44.4)	0.25
Solid tumors	9 (47.4)	21 (33.3)	0.40
Others	5 (26.3)	14 (22.2)	0.95
White blood count, cells/mm^3 median (IQR)	1,990 (20–11,410)	2,700 (672–8,340)	0.40
Neutrophils, %, median (IQR)	39 (0–71)	40 (0–73)	0.66
ANC, cells/mm^3, median (IQR)	1,190 (0–7,968)	1,082 (0–5,629)	0.81
Hemoglobin, %, median (IQR)	8.6 (7.4–11)	8.6 (7.8–10.1)	0.96
Platelets $\times 10^3$/mm^3, median (IQR)	70 (22–349)	92 (30–294)	0.80
Lowest ANC, cells/mm^3, median (IQR)	0 (0–2,789)	340 (0–2,278)	0.69
Duration of ANC <100 cells/mm^3, n (%)			0.83
<1 week	7 (63.6)	19 (67.9)	
1–2 weeks	2 (18.2)	6 (21.4)	
>2 weeks	2 (18.2)	3 (10.7)	

ANC=absolute neutrophil count, IQR=interquartile range

Table 3 Types of infections, related clinical factors, and treatment outcomes between the carbapenem and non-carbapenem groups

Types of infections and treatment outcomes	Meropenem N=19	Non-carbapenems N=63	p-value
Fever without source	7 (36.8)	36 (57.1)	0.20
Clinically documented infection	6 (31.6)	10 (15.9)	0.24
Microbiologically documented infection	6 (31.6)	17 (27.0)	0.92
CRE	2 (33.3)	5 (29.4)	
Other gram-negative bacteria	3 (50.0)	6 (35.3)	
Gram-positive bacteria	1 (16.7)	6 (35.3)	
Susceptible to initial antibiotics, n (%)	3/6 (50.0)	12/17 (70.6)	0.62
Duration of antibiotics, days	11 (8–16)	7 (5–12)	0.03
Length of stay, days	19 (14–30)	14 (8–23)	0.03
Duration of fever, days	5 (3–9)	4 (1–7)	0.12
Step-up antibiotics, n (%)	4 (21.1)	23 (36.5)	0.27
Antifungal use, n (%)	4 (21.1)	10 (15.9)	0.73
Sepsis, n (%)	1 (5.3)	10 (15.9)	0.44
Respiratory failure, n (%)	1 (5.3)	3 (4.8)	>0.99
Acute kidney injury, n (%)	3 (15.8)	3 (4.8)	0.13
Hepatic failure, n (%)	1 (5.3)	1 (1.6)	0.41
Death within 30 days, n (%)	1 (6.6), n=15	4 (9.8), n=41	>0.99

CRE=carbapenem-resistant Enterobacteriaceae

Table 4 Risk factors of sepsis in febrile study patients with CRE colonization

	Sepsis N=11	Non-sepsis N=71	p-value
Underlying diseases, n (%)			
Hematologic malignancy	7 (63.6)	26 (36.6)	0.17
Solid tumors	2 (18.2)	28 (39.4)	0.31
Others	2 (18.2)	17 (23.9)	>0.99
Source of infection, n (%)			
Fever without source	5 (45.5)	37 (52.1)	0.68
Clinically documented infection	2 (18.2)	15 (21.1)	>0.99
Microbiologically documented infection	4 (36.4)	19 (26.8)	0.49
CRE	3 (75.0)	4 (21.1)	0.07
Susceptible to empirical therapy	1 (25.0)	14 (73.7)	<0.01
White blood count, cells/mm^3	3,760 (30–11,620)	2,830 (550–9,430)	0.69
ANC, cells/mm^3	597 (0–8,494)	1,190 (0–5,942)	0.66
Lowest ANC, cells/mm^3	0 (0–340)	473 (0–2,538)	0.07
Duration of ANC <100 cells/mm^3, n (%)			<0.01
<1 week	1 (14.3)	25 (78.1)	
1–2 weeks	3 (42.9)	5 (15.6)	
>2 weeks	3 (42.9)	2 (6.3)	

CRE=carbapenem-resistant Enterobacteriaceae, ANC=absolute neutrophil count

Discussion

In our study, the overall percentage of CRE infections in patients with CRE colonization was 9.8%. The treatment outcomes in patients who were empirically treated with and without carbapenems, including the proportions of patients who needed stepped-up antibiotic treatments, patients who developed sepsis, and/or organ failure were not significantly different. Resistance against empirical antibiotics and severe neutropenia exceeding 1 week were risk factors for sepsis.

We found CRE infections in 9.8% of the patients with CRE colonization, which was lower than reported in a previous systematic study (16.5%)[16]. The variations in CRE infection rates in patients with CRE colonization could be explained by differences in immune status and disease severity of the enrolled subjects. Previous studies in critically ill adult patients and pediatric liver transplant recipients reported CRE infection rates of 47.2%[14] and 53.0%[15].

When comparing the treatment outcomes in patients without sepsis initially treated with meropenem or non-carbapenems, we found that the proportions of patients who required stepped-up antibiotics and those with overall complications were not significantly different. However, the duration of antibiotic treatment and length of stay were significantly longer in the carbapenem than in the non-carbapenems. In the meropenem group, higher proportions of Gram-negative bacteria and CDI were observed, which could explain these results.

The proportion of patients who developed sepsis was higher in the non-carbapenem group than in the meropenem group, although the difference was not statistically significant (15.9% vs. 5.3%, p-value=0.44). We found that an ANC ≤100 cells/mm^3 persisting for more than 1 week increased the risk of sepsis.

Meropenem did not demonstrate better efficacy than non-carbapenems, which can be explained by the low incidence of CRE infections (9.8%) in patients with CRE colonization. CRE may produce NDM causing high minimal inhibitory concentrations of meropenem (>8 mg/

mL)[9,10]. Therefore, EI with high-dose meropenem was not better than non-carbapenems.

Taken together, our results suggest that patients with CRE colonization who have a fever without clinical sepsis and have a low risk of developing severe infection (ANC >100 cells/mm^3 and duration of severe neutropenia <1 week) can be empirically treated with non-carbapenems.

In this study, the overall mortality rate within 30 days after febrile illness in patients with CRE colonization was 8.2% (5/61 patients), while the mortality rate of patients with CRE infections was 50% (3/6 patients). Our findings were similar to previous studies that reported mortality rates of 10% in colonized patients and 30–75% in patients with infections[20-22]. High mortality rates in patients with CRE infections have been associated with delays in appropriate antibiotic therapy, a lack of available antibiotics active against CRE, and underlying comorbid conditions[14-17,20-22].

In a previous study conducted between 2001 and 2003, we found that in a febrile neutropenic patients, all gram-negative organisms susceptible to meropenem, as well as *S. aureus*, were susceptible to cloxacillin[23,24]. In the current study, unlike gram-negative organisms, all isolated *S. aureus* specimens were susceptible to cloxacillin. We, therefore, suggest that empirically treating methicillin-resistant *S. aureus* be avoided in patients without methicillin-resistant *S. aureus* colonization.

A notable limitation of this study was the retrospective design, thus, decisions concerning patient management and antibiotic prescriptions depended on the individual physician's experience and clinical judgment.

Conclusion

In conclusion, the incidence of CRE infections in pediatric patients with CRE colonization in our institution during the study period was 9.8%. The proportions of patients requiring stepped-up antibiotics and having overall complications were not significantly different between those empirically treated with meropenem and those treated with non-carbapenems. Based on our findings, we conclude that to prevent further CRE colonization, patients with a non-septic presentation, including an ANC >100 cells/mm^3, can be safely empirically treated with non-carbapenem antibiotics.

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Conflict of Interest

The authors declare there are no conflict of interests.

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