RECURRENT URINARY TRACT INFECTIONS: *WHAT AN INTERNIST MUST KNOW*

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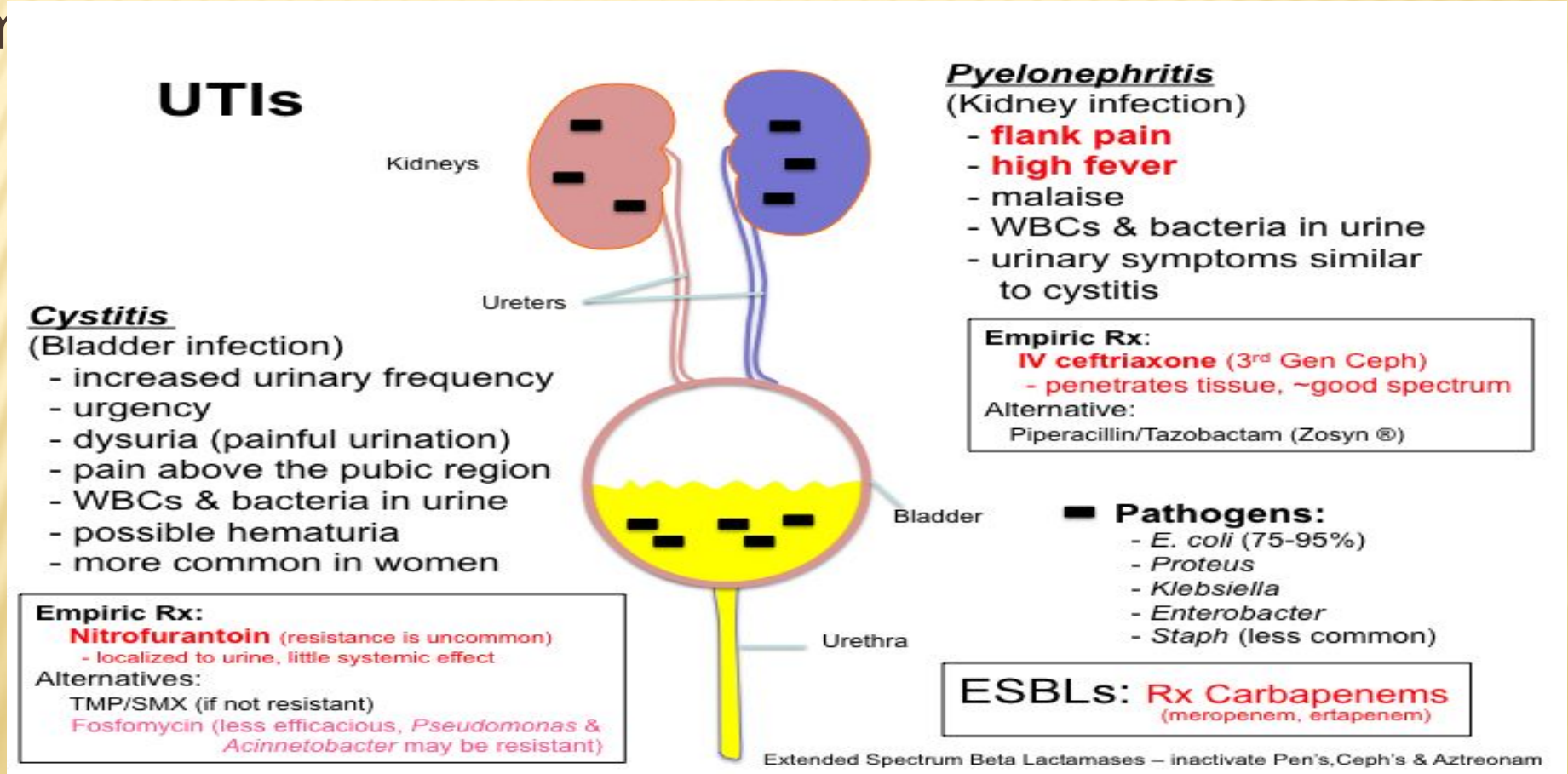
INTRODUCTION

- **Urinary tract infection (UTI)** is one of the commonest bacterial infections globally encountered by women**. I will concentrate only on recurrent UTIs in females**. The risk of women acquiring a UTI in their lifetime has been estimated to be over 50 %, with about 25 % having a recurrence. **Recurrent UTIs are symptomatic infections that follow complete resolution of a previous UTI**. In a primary care setting, 53 % of women above the age of 55 years and 36 % of younger women report a recurrence within 1 year. Hence, its management and prevention is of utmost significance for all clinicians including non-specialists and those in the primary care setting.
- In this paper, I will attempt to provide an overview of recurrent urinary tract infections and their management, using the latest information from systematic reviews, randomized controlled trials and current clinical guidelines. We recommend a pathway for the management of recurrent UTIs, based on current evidence.

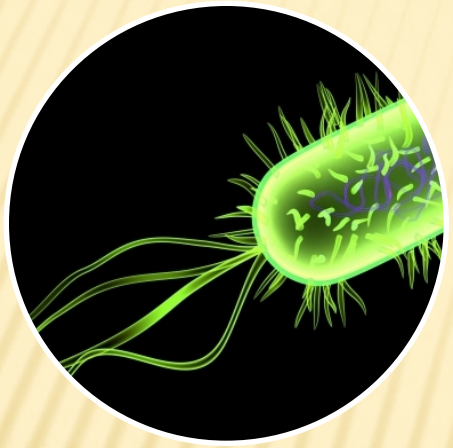
DEFINITIONS

- UTI can manifest as either **cystitis (lower UTI)** or **pyelonephritis (upper UTI)** and may also be classified as **complicated** or **uncom**



- A **complicated UTI** is associated with a structural or functional urinary tract abnormality or an underlying pathology, both of which can subsequently increase risks of acquiring an infection or failure of therapy.
- **Uncomplicated UTIs** are sporadic, community-acquired episodes of cystitis and pyelonephritis in otherwise healthy individuals, but could lead to more serious outcomes and thus require additional attention.
- A recurrent UTI is widely defined as ***more than two episodes of uncomplicated UTI in the last 6 months*** or ***more than three in the last 12 months***, documented by culture.

PATHOPHYSIOLOGY

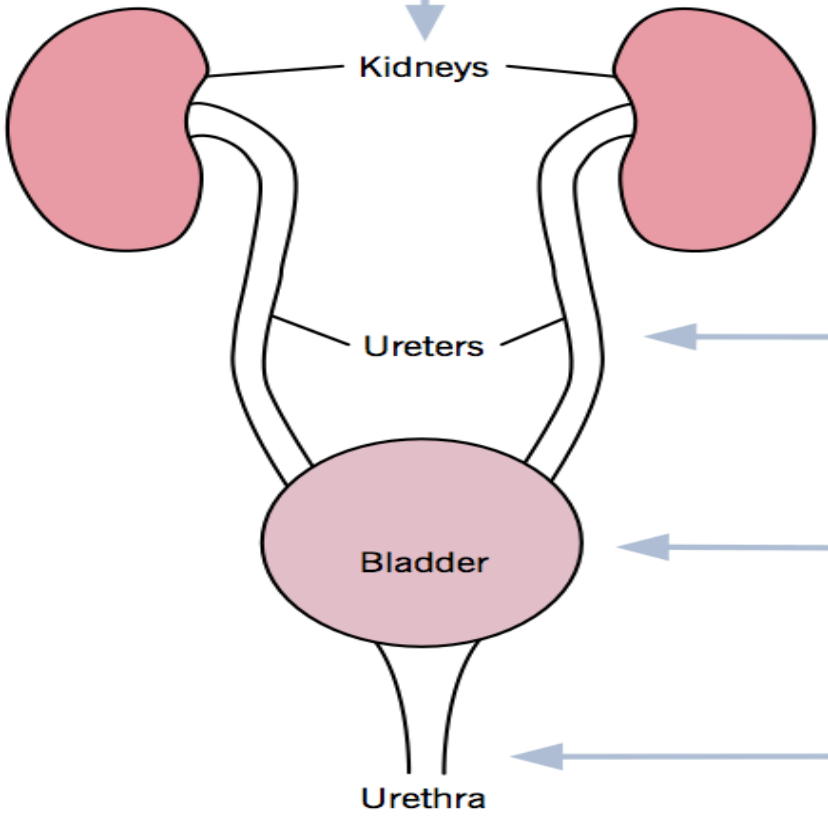


Escherichia coli is the predominant uropathogen responsible for both sporadic and recurrent UTI, seen in 70–95 % of cases.

- Other causative organisms include:
  - *Staphylococcus saprophyticus* (10–15 % of cases)
  - *Klebsiella pneumoniae*
  - *Proteus mirabilis*
- Following the resolution of a UTI, small numbers of the original strain of uropathogens may persist in the host and lead to infection stones (e.g. P. mirabilis).

PATHOGENESIS

Pathogenesis of urinary tract infection



Acute kidney injury

- If the inflammatory cascade continues, tubular obstruction and damage occur, leading to interstitial edema.
- This may lead to interstitial nephritis, causing acute kidney injury (AKI).

Pyelonephritis

- Infection of the renal parenchyma causes an inflammatory response called pyelonephritis
- While infection of the renal parenchyma is usually the result of bacterial ascension, it can also occur from hematogenous spread.

Ascension

- Once sufficient bacterial colonization occurs, bacteria may ascend on the ureter towards the kidney.
- Fimbria may aid in the ascension process
- Bacterial toxins may also play a role by inhibiting peristalsis (reducing the flow of urine)

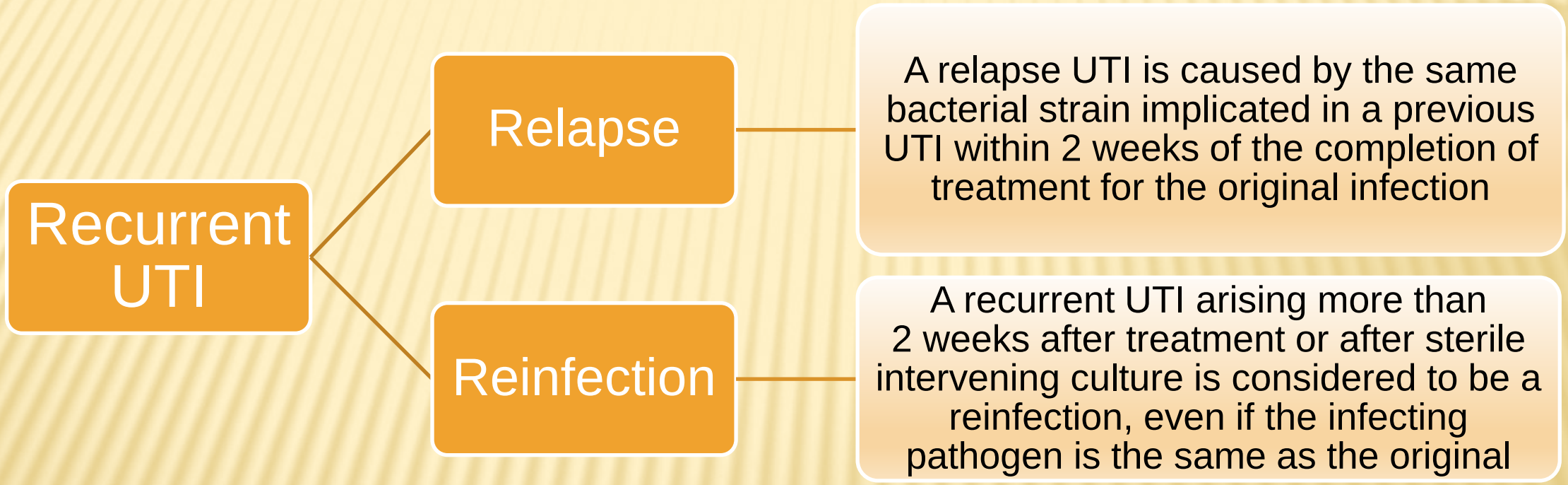
Uroepithelium penetration

- Fimbria allow bladder epithelial cell attachment and penetration
- Following penetration, bacteria continue to replicate and may form biofilms.

Colonization

- Pathogen colonizes the periuretheral area and ascends through the urethra upwards towards the bladder.

RELAPSE VS REINFECTION

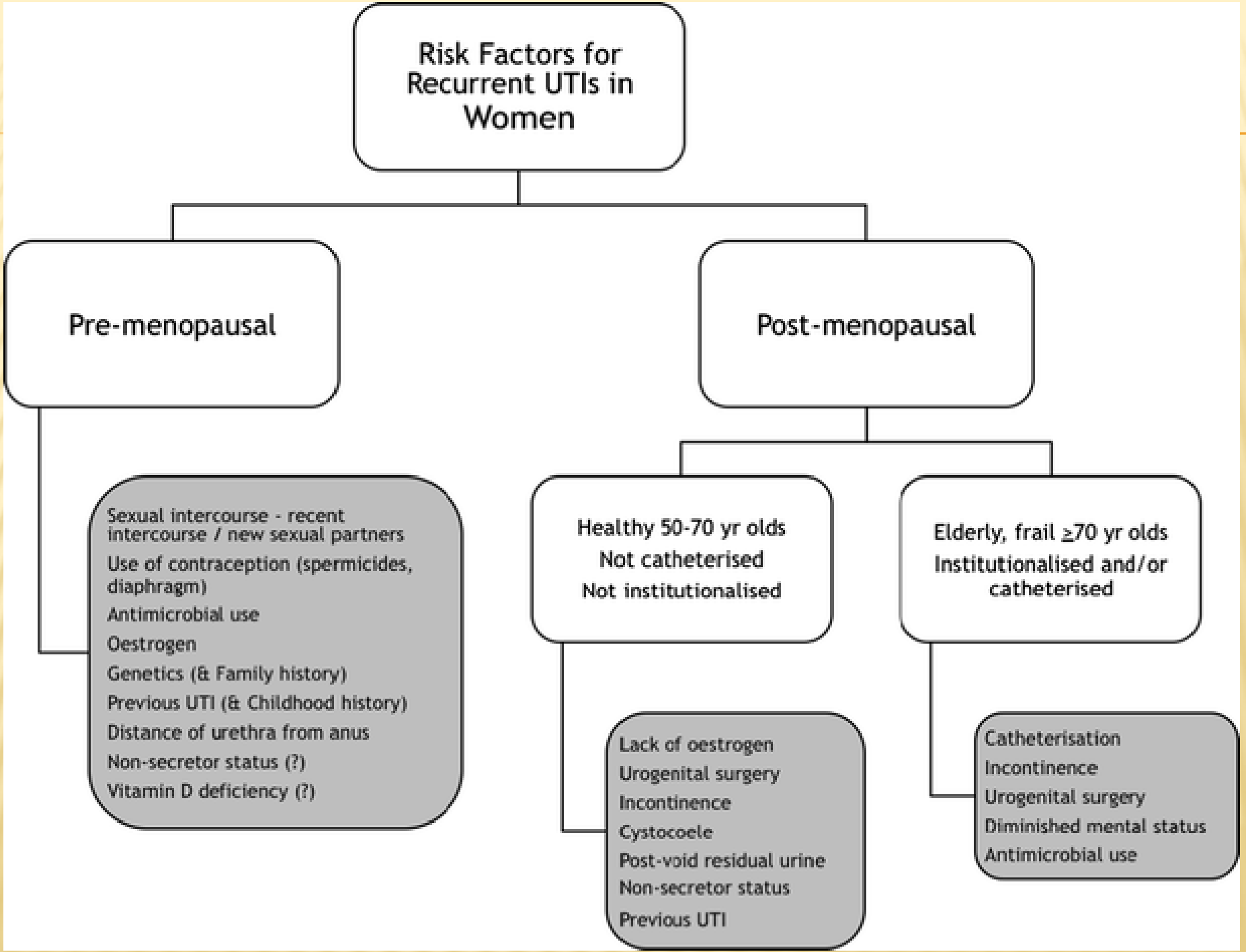


- Recurrent UTI are most commonly seen in women and girls and are associated with ascending colonization from the faecal flora. Infection occurs through bacterial colonization of the vagina and distal urethra, which subsequently ascends into the bladder. Reservoirs of bacteria may remain in the vagina and gastrointestinal tract of susceptible patients. It has been suggested that household contacts may also act as reservoirs for the recolonization of these UTI-susceptible patients

RISK FACTORS

THE RISK FACTORS FOR RECURRENT UTI IN WOMEN VARY BETWEEN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN:

- Premenopausal
  - **Frequency of sexual intercourse.**
  - **Use of contraception(spermicides, diaphragm)**
  - **Antimicrobial use**
  - All of these risk factors have been found to increase vaginal and urethral colonization with *E. coli*
  - **Other factors:**
    - **Oestrogen**
    - **Genetics**
    - **Previous UTI**
    - **Distance of urethra from anus**
- Postmenopausal
  - For postmenopausal women,the risk factors include: oestrogen deficiency, cystocoele, urogenital surgery, high post-void residual volume and a previous UTI
  - These women also have a relative depletion of vaginal lactobacilli and an increase in vaginal *E. coli* compared with premenopausal women. This age-related alteration of the normal vaginal flora, especially loss of hydrogen peroxide producing lactobacilli, may predispose women to introital colonization with *E. coli* and also to UTI.


Risk Factors for Recurrent UTIs in Women
Pre-menopausal
Post-menopausal
Sexual intercourse - recent intercourse / new sexual partners
Use of contraception (spermicides, diaphragm)
Antimicrobial use
Oestrogen
Genetics (& Family history)
Previous UTI (& Childhood history)
Distance of urethra from anus
Non-secretor status (?)
Vitamin D deficiency (?)
Healthy 50-70 yr olds
Not catheterised
Not institutionalised
Elderly, frail ≥70 yr olds
Institutionalised and/or catheterised
Lack of oestrogen
Urogenital surgery
Incontinence
Cystocoele
Post-void residual urine
Non-secretor status
Previous UTI
Catheterisation
Incontinence
Urogenital surgery
Diminished mental status
Antimicrobial use

UROLOGICAL EVALUATION

1. Clinical presentation
2. **Investigations**

❖CLINICAL PRESENTATION

- The clinical presentation of recurrent UTI is similar to sporadic UTI. Most patients present with classic symptoms of cystitis which include:
  - frequency,
  - polyuria,
  - dysuria,
  - suprapubic tenderness
  - and haematuria.
- On the basis of prospective cohort studies, the Health Protection Agency and British Infection Association recommend that **UTIs be diagnosed** when **at least three of these symptoms are present**.
- Fever and flank pain may also be evident with an episode of acute pyelonephritis.

INVESTIGATIONS

- Diagnostic evaluation for recurrent UTIs should begin with a detailed **history** and **physical examination**.
- **Urinalysis** is usually the next step. **A leucocyte and nitrite positive urine dipstick** has been considered **a highly sensitive test** in predicting a UTI. However, since some bacteria, such as *S. saprophyticus*, lack the enzymes to reduce nitrates into nitrites, false-positive results are fairly common.
- **Urine microscopy and culture of midstream urine sample is the gold standard test for a definitive diagnosis.**
  - Historically, UTI has been defined as $>10^5$ colony units of bacteria/ml on culture; however, according to European Association of Urology (EAU) guidelines a count of $>10^3$ cells/ml in symptomatic patients is sufficient to diagnose suspected cystitis or $>10^4$ cells/ml for suspected pyelonephritis.
  - In order to assess for bacterial persistence, the urine sample should be re-cultured 2 weeks after initiating therapy
- Although there are no guidelines for imaging studies in women with uncomplicated recurrent UTIs, patients who present with atypical symptoms of either acute uncomplicated cystitis or acute uncomplicated pyelonephritis, as well as those who fail to respond to appropriate antimicrobial therapy and remain febrile after 72 h of treatment, should be considered for **additional diagnostic investigations** such as **unenhanced helical computed tomography (CT), excretory urography or dimercaptosuccinic acid (DMSA) scanning**
- They also need to be screened for any predisposing factors for complicated UTIs and may need a specialist referral

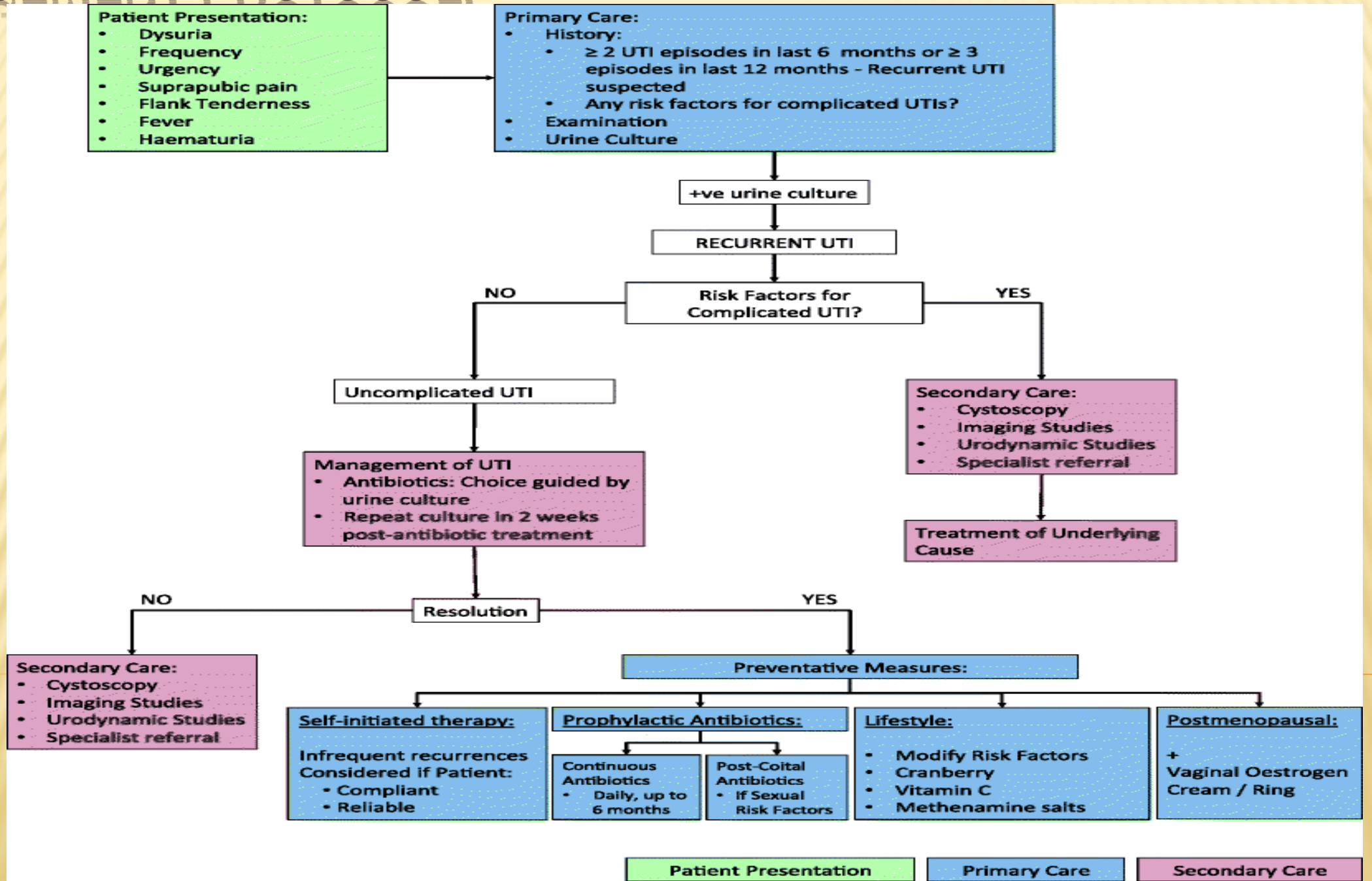
History:

- Age of first UTI
- No of previous UTI episodes, investigations and treatment
- Lower or Upper UTI symptoms
- Urinary continence
- Sexual and Contraceptive history
- Past Medical History: Diabetes, Neurological Disease, any previous urolithiasis, previous surgeries, any urinary tract instrumentation
- Any medications

Assessment:

- General and neurological examination, assessing
- Renal size and tenderness
- Is the bladder palpable
- Vaginal examination: Prolapse ?

MANAGEMENT PROTOCOL:



PREVENTATIVE MEASURES

Lifestyle modifications

Patients should be informed and educated about behavioural risk factors, such as sexual activity. Likewise, premenopausal women on spermicides or vaginal diaphragms should be offered alternative forms of contraception.

Antibiotic therapy

- **Continuous antibiotic prophylaxis:**

In women with recurrent UTI, continuous antibiotic prophylaxis (once daily) has been recommended for prevention of any future episodes. Public Health England recommends low-dose antibacterial prophylaxis (**trimethoprim 100 mg or nitrofurantoin 50–100 mg**) nightly for women with frequent symptomatic recurrent infections. Other antibiotics that have been suggested include **cephalexin and norfloxacin**.

Trimethoprim/sulfamethoxazole (TMP-SMX) and fluoroquinolones prevent recurrent UTIs by inhibiting the recovery rate of uropathogens (especially *E. coli*) from the faecal reservoir, while nitrofurantoin plays a role in sterilizing the urine and inhibiting bacterial attachment.

Prior to prophylactic treatment, patients should have the elimination of a previous UTI confirmed by a negative urine culture 1–2 weeks post-treatment. As per EAU guidelines, antibiotic prophylaxis should be considered only after counselling and where appropriate behavioral modifications have failed to prevent the recurrences.

Continuous antibiotic prophylaxis has been associated with a number of side effects, the most common of which are nausea and candidiasis. Although rare, trimethoprim, especially in combination with sulphamethoxazole, can lead to Lyell's syndrome, Stevens-Johnson syndrome and pancytopenia.

For those requiring >6 months of nitrofurantoin, it is recommended to perform liver function tests to

- **Post-coital prophylaxis**

Post-coital therapy consists of a single dose of antibiotics following sexual activity and may be a more acceptable method of prevention in women where frequency of sexual intercourse is a risk factor.

Depending upon the frequency of sexual activity, post-coital prophylaxis is required in smaller amounts than continuous prophylaxis and is associated with fewer side effects.

- **Patient-initiated therapy**

This is also referred to as self-start therapy and is ideal for women who are not suitable candidates for long-term prophylaxis or for those who do not wish to take the long-term therapy. Through this method, patients can identify episodes of infection on the basis of symptoms, perform their own culture and begin a standard 3-day course of antibiotics. However, it has been associated with a higher rate of infection compared with continuous prophylaxis. **It is advised that the use of this method be restricted to patients** who have documented previous infections and are motivated and compliant with given medical instructions.

The Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases recommends **nitrofurantoin monohydrate/macrocrystals** (100 mg, twice daily for 5 days), TMP-SMX [160/800 mg (one double-strength tablet), twice daily for 3 days], **fosfomycin trometamol** (3 g, single dose) or pivmecillinam (400 mg, twice daily for 5 days).

Non-antibiotic prevention strategies

1. **Oestrogen therapy**- Oestrogen has been associated with colonization of vagina with lactobacilli, which has been found to be protective against UTIs. With menopause, there is a change in the vaginal pH and flora, increasing the risk of UTI
2. **Cranberry juice and tablets-** cranberry juice inhibits adherence of uropathogens to uroepithelial cells
3. **Ascorbic acid-** Ascorbic acid (vitamin C) is often recommended as a supplement that can prevent recurrent UTIs by acidification of the urine
4. **Methenamine salts-** Methenamine is hydrolysed to ammonia and formaldehyde when in acidic urine, which act as a bactericide to some strains of bacteria.

EMERGING THERAPIES

D-Mannose- is a sugar normally present in human metabolism and has an important role. It is thought that its mechanism of action is through inhibition of bacterial adherence to urothelial cells.

Lactobacillus (probiotics)- The use of probiotics has been suggested and trialed as a novel approach to reducing the risk of recurrent UTIs. A recent phase 2 trial has found that treatment with probiotics following cystitis is associated with a decrease in recurrent UTIs.

Vaccination-

Another alternative prophylactic measure that has been a subject of extensive research is use of systemic or mucosal vaccines. **Uro-Vaxom** is an oral capsular vaccine comprising 18 heat killed *E. coli* strains. It has been found to be an effective prophylaxis for prevention of UTI. A meta-analysis of four studies comprising 891 patients demonstrated that Uro-Vaxom significantly reduced the risk for development of UTI, as the mean number of UTI were halved in the participants taking Uro-Vaxom capsule daily in comparison to those on a placebo capsule daily.

Research in use of **Urovac**, which is a vaginal suppository vaccine, has yielded positive results so far. Urovac comprises ten uropathogenic strains of bacteria (six *E. coli* strains and one strain each of *Proteus*, *Mirabilis*, *Morganella morganii*, *K. pneumoniae* and *Enterococcus faecalis*). Currently this vaccine has successfully completed a phase 2 trial, where it has been demonstrated that administration of this vaccine as primary immunization plus its booster vaccination is effective in prolonging the time until first recurrence of UTI as compared to those participants who were administered primary immunization or placebo only.

CONCLUSION

Recurrent UTIs are common phenomena amongst pre- and postmenopausal women. It is important that patients with recurrences are recognized through thorough history and examination.

Although risk factors should be identified and addressed accordingly, antibiotics remain the most effective method of management. The type and regimen of antibiotic agent should be individualized to each patient. Non-antibiotic prevention strategies such as cranberry, vitamin C and methenamine salts lack strong evidence to be introduced as routine management options and as alternatives to antibiotics. However, they may be used as adjuvant measures, where the patient is able to tolerate them.

There are also a number of emerging therapies including D-mannose, probiotics and vaccination. However, further basic science and randomized controlled trials are necessary before they can be recommended.