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Eligibility and Outcomes of Conversion to Oral (PO) Therapy in Patients Hospitalized with Enterobacteriaceae (ENT) Urinary Tract Infection (UTI) in the United States (US): A Multicenter Analysis

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ABSTRACT

Background: Rising rates of fluoroquinolone resistance (FQ-R) and third-generation cephalosporin resistance/extended-spectrum beta-lactamases (ESBL+) have left patients with urinary tract infections (UTI) few oral options. Here, we evaluate the eligibility of hospitalized UTI patients to take PO medications and estimate the potential impact on hospital cost and length of stay (LOS).

Methods: We analyzed the first positive Enterobacteriaceae (ENT) urine culture ≤ 3 days from hospital admission in patients with a primary or secondary UTI ICD10 discharge diagnosis from 68 US hospitals admitted October 1, 2015-2017. Eligibility for PO was classified as: (1) received at least 24 hours intravenous (IV) antimicrobial, (2) ability to tolerate PO drug as evidenced by a pharmacy order for non-antibiotic PO medication, (3) stable/normal white blood count (WBC). Fisher's exact test was used to test for significance; results were examined by severity quartile, PO conversion and resistance status (FQ-R and ESBL+)

Results: 5,842 patients were eligible for PO conversion and analysis; 1,890 (32.5%) actually converted to PO during their hospital stay; 2,199 (37.6%) were either FQ-R, ESBL+, or both. Baseline demographics were similar between groups. Highly resistant patients (FQ-R and ESBL+) were less likely to transition to PO compared to those with neither FQ-R nor ESBL infections (16.7% vs. 37.0%). Among patients who did convert to PO, post-PO-eligible LOS was shorter across all severity strata compared to patients who did not convert (p< 0.0001). For those who did not convert, post PO-eligible LOS was 2.6, 2.9, 3.3, and 4.0 days by severity quartile, respectively. Among patients who did convert to PO, the total cost was $1,043 less (p=0.024) for patients in the 3rd quartile of severity and $1,512 less (p=0.004) for patients in the 4th quartile of severity, compared to the patients who did not convert.

Conclusion: Only ~1/3 of patents eligible for PO therapy are converted during hospitalization. Reduced LOS and substantial cost savings could be recognized by efficient PO conversion and hospital discharge. Lack of PO therapies with activity against resistant pathogens has made this challenging; new PO options may help reduce hospital costs and resources required to treat these UTI patients.

INTRODUCTION

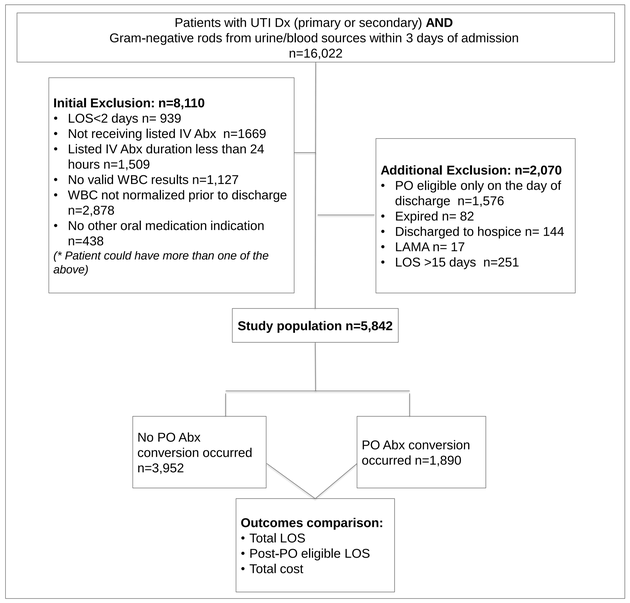
- **Fluoroquinolone-non-susceptible (FQ NS) and ESBL-producing (ESBL+) Enterobacteriaceae (ENT) are increasing in frequency as a cause of urinary tract infections in the US and globally.[1,2]**
- **These strains are generally susceptible to intravenous (IV) carbapenems; however there are a lack of oral 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.**
- **Here, we examine frequency and compare outcomes in hospitalized patients with UTI who were eligible for PO conversion, who did versus those who did not actually convert.**

METHODS

- **Adult patients were included for analysis if they had 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]**
- **Admissions were excluded that underwent surgical procedures or had another cause of infection during index admission using the following ICD10 code categories: any surgical procedure, concomitant skin and skin structure infection, pneumonia or intra-abdominal 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:**
  - Extended spectrum beta-lactamases (ESBLs): confirmed as ESBL+ per commercial panels or intermediate/resistant to extended spectrum cephalosporins (either ceftriaxone, cefotaxime, ceftazidime or cefepime).
  - Fluoroquinolone (FQ) non-susceptible (NS): intermediate or resistant to ciprofloxacin, levofloxacin or moxifloxacin.
- **PO eligibility was identified if, after at least 24 hours of IV therapy, the patient was tolerating PO (identified by pharmacy order for PO medications other than antibiotics) and were clinically stable (white blood cell count of either (a) 2.0-11.0 if baseline was >11 or (b) 2.0-10.0 if baseline was <10.9 24 hours after starting IV antibiotics).**
- **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 positivity and FQ susceptibility status in patients that received IV antimicrobials only and/or IV with step-down PO antimicrobial therapy during their hospitalization.**
- **Patient demographics were identified using Agency for Healthcare Research and Quality Clinical Classifications Software (AHRQ CS/CCS) to assess for specific risk factors.[4]**
- **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 hospital 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

Figure 1. Patient Cohort



UTI; Urinary Tract Infection. Dx; Diagnosis. LOS; Length of Stay. IV; Intravenous. Abx; Antibiotics. WBC; White Blood Cell. PO; Oral. LAMA; Leave Against Medical Advice.

Table 1: Patient Demographics

Variable	Overall n=5,842		IV to PO=Yes (n=1,890)		IV to PO=No (n=3,952)		
	n	%	n	%	n	%	P
Age							
Mean (SD)	70.9	(16.7)	71.8	(16.1)	70.4	(16.9)	0.0023
Median (1st, 3rd quartile)	74	(62,83)	75	(62,84)	74	(61,83)	
Male	1430	24.5	478	25.3	952	24.1	0.3175
ALaRMS (aggregated severity score)							
Mean (SD)	50.8	(18.4)	51	(18.3)	50.7	(18.5)	0.5339
Median (1st, 3rd quartile)	49	(40,61)	49	(39,60)	49	(40,61)	
Positive blood culture	1106	18.9	321	17.0	785	19.9	0.0086
ICU admission	1193	20.4	396	21.0	797	20.2	0.4860
Healthcare associated infections	1674	28.7	510	27.0	1164	29.5	0.0508
Carbapenem non-susceptible	31	0.5	7	0.4	24	0.6	0.2436
Urinary catheter/device	65	1.1	23	1.2	42	1.1	0.5992
Neurogenic bladder	252	4.3	93	4.9	159	4.0	0.1143

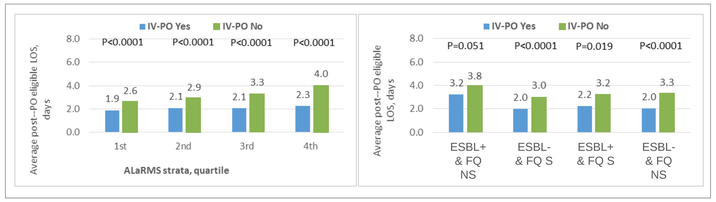
IV; Intravenous. PO; Oral. SD; Standard Deviation. ICU; Intensive Care Unit.

Table 2: PO Conversion by Resistance Profile

ESBL and FQ category (mutually exclusive)	Overall n=5,842	IV to PO=Yes (n=1,890)		IV to PO=No (n=3,952)	
	n	n	%	n	%
ESBL+ & FQ NS	708	118/708	16.7	590/708	83.3
ESBL- & FQ S	3643	1347/3643	37.0	2296/3643	63.0
ESBL+ & FQ S	120	38/120	32.0	82/120	68.3
ESBL- & FQ NS	1371	3871371	28.2	984/1371	71.8

ESBL; Extended Spectrum Beta-Lactamase. FQ; Fluoroquinolone. IV; Intravenous. PO; Oral. NS; Non-Susceptible. S; Susceptible

Figure 2. Post-PO-Eligible LOS stratified by Conversion Status, Severity, and Resistance Profile



PO; Oral. LOS; Length of Stay. IV; Intravenous. PO; ESBL; Extended Spectrum Beta-Lactamase. FQ; Fluoroquinolone. NS; Non-Susceptible. S; Susceptible

- **Patients' baseline characteristics were generally comparable between those who actually received oral antibiotic conversion versus those who didn't (Table 1).**
- **80% of all PO eligible patients became eligible by day 3 after admission; there was no significant difference between actually converted versus not-converted groups .**
  - **For those actually converted to PO, 63% converted between 1 day prior and 1 day after the PO-eligible day.**
  - **67% of all PO-eligible patients were discharged by day 3 after becoming PO-eligible.**
- **For patients who were eligible for oral antibiotic conversion, only one out of three actually converted in this analysis (1,890/5,842; 32.5%).**
- **Among patients receiving oral conversion, the overall hospital LOS was significantly shorter in 4th quartiles in severity, compared to the patients who did not convert.**
- **For those who received oral conversion, there was approximately one day shorter post-PO eligible length of stay overall (Figure 2).**
  - **The oral conversion effect on post-PO eligible length of stay was most prominent among patients more severely ill (3rd or 4th quartile of severity).**
  - **There was a favorable oral conversion effect in post-PO LOS across the 4 ESBL/FQ categories.**
- **Among patients receiving oral conversion, the total cost was $1,043 less (P=0.024) for patients in the 3rd quartile of severity and $1,512 less (P=0.004) for patients in the 4th quartile of severity, compared to the patients who did not convert.**
- **There was no significant total cost difference between PO conversion groups across 4 ESBL/FQ categories.**

CONCLUSIONS

- **Only ~1/3 of patents eligible for PO therapy are converted during hospitalization. Reduced LOS and substantial cost savings could be recognized by efficient PO conversion and hospital discharge.**
- **Lack of PO therapies with activity against resistant pathogens has made this challenging; new PO options may help reduce hospital costs and resources required to treat these UTI patients.**

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