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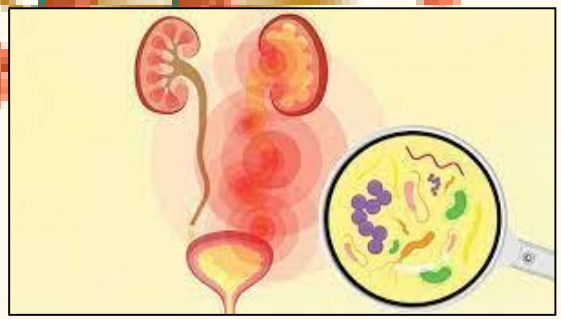
BRIHANMUMBAI MAHANAGARPALIKA

- **Professor & Unit Head, HBT Medical College & Dr RN Cooper Hospital, Mumbai**
- **Core committee, FOGSI Violence against Women Cell 2015-21**
- **Member, FOGSI GCPR for COVID guidance and Vaccination 2020-21**
- **President, Mumbai Breastfeeding Promotion Committee 2019-22**
- Chairperson, FOGSI Perinatology Committee 2015-2017
- **ICOG Governing Council Member 2021-22**
- 50+ chapters in FOGSI/ other books, over 75 publications in journals
- **2 gold medals, 5 distinctions, 25 prizes and awards**
- **Editor/ Co-editor of 14 books, author of 2 textbooks**
- **MOGS Personality of the Year Award 2020-21**
- **Awarded MOGS SN Pandit award for Women's Empowerment 2017, MOGS Ganatra trust Prize for contribution to Social Issues, Dr RD Pandit Prize twice & Dr Duru Shah Best committee member Prize three times from MOGS**
- **PG/ UG Teacher for DNB, DGO and MBBS, Referee for MRCOG**



UTI IN PREGNANC

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विद्या नो रुग्विमुक्तये

Urinary tract host defences

Urine

1. Acidic pH: Intolerable by pathogens
2. High urine osmolality
3. Mechanical flushing of urine flow

Mucosal immunity

1. Urothelial secretion of cytokines & chemokines
2. Mucopolysaccharide lining: Increases difficulty of bacterial penetration
3. Mucosal IgA
4. In men: Prostatic secretions contain bactericidal zinc & urethra is longer

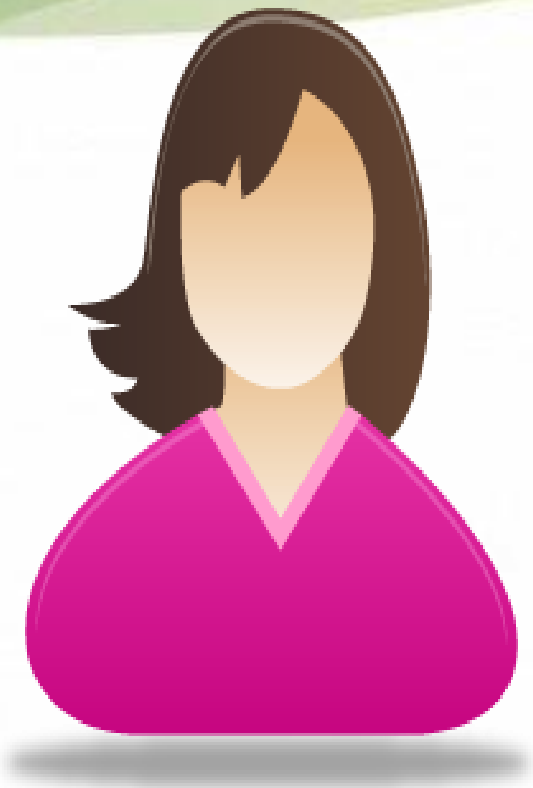
Hooton, T. NEJM. 2012; 366 (11): 1028-037./ Stamey TA, et al. Nature. 1968; 218: 444–447. / Naber KG. BJUI. 2008; 101(Suppl 3): 7–10./ Parsons CL, et al. Invest Urol. 1978; 6: 196–200.

UTI: Introduction

- Urinary tract infections (UTIs): 2nd most common infectious presentation in community practice
- Common infections diagnosed in outpatients as well as hospitalized patients
- Self-limiting
- Recurrence
- Occurs in males & females, in all age groups

UTI: Infection of urinary system causing inflammatory response

Dason S, et al. Can Urol Assoc J. 2011; 5(5): 316-22./ Campbell Walsh. 2007; 9th ed/ Akram M, et al. Ann Clin Microbiol Antimicrob. 2007; 6: 4.



Incidence of UTI is more common in females 53.3% as compared to males 46.7%

- Mittal S, et al. Infectious Disorders – Drug Targets, 2015, Vol. 15, No. 3

↑ with increasing age
Postmenopausal women

It is estimated that about 35% of healthy women suffer symptoms of UTI at some time in their life

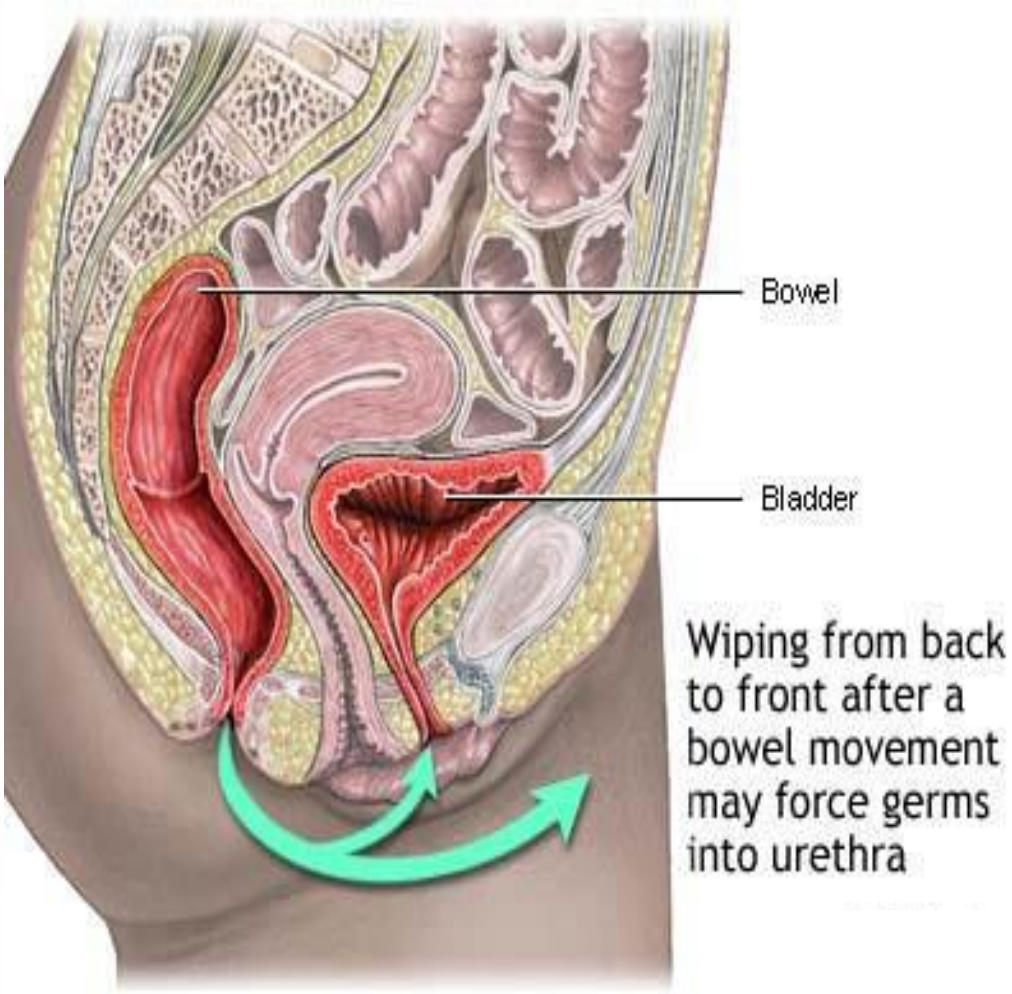
- Ponnusamy P, et al. International Journal of Microbiological Research 4 (2): 101-118, 2013

Ahmed SM, et al. Journal of Clinical and Diagnostic Research. 2012; 6(7): 1192-1195./ 2. Brusch JL, et al. Cystitis in Females: Practice Essentials, Background, Pathophysiology. Medscape.

Why greater susceptibility of UTI in women?

Female urethra

- Short length (~ 4 cm)
- Proximity to anus

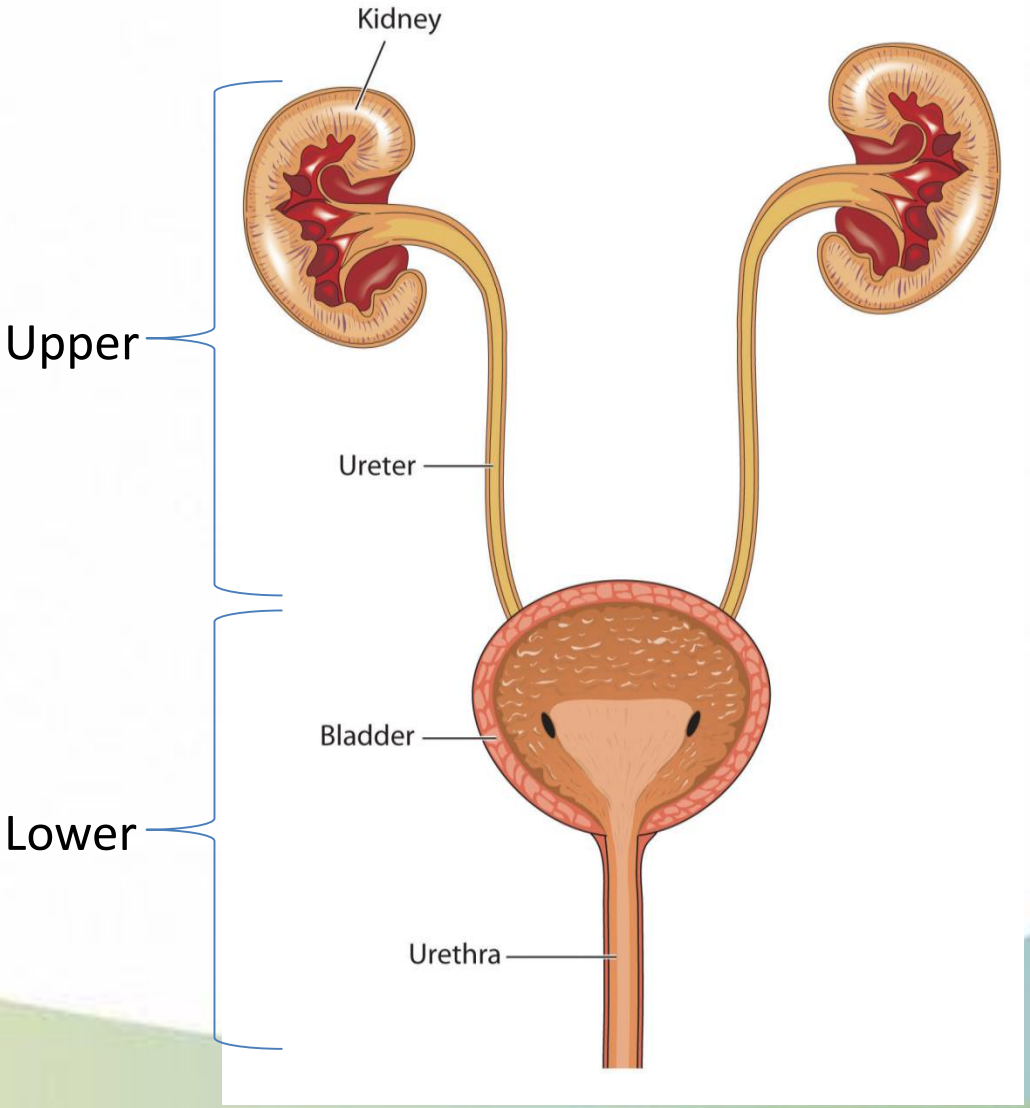


Urethra is prone to colonization with bacteria (faecal bacteria)

Minardi D, et al. International Journal of General Medicine. 2011: 4; 333–343.

Upper & Lower UTI

- **Lower UTI (urethra & bladder)**
  - Urethritis
  - Cystitis
- **Upper UTI (Ureter & kidney)**
  - Pyelonephritis



Definitions

Asymptomatic bacteriuria or asymptomatic urinary infection

Isolation of specified quantitative count of bacteria in appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection (2 consecutive voided urine specimens, bacterial strain: 10^5 cfu/mL)

Acute uncomplicated urinary tract infection

Symptomatic bladder infection characterized by frequency, urgency, dysuria, or suprapubic pain in a woman with normal genitourinary tract and it is associated with both genetic & behavioral determinants

IDSA Guidelines. Nicolle LE, et al. Clinical Infectious Diseases. 2005; 40: 643–54.

Risk factors

- Healthy pre-menopausal women
- Sexual behaviour & contraceptive device
- Hormonal deficiency in postmenopausal women
- DM
- Pregnancy
- Relevant immunosuppression
- Long-term urinary catheter treatment
- Ureteral obstruction (stone, stricture)

Grabe M, et al. EAU guidelines on Urological Infections. 2015.

Urinary tract infection

Most common bacterial infections during pregnancy

ASYMPTOMATIC

Asymptomatic Bacteriuria

SYMPTOMATIC

Acute Cystitis

Acute Pyelonephritis

William Obstetrics, 25th Edition.

Route of infection

- **Common route:**
  - Ascending through urethra [especially organisms of enteric origin (e.g. *E. coli* and other Enterobacteriaceae)]

- **Other routes:**
  - Blood (*S. aureus*, *Candida sp.*, *Salmonella sp*. & *M. tuberculosis*) & lymphatic

Grabe M, et al. EAU Guidelines on Urological Infections. 2015.

Is it any different in pregnant women??

- Incidence in pregnancy is only slightly higher as non-pregnant women.
- Recurrent UTI is more common in pregnancy
- Incidence of Pyelonephritis is higher.
- Serious maternal and fetal effects

Epidemiology

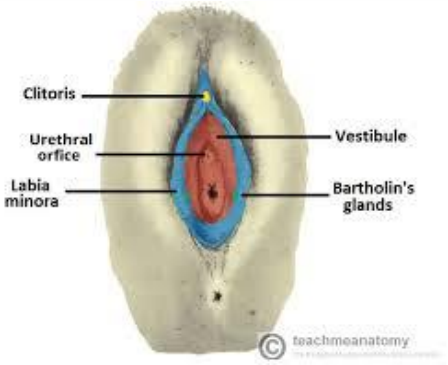
- Asymptomatic bacteria 10 - 13%
- Acute Cystitis 1 - 4%
- Acute Pyelonephritis 0.5 - 2%
- Recurrent UTI maybe defined as 3 or more UTIs in pregnancy
- Recurrent UTIs occur due to bacterial re-infection or persistent bacteriuria
- **Re-infection** is a recurrence with a different organism or the same organism in more than two weeks interval or a sterile intervening culture
- **Persistence** involves the same bacteria not being eradicated in the urine two weeks after sensitivity adjusted treatment

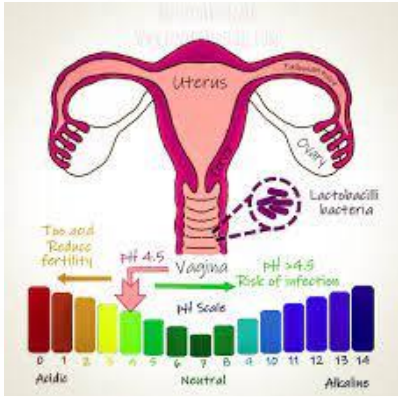
Epidemiology

- Most common medical disorder in pregnancy
- 3.5% antepartum admissions ***(Gazmararian JA, Obstet Gynecol 2002)***
- Typically occurs in 1st trimester with a quarter in the 2nd and 3rd trimester ***(Sobel JD. Urinary tract infections. In: Mandell, Douglas, and Bennett's Principles and practice of infectious diseases, 2010)***
- 28.7% in whites and Asians, 30.1% in blacks, and 41.1% in Hispanics. ***(Whitehead NS et al. Maternal Child Health J. 2009)***

Etiology

- Proximity to vagina and anal microflora
- Short length of urethra
- Urinary stasis due to gravid uterus compressing the ureters (80% pregnant women)
- High progesterone-ureteric smooth muscle relaxation- dilatation and hydronephrosis
- Increased urinary pH- high amounts of glucose, amino acids and hormone degradation products
- Relative immunosuppression
- Increased vesicoureteral reflux





- ***Ref: Matuszkiewicz-rowińska J et al. Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. Arch med sci 2015***

Predisposing factors

- Urinary catheterization- during labour/caesarean section
- Asymptomatic bacteriuria
- Poor hygiene
- Low socioeconomic (SE) status
- Nulliparity
- Young age
- Anaemia (esp. Sickle cell anaemia)
- Pre-existing Diabetes mellitus

Ref: Alvarez JR et al. Asymptomatic bacteriuria in pregestational diabetic pregnancies and the role of group B streptococcus. Am J Obstet Gynecol 2010.

Risk factors

- **Pre-pregnancy history of UTI**
- **lower socio-economic status**
- **sexual activity**
- **older age**
- **Multiparity**
- **Anatomical urinary tract abnormalities**
- **sickle-cell disease**
- **Diabetes**

UTI: Diagnosis

- Based on detection of pyuria (WBC/ pus in urine)
- Urinalysis (routine & microscopy)
  - Urine test strips (dipstick)
- Culture

Causative Micro-organisms

- *Escherichia* Coli (Most common)
  - An 18-year retrospective analysis – E.coli most common organism in 82.5% pregnant women

Ref: Wing DA, Am J Obstet Gynecol. 2014

- *Klebsiella pneumoniae* (5%)
- *Proteus mirabilis* (5%)
- *Enterobacter* species (3%)
- *Staphylococcus saprophyticus* (3%)
- Group B beta-hemolytic *Streptococcus* (GBS; 2-5%)
- *Proteus* species (2%)

Ref: Patricia J etal. Urinary Tract Infections in Pregnancy: Practice Essentials, Pathophysiology, Etiology. 2021

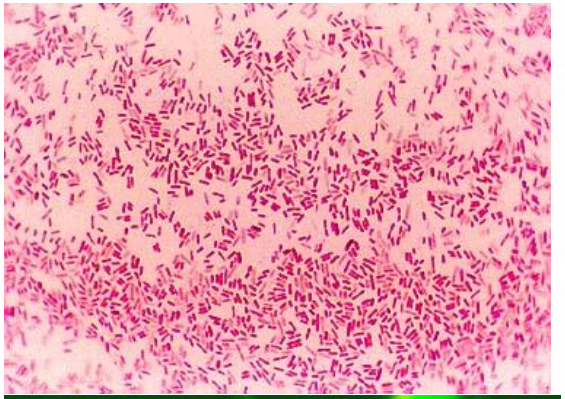
UTI: Etiology

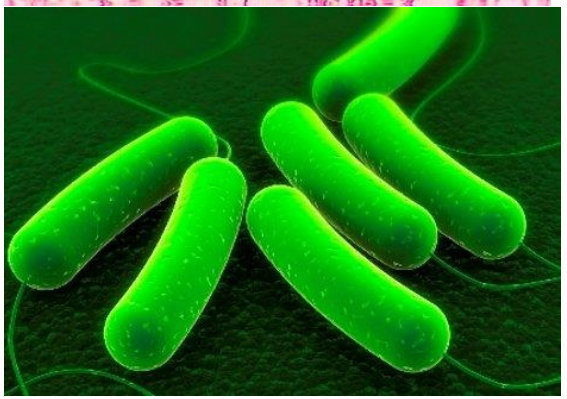
- Most common:
  1. E. coli predominant pathogen: 80-85%
  2. Staphylococcus saprophyticus: 5-10%
- ***In addition:***
  1. Klebsiella
  2. Proteus
  3. Pseudomonas
  4. Enterobacter
- **Rare:** Viral or fungal agents

Ranganathan Vasudevan. J Microbiol Exp. 2014; 1(2): 00008.

Escherichia coli (E. Coli)

- Gram-ve, facultative anaerobic, exists in single or pairs
- Rod-shaped bacterium
- Commonly found: Large intestine
- Pathogenic or non-pathogenic
- Pathogenic: Cholecystitis, bacteremia, urinary tract infection (UTI), traveler's diarrhea, etc.

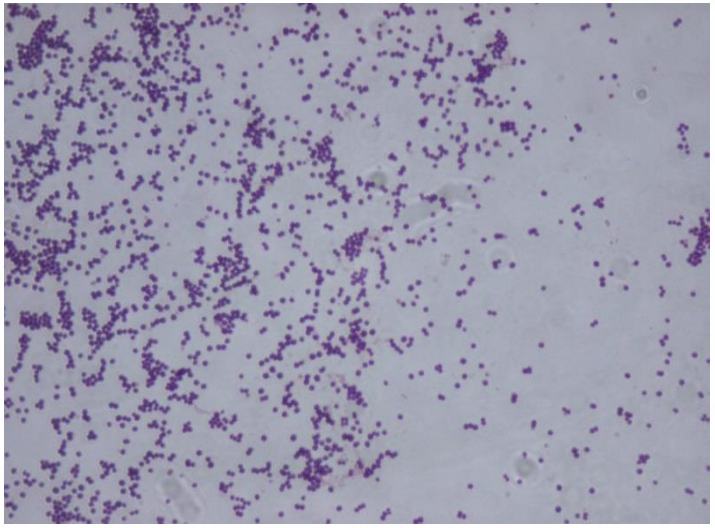




Madappa T, et al. Escherichia Coli infections. Medscape. Jan 2016.

Staphylococcus saprophyticus (S. saprophyticus)

- Gram+ve bacteria
- 2nd most frequent causative agent of acute UTI
- Has capacity for selective adherence to human urothelium
- Found: Normal flora of female genital tract & perineum



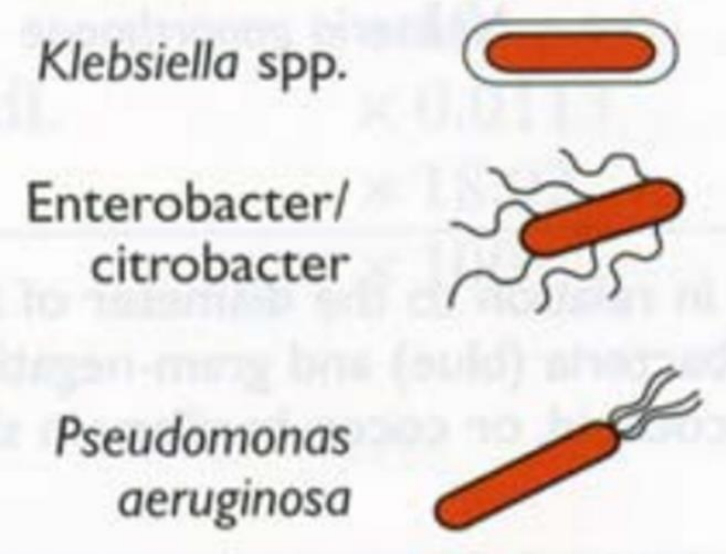
Hovelius B, et al. Rev Infect Dis. 1984; 6(3): 328-37/ Widerstrom M, et al. Eur J Clin Microbiol Infect Dis. 2012; 31(1): 7-20/ Harvey RA. Microbiology. 2nd edition. Lippincott Williams & Wilkins. Pg. 76.

Other bacteria

- Klebsiella
- Proteus
- Enterobacter
- Pseudomonas

Gram-ve, facultative anaerobic, rod-shaped

Gram-ve, rod-shaped, aerobic (sometimes facultative anaerobic)



Qureshi S, et al. Klebsiella Infections. Medscape. Oct 2015/ Gonzalez G, et al. Medscape. Oct 2015/ Fraser SL, et al. Medscape. Oct 2015.

Microbiology of UTI in pregnancy

Common organisms causing UTI (as per ICMR – AMRSN data 2017)

- Enterobacteriaceae. 73.2%
  - E.coli. 49.24%
  - Klebsiella spp 17.44%
  - Proteus spp 1.4%
  - Citrobacter. 1.3%
- Enterococcus species. 10.9%
- Non-fermenting gram-negative bacilli. 8.2%
- Staphylococcus aureus. 0.9%

Classification & Incidence

- ASYMPTOMATIC BACTERIURIA- limited to bacterial growth in urine (**2-7%**);
- SYMPTOMATIC BACTERIURIA- when bacteria invade urinary tract tissues, inducing an inflammatory response.
  - Acute cystitis (**1-4%**);
  - Acute pyelonephritis (**0.5-2%**)

ASYMPTOMATIC BACTERIURIA

- **$>10^5$ CFU/ml** two consecutive mid-stream clean-catch urine specimens or **≥ 100 CFU/ml** in urine collected from single urinary bladder catheterization
- 2-7% rate in pregnant women; more common in parous, low SE women
- If untreated,
  - risk of **cystitis is 30%** (*UTI in pregnancy. Tog 2008*)
  - subsequent **pyelonephritis in 30-40%;** on treatment, this reduces to **3-4%.** *(Patricia J Henek et al, UTI in preg :practice essentials 2021)*

Other complications

- Fetal complications- Premature delivery (12.8%), low birth weight: studies show controversial results
  - Many studies -increased risk of the fetal complications in pregnant women with ASB
  - few studies- denied of any such risks.

Ref: Chen YK et al. No increased risk of adverse pregnancy outcomes in women with urinary tract infections: a nationwide population-based study. Acta Obstet Gynecol Scand. 2010

-Schnarr J. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. Eur J Clin Invest. 2008

Baer RJ, Nidey N, Bandoli G, Chambers BD, Chambers CD, Feuer S, et al. Risk of Early Birth among Women with a Urinary Tract Infection: A Retrospective Cohort Study. AJP Rep. 2021 Jan. 11 (1):e5-e14.

- Antibiotic treatment was effective in reducing the incidence of low-birth-weight infants **but not** of preterm deliveries

Ref: Smaill F, Vazquez JC. Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev. 2007;18:CD000490)

Hence,

- Mandatory at first prenatal visit or 12-16 weeks- whichever is earlier. (Grade A-RCOG)
  - Routinely done; although one study questions the benefit of screening for ASB in the first trimester- found no association with the fetal risks.
    (Kazemier BM et al. Lancet Infect Dis. 2015)

Predictors of UTI at the first prenatal visit

Predictors of Urinary Tract Infection at the First Prenatal Visit

Lisa M. Pastore,[1] David A. Savitz,[1] and John M. Thorp, Jr.[2]

We identified maternal demographic, behavioral, and medical history factors that predict bacteriuria (that is, symptomatic and asymptomatic urinary tract infection) at prenatal care initiation. We applied logistic regression modeling to data from all prenatal care recipients who delivered during 1990–1993 and resided in selected North Carolina counties (N = 8037), omitting those with diabetes mellitus, human immunodeficiency virus, or structural urologic abnormalities. The two strongest predictors of bacteriuria at prenatal care initiation were an antepartum urinary tract infection prior to prenatal care initiation (for whites, adjusted prevalence odds ratio (POR)=2.5, 95% CI 0.6–9.8; for blacks, POR = 8.8, 95% CI 3.8–20.3) and a pre-pregnancy history of urinary tract infection (POR = 2.1, 95% CI 1.4–3.2). For white women only, education beyond high school and age ≥30 years were inversely associated (POR ≤ 0.6). Sickle cell hemoglobin nearly doubled the prevalence odds for bacteriuria among African-Americans (POR = 1.9, 95% CI 1.0–3.5), whereas African-Americans with normal hemoglobin had reduced prevalence odds compared with whites (POR = 0.6, 95% CI 0.4–0.9). This study suggests predictors not considered before, including race controlling for sickle cell disease or trait and antepartum urinary tract infections prior to prenatal care. (Epidemiology 1999;10:282–287)

A large retrospective analysis with logistic regression modelling, embracing 8037 women from north Carolina, revealed that the **two strongest predictors of bacteriuria** at prenatal care initiation were:

- UTI prior to prenatal care initiation and
- pre-pregnancy history of UTI

Asymptomatic Bacteriuria

- Isolation of significant colony count of bacteria in the urine from a person without symptoms of a UTI

What is SIGNIFICANT?

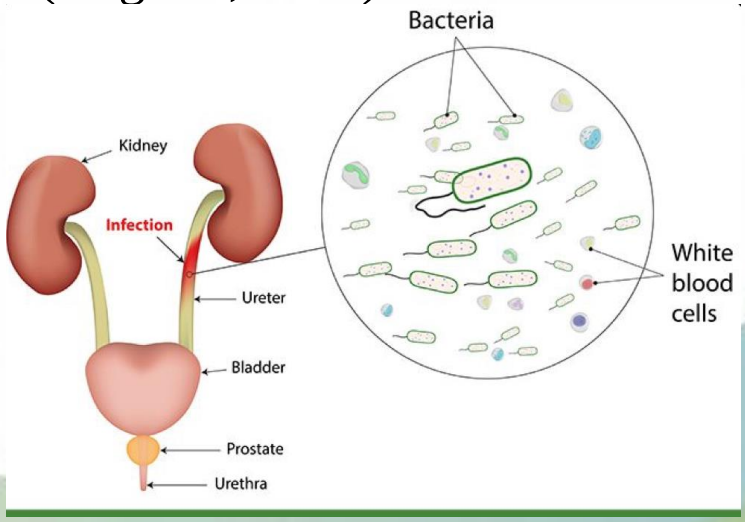
- Bacterial monoculture in the quantity of more than equal to 10^5 CFU/ml in 2 consecutive midstream clean-catch urine specimens

OR

- 10^2 CFU/ml in urine collected from single categorisation of urinary bladder

Asymptomatic Bacteriuria

- If **not treated:** apprx 25% will develop symptomatic infection during pregnancy
- Only 2.4% **treated** women develop pyelonephritis
- Recommended screening for bacteriuria at the first prenatal visit or at 12 weeks whichever is earlier
- **Urine culture** is the gold standard but may not be cost-effective when prevalence is low
- **Leucocyte esterase/nitrate** dipstick is cost-effective. It has excellent positive and negative predictive values. (Mignini, 2009)



GBS bacteriuria in pregnancy- a special mention

- Marker for genital tract colonization with this organism which poses a significant risk of preterm rupture of the membranes, premature delivery and early-onset severe neonatal infection.
- likelihood of maternal GBS carriage in this pregnancy is 50%.
- Women with GBS UTI (growth of greater than 10^5 cfu/ml) during pregnancy should receive appropriate treatment at the time of diagnosis as well as IAP.
- Routine screening is not recommended for GBS

Ref: GTG no 36 ,

Verani JR et al. Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010.

Complications of Asymptomatic Bacteriuria

Maternal Complications	Foetal Complications
Hypertension	IUGR
Pre-eclampsia	IUD
Anemia	Low Birth weight
Chorioamnionitis	Prematurity
Acute Cystitis	
Acute Pyelonephritis	

SYMPTOMATIC BACTERIURIA

- Pregnancy- UTI symptoms may vary. In some cases, vomiting and increased frequency of urine may be the only indications for underlying infection.
- **Acute cystitis**: dysuria, frequency, urgency and suprapubic pain in the absence of systemic illness;
- **Pyelonephritis** presents with all of the above along with systemic signs and symptoms of sepsis.

Acute Cystitis in pregnancy

- **Dysuria, urgency and frequency**
- Pyuria and bacteriuria usually found
- Microscopic haematuria is common
- Occasionally gross haematuria from haemorrhagic cystitis
- Acute Cystitis in pregnancy almost always results from ascending infection in long-standing asymptomatic bacteria
- 40% of pregnant woman with acute pyelonephritis have symptoms of lower tract infection
- Lower urinary tract symptoms with pyuria accompanied by a sterile urine culture maybe from urethritis caused by **chlamydia trachomatis.**

Acute Pyelonephritis in pregnancy

- Infection of Renal papillae and occasionally of renal cortex
- Most common serious medical complications of pregnancy
- Pyelonephritis is the leading cause of septic shock during pregnancy
- Pyelonephritis is unilateral and right-sided is more than half of cases and it is bilateral in a fourth of cases.

Asymptomatic Bacteriuria

Single-dose treatment

Amoxicillin 3g

Ampicillin 2g

Cephalosporin 2g

Nitrofurantoin 200mg

Trimethoprim-sulfamethoxazole 320/1600mg

Other

Nitrofurantoin 100mg 4 times daily for 10days

Nitrofurantoin 100mg twice daily for 5 to 7 days

Nitrofurantoin 100mg at bedtime for 10days

Treatment Failure

Nitrofurantoin 100mg 4 times daily for 21 days

3- Day course

Amoxicillin 500mg 3 times times daily

Ampicillin 250mg 4 times daily

Cephalosporin 250 mg 4 times daily

Ciprofloxacin 250mg twice daily

Levofloxacin 250 or 500 mg daily

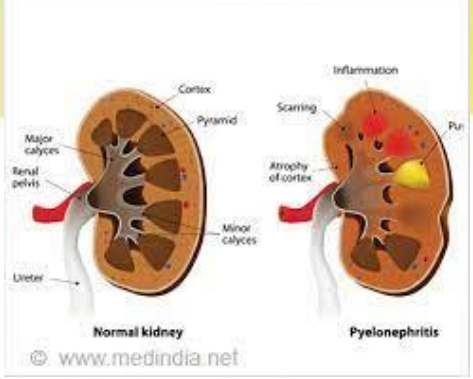
Nitrofurantoin 50-100mg 4 times daily or 100mg twice daily

Trimethoprim-sulfamethoxazole 160/800 mg two times daily

Clinical Diagnosis of Severity

	Asymptomatic bacteriuria	Acute cystitis	Pylonephritis
Urine culture	Positive	Positive	Positive
Urgency, frequency, burning	No	Yes	Yes
Fever	No	No	Yes
Costovertebral Angle tenderness	No	No	Yes

Pyelonephritis- infection of a renal papilla



- 90% cases – second and third trimesters
- Initially, Lower urinary tract symptoms predominate
- **LOOK FOR-** pyrexia, rigors, nausea and vomiting and renal angle pain to make an early accurate diagnosis.
- Fetal tachycardia assessed as a part of clinical evaluation
- prior antenatal UTI was found to be the strongest predictor of pyelonephritis after 20 weeks' gestation (OR = 5.3, 95% CI: 2.6–11.0).

Ref:Matuszkiewicz-RJ et al.Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. Arch Med Sci. 2015

Complications:

- **Medical:**
  - Anaemia –Most common complication occurring in upto 25% cases (typically resolves spontaneously following treatment).

  Ref:UTI in preg. Practise essentials. 2021
  - Pyonephrosis (infection of whole kidney) can lead to perinephric abscess ;if the capsule ruptures.
  - Gram-negative septicaemia and septic shock, leading to multiple organ failure.
  - Acute respiratory distress.
- *Ref: John E. Delzell J, LeFevre M. Urinary Tract Infections During Pregnancy. Am Fam Physician. 2000 Feb 1;61(3):713–20.*

Obstetric:

- **Preterm labour**:
  Endotoxin release > uterine contractions
  - Pyelonephritis is an important independent risk factor for delivery before 37 weeks' gestation
  - Exact risk difficult to predict, significant heterogeneity between studies.

  Ref: The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity.Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PF.Bull World Health Organ. 2010

  – patients should be monitored for preterm labor; treated when indicated.
  – **Caution** with tocolytic therapy> risk of pulmonary oedema is increased in the setting of UTI
- **Preeclampsia**

  Ref Association of UTI in pregnancy and preeclampsia. A meta-analysis. Medicine-baltimore-2018

Differential diagnosis of UTI

- Gonococcal and non-gonococcal urethritis
  - dysuria, frequency, pyuria and sometimes haematuria but without significant bacteriuria upon culture and presence of urethral discharge
- Nonurethral, non-urinary tract infections and chemical cystitis
- vulvitis, vaginitis or cervicitis secondary to conditions such as herpes simplex.
- appendicitis, pancreatitis, or cholecystitis
- pregnancy-related complications such as preterm labor, chorioamnionitis, or placental abruption.

Investigations

1. Urine microscopy and culture: Gold standard in detection of asymptomatic bacteriuria, identifies the organism and suitable antibiotic but 48 hours to obtain a result.
2. Urine reagent dipstick testing- affordable,rapid and easy available; presence of nitrites in the urine of symptomatic women is strongly suggestive of significant bacteriuria; but high false negative rates (52.8%) when compared with the reported 80% sensitivity with urine culture
3. Imaging of the renal tract: if not responding to treatment and recurrent UTI

Ref:Shelton et al., 2001, UTI in pregnancy:review .tog 2008

UTI: Management

- Appropriate antibiotic treatment in women with uncomplicated cystitis leads to:
  - ***Significantly higher symptomatic and Bacteriologic cure rates***
  - ***Better prevention of reinfection***

- Empirical antibiotic treatment: Usually 1st treatment to be administered to patients with UTI

Brusch JL, et al. Cystitis in Females Treatment and Management. Medscape. Aug 2015/ Tandogdu Z, et al. Curr Opin Infect Dis. 2016; 29: 73–79.

UTI Management: Antibiotics

Oral antibiotics used in UTI

- **Nitrofurantoin**
- **Trimethoprim-sulfamethoxazole**
- ***Fosfomycin***
- **Pivmecillinam** (where available)

- **Fluoroquinolones**
  - Ofloxacin
  - Ciprofloxacin
  - Levofloxacin
  - Norfloxacin
- **β-Lactam**
  - Amoxicillin-clavulanate
  - Cefdinir
  - Cefaclor
  - Cefpodoxime-proxetil
  - Cephalexin

Gupta K, et al. CID 2011:52 (1 March) d e103.

Rationale of Treatment

- Usually easy to treat and respond well
- A full maternal clinical history and examination is mandatory, along with an assessment of fetal wellbeing
- Do not prescribe trimethoprim for pregnant women with established folate deficiency or women taking folate antagonists.
- Take a single sample for urine culture before empirical treatment is started.
- Women with symptomatic bacteriuria with systemic signs of infection should be admitted for intravenous antibiotics pending the result of blood cultures and the urine culture

- When choosing an antimicrobial regimen it is important to consider issues of teratogenicity and absorption as well as local antimicrobial resistance.
- If no clinical improvement in 24 hours of instigating treatment or where there are additional co-morbidities additional senior medical and microbiology advice should be sought.
- A repeat urine culture should be sent a week after the antimicrobial treatment is finished to ensure that the bacteriuria has cleared.

UTI: Management

- **β-lactam antibiotics may be used when other recommended agents cannot be used**

- **Fosfomycin& nitrofurantoin monohydrate/macrocrystals should be avoided in patients with possible early pyelonephritis**
- **Fluoroquinolones are typically reserved for complicated cystitis**
- Empiric antibiotic selection is determined in part by local resistance patterns. Clinicians may wish to limit use of TMP-SMX in order to reduce emergence of resistant organisms

Brusch JL, et al. Cystitis in Females Treatment and Management. Medscape. Aug 2015.

Limitations of present antibiotics

- Emergence of extended spectrum beta-lactamases (ESBL), AmpC production by Gram-negative bacteria & methicillin resistant Staphylococcus species ***limits choice of antimicrobials***
- Longer duration of therapy (3-7 days)
  - Compliance issue

Sultan A, et al. Urol Ann. 2015; 7(1): 26–30.

- Pregnancy-increased GFR + increased maternal plasma volume- reduces serum drug concentrations –lessens bio-availability. This is especially a problem with ß-Lactam antibiotics, including penicillins and cephalosporins.
- Nitrofurantoin can be used for prophylaxis but should be avoided near term or when delivery is imminent because of the risk of neonatal haemolysis.

- Urine alkalinising agents – risk of hypernatraemia with the use of sodium citrate in pregnancy.

- **NSAIDS- risk of oligohydramnios and premature closure of ductus in foetus- should be avoided**
- **Thromboprophylaxis- strongly considered along with graduated compression stockings**
- **Antenatal corticosteroids- high chances of preterm labour**

Ref: Patricia et al. UTI in pregnancy. Practice essentials.2021,

John E. Delzell J, LeFevre M. Urinary Tract Infections During Pregnancy. Am Fam Physician. 2000

CURRENT OPINION

Nonantibiotic treatments for urinary cystitis: an update

Bianca M. Barea, Rajan Veeratterapillay, and Chris Harding

Purpose of review
Urinary tract infections (UTIs) are one of most common infections in everyday clinical practice. Given the increase in antimicrobial therapy resistance, there has been an increased interest in nonantibiotic treatment options for common infections.

Recent findings
A review of the recent literature including on nonantibiotic options for management of UTIs, symptoms of cystitis and prevention of recurrent UTIs.

Summary
The article provides an overview on alternative therapy to antibiotics in the treatment of cystitis and recurrent UTI prophylaxis, including alkalinization of urine, cranberry products, probiotics, NSAIDS, D-mannose, herbal medicine, methenamine hippurate, oral immunostimulants (immunotherapy), topical oestrogens, vitamins and acupuncture. The last few years of intense research has focused on an effort to find evidence to corroborate pote
treatments for UTIs have not brou
by nonantibiotic options. The rea
trials on this subject.

Curr Opin Urol 2020, 30:845–852
DOI:10.1097/MOU.0000000000000821

KEY POINTS

- Emerging non antibiotic treatment for UTIs such as Canephron N (Bionorica SE Kerschensteinerstraβe, Neumarkt, Germany), methenamine hippurate, vaccines, D-mannose and acupuncture showed promising results in reducing recurrent UTIs.
- Alternative therapies are usually better tolerated and associated with less side effects.
- Well designed randomized trials are still required to establish definitive recommendations to alternative treatments.

Options for Recurrent UTI

Table 1. Clinical practice guideline recommendations for the prevention and treatment of recurrent urinary tract infections in women

Prevention or treatment recommendations for women with rUTIs	European Association of urology 2019*	American urological association 2019**	Level of recommendation
Clinicians may offer cranberry prophylaxis for women with rUTIs	No recommendation	X	**Conditional recommendation, evidence level: Grade C
Use vaginal oestrogen replacement in peri and postmenopausal women to prevent recurrent UTI	X	X	*Weak/**Moderate recommendation, evidence level: Grade B
Use immunoactive prophylaxis to reduce rUTI in all age groups	X	No recommendation	XStrong
Lactobacillus probiotics	No recommendation	No recommendation	*/**Lack of data indicating benefit
Prophylaxis with D mannose	No recommendation	No recommendation	*Acknowledgement of one good trial study but not sufficient to recommend **Refers 2 good trials but high risk of bias
Endovesical instillation	No recommendation	No recommendation	Promising studies further date required to establish long-term outcomes and overall feasibility
Prophylaxis with methenamine	No recommendation	No recommendation	**Refers 2 good trials but high risk of bias
Herbal therapies	No recommendation	No recommendation	**Insufficient data

rUTI, recurrent urinary tract infection; UTI, urinary tract infection.
*European Association of urology 2019.
**American urological association 2019.

VITAMIN C

Vitamin and mineral requirements in human nutrition. Second edition. World Health Organization and Food and Agriculture Organization of the United Nations 2004. ISBN 92-4-154612-3.

Vitamin C is an electron donor (reducing agent or antioxidant), and probably all of its biochemical and molecular roles can be accounted for by this function. Vitamin C acts as an electron donor for 11 enzymes. Three of those enzymes are found in fungi but not in humans or other mammals and are involved in reutilization pathways for pyrimidines and the deoxyribose moiety of deoxynucleosides. Of the eight remaining human enzymes, three participate in collagen hydroxylation and two in carnitine biosynthesis; of the three enzymes which participate in collagen hydroxylation, one is necessary for biosynthesis of the catecholamine norepinephrine, one is necessary for amidation of peptide hormones, and one is involved in tyrosine metabolism.

Natural Remedies for UTI

Fazly Bazzaz, B. S. et al. Deep insights into urinary tract infections and effective natural remedies. Afr J Urol (2021) 27:6.

Vitamin C possesses antimicrobial activities and is frequently used as an important supplement to antibiotic therapy for UTI. Vitamin C is considered as a nonenzymatic antioxidant that slows down the production of free radicals and oxidation, which leads to strengthening the immune system and the deficiencies of vitamin C could place the persons at risk for infections due to the negative impacts on immune function. Various studies have been conducted to show the efficacy of vitamin C in the management of UTIs. Yousefichaijan et al. studied the efficacy of vitamin C supplementation on UTI in children for 14 days. The results showed that vitamin C supplementation was able to control the symptoms of UTI, including dysuria, fever, urinary urgency, and also dribbling urine.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Effectiveness of a Combination of Cranberries, *Lactobacillus rhamnosus*, and Vitamin C for the Management of Recurrent Urinary Tract Infections in Women: Results of a Pilot Study

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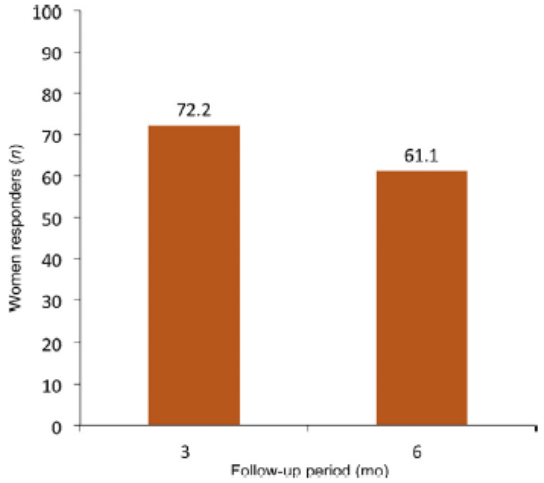

Fig. 1 – Proportion of women with recurrent urinary tract infections considered as responders after treatment with 120 mg cranberries, 1 billion heat-killed *Lactobacillus rhamnosus* SGL06, and 750 mg vitamin C thrice daily for 20 consecutive d monthly for 3 mo at 3-mo and 6-mo follow-up.

Concluding, the administration of 120 mg cranberries, 1 billion heat-killed *L. rhamnosus* SGL06, and 750 mg vitamin C thrice daily for 20 consecutive d monthly for 3 mo might represent a safe and effective option for the prevention of recurrent UTIs in women. Nonetheless, randomized placebo-controlled trials are needed to confirm the results of our pilot study.

Cranberry: a potent uroprotective agent

- For centuries, cranberries have been used as a treatment for urinary tract diseases and its antibacterial activity was reported long back. It contains > 80% water, 10% carbohydrates (glucose and fructose), and other phytoconstituents like anthocyanins, flavonoids, terpenoids, catechins, organic acids (citric acid, malic acid, and quinic acid, etc.) with small amount of ascorbic acid, benzoic acid, glucuronic acids.
- Clinical trials were often complicated, and results are not satisfactory in patients with complicated UTI, whereas, cranberry uptake significantly prevented acute cystitis in high-risk females.
- *Das, S. Natural therapeutics for urinary tract infections—a review Future Journal of Pharmaceutical Sciences (2020) 6:64.*

Molecular mechanism of action of Proanthocyanins

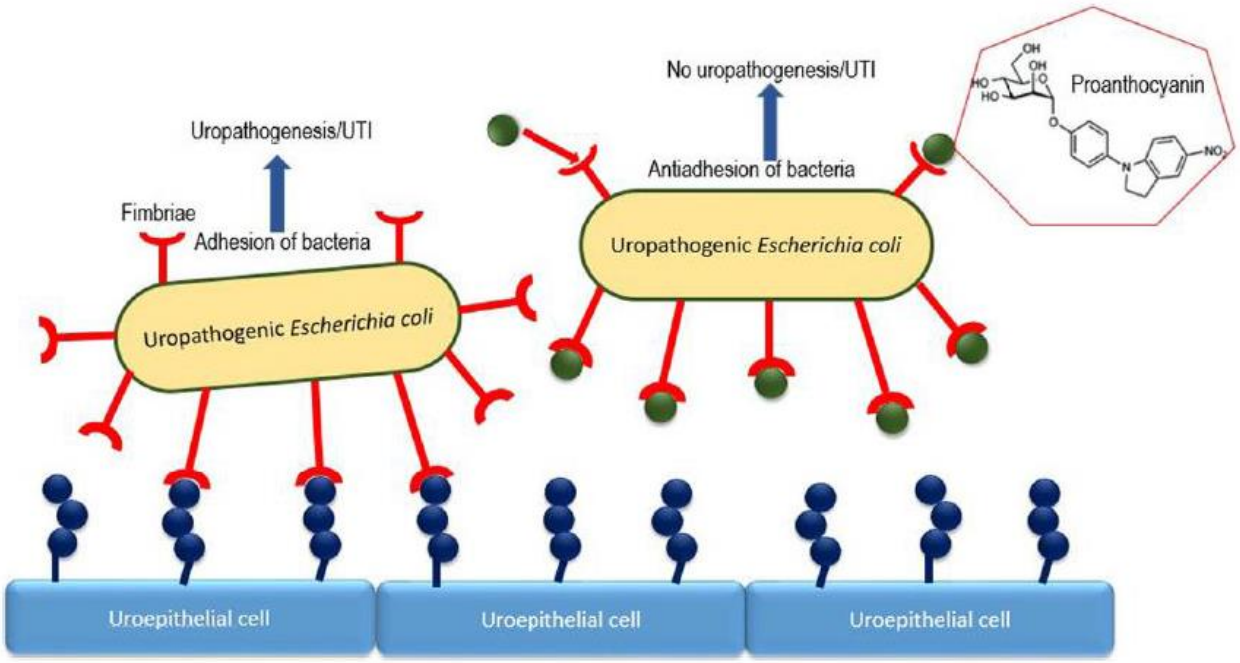

Fig. 1 Type 1 or P-fimbriae inhibitors (e.g., proanthocyanins) are shown as green balls interfering with binding of bacterial fimbriae to uroepithelial cell

Due to lack of proper standardization of cranberry products, it becomes extremely complicated to compare products or correlate the results. The recurrence of UTI rates was reduced up to 35% in young to middle-aged women, after the use of cranberry-based compounds. But, in groups with complicated UTI (i.e., young and elderly patients, or patients with neurogenic bladder or with chronic indwelling catheters), the potency of cranberry was unclear. However, these

Prevention of UTI –Other Options

JAMDA

journal homepage: www.jamda.com

Review Article

A Review of Nonantibiotic Agents to Prevent Urinary Tract Infections in Older Women

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Keywords:
Ascorbic acid
cranberry
D-mannose
estrogens
lactobacillus
methenamine hippurate
older adult women
prevention of urinary tract infections

ABSTRACT

Objective: This article provides a comprehensive literature review on nonantibiotic agents used for the prevention of urinary tract infections (UTIs) in women >45 years of age.
Design: A structured
pertaining to the u
through postmenop
agent, unless data w
Setting and participa
community, inpatier
Measure: The efficac
tobacilli, and methe

Conclusion and Implications

There have been several nonantibiotic agents studied in the setting of UTI for prevention of UTIs in women ≥45 years of age. Cranberry capsules and vaginally applied estrogens (if postmenopausal) have been shown to be effective in preventing UTIs in this population and therefore may have the advantage of potentially deterring overuse of antibiotics. Current data is lacking to make recommendations for or against the use of ascorbic acid, cranberry juice, cranberry capsules with high PAC content, D-mannose, lactobacilli, and methenamine hippurate in this specific patient population.

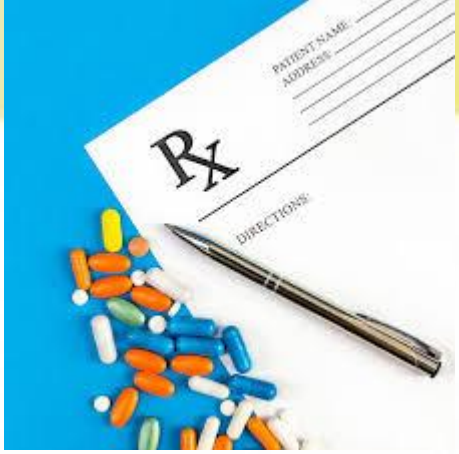
FDA category

Antibiotic	FDA risk category	Antibiotic	FDA risk category
Amoxicillin	B	Trimethoprim/sulfamethoxazol	C
Cephalosporins	B	Ciprofloxacin	C
Piperacillin/tazobactam	B	Levofloxacin	C
Daptomycin	B	Imipenem/cilastatin	C
Azithromycin	B	Linezolid	C
Erythromycin	B	Clarithromycin	C
Meropenem	B	Spiramycin	C
Clindamycin	B	Gentamycin	C
Nitrofurantoin	B	Amikacin	D
Vankomycin *iv*.	B	Tobramycin	D
Metronidazol *iv*.	B	Netilmycin	D
Trimethoprim	C	Tetracyclines	D

Role of surgery?

- Rarely needed
- Cystoscopy may aid in establishing the diagnosis of urethral or bladder diverticulum, bladder stones, urethral syndrome, lower urinary tract trauma, interstitial cystitis, or bladder cancer.
- A retrograde stent or a percutaneous nephrostomy tube --- relieve ureteral colic or decompress an obstructed infected collecting system
- Extracorporeal shock wave lithotripsy (ESWL) is contraindicated in pregnancy.

General instructions



- Preventative hygiene behaviour, such as washing the genitals after sexual intercourse, is the only evidence-based intervention linked to a reduced incidence of UTIs in pregnancy and therefore the most effective method of avoiding antibiotics

Ref: Ghouri F, Hollywood A, Ryan K. A systematic review of non-antibiotic measures for the prevention of urinary tract infections in pregnancy. BMC pregnancy and childbirth. 2018

- Paracetamol for pain (No much evidence)
- Plenty of oral fluids

Recurrent UTI

- 4–5% of pregnancies.
- The risks of developing pyelonephritis and its potential consequences are the same as for the primary infection.
- The exact aetiology is uncertain but re-infection by coliform bacteria from the vaginal reservoir can occur as a result of sexual activity.
- Urinary tract anomalies must be excluded
- Long-term, lowdose antimicrobial cover, or single postcoital doses, have been advocated for the remainder of pregnancy

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KEY MESSAGES

- UTI in pregnancy can lead to serious consequences
- Screening for Asymptomatic Bacteriuria is important
- Treatment options are many, but to be chosen carefully after evaluation
- Additional therapies have a role in prevention and in recurrent cases

FOGSI FOR ALL, ALWAYS

DHEERA

STOP VIOLENCE AGAINST WOMEN

Thank You!

ACKNOWLEDGEMENTS:

- **SCGO**
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TEAM HBTMC & COOPER HOSPITAL, Mumbai