

## ABSTRACT (revised)

**Background:** In response to increasing rates of antimicrobial resistance, carbapenems have become first-line treatments for many infections. This, in turn, fosters the potential for resistance (CR). Efforts to mitigate the emergence of CR through carbapenem-sparing strategies must rest on a fundamental understanding of antibiotic resistance patterns among commonly encountered pathogens. Therefore, we examined the microbiology of complicated urinary tract infections (cUTI) in hospitalized patients in the US.

**Methods:** We performed a multicenter retrospective cohort study in the Premier database of approximately 180 hospitals, 2013–2018. Using an ICD-9/10 based algorithm we identified all adult patients hospitalized with cUTI and included those with a positive blood or urine culture. Patients with carbapenem resistant organisms were excluded. We examined the microbiology and susceptibilities to common cUTI antimicrobials (3<sup>rd</sup> generation cephalosporin [C3], fluoroquinolones [FQ], trimethoprim-sulfamethoxazole [TMP/SMX], fosfomycin [FFM], nitrofurantoin [NFT], and triple-resistant [TR]) over time.

**Results:** Among 28,057 organisms from 23,331 patients, the 3 most common pathogens were *E. coli* (EC, 41.0%), *K. pneumoniae* (KP, 12.1%), and *P. aeruginosa* (PA, 11.0%). Among these 3 organisms, resistance to C3 was 15.1% among EC, 13.2% KP, and 12.0% PA. EC was most frequently resistant to FQ (43.5%) and least to NFT (6.7%). KP was most frequently resistant to NFT (60.8%) and least to FFM (0.1%). PA was most frequently resistant to FQ (34.4%) and least to TMP/SMX (4.2%). The prevalence of TR among EC was 12.8%, among KP 15.6%, and among PA 7.9%. The prevalence of TR in 2013–2014 and 2017–2018, respectively was 11.7% and 17.3% among EC, 15.2% and 17.1% among KP, and 10.2% and 5.3% among PA.

**Conclusions:** Among the most common pathogens isolated in hospitalized patients with cUTI, and particularly in EC, substantial and increasing single resistance and TR rates to common antimicrobials were evident. Current empiric treatment strategies may be insufficient against the growing threat of TR.

## INTRODUCTION

- In the face of rising antimicrobial resistance, carbapenems have become a first-line therapy in multiple serious infections
- Of particular concern are increasing rates of resistance to commonly used first-line agents in the treatment of complicated urinary tract infections (cUTI), including 3<sup>rd</sup>-generation cephalosporins (C3), fluoroquinolones (FQ), and trimethoprim-sulfamethoxazole (TMP-SMX)
- The tension between the need to target appropriate empiric therapy and avoiding use of overly broad agents calls for understanding the microbiology of specific infectious syndromes
- We examined microbiology and susceptibilities to commonly used antimicrobial regimens among patients hospitalized with cUTI

## STUDY AIMS

- To understand the current microbiology of cUTI in the US acute care hospitals
- To estimate the prevalence of overlapping resistance to commonly utilized antibiotics in cUTI
- To examine temporal trends in overlapping resistance to commonly utilized antibiotics in cUTI

## Design and data source

- Retrospective cohort study within Premier Research database [1]
- 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 [1]

## Exclusion criteria

- Age < 18
- Hospital length of stay (LOS) < 2 days
- Fit the definition for a complicated intra-abdominal infection [1]
- Transferred from another acute care facility
- An organism resistant to at least one carbapenem.

## Organisms

- Enterobacteriaceae
- P. aeruginosa*

## METHODS

- A. baumannii*
- E. faecium*
- E. faecalis*

## Antimicrobials and resistance definitions

- Agents commonly used to treat cUTI
  - 3<sup>rd</sup> generation cephalosporins (C3)
  - Fluoroquinolones (FQ)
  - Trimethoprim-sulfamethoxazole (TMP/SMX)

- Fosfomycin (FFM)
- Nitrofurantoin (NFT)
- 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

- Prevalence of resistance to above antimicrobials among organisms of interest

- Changes in the prevalence of resistance to above antimicrobials among organisms of interest over the study time frame
  - Time periods 2013–2014, 2015–2016, 2017–2018

## Statistical analyses

- Prevalence estimates are given as percentages
- No formal hypothesis testing was undertaken

## 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

## CONCLUSIONS

- EC, KP, and PA remain top three pathogens in cUTI
- NFT, followed by FQ and TMP/SMX, exhibit some of the highest rates of resistance across most cUTI pathogens
- Although TR has fallen among some of the cUTI organisms, it is on the rise among EC and KP, the two most common pathogens comprising over 50% of all cUTI

## REFERENCES

- Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Infect Control Hosp Epidemiol 2018;39:1112–4

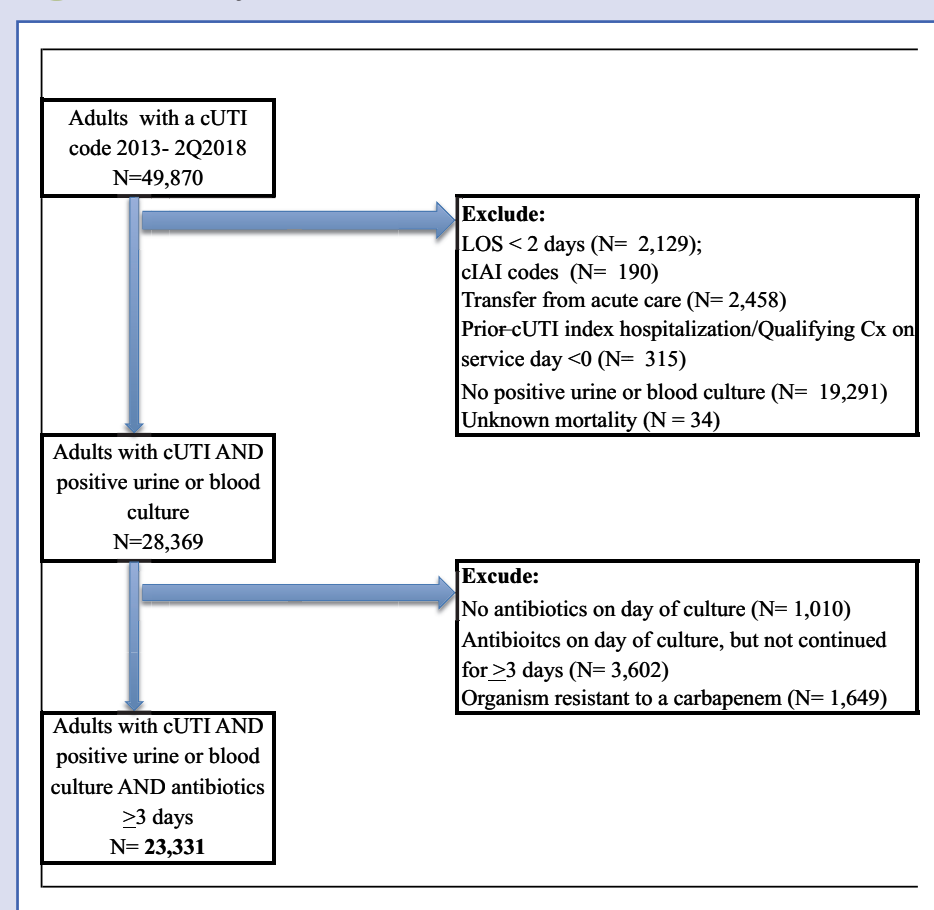
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## RESULTS

- Study enrollment schema in Figure 1

- Among 23,331 patients meeting enrollment criteria, 28,057 organisms of interest were isolated

Figure 1 Study enrollment



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

- The 3 most common pathogens were (Table 1):

- E. coli* (EC)
- K. pneumoniae* (KP)
- P. aeruginosa* (PA)
- Together they comprised nearly 2/3 of all isolates

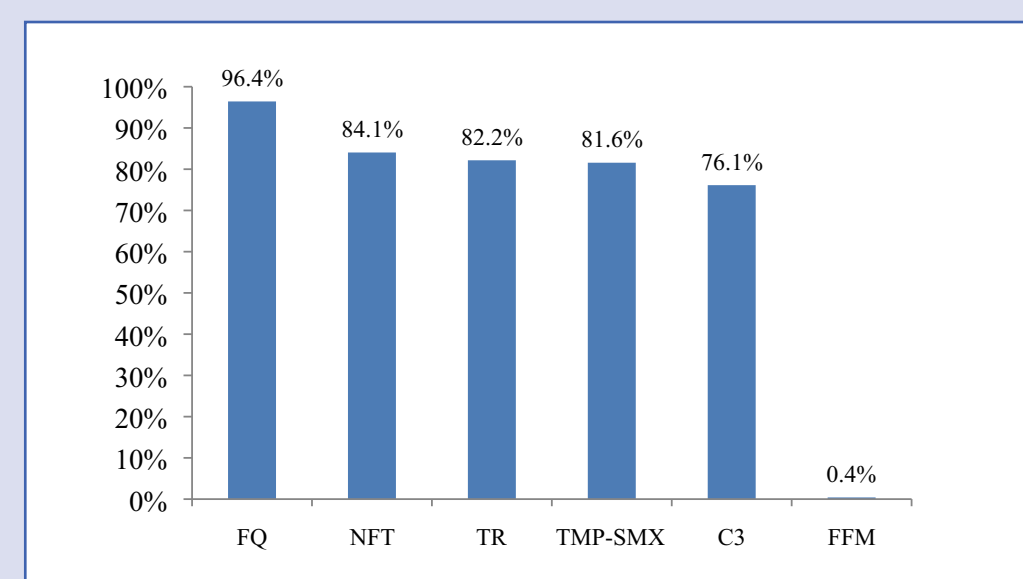
- The 10 most commonly isolated organisms accounted for over 90% of all cUTIs (Table 1)

TABLE 1 Organism distribution

Organism	N=28057	
	n	%
<i>Escherichia coli</i>	11510	41.02%
<i>Klebsiella pneumoniae</i>	3395	12.10%
<i>Pseudomonas aeruginosa</i>	3080	10.98%
<i>Proteus mirabilis</i>	2739	9.76%
<i>Enterococcus faecalis</i>	2446	8.72%
<i>Enterococcus spp</i>	936	3.34%
<i>Enterobacter cloacae</i>	665	2.37%
<i>Klebsiella oxytoca</i>	501	1.79%
<i>Providencia spp</i>	473	1.69%
<i>Citrobacter freundii</i>	433	1.54%
<i>Morganella morganii</i>	402	1.43%
<i>Serratia marcescens</i>	360	1.28%
<i>Enterococcus faecium</i>	339	1.21%
<i>Enterobacter aerogenes</i>	284	1.01%
<i>Citrobacter spp.</i>	240	0.86%
<i>Acinetobacter baumannii</i>	150	0.53%
<i>Proteus spp.</i>	119	0.42%
<i>Enterobacter spp.</i>	46	0.16%
<i>Klebsiella spp.</i>	39	0.14%
<i>Serratia spp.</i>	35	0.12%

- FQ susceptibility was most and FFM least frequently tested (Figure 2)

Figure 2 Frequency of susceptibility testing



C3 = 3<sup>rd</sup> generation cephalosporin; FQ = fluoroquinolone; TMP/SMX = trimethoprim-sulfamethoxazole; FFM = fosfomycin; NFT = nitrofurantoin

TABLE 2 Prevalence of resistance among top 3 cUTI pathogens\*

	C3R	FQR	TMP/SMX-R	FFMR	NFTR	TR
<i>Escherichia coli</i>	15.1%	43.5%	36.9%	0.0%	6.7%	12.8%
<i>Klebsiella pneumoniae</i>	13.2%	15.3%	20.4%	0.1%	60.8%	15.6%
<i>Pseudomonas aeruginosa</i>	12.0%	34.4%	4.2%	0.0%	8.8%	7.9%
<i>Proteus mirabilis</i>	7.9%	55.6%	40.7%	0.1%	73.7%	33.4%
<i>Enterococcus faecalis</i>	0.2%	34.8%	0.2%	0.0%	1.3%	8.0%
<i>Enterococcus spp</i>	0.0%	41.7%	0.1%	0.1%	9.7%	8.5%
<i>Enterobacter cloacae</i>	32.6%	18.8%	23.0%	0.6%	64.5%	17.7%
<i>Klebsiella oxytoca</i>	8.8%	9.2%	8.4%	0.0%	18.0%	6.4%
<i>Providencia spp</i>	10.4%	60.0%	19.9%	0.0%	78.0%	28.1%
<i>Citrobacter freundii</i>	25.6%	19.2%	20.6%	0.0%	8.1%	9.2%

C3 = 3<sup>rd</sup> generation cephalosporin; FQ = fluoroquinolone; TMP/SMX = trimethoprim-sulfamethoxazole; FFM = fosfomycin; NFT = nitrofurantoin; TR = triple resistant; R = resistant

\*Low resistance prevalence may reflect low prevalence of testing of the particular organism to the particular drug/class

- Among the top 3 organisms, resistance to C3 was (Table 2)

- 15.1% EC
- 13.2% KP
- 12.0% PA

- EC was (Table 2)

- Most frequently resistant to FQ (43.5%)
- Least frequently resistant to NFT (6.7%)
- Never tested for susceptibility to FFM

- KP was (Table 2)

- Most frequently resistant to NFT (60.8%)
- Least frequently resistant to FFM (0.1%)

- PA was (Table 2)

- Most frequently resistant to FQ (34.4%)
- Least frequently resistant to TMP/SMX (4.2%)
- Never tested for susceptibility to FFM

- The highest prevalence of TR occurred among *P. mirabilis* (33.4%) and lowest among *K. oxytoca* (6.4%) (Table 2)

- NFT and FQ exhibited some of the highest rates of resistance across multiple cUTI pathogens (Table 2)

- The prevalence of TR in 2013–2014 and 2017–2018, respectively was (Table 3)

- 11.7% and 17.3% for EC
- 15.2% and 17.1% for KP
- 10.2% and 5.3% for PA

TABLE 3 Prevalence of triple resistance over time

Time period	2013–2014	2015–2016	2017–2018
<i>Escherichia coli</i>	11.7%	11.0%	17.3%
<i>Klebsiella pneumoniae</i>	15.2%	14.6%	17.1%
<i>Pseudomonas aeruginosa</i>	10.2%	7.8%	5.3%
<i>Proteus mirabilis</i>	34.8%	30.2%	34.4%
<i>Enterococcus faecalis</i>	9.1%	6.8%	7.7%
<i>Enterococcus spp</i>	9.6%	6.4%	7.1%
<i>Enterobacter cloacae</i>	22.0%	13.4%	17.1%
<i>Klebsiella oxytoca</i>	8.3%	4.0%	6.3%
<i>Providencia spp</i>	29.6%	27.8%	26.7%
<i>Citrobacter freundii</i>	10.5%	8.1%	8.3%
<i>Morganella morganii</i>	51.1%	40.6%	32.8%
<i>Serratia marcescens</i>	12.8%	9.5%	9.2%
<i>Enterococcus faecium</i>	8.1%	12.2%	3.8%
<i>Enterobacter aerogenes</i>	2.3%	1.2%	5.4%
<i>Citrobacter spp.</i>	8.8%	5.4%	6.3%
<i>Acinetobacter baumannii</i>	18.2%	27.5%	4.5%
<i>Proteus spp.</i>	10.5%	3.8%	25.0%
<i>Enterobacter spp.</i>	7.1%	5.6%	7.1%
<i>Klebsiella spp.</i>	18.2%	0.0%	40.0%
<i>Serratia spp.</i>	20.0%	22.2%	9.1%