Clinical Features and Mechanisms of Carbapenem Resistance in *Enterobacteriaceae* in Pediatric Patients in the United States

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INTRODUCTION

- Carbapenem-resistant *Enterobacteriaceae* (CRE) carrying a broad range of carbapenemase enzymes, are on the rise.
- Global spread of these highly-resistant bacteria have led to emergence in pediatric populations in the United States.
- Risk factors, resistance characteristics and outcomes in pediatric patients are not well described.

AIM

To describe clinical, phenotypic and genotypic characteristics of CRE infections at a free-standing U.S. children's hospital

METHODS

- CRE isolates, detected by a positive modified Hodge test, were identified through active surveillance in the clinical microbiology laboratory at Children's Hospital Los Angeles since 2005.
- Medical records were reviewed.
- Resistance testing and molecular characterization of phylogenetic and resistance-associated traits were carried out for each isolate including:
  - Antimicrobial susceptibility testing by Etest or disk diffusion per CLSI guidelines
  - Polymerase chain reaction (PCR) screening and sequencing of genes encoding AmpC, ESBL and carbapenemase enzymes and the KPC Tn4401 platform.
  - Multilocus sequence typing was performed for *E. coli* and *K. pneumoniae* isolates.
  - PCR-based replicon typing was performed for IncF related plasmid backbones.
  - Outer membrane porin amplification and sequencing is currently underway and is not reported here.

Clinical Features								Susceptibility testing						Resistance Characteristics						Outcome	
Pt	Year	Age (yr)	Presen-tation	Underlying Conditions	ICU	Travel history	Source	Species	Cef	Cip	Col	Gm	Tig	T/S	Carbapen-emase	Other genes	MLST	PCR-based replicon type	Plasmid ST	Tn4401	Treatment	Death
1	2011	20	Abd pain	Abd gunshot wound	no	none	Abd wound	*K. pneumoniae*	R	S	S	S	-	S	KPC-3	--	ST18	IncFIIK	K4	Tn4401b	none	no
2	2011	16	UTI	Spina bifida	no	Unk	Urine	*E. coli*	R	R	S	R	-	R	-	CTX-M-15	ST10	IncFII, FIA, FIB	F31:A4:B1	-	Mer	no
3	2011	24	UTI	Blue rubber bleb nevus syndrome, neurogenic bladder	no	Unk	Urine	*E. coli*	S	R	-	R	-	R	KPC-3	CTX-M-15	ST131	IncFIA, FIB	F-:A2:B20	Tn4401b	Nit	no
4	2012	5	Resp failure	Drowning, mild asthma	yes	Unk	BAL	*E. cloacae*	I	S	S	S	-	S	-	-	-			-	None	yes
5	2012	0.6	Sepsis	Hemophagocytic lymphohistiocytosis	no	Lebanon	Blood	*K. pneumoniae*	I	R	S	R	S	R	KPC-3	SHV	ST258			Tn4401d	Ert, Mer, Col	yes
6	2012	2	Sepsis	Myelodysplastic syndrome	no	India	Blood	*E. coli*	R	R	S	R	-	R	NDM-1	CTX-M-15, CMY-2	ST101	IncFII, FIA, FIB	F2:A1:B20	-	Imp, Amik	yes
7	2012	0.3	↑ Resp secretions	Neuroblastoma	yes	None	TA	*E. cloacae*	S	S	S	S	S	S	-	-	-			-	None	no
8	2012	0.1	Abd abscess	Trisomy 21, ex-34 week premie, Necrotizing enterocolitis	yes	None	Abd wound	*E. cloacae*	S	S	S	S	S	S	-	-	-			-	Cef, Tob	yes
9	2012	11	None	Lipomeningocele, neurogenic bladder	No	Unk	Urine	*E. coli*	S	S	S	S	S	S	-	CMY-2	ST457			-	None	no
10	2013	3	UTI	Gangliosidosis	Yes	Unk	Urine	*K. pneumoniae*	R	R	S	R	S	R	NDM-1	CTX-M-15, CMY-4	ST37			-	Levo	no
	2013	"	Sepsis	"	Yes	"	Blood	*K. pneumoniae*	R	R	S	R	S	R	NDM-1	CTX-M-15, CMY-4	ST37			-	Imp, Col	no

Abbreviations: **Yr**, year. **ICU**, intensive care unit. **Cef**, cefepime. **Cip**, ciprofloxacin. **Col**, colistin. **Gm**, gentamicin. **Tig**, tigecycline. **T/S**, trimethoprim/sulfamethoxazole. **MLST**, multilocus sequence type. **Abd**, abdominal. **UTI**, urinary tract infection. **Resp**, respiratory. **Unk**, unknown. **KPC**, Klebsiella pneumoniae carbapenemase. **NDM**, New Delhi metallo-β-lactamase. **Mer**, meropenem. **Nit,** nitrofurantoin. **Ert**, ertapenem. **Imp**, imipenem. **Amik,** amikacin. **Tob**, tobramycin. **Levo**, levofloxacin.

RESULTS

Patient Characteristics

- Eleven isolates from 10 patients demonstrated a positive Modified Hodge test.
- All patients except one (pt #4) had underlying conditions as risk factors for prolonged hospitalizations or recurrent infections.
- All patients had indwelling devices (central lines, surgical drains, endotracheal tube, surgical drain, foley catheter) or had intermittent urinary catheterization multiple times daily.
- Travel history was significant in two patients.

Novel Isolates in U.S. Pediatric Patients

- Three isolates carried **KPC-3** carbapenemases:
  - *K. pneumoniae* from ST18
  - *K. pneumoniae* from **disseminated clone ST258**
  - *E. coli* from **international clone ST131**
- Three isolates from 2 patients carried **NDM-1** carbapenemases:
  - *E. coli* from ST101 in patient who travelled from India.
  - *K. pneumoniae* from ST37 initially isolated from urine and then blood two weeks later in same patient

Outcomes

- No evidence of epidemiologic or molecular relatedness was evident between any two isolates from different patients.
- The CRE isolate was considered to be a colonizer in 3 patients.
- Isolates producing carbepenemases tested for susceptibility to colistin and tigecycline remained susceptible.
- Two of three (67%) patients died during treatment for bacteremia. Repeat blood cultures were negative in one (Pt #6) and persistently positive in the other (Pt #5).

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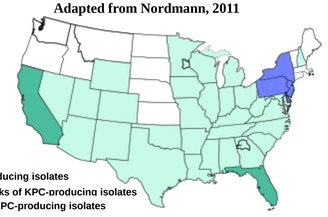
Distribution of KPC carbapenemase in the US. Adapted from Nordmann, 2011



SUMMARY

- ***E. coli*** **ST131 carrying the KPC-3 carbapenemase** have previously been reported in adult infections in the US (Kim, 2012), but this is the **first report** in **pediatric patients**.
- To the best of our knowledge, this is the **first report** of **NDM carbapenemase-producing *Enterobacteriaceae*** associated with **pediatric** infection or colonization in the US.
- This cluster of epidemiologically unlinked cases in **Los Angeles,** where KPC-producing *Klebsiella pneumoniae* appear to have become endemic (Marquez, 2013), reflects the highly dynamic nature of the spread of CRE in the US and across the globe.
- Detailed understanding of the distribution and spread of CRE enzymes is essential to the timely detection and containment of these **perilous pathogens**.

References

Kim YA *et al* (2012) *CID* 55(2):224-31.
Marquez P *et al* (2013) ICHE 34(2):144-50.
Nordmann P *et al* (2011) EID 17(10): 1791-8.