

# Predictors of empiric carbapenem therapy in complicated intra-abdominal infections in the US, 2013–2017: a retrospective cohort study

Marya Zilberberg, MD, MPH,<sup>1</sup> Brian Nathanson, PhD,<sup>2</sup> Kenneth Lawrence, PharmD,<sup>3</sup> Colby Johnson,<sup>1,4</sup> Kristen Ditch, PharmD,<sup>3</sup> Melanie Olesky, PhD,<sup>3</sup> Andrew Shorr, MD, MPH, MBA<sup>5</sup>

<sup>1</sup>EviMed Research Group, LLC, Goshen, MA; <sup>2</sup>OptiStatim, LLC, Longmeadow, MA; <sup>3</sup>Tetraphase Pharmaceuticals, Watertown, MA; <sup>4</sup>Massachusetts College of Pharmacy and Health Sciences, Boston, MA; <sup>5</sup>Washington Hospital Center, Washington, DC

## ABSTRACT

**Background:** Complicated intra-abdominal infections (cIAI) remain an important cause for hospitalization. Evidence-based guidelines recommend reserving broad-spectrum antibiotic coverage for high-risk cases in order to reduce overuse of certain antibiotic classes, particularly in the face of emerging carbapenem resistance. We examined the factors associated with use of empiric carbapenem treatment (ECT) among hospitalized patients with cIAI.

**Methods:** We performed a multicenter retrospective cohort study in the Premier database of approximately 180 hospitals, 2013–2017. Using an ICD-9/10 based algorithm, including a requirement for a laparotomy/laparoscopy, we identified all adult patients hospitalized with cIAI and included those with a positive blood or abdominal culture. We derived and tested a multivariable logistic regression model to examine predictors of ECT.

**Results:** Among 321,317 hospitalized patients with cIAI, 4,453 (1.4%) were culture-positive, 1,185 (26.6%) of whom received ECT. Among those given ECT, >50% (682) had no risk factors for resistance, and in only 120 (10.1%) was an organism resistant to a 3rd generation cephalosporin (C3R extended spectrum beta-lactamase [ESBL] phenotype) isolated. The top 5 variables associated with ECT use were: pre-cIAI anti-fungal therapy (OR 2.57, 95% CI 1.91, 3.45), urgent (vs. emergent) admission (OR 1.56, 95% CI 1.21, 2.01), corticosteroids (OR 1.50, 95% CI 1.13, 1.99), ICU admission (OR 1.46, 95% CI 1.17, 1.82), and presence of sepsis/septic shock (OR 1.43, 95% CI 1.18, 1.74). The model had a moderately good fit (c-statistic = 0.683; 95% CI (0.665, 0.700), Hosmer-Lemeshow p value = 0.411).

**Conclusions:** Among patients hospitalized with a cIAI, 26.6% received ECT despite >50% lacking risk factors for resistance, and an only 10% prevalence of C3R in this cohort. This suggests that there remains an opportunity for carbapenem-sparing strategies. Further stratification of the risk for resistance is needed among patients with markers of high illness severity, such as those identified in our model.

## INTRODUCTION

- Complicated intra-abdominal infections (cIAI) remain an important cause for hospitalization in the US
- Because antimicrobial resistance is on the rise, carbapenems are often recommended as broad-spectrum empiric treatment in high-risk cIAI patients
- Broad use of carbapenems is leading to subsequent loss of *in vitro* activity

## STUDY AIMS

- To explore factors associated with the use of carbapenems as empiric treatment in hospitalized cIAI patients

## Study population

- Adults 18 years or older
- Hospitalized for 2+ days
- Diagnosis of cIAI by ICD-9/10 algorithm [1]
- Positive abdominal and/or blood culture from within 48 hours after laparotomy/laparoscopy
- Antibiotic treatment on the day of surgery or index culture
  - Continued for ≥3 consecutive days

## Data source

- Premier database, 2013–2017 [2]

## Baseline measures

- Standard baseline demographic and clinical measures, as well as hospital characteristics
- cIAI classified as community-onset (CO) if present on admission or if the index culture was obtained within the first 2 hospital days
  - CO cIAI was further classified as
    - healthcare-associated (HCA) if one or more risk factors were present:
      - Prior hospitalization with 90 days of the index hospitalization
      - Hemodialysis
      - Admission from a long-term care facility
      - Immune suppression

## METHODS

- All other CO infections were defined as community-acquired (CA)
- All cIAI occurring on or after hospital day 3 were considered hospital-onset (HO)

## Organisms of interest

- Gram-negatives
  - Pseudomonas aeruginosa*
  - Acinetobacter baumannii*
  - Stenotrophomonas maltophilia*
  - Enterobacteriaceae

## Other

- Enterococcus spp*
- Staphylococcus aureus* (including methicillin resistant, MRSA)
- Bacteroides fragilis*
- Candida spp*
- Polymicrobial infection noted if present

## Outcomes

- Empiric carbapenem treatment (ECT) was the primary outcome

## Statistical analyses

- Standard descriptives to compare ECT and non-ECT groups across all demographics, comorbidities, and hospital characteristics
- Derived and tested a multivariable logistic regression model to examine predictors of ECT
  - Model fit tested with
    - C-statistic (model discrimination)
    - Hosmer Lemeshow goodness of fit test (model calibration)

## RESULTS

- Microbiology and baseline infection characteristics are in Table 2
- Compared to those on non-ECT, patients receiving ECT were more likely to have
  - Hospital-onset cIAI
  - Antibiotics within 90 days prior to admission
  - Carbapenem resistant organism within 90 days prior to admission
  - Third generation cephalosporin-resistant organism within 90 days prior to admission

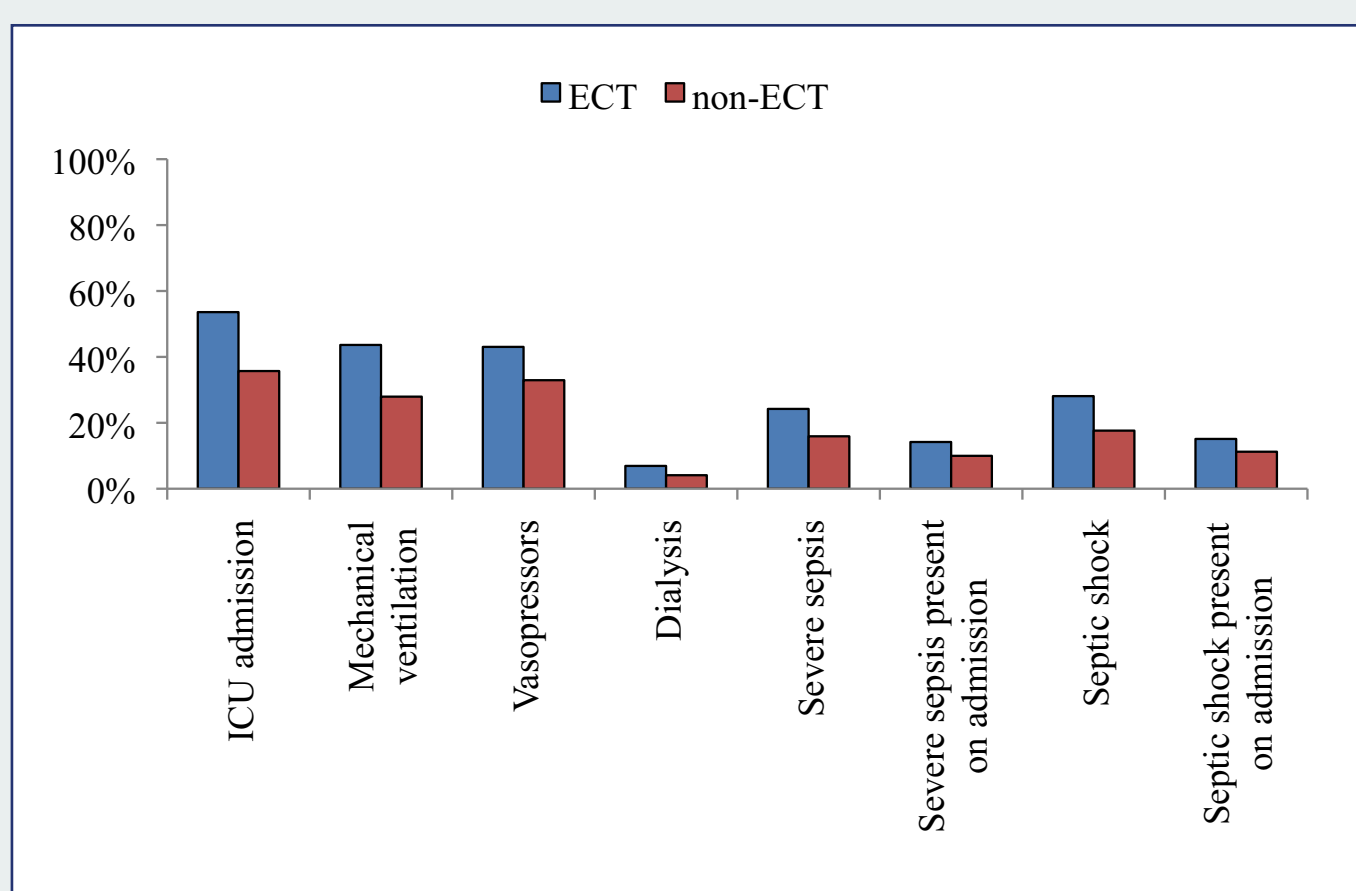
**TABLE 2** Infection-related characteristics at cIAI onset among patients with > 1 gram-negative organism

	ECT		Non-ECT		P-value
	N = 1185	%	N = 3268	%	
Community-onset cIAI	1028	86.75%	2976	91.06%	<0.001
Community-acquired	682	57.55%	2116	64.75%	
Healthcare-associated	346	29.20%	860	26.32%	
Hospital-onset cIAI	157	13.25%	292	8.94%	
Time to cIAI					
Mean (SD)	5.5 (11.8)		3.2 (5.2)		<0.001
Median [IQR]	2 [1, 6]		2 [1, 3]		<0.001
Antibiotics within 90 days prior to admission	199	16.79%	414	12.67%	<0.001
Antibiotics during index hospitalization prior to cIAI onset	672	56.71%	1738	53.18%	0.037
CR organism within 90 days prior to admission	3	0.25%	4	0.12%	0.392
C3R organism within 90 days prior to admission	11	0.93%	12	0.37%	0.032

ECT = empiric carbapenem treatment; cIAI = complicated intra-abdominal infection; CR = carbapenem resistant; C3R = resistant to 3rd generation cephalosporin; SD = standard deviation; IQR = interquartile range

- All illness severity measures were higher in ECT than non-ECT group (Figure 3)

**Figure 3** Illness severity measures at cIAI onset\*

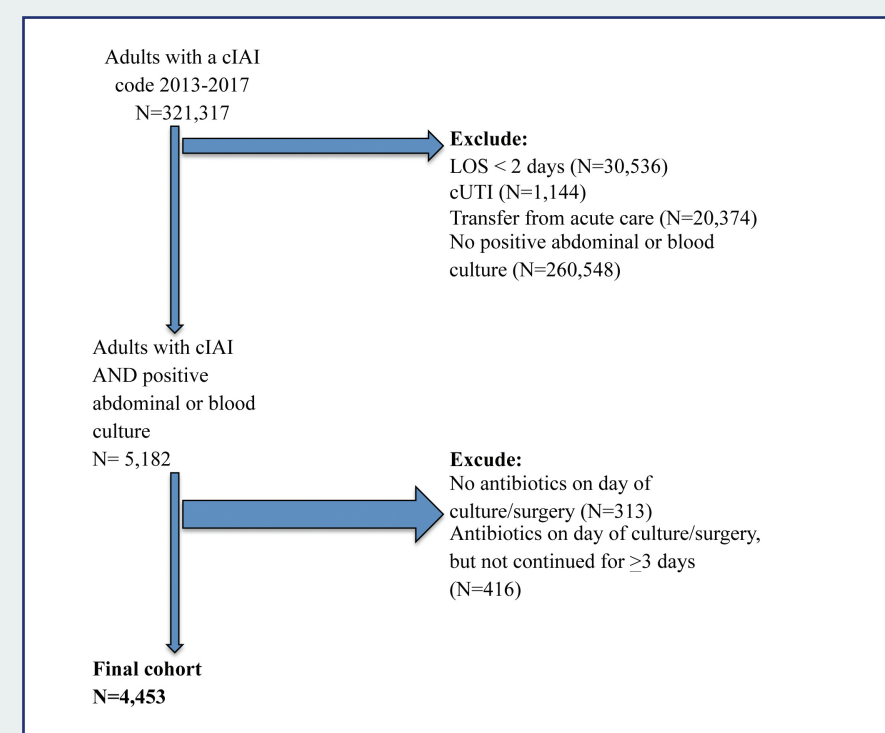


ECT = empiric carbapenem treatment; ICU = intensive care unit

\*All p values <0.001

- Among 321,317 hospitalized patients with cIAI, 4,453 (1.4%) were culture-positive (Figure 1)
- 1,185 (26.6%) received ECT

**Figure 1** Study enrollment



cIAI = complicated intra-abdominal infection; LOS = length of stay; cUTI = complicated urinary tract infection

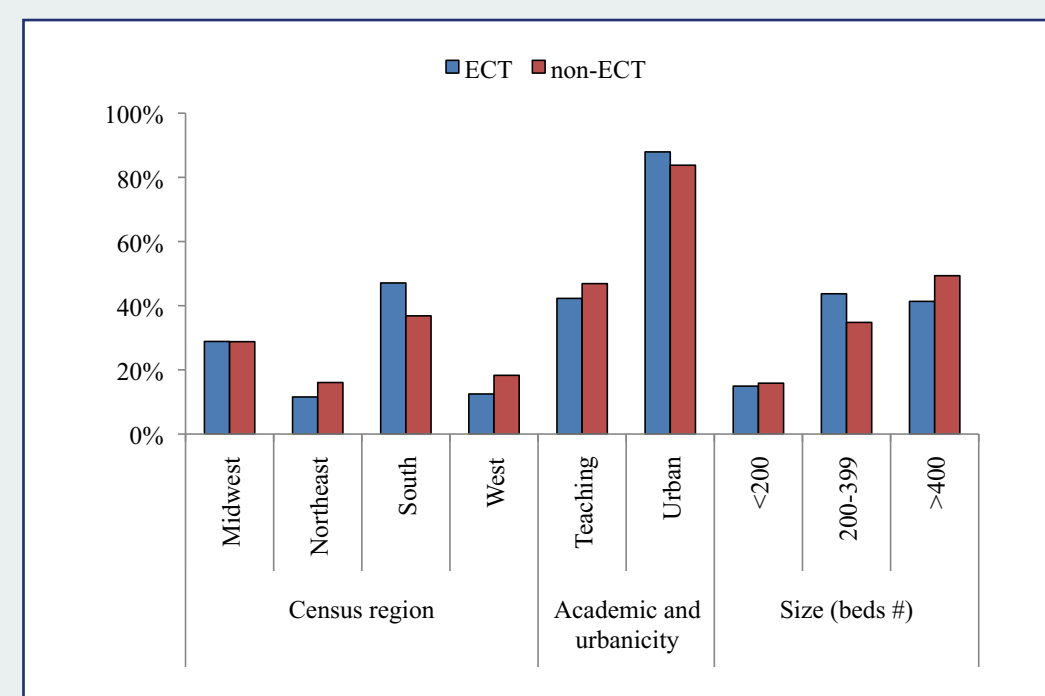
- Compared to those on non-ECT, patients receiving ECT were (Table 1)

- Less likely admitted from home
- Less likely emergent
- Shown to have a higher comorbidity burden

- As for hospital characteristics, patients receiving ECT were (Figure 2)

- Less likely to be in the Northeast & West and more likely in the South
- Less likely at teaching hospitals
- More likely at urban hospitals
- More likely in large (>400 beds) hospitals

**Figure 2** Hospital characteristics\*



ECT = empiric carbapenem treatment

\*All p values <0.001 except for academic status, whose p=0.006

**TABLE 1** Demographic, clinical, and hospital characteristics present at hospital admission among patients with > 1 gram-negative organism

	ECT		Non-ECT		P-value
	N = 1185 (26.61%)	%	N = 3268 (73.31%)	%	
Mean age, years (SD)	61.1 (17.0)		61.0 (17.0)		0.910
Gender: male	617	52.07%	1765	54.01%	0.251
Race					0.439
White	910	76.79%	2435	74.51%	
Black	114	9.62%	331	10.13%	
Hispanic/Other	150	12.66%	470	14.38%	
Unknown	11	0.93%	32	0.98%	
Admission Source					0.014
Home	978	82.53%	2810	85.99%	
Clinic	94	7.93%	247	7.56%	
Transfer from another non-acute healthcare facility	76	6.42%	150	4.59%	
Other	37	3.12%	59	1.80%	
Admission type					<0.001
Emergency	900	75.95%	2659	81.36%	
Urgent	120	10.13%	237	7.25%	
Elective	155	10.95%	358	10.95%	
Trauma	4	0.34%	9	0.28%	
Unknown	6	0.51%	5	0.15%	
Charlson comorbidity score					0.011
Mean (SD)	1.8 (2.2)		1.6 (2.1)		
Median [IQR]	1 [0, 3]		1 [0, 2]		0.006

ECT = empiric carbapenem treatment; SD = standard deviation; IQR = interquartile range

## STRENGTHS AND LIMITATIONS

- Large generalizable multi-hospital database
  - Since we examined only culture-positive cIAI, our results may not apply to those without a positive culture
- Observational study prone to selection bias
  - Mitigated magnitude by defining the cohort prospectively
- Misclassification, particularly when using administrative data
  - To minimize
    - Used a previously published algorithm
    - Excluded other potential sources of infection
    - Included microbiology specimens, pharmacy data, and dates of cultures and treatments

## CONCLUSIONS

- Among patients hospitalized with a cIAI, 26.6% received ECT despite
  - >50% lacking risk factors for resistance
  - 10% prevalence of C3R
- Further risk stratification for resistance among patients with markers of high illness severity, such as those identified in our model, could aid in developing more robust carbapenem-sparing strategies

## REFERENCES

- Edelsberg J, Berger A, Schell S, Mallick R, Kuznik A, Oster G. Economic consequences of failure of initial antibiotic therapy in hospitalized adults with complicated intra-abdominal infections. *Surgical Infections* 2008;9:335–47
- Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. *Infect Control Hosp Epidemiol* 2018;39:1112–4

Study supported by a grant from  
Tetraphase Pharmaceuticals,  
Watertown, MA, USA