Epidemiology and natural history of ESBL-producing and carbapenem-resistant Enterobacteriaceae rectal colonization among solid organ transplant recipients

M. Hong Nguyen, Ryan K. Shields, Liang Chen, Barry N. Kreiswirth, Cornelius J. Clancy

Department of Medicine, University of Pittsburgh, University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; PHRI, Rutgers, New Jersey Medical School, NJ

Contact Information:
M. Hong Nguyen, MD
Professor of Medicine
3601 Fifth Avenue
Falk Medical Building, Suite 3A
Pittsburgh, PA 15213
Phone: (412) 383-5193
E-mail: mhn5@pitt.edu

INTRODUCTION

- ESBL-Enterobacteriaceae (ESBL-E) and CRE infections carry high mortality in solid organ transplant patients (SOT pts). Natural history of rectal colonization (R-COL) and subsequent disease (Dz) by ESBL-E and CRE post-SOT is unclear.

OBJECTIVE

- The objective of the CRE Carriage in Solid Organ Transplant (CREST) study is to prospectively investigate the natural history of ESBL-E and CRE GI colonization among SOT recipients at the University of Pittsburgh Medical Center (UPMC).

HYPOTHESES

- GI colonization rates will be highest among liver and lung transplant recipients, and lowest among kidney transplant recipients.
- GI colonization will be a risk factor for ESBL-E and CRE invasive infections.
- Invasive infections will be caused by isolates that are colonizing the GI tract.

METHODS

- Pts who underwent SOT from 8/15-10/16 were consented.
- Peri-rectal swabs were collected each week (wk) until 90 days (d) post-SOT, and cultured using KPC and ESBL CHROMagar plates.
- Resistance was confirmed by MIC.
- ESBLs and KPCs were detected by PCR.
- Pts were followed until 6 months (m) post-SOT.
- 18 longitudinal isolates from GI and other sites underwent MiSeq whole genome sequencing (WGS).
  - WGS compared to other UPMC isolates, and US isolates in the Kreiswirth repository.
- Primary endpoint was ESBL-E or CRE Dz.

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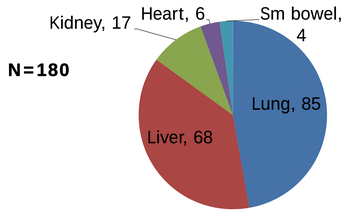
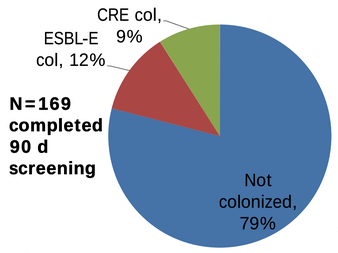
RESULTS

SOT recipients



- Median age: 58 years
- 56% men
- 88% white
- Median time to first swab: 3 d post-SOT
- Median: 3 swabs/patient

GI colonization



- 15 colonized with CRE (KPC-*K. pneumoniae*)
- 21 colonized with ESBL-E (*E. coli, K. pneumonia, E. cloacae, C. freundii*)
- 1 patient colonized with 2 CRE
- 2 patients colonized with 2-3 ESBL-E

GI colonization rates

	CRE	ESBL-E	Either
Liver	7%	21%	25%
Lung	12%	14%	22%
Small bowel	0%	25%	25%

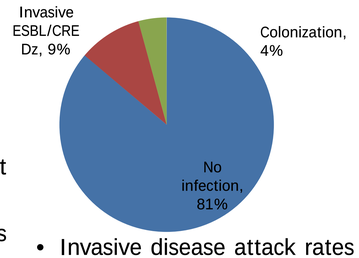
No colonization in other types of SOT

- Median time from SOT to first + rectal swab:
  - CRE: 17 days (3-59 days)
    - 0% present on admission
  - ESBL-E: 17 days (1-83 days)
    - 18% present on admission

	CRE	ESBL-E
Persistent (≥3+)	60%	54%
Transient	20%	14%
Only 1 sample	13%	25%
Intermittent	7%	7%

ESBL-E and CRE infections

N=125 lung and liver pts at 6 mo post-SOT



- 13% (16/125) were infected with ESBL/CRE post-SOT
  - 9% (11) with invasive disease, 4% (5) non-GI colonized
  - Invasive disease included urinary tract (3), intra-abdominal (2), bacteremia (2), pneumonia (2), empyema (1), surgical site (1)
- 25% (9/36) of GI colonized pts developed invasive infection, *vs.* 1% (2/89) of non-colonized pts (p=0.0002)
- Invasive disease attack rates among GI colonized Liver and Lung recipients were 29% (5/17) and 21% (4/19), respectively
- GI colonization was the only independent risk factor for invasive disease

Whole genome sequencing

- CREST isolates clustered tightly together, forming a novel ST258 sublineage that was distinct from other clade II isolates recovered previously from UPMC and elsewhere.
  - Plasmid sequencing of these isolates revealed a pBK30683-like IncFIA plasmid, a common *bla*$_{KPC}$-harboring plasmid circulating in the NY/NJ area
- Isolates within this new sublineage differed on average by 17 SNPs
  - Differed from other clade II and clade I isolates by an average of 85 and 240 SNPs, respectively.

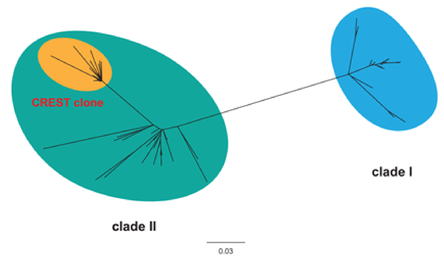


Figure 3. SNP based phylogenetic analysis of CREST clone.

Table. Invasive KPC-*K. pneumoniae* infections were caused by GI colonizing isolates

	P1-Wk3	P1-W5	P1-W6	P1-W9	Sputum-W	BAL-W3	PF-W6
P1-Wk3		5	75	4	8	5	2
P1-W5	5		48	8	12	8	4
P1-W6	75	48		37	46	57	35
P1-W9	4	8	37		15	8	12
Sputum-W	8	12	46	15		8	16
BAL-W3	5	8	57	8	8		9
PF-W6	2	4	35	12	16	9	

Table. Genetic evidence of nosocomial spread of ST258 KPC-*K. pneumoniae*

	CREST-F1	CREST-F7	CREST-G6	CREST-H2	CREST-H3	CREST-H7	CREST-H9	CREST-I2	CREST_119
CREST-F1		57	44	48	55	66	57	44	207
CREST-F7	57		17	21	28	39	30	17	228
CREST-G6	44	17		8	15	26	17	4	270
CREST-H2	48	21	8		19	30	21	8	397
CREST-H3	55	28	15	19		37	28	15	401
CREST-H7	66	39	26	30	37		39	26	406
CREST-H9	57	30	17	21	28	39		17	408
CREST-I2	44	17	4	8	15	26	17		418
CREST_119	207	228	270	397	401	406	408	418	

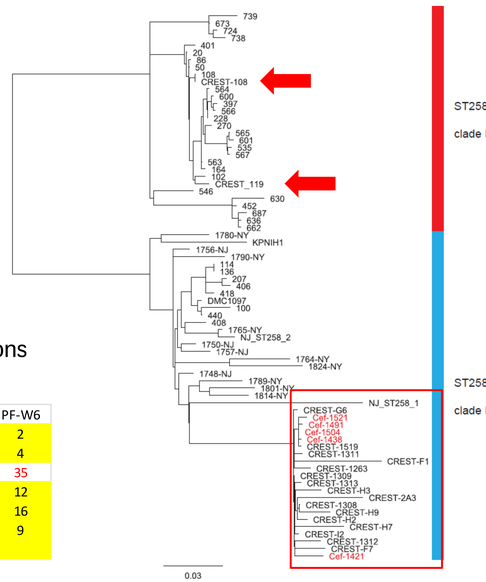
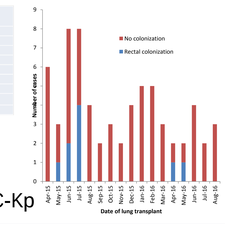


Figure. Phylogenetic tree including CREST isolates.

Table and Figure. Cryptic nosocomial spread of ST258 KPC-Kp

DATE OF TX	Time of first swab+ For CRE	CRE NAME
5/3/2015	6/3/2015	CR-Kp
6/6/2015	8/4/2015	CRE-KP
6/13/2015	6/24/2015	CRE-KP
7/4/2015	7/21/2015	CRE-KP
7/9/2015	7/29/2015	CRE-ENTA
7/17/2015	7/28/2015	CRE-Kp
7/27/2015	8/5/2015	CRE-Kp
4/26/2016	5/17/2016	CRE-E. cloaca
5/6/2016	5/24/2016	CRE-SM



Outcomes

- 17% of pts with invasive infections died
- Length of stay was significantly prolonged in survivors (median: 75 d vs 22 d)

CONCLUSIONS

- The data from CREST establish that liver and lung transplant recipients are at high-risk for GI colonization by ESBL-E and CRE, which is a significant risk factor for subsequent invasive infection
- Invasive ESBL-E and CRE infections are caused by isolates colonizing the GI tract
- In most instances, GI colonization occurs >2 weeks post-SOT, consistent with nosocomial transmission
- WGS showed that an ST258 *K. pneumoniae* sublineage that is prone to ceftazidime-avibactam resistance was introduced to UPMC in 2015 and likely spread cryptically in liver and lung transplant recipients as a GI tract colonizer
- Rectal screening and infection prevention interventions deserve further investigation among liver and lung transplant recipients