

CLINICAL ALERT

Invasive carbapenem-resistant Enterobacteriaceae infection at a paediatric hospital: A case series

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Background. There are no paediatric reports of invasive infection caused by carbapenem-resistant Enterobacteriaceae (CRE) from Africa.

Objectives. To document a series of cases of CRE infections at a tertiary children's hospital in Cape Town, South Africa, describing the clinical and microbiological findings in these children.

Methods. A retrospective, descriptive study was completed using data from a series of children with invasive CRE infection between 2010 and 2015, sourced from their clinical notes and microbiology results.

Results. The first of 10 invasive CRE infections during the study period occurred in November 2012. Nine CRE infections were caused by *Klebsiella pneumoniae*, and one by both *K. pneumoniae* and *Escherichia coli*. The median age was 25 months (interquartile range (IQR) 5 - 60). All 10 CRE infections were hospital acquired. The median length of hospitalisation before CRE infection was 28.5 days (IQR 20 - 44). Eight of the children were exposed to carbapenems during the 12-month period prior to invasive CRE infection. Six were treated with colistin and carbapenem combination therapy, of whom 2 died, including 1 of a non-CRE event. The other 4 children received colistin monotherapy. All these children died, including 2 from non-CRE events.

Conclusions. Children with invasive CRE infection and severe underlying disease must be treated with combination antibiotic therapy. Strict infection control practice and antibiotic stewardship are necessary to contain the spread of CRE and limit the number of new infections.

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Invasive infection caused by carbapenem-resistant Enterobacteriaceae (CRE), first documented in the late 1990s, has become a serious global public health problem.^[1] Resistance to carbapenems may result from several mechanisms, including alteration of outer membrane permeability due to loss of porins, upregulation of efflux systems together with extended-spectrum β-lactamases (ESBLs), or commonly the production of carbapenemases.^[2] A large number of carbapenemases belonging to all four classes of β-lactamases have been described. However, clinically relevant carbapenemases belong to three of these classes, namely class A β-lactamases such as *Klebsiella pneumoniae* carbapenemase (KPC) and Guiana extended-spectrum carbapenemase (GES), class B metallo-β-lactamases such as Verona integron-mediated metallo-β-lactamase (VIM), imipenemase (IMP) and New Delhi metallo-β-lactamase (NDM), and class D β-lactamases including oxacillinase (OXA) subtypes such as OXA-48.^[3,4] The first CRE invasive infections in South Africa (SA) were reported in adult patients from Gauteng Province in 2011, caused by NDM-1- and KPC-2-expressing *K. pneumoniae* isolates.^[5] Since then, invasive infections caused by CRE-carrying resistance genes of these three classes of β-lactamases have been reported in SA.^[6]

Publications from the USA, Europe, Asia and the Middle East have begun to describe CRE infection in children.^[7-15] Age at presentation ranged from 0 to 18 years, and ~40% (32/79) were <12 months of age. The main types of infection were bloodstream infection, urinary tract infection and soft-tissue infection.^[7-15] The crude case fatality rate was 7.4% (5/68).^[13-15] A wide spectrum of potential risk factors for CRE infection was identified, including previous admission to an intensive care unit (ICU), hospitalisation for >48 hours, the presence of an indwelling device, underlying medical conditions, necrotising enterocolitis and/or

short-bowel syndrome, solid organ or stem cell transplantation, exposure to immunosuppressants, previous exposure to antibiotics, including third-generation cephalosporins, fluoroquinolones or carbapenems, and previous infection by a multidrug-resistant organism.^[13,15] None of these reports was from Africa.

Objectives

To describe a series of cases of CRE at a paediatric hospital and document the clinical and microbiological experience of children with invasive CRE infection in an SA context.

Methods

A retrospective study was completed at Red Cross War Memorial Children's Hospital (RCWMCH), a tertiary referral hospital in Cape Town that cares for sick children. Microbiology specimens from children treated at RCWMCH are processed at the central National Health Laboratory Service (NHLs) laboratory at Groote Schuur Hospital (GSH), Cape Town. The NHLs microbiology database at GSH was searched for minimum inhibitory concentration (MIC) breakpoints confirming the presence of phenotypic carbapenem resistance of Enterobacteriaceae isolates in patients hospitalised at RCWMCH during the period January 2010 - December 2015. The Clinical Laboratory Standards Institute (CLSI) MIC breakpoints used to establish carbapenem susceptibility or resistance in Enterobacteriaceae isolates are summarised in the next section.^[16]

Microbiological evaluation

All testing was completed at the NHLs microbiology laboratory, GSH. Identification and susceptibility testing of Enterobacteriaceae

was carried out primarily with the Vitek 2 system (bioMérieux, France) using the GN and N133 cards, respectively, supplemented where necessary with E-test (bioMérieux) to confirm the MICs of ertapenem, imipenem and meropenem.

The susceptibility of bacterial isolates was evaluated for the following antibiotics: ampicillin, amoxicillin plus clavulanic acid, piperacillin-tazobactam, cefuroxime, cefoxitin, ceftriaxone, ceftazidime, cefepime, ertapenem, meropenem, imipenem, ciprofloxacin, gentamicin, amikacin, co-trimoxazole, tigecycline and colistin.

Carbapenem susceptibility tests were conducted and interpreted according to the CLSI 2010 - 2015 criteria.^[16] MIC breakpoints for Enterobacteriaceae were $\leq 1 \mu\text{g/mL}$ (imipenem and meropenem) and $\leq 0.5 \mu\text{g/mL}$ (ertapenem) for susceptible isolates, $2 \mu\text{g/mL}$ (imipenem and meropenem) and $1 \mu\text{g/mL}$ (ertapenem) for intermediately resistant isolates, and $\geq 4 \mu\text{g/mL}$ (imipenem and meropenem) and $\geq 2 \mu\text{g/mL}$ (ertapenem) for resistant isolates.

Detection of specific carbapenemase genes was carried out by the Centre for Opportunistic, Tropical and Hospital Infections of the National Institute of Communicable Diseases, using in-house polymerase chain reaction assays. DNA was extracted from cultured isolates using the ZR-96 Fungal/Bacterial DNAkit (Zymo Research, Inqaba, SA). The following carbapenemase genes were targeted: *bla*_{NDM}, *bla*_{VIM}, *bla*_{IMP}, *bla*_{KPC}, *bla*_{GES} and *bla*_{OXA-48-like}.

Case definitions

Invasive CRE infection was diagnosed when CRE was isolated from any given body site (other than rectal/faecal swab culture) that was associated with clinical manifestations of infection. Hospital-acquired infection was defined as CRE infection detected ≥ 48 hours after hospital admission and not incubating at the time of hospitalisation. Healthcare-associated infection was defined as CRE infection detected within 48 hours of hospitalisation in children who had contact with the healthcare service, including admission to an intermediate-care facility within the previous 12 months. Community-acquired infection was defined as CRE infection detected within 48 hours of hospital admission without previous contact with the healthcare service.^[17]

Data collection

Clinical information was extracted from the hospital records of children with infection caused by CRE, including age, gender, clinical manifestations at the time of the CRE culture result, HIV status, and antibiotic use during the 12-month period preceding CRE infection, antibiotic treatment of the CRE infection and outcome of the CRE infection. Microbiological information on the CRE isolates cultured from children infected or colonised with CRE was extracted from the NHLs microbiology database and included genus and species, results of selective carbapenemase gene screening and the antibiotic sensitivity pattern. All data were entered on standardised datasheets.

Data analysis

Data were transferred anonymously to an Excel 2010 spreadsheet (Microsoft, USA) and analysed using descriptive statistical methods.

Ethical considerations

The study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (reference number: HREC/REF 909/2014), and was conducted in accordance with the Declaration of Helsinki.

Results

The first invasive CRE infection at RCWMCH was recorded in November 2012. A further 9 children developed invasive infection caused by CRE during the study period, 1 in 2013, 3 in 2014 and 5 in 2015.

Clinical features of CRE infections

The 10 cases in this series are described in detail in Table 1. The median age was 25 months (interquartile range (IQR) 5 - 60). All 10 children were hospitalised for >48 hours before the onset of their CRE infection, implying that all 10 CRE infections were hospital acquired. The median length of hospitalisation before CRE infection was 28.5 days (IQR 20 - 44). Six of the children developed bloodstream infection, 2 manifested with intra-abdominal sepsis, 1 had sepsis and empyema and 1 had deep-seated burn wound infection (Table 1). Four of the 10 children developed CRE infection in the paediatric ICU. Table 2 summarises potential factors contributing to CRE infection.

Five children with CRE infection were treated with parenteral colistin (colistimethate sodium, Sanofi), hereafter referred to as colistin) and imipenem combination therapy, and 1 child with colistin and meropenem combination therapy. Of these 6 patients, 1 died of a non-CRE event and one from CRE infection. The remaining 4 children were treated with colistin monotherapy. All died, 2 from CRE infection (patients 3 and 5) and 2 from non-CRE events after treatment with colistin monotherapy (patients 8 and 9) (Table 1). According to the susceptibility profiles of the pathogens causing invasive CRE infection in these patients (Table 3), 1 might have benefited from colistin-carbapenem combination therapy (patient 5), and 2 from colistin-amikacin combination therapy (patients 3 and 8).

Microbiological characterisation of CRE isolates

Nine CRE infections were caused by *K. pneumoniae*, while the infection in patient 2 was caused by both *K. pneumoniae* and *Escherichia coli* (Table 3). Carbapenamase genes were identified in isolates from 4 of the 8 patients screened. Three and 5 of the 11 isolates were sensitive to meropenem and imipenem, respectively. None of the isolates was sensitive to ertapenem. Furthermore, 6/11 (54.5%) and 7/11 (63.6%) of the isolates had MICs $\leq 4 \mu\text{g/mL}$ for meropenem and imipenem, respectively. All 11 isolates were susceptible to colistin and 5 were sensitive to amikacin.

CRE gastrointestinal colonisation

Between 18 May and 29 July 2013, 48 children who had been treated in the ward where patient 2 manifested with CRE were screened for CRE colonisation by rectal swab culture. Faecal colonisation with CRE isolates carrying the NDM gene was documented in 4/48 (8.3%). One was colonised by a *K. oxytoca* isolate, 1 by a *K. pneumoniae* isolate and 2 by *E. coli* isolates. Of the remaining 44 children, 1 was colonised by a carbapenem-resistant *K. pneumoniae* isolate carrying a GES gene, and another by a carbapenem-resistant *E. coli* isolate. This *E. coli* isolate was Hodge test-positive, suggesting that it produced a carbapenemase, but none of the six common carbapenemase genes was detected.

Discussion

This is one of the very first studies to report on the outcome of invasive CRE infection among children in an African setting. Since the first invasive CRE infection was diagnosed at our hospital in November 2012, there has been a steady increase in the annual number of cases. The emergence of CRE infection to some extent follows a change in the empirical antibiotic policy for hospital-acquired sepsis. At the beginning of 2012, because of escalating numbers of hospital-acquired infections caused by ESBL-producing Enterobacteriaceae, empirical antibiotic cover for hospital-acquired infections was changed from piperacillin-tazobactam plus amikacin to a carbapenem, usually ertapenem or, where appropriate, meropenem.^[18,19] High carbapenem exposure during the 12-month period before the development of CRE infection in the 10 patients, together with a general increase in carbapenem use at our hospital over time (data not shown), probably

Table 1. Description of the case series of CRE infections

Patient	Age (mo), gender	Clinical course	CRE infection	Treatment and outcome
1	60, female	This child was hospitalised on 28/10/2012 with multiple liver abscesses due to <i>Entamoeba histolytica</i> , requiring laparotomy and ICU admission. On day 5, ESBL-producing <i>Klebsiella pneumoniae</i> BSIs were diagnosed, requiring ertapenem for 12 days. Poor wound healing and dehiscence necessitated 12 additional laparotomies.	On day 28 of admission while still in the ICU, intra-abdominal infection developed. A peritoneal swab obtained at laparotomy cultured CRE. This infection was complicated by septic shock, coagulopathy and deranged liver function.	The CRE infection was successfully treated with colistin for 16 days plus imipenem for 14 days. The child was discharged 48 days after CRE diagnosis and 78 days after hospitalisation.
2	4, female	This child was admitted directly to the ICU on 27/2/2013 with bowel perforation due to NEC. She had been discharged from the GSH-NICU 5 days earlier, having been managed for prematurity and HIV exposure. Partial colectomy and ileostomy were done on 27/2/2013, and meropenem was administered for 21 days for presumed bacterial sepsis. After 3 days in the ICU, she was transferred to a general ward for ongoing care. On 21/4/2013 she was readmitted to the ICU with fever and wound infection; meropenem was re-started and continued for 9 days until 29/4/2013, when she was transferred back to the general ward. On day 84 of admission, culture of the laparotomy wound site documented colonisation by CR <i>K. oxytoca</i> and CR <i>Escherichia coli</i> .	On day 90 of admission fever and wound infection recurred, accompanied by elevated septic markers and a purulent discharge from the incision site, necessitating a laparotomy. A pus swab from the peritoneal cavity cultured CRE. This infection was complicated by coagulopathy and deranged liver function.	The CRE infection was treated successfully with colistin and imipenem for 10 days. The child was discharged 10 days after CRE diagnosis and 100 days after hospitalisation.
3	6, male	This child with dilated cardiomyopathy, known to the cardiology service, was admitted from home on 29/1/2014 into the ICU with congestive cardiac failure.	On day 20 of admission, while in the ICU, the child developed septic shock. CRE was documented on blood culture. The infection was complicated by renal failure and coagulopathy.	The CRE infection was treated with 14 days of colistin monotherapy. The clinical condition worsened, and the child died 15 days after CRE diagnosis, and 35 days after admission, from progressive sepsis.
4	4, female	This child was admitted to a general paediatric ward on 16/7/2014 with pneumonia complicated by a right-sided empyema. She had had a successful liver transplantation at 1 month of age and was receiving tacrolimus and methylprednisolone. Treatment with cefotaxime and ampicillin was commenced. There was no growth on the admission blood culture.	On day 6 of admission, repeat blood culture for persistent fever and elevated septic markers cultured CRE. This infection was complicated by deranged liver function.	The CRE infection was treated successfully with colistin and imipenem for 14 days. The child was discharged 16 days after CRE diagnosis. The total duration of hospitalisation was 24 days.
5	15, female	This child with Crigler-Najjar syndrome type 1 was hospitalised on 16/7/2014. After a liver transplantation on 16/7/2014 she was admitted to the ICU and treatment with tacrolimus and methylprednisolone was commenced. She was transferred to a general ward 6 days later in a stable condition. Four days later she experienced fever and deranged liver enzymes, and was commenced on meropenem for presumed sepsis. A blood culture done before meropenem was started was negative.	On day 23 of admission, while still on meropenem, the child developed fever and raised septic markers. A repeat blood culture cultured CRE. This infection was complicated by neutropenia, coagulopathy and deranged renal and liver function.	Colistin was commenced for the CRE infection. Meropenem was discontinued. However, the child's condition deteriorated and she died 4 days after diagnosis of CRE infection and 26 days after hospital admission. The cause of death was liver failure with coagulopathy.
6	93, female	This child was admitted to the ICU on 22/12/2014 with a hot-water burn involving 80% of her body surface area. Initial culture results were negative, and she was transferred to the burns ward on 28/12/2014. Eight days later she developed ESBL-producing <i>K. pneumoniae</i> BSI requiring ceftazidime and ciprofloxacin for 14 days. A repeat blood culture on 15/1/2015 was negative, indicating that the BSI had been effectively treated. CR <i>K. pneumoniae</i> colonisation was documented on a rectal swab on 13/1/2015.	On day 29 of admission, while in the paediatric burns ward, the child developed CR- <i>K. pneumoniae</i> BSI.	This infection was successfully treated with colistin and imipenem for 10 days. A repeat blood culture on 31/1/2015 was negative. Three days after completing antibiotics the child developed wound sepsis caused by a drug resistant <i>Pseudomonas aeruginosa</i> isolate. Despite appropriate antibiotic therapy, she died of this new infection on 13/2/2015, 53 days after hospitalisation and 24 days after CRE diagnosis.

Continued...

Table 1. (continued) Description of the case series of CRE infections

Patient	Age (mo), gender	Clinical course	CRE infection	Treatment and outcome
7	44, female	This child was hospitalised on 29/1/2015 with a hot-water burn involving 75% of her body surface area. On day 8 she was transferred to the ICU after surgical grafting. Two days later while in ICU she developed <i>P. aeruginosa</i> <td>On day 18 of hospitalisation and day 6 of ICU admission, she experienced persistent fever while still on antibiotic therapy. Repeat blood culture cultured CR <i>K. pneumoniae</i>.</td> <td>The CRE infection was treated successfully with colistin and imipenem for 14 days. The child was discharged 48 days after CRE infection and 63 days after hospitalisation.</td>	On day 18 of hospitalisation and day 6 of ICU admission, she experienced persistent fever while still on antibiotic therapy. Repeat blood culture cultured CR <i>K. pneumoniae</i> .	The CRE infection was treated successfully with colistin and imipenem for 14 days. The child was discharged 48 days after CRE infection and 63 days after hospitalisation.
8	198, female	This child, on tacrolimus and methylprednisolone following liver transplantation in 2000, was hospitalised on 26/1/2015 with presumed sepsis and started empirically on ampicillin and cefotaxime. She developed pneumonia 4 days later, complicated by left-sided empyema. Antibiotic therapy was changed to ertapenem, and a percutaneous chest drain inserted. Analysis of the pleural fluid showed the presence of acid-fast bacilli; four-drug antituberculosis therapy was commenced and ertapenem changed to meropenem, which was continued for 10 days. Drug-susceptible tuberculosis was confirmed on pleural fluid culture. On 19/2/2015 she received another 8-day course of meropenem for recurrent sepsis.	On day 44 of admission the child developed septic shock necessitating ICU admission. Blood cultures were negative, but pleural empyema fluid cultured CRE. This infection was complicated by coagulopathy and deranged liver function.	CRE infection was treated with colistin for 8 days. The child improved in response to antibiotic therapy. However, 14 days after CRE was diagnosed she deteriorated with worsening liver function, coagulopathy and renal failure. She died of liver and renal failure on 14/4/2015, 39 days after CRE diagnosis and 78 days after hospitalisation.
9	35, female	This child was admitted to the ICU on 7/4/2015 after a hot-water burn involving 40% of her body surface area. She was transferred to the burns ward 5 on 12/4/2015. Two days later she developed a BSI caused by a sensitive <i>K. pneumoniae</i> isolate that was effectively treated. On 2/5/2015, she developed another BSI caused by an ESBL-producing <i>K. pneumoniae</i> isolate, successfully treated with meropenem for 10 days. On 26/5/2015 she developed ESBL-producing <i>Enterobacter cloacae</i> BSI that was successfully treated with colistin and imipenem for 7 days.	On day 135 of admission while in the burns ward, the child developed deep burn wound infection caused by CRE.	This infection was successfully treated with colistin for 14 days. On 16/9/2015, the child developed a left-sided corneal abscess caused by <i>P. aeruginosa</i> and treated with gentamicin. However, her general condition deteriorated, resulting in death on 19/9/2015, 165 days after hospitalisation and 30 days after CRE was diagnosed.
10	5, male	This child was referred to a general ward from a secondary hospital on 16/8/2015 with newly diagnosed HIV infection and worsening respiratory infection. Two days later he was transferred to the ICU for IPPV. On 29/8/2015 he was started on a 10-day course of ertapenem for a <i>K. pneumoniae</i> BSI. On 9/9/2015 while still in the ICU meropenem and vancomycin was commenced for presumed line sepsis. Despite negative blood cultures, these antibiotics were continued. On routine tracheal aspirate on 7/9/2015, CR <i>K. pneumoniae</i> was cultured.	On 18/9/2015 the child developed septic shock. The blood culture grew CRE. This infection was complicated by coagulopathy, renal failure and liver failure.	The child was commenced on colistin on 18/9/2015 and meropenem was continued. However, his condition deteriorated and he died on the same day that CRE infection was diagnosed and 33 days after hospitalisation.

BSI = bloodstream infection; NEC = necrotising enterocolitis; GSH-NICU = Groote Schuur Hospital neonatal intensive care unit; CR = carbapenem-resistant; IPPV = intermittent positive-pressure ventilation.

Table 2. Potential factors contributing to CRE infection (N=10)

Factor	n (%)	Corresponding cases as shown in Table 1
Transfer in from another hospital	2 (20)	1, 10
Colonisation with CRE within 6 months of invasive CRE infection	3 (30)	2, 6, 10
HIV infection	1 (10)	10
Parenteral nutrition at the time of CRE infection	2 (20)	1, 2
Exposure to carbapenems during the preceding 12 months	8 (80)	1, 2, 3, 4, 5, 8, 9, 10
Exposure to cephalosporins during the preceding 12 months	5 (50)	2, 3, 4, 5, 6
Exposure to fluoroquinolones during the preceding 12 months	5 (50)	3, 4, 5, 6, 9
Age <1 year	4 (40)	2, 3, 4, 10
ICU admission within the month preceding CRE infection	8 (80)	1, 2, 3, 5, 6, 7, 9, 10
Surgical procedures/operations within the month preceding CRE infection	6 (60)	1, 2, 4, 6, 7, 8
Central intravenous catheterisation within the month preceding CRE infection	4 (40)	2, 3, 5, 6
Hospitalisation for a period of >14 days within the 6 months preceding CRE infection	8 (80)	1, 2, 3, 5, 7, 8, 9, 10
Two or more hospital admissions within the 12 months preceding CRE infection	3 (30)	3, 5, 8
Immunosuppressive therapy, including glucocorticosteroid therapy, for ≥3 months at the time of CRE infection	3 (30)	4, 5, 8

Table 3. Microbiological characteristics of CRE isolates

Patient	Specimen type	Carbapenem-resistant pathogens	Carbapenemase gene	MICs	Antibiotic susceptibility profile
1	Peritoneal swab	<i>K. pneumoniae</i>	Negative	Meropenem: 1 µg/mL Imipenem: 1 µg/mL Ertapenem: >8 µg/mL	Meropenem, imipenem, colistin
2	Peritoneal swab	<i>E. coli</i>	<i>bla</i> _{NDM}	Meropenem: 2 µg/mL Imipenem: 4 µg/mL Ertapenem: >8 µg/mL	Tigecycline, colistin
2	Peritoneal swab	<i>K. pneumoniae</i>	<i>bla</i> _{NDM}	Meropenem: <1 µg/mL Imipenem: <1 µg/mL Ertapenem: 1 µg/mL	Amikacin, imipenem, meropenem, tigecycline, colistin
3	Blood culture	<i>K. pneumoniae</i>	<i>bla</i> _{GES}	Meropenem: >32 µg/mL Imipenem: >32 µg/mL Ertapenem: >8 µg/mL	Amikacin, colistin
4	Blood culture	<i>K. pneumoniae</i>	Negative	Meropenem: 8 µg/mL Imipenem: 2 µg/mL Ertapenem: >8 µg/mL	Ciprofloxacin, tigecycline, colistin
5	Blood culture	<i>K. pneumoniae</i>	Negative	Meropenem: 4 µg/mL Imipenem: 1 µg/mL Ertapenem: >8 µg/mL	Imipenem, tigecycline, colistin
6	Blood culture	<i>K. pneumoniae</i>	<i>bla</i> _{NDM}	Meropenem: >16 µg/mL Imipenem: >16 µg/mL Ertapenem: >8 µg/mL	Colistin
7	Blood culture	<i>K. pneumoniae</i>	Negative	Meropenem: 2 µg/mL Imipenem: 0.5 µg/mL Ertapenem: >8 µg/mL	Amikacin, imipenem, colistin
8	Pleural fluid	<i>K. pneumoniae</i>	<i>bla</i> _{NDM}	Meropenem: >32 µg/mL Imipenem: >32 µg/mL Ertapenem: >8 µg/mL	Amikacin, colistin
9	Burn tissue swab	<i>K. pneumoniae</i>	Not done	Meropenem: >16 µg/mL Imipenem: >32 µg/mL Ertapenem: >8 µg/mL	Colistin
10	Blood culture	<i>K. pneumoniae</i>	Not done	Meropenem: 0.5 µg/mL Imipenem: 0.5 µg/mL Ertapenem: >8 µg/mL	Ciprofloxacin, amikacin, imipenem, meropenem, gentamicin, colistin

contributed to the emergence of carbapenem-resistant isolates in the local microflora. Other contributory factors include exposure to other antibiotic classes, particularly cephalosporins and fluoroquinolones, prolonged hospitalisation (for ≥ 4 weeks) before the development of CRE infection in 6 of the 10 children, prior faecal colonisation with CRE in 3 patients, and suboptimal infection control practice.^[20]

Inadequate infection control practice was demonstrated during the investigation of contacts of patient 2. Of 48 children who were in contact with this patient, 4 were asymptotically colonised with Enterobacteriaceae carrying the same carbapenemase gene as patient 2. We cannot be certain that colonisation occurred as a result of direct transfer from patient 2. However, it is likely that some were colonised through direct transfer, given that CRE is easily transmitted between humans if adequate containment measures are not implemented, and because these children were managed in close proximity to patient 2.^[21] Colonisation of multidrug-resistant pathogens, including CRE, may persist for lengthy periods. In one study of 51 infants colonised with ESBL-producing *K. pneumoniae*, the median faecal carriage time was 12.5 months and carriage persisted for up to 24 months.^[22] In another study, of adults in post-acute facilities, faecal carriage of carbapenem-resistant *K. pneumoniae* persisted for >10 months in 30% of colonised patients.^[23] Persistent carriage is therefore an important reservoir for the spread of these organisms. Screening also identified 2 patients in contact with patient 2 who were colonised by CRE isolates unrelated to that of patient 2, indicating that asymptomatic faecal carriage among hospitalised children may be widespread, and may have contributed to the emergence of CRE infections at our hospital. Prolonged hospitalisation and previous admission to an ICU in most of our patients provided the opportunity for acquiring CRE from asymptomatic carriers.

In vitro studies have shown enhanced activity against CRE isolates with antibiotic combination therapy.^[4] Observational studies have documented inconsistent outcomes following mono- or combined therapy. In one review of case reports and case series, polymyxin monotherapy was associated with higher treatment failure rates than combination therapy.^[24] However, a systematic review of 20 non-randomised studies showed a mortality rate of up to 67% among patients who received colistin-carbapenem combination therapy; among patients treated with monotherapy, the mortality rate was up to 57% for colistin and up to 80% for tigecycline.^[25] Observational studies suggest that combination therapy is superior in patients with severe infections caused by CRE.^[4,26] Despite these inconsistencies, there is strong support for using combination therapy when treating invasive CRE infection. Various combinations have been used, including colistin plus a carbapenem, colistin plus tigecycline, colistin plus an aminoglycoside, or colistin plus a carbapenem plus tigecycline. When combining colistin with a carbapenem, an additive effect may be achieved if the carbapenem MIC is ≤ 4 µg/mL and possibly if it is ≤ 8 µg/mL.^[4] Six of the children in the current case series were treated with combination therapy comprising colistin plus a carbapenem. In 5 of these, the MICs of the carbapenem-resistant isolates for imipenem and/or meropenem were ≤ 4 µg/mL. The isolate of the remaining child (patient 6) had very high meropenem and imipenem MICs. This child's CRE infection was treated successfully, but she died of a subsequent *Pseudomonas aeruginosa* infection (Table 1). All 4 children who were treated with colistin monotherapy died. The antibiotic sensitivity profiles of their isolates (Table 3) showed that combination antibiotic options existed for 3 of these children. Why combination therapy was not prescribed is not clear from their clinical notes.

Six of the 10 children died, 3 from non-CRE-related events after the treatment of their CRE infections. The CRE-related mortality rate of 30% was higher than the crude mortality reported in recent paediatric studies, but lower than the mortality recorded in many

adult studies.^[4,13-15,25] Higher mortality in the present case series may be due to the small sample size, severe underlying illness, and the administration of colistin monotherapy to 40% of the children.

Conclusions

This study has provided useful insights about the patients who acquire CRE infection at our hospital and their response to treatment. Until randomised controlled trials define optimal treatment strategies, CRE infection manifesting in children with severe underlying disease such as those described in our case series must be treated with combination antibiotic therapy to optimise outcomes. Attention should be focused on improving infection control practice to contain the spread of CRE isolates, and intensifying antibiotic stewardship to reduce unnecessary antibiotic selection pressure and in so doing restrict the number of CRE infections.

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