

Risk factors for treatment failure in patients with uncomplicated urinary tract infection

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ABSTRACT

Background
Outpatients presenting with signs and symptoms of uncomplicated urinary tract infection (uUTI) are typically managed with an empiric course of antibiotic therapy. Treatment failure resulting in the need for repeated courses of antibiotics may occur in patients with certain baseline characteristics. In the absence of microbiologic data, typically not available to the prescribing clinician at the time of the clinical encounter, there is a need to define baseline variables predictive of treatment failure in patients with clinical evidence of uUTI. We recently completed two phase 3 studies, SURE-1 and REASSURE, evaluating 3,874 adult women with uUTI.

Methods
SURE-1 and REASSURE were randomized, double-blinded, double-dummy, multicenter Phase 3 clinical trials. In the SURE-1 trial, patients with uUTI were randomized to five days of oral sulopenem or three days of ciprofloxacin. In the REASSURE trial, patients with uUTI were randomized to five days of oral sulopenem or five days of amoxicillin/clavulanate. For both trials, the primary endpoint was overall success, defined as both clinical and microbiologic response, at the Day 12/Test of Cure (TOC) visit. Post hoc analyses were performed to determine if there was a relationship between baseline characteristics and overall success for these clinical trial patients.

Results
In the SURE-1 and REASSURE trials combined, there were 2,061 adult female patients with uUTI in the microbiologic Modified Intent to Treat (mMITT) population. The majority of baseline uropathogens recovered were *Escherichia coli* (83.4%) and *Klebsiella pneumoniae* (10.0%). Overall response could be determined for 1,958 (95%) of the patients in the mMITT population. For these clinical trial patients, age ≥65 years, BMI >30 kg/m², creatinine clearance <60 mL/min and Diabetes mellitus were associated with treatment failure (Table).

Conclusion
Older age, higher BMI, lower creatinine clearance and the presence of Diabetes mellitus identified uUTI patients at increased risk for treatment failure. These variables, plus infection known or suspected to be resistant to one or more commonly prescribed oral antibiotic, may serve to guide clinicians when choosing empiric antibiotic therapy for adult women with uUTI.

Baseline variable / category	Patients with failure (N=668) n (%)	Patients without failure (N=1,293) n (%)	p-value
Age (years)			
<65	431 (64.8)	1001 (77.4)	<.0001
≥65	234 (35.2)	292 (22.6)	
Race			
White	508 (85.4)	1009 (85.0)	0.6301
Black/African American	81 (12.2)	164 (12.7)	
Asian	6 (0.9)	17 (1.3)	
American Indian/Alaska Native	3 (0.5)	3 (0.2)	
Other	7 (1.1)	10 (0.8)	
Ethnicity			
Hispanic or Latina	297 (44.7)	586 (45.3)	0.7702
Not Hispanic or Latina	366 (55.3)	707 (54.7)	
BMI (kg/m ²)			
<25	193 (29.0)	491 (38.0)	<.0001
25-30	192 (28.9)	410 (31.7)	
≥30	277 (41.9)	388 (30.2)	
Creatinine clearance (mL/min)			
≥60	217 (32.8)	270 (20.9)	<.0001
<60	444 (66.9)	1015 (78.9)	
Diabetes mellitus			
Present	135 (20.3)	145 (11.2)	<.0001
Absent	530 (79.7)	1148 (88.8)	

*502 patients with indeterminate overall response are not included

INTRODUCTION

Oral antibiotics are typically prescribed empirically for the treatment of uUTI in the outpatient setting and are associated with a high frequency of treatment failure due to rising prevalence of antimicrobial resistant uropathogens. Defining baseline factors predictive of treatment failure would be valuable in the absence of culture data at the time of diagnosis to help prescribers select appropriate antibiotics for successful treatment of uUTI caused by MDR uropathogens. We recently completed two phase 3 studies, SURE1 and REASSURE, assessing the safety and efficacy of oral sulopenem or comparator in 3,874 adult women with uUTI. Here, we present results from a post-hoc pooled analysis of data from the two trials to identify baseline variables associated with treatment failure.

METHODS

SURE1 & REASSURE

- Multicenter, double-blind, double-dummy, active-controlled, Phase 3 randomized trials
- 3874 adult women with uUTI
 - Pyuria, bacteriuria, and clinical signs/symptoms of uUTI
- Compared sulopenem etzadroxil/probenecid (oral sulopenem) 500 mg/500 mg PO BID x 5 days to ciprofloxacin 250 mg PO BID for 3 days (SURE1) or amoxicillin/clavulanate 875 mg/125 mg PO BID x 5 days (REASSURE)
- Primary endpoint: overall (clinical + microbiologic) response in the micro-MITT population at the Test-of-Cure (Day 12) Visit
- Sensitivity and subgroup analyses of the primary efficacy variable were also conducted, including post hoc analyses, not prespecified, to determine if there was a relationship between antibiotic resistance and advancing age, as well as the impact of treatment by age group with oral sulopenem versus comparator in these two trials combined.

Table 1: SURE-1 and REASSURE Studies Combined: Baseline Demographics, mMITT Population

Parameter	Sulopenem N = 1039 n (%)	Comparator N = 1022 n (%)	Total N = 2061 n (%)
Age (years)			
Mean (SD)	51.1 (18.26)	50.2 (18.32)	50.7 (18.29)
Range	18, 91	18, 96	18, 96
Age group			
<65 years	753 (72.5)	753 (73.7)	1506 (73.1)
≥65 years	286 (27.5)	269 (26.3)	555 (26.9)
65-74 years	172 (16.6)	160 (15.7)	332 (16.1)
75-84 years	99 (9.5)	94 (9.2)	193 (9.4)
≥85 years	15 (1.4)	15 (1.5)	30 (1.5)
Ethnicity			
Hispanic or Latina	474 (45.6)	450 (44.0)	924 (44.8)
Race			
Black	131 (12.6)	130 (12.7)	261 (12.7)
White	879 (84.6)	872 (85.3)	1751 (85.0)
Other	9 (0.9)	7 (0.7)	16 (0.8)
Diabetes mellitus	155 (14.9)	143 (14.0)	298 (14.5)
Body mass index, mean (SD), kg/m ²	28.47 (6.6)	28.33 (6.6)	28.40 (6.6)
Creatinine clearance, mean (SD), (mL/min)	79.97 (28.0)	81.02 (27.8)	80.49 (27.9)

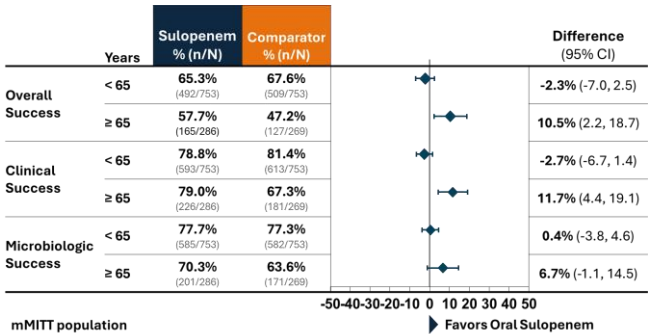
Table 2: SURE-1 and REASSURE Studies Combined: Baseline Study Uropathogens, mMITT Population

Number of Patients with at Least One Study Uropathogen at Baseline	Sulopenem N = 1039 n (%)	Comparator N = 1022 n (%)	Total N = 2061 n (%)
<i>Escherichia coli</i>	863 (83.1)	856 (83.8)	1719 (83.4)
<i>Klebsiella pneumoniae</i>	109 (10.5)	98 (9.6)	207 (10.0)
<i>Proteus mirabilis</i>	31 (3.0)	30 (2.9)	61 (3.0)
<i>Klebsiella aerogenes</i>	8 (0.8)	9 (0.9)	17 (0.8)
<i>Staphylococcus saprophyticus</i>	5 (0.5)	8 (0.8)	13 (0.6)
<i>Enterobacter hormaechei</i>	4 (0.4)	8 (0.8)	12 (0.6)
<i>Citrobacter freundii</i>	5 (0.5)	6 (0.6)	11 (0.5)
<i>Klebsiella varicola</i>	9 (0.9)	2 (0.2)	11 (0.5)
<i>Citrobacter koseri</i>	7 (0.7)	3 (0.3)	10 (0.5)
<i>Morganella morganii</i>	5 (0.5)	5 (0.5)	10 (0.5)
<i>Klebsiella oxytoca</i>	2 (0.2)	5 (0.5)	7 (0.3)
<i>Enterobacter cloacae</i> complex	4 (0.4)	2 (0.2)	6 (0.3)
<i>Serratia marcescens</i>	3 (0.3)	2 (0.2)	5 (0.2)
<i>Leifliotia amnigena</i>	1 (0.1)	3 (0.3)	4 (0.2)
<i>Providencia stuartii</i>	2 (0.2)	2 (0.2)	4 (0.2)
<i>Klebsiella sp</i>	1 (0.1)	1 (0.1)	2 (0.1)
<i>Raoultella planticola</i>	0 (0)	2 (0.2)	2 (0.1)
<i>Enterobacter cloacae</i>	1 (0.1)	0 (0)	1 (0)
<i>Enterobacter kobei</i>	1 (0.1)	0 (0)	1 (0)
<i>Escherichia sp</i>	1 (0.1)	0 (0)	1 (0)
<i>Pantoea sp</i>	1 (0.1)	0 (0)	1 (0)
<i>Enterobacter bugandensis</i>	0 (0)	1 (0.1)	1 (0)
<i>Enterobacter aerogenes</i>	0 (0)	1 (0.1)	1 (0)
<i>Pantoea septic</i>	0 (0)	1 (0.1)	1 (0)

Table 3: Summary of Study Outcomes, SURE-1, REASSURE and Both Studies Combined, mMITT Population

SURE-1			
Response at TOC (Day 12)	Sulopenem N = 517 n (%)	Ciprofloxacin N = 554 n (%)	Difference (95% CI)
Overall success	339 (65.6)	376 (67.9)	-2.3% (-7.9, 3.3)
Clinical success	422 (81.6)	436 (78.7)	2.9% (-1.9, 7.7)
Microbiologic success	396 (76.6)	438 (79.1)	-2.5% (-7.5, 2.5)
REASSURE			
Response at TOC (Day 12)	Sulopenem N = 522	Amoxicillin/clavulanate N = 468	Difference (95% CI)
Overall success	318 (60.9)	260 (55.6)	5.4% (-0.8, 11.5)
Clinical success	397 (76.1)	358 (76.5)	-0.4% (-5.7, 4.9)
Microbiologic success	390 (74.7)	315 (67.3)	7.4% (1.8, 13.1)
SURE-1 AND REASSURE COMBINED			
Response at TOC (Day 12)	Sulopenem N = 1039	Comparator N = 1022	Difference (95% CI)
Overall success	657 (63.2)	636 (62.2)	1.0 (-3.2, 5.2)
Clinical success	819 (78.8)	794 (77.7)	1.1 (-2.4, 4.7)
Microbiologic success	786 (75.6)	753 (73.7)	2.0 (-1.8, 5.7)

Table 4: SURE-1 and REASSURE Studies Combined: Treatment Response in Women ≥ 65 Years vs <65 Years of Age



RESULTS

Figure 1: Prevalence of antibiotic resistance by age group in *E. coli* in SURE1 and REASSURE Studies Combined

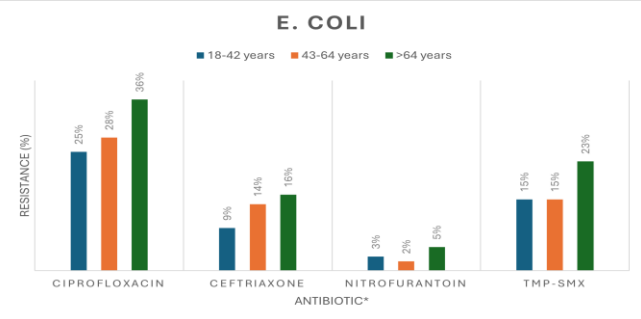
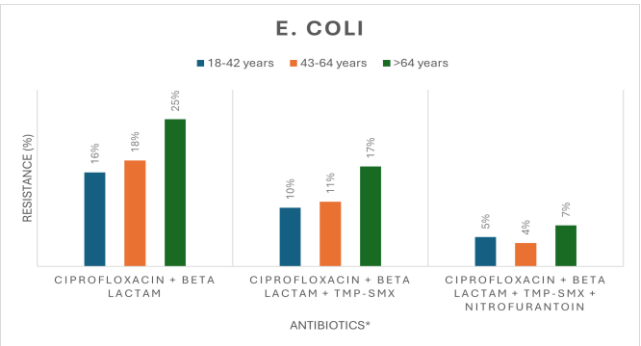


Figure 2: Prevalence of antibiotic resistance by age group in MDR *E. coli* in SURE1 and REASSURE Studies Combined



CONCLUSIONS

Data from two large recently conducted registrational studies in uUTI indicate that a direct correlation exists between antibiotic resistance and age for adult women with uncomplicated urinary tract infection

- women older than 65 years were more likely to have a resistant pathogen for all antibiotics compared to women aged 18-42 years and 43-64 years.
- E. coli* resistance to multiple antibiotics also correlated with increasing age.
- Treatment outcomes for patients over the age of 65 years showed that sulopenem had a higher success rate than those treated with the comparators