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Recurrent urinary tract infections

Speaker

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Disclosures

Advisory Boards: Coloplast, Astellas, Allergan

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Objectives

1. Define and identify recurrent uncomplicated urinary tract infections in women
2. Establish the appropriate evaluation and treatment of rUTI
3. Integrate the different prevention strategies for rUTI
4. Apply the principles of antimicrobial stewardship to the treatment of rUTI
5. Identify the indications to refer to a specialist in a context of rUTIs

Outline

- Definition
- Epidemiology
- Diagnosis
- Treatment
- Prevention
- Antibiotic stewardship
- When to refer?

https://choosingwiselycanada.org/antibiotics-urinary-tract-infections/

Definitions

- Urinary tract infection (**UTI**): inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria
  - Acute bacterial cystitis

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- **Bacteriuria**: presence of bacteria in the urine which is normally free of bacteria
  - Asymptomatic or symptomatic

- **Pyuria**: presence of ***white blood cells*** in the urine

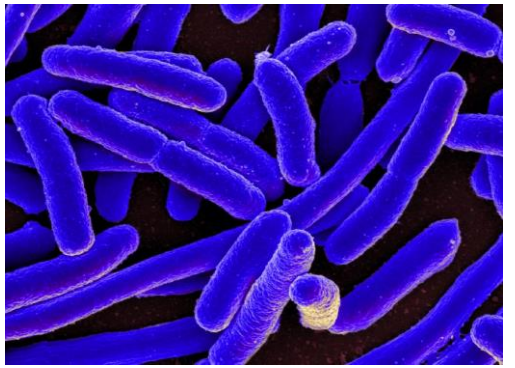
Definitions

- **Uncomplicated:** infection in a healthy patient with a anatomically and functionally normal urinary tract (in nonpregnant immune competent woman)
- **Complicated:** infection with factors that increase the chance of acquiring bacteria and decrease the efficacy of therapy
  - Urinary tract is structurally or functionally abnormal, host is immunocompromised, multi-drug resistant bacteria
  - Majority of these patients are men
- **Recurrent UTI (rUTI):** recurrent episodes of uncomplicated cystitis in women
  - Two separate culture-proven episodes of acute bacterial cystitis and associated symptoms within six months, or (***2 UTIs/6 months***)
  - Three episodes within one year (***3 UTIs/1 year***)

Definitions

- **Reinfection**: recurrence with a different organism, the same organism in more than 2 weeks after treatment, or a sterile intervening culture
  - Usually different organisms – variable intervals
  - Uncommon in men – usually with GU tract abnormality
  - Common in women – usually don't have correctable cause

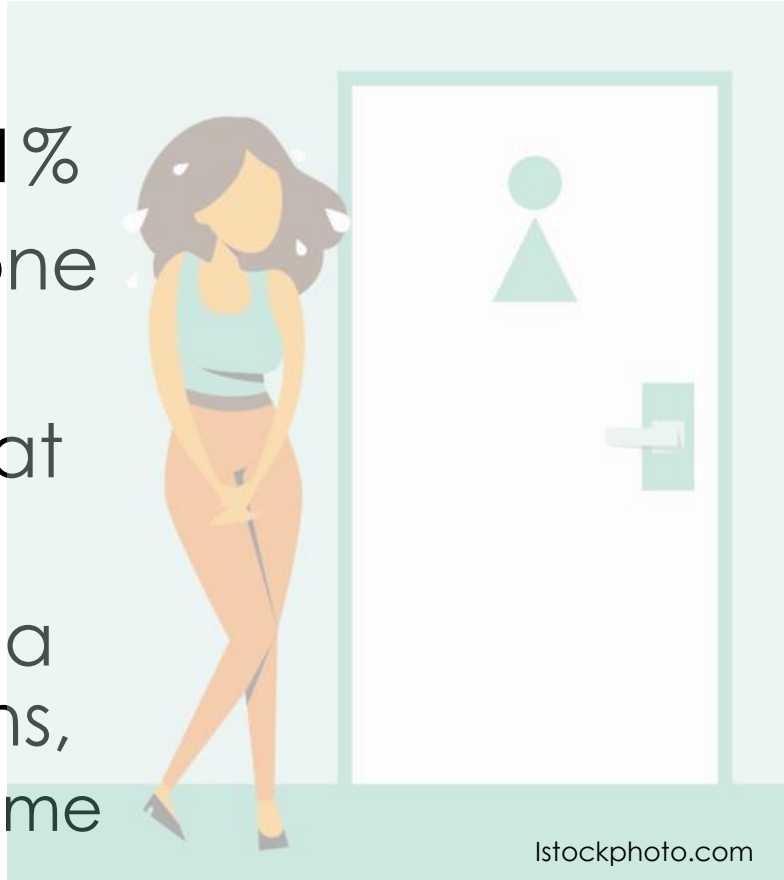
- **Bacterial persistence**: same bacteria cultured within 2 weeks after initiating sensitivity-adjusted therapy,
  - Same organism – short interval
  - could be from a nidus



https://www.niaid.nih.gov/diseases-conditions/e-coli

Epidemiology

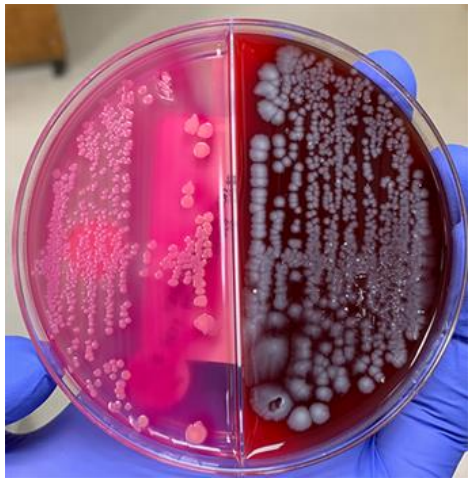
- Prevalence of UTI in women >65 y.o.: 20%,
- Prevalence of UTI in the overall population: 11%
- 50% - 60% of adult women will have at least one UTI in their life
- ~10% of postmenopausal women indicate that they had a UTI in the previous year
- After first episode of UTI, 27% of women have a confirmed recurrence within the next 6 months,
  - and 2.7% have a second recurrence within the same period of time



Chu CM et al. Am J Obstet Gynecol 2018

Diagnosis

- *Symptoms*: Dysuria (acute onset), with increased urinary urgency and frequency, hematuria, and new or worsening incontinence
- Non specific symptoms in older women
- Uropathogen in the urine (E.Coli 75-95%) with urine culture
  - Traditional threshold: $>10^5$ CFU/mL bacteria in a clean-catch midstream specimen
  - Lower threshold if strong suspicion: $\geq 10^2$ CFU/mL of a single uropathogen
  - Consider urinalysis results to determine if infection or contaminant



Asm.org

Diagnosis

- ***Urinalysis***
  - *Bacteriuria:*
    - Sensitivity for UTI of 40 – 70 %
    - Specificity for UTI of 85 – 95 %
    - > 90% of infection with **>= 10^5 CFU/ml**
    - Not detectable with 10^2 – 10^4 cfu/ml – error (false negative result) due to limitation by the microscope on the volume of urine that can be observed
    - Bacteria on the microscopic analysis but culture is negative – error (false positive result)
  - *Nitrites:*
    - Sensitivity for UTI of 35 – 85 %
    - Specificity for UTI of >90 %
  - *Pyuria* (WBC): inflammatory response
    - Sensitivity for UTI of 80 – 95%
    - Specificity for UTI of 50 – 76%
  - *Hematuria*: inflammatory response (consider microscopy)

Medicinenet.com

Evaluation

- Clinicians should obtain a complete patient history and perform a pelvic examination in women presenting with rUTIs. (Clinical Principle)

- To make a diagnosis of rUTI, clinicians must document positive urine cultures associated with prior symptomatic episodes. (Clinical Principle)

- Clinicians should obtain repeat urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen. (Clinical Principle)

Anger J et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline 2019

Evaluation

- Cystoscopy and upper tract imaging should not be routinely obtained in the index patient presenting with rUTI. (Expert Opinion)

- Clinicians should obtain urinalysis, urine culture and sensitivity with each symptomatic acute cystitis episode prior to initiating treatment in patients with rUTIs. (Moderate Recommendation; Evidence Level: Grade C)

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When to refer

- Bacterial persistence after sensitivity-based therapy
- Prior urinary tract surgery or trauma
- Gross hematuria after resolution of infection
- Previous bladder or renal calculi
- Obstructive symptoms (straining, weak stream, intermittency, hesitancy, low uroflowmetry or high PVR
- Urea-splitting bacteria on culture (e.g., Proteus, Yersinia)
- Prior abdominopelvic malignancy
- Diabetes or immunocompromised
- Pneumaturia, fecaluria
- Repeated pyelonephritis

Dason S, et al. CUAJ 2011

Principles of antimicrobial therapy

- Eradicate bacterial growth in the urinary tract
- Efficacy depends on the antimicrobial levels in the urine and the duration that this level remains above the MIC (minimal inhibitory concentration) of the infecting organism
- Selection of antibiotics depends on spectrum of activity or the most probable uropathogen based on the source of acquisition of infection
- Blood levels of antimicrobial is important when bacteremia and febrile UTI
- Beware of renal insufficiency for antibiotics primarily cleared by the kidneys

Treatment

First-line therapy for the treatment of uncomplicated symptomatic UTI

Treatment effects	Nitrofurantoin	TMP-SMX	Fosfomycin
Cure rate	88-93%	90-100%	83-91%
Antimicrobial spectrum	narrow: *E. coli, S. saprophyticus*	typical uropathogens	Covers VRE, ESBL GNRs
Collateral damage	No	Minimal	No
Resistance	Low, stable X 50y	Increasing	Currently low
Dose & duration	100 mg BID X 5d	One DS BID X 3d	3 g single dose

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Antimicrobial resistance

2018 NATIONAL Antimicrobial Susceptibility Testing Results: *Escherichia coli*

Source: http://www.can-r.com

Escherichia coli (554)	SUSCEPTIBILITY					RANGE	
	% SUS	% INT	% RES	MIC_{50}	MIC_{90}	MIN	MAX
Amikacin	99.5	0.4	0.2	2	4	≤ 1	> 64
Amoxicillin Clavulanate	68.8	19.3	11.9	8	32	1	> 32
Aztreonam	87.0	2.3	10.6	≤ 0.12	16	≤ 0.12	> 64
Cefazolin	59.9	15.2	24.9	2	> 128	≤ 0.5	> 128
Cefepime	89.4	2.5	8.1	≤ 0.25	4	≤ 0.25	> 64
Cefoxitin	85.9	7.9	6.1	4	16	0.25	> 32
Ceftazidime	86.3	2.7	11.0	0.5	16	≤ 0.25	> 32
Ceftobiprole *	87.7		12.3	≤ 0.06	> 32	≤ 0.06	> 32
Ceftolozane Tazobactam	97.8	0.2	2.0	0.25	0.5	≤ 0.12	> 64
Ceftriaxone	85.6	0.2	14.3	≤ 0.25	> 64	≤ 0.25	> 64
Ciprofloxacin	73.1	1.8	25.1	≤ 0.06	> 16	≤ 0.06	> 16
Colistin	No breakpoints defined			0.5	0.5	0.12	> 16
Doxycycline	71.1	4.5	24.4	2	32	0.5	> 32
Ertapenem	98.9	0.5	0.5	≤ 0.03	0.06	≤ 0.03	> 32
Gentamicin	91.2	0.9	7.9	≤ 0.5	2	≤ 0.5	> 32
Imipenem	99.5	0.4	0.2	0.25	0.5	0.06	> 32
Meropenem	99.8		0.2	≤ 0.03	≤ 0.03	≤ 0.03	> 32
Moxifloxacin	No breakpoints defined			≤ 0.06	16	≤ 0.06	> 16
Nitrofurantoin	97.3	1.4	1.3	16	32	2	> 512
Piperacillin Tazobactam	95.5	1.6	2.9	2	4	≤ 1	> 512
Tigecycline *	100.0			0.25	0.5	0.06	2
Tobramycin	92.8	2.3	4.9	≤ 0.5	2	≤ 0.5	> 64
Trimethoprim Sulfa	72.4		27.6	≤ 0.12	> 8	≤ 0.12	> 8

CLSI M100-29th Ed. breakpoints were used to interpret MIC values
*Interpretive breakpoints defined by FDA (tigecycline) and Health Canada (ceftobiprole)

Antibiotic treatment

- Clinicians may offer patient-initiated treatment (self-start treatment) to select rUTI patients with acute episodes while awaiting urine cultures. (Moderate Recommendation; Evidence Level: Grade C)

- Clinicians should use first-line therapy (i.e., nitrofurantoin, TMP-SMX, fosfomycin) dependent on the local antibiogram for the treatment of symptomatic UTIs in women. (Strong Recommendation; Evidence Level: Grade B)

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Antibiotic treatment

- Clinicians should treat rUTI patients experiencing acute cystitis episodes with as short a duration of antibiotics as reasonable, generally no longer than seven days. (Moderate Recommendation; Evidence Level: Grade B)

- Inpatients with rUTIs experiencing acute cystitis episodes associated with urine cultures resistant to oral antibiotics, clinicians may treat with culture-directed parenteral antibiotics for as short a course as reasonable, generally no longer than seven days. (Expert Opinion)

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Prevention

- Conservative measures
  - Limited use of spermicide : lack evidence – but not harmful
  - Pre or post-coital voiding : lack evidence – but not harmful
  - Lactobacillus probiotics : inconclusive studies
  - Cranberry products
- Antibiotics
  - Continuous low-dose
  - Self-start : 3 day treatment
    - Contact their physician if no improvement within 48 hours
  - Postcoital within 2 hours of coitus
- Other
  - Estrogens in post-menopausal
    - Vaginal rings changed every 12 weeks for a total of 36 weeks
    - Vaginal creams : 0.5 mg of estriol every night for 2 weeks, then twice a week for 8 months

Table 3. Suggested antibiotic prophylaxis[39]

Continuous	Postcoital (within 2 hours of coitus)
Trimethoprim/sulfamethoxazole (TMP/SMX) (40 mg/200 mg daily or thrice weekly)[45]	TMP/SMX (40 mg/200 mg to 80 mg/400 mg)[46]
Trimethoprim (100 mg daily)[45,47]	
Ciprofloxacin (125 mg daily)[48]	Ciprofloxacin (125 mg)[48]
Cephalexin (125 mg to 250 mg daily)[49]	Cephalexin (250 mg)[50]
Cefaclor (250 mg daily)[51]	
Nitrofurantoin (50 mg to 100 mg)[52]	Nitrofurantoin (50 mg–100 mg daily)[46]
Norfloxacin (200 mg daily)[53]	Norfloxacin (200 mg)[56]
Fosfomycin (3 g every 10 days)[55]	
	Ofloxacin (100 mg)[56]

Prevention

Antibiotic Prophylaxis

- Following discussion of the risks, benefits, and alternatives, clinicians may prescribe antibiotic prophylaxis to decrease the risk of future UTIs in women of all ages previously diagnosed with UTIs. (Moderate Recommendation; Evidence Level: Grade B)

  - 6-12 months

    - TMP 100mg daily
    - TMP-SMX 40mg/ 200mg daily
    - TMP-SMX 40mg/ 200mg thrice weekly
    - Nitrofurantoin monohydrate/macrocrystals 50mg daily
    - Nitrofurantoin monohydrate/macrocrystals 100mg daily
    - Cephalexin 125mg once daily
    - Cephalexin 250mg once daily
    - Fosfomycin 3g every 10 days

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Prevention

Non-Antibiotic Prophylaxis

- Clinicians may offer cranberry prophylaxis for women with rUTIs. (Conditional Recommendation; Evidence Level: Grade C)
  - oral juice (high in sugar content)
  - tablet formulations
    - 500 mg daily of cranberry fruit powder
    - Standardized formulation of 36 mg of PAC (proanthocyanidins)
- Increased water intake
- Lactobacillus probiotics
- Other supplements: D-mannose, methenamine

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Prevention

Estrogen

- In ***peri-*** and ***post-menopausal*** women with rUTIs, clinicians should recommend vaginal estrogen therapy to reduce the risk of future UTIs if there is no contraindication to estrogen therapy. (Moderate Recommendation; Evidence Level: Grade B)

Commonly used vaginal estrogen therapy

Formulation	Composition	Strength and Dosage
Vaginal tablet	Estradiol hemihydrate*	10 mcg per day for 2 weeks, then 10 mcg 2-3 times weekly
Vaginal ring	17b-estradiol	2 mg ring released 7.5 mcg per day for 3 months (changed by patient or provider)
Vaginal cream	17b-estradiol	2 g daily for 2 weeks, then 1 g 2-3 times per week
	Conjugate equine estrogen	0.5 g daily for 2-weeks, then 0.5 g twice weekly

* Estradiol hemihydrate comes in a 4mcg tablet; however, this has not been studied for prevention of rUTI.

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Vaginal estrogen therapy

- Vaginal estrogen therapy has **not been shown to increase risk of cancer** recurrence in women undergoing treatment for or with a personal history of ***breast cancer***.
  - Therefore, vaginal estrogen therapy should be considered in prevention of UTI women with a personal history of breast cancer in coordination with the patient's oncologist

- Systematic review supports the use of low-dose vaginal estrogens for treating vulvar and vaginal atrophy in menopausal women *without a concomitant progestogen.*
  - This review does not support increased endometrial hyperplasia or cancer risk with low-dose, unopposed vaginal estrogens

Anger J et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline 2019
Constantine GD et al. Endometrial safety of low-dose vaginal estrogens in menopausal women: a systematic evidence review. Menopause. 2019

Antimicrobial stewardship

- Obtain cultures for each symptomatic episode
- Reduce inappropriate treatment, decrease broad-spectrum antibiotic use, and appropriately tailor necessary treatment to the shortest effective duration
- Local antibiogram with the selection of antimicrobial agents with the least impact on normal vaginal and fecal flora (nitrofurantoin, fosfomycin)

Take-home points

- Uncomplicated rUTIs are 2 ***symptomatic*** UTIs in a women in 6 months or 3 UTIs in 1 year, ***culture-proven***
- Treatment should be guided by sensitivity profile of urine culture, with either *nitrofurantoin*, *TMP-SMX* or *fosfomycin*, following the principles of antimicrobial stewardship
- Prevention strategies include non-antibiotics with cranberry supplements or vaginal estrogen, or antibiotic regimen (low-dose or post-coital)
- Referral to a specialist should be considered in a context of *bacterial persistence*, or concerns for other possible diagnosis or complicating factors