Pilot Surveillance for Carbapenemase-producing Carbapenem-resistant Organisms Among Hospitalized Solid Organ Transplant Recipients

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Introduction

Multidrug-resistant organisms (MDROs) are a global public health challenge. Carbapenemase-producing carbapenem-resistant organisms (CP-CROs) typically carry numerous drug resistance profiles, along with carbapenem resistance. Organisms, including carbapenem-resistant *Acinetobacter* and carbapenem-resistant Enterobacterales have been deemed urgent threats in the United States.[1] Infections by CP-CROs can be particularly deadly in patients that are immunocompromised.

Recipients of solid organ transplants (SOT) are at a disproportionately higher risk for acquisition of and potential infection by CP-CROs. Prolonged hospital stays, frequent exposure to broad-spectrum antimicrobial therapy, sustained use of immunosuppressive drugs, and the potential need for mechanical ventilation are all contributing factors to this infection risk.[2] Complicating matters, an organ donor's own declining health status and hospitalizations, the limited supply of donor organs available, and the urgency of organ transplantation to maintain graft viability (e.g., screening assays of donor organs must be completed within 4-12 hours), pose significant risks to the development of donor infections and the potential transfer of infected organs from donor to recipient.[3] The outcomes of CP-CRO infection in SOT recipients also tend to be worse, with reported mortality rates in patients with carbapenem-resistant Enterobacterales (CRE) infections ranging from 30-50%.[4]

Objectives

PROBLEMS:

- From passive reporting to the CDC, CP-CROs are being identified with increasing frequency in SOT recipients
- This may represent an emerging source of spread of CP-CROs in this high-risk population

SOLUTIONS:

- Determine the prevalence of CP-CRO colonization in SOT recipients
- Describe the types of carbapenemase genes and organisms carrying them present in SOT recipients
- Inform public health actions aimed at preventing and limiting the spread of CP-CROs

ARLABnetwork

CP-CRO Screening Locations: September 2019 to June 2020

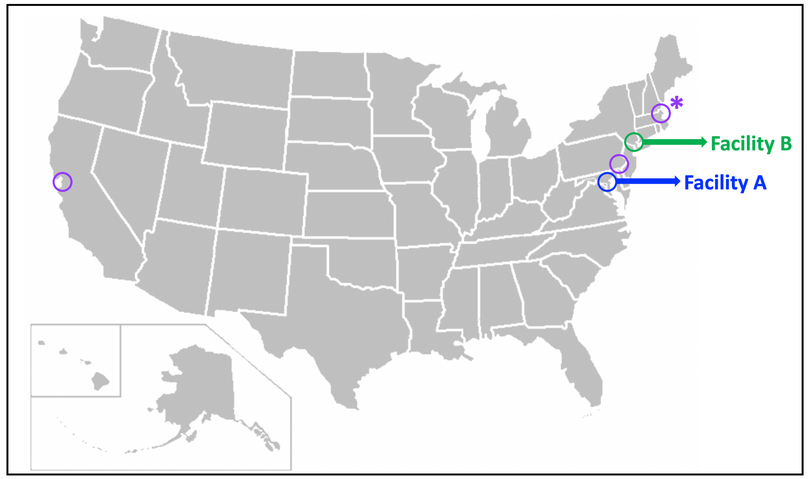

Figure 1. Locations of hospitals participating in SOT recipient pilot CP-CRO screening. From September 2019 to June 2020, five academic hospitals conducted colonization screening point prevalence surveys (PPS) on units where SOT recipients received inpatient care. Each facility conducted two PPS, approximately one month apart. Rectal swabs were collected from all consenting patients, regardless of transplant status; 154 patients were sampled. Intensive care units (ICUs) were excluded. °: Denotes hospital conducting PPS. *: Denotes hospital that conducted 1 PPS. Carbapenemase gene-positive specimens were only detected from Facilities A and B.

Commercially Available & Laboratory-Developed Molecular Testing

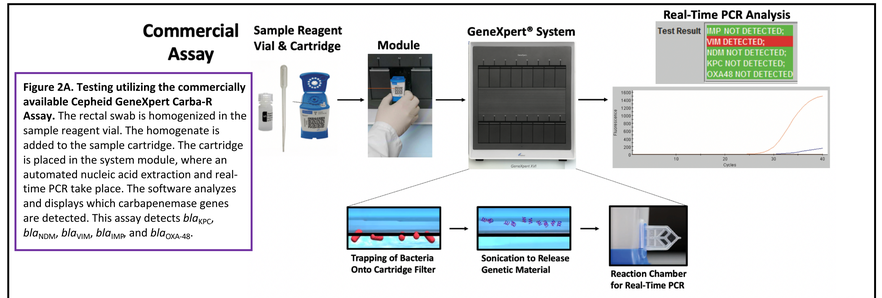

Figure 2A. Testing utilizing the commercially available Cepheid GeneXpert Carba-R Assay. The rectal swab is homogenized in the sample reagent vial. The homogenate is added to the sample cartridge. The cartridge is placed in the system module, where an automated nucleic acid extraction and real-time PCR take place. The software analyzes and displays which carbapenemase genes are detected. This assay detects *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$, and *bla*$_{OXA-48}$.

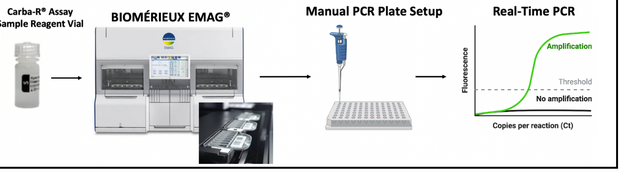

Figure 2B. Testing utilizing laboratory-developed tests (LDTs). LDTs were used to retrospectively screen specimens for all *bla*$_{IMP}$ and *bla*$_{OXA-23, -24/40, -58-like}$ gene variants not detected by the Carba-R® assay. Sample homogenate nucleic acids were extracted with the BIOMÉRIEUX EMAG®. Real-time PCR setup and analyses were performed manually.

Positive Swab Culture & Downstream Analyses

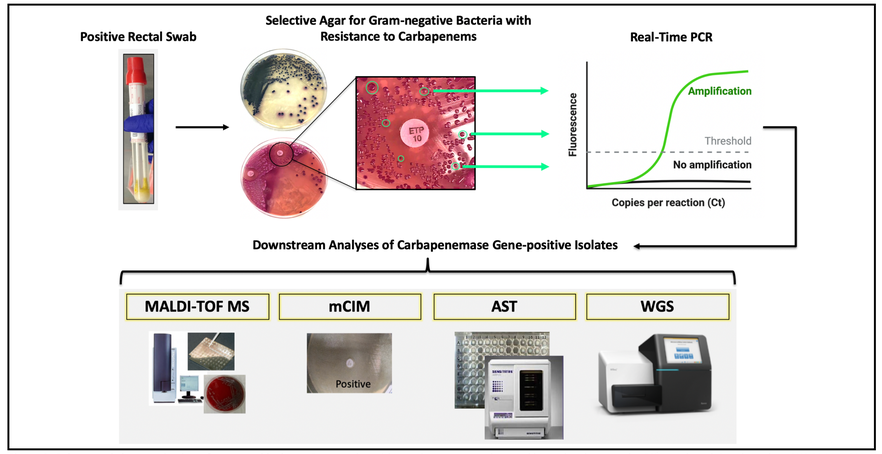

Figure 3. Culture and characterization of recovered isolates. For samples with a carbapenemase detected by molecular test, the 2nd rectal swab is cultured on CHROMagar™ mSuperCARBA™ agar and MacConkey agar (with an ertapenem and meropenem antibiotic disc) to recover gram-negative bacteria resistant to carbapenems. Isolates are screened by real-time PCR for carbapenemase gene confirmation. The isolate is identified with MALDI-TOF mass spectrometry and whole-genome sequencing. The modified carbapenem inactivation method (mCIM) is performed to assess carbapenemase production from the isolate. Broth microdilution antimicrobial susceptibility testing (AST) is performed with the Thermo Scientific™ Sensititre™ GNX2F AST Plate to assess isolate drug susceptibilities to 21 antimicrobial compounds, including carbapenems.

Acknowledgements

This work was supported by the New York State Department of Health and by Cooperative Agreement Number NU50CK000423 funded by the Centers for Disease Control and Prevention (CDC). This research was supported in part by an appointment to the Antimicrobial Resistance Fellowship Program administered by the Association of Public Health Laboratories (APHL) and funded by the CDC. This poster uses some free-text images from BioRender.com

Results: CP-CRO Screening of 154 Total Patients

TABLE 1: Characteristics of Carbapenemase-producing Carbapenem-resistant Organism (CP-CRO) Pilot Surveillance Participants

	Solid Organ Transplant Recipients (N = 92)
Age (median years, range)	57 (18-77)
Male	51 (55%)
Transplant organ[a]	
kidney	44 (48%)
liver	39 (42%)
pancreas	9 (10%)
lung	6 (7%)
Patients with carbapenemase genes detected	7 (8%)
Detected by CARBA-R: *bla* $_{KPC}$	4 (57%)
Organisms[b]	*Enterobacter cloacae* complex[c], *Klebsiella pneumoniae*[c], *Klebsiella oxytoca;* organisms were not recovered from 2 patients
bla $_{NDM}$	1 (14%)
Organisms[b]	*Klebsiella oxytoca*
Detected by LDT: *bla* $_{OXA-23}$	2 (29%)
Organisms[b]	not recovered
Time from transplantation to point prevalence survey (PPS) date among all solid organ transplant (SOT) recipients, N = 92; median days (range)[d]	40 (0-7151)
Time from transplantation to PPS date among SOT recipients with carbapenemase genes detected, N = 7; median days (range)[d]	108 (4-1529)

- 8% (7 of 92) of SOT recipients were positive for carbapenemase genes
- 3% (2 of 62) of non-transplant patients were positive for carbapenemase genes

[a]Some patients received dual SOTs

[b]Carbapenemase genes detected & associated organisms

[c]Organisms were cultured from the same patient

[d]Time interval = # of days from SOT to specimen collection for screening

Table 1. Characteristics of pilot surveillance participants who were SOT recipients. Five carbapenemase gene-positive patients were detected by the Carba-R® Assay: 4 *bla*$_{KPC}$ and 1 *bla*$_{NDM}$ (blue). Two additional positive patients were detected by the LDT: 2 *bla*$_{OXA-23}$ (green).

TABLE 2: Patient Demographics, Culture and Phenotypic Testing Results from Carbapenemase Gene-Positive Specimens

Patient	Carbapenemase Gene	Organism	Interval	mCIM	Doripenem	Ertapenem	Imipenem	Meropenem
SOT[a] (liver)	*bla* $_{NDM-5}$	*Klebsiella oxytoca*	12	POS	R	R	R	R
SOT[a] (kidney)	*bla* $_{KPC-3}$	*Enterobacter cloacae* complex[c]	323	POS	S	R	I	S
	bla $_{KPC-3}$	*Klebsiella pneumoniae*[c]		POS	I	R	R	I
SOT[a] (liver)	*bla* $_{KPC-3}$	*Klebsiella oxytoca*	33	POS	S	S	I	S
SOT[a] (liver)	*bla* $_{KPC}$	not recovered	108					
SOT[a] (liver)	*bla* $_{KPC}$	not recovered	185					
SOT[a] (liver)	*bla* $_{OXA-23}$	not recovered	1529					
SOT[b] (kidney)	*bla* $_{OXA-23}$	not recovered	4					
non-transplant[b]	*bla* $_{OXA-23}$	not recovered						
non-transplant[b]	*bla* $_{KPC-19}$	*Citrobacter farmeri*		POS	R	R	R	R

Interval = # of days from SOT to specimen collection for screening

[a] Individuals received treatment at Facility A

[b] Individuals received treatment at Facility B

[c] Organisms were cultured from the same patient

Table 2. Patient demographics, culture and phenotypic testing results of all recovered isolates. Patients receiving treatment at Facility A (blue) or Facility B (green). POS = mCIM-positive test result with a <6mm meropenem inhibition zone. S, I, R = Susceptible, Intermediate, or Resistant AST result to respective carbapenem antibiotics.

Conclusions

- Carbapenemase genes were detected in **8%** (7 of 92) of SOT recipients
- CP-CRO colonization by Enterobacterales was confirmed in **3%** (3 of 92) of SOT recipients
- Carbapenemase genes were detected in **3%** (2 of 62) of non-transplant patients
- All cultured isolates produced functional carbapenemases and exhibited non-susceptibility to at least one carbapenem tested
- We did not identify carbapenemase gene-positive patients in 3 out of 5 of the pilot surveillance participating hospitals

References

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