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 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
- Median time from SOT to first + rectal swab:
  - CRE: 17 days (3-59 days)
  - ESBL-E: 17 days (1-93 days)
- 9% (11) with invasive disease, 4% (5) non-GI

ESBL-E and CRE infections
- 13% (16/125) were infected with ESBL/CRE post-SOT
- 9% (11) with invasive disease, 4% (5) non-GI
- 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% (2/209) 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
- ESBL 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 blaKPC-harboring plasmid circulating in the NY/NJ area.
- Isolates within this new sublineage differed on average by 17 SNPs
- Different from other clade II and clade I isolates by an average of 85 and 240 SNPs, respectively

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

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

Figure. Phylogenetic tree including CREST isolates.

Figure. Cryptic nosocomial spread of ST258 KPC-Kp.