March 23, 2021

Are male urinary tract infections always complicated?

Funnce Liu, PharmD
PGY2 Infectious Diseases Pharmacy Resident
UW Medical Center

Objectives

- Describe definitions of complicated and uncomplicated UTIs
- Review current guideline recommendations for treatment of UTIs in males
- Discuss literature on treatment of UTIs in males

Anatomy of UTIs

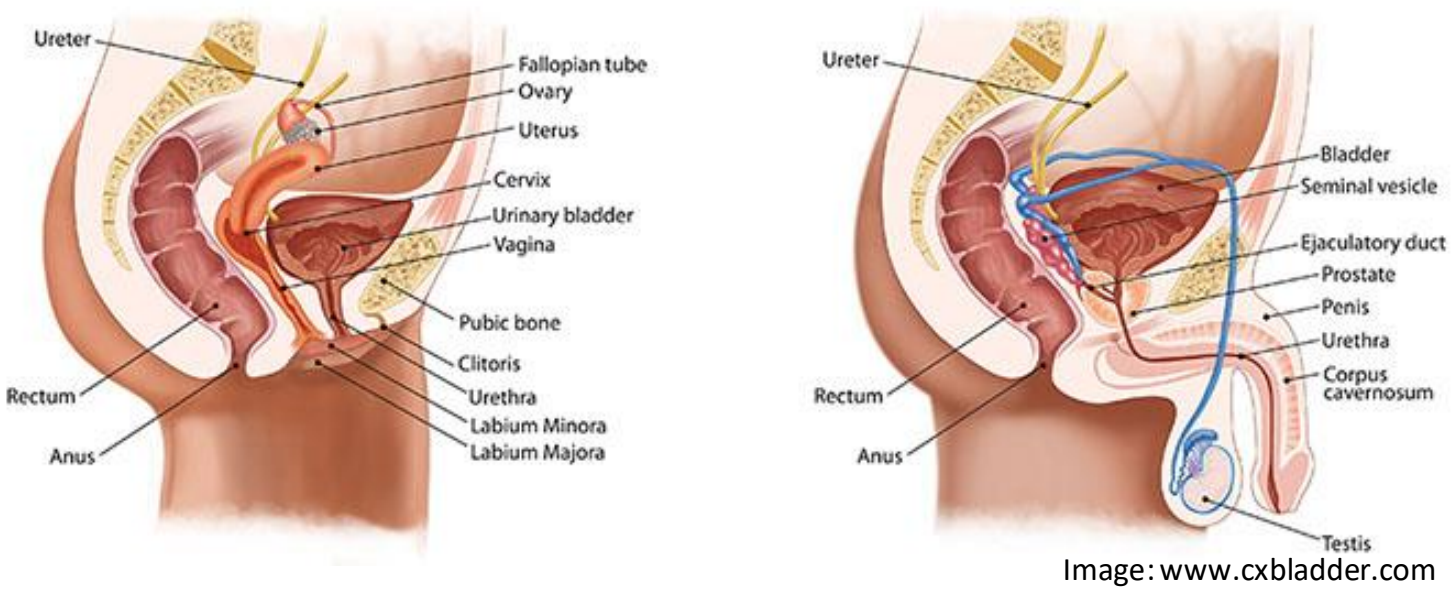


Image: www.cxbladder.com

- UTIs are more common in women than men
  - Urethral distance shorter in women
  - Closer urethral proximity to moist, warm vulvar and perianal area
- Given infrequent UTIs in men, symptomatic UTIs are assumed to be due to anatomical issue or other complicating factor

[edited by] John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, And Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

Uncomplicated vs Complicated UTI

Uncomplicated[1]	Complicated (generally accepted)[1]
Infection in a structurally and neurologically normal urinary tract	Infection and factors that predispose to persistent or relapsing infection • Foreign bodies (e.g., calculi, IUC, drainage device) • Obstruction • Immunosuppression • Renal transplant • Retention from neurologic disease • Renal failure

- Definitions of uncomplicated and complicated UTI are not agreed upon by all experts[2]
- Some definitions may include signs/symptoms of systemic infection (e.g., fever, sepsis), postmenopause, or preadolescence[3]

[1][edited by] John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, And Bennett's Principles and Practice of Infe ctious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.
[2]CID 2017;64(4):529 [3]Am Fam Physician. 2011 Oct 1;84(7):771-776.

UTI Definitions in Males

- Historically, male UTIs have been considered complicated due relative low rates of UTI and high proportion of complicated UTI in men who get infected[1,2]
- Some experts only consider a UTI as complicated if the patient has signs/symptoms suggesting an infection extending beyond the bladder in men[3]

[1][edited by] John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, And Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.
[2]Colgan R, Williams M. Diagnosis and treatment of acute uncomplicated cystitis. Am Fam Physician. 2011 Oct 1;84(7):771-6. PMID: 22010614.
[3]Hooton TM. Acute cystitis in men. UpToDate. Waltham, MA. (Accessed on March 15, 2021)

Current Recommendations

- IDSA has only published guidelines for female cystitis and pyelonephritis
- Men have historically been treated with complicated UTI regimens studied in females

EAU Guidelines

European Association of Urology

Cystitis in men

Cystitis in men without involvement of the prostate is uncommon and should be classed as a complicated infection. Therefore, treatment with antimicrobials penetrating into the prostate tissue is needed in males with symptoms of UTI. A treatment duration of at least seven days is recommended, preferably with trimethoprim sulfamethoxazole or a fluoroquinolone if in accordance with susceptibility testing.

- Treat as complicated for ≥ 7 days
- Choose prostate penetrating antibiotic
- Fluoroquinolone or SMX/TMP preferred

Bonkat G et al. Urological Infections Guideline. European Association of Urology. 2020.

Treatment Duration in Male UTI

Study	Design
Urinary Tract Infection in Male Veterans Treatment Patterns and Outcomes Drekonja D et al. 2013	Retrospective review of outpatient male UTI treatment (n = 33,336) <u>Parameters Measured</u>: Early recurrence (≤30 days) Late recurrence (>30 days) Antibiotic duration (≤ 7 days, >7 days) Antimicrobial use *C. difficile* infection

ICD9 Codes for outpatient UTIs were pulled → Filtered for patients with typical UTI antimicrobial prescription within 72 h of encounter

Drekonja DM et al. Urinary tract infection in male veterans: treatment patterns and outcomes. JAMA Intern Med. 2013 Jan 14;173(1):62-8. doi: 10.1001/2013.jamainternmed.829.

Duration and Antimicrobials

Shorter Duration (≤7 days, 35%)	Longer Duration (>7 days, 65%)
7 days (77.2%)	**10 days (66.2%)**
5 days (14.2%)	14 days (18.7%)
3 days (6.6%)	30 days (3.5%)
1-6 days (2.0%)	8-173 days (11.6%)

- Most common durations
  - Short = 7 days
  - Long = 10 days
- 84.4% of cases fells within 7-14 days

Antimicrobial	Percent Use
Ciprofloxacin	**62.7%**
SMX/TMP	**26.8%**
Nitrofurantoin	6.1%
Amoxicillin or Amox/Clav	5.6%
Levofloxacin	3.9%
Other	<3%

- Ciprofloxacin and SMX/TMP most commonly used

Factors Associated with Early Recurrence

Table 3. Multivariate Associations of Demographic, Clinical, and Treatment Characteristics Among Outpatient Male Veterans in Fiscal Year 2009

Characteristic	Odds Ratio (95% CI)
Association With Risk of Early Recurrence (<30 Days) of Urinary Tract Infection[a]	
β-Lactam treatment[b]	1.81 (1.52-2.17)
History of prior urinary tract infection	1.49 (1.32-1.68)
Incontinence	1.18 (1.00-1.36)
Prostate hypertrophy	1.22 (1.08-1.38)

- Duration NOT associated with early recurrence in (OR 1.01, 95% CI 0.90-1.14)
- Beta-lactam use was associated with INCREASED risk of early recurrence (OR 1.81, 95% CI 1.52-2.17)

Factors Associated With Late Recurrence

Table 5. Multivariate Associations of Demographic, Clinical, and Treatment Characteristics With Risk of Late Recurrence (≥30 Days) of Urinary Tract Infection Among Outpatient Male Veterans in Fiscal Year 2009

Characteristic[a]	Odds Ratio (95% CI)
Age	1.01 (1.00-1.01)
Charlson Comorbidity Index[b]	
1	1.13 (1.01-1.27)
2	1.22 (1.07-1.40)
≥3	1.16 (1.01-1.34)
History of prior urinary tract infection	2.74 (2.52-2.97)
Incontinence	1.44 (1.30-1.59)
Prostate hypertrophy	1.15 (1.05-1.25)
Prostatitis	1.37 (1.12-1.67)
Spinal cord injury	1.68 (1.43-1.96)
Treatment duration >7 d	1.20 (1.10-1.30)
Urethral stricture	1.23 (1.09-1.39)
Urinary calculi	1.21 (1.06-1.38)

[a] Variables included in the model but not significantly associated with late recurrence were stroke, dementia, β-lactam treatment, prostate cancer, diabetes mellitus, multiple sclerosis, vesicoureteral reflux, chronic renal disease, prostate disease (other), fluoroquinolone treatment, human immunodeficiency virus infection, and trimethoprim-sulfamethoxazole treatment.

[b] Charlson Comorbidity Index of 0 was used as the reference group.

- Treatment duration >7 days associated with INCREASED risk of late recurrence (OR 1.20; 95% CI 1.10-1.30)
- Prostatitis associated with INCREASED risk of late recurrence (OR 1.37; 95% CI 1.12-1.67)

Factors Associated With CDI

Table 3. Multivariate Associations of Demographic, Clinical, and Treatment Characteristics Among Outpatient Male Veterans in Fiscal Year 2009

Characteristic	Odds Ratio (95% CI)
Association With Risk of *Clostridium difficile* Infection Within 90 Days of the Index Urinary Tract Infection Episode[c]	
β-Lactam treatment[b]	2.05 (1.27-3.30)
Charlson Comorbidity Index[d]	
2	2.58 (1.42-4.68)
≥3	3.40 (1.82-6.35)
History of prior *C difficile* infection	8.82 (5.45-14.27)

[b]Fluoroquinolones used as reference group

- Beta lactam treatment associated with INCREASED risk of CDI
- History of CDI was greatest predictor of CDI

CDI = *Clostridioides difficile* infection

Takeaway Points

- Male UTI treatment of ≤7 days is not associated with increased risk of early recurrence
- Beta-lactams associated with subsequent CDI and early recurrence

No Benefit Treating >7 Days

Study	Design
No Clinical Benefit to Treating Male Urinary Tract Infection Longer Than Seven Days: An Outpatient Database Study Germanos GJ et al. 2019	Retrospective outpatient database study (n = 637) Primary Exposure: Short (≤7 days) or long (>7 days) treatment duration Outcome Variables: Early recurrence Late recurrence

UTIs identified by ICD9 codes in outpatient clinics → Split into short and long duration groups → Further classified by having or not having complicating factors → Analyzed for association with recurrence

Complicating factors: pyelonephritis, prostatitis, nephrolithiasis

Germanos GJ et al. No Clinical Benefit to Treating Male Urinary Tract Infection Longer Than Seven Days: An Outpatient Database Study. Open Forum Infect Dis. 2019 May 6;6(6):ofz216. doi: 10.1093/ofid/ofz216.

Antibiotic Use and Duration

Antibiotic	Visits Without Complicating Factors (n = 518)	Visits With Complicating Factors (n = 119)
Fluoroquinolone	69.9%	68.9%
SMX/TMP	21.4%	20.2%
Nitrofurantoin	5.2%	5.9%
Beta-lactams	3.5%	5.0%

Treatment Duration	Visits Without Complicating Factors (n = 518)	Visits With Complicating Factors (n = 119)
≤5 days	69.9%	68.9%
6 days to 7 days	21.4%	20.2%
8 days to 10 days	5.2%	5.9%
11 days to 14 days	3.5%	5.0%
>14 days	0%	32.8%

Bivariate Analysis: Predictors of UTI Recurrence

	Overall Cohort	No Prostatitis	No Prostatitis or Pyelonephritis	No Prostatitis, Pyelonephritis, Nephrolithiasis, or BPH
Longer duration (OR, 95% CI)	1.95 (0.91-4.21)	**2.26 (1.03-4.96)**	**2.31 (1.05-4.68)**	**2.62 (1.04-6.61)**

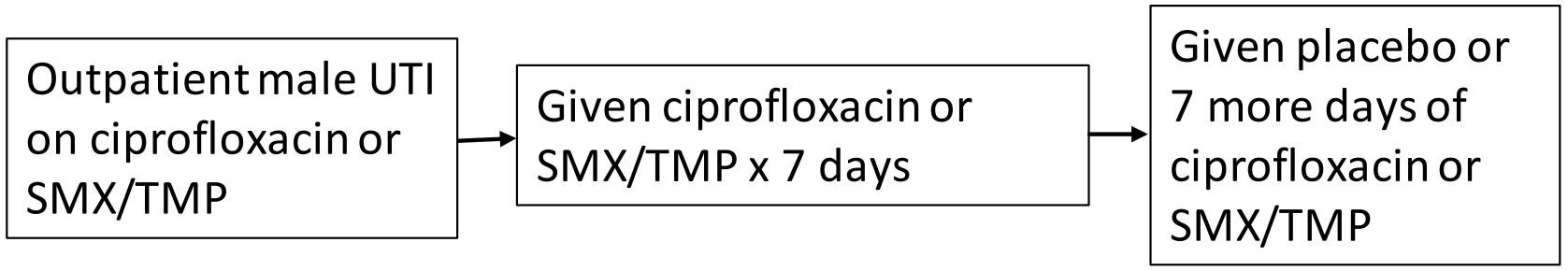
- Age, antibiotic type, race, and CCI were not predictive of UTI recurrence
- In the overall cohort, longer duration was not associated with recurrence
- In subgroup analysis, the group that excluded BPH in addition to complicating factors had greatest magnitude of association

Takeaway

- Fluroquinolones and SMX/TMP were most used; however, no class of antibiotic was associated with recurrence
- Generally, longer durations were associated with recurrence in the absence of complicating factors (i.e., prostatitis, pyelonephritis, nephrolithiasis)

Treatment Duration in Male UTI

Study	Design
Seven vs. 14 Days Treatment Duration for Afebrile Men with Urinary Tract Infections; A Randomized Clinical Trial Drekonja D et al. 2020 **ABSTRACT ONLY**	Randomized controlled trial (n = 273) **Primary Outcome**: Percentage of subjects with symptom resolution 14 days after completion of therapy (10% difference, p-value 0.05 for significance) **Secondary Outcome**: Recurrent of UTI Adverse Events



Drekonja D et al. Seven vs. 14 Days Treatment Duration for Afebrile Men with Urinary Tract Infections; A Randomized Clinical Trial, OFID Vol 7, Issue Supplement_1, Oct 2020, Pages S220–S221,

Treatment Duration in Male UTI

Per-Protocol (n = 254)	7 days (n = 136)	14 days (n = 136)	P-value
Symptom resolution	93.1%	90.2%	P = 0.5

Note: Intention to treat yielded similar results (n = 272)

Authors' Conclusion:
Treatment with 7 days was non-inferior to 14 days for symptom resolution. Afebrile men with UTI should not be treated beyond 7 days.

Nitrofurantoin Use in Male UTI

- A large retrospective study (n = 485) showed that there may be an association between clinical cure and CrCl; however, results are difficult to interpret due to confounding factors and definitions of cure[1]
- A small retrospective study showed failure in 8/26 uncomplicated male UTI patients[2]
  - 6 failures explained by resistance and alkaline urine pH
  - 2 failures explained by CrCl <30 mL/min

[1]Ingalsbe ML, Wojciechowski AL, Smith KA, Mergenhagen KA. Effectiveness and safety of nitrofurantoin in outpatient male veterans. Ther Adv Urol. 2015 Aug;7(4):186-93.
[2]Cunha BA et al. Nitrofurantoin safety and effectiveness in treating acute uncomplicated cystitis (AUC) in hospitalized adults with renal insufficiency: antibiotic stewardship implications. Eur J Clin Microbiol Infect Dis. 2017 Jul;36(7):1213-1216.

Final Thoughts

- Not all male UTIs are complicated
- Observational data and preliminary RCT data demonstrates that 7 days is non-inferior to 14 days
- Most commonly used antibiotics are fluoroquinolones and SMX/TMP
- Beta lactams may have increased association with CDI and recurrence but are reasonable as second line agents
- Prostatitis and complicated UTIs were often excluded in studies
- Nitrofurantoin may be considered if adequate CrCl (>30 mL/min) and without complicating factors

UWTASP
tele-antimicrobial stewardship program

March, 2021

Are male urinary tract infections always complicated?

Funnce Liu, PharmD
PGY2 Infectious Diseases Pharmacy Resident
UW Medical Center