

The impact of antibiotic resistance on hospitalized patients with Enterobacteriaceae (ENT) urinary tract infections (UTI): A multicenter analysis

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ABSTRACT

Background: Fluoroquinolone resistance (FQ NS) and ESBL + rates in UTI are high with strains being most susceptible to intravenous (IV) carbapenems, however there are a lack of oral alternatives. We evaluated the epidemiology of IV to PO transition in ENT ESBL + and/or FQ NS UTI admissions.

Material/methods: We analyzed the first positive ENT urine culture \leq 3 days from admission in those with a discharge primary or secondary UTI ICD10 code from 68 US hospitals from October 1, 2015-2017 (BD Insights, Franklin Lakes, NJ). Patient characteristics and outcomes were categorized by ESBL and FQ resistance status. IV to PO was identified as PO therapy after 24 hours of IV. The Fisher's exact test was used to test for significance.

Results: Of 16,022 adult inpatients (mean 69.5 years; 77.7% female) with culture positive ENT UTI were identified; 11.0% (n=1763) were ESBL +, 31.3% (n=5017) were FQ NS & 8.9% (n=1433) were both ESBL + and FQ NS. IV to PO was more common in susceptible vs. non-susceptible UTIs as follows: 15.1% vs. 12.1% for ESBL- vs. ESBL+, 15.6% vs. 12.9% for FQ S vs. FQ NS, and 15.5% vs. 10.9% for ESBL-/FQ S vs. ESBL+/FQ NS, $p < .001$ for all. ESBL+/FQ NS UTI admissions are associated with a higher hospital mortality, LOS & cost with other differences noted compared to ESBL-/FQ S & Other (ESBL + or FQ NS) admissions.

Conclusions: Urinary tract infections with Enterobacteriaceae which are ESBL+, FQ-R, or both are associated with a trend toward increased mortality, increased hospital length of stay, increased cost of care, and a lower rate of transition from IV to PO antibiotic therapy.

INTRODUCTION

Fluoroquinolone-resistant (FQ NS) and ESBL-producing (ESBL+) Enterobacteriaceae are increasing in frequency as a cause of urinary tract infections in the US and globally^{1, 2}. These strains are generally susceptible to intravenous (IV) carbapenems; however there are a lack of oral carbapenem alternatives. The loss of susceptibility to the commonly used oral antibiotic treatment alternatives such as quinolones, cephalosporins, trimethoprim/sulfamethoxazole, and nitrofurantoin limits the opportunity to transition these patients home, leading to increased length of stay (LOS) and higher costs. We evaluated the epidemiology of IV to PO transition during hospitalization in ENT ESBL + and/or FQ NS UTI admissions.

METHODS

- We analyzed adult patients with a primary or secondary discharge diagnosis of UTI (ICD10 codes) who also had a positive urine culture for the following Enterobacteriaceae (ENT) within 3 days of admission: *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Enterobacter aerogenes*.³
- We excluded other causes of infection and surgical procedures during index admission using the following ICD10 codes: any surgical procedure, concomitant skin and skin structure infection, pneumonia or intraabdominal infection.
- Patients from 68 US acute care hospitals in the period between 2015-2017 were included (BD Insights Research Database, Franklin Lakes, NJ USA; [formerly CareFusion Research Database]).
- Resistant phenotypes were identified for the following pathogens, where applicable:
 - ESBLs: confirmed as ESBL-positive per commercial panels or intermediate/resistant to extended spectrum cephalosporins (either ceftriaxone, cefotaxime, ceftazidime or cefepime).
 - Quinolone NS: intermediate or resistant to ciprofloxacin, levofloxacin or moxifloxacin.
- IV to PO was identified as conversion to a PO antibiotic that had a duration of at least 24 hours where PO conversion occurred after at least 24 hours of IV antibiotic therapy.
- Patient characteristics and outcomes were categorized by ESBL and FQ resistance status (ESBL -/FQ S, Other [ESBL + OR FQ NS], and ESBL +/FQ NS) in patients that received IV antimicrobials only and/or IV with step-down PO antimicrobial therapy during their hospitalization.
- Healthcare-associated (HCA) episodes were defined as admitted from another acute care facility (e.g., skilled nursing facility, long-term acute care hospital, rehabilitation hospital, hospice), admission in the prior 30 days, dialysis ICD10 code Z99.2 (dependence on renal dialysis), or cancer comorbidity as identified in the AHRQ CCS classification.
- Unadjusted mortality, cost and length of stay were determined from financial, outcomes and billing data as calculated by each facility.
- The Fisher's exact test was used to test for significance.

RESULTS

- Of 16,022 adult inpatients (mean 69.5 years; 77.7% female) with culture positive ENT UTI identified across 68 hospitals (Table 1); 11.0% (n=1763) were ESBL +, 31.3% (n=5017) were FQ NS & 8.9% (n=1433) were both ESBL + and FQ NS.
- Over 80% of patients with ENT UTIs were able to tolerate oral medications as evidenced by receipt of a non-antibiotic oral medication for $>$ 24 hours within 3 days of admission (Table 2).
- Overall, IV to PO conversion during hospitalization was more common in patients with susceptible vs. Non-susceptible organisms across all three categories of comparison (Table 2).
- ESBL+/FQ NS UTI admissions are associated with a trend toward higher hospital mortality, LOS & cost with other differences noted compared to ESBL-/FQ S & Other (ESBL + or FQ NS) admissions.
- Admissions with ESBL + /FQ NS were significantly more likely to be male and admitted with HCA risk factors (Table 2).

TABLE 1. US HOSPITAL CHARACTERISTICS.

BD Sites: n=68	
Region	
Northeast	5 (7.4%)
South	32 (47.1%)
Midwest	26 (38.2%)
West	5 (7.4%)
Urban/Rural	
Urban	62 (91.2%)
Rural	6 (8.8%)
Medical School Affiliation	
Major	4 (5.9%)
Limited	12 (17.6%)
Graduate	2 (2.9%)
No Affiliation	50 (73.5%)
Bed size	
<100	12 (17.6%)
100-300	27 (39.7%)
>300	29 (42.6%)

Short-term acute hospitals: Acute & Critical Access, excludes Children's & Specialty sites

TABLE 2. PATIENT CHARACTERISTICS AND OUTCOMES BY ESBL AND FQ RESISTANCE STATUS.

Measure (avg \pm SD)	ESBL - / FQ S	Other (ESBL + OR FQ NS)	ESBL + / FQ NS
N	10,784 (67.3%)	3,805 (23.7%)	1,433 (8.9%)
Age	68.6 \pm 18.8	71.6 \pm 16.8 \yen	70.7 \pm 16.2*
% Male	2,252 (20.9%)	921 (24.2%) \yen	401 (28.0%) \yen^{\wedge}
% In hospital mortality	203 (1.9%)	94 (2.5%) \yen	44 (3.1%) *
% Positive blood culture	1,585 (14.7%)	381 (10.0%) \yen	233 (16.3%) \wedge
% In ICU in admission period	1,821 (16.9%)	687 (18.1%)	242 (16.9%)
% HCA	2,716 (25.3%)	1,073 (28.2%) \yen	489 (34.1%) \yen^{\wedge}
Other scheduled PO meds in admission period	85.00%	86.30%	87.50%
% IV-to-PO	1,676 (15.5%)	535 (14.1%) \yen	156 (10.9%) \yen^{\wedge}
LOS	5.0 \pm 4.4, 4.0	5.3 \pm 4.4, 4.0 \yen	6.3 \pm 5.0, 5.0 \yen^{\wedge}
Payments (\$)	8,394 \pm 9,320, 6,448	8,722 \pm 11,630, 6,620	9,180 \pm 9,277, 6,897*
Total Cost (\$)	8,909 \pm 9,708, 6,091	9,696 \pm 11,835, 6,696 \yen	11,226 \pm 16,801, 8,126 \yen^{\wedge}
Total Gain (\$)	-628 \pm 7,369, 53	-1,065 \pm 7,081, -20 \yen	-2,279 \pm 16,180 -913 * \wedge

* $p < .0049$ ESBL+/FQ NS vs. ESBL-/FQ S; \wedge $p < .0089$ ESBL +/FQ NS vs. Other; \yen $p < .0324$ Others vs. ESBL -/FQ S

CONCLUSIONS

- Approximately one-third of hospitalized patients with UTI (5238/16022) have urine cultures demonstrating resistance to cephalosporins (ESBL+), fluoroquinolones, or both classes of antibiotics. As compared to patients with antibiotic susceptible uropathogens, these patients are more likely to be male and have health care-associated infections.
- Urinary tract infections with Enterobacteriaceae which are ESBL+, FQ-R, or both are associated with a trend toward increased mortality, increased hospital length of stay, increased cost of care, and a lower rate of transition from IV to PO antibiotic therapy.

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