住院醫師課程

Evaluation and Management of Recurrent UTI (rUTI)

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Introduction

- Urinary tract infections (UTI) is the most common adult bacterial infection in the world.
- Approximately **60%** of women will be diagnosed with symptomatic acute bacterial cystitis in their lifetime.
- Considering that the majority of women presenting with UTI have a history of more than two previous infections, recurrence represents a substantial social cost.
- Recurrent UTI (rUTI) is a highly prevalent, costly, and burdensome condition affecting women of all ages, races, and ethnicities without regard for socioeconomic status, or educational level.
- Recurrence also poses significant clinical challenges and has a major impact on quality of life.

Introduction

- It is well established that one of the most significant risk factors for development of a UTI is a prior recent UTI.
- Interestingly, the majority of women experience recurrence despite culture directed antibiotic treatment, have no anatomical abnormalities in the lower and upper urinary tracts, and are otherwise healthy individuals.

Current evidence indicates that the rate of recurrence following an initial UTI is high

- A 1990 study at the University of Michigan involving female students aged 17-39 years showed that after a single UTI event, 27% of women will experience a second recurrence in the following 6 months with a further 3% experiencing a third UTI within the same time period.
- Another study from Denmark showed that for women aged 16-65 years, rate of recurrence is highest during the first 2 months post-treatment and 25%-35% of women will have recurrence within 3-6months.
- A single study in Finnish indicated that 44% of women aged 17-82 years will experience recurrence within 12 months.
- An estimated **20-40%** of women who have had one previous cystitis episode are likely to experience an additional episode, **25-50%** of whom will experience multiple recurrent episodes.

Definition

- rUTIs are defined in most guidelines as **≥ 2 episodes in 6 months** or **≥ 3 episodes in 12 months**. Importantly, patients must be symptom free between episodes.
- Proof of a **positive urine culture** was also frequently incorporated in the definition.
- rUTIs are hypothesized to be secondary to either **bacterial persistence** within the urinary tract or, more commonly, novel **reinfections**.
- Persistence caused by **the same bacterial strain**, usually leads to recurrent infections in a short time frame.
- Reinfections are caused by either the same organism **more than 2 weeks** after treatment or **a different organism**.
- Reinfection is likely secondary to ascent or uropathogens from fecal flora into the urinary tract or from reemergence of bacteria from uroepithelial intracellular colonies.
- Reinfections in men are uncommon and my be associated with an underlying **anatomic abnormality.**

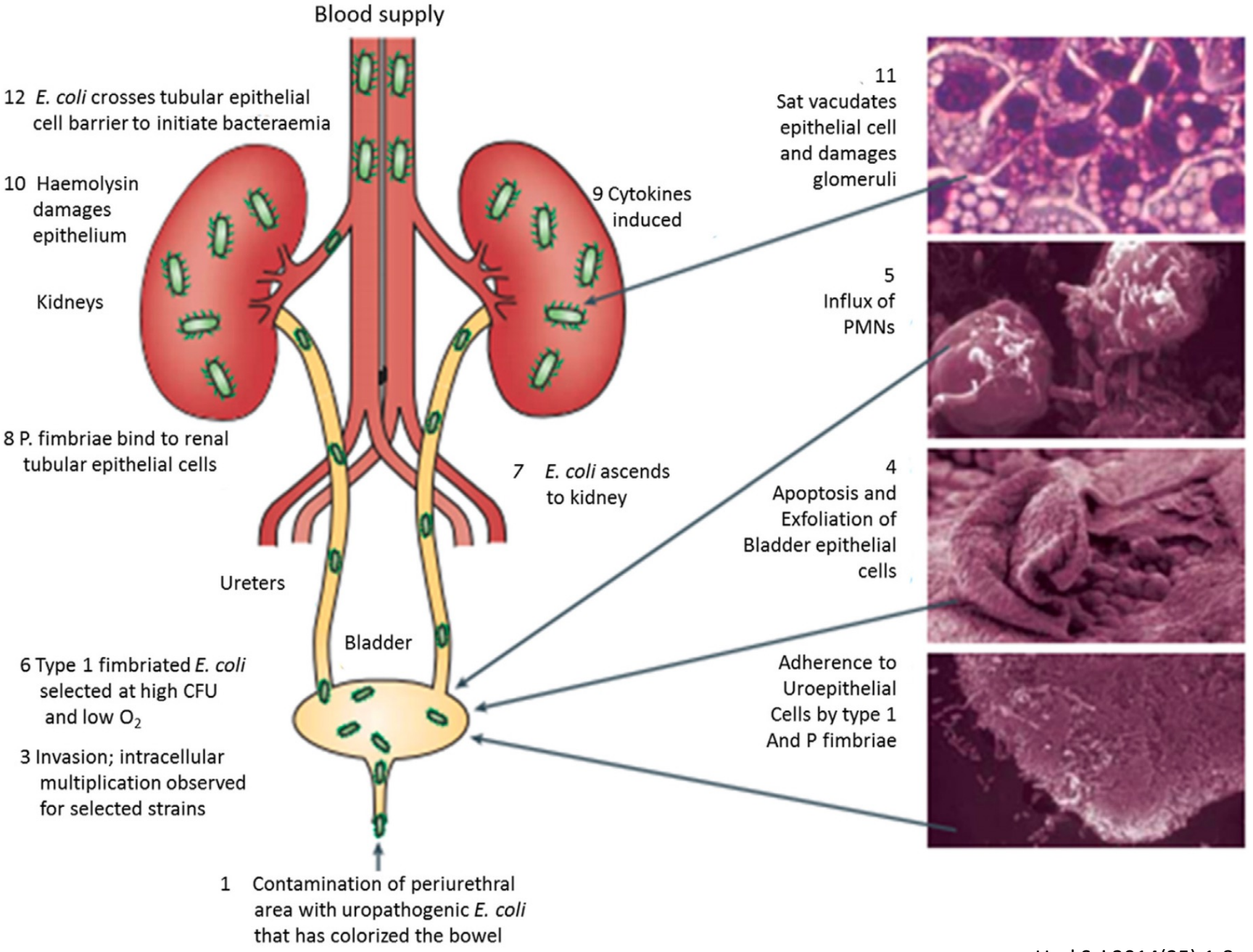
Urinary tract infection (UTI)	A variety of clinical conditions ranging from localized infection of the bladder with lower urinary tract symptoms to pyelonephritis with severe infection of the kidney and the potential for resultant urosepsis
	An inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria
Complicated UTIs	UTIs with factors that increase bacterial acquiring and decrease therapy efficacy
	The urinary tract is structurally or functionally abnormal, the host is compromised, and/or the bacteria have increased virulence or antimicrobial resistance
First or **isolated infection**	Never had a UTI or has one remote infection from a previous UTI
Unresolved infection	Not responded to antimicrobial therapy and is documented to be the same organism with a similar resistance profile
Recurrent infection	Occurs after documented, successful resolution of an antecedent infection
	Two different types of recurrent infection: reinfection and bacterial persistence
Reinfection	A new event with reintroduction of bacteria into the urinary tract from outside
Bacterial persistence	Caused by the same bacteria reemerging from a focus within the urinary tract, such as an infectious stone or the prostate
	Relapse is frequently used interchangeably

Etiology

- rUTIs may be caused by one of two mechanisms: ascending reinfections or chronic/ persistent infection in the bladder.
- **Repeated ascending infections** are thought to occur by the endogenous rectal flora via a fecal-perineal-urethral route.
- Women who suffer from rUTI have been found to have a higher frequency of infection with endogenous rectal flora, specifically *E. coli* and *Enterococcus faecalis*.
- Another mechanism is the survival of bacteria in the urinary bladder through the progression of **transient intracellular bacterial communities** (IBC) into persistent **quiescent intracellular reservoirs** (QIR).
- Current evidence supports both **ascending reinfection** and **QIR recurrence** as models for rUTI.

Ascending reinfection

Uropathogens originate from the rectal flora and colonize the periurethral area leading to ascension through the urethra into the bladder.



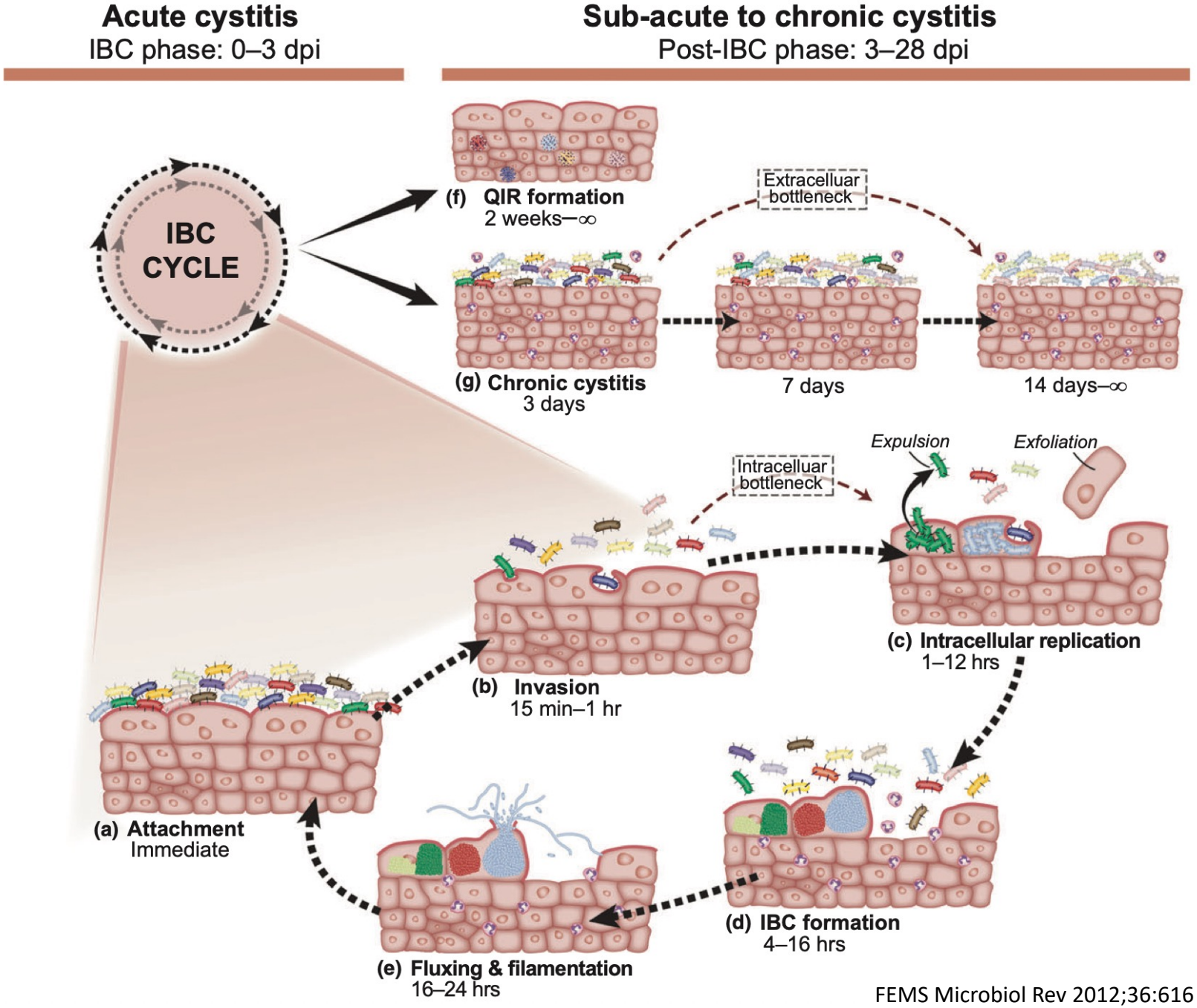
Urol Sci 2014(25):1-8

IBCs and QIRs

Intracellular bacterial community (IBC) formation starts when bacteria attach onto the apical transitional epithelium of the bladder via type 1 pili. These bacteria are then enveloped and invade the epithelium: replicating and forming IBCs.

As a host response to infection, the urothelium typically exfoliates, resulting in IBC liberation and IBC recreation in a clonal fashion.

IBCs may also progress to quiescent intracellular reservoirs (QIR), which are not metabolically active and do not produce a measurable inflammatory response.



FEMS Microbiol Rev 2012;36:616

IBC (Intracellular bacterial community)

- IBCs are initially created when bacteria ascend the urethra and attach onto the bladder urothelium. This luminal attachment results in **urothelial envelopment**.
- Initial IBC formation is rapid and can be seen as early as **3 hours** post-inoculation. By 12 hours post-infection, over half of all bacteria are intracellular. This **biofilm** allows bacteria to replicate while protected from innate immune defenses such as neutrophil phagocytosis.
- The majority of the bacteria are expelled from the bladder through **TLR-4 dependent** urothelial hyperplasia. **Lipopolysaccharide (LPS)** released by *E. coli* is sensed by TLR-4 receptor, which induces cAMP production, resulting in **exocytosis of vesicular UPEC** across the apical plasma membrane.
- The bacteria that escape this expulsion remain to create clonal recurrent IBCs.
- Acute IBC formation can result in a simple resolution, but the infection may also persist in the form of either chronic cystitis or QIRs.
- IBC expulsion is limited by urothelial hyperplastic. Each round of IBC formation is associated with slower bacterial replication and smaller IBCs with eventual resolution of infection.
- IBC formation provides UPEC with the ability to survive stringent bottlenecks in the urinary tract, including TLR4-mediated expulsion, umbrella cell exfoliation, and ascension to the kidneys.

QIR (quiescent intracellular reservoir)

- Although the IBC cycle is self-limited, invasion of urothelial cells can result in recurrence through the creation of quiescent intracellular reservoirs (QIRs).
- QIRs consist of 4–10 **non-replicating bacteria** within membrane-bound compartments encased in F-actin.
- In contrast to IBCs, these quiescent bacteria are non-replicating and do not elicit an immune response.
- QIRs can remain viable for months and can be re-activated to serve as seeds that initiate a recurrent UTI.
- As the epithelium turns over, these quiescent bacteria are released and emerge to create new acute infections. These recurrences may occur for **months after** the initial acute infection.
- In this fashion, some species of *E. coli* possess the ability to create a state of quiescent infection in the bladder that may be responsible for **multiple recurrences**.

Evaluation of rUTIs

- Identification of the cause of the recurrent infection is important, because the **management** of bacterial persistence and reinfection are distinct.
- If bacterial persistence is the cause of rUTI, the **removal of the infected source** is often curative, whereas **preventive therapy** is effective in treating reinfection.
- In evaluation of a woman with rUTI, the clinical focus should be on preventing recurrence by **identifying risk factors** for, and **altering behaviors** that contribute to, recurrent infections.
- Obtaining a thorough medical history is imperative.
- The physical examination is equally important. As recommended in the AUA guidelines, all women should be examined with a **pelvic examination** at the time of the first visit and as indicated.

Evaluation: History

- Emphasis should be on ascertaining the prior number of infections and their frequency, culture results and associated symptoms.
- Symptoms such as pneumaturia, fecaluria, as well as prior history of diverticulitis, prior pelvic surgery or radiation should raise suspicion for **fistula**.
- Identifying triggers, risk factors, contributory behaviors, prior UTI work-up, diagnosis, and treatments allows for an in-depth assessment of the patient.
- A review of all **available urine culture data** is crucial and may determine not only a pattern of pathogenic organisms, but can differentiate persistent from recurrent infections.

Key features to elicit in history of patients with rUTIs

Duration of symptoms
Frequency of infections
Complicated UTIs (i.e. pyelonephritis, urosepsis)
Lower urinary tract symptoms – storage and voiding
Incontinence
Previous investigations and treatment for infections
Sexual and contraceptive history
Childhood UTIs
Dietary pattern/fluid intake
Triggers/precipitants
Neurological disease (cerebrovascular accidents, multiple sclerosis, Parkinson disease, etc.)
Co-morbidities: diabetes, immunosuppression (steroid use)
Red flags: hematuria, persisting bladder/pelvic pain

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Risk factors for RUTIs

Young and pre-menopausal women	Post-menopausal and elderly women
Sexual activity	History of UTI before menopause
New sexual partner within past year	Menopause
Recent antimicrobial use	Incontinence
Family history of UTI in first-degree female relative	Atrophic vaginitis due to estrogen deficiency
History if UTI during childhood	Cystocele
Contraceptive use (spermicides, diaphragm, oral contraceptives)	Urine catheterization in elderly institutionalized women
Voluntary deferral of micturition	Functional status deterioration in elderly institutionalized women
Blood group antigen secretory status (women who are nonsecretors of blood group antigens B or AB are up to four times more susceptible to rUTI)	
Urinary tract abnormality: obstruction, calculi, VUR, fistula	
Voiding dysfunction: elevated residuals, abdominal straining in voiding, reduced flow rate	
Immunodeficiency: DM, organ transplants, chronic renal insufficiency	

Campbell Walsh Wein Urology, 2020, 12th Ed. Ch 55
EAU guidelines 2022
Tzu Chi Med J 2017;29:131
Urol Sci 2014(25):1-8

Evaluation: Physical examination

- A physical examination including an **abdominal exam** and a detailed **pelvic examination** should be performed to look for any structural or functional abnormalities.
- Palpating the suprapubic area may identify a distended bladder, a significant postvoid residual contributes to bacteriuria.
- On pelvic examination, the appearance of vaginal epithelium, particularly in postmenopausal women, should be characterized.
- The presence of pelvic organ prolapse, urethral diverticulum, labial fusion, or pelvic mesh complications could help establish the cause of rUTIs.

Evaluation: Laboratory data

- Obtaining laboratory data, specifically urinalysis and urine culture, is imperative in patients with RUTI.
- To make a diagnosis of rUTI, clinicians must document **positive urine cultures** associated with prior symptomatic episodes.
- Clinicians should obtain **repeat** urine studies when an initial urine specimen is suspect for contamination, with consideration for obtaining a catheterized specimen.
- Clinicians should obtain **urine culture and sensitivity** with each symptomatic episode prior to initiating treatment in patients with rUTI.

Evaluation: Imaging and cystoscopy

- Imaging and cystoscopic evaluation are not warranted in all women with rUTI.
- The yield of imaging in women without complicated UTI is low and is not recommended by AUA and EAU Guidelines.
- However, it should be performed without delay in atypical cases, for example, if renal calculi, outflow obstruction, interstitial cystitis or urothelial cancer is suspected.
- In women with risk factors for a complicated UTI the evaluation should include imaging and cystoscopy. In patients who have frequent rUTI, **bacterial localization studies** and more extensive radiologic evaluation (such as retrograde pyelograms) are warranted.
- When **bacterial persistence** is the suspected cause, radiologic imaging is indicated.
- **Ultrasonography** can be obtained to provide a **screening evaluation** of the genitourinary tract. More detailed assessment with intravenous pyelogram, cystoscopy, and CT scans may occasionally be necessary.
- When **bacterial reinfection** is the suspected cause of recurrent cystitis, the patient should be carefully evaluated for evidence of vesicovaginal or vesicoenteric **fistula**. Otherwise, radiologic examination is rarely necessary in these patients.

Indications for further investigation of rUTI

Previous urinary tract trauma or surgery
Previous bladder or renal calculi
Gross hematuria after resolution of infection
Obstructive symptoms, low uroflowmetry, or high postvoid residual
Urea-splitting bacteria or culture
Previous abdominopelvic malignancy
Bacterial persistence after sensitivity-based therapy
Diabetes or other immune compromise
Pneumaturia, fecaluria, anaerobic bacteria, or history of diverticulitis
Repeated pyelonephritis
Asymptomatic microhematuria after resolution of infection

Campbell Walsh Wein Urology, 2020, 12th Ed. Ch 55

Management for bacterial persistence

- The incidence of bacterial persistence in the rUTI population is very small, but when present, it is critical to diagnose **the source of persistence**.
- For culture-documented infection with acute symptoms, if patients fail to respond to an **appropriate course of antibiotics**, then bacterial persistence may be present.
- With persistence there are usually correctable **urological abnormalities** that may be reversible. Such abnormalities often immune from treatment because of the inability of antibiotics to penetrate or eliminate the nidus of infection.
- In select instances, **surgical treatment** of the source of infection has been shown to eradicate the infections, such as infection stones and fistulas.

Correctable urological abnormalities that cause bacterial persistence

Infection stones
Chronic bacterial prostatitis
Unilateral infected atrophic kidney
Ureteral duplication and ectopic ureters
Foreign bodies
Urethral diverticula and infected periurethral glands
Unilateral medullary sponge kidney
nonrefluxing, normal-appearing, infected ureteral stumps after nephrectomy
Infected urachal cysts
Infected communicating cysts of the renal calyces
Papillary necrosis
Perivesical abscess with fistula to bladder

Campbell Walsh Wein Urology, 2020, 12th Ed. Ch 55

Management for bacterial persistence

- One of the most common causes of bacterial persistence are **struvite renal calculi**.
- **Urea-splitting organisms**, such as *P. mirabilis*, contribute to such infection stones. Urea-splitting organisms cause alkalinization of urine with precipitation of calcium, magnesium, ammonium, and phosphate salts.
- **Surgical treatment** of the infection stones is recommended in all patients safe for intervention, per the AUA Guideline.
- In those patients with residual or recurrent struvite stones who are not surgical candidates, **acetohydroxamic acid** in conjunction with **antibiotics suppression** may be offered.
- Management of non-obstructing stones in rUTI is controversial.

Management for reinfection

- The majority of women with rUTI do not have identifiable and/or correctible anatomic abnormalities.
- Options for minimizing rUTI include **behavioral modifications**, use of **non-antibiotics therapies**, and as a last resort, **antibiotics treatment** and prophylaxis.
- Treatments for UTI and rUTI are similar in that the first line of defense involves antibiotic therapy.
- Trimethoprim/sulfamethoxazole (TMP-SMX), fluoroquinolones (Ciprofloxacin), β-lactams, and nitrofurantoin (Macrobid) are the most common antimicrobial agents used in daily practice.
- However, dosing regimens may differ in women with frequent rUTI, favoring **patient-initiated treatment** when symptoms start, **postcoital therapy**, and long-term **daily prophylaxis**.

Management for reinfection: behavioral modifications

- Employing behavioral modification is a reasonable strategy to minimize rUTI, despite the lack of scientific evidence in support.
- Women with rUTI should be counselled on avoidance of risks (insufficient hydration, habitual and postcoital delayed urination, wiping from back to front after defecation, douching and wearing occlusive underwear) before initiation of long-term prophylactic drug treatment.
- **Hydration** is recommended to augment innate immunity by sloughing of urothelial cells and flushing of adherent bacteria.
- **Frequent voiding** helps to continually empty the bladder, which is particularly important if women have a tendency to hold urine for extended periods.
- **Emptying the bladder after intercourse** help to minimize the likelihood that the transient bacteriuria will progress to clinical symptomatology of a UTI. By the same logic, voiding pre-intercourse may also be beneficial.

Management for reinfection: behavioral modifications

- Spermicides (nonoxynol-9) have been associated with an increased risk of developing a UTI because they contribute to decreased population of normal vaginal flora and subsequently alter the vaginal pH.
- Clinicians have speculated that shaving pubic hair and wearing thong underwear may contribute to rUTI; however, scientific data confirming this do not exist.

Management for reinfection: non-antimicrobial prophylaxis

Hormonal replacement
EAU guideline: Use vaginal estrogen replacement in post-menopausal women to prevent rUTI (Strong Recommendation)
AUA guideline: 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 (Moderate Recommendation; Evidence Level: Grade B)
Vaginal admission has no systematic side effects, but local irritation and minor bleeding can occur
The use of oral estrogens was not effective for rUTI prophylaxis
Immunoactive prolphylaxis (Vaccines)
EAU guideline: Use immunoactive prophylaxis to reduce rUTI in all age groups (Strong Recommendation)
Endovesical instillation
Endovesical instillations of hyaluronic acid (HA) and chondroitin sulphate (CS) have been used for glycosaminoglycan (GAG) layer replenishment
EAU guideloine: Use endovesical instillations of HA or HA-CS to prevent rUTIs in patients where less invasive preventive approaches have been unsuccessful (Weak recommendation)

Management for reinfection: non-antimicrobial prophylaxis

Prophylaxis with cranberry
EAU guideline: Advise patients on the use of cranberry products to reduce rUTI episodes; however, patients should be informed that the quality of evidence underpinning this is low with contradictory findings (Weak Recommendation)
AUA guideline: Clinicians may offer cranberry prophylaxis for rUTIs (Conditional Recommendation; Evidence Level: Grade C)
Prophylaxis with D-mannose
EAU guideline: D-mannose can significantly reduce the number of UTI episodes and can be an effective agent for UTI prevention in selected patients (Weak recommendation)
Prophylaxis with probiotics (Lactobacillus spp.)
EAU guideline: Advise patients on the use of local or oral probiotics containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs (Weak Recommendation)
Not all Lactobacillus strains are effective for vaginal flora restoration and rUTI prevention
The quality of available data was too low to make recommendations on the route of admission, optimal dosage, and treatment duration

Management for reinfection: continuous low-dose antimicrobial prophylaxis

- Antibiotic prophylaxis is the most effective approach against rUTI compared with placebo or no treatment
- There is no consensus about the optimal duration of continuous antimicrobial prophylaxis, with studies reporting of **3-12 months**.
- After discontinuation, UTIs **tend to re-occur**, especially among those who have had three or more infections annually.
- AUA guideline: 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)
- EAU guideline: Use continuous antimicrobial prophylaxis to prevent recurrent UTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects. (Strong Recommendation)
- The choice of agent should be based on the local resistance patterns.
- Regimens include nitrofurantoin, fosfomycin trometamol, trimethoprim and cephalexin or cefaclor during pregnancy .

Management for reinfection: postcoital prophylaxis

- Postcoital antibiotic use In women with rUTI secondary to intercourse, is an effective strategy and is preferable to daily antibiotic use.
- A single dose of antibiotic taken **within 2 hours** of sexual intercourse can significantly reduce the incidence of recurrent infection.
- AUA guideline: In women who experience UTIs temporally related to sexual activity, antibiotic prophylaxis taken **before or after** sexual intercourse has been shown to be effective and safe.
- EAU guideline: Use **postcoital** antimicrobial prophylaxis to prevent rUTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects. (Strong Recommendation)

Antibiotic prophylaxis dosing

Continuous prophylaxis	
TMP	100 mg once daily
TMP-SMX	40 mg/200 mg once daily, 40 mg/200 mg thrice weekly
Nitrofurantoin	50 mg daily, 100 mg daily
Cephalexin	125 mg once daily, 250 mg once daily
Fosfomycin	3 gm every 10 days
Intermittent prophylaxis	
TMP-SMX	40 mg/200 mg, 80 mg/400 mg
Nitrofurantoin	50-100 mg
Cephalexin	250mg

AUA Guideline. J Urol 2019;202:282

Management for Reinfection: self-start Therapy

- EAU guideline: In patients with good compliance, self-diagnosis and self-treatment with a short course regimen of an antimicrobial agent should be considered. (Strong Recommendation)
- AUA guideline: Clinicians may offer self-start treatment to select rUTI patients with acute episodes while awaiting urine cultures. (Moderate Recommendation; Evidence Level: Grade C)
- Motivated patients self-identify episodes of infection by their typical UTI symptoms and get instant access to antibiotics.
- The choice of antimicrobials is the same as for sporadic acute uncomplicated UTI.
- However, it countermands the principles of **antibiotic stewardship** and meaningful use of culture-specific antibiotics justification.
- Many experienced clinicians encourage patients to medicate the **urinary analgesics** with the onset of symptoms, provide a urine sample, and continue observation.

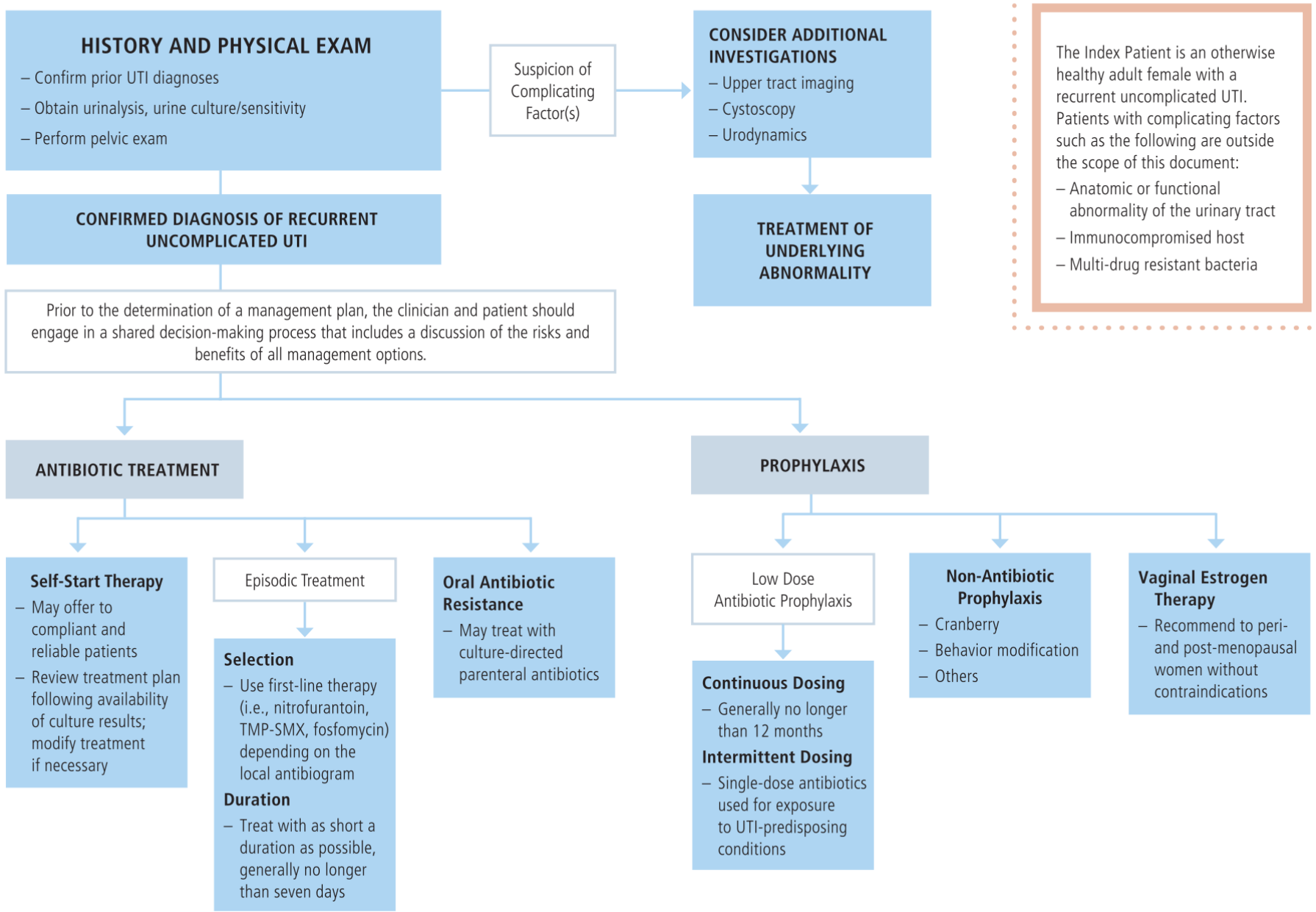
Antibiotics for rUTI

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

Suggested regimens for antimicrobial therapy in uncomplicated cystitis

Antimicrobial	Daily dose / Duration of therapy		Comments
First-line			
Fosfomycin trometamol	3g SD	1 day	Recommended only in women with uncomplicated cystitis
Nitrofurantoin macrocrystal	50-100 mg four times a day	5 days	
Nitrofurantoin monohydrate/ macrocrystals	100 mg bid	5 days	
Nitrofurantoin microcrystal ER	100 mg bid	5 days	
Pivmecillinam	400 mg tid	3-5 days	
Alternatives			
Cephalosporins	500 mg bid	3 days	Or comparable
If the local resistance pattern for E. coli is < 20%			
Trimethoprim	200 mg bid	5 days	Not in the first trimenon of pregnancy
Trimethoprim-sulfamethoxazole	160/800 mg bid	3 days	
Treatment in men			
Trimethoprim-sulfamethoxazole	160/800 mg bid	7 days	

Recurrant Uncomplicted Urinary Tract Infections in Women: AUA/CUA/SUFU Diagnosis & Treatment Algorithm



1. Obtaining a thorough history is critical, with emphasis on prior symptoms, urinalysis and culture results, and triggers for infections.
2. Sources of possible bacterial persistence must be identified and eradicated.
3. Image and cystoscopy are not recommended for uncomplicated rUTIs.
4. Prevention of recurrence should focus on non-antibiotic interventions.
5. In patients with good compliance, self-start treatment with a short course regimen of an antimicrobial agent should be considered while awaiting urine cultures.
6. In women who experience UTIs temporally related to sexual activity, postcoital antimicrobial prophylaxis has been shown to be effective and safe.

Take home message

Reference

1. Bacterial Infections of the Genitourinary Tract. Smith & Tanagho's General Urology. 2020, 19th Ed, Ch 14
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