1455

Epidemiology, empiric treatment, and outcomes among hospitalized patients with complicated urinary tract infections in the US, 2013–2018

Marya Zilberberg, MD, MPH,[1] Brian Nathanson, PhD,[2] Kate Sulham, MPH,[3] Andrew Shorr, MD, MPH, MBA[4]

[1]Evi*Med* Research Group, LLC, Goshen, MA; [2]OptiStatim, LLC, Longmeadow, MA; [3]Spero Therapeutics, Cambridge, MA; [4]Washington Hospital Center, Washington, DC

ABSTRACT

Background: Complicated urinary tract infection (cUTI) is common among hospitalized patients. Though carbapenems are an effective treatment in the face of rising resistance, overuse drives carbapenem resistance (CR). We hypothesized that resistance to routinely used antimicrobials is common, and, despite frequent use of carbapenems, associated with an increased risk of inappropriate empiric treatment (IET), which in turn worsens clinical outcomes.

Methods: We performed a multicenter retrospective cohort study in ~180 hospitals in the Premier database, 2013–2018. Using an ICD-9/10 based algorithm we identified all adult patients hospitalized with cUTI and a positive blood or urine culture (CR excluded). We examined with the impact of triple resistance (TR; resistance to ≥3 of the following drugs/classes: 3rd generation cephalosporin [C3R], fluoroquinolones, trimethoprim-sulfamethoxazole, fosfomycin, and nitrofurantoin), on the risk of receiving IET. We derived multivariate models to compute the impact of IET on hospital outcomes.

Results: Among 23,331 patients with cUTI (96.2% community-onset), 3,040 (13.0%) had a TR pathogen. Compared to those with non-TR, patients with TR were more likely male (57.6% vs. 47.7%), black (17.9% vs. 13.6%), and in the South (46.3% vs. 41.5%), p<0.001 each; had a higher median Charlson score (3 vs. 2), and were more likely to need early ICU (22.3% vs. 18.6%) and mechanical ventilation (7.0% vs. 5.0%), p<0.001 each. Patients with TR were hospitalized at centers with higher median prevalence of both C3R (16.3% vs. 14.4%) and TR (15.1% vs. 12.2%), p<0.001 each. IET was more frequent in TR than non-TR group (19.6% vs. 5.4%) despite greater empiric carbapenem use in TP (43.3% vs. 16.2%), p<0.001 each. Though IET did not have an impact on adjusted hospital mortality or 30-day readmission rate, it was associated with excess adjusted resource utilization ($1,364 in costs and 0.66 day in length of stay).

Conclusions: Among hospitalized patients with cUTI, TR is common, and is associated with a near 4-fold increase in exposure to IET, which in turn contributes to excess resource utilization. Given the high prevalence of TR, clinicians should consider a lower threshold for broader empiric treatment in appropriate patients.

INTRODUCTION

- Complicated urinary tract infections (cUTI) are a common cause and complication of hospitalization
- Rising prevalence of antimicrobial resistance (AMR) makes inappropriate empiric treatment (IET) and its attendant worsened outcomes more likely [1–5]
- Of particular concern are increasing rates of resistance to commonly used first-line agents in the treatment of cUTI, including 3rd-generation cephalosporins (C3), fluoroquinolones (FQ), and trimethoprim-sulfamethoxazole (TMP-SMX)
- For a clinician at the bedside, it is critical to understand AMR patterns to commonly utilized antimicrobials in cUTI in order to predict when a standard approach may fail and another empiric strategy is necessary

STUDY AIMS

- To estimate the prevalence of overlapping resistance to commonly utilized antibiotics in cUTI and its impact on the outcomes
- To examine the rate of IET as a function of compound resistance in cUTI, and of its impact on morbidity and mortality

METHODS

Design and data source

- Retrospective cohort study within Premier Research database [6]
- Years 2013 through 2018
- Data from a subset of ~180 US institutions who submitted microbiology data

Setting

- US acute care hospitals

Patients and Participants

Inclusion criteria

- Adults (age ≥ 18 years)
- Urine culture obtained at any time during hospitalization
- Received antibiotic treatment on the day of the index culture and continued for ≥3 consecutive days
- Met the definition for cUTI [6]

Exclusion criteria

- Age < 18
- Hospital length of stay (LOS) < 2 days
- Fit the definition for a complicated intra-abdominal infection [6]
- Transferred from another acute care facility
- An organism resistant to at least one carbapenem.

Infection and treatment characteristics

cUTI classification

- Community-onset (CO): present on admission (POA) or if index culture drawn within first 2 hospital days
  - CO cUTI further classified as
    - Healthcare-associated (HCA) if one or more of the following risk factors present:
      1. Hospitalization within prior 90 days
      2. Hemodialysis
      3. Admission from a long-term care facility
      4. Immune suppression
    - All other CO infections community-acquired (CA)
  - All cUTIs occurring on or after hospital day 3 considered hospital-onset (HO)

Empiric treatment

- Empiric antibiotic treatment considered appropriate if the patient received coverage that included the corresponding organism within two days of the culture being obtained
- All other coverage considered inappropriate empiric treatment (IET)

Organisms

- Enterobacteriaceae
- *P. aeruginosa*
- *A. baumannii*
- *E. faecium*
- *E. faecalis*

Antimicrobials and resistance definitions

- Agents commonly used to treat cUTI
  - 3rd generation cephalosporins
  - Fluoroquinolones
  - Trimethoprim-sulfamethoxazole
  - Fosfomycin
  - Nitrofurantoin
- Triple-drug resistance (TR) defined as resistance to at least three separate antimicrobials or classes of interest (i.e., resistance to at least one of the member drugs within the class)

Outcome variables

- Primary outcome
  - Hospital mortality served as the primary outcome, and
- Secondary outcomes
  - 30-day readmission
  - Hospital LOS
  - Hospital costs

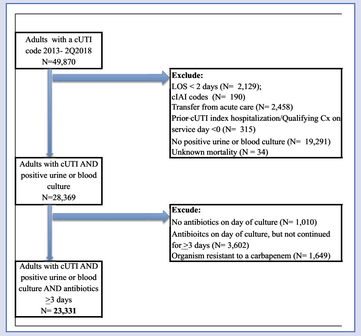
Statistical analyses

- Standard descriptive statistics to compare TR and non-TR groups across all demographics, comorbidities, infection characteristics, hospital characteristics and processes, and hospital outcomes
- Multivariable models to quantify the impact of TR and inappropriate empiric therapy (IET) on mortality, hospital LOS, and costs

RESULTS

- Study enrollment schema in Figure 1

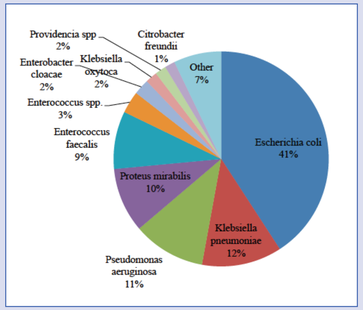
Figure 1 Study enrollment



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

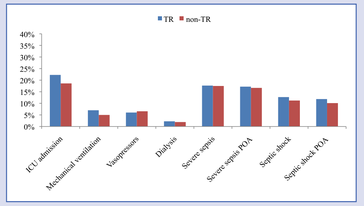
- Top 10 organisms among 23,331 patients with cUTI depicted in Figure 2

Figure 2 Organism distribution



- TR prevalence
  - Overall 13.0% (n=3,040)
    - *E. coli* 12.8% TR
    - *K. pneumoniae* 15.6% TR
    - *P. aeruginosa* 7.9% TR
- Patients with TR vs. non-TR more likely
  - Male (57.6% vs. 47.7%, p<0.001)
  - Black (17.9% vs. 13.6%, p<0.001)
  - In the South (46.3% vs. 41.5%, p<0.001)
  - Higher median [IQR] Charlson score (3 [2, 4] vs. 2 [1, 4], p<0.001)
  - Hospitalized at centers with higher median prevalence of
    - 3rd generation cephalosporin resistance (C3R, 16.3% [12.4%, 20.9%] vs. 14.4% [10.2%, 17.7%], p<0.001)
    - TR (15.1% [11.3%, 18.8%] vs. 12.2% [9.4%, 16.1%], p<0.001)
  - Higher severity of acute illness (Figure 3)

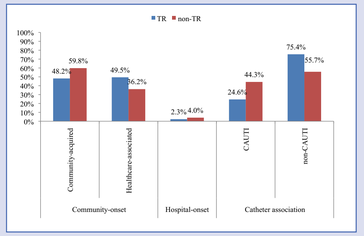
Figure 3 Measures of illness severity*



TR = triple resistant; POA = present on admission
*ICU admission and mechanical ventilation p < 0.001; septic shock POA = 0.003; septic shock p = 0.016; all other comparisons p ≥ 0.5

- UTI classification in Figure 4
  - Over 95% of all cUTI was CO
  - HCA infections more frequent among TR patients compared with non-TR patients
  - Catheter-associated cUTI (CAUTI) more prevalent in TR than in non-TR
- TR more likely than non-TR to receive IET (19.6% vs. 5.4%, p<0.001)

Figure 4 cUTI classification*



TR = triple resistant; CAUTI = catheter-associated UTI
*p < 0.001 for each comparison

Outcomes

- Unadjusted hospital mortality (2.6% vs. 2.0%, p=0.046) and 30-day readmission (19.7% vs. 15.4%, p<0.001) higher in TR than non-TR
  - Differences disappeared in adjusted analyses (Table 1)
- TR associated with increased adjusted costs and LOS (Table 1)

TABLE 1 Adjusted outcomes associated with triple resistance

Outcome	*Metric*	*Point estimate*	*95% confidence interval*	*P value*
Mortality	Odds ratio	1.03	(0.78, 1.35)	0.844
30-day readmission	Odds ratio	1.04	(0.94, 1.16)	0.429
Hospital cost	Excess $	$754	($406, $1103)	<0.001
Total LOS	Excess days	0.28 days	(0.12, 0.44)	<0.001
Post-infection onset LOS	Excess days	0.34 days	(0.18, 0.49)	<0.001

LOS = length of stay

- TR affected both LOS and costs differently among patients with CAUTI vs. those with cUTI that is not CAUTI
  - Mean marginal increase in costs attributable to TR
    - $125 (95% CI -$275, $525, p= 0.540) CAUTI
    - $1,637 (95% CI $1,045, $2,229, p<0.001) non-CAUTI cUTI
  - Mean marginal increase in post-infection onset LOS attributable to TR
    - 0.34 days (95% CI 0.18, 0.49, p<0.001) CAUTI
    - 0.62 days (95% CI 0.35, 0.88, p<0.001) non-CAUTI cUTI
- IET associated with increases in
  - Marginal hospital costs ($1,364; 95% CI $923, $1,805, p<0.001)
  - Post-infection onset LOS (0.73 days; 95% CI 0.52, 0.94, p<0.001)
- IET interacted with the type of cUTI in the mortality estimate
  - Mortality
    - Not increased in CAUTI
      - Unadjusted mortality: non-IET 2.52% vs. IET 2.04%
      - Adjusted OR=1.26 (95% CI 0.77, 2.04, p= 0.355)
    - Increased in non-CAUTI cUTI
      - Unadjusted mortality: non-IET 1.55% vs. IET 3.31%
      - Adjusted OR=2.44 (95% CI 1.30, 4.56, p = 0.005)

STRENGTHS AND LIMITATIONS

- Large generalizable multihospital database
- 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
- Confounding a potential problem in all observational studies
  - Minimized via statistical modeling
  - Likely that some residual confounding remains

CONCLUSIONS

- Resistance to combinations of frequently used antimicrobials in cUTI is prevalent across the US institutions
- TR is associated with an increased risk of receiving IET
- Both TR and IET are associated with worsening of some outcomes among subsets of hospitalized patients with cUTI, particularly among those whose cUTI is not catheter-associated

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