Metallo-β-Lactamase (MBL)-Producing Enterobacteriaceae in United States Children

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Metallo-β-lactamases (MBLs) are emerging as the most notable resistance determinants in Enterobacteriaceae. In many cases, the genes encoding MBLs are part of complex, mobile genetic elements that carry other resistance determinants. In the United States, there are increasing reports of MBL-producing Enterobacteriaceae, with New Delhi MBLs (NDMs) accounting for the majority of transmissible MBL infections. Many infections caused by NDM-producing bacteria are associated with international travel and medical tourism. However, little recognition of the introduction of MBL-producing Enterobacteriaceae into the pediatric community has followed. Reports suggest that this occurred as early as 2002. Here, we re-following reports that include the most readily transmissible MBLs, blaIMP, blaVIM, and blaNDM types. In the majority of children with available data, a history of foreign travel is absent.

Keywords. carbenamase; child; drug resistance; Enterobacteriaceae; epidemiology.

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What has gone relatively unrecognized is the dissemination of these organisms in our most vulnerable population, children.

Since the discovery of NDM-type MBLs in Enterobacteriaceae in 2008 from a patient returning to Sweden after healthcare in India, there have been widespread reports of these organisms in multiple countries, and NDM-type MBLs have become the most prevalent MBL gene circulating worldwide [1]. In India where MBL-producing GNB are endemic, reports of newborn and infant-related deaths caused by multidrug-resistant infections, including NDM-producing Enterobacteriaceae, continue to increase. Although a majority of reports suggest that the global spread of blaNDM in GNB is predominantly related to international travel and medical tourism, the horizontal gene transfer of blaNDM in endemic areas occurs outside of hospitals and has been linked to household transmission and exposure from environmental sources, which may play an important role in childhood acquisition of drug-resistant organisms [1].

In the United States, a recent national study of trends of carbapenem-resistant Enterobacteriaceae (CRE) in children using antimicrobial susceptibility data from 300 US laboratories reported (1) that 266 isolates were identified as CRE
and (2) that the prevalence of CRE isolated from children increased between the years of 1999 and 2012; however, little is known about the molecular mechanisms associated with these increases [3].

In this commentary, we reviewed the literature of MBL-producing _Enterobacteriaceae_ in US children and found extremely disturbing reports [4–9]. In addition, there are 2 additional recent cases for which publications are submitted or in press. We also describe an additional unreported pediatric case in the Study for Monitoring Antimicrobial Resistance Trends (SMART) data [S. Bouchillon, MD, personal communication was written on 12 January 2016]. In total, we found that 12 pediatric patients, ages 0–11 years, with 15 MBL-producing _Enterobacteriaceae_ isolates recovered during clinical care.

Metallo-β-lactamase-producing _Enterobacteriaceae_ were first described in US children in 2011; however, infections with _blaIMP-4_ -producing _Escherichia coli_ were discovered in pediatric patients as early as 2002, and an _Enterobacter cloacae_ harboring _blaVIM-2_ was recovered from a child in 2005 (Table 1). Of the 15 MBL-producing isolates, the predominant organism was _Klebsiella pneumoniae_ in 9 cases (60%), followed by _E. coli_ in 5 (33.3%) isolates, and in 1 (6.7%) patient, there was an _E. cloacae_ harboring an MBL gene. All MBL genes ( _blaIMP_ , _blaVIM_ , _blaNDM_ ) were associated with more than one species, and of importance, the presence of additional plasmid-borne beta-lactamases, including extended-spectrum beta-lactamas ( _blaCTX-M, blaTEM, blaSHV_ ) and AmpC cephalosporinases ( _blaCMY_ ), were reported in 50% of MBL harboring patients. Multilocus sequence types (STs) were reported for 6 patients and were associated with different STs. For _K pneumoniae_ , a _blaVIM-4_ was ST14, a _blaNDM_ was ST37, whereas a _blaIMP-13_ was found in ST253. For _E. coli_ , the 2 _blaIMP_ - were ST648 and ST1061, and the _blaNDM_ was ST101.

The median age of children with MBL-producing _Enterobacteriaceae_ was 2.5 years (range, 4 months–11 years); 67% were male, and 83% were cared for in medical centers on the Western Coast of the United States (California and Washington) at the time of infection. Unit-level data were available for 10 patients, and 6 (60%) patients were located in the intensive care unit at the time of the culture. The most common source was urine (40%), followed by blood (26.7%) and respiratory cultures (20%). All positive blood cultures were recovered from central venous catheters.

Clinical data were available for 10 of 12 (83.3%) children. All 10 (100%) suffered from serious underlying medical conditions with 40% having hematologic-oncologic comorbidities or were immunosuppressed (including organ transplant), 40% had a neurologic comorbidity, 30% had respiratory comorbidities (including tracheostomy and ventilator dependence), and 20% had a history of early preterm birth of less than 30 weeks gestation. In each case, there was a previous history of hospitalization and/or frequent medical care, and most reported previous exposure to antibiotics. It is interesting to note that travel outside the United States in 6 (50%) patients, which included 5 cases involving _blaIMP_ and in 1 of the _blaNDM_ cases was not present. Data on hospital type were available for 7 children, and 6 (85.7%) children were cared for in free-standing children’s hospitals.

Treatment and outcome data were available for 11 of 12 children. Antibiotic choices were varied and included combination therapy in 5 (45.4%) children. A carbapenem was used in the treatment of 5 children (45.4%); an aminoglycoside (gentamicin or amikacin) was used in the treatment of 4 (36.3%) children; colistin and trimethoprim-sulfamethoxazole were each used in 2 (18.1%) cases; and fosfomycin, levofloxacin, or tigecycline were part of therapy each in 1 (9%) case. Two deaths were reported, with an attributable mortality of 18% due to infections by MBL-producing organisms.

Metallo-β-lactamase-producing _Enterobacteriaceae_ infections have been occurring in US children, but for the most part infections have been “under the radar”. Consistent with adult data is the heterogeneity of clonal strains associated with MBL dissemination. As a result, spread is likely attributed to “promiscuous plasmids” of multiple types associated with integrons (and transposons in some cases). What is most shocking is that there are reports of cases of MBL-producing _Enterobacteriaceae_ infections in young children as early as 2002, even though the first reports were not published in the United States until 2010. Even more surprising is that half of these organisms were found in children who do not have a history of travel. So where are the children acquiring these infections? Other than the 2 cases of _blaIMP_ with evidence of a neonatal intensive care unit stay overlapping the sentinel case [5], the available evidence does not shed clear light on this. We additionally hypothesize that because there appears to be a higher proportion of isolates in children recovered from the Western region of the United States, that there may have been an introduction of MBLs via Southeast Asia and Japan.

Most disturbingly, the limited literature available suggests that children may be silently harboring MDR _Enterobacteriaceae_, including MBL-producers, and that colonization is often prolonged, which means that children may serve as potential reservoirs for these organisms in the community [10–12]. Why children are more likely to become colonized but not infected is poorly understood. The long-term consequences of this prolonged colonization are unthinkable.

In summary, MBL-producing _Enterobacteriaceae_ are a real and present danger in children. Regional and national surveillance, as well as the analysis of molecular mechanisms in MDR _Enterobacteriaceae_ are critical to identifying and halting the spread of these organisms in our most vulnerable populations. We posit that a targeted surveillance program should be undertaken in critically ill and immunocompromised children who are cared for in tertiary care settings.
### Table 1. Characteristics of 12 Pediatric Patients With 15 MBL-Producing *Enterobacteriaceae* Isolates

| Year Isolated | Age, Years | Sex | Race/ Ethnicity | Region | Organism | Source | Unit | MBL Gene | Other bla Genes | Underlying Conditions | Travel Outside of United States | Treatment | Outcome | Ref. |
|---------------|------------|-----|----------------|--------|----------|--------|------|----------|----------------|---------------------|-----------------------------|------------|---------|------|
| 2002          | 3.5        | M   | White          | Seattle, WA | *E coli* | Blood | Heme-onc | IMP-4 | CMY-2 | AML | None | GNT | Survived | [6] |
| 2003          | 11         | M   | Hispanic       | Seattle, WA | *E coli* | Blood; Stool | Heme-Onco | IMP-4 | CMY-2 | ALL | Mexico | GNT, TMP/SMX | Survived | [6] |
| 2005          | 3          | F   | ND             | Los Angeles, CA | *E cloacae* | Respiratory | PICU | VIM-2 | TEM-15, ACT | ND | ND | ND | PC |
| 2009          | 0.33       | M   | ND             | CA | *K pneumonia* | Urine | NICU | IMP-4 | NR | Premature birth, (25 wks) | None | NT | Survived | [5] |
| 2010          | 0.42       | F   | ND             | CA | *K pneumonia* | Urine | NICU | IMP-4 | NR | Premature birth (29 wks); CHD | None | NT | Survived | [5] |
| 2011          | 1.1        | M   | Asian          | Los Angeles, CA | *K pneumonia* | Respiratory | ED | NDM-1 | NR | RA; CSA; DD, Multi-abx courses | Pakistan | COL | Survived | [7] |
| 2012          | 4          | M   | White          | Chicago, IL | *K pneumonia* | Peritoneal | PICU | IMP-13 | None | SBT | None | MEM | Survived | [4] |
| 2012          | 2          | F   | Asian          | Stanford, CA | *K pneumonia* | Urine | NR | NDM-1 | NR | Neurogenic bladder | India | MEM, Tig, FOS | Survived | [4] |
| 2012          | 2          | F   | Asian          | Los Angeles, CA | *E coli* | Blood | NR | NDM-1 | CTX-M-15; CMY-42 | MDS | India | IMI, AMK | Died | [8] |
| 2013          | 3          | M   | NR             | Los Angeles, CA | *K pneumonia* | Urine; Blood | PICU | NDM-1 | CTX-M-15; CMY-42; SHV-11 | Gangliosidosis; Trach/Vent dep | None | LEV, IMI, COL | Survived | [8] |
| 2014          | 2          | M   | Mideastern     | Baltimore, MD | *K pneumonia* | Respiratory | PICU | VIM-4 | CMY-4 | Vent dep, Dandy-Walker | Kuwait | MEM, AMK | Died | [9] |

Abbreviations: abx, antibiotics; ALL, acute lymphoblastic leukemia; AMK, amikacin; AML, acute myelogenous leukemia; CHD, congenital heart defect; COL, colistin; CSA, congenital skeletal abnormality; E coli, *Escherichia coli*; E cloacae, *Enterobacter cloacae*; ED, emergency department; FOS, fosfomycin; GNT, gentamicin; Heme-Onco, hematol- oncology ward; IMI, imipenem; K pneumonia, *Klebsiella pneumoniae*; LEV, levofloxacin; MDS, myelodysplastic syndrome; MEM, meropenem; Multi, multiple; ND, no data; NICU, neonatal intensive care unit; NR, none reported; NT, no specific *Enterobacteriaceae* treatment; PC, personal communication; PICU, pediatric intensive care unit; RAD, reactive airway disease; Ref., reference; SBT, small bowel transplant; Tig, tigecycline; TMP/SMX, trimethoprim/sulfamethoxazole; Trach/Vent dep, tracheostomy/ventilator dependent; Unit, hospital location.

* If year isolated not available, year of publication reported.
* Presented to the ED; however, history of NICU stay overlapping with 2 other California *K pneumoniae* harboring *bla*<sub>IMP</sub>-4 NICU cases.
* L. K. Logan et al (unpublished data).
Targeted molecular surveillance can be cost effective and prevent unrecognized dissemination.

As in adults, the consequences of infection by MBL-producing GNB are likely to exact a disturbing toll. No one is safe.

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