Epidemiology of the β-lactamase resistome among *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* in the Chicago region

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Background

- *Enterobacteriaceae* that produce *Klebsiella pneumoniae* carbapenemase (KPC) often carry multiple β-lactamase genes, some conferring broad spectrum β-lactam resistance

- When 2 or more KPC-producing *Enterobacteriaceae* are recovered from the same ward or facility, a practical infection control question is whether the strains are related, suggesting an outbreak

- Distinct β-lactamase gene collections, or resistomes, may serve as markers of strain relatedness

Objectives

1) Characterize the β-lactamase resistomes of KPC-producing *Enterobacteriaceae* from the Chicago region

2) Assess whether resistome typing can identify significant clusters

Methods

- Design: Retrospective cohort analysis of 363 KPC-producing *Enterobacteriaceae* recovered from 177 distinct hospital point prevalence surveys from 2010-2014 in Chicago region
  - For each isolate, we had epidemiologic information about hospital identity and date of surveillance

Blue = 25 Hospitals (ICU); red = 7 LTACHs

Methods (cont.)

- β-lactamase resistome characterization: multiplex PCR targeting 49 gene families (Acuitas® Resistome Test, OpGen)
  - Carbapenemases
  - Extended spectrum β-lactamase (ESBL)
  - Plasmid-mediated AmpC-type β-lactamases
  - Narrow spectrum β-lactamases

Methods (cont.)

- Distinct combinations of β-lactamase genes = ‘resistome types’
- For minority resistome types, we assessed temporal-spatial clusters (2 or more KPC-producing *Enterobacteriaceae* of identical species and resistome type recovered from the same facility/survey date)
- We tested cluster significance using exact statistical tests

Results

- 363 KPC-producing *Enterobacteriaceae* were recovered from 44% (77/177) of distinct hospital point prevalence surveys:
  - 86% *K. pneumoniae*, 7% *E. coli*, 6% *Enterobacter* spp.

- 24% (43/177) hospital surveys had 2 or more patients carrying KPC-producing *Enterobacteriaceae*

β-lactamase resistome

- Including *bla*$_{KPC}$, isolates carried a median of five β-lactamase genes (range, 1 to 8)

β-lactamase types	n	%
SHV-type ESBL	167	46
TEM-type ESBL	17	5
CTX-M-type ESBL	12	3
Plasmid mediated AmpC-type	48	13

Using 23 resistance genes detected, we identified 38 unique resistome types (top 10 shown)

		Resistome type									
		1	2	3	4	5	6	7	8	9	10
Type	**Gene family**										
Carbapenemase	KPC	■	■	■	■	■	■	■	■	■	■
ESBL	SHV G238S E240K	■						■			■
	TEM R164S						■				
	TEM E104K						■				
	CTX-M (CTX-M-1 subgroup)					■					
pAmpC	CMY-2/CFE-1			■						■	
Narrow spectrum β-lactamase	VEB								■		
	SHV G238 E240 (WT)		■		■		■		■	■	■
	TEM G238 E240 (WT)	■	■	■		■	■		■		
	TEM R164 (WT)	■	■	■		■	■		■		■
	TEM E104 (WT)	■	■	■		■	■		■		■
	Count (% of total [N=363])	139 (38)	120 (33)	17 (5)	9 (2)	7 (2)	7 (2)	5 (1)	5 (1)	5 (1)	4 (1)

- Two most frequent resistome types accounted for 71% of all isolates
- 20 types were represented by at least 2 or more isolates

Cluster analysis

- Resistome types affecting 9 or less patients (from type 20 [n=2] to type 4 [n=9]) were analyzed for evidence of clustering

Example: Resistome 20 (n=2)

Obs	Organism	Facility	Date (coded)
17	*E. cloacae*	P	19891
79	*E. cloacae*	B	19569

No cluster identified

Example: Resistome 19 (n=2)

Obs	Organism	Facility	Date (coded)
156	*K. pneumoniae*	LC	18700
293	*K. pneumoniae*	LC	18700

1 cluster identified, $P = 0.02$

Example: Resistome 6 (n=7)

Obs	Organism	Facility	Date (coded)	
122	*K. pneumoniae*	LC	18700	
125	*K. pneumoniae*	LC	18700	
154	*K. pneumoniae*	LC	18700	1
200	*K. pneumoniae*	LC	18700	
229	*K. pneumoniae*	LC	18700	
232	*K. pneumoniae*	LD	19821	
264	*K. pneumoniae*	LD	19821	2

2 clusters identified. Cluster 1, $P < 0.001$; Cluster 2, $P = 0.006$

Cluster analysis results

- We found 17 temporal-spatial clusters (same resistome type, species, hospital, date of survey), involving 39/69 (57%) analyzed isolates
- Of 17 clusters, 15/17 (88%) were statistically significant ($P < 0.05$)

Limitations and Strengths

- Limitations
  - Did not include analysis of non-β-lactamase resistome; inclusion of a broader resistome could improve strain differentiation
  - Did not assess for outbreaks spanning more than 1 facility
  - More discriminatory genetic testing (e.g., whole genome sequencing) is needed to confirm clustering as suggested by resistome and epidemiologic data
- Strength
  - Isolates were obtained by point prevalence surveys, allowing recovery of KPC-producing *Enterobacteriaceae* from asymptomatic and symptomatic patients at a given time and location

Conclusions

- KPC-producing *Enterobacteriaceae* carry multiple β-lactamases, including ESBLs (SHV, TEM, CTX-M) and plasmid-mediated AmpC
- In the Chicago region, about 70% of isolates were associated with 2 dominant resistome types that would require whole genome sequencing to resolve transmission linkages
- Facility clustering of minority resistome types suggests that a resistome-based surveillance system can identify some potential outbreaks

Thank you