Impact of age on antibiotic resistance and efficacy of antibiotics for women with uncomplicated urinary tract infection

Steven I. Aronin, MD, Sailaja Puttagunta, MD, Jayanti Gupta, PhD, and Michael Dunne, MD
Iterum Therapeutics, Old Saybrook, CT 06475

ABSTRACT

Background
Epidemiologic data suggests that there's a correlation between age and antibiotic resistance among urinary isolates from female outpatients in the United States. Sulopenem etzadroxil/probenecid (oral sulopenem) is a thiopenem antibiotic active against multidrug-resistant pathogens, approved for the treatment of adult women with uncomplicated uUTI.
Methods
In SURE-1, patients with uUTI were randomized to five days of oral sulopenem or three days of ciprofloxacin. In REASSURE, 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 (both clinical and microbiologic response), at the Day 12/Test of Cure (TOC) visit. Posthoc analyses were performed to determine if there was a relationship between antibiotic resistance and age, as well as the impact of treatment by age group with oral sulopenem versus comparator in the two trials combined.
Results
In SURE-1 and REASSURE combined, there were 2,061 adult women 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%). For patients with infection due to *E. coli* and *K. pneumoniae*, the prevalence of antibiotic resistance to ciprofloxacin, ceftriaxone, nitrofurantoin, and trimethoprim-sulfamethoxazole increased by age group. This trend was also seen in patients with infection due to *E. coli* strains resistant to two, three and four classes of antibiotics. Patients in the oldest age group (≥65 years) treated with oral sulopenem had higher success rates at the TOC assessment than those treated with the comparators. The lower limit of the confidence interval on the difference in outcomes does not include zero for both overall success (57.7% vs 47.2%, difference 10.5%, 95%CI: 2.2, 8.7) and clinical success (79.0% vs 67.3%, difference 11.7%, 95%CI: 4.4, 19.1).

Table. Prevalence of antibiotic resistance by age group for patients with uUTI due to E. coli and K. pneumoniae

	Escherichia coli (N=1,719)			*Klebsiella pneumoniae* (N=207)		
	Age group (years)					
Resistance, n/N (%)	17-42	43-64	≥65	17-42	43-64	≥65
Ciprofloxacin	157/621 (25.3)	177/637 (27.8)	166/461 (36.0)	11/67 (16.4)	8/75 (10.7)	14/65 (21.5)
Ceftriaxone	58/621 (9.3)	86/637 (13.5)	73/461 (15.8)	4/67 (6.0)	6/75 (8.0)	8/65 (12.3)
Nitrofurantoin	16/621 (2.6)	10/637 (1.6)	24/461 (5.2)	25/67 (37.3)	26/75 (34.7)	30/65 (46.2)
Trimethoprim-sulfamethoxazole	95/621 (15.3)	97/637 (15.2)	106/461 (23.0)	6/67 (9.0)	7/75 (9.3)	11/65 (16.9)
Ciprofloxacin + β-lactam	96/621 (15.5)	116/637 (18.2)	113/461 (24.5)			
Ciprofloxacin + β-lactam + TMP-SMX	60/621 (9.7)	70/637 (11.0)	79/461 (17.1)			
Cipro + β-lactam + TMP-SMX + nitrofurantoin	30/621 (4.8)	27/637 (4.2)	32/461 (6.9)			

Conclusions
There is a direct correlation between antibiotic resistance and age for women with uUTI. For patients with uUTI ≥65 years, those treated with oral sulopenem had a higher success rate than those treated with comparators. These findings help to inform the empiric treatment of women with uUTI.

INTRODUCTION

Uncomplicated urinary tract infections (uUTI) are one of the most common causes for ambulatory clinical care among women. While several oral antibiotics are available to treat uUTI, including β-lactams, quinolones, TMP-SMX, fosfomycin and nitrofurantoin, resistance rates are now at or exceed 20% for some of these agents, a rate at which a urine culture should be considered to guide therapy. Increasing resistance, including multidrug resistance (MDR), among UTI pathogens in the community complicates the choice of appropriate empiric therapy. Ineffective treatments may prompt additional testing and necessitate a second prescription, incurring additional costs on both counts. More antibiotics may mean the risk of more adverse events, as well as the selection of resistant pathogens among colonizing flora, all of which can contribute to morbidity. Risk factors identified for MDR UTI include prior antimicrobial therapy exposure, prior infection with a MDR pathogen, recent stay at a health care facility, prior history of UTIs, recent international travel and chronic medical conditions. New, safe and well-tolerated orally bioavailable antibacterials with in vitro activity against MDR pathogens will be needed to address this problem. Sulopenem etzadroxil, the prodrug of the parent intravenous compound sulopenem, is an oral thiopenem antibiotic active against MDR Gram-negative pathogens, including those producing an extended spectrum beta-lactamase (ESBL), and with an in vitro antimicrobial spectrum similar to ertapenem. Combined with probenecid to extend its half-life in plasma, sulopenem obtains high concentrations in urine and is approved for the treatment of uUTI in women.

METHODS

SURE-1 and REASSURE were prospective, phase 3, randomized, multicenter, double-blind, double-dummy studies in adult women with uUTI conducted from August 2018 through January 2020 (SURE-1) and October 2022 through November 2023 (REASSURE). In SURE-1, oral sulopenem was compared to oral ciprofloxacin in patients at 142 study centers in 4 countries: the United States (U.S.) (102), Russia (20), Ukraine (15) and Italy (5). In REASSURE, sulopenem was compared to amoxicillin/clavulanate in patients at 139 U.S. centers.

Eligible patients were women, aged ≥18 years old with signs and symptoms of uUTI and a urinalysis consistent with uUTI based on the results of nitrite, leukocyte esterase and microscopy. Qualifying signs and symptoms included urinary frequency, urinary urgency, pain or burning on micturition and suprapubic pain.

Randomization, Treatment, and Monitoring

SURE-1 and REASSURE patients were randomized 1:1 to receive either a bilayer tablet with sulopenem etzadroxil/probenecid 500 mg/500 mg twice daily for 5 days or comparator (oral ciprofloxacin 250 mg twice daily for 3 days in SURE-1 and amoxicillin/clavulanate 875 mg/125 mg twice daily for 5 days in REASSURE). Each regimen included a matched placebo to maintain the blind.

Efficacy Endpoints

For both SURE-1 and REASSURE, the primary efficacy endpoint, overall response at the Test of Cure (TOC) visit (Day 12), was a composite of clinical and microbiologic outcomes. A patient was assigned an outcome of success if she was alive, her baseline signs and symptoms of uUTI had resolved, had no new UTI symptoms, if the bacterial pathogen found at $\geq 10^5$ CFU/mL in the baseline urine culture was reduced to $<10^3$ CFU/mL in the TOC urine culture and she had received no non-study antibacterial therapy for uUTI.

Safety

In both studies, the safety endpoints included assessment of treatment-emergent adverse events, serious adverse events and evaluation of changes from baseline in laboratory test results and vital signs.

Statistical Analyses

In both SURE-1 and REASSURE, the primary efficacy population, microbiologic-modified intent-to-treat (mMITT), comprised all randomized patients who received any study medication and with a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen and no more than 2 species of microorganisms, regardless of colony count. Efficacy was also assessed in the mMITT-susceptible population consisting of all patients in the mMITT population with the baseline uropathogen(s) susceptible to the comparator agent, and in the mMITT-resistant population consisting of all patients in the mMITT population with the baseline uropathogen(s) non-susceptible to the comparator agent. The number and percentage of patients in each treatment group with an overall outcome of success, failure and indeterminate was determined in the mMITT population. A 2-sided 95% confidence interval (CI) for the observed difference in the overall success rates (sulopenem minus comparator) was computed using the method proposed without stratification by Miettinen and Nurminen. Non-inferiority of sulopenem to comparator was to be concluded if the lower bound of the 95% CI was greater than -10%. Using the hierarchical testing procedure of Westfall and Kishen to control for inflation of the overall type I error, further comparisons of the primary efficacy endpoint were to be statistically tested in the order presented in a prespecified sequence. Sensitivity and subgroup analyses of the primary efficacy variable were also conducted, including post hoc analyses 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.

RESULTS

Table 1: Baseline Demographics, mMITT Population, Phase 3 uUTI Studies

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/m²	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: Baseline Study Uropathogens, mMITT Population, Phase 3 uUTI Studies

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

RESULTS

Figure 1: SURE-1 and REASSURE Phase 3 uUTI Studies: Treatment Response at Test-Of-Cure in Women ≥ 65 Years of Age, Sulopenem vs Comparators, mMITT Population

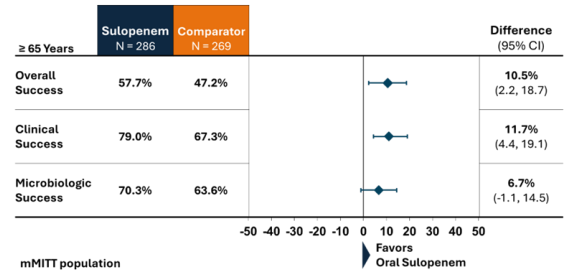


Figure 2: SURE-1 and REASSURE Phase 3 uUTI Studies: Treatment Response in Women ≥ 65 Years vs <65 Years of Age

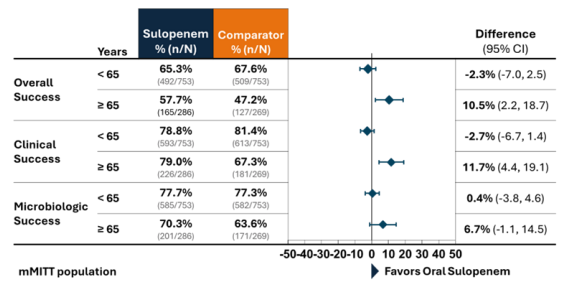


Figure 3: Treatment Response in Women ≥ 65 Years of Age, All Treatment Populations, Phase 3 uUTI Studies

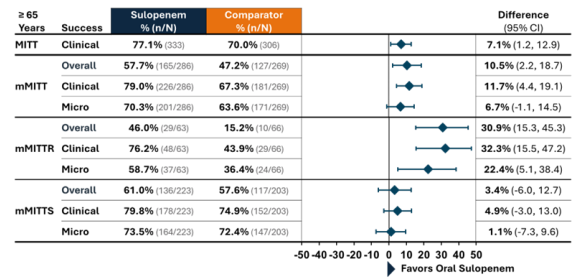


Figure 4a: SURE-1 and REASSURE Phase 3 uUTI Studies: Prevalence of E. coli Resistance to Individual Antibiotics By Age Group

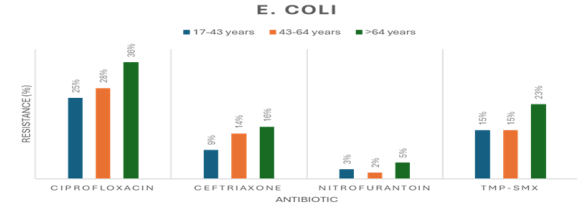


Figure 4b: SURE-1 and REASSURE Phase 3 uUTI Studies: Prevalence of K. pneumoniae Resistance to Individual Antibiotics By Age Group

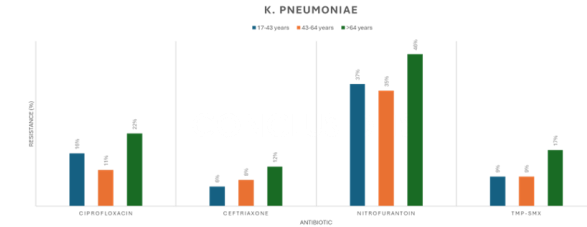
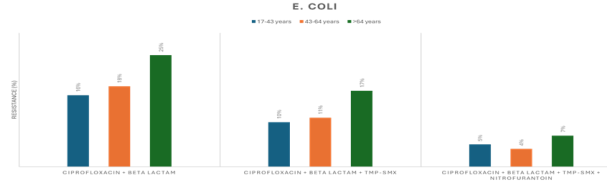


Figure 4c: SURE-1 and REASSURE Phase 3 uUTI Studies: Prevalence of E. coli Resistance to Two or More Antibiotics By Age Group



CONCLUSIONS

- Previously identified risk factors for MDR UTI include recent antibiotic exposure, known colonization with a MDR pathogen, recent stay at a health care facility, prior history of UTIs, and host factors including chronic medical conditions
- Women ≥65 years of age are more likely to have uUTI due to uropathogens resistant to individual antibiotics and with multidrug resistance
- For patients with uUTI ≥65 years, those treated with oral sulopenem had a higher success rate than those treated with comparators, including patients in the MITT population which is the population most similar to patients evaluated in the ambulatory setting
- These findings help to inform the empiric treatment of women with uUTI and support the use of oral sulopenem for the treatment of women with uUTI with limited oral antibacterial treatment options

REFERENCES

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- Puttagunta S, Aronin SI, Gupta J, Das AF, Gupta K, Dunne MW. Oral sulopenem/probenecid for uncomplicated urinary tract infections (uUTI): Results from the REASSURE trial. Open Forum Infectious Diseases. Volume 12, Issue Supplement_1, February 2025, ofae631.1295, https://doi.org/10.1093/ofid/ofae631.1295