

# Predicting carbapenem resistance among gram-negative pathogens in complicated urinary tract infections

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## ABSTRACT

**Introduction:** Rising antimicrobial resistance increases the risk of exposure to inappropriate empiric treatment. Carbapenem resistance (CR) is a concern in complicated urinary tract infections (cUTI). To facilitate improved empiric antimicrobial targeting in cUTI, we developed a bedside instrument to predict CR.

**Methods:** We developed a predictive model using a 60/40 split cohort approach within the Premier Research database (2009-2016) of 178 US hospitals. We included all hospitalized adult patients with a gram-negative organism in at least one urine culture, who fit our algorithm for cUTI, and were treated with an antibiotic starting on the day of the index culture and continued for >3 days. CR was defined as any organism with an I or R in the susceptibility category to imipenem, meropenem, ertapenem, or doripenem.

**Results:** Among 25,285 patients with cUTI, 1,357 (5.4%) were CR. The median (IQR) hospital rate of CR was 4.0% (1.6%, 6.6%). Patients with CR were more likely male (63.0% vs. 44.0%, p<0.001), black (18.1% vs. 15.0%, p=0.11), and transferred from an extended care facility (ECF) (13.2% vs. 7.6%, p<0.001) than those with carbapenem-susceptible [CS] organisms. Patients with CR also had higher comorbidity burden than CS (median [IQR] Charlson Comorbidity Index 3 [2, 4] vs. 2 [1, 3], p<0.001). Overall E. coli was the most frequent cUTI organism. Among CR pathogens P. aeruginosa predominated (54.5%), with E. coli accounting for 11.5% of all CR infections. Patients with CR were more likely than CS to have previously received antibiotics (50.3% vs. 26.1%, p<0.001), and grown a CR organism (11.8% vs. 0.9%, p<0.001). In a model assigning weighted points for: admission from ECF (1), history of weight loss (1), early mechanical ventilation (1), age<50 (2), male gender (3), catheter-associated UTI (4), prior antibiotics treatment (4) and prior CR (8), the model exhibited good discrimination (c-statistic 0.721), performing better among hospitals with low rates of CR.

**Conclusions:** In this large US cohort of cUTI hospitalizations, CR occurred in ~5% of all cases. A model including eight easily available factors was able to predict the risk of CR at the onset of infection with good discrimination.

## BACKGROUND

- In the US, urinary tract infection (UTI) hospitalizations rose by 50% over the 2000s
  - Over 3 million UTI admissions in 2009<sup>1</sup>
- Pathogens<sup>2</sup>
  - Enterobacteriaceae - common
  - P. aeruginosa - common
  - A. baumannii - rare, but often resistant to carbapenems
- Carbapenem resistance (CR) has grown rapidly
  - Over 3% of Enterobacteriaceae carbapenem non-susceptible<sup>2-4</sup>
  - CR among PA and AB substantially higher<sup>1</sup>
  - Resistance associated with inappropriate empiric therapy (IET)<sup>5-6</sup>
  - IET associated with worsened outcomes

## STUDY AIM

- To develop and validate a predictive score to be used at the bedside to identify hospitalized patients with complicated UTI (cUTI) who are at risk for a CR pathogen

## METHODS

**Design:** multi-center retrospective cohort

**Data source:** Premier Research database, years 2009-2016

- 178 US institutions that submit microbiology data

**Population:** hospitalized patients with cUTI

**Inclusion criteria:**

- Adults (age ≥ 18 years)
- Urine culture at any time during hospitalization
- Antibiotic treatment on the day index culture is drawn and continued for ≥3 consecutive days
- Meets the definition of cUTI (algorithm available upon request)

**Exclusion criteria:**

- Age < 18
- Hospital length of stay (LOS) < 2 days
- Patients fits the definition for complicated intra-abdominal infection (algorithm available upon request)
- Patient transferred from another acute care facility
- cUTI episode is a repeat bout during the index hospitalization (as evidenced by a ≥3-day hiatus in antimicrobial regimen administration and a new positive culture)

**Microbiology and antimicrobial treatment variables and definitions**

- Included if had at least one urine or blood organisms below:

- Pseudomonas aeruginosa
- Acinetobacter baumannii
- Stenotrophomonas maltophilia (assumed always to be CR)
- Enterobacteriaceae
  - Escherichia coli
  - Klebsiella pneumoniae
  - Klebsiella oxytoca
  - Enterobacter cloacae

Enterobacter aerogenes  
Proteus mirabilis  
Proteus spp.  
Serratia marcescens  
Citrobacter freundii  
Morganella morganii  
Providencia spp.

- First detection of a CR organism served as the index culture
  - If no CR organism, then first culture growing out one of the organisms of interest served as the index culture

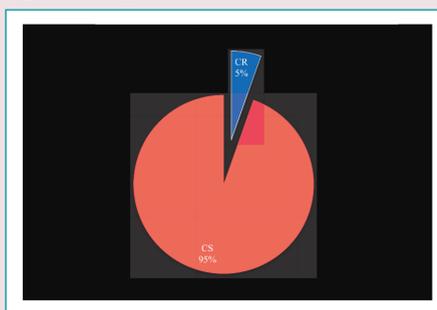
**Primary outcome:** CR

- Modeling
  - Split cohort method
    - 60% training
    - 40% validation
  - Limited to ≤10 predictors
  - Score weighted to each predictor's regression coefficient
  - Predictors: baseline factors, hospital characteristics, processes prior to infection onset

## RESULTS

- N=25,285 cUTI patients
  - 92% community-onset
  - 5% CR (Figure 1)
  - Median (IQR) hospital rate of CR: 4.0% (1.6%, 6.6%)

**Figure 1** CR prevalence in cUTI



CR = carbapenem-resistant; CS = carbapenem-susceptible

- Patient with CR older and with higher comorbidity burden than CS (Table 1)

**TABLE 1** Age and chronic disease burden

	CR	CS	P-value
Mean age	64.1 (17.9)	64.0 (18.7)	0.86
Mean Charlson	2.9 (2.2)	2.3 (2.2)	<0.001

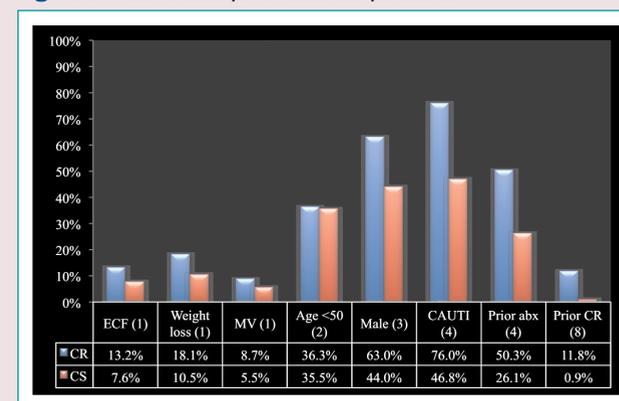
CR = carbapenem-resistant; CS = carbapenem-susceptible

- CR also more likely than CS among
  - Male (63.0% vs. 44.0%, p<0.001)
  - Black (18.1% vs. 15.0%, p=0.11)
  - Those transferred from an extended care facility (ECF) (13.2% vs. 7.6%, p<0.001)
- Higher prevalence of catheter-associated UTI (CAUTI) among CR than CS (76.0% vs. 46.8%, p<0.001)
- CR more likely than CS to have
  - Received antibiotics (50.3% vs. 26.1%, p<0.001) within 90 days prior to the index infection, and
  - Grown a CR organism (11.8% vs. 0.9%, p<0.001) within 90 days prior to the index infection
  - Require mechanical ventilation (8.0% vs. 5.1%, p<0.001) or dialysis (2.3% vs. 1.5%, p=0.025) during their hospitalization

**Model to predict the likelihood of CR in cUTI**

- Assigned weighted points proportional to the regression coefficients of the following factors (Figure 2)

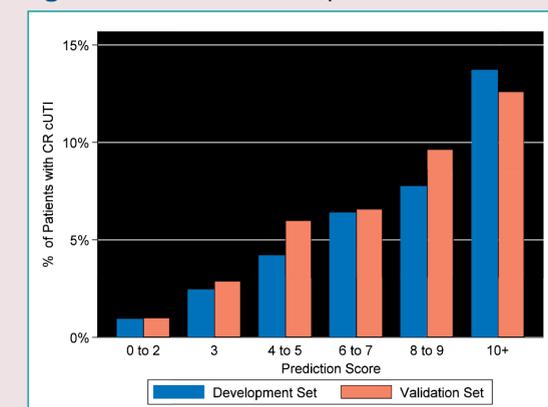
**Figure 2** Model factors' point values and prevalence



CR = carbapenem-resistant; CS = carbapenem-susceptible, ECF = extended care facility; MV = mechanical ventilation; CAUTI = catheter-associated UTI; abx = antibiotics

- Admission from ECF (1)
- History of weight loss (1)
- Mechanical ventilation within two days of infection onset (1)
- Age<50 (2), male gender (3)
- Catheter-associated UTI (4)
- Prior antibiotics treatment (4)
- Prior CR (8)
- Model exhibited good discrimination in both the training (c-statistic 0.746) and validation (c-statistic 0.721) sets
- Model performed better among hospitals with lower prevalence of CR (Figure 3)
  - Tertile 1 - 0.752 [CR prevalence 2.1%]
  - Tertile 2 - 0.725 [CR prevalence 4.7%]
  - Tertile 3 - 0.703 [CR prevalence 9.2%]
  - NPV 99% for score <3

**Figure 3** Prediction score for carbapenem resistance in cUTI



CR = carbapenem-resistant; cUTI = complicated UTI

## STRENGTHS AND LIMITATIONS

- Large multicenter cohort representative of US institutions
- Broadly generalizable
- Selection bias
  - Dealt with it by setting a priori enrollment criteria and definitions for exposures and outcomes
- Misclassification
  - Our cUTI algorithm designed to maximize specificity
  - Outcome of interest minimally susceptible to misclassification
- Confounding
  - Attempted to eliminate through regression analyses using a large number of potentially confounding variables
  - Possibility of residual confounding remains

## CONCLUSIONS

- CR is prevalent in 5% of hospitalized patients with cUTI
- Our simple bedside score was able to identify cUTI patients at low risk for CR
- Using our score may help reduce overuse of broad-spectrum antibiotics in patients with cUTI

## REFERENCES

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