

Figure 1: Primary and Secondary Endpoints

| Antimicrobial exposure | Cases n = 106 (%) | Controls n = 119 (%) | Odds Ratio (95% CI) |
|---|----------------------|-------------------------|------------------------|
| ≥ 48 hours of meropenem | 21 (19.8) | 5 (4.2) | 5.63 (2.04 – 15.54) |
| ≥ 7 days of meropenem | 15 (14.2) | 4 (3.4) | 4.74 (1.52 – 14.77) |
| ≥ 7 days of other antipseudomonal antibiotics | 37 (34.9) | 18 (15.1) | 3.01 (1.59 – 5.71) |

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484. Metallo-β-Lactamase-Positive Carbapenem-Resistant Enterobacteriaceae and Pseudomonas aeruginosa in the Antibiotic Resistance Laboratory Network, 2017–2018
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Background. Infections with metallo-β-lactamase (MBL)-producing organisms are emerging in the United States. Treatment options for these infections are limited. We describe MBL genes among carbapenemase positive carbapenem-resistant Enterobacteriaceae (CP-CRE) and *Pseudomonas aeruginosa* (CP-CRPA) isolates tested during the first two years of the Antibiotic Resistance Laboratory Network (AR Lab Network).

Methods. State and local public health laboratories tested CRE and CRPA isolates for organism identification, antimicrobial susceptibility, and PCR-based detection of *bla*_{KPC}, *bla*_{NDM}, *bla*_{OXA-48-like}, *bla*_{VIM}, and *bla*_{IMP} carbapenemase genes. All testing results were sent to CDC at least monthly.

Results. Since January 2017, the AR Lab Network tested 21,733 CRE and 14,141 CRPA. CP-CRE were detected in 37% of CRE; 2% of CRPA were CP-CRPA. Among CP-CRE, 9% (686/8016) were MBL-producers (NDM, VIM, or IMP). Among MBL-producers, a *bla*_{NDM} gene was detected most often (81%; 551/686). *bla*_{NDM} were most common among *Klebsiella* spp. (47%; 261/551), *bla*_{IMP} were most common among *Providencia* spp. (53%; 40/75), *bla*_{VIM} was most common among *Enterobacter* spp. (19%; 25/62). Twelve percent (96) of MBL CP-CRE contained more than one carbapenemase gene. Among CP-CRPA, 73% (218/300) were MBL producers and *bla*_{VIM} was the most common gene (62%; 186). Three (1%) MBL CP-CRPA contained more than one carbapenemase.

Conclusion. Increased testing of CRE and CRPA isolates through the AR Lab Network has facilitated early and rapid detection of hard-to-treat infections caused by MBL-producing organisms across the United States. The widespread distribution of MBL genes highlights the continued need for containment strategies that help prevent transmission between patients and among healthcare facilities. To support therapeutic decisions for severe infections caused by MBL-producing organisms, the AR Lab Network is now offering rapid susceptibility testing against aztreonam/avibactam, using digital dispenser technology. This testing program aims to close the gap between the availability of new drugs or drug combinations and the availability of commercial AST methods, thereby improving patient safety and antimicrobial stewardship.



Antimicrobial susceptibility testing for Enterobacteriaceae producing a metallo-beta-lactamase (MBL)

Clinicians, hospital laboratories, and public health labs can request expanded antimicrobial susceptibility testing (EAST) from CDC's Antibiotic Resistance Lab Network (AR Lab Network) to find new, effective treatment options for their patients' most resistant infections.

- Enterobacteriaceae are resistant to new drugs for carbapenem-resistant Enterobacteriaceae (CRE) treatment, specifically ceftazidime-avibactam and meropenem-vaborbactam. However, these bacteria may be susceptible to the combination therapy ceftazidime + avibactam + aztreonam*.
- Susceptibility testing is CLIA-compliant and results will be reported for ceftazidime + avibactam, aztreonam, and aztreonam + avibactam to help assess utility of combination therapy.
- CDC plans to expand testing as new antimicrobial treatment options become available for other hard-to-treat bacterial infections.
- There is no cost for this service.

*Ceftazidime + avibactam + aztreonam is a combination of drugs recommended by the 2015 Sanford Guide for treatment of various infections caused by MBL-producing Enterobacteriaceae.

- 1 What isolates can I submit?
Hospital laboratories and clinicians are encouraged to submit Enterobacteriaceae isolates that:
• Test non-susceptible to all beta-lactams, including other ceftazidime-avibactam or meropenem-vaborbactam. These isolates may be MBL-producing isolates with few effective treatment options.
-OR-
• Enterobacteriaceae with NDM, VIM, or IMP genes confirmed by a molecular test and are highly resistant to all or the majority of antimicrobials already tested.

- 2 What is the testing process?
• AST turn-around time is 3 business days (once isolate received) for therapy decisions.
• Isolates will be tested to confirm carbapenem resistance, carbapenemase production, and to identify carbapenemase gene-coded resistance.
• Isolates that meet the inclusion criteria will be tested for susceptibility to ceftazidime + avibactam, aztreonam and avibactam + aztreonam.

- 3 How do I request the test and receive results?
• Healthcare providers, hospital laboratories, and public health labs should email their regional lab to request testing and instructions for submitting the bacterial isolate.
• Provide preliminary lab testing results and confirm that the facility's infection control department has been notified and/or infectious disease physician has been consulted.
• See regional lab map and contact information on the right.

AS PART OF THE AR LAB NETWORK, YOUR STATE & REGIONAL LAB WORK TO:
DETECT RESISTANT SPECIES & NEW THREATS | PERFORM SUSCEPTIBILITY TESTING TO TRACK RESISTANCE | HELP RESPOND TO OUTBREAKS

www.cdc.gov/DrugResistance/Solutions-Initiative/AR-Lab-Network

485. Clinical and Molecular Epidemiology of Carbapenem Non-susceptible *Citrobacter* sp.

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Background. Carbapenem non-susceptible *Citrobacter* sp. (CNSC) are becoming increasingly recognized as healthcare-associated (HA) pathogens, but data on clinical and molecular epidemiology, species diversity and mechanisms of carbapenem resistance are lacking.

Methods. We reviewed patients at University of Pittsburgh Medical Center with CNSC positive cultures from 2000 to 2018. The diversity of CNSC species among a subset of isolates from all UPMC sites was confirmed by 16S rRNA typing, and the presence of carbapenemase enzymes in the same isolates was determined by PCR amplification. Minimum inhibitory concentrations (MICs) were determined by broth microdilution. Significance of epidemiological trends over time was determined by linear regression, and correlation with antibiotic consumption was determined by cross-correlation using STATA v15.

Results. Between 2000 and 2018, 3% (78/2817) of all *Citrobacter* sp. were CNS. CNSC rates increased from 4% in 2000 to 10% in 2018 ($R^2 = 0.206$, $P = 0.05$), as did carbapenem consumption (6.5–34.5 DDDs/1000, $R^2 = 0.831$, $P < 0.001$) (Figure 1). Twenty-one isolates from 19 patients were available for additional analysis. Patients had multiple comorbidities (84%), frequently acquired CNSC in the healthcare setting (84%), were colonized with other organisms (68%), and had high rates of in-hospital mortality/discharge to hospice (47%) (Table 1). *C. freundii* was the dominant species identified (16/21), followed by *C. farmeri* (2/21), *C. koseri* (2/21), and *C. werkmanii* (1/21). Carbapenemases were identified in 14 isolates, including KPC ($n = 12$), NDM ($n = 2$), and OXA-48 ($n = 1$) (Table 2). Isolates were frequently susceptible to ceftazidime-avibactam (MIC median [IQR]: 2[0.5,8] 81%) and meropenem-vaborbactam (86%) (MIC median [IQR] 0.12[0.3,0.5]) (Table 2).

Conclusion. CNSC species are diverse, have emerged as an HA pathogen at our center, and cause high rates of mortality. Further studies, including ongoing genome sequencing and analysis, are required to better elucidate CNSC diversity and resistance mechanisms.

Figure 1: Rates of CNSC and Carbapenem Consumption from 2000-2018.

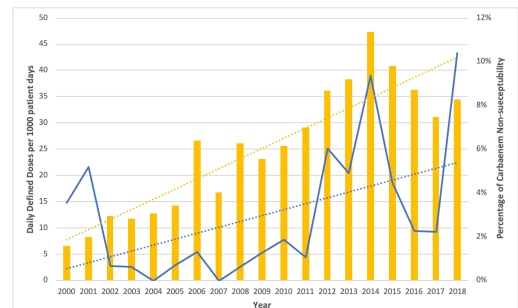


Figure 1 Legend: Carbapenem consumption (daily defined doses) and carbapenem non-susceptibility (non-susceptible isolates/total isolates tested) between 2000-2018. Trends evaluated by linear regression.

Table 1: Clinical characteristics of patients with CNSC.

| Isolate ID | Age | Gender | Major Comorbid Condition | Year | Source | Organism | Culture site | Clinical Infection | Polymicrobial culture (%) | Other orgs | Outcome of hospitalization |
|------------|-----|--------|--|------|-----------|---------------------|----------------------------|--------------------|---------------------------|---|----------------------------|
| RS-102 | 74 | F | ESLD, liver transplant | 2018 | HA | <i>C. freundii</i> | Rectal swab | Colonization | N | N/A | In-hospital death |
| RS-189 | 66 | F | Divericulosis | 2017 | HA | <i>C. freundii</i> | BAL | Pneumonia | N | N/A | Discharge to facility |
| RS226 | 76 | F | Cytoplast dysentery, CMV, HTN | 2018 | HA | <i>C. freundii</i> | Urine | Colonization | Y | <i>E. coli</i> | In-hospital death |
| RS236 | 70 | M | Pancreatic cancer, COPD, DM, HTN | 2018 | HA | <i>C. freundii</i> | Peritoneal fluid | Intra-Abdominal | Y | <i>C. freundii</i> (ESBL), <i>B. cereus</i> (VRE), <i>C. parvulus</i> | Transfer to hospice |
| RS237 | 80 | F | Sinus OM | 2018 | Community | <i>C. freundii</i> | Urine | Colonization | N | N/A | Discharge to home |
| RS240 | 29 | F | Nephrolithiasis obstructive uropathy | 2017 | Community | <i>C. freundii</i> | Urine | Colonization | Y | <i>S. maltophilia</i> , <i>S. pneumoniae</i> , <i>E. faecalis</i> | Discharge to home |
| RS259 | 61 | F | Metastatic lung cancer, COPD, DM | 2018 | HA | <i>C. freundii</i> | Peritoneal fluid | Intra-Abdominal | Y | <i>E. coli</i> , <i>P. aeruginosa</i> , <i>E. cloacae</i> | In-hospital death |
| RS289 | 92 | M | Bladder cancer, dementia, CAD | 2018 | Community | <i>C. koseri</i> | Urine | UTI | Y | <i>E. faecalis</i> | Discharge to home |
| RS77 | 49 | M | ESLD, Crohn's disease, PSC, liver transplant | 2018 | HA | <i>C. freundii</i> | Rectal swab | Colonization | N | N/A | Discharge to home |
| YOC62 | 54 | M | ESLD, HCC | 2012 | HA | <i>C. freundii</i> | Abdominal drain | Intra-Abdominal | Y | <i>E. aerogenes</i> | In-hospital death |
| YOC68 | 57 | M | HLD | 2013 | HA | <i>C. freundii</i> | BAL | Colonization | N | N/A | Transfer to hospice |
| YOC69-2 | 27 | M | ESLD, Crohn's disease, PSC, liver transplant | 2013 | HA | <i>C. freundii</i> | Biliary drainage | Intra-Abdominal | Y | <i>E. faecium</i> (VRE) | Discharge to home |
| YOC65 | 47 | F | CAD, CHF, DM, ESRD, Ascites | 2013 | HA | <i>C. freundii</i> | Blood | SSTI | Y | <i>Bacteroides</i> , <i>Endocarditis</i> , <i>Pseudomonas</i> | Transfer to hospice |
| YOC61 | 64 | M | Heart transplant | 2014 | HA | <i>C. freundii</i> | BAL | Pneumonia | Y | <i>S. maltophilia</i> | Discharge to facility |
| YOC67-4 | 73 | M | CHF, DM, CAD, CKD | 2014 | HA | <i>C. freundii</i> | BAL | Pneumonia | Y | <i>K. pneumoniae</i> (ESBL) | In-hospital death |
| YOC69-2 | 61 | M | ESLD, liver transplant | 2015 | HA | <i>C. koseri</i> | BAL | Pneumonia | N | N/A | Discharge to hospice |
| YOC69-1 | 65 | M | SBT, adrenal insufficiency | 2015 | HA | <i>C. freundii</i> | BAL | Pneumonia | Y | <i>ESBL-E. coli</i> | In-hospital death |
| YOC69-2* | 65 | M | SBT, adrenal insufficiency | 2015 | HA | <i>C. freundii</i> | BAL | Pneumonia | Y | <i>ESBL-E. coli</i> | In-hospital death |
| YOC69-2* | 65 | M | SBT, adrenal insufficiency | 2015 | HA | <i>C. freundii</i> | Tracheostomy site drainage | Intra-Abdominal | Y | <i>K. oxytoca</i> (KPC) | In-hospital death |
| YOC70 | 71 | M | Multiple myeloma | 2015 | HA | <i>C. werkmanii</i> | Urine | UTI | Y | <i>E. faecium</i> (VRE) | Discharge home |
| YOC69-1 | 26 | F | COVID | 2018 | HA | <i>C. freundii</i> | Urine | UTI | Y | <i>C. freundii</i> (NDM) | In-hospital death |

Abbreviations: BAL: Bronchoalveolar lavage; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; COPD: chronic pulmonary disease; COVID: common variable immunodeficiency; ESBL: Extended spectrum β-lactamase; ESLD: end stage liver disease; ESRD: end stage renal disease; DM: diabetes mellitus; F: female; HAP: hospital acquired pneumonia; HCC: hepatocellular carcinoma; HTN: hypertension; KPC: Klebsiella pneumoniae carbapenemase; OM: otitis media; N/A: Not available; NDM: New Delhi metallo-beta-lactamase; PSC: primary sclerosing cholangitis; SBT: small bowel transplant; SSTI: skin and soft tissue infection; VRE: Vancomycin-resistant Enterococcus; UTI: urinary tract infection

*Same patient

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