

Impact of ESBL-positivity and Quinolone Non-Susceptibility on Outcome for Inpatients with Complicated Urinary Tract Infection: A Multicenter Evaluation in the U.S

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ABSTRACT

Background: The rates of gram-negative Enterobacteriaceae resistance and the incidence of hospitalization attributable to complicated urinary tract infection (cUTI) have been rising. Understanding the correlation between comorbidities, such as Diabetes mellitus, antibiotic resistance and outcomes in cUTI may help devise strategies to improve patient care.

Materials/methods: The BD Insights Research Database (Franklin Lakes, NJ US) was queried from October 2015 forward to identify adult inpatients from 68 U.S. institutions with an ICD-10 code indicative of cUTI and a positive urine culture for an Enterobacteriaceae within the first three days of admission. Patient mortality was compared based on presence/absence of baseline variables, including severity of illness, need for ICU care, comorbid conditions, ESBL status and fluoroquinolone resistance.

Results: A total of 62,270 adult inpatients with a cUTI were identified, of which 22,752 (mean age 70.3 years; 76.1% female) had a positive urine culture for an Enterobacteriaceae. Of the positive cultures, 11.7% were ESBL-positive and 34% were fluoroquinolone non-susceptible (QNS). Patients admitted from a skilled nursing facility or long-term care facility were more likely to have resistant pathogens. Patients with cUTI due to ESBL-positive and/or QNS strains are more likely to have Diabetes mellitus, increased frequency of ICU care, or have a higher unadjusted mortality rate.

Variable	ESBL			Fluoroquinolone		
	Positive	Negative	P value	Non-susceptible	Susceptible	P value
N (%)	2,669 (11.7)	20,083 (88.3)	-	7,747 (34.0)	15,005 (66.0)	-
Diabetes mellitus (%)	43.9	37.8	<0.0001	42.2	36.7	<0.0001
ICU stay (%)	23.6	21.8	0.0384	24.0	21.0	<0.0001
Mortality (%)	4.2	3.2	0.0067	3.9	2.9	<0.0001

Conclusions: Patients with Diabetes mellitus are more likely to have antibiotic resistant uropathogens. Overall, patients with cUTI caused by resistant pathogens have a higher ICU admission and unadjusted mortality rate. Further analysis is justified to assess the impact of inappropriate initial empiric antibiotic treatment for cUTI caused by non-susceptible pathogens, especially in diabetic patients.

INTRODUCTION

- The prevalence of urinary tract infection (UTI) caused by ESBL-producing or fluoroquinolone non-susceptible Enterobacteriaceae has been increasing worldwide and includes both hospital-acquired and community-onset infections.
- In U.S. hospitals, 13.4% ESBL resistance has been reported nationally, with rates as high as 24% reported in some Northeastern, Southern and Western states. Further, over a third of *E. coli* isolates in 2014 were resistant to fluoroquinolones.
- While the majority of UTIs in the U.S. are ambulatory in nature, the incidence of hospitalization for cUTI has more than doubled since the late 1990s. This rise in hospitalization has taken place in parallel with the rise in resistance to first-line oral antimicrobial agents.
- However, the impact of antibiotic resistance on outcomes in hospitalized cUTI patients has not been fully described. We queried the BD Insights research Database from October 2015 forward to identify adult inpatients with cUTI to describe the impact of resistance on patient outcomes.

METHODS

- We analyzed all adult patients with a primary or secondary discharge diagnosis of cUTI (ICD10 codes) who also had a positive urine culture for Enterobacteriaceae (ENT) within 3 days of admission. Patients from 68 US acute care hospitals in the period between 2015-2017 were included (BD Insights Research Database, Franklin Lakes, NJ, USA).
- Resistant phenotypes were identified for the following pathogens, where applicable:
 - Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Enterobacter cloacae*, *E. aerogenes*, *Proteus mirabilis*, *Serratia marcescens*, *Citobacter freundii*, *Morganella morganii*
 - ESBLs: confirmed as ESBL-positive per commercial panels or intermediate/resistant to ESC4 (either ceftriaxone, cefotaxime, ceftazidime or cefepime)
 - Quinolone NS: intermediate or resistant to ciprofloxacin, levofloxacin or moxifloxacin
- Inappropriate empiric antimicrobial therapy (IET) was defined as the receipt of any antimicrobial with a duration \geq 24 hours within 5 days prior to final culture result where the regimen did not cover or was proven inactive against the cultured pathogen
- Patient demographics were identified using AHRQ CS and CCS classifications to assess for specific risk factors
- Unadjusted mortality, cost and length of stay were determined from financial, outcomes and billing data as calculated by each facility

RESULTS

Table 1: Demographics of cUTI Patients

Characteristic	ESBL Status		Quinolone Susceptibility	
	Positive N=2,669	Negative N=20,083	Non-Susceptible N=7,747	Susceptible N=15,005
Mean Age (years, SD)	69.7 (16.7)	70.4 (17.5)	71.8 (16.0)	69.5 (18.2)
Male Gender, (%)	28.8	23.2	28.1	21.7
Alarms risk score average, (SD)	51.0 (20.4)	49.4 (20.1)	51.7 (20.1)	48.5 (20.1)
Diabetes Mellitus, n (%)	576 (21.6)	3821 (19.0)	1666 (21.5)	2731 (18.2)
	p value = 0.0019		p value = <0.0001	
Renal Failure, n (%)	740 (27.7)	4517 (22.5)	1980 (25.6)	3277 (21.8)
	p value = <0.0001		p value = <0.0001	
Paralysis, n (%)	382 (14.3)	1673 (8.3)	1024 (13.2)	1031 (6.9)
	p value = <0.0001		p value = <0.0001	
Pathogen, n (%)				
<i>E. coli</i>	1547 (78)	9546 (63)	4533 (78)	6560 (59)
<i>Klebsiella</i> spp.	330 (17)	2902 (19)	313 (6)	2919 (26)
<i>P. mirabilis</i>	114 (6)	1402 (9)	791 (14)	725 (6)

RESULTS

Table 2: Location Prior to Hospitalization

Location prior to hospitalization	ESBL Status		Quinolone Susceptibility	
	Positive N=2,669 (%)	Negative N=20,083 (%)	Non-Susceptible N=7,747 (%)	Susceptible (N=15,005) (%)
Home	43.2	45.3	44.2	45.5
ER	23.9	25.0	24.4	25.1
Physician/HMO Referral	18.4	17.3	17.0	17.6
Not Provided	2.4	4.2	3.7	4.1
SNF/LTACH/Hospice/Rehab*	6.9	3.3	5.8	2.7
Acute Care Facility	2.8	2.7	2.6	2.7
Other	2.3	2.2	2.2	2.3

* P value = <0.0001 for ESBL positive vs negative, and quinolone non-susceptible vs susceptible pathogens

Table 3: Impact of Resistance on Outcomes

	ESBL Status			Quinolone Susceptibility		
	Positive N=2,669	Negative N=20,083	P Value	Non-Susceptible N=7,747	Susceptible N=15,005	P Value
ICU Admissions	23.6%	21.8%	0.0384	24.0%	21.0%	<0.0001
Mortality	4.2%	3.2%	0.0067	3.9%	2.9%	<0.0001

Table 4: Initial Empiric Antibiotic Therapy for cUTI Caused by Enterobacteriaceae

	Appropriate N	Inappropriate N	Initial Inappropriate Therapy (%)
Grand Total	14,174	2,076	11.6
β-Lactams	10,652	926	
Ceftriaxone-IV	5,598	454	7.3
Piperacillin/tazobactam-IV	2,867	240	8.0
Cefepime-IV	1,082	79	7.0
Aztreonam-IV	347	29	7.7
Cefazolin-IV	309	67	20.5
Quinolones	2371	691	
Levofloxacin-IV	1,331	386	27.8
Ciprofloxacin-IV	547	162	28.9
Ciprofloxacin ORAL	309	78	24.0
Levofloxacin ORAL	213	75	34.0
Carbapenems	1627	9	
Meropenem-IV	1,225	8	0.5
Ertapenem-IV	342	0	0.0
Other	359	780	
Vancomycin	2	345	100.0
Sulfamethoxazole/Trimethoprim ORAL	187	77	31.3

Table 5: Clinical Features of Patients with cUTI

Characteristic	Inappropriate Therapy N=2,076	Appropriate Therapy N=14,154
Bacteremia (%)	7.6	12.9
ICU (%)	20.1	23.4

Table 6: Outcomes of Inappropriate Therapy for cUTI

Characteristic	Inappropriate Therapy N=2,076	Appropriate Therapy N=14,154
Expired (%)	3.0	2.9
Avg. LOS (days: SD)	6.8 (5.5)	6.2 (5.9)
Median Total Cost (\$)	9,053	7,999

CONCLUSIONS

- Patients more likely to have cUTI caused by antibiotic resistant uropathogens are those:
 - With Diabetes mellitus, renal failure and/or paralysis
 - Admitted from long-term care or rehabilitation facilities
- Overall, patients with cUTI caused by resistant pathogens have a higher ICU admission rate and unadjusted mortality rate.
- Prescription of inappropriate empiric antibiotic therapy was:
 - Overall, most frequently as a result of β -lactam use
 - Observed in 29% of patients when quinolones are prescribed
- Patients who received appropriate initial antibiotic therapy were more likely to have bacteremia and admission to ICU at baseline
- Inappropriate empiric antibiotic therapy resulted in an increase in length of stay and increased total cost of care
- Further analysis of these data should be performed in order to identify patients at higher risk of receiving initial empiric inappropriate therapy in order to avoid these negative consequences to both the patient and the healthcare system.