Nitrofurantoin Use and Resistance in Urinary Tract Infections Across a Large, Integrated Health System

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Background

- Nitrofurantoin is a preferred empiric antibiotic for the treatment of acute cystitis
- Limited data exists on utilization patterns and bacterial resistance
- Nitrofurantoin:
  - is bactericidal in urine at therapeutic doses[1]
  - is active against gram-negative and gram-positive bacteria
  - has limited efficacy in impaired renal function
  - is well-tolerated except pulmonary toxicity long-term
  - does not penetrate tissue well[2]
  - has a unique mechanism of action[1,3]
- Since introduction in 1953, resistance to nitrofurantoin has remained relatively unchanged[1,2]
  - Study of common urinary isolates found overall susceptibility of nitrofurantoin was 89.3% in uropathogens[4]
- Mechanisms of nitrofurantoin resistance may include the
  - nfsA gene
  - nfsB gene
  - overexpression of oqxAB gene[5]

Objectives

- Describe nitrofurantoin utilization patterns and opportunities for antibiotic stewardship in an integrated health system
- Evaluate rate of and clinical outcomes associated with nitrofurantoin resistance

Methods

Study Design: retrospective cohort study of patients prescribed nitrofurantoin at Denver Health from January 1, 2017 to December 31, 2021 in 9 community health centers, 2 urgent cares, and the ED

Patients (n = 634, with 934 positive urine cultures):

- *Inclusion*: Received nitrofurantoin within 72 hours of a positive urine culture, defined as >100,000 cfu/mL of a single organism (*Escherichia coli*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, or *Klebsiella oxytoca*)
- *Exclusion*: Patients less than 18 years old and patients with confirmed or suspected pyelonephritis

Primary Outcome:

- Clinical outcomes of nitrofurantoin-resistant compared with nitrofurantoin-susceptible urinary tract infections
  - Repeat clinic, ED, urgent care, or hospital admission within 30 days of culture

Secondary Outcome:

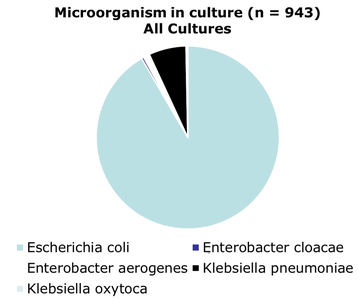
- Proportion of urinary isolates resistant to nitrofurantoin

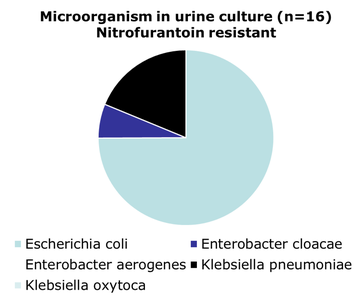
Results

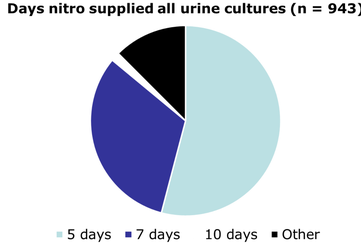
Table 1. Demographics of Patients Prescribed Nitro for Suspected UTIs

Variable	Patients Receiving Nitro (n = 634) No. (%)*	Subset Nitro-R (n = 13) No. (%)*
Age (years), mean (SD)	42.7 (17.0)	41.9 (12.1)
BMI (kg/m²), mean (SD)	30.3 (7.3)	28.2 (7.2)
Weight (kg), mean (SD)	77.2 (19.4)	66 (18.8)
Gender		
Female	628 (99.0)	13 (100)
Race		
White or Caucasian	466 (73.5)	10 (76.9)
Other	95 (15.0)	2 (15.4)
Black or African American	48 (7.6)	1 (7.7)
American Indian or Alaska Native	14 (2.2)	0 (0)
Asian	11 (1.7)	0 (0)
Ethnicity		
Hispanic, Latinx, or Spanish Origin	475 (74.9)	10 (76.9)
Comorbid Conditions		
Pregnancy	257 (40.5)	5 (38.5)
Diabetes	156 (24.6)	5 (38.5)
Kidney Stones	74 (11.7)	3 (23.1)
Heart Failure	33 (5.2)	0 (0)

Nitro = nitrofurantoin; R = resistant; *: unless otherwise noted







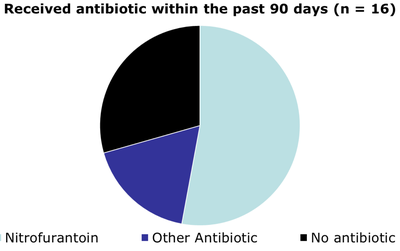
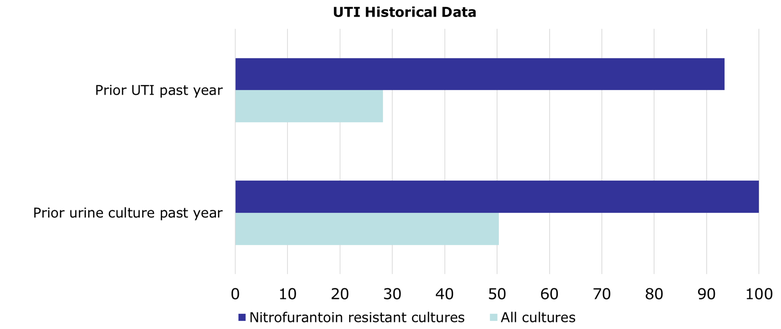


Table 2. Antibiotics Prescribed in Nitrofurantoin Resistant Cultures (n = 16)

Variable	No. (%)
New Antibiotic After Culture Resulted	
Cephalexin	7 (43.8)
Levofloxacin	3 (18.8)
Sulfamethoxazole/trimethoprim	2 (12.5)
Other (Fosfomycin, cefdinir, amoxicillin/clavulanate)	3 (18.8)

Results Continued



Discussion

- Increasing guideline-concordant durations is an important antibiotic stewardship opportunity
  - Institutional guidance is 5-day nitrofurantoin courses
  - Prescribed durations were discordant in about 46% of cases
- Despite widespread use, resistance among urinary pathogens remains uncommon (1.7% resistance)
  - May be associated with recent nitrofurantoin exposure
- **Limitations:**
  - Overall, there were few cases of nitrofurantoin resistance
  - Outpatient prescriptions are difficult to monitor for adherence
  - Retrospective
  - Over 90% of organisms identified were *Escherichia coli*
  - Nearly 75% of patients were Hispanic, Latinx, or Spanish ethnicity

Conclusion

- These results could be used to guide empiric nitrofurantoin treatment for urinary tract infections
- In addition, durations of antibiotics could be targeted to ensure that patients are receiving guideline concordant prescriptions outpatient

References:

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5. Zhang X, Zhang Y, Wang F, et al. Unravelling mechanisms of nitrofurantoin resistance and epidemiological characteristics among Escherichia coli clinical isolates. *Int J Antimicrob Agents.* 2018 Aug;52(2):226-232. doi: 10.1016/j.ijantimicag.2018.04.021.

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