實習醫師課程

# Urinary Tract Infections (UTIs)

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# 1. Definitions

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|---|---|
| **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 |
| **Pyuria** | The presence of WBCs in the urine; indicative of infection and/or an inflammatory response of the urothelium to the bacterium, stones, or other indwelling foreign body |
| **Bacteriuria** | The presence of bacteria in the urine, it can be symptomatic or asymptomatic |
| | Bacteriuria without pyuria is generally indicative of bacterial colonization without infection |
| | Pyuria without bacteriuria warrants evaluation for tuberculosis, stones, or cancer |
| **Cystitis** | Syndrome of dysuria, frequency, urgency, and occasionally suprapubic pain |
| **Acute pyelonephritis (APN)** | Syndrome of chills, fever, and flank pain that is accompanied by 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 |

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|---|---|
| **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 |
| **Domiciliary UTIS** or **Outpatient UTIs** | Occur in patients who are not hospitalized or institutionalized |
| | Generally caused by common bowel bacteria (e.g., Enterobacteriaceae or Enterococcus faecalis) which are susceptible to most antimicrobial agents |
| **Nosocomial UTIS** or **Health care–associated UTIs** | Occur in hospitalized or institutionalized patients |
| | Typically caused by Pseudomonas and other more antimicrobial-resistant strains |

# 2. Incidence and Epidemiology

- UTIs are considered to be the most common bacterial infection.
- The overall lifetime prevalence was 14,000 per 100,000 men and 53,000 per 100,000 women.
- Overall, UTIs are more common in females,  and increasing with age in a linear trend.
- Upward of **60%** of adult women will report having a UTI during their lifetime, and 11% will report having at least one infection per year.
- 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.
- UTIs account for approximately 38% of the 2 million nosocomial infections each year. **Catheter-associated UTIs (CAUTIs)** are the most common nosocomial infection. More than 80% of nosocomial UTIs are secondary to an indwelling urethral catheter.
- Prophylactic antimicrobial therapy reduces morbidity and the time to recurrent bacteriuria, but the risk of recurrence remains the same.

# Epidemiology of UTI by age, group, and sex

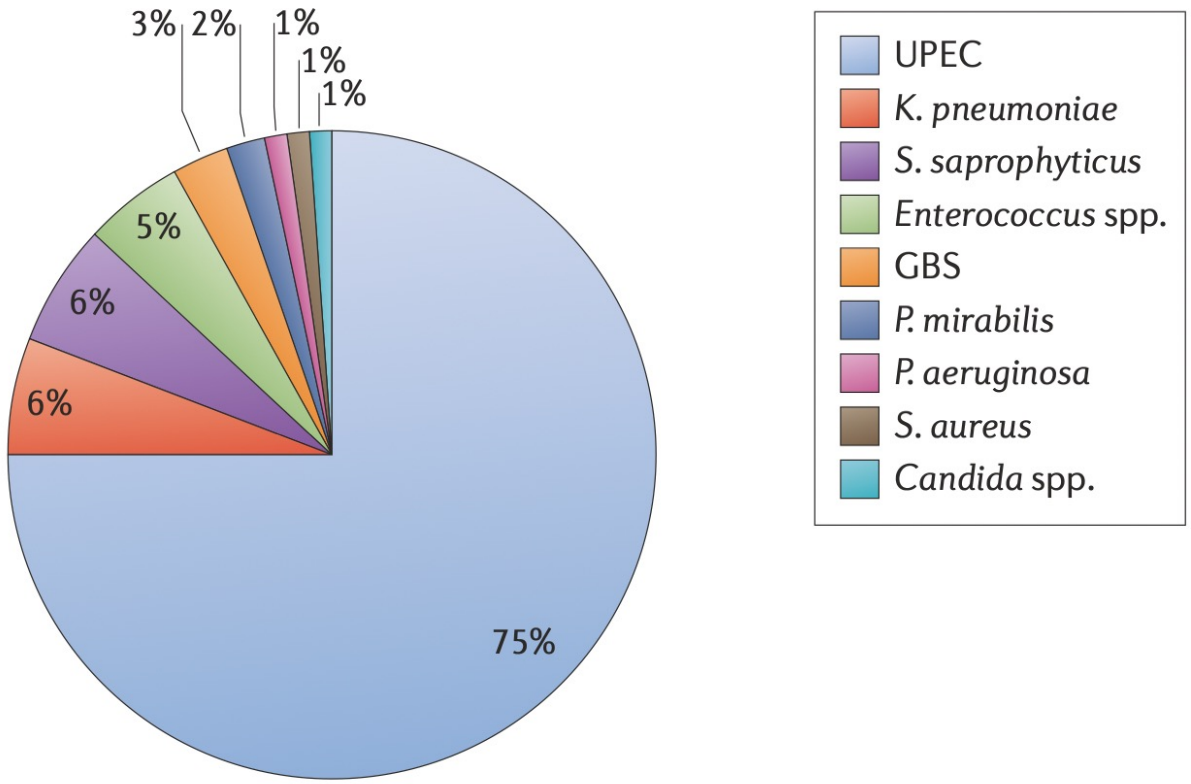
| Incidence (%) | | | |
|---|---|---|---|
| **Age (y)** | **Female** | **Male** | **Main risk factors** |
| < 1 | 0.7 | 2.7 | Foreskin, anatomic GU abnormalities |
| 1-5 | 4.5 | 0.5 | Anatomic GU abnormalities, functional GU abnormalities |
| 6-15 | 4.5 | 0.5 | Functional GU abnormalities |
| 16-35 | 20 | 0.5 | Sexual intercourse, diaphragm use |
| 36-65 | 35 | 20 | Surgery, prostate obstruction, catheterization |
| > 65 | 40 | 35 | Incontinence, catheterization, prostate obstruction |

Smith & Tanagho's general urology, 2020, 19Ed, Ch 14

# 3. Pathogenesis

- UTIs are a result of interactions between the uropathogen and the host.
- Successful infection of the urinary tract is determined in part by the **virulence factors** of the bacteria, the inoculum size, and the inadequacy of **host defense mechanisms**.
- Whereas increased bacterial virulence appears to be necessary to overcome strong host resistance, bacteria with minimal virulence factors are able to infect patients who are significantly compromised.
- There are four possible modes of bacterial entry into the genitourinary tract: ascending route, hematogenous route, lymphatic route, and direct extension.
- Most UTIs are caused by facultative anaerobes usually originating from the bowel flora. ***E. coli*** is by far the most common cause of UTIs, accounting for **85%** of community-acquired and **50%** of hospital-acquired infections.

# Uncomplicated UTIs

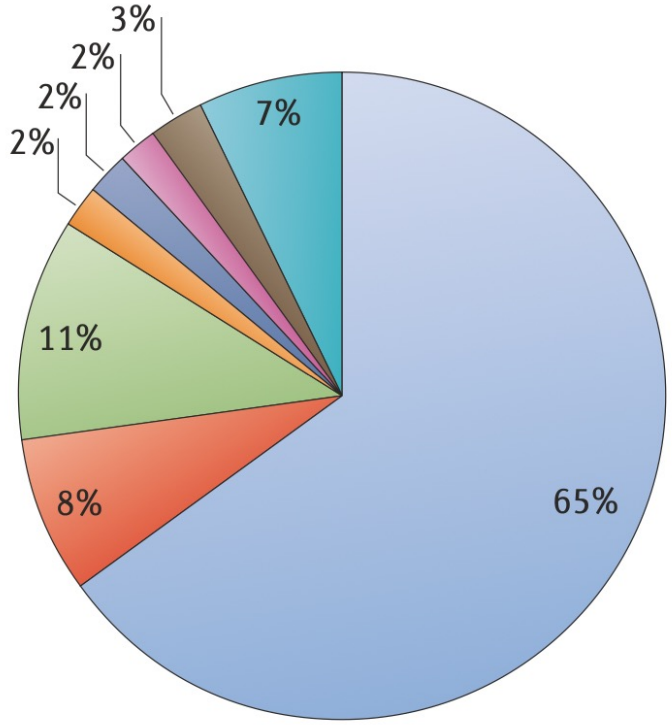



Risk factors

Female gender
Older age
Younger age

1 UPEC
2 *Klebsiella pneumoniae*
3 *Staphylococcus saprophyticus*
4 *Enterococcus faecalis*

# Complicated UTIs




Risk factors

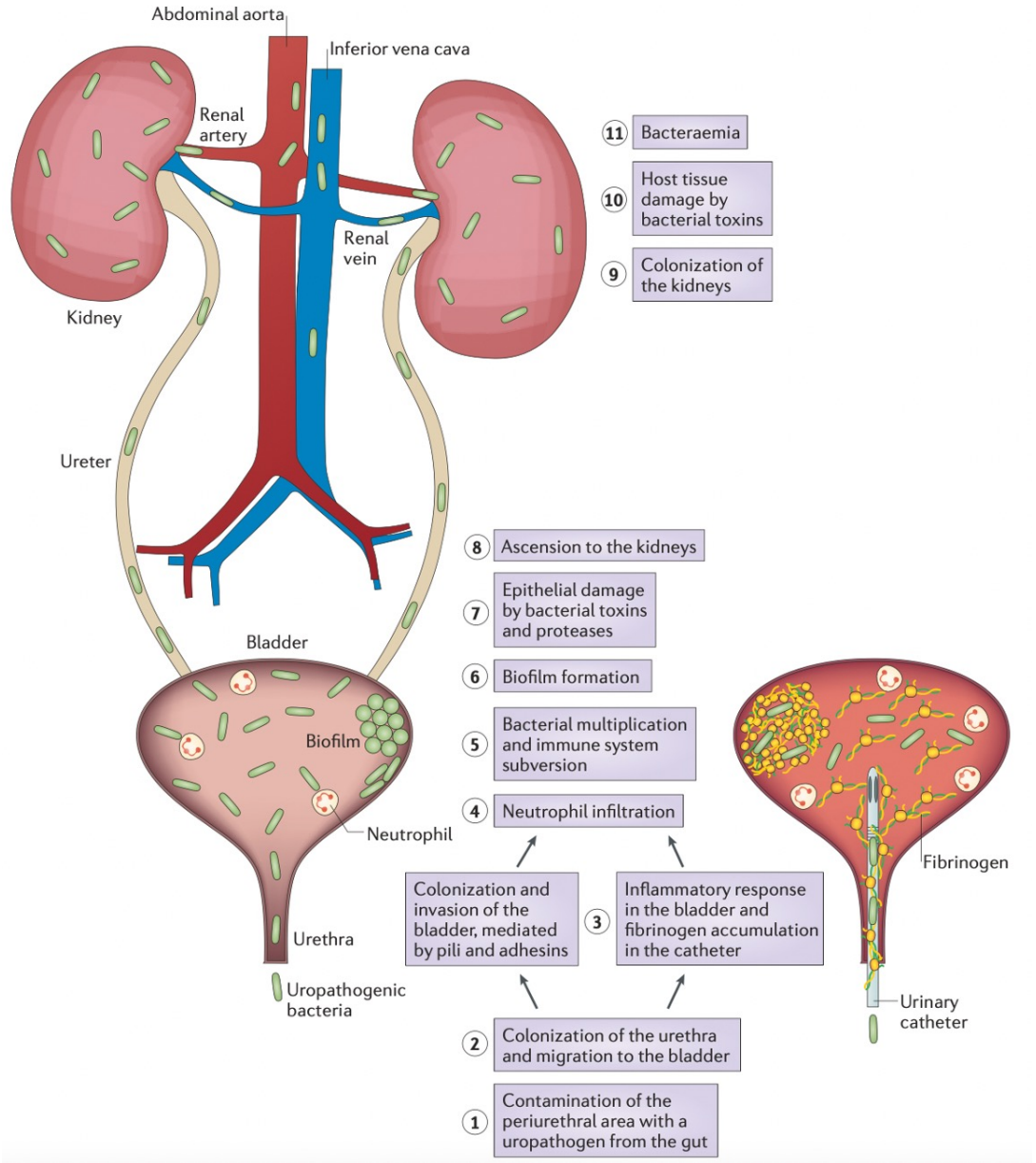
Indwelling catheters
Immunosuppression
Urinary tract abnormalities
Antibiotics exposure

1 UPEC
2 *Enterococcus* spp.
3 *Klebsiella pneumoniae*
4 *Candida* spp.

Nat Rev Microbiol 2015;13:269

# Pathogenesis of urinary tract infection

Uncomplicated UTIs




Complicated UTIs

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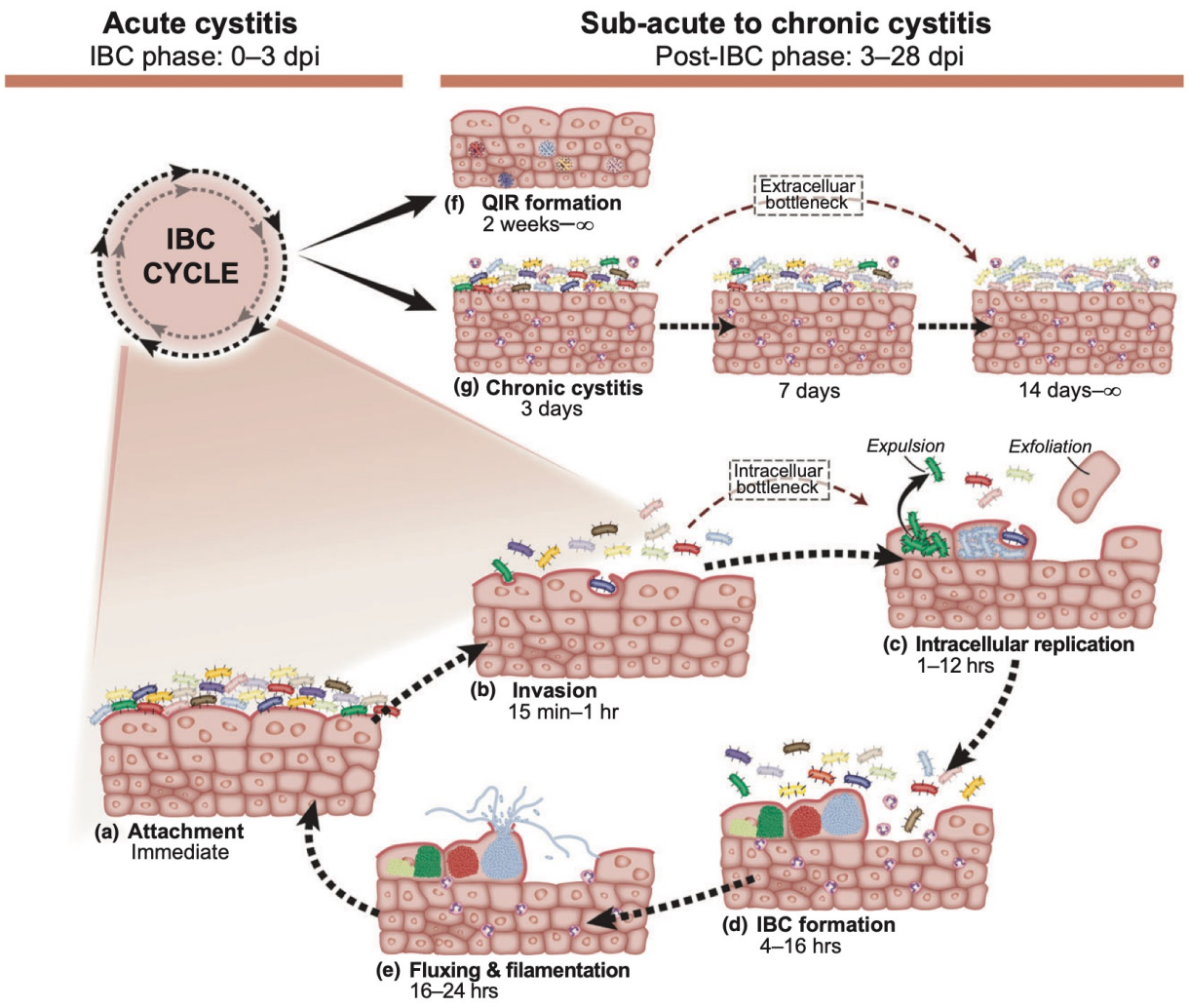
# Host defenses

- The **normal flora** of the vaginal introitus, the periurethral area, and the urethra usually contain microorganisms such as lactobacilli, coagulase-negative staphylococci, corynebacteria, and streptococci that form a barrier against uropathogenic colonization.
- In men, the **prostate secretes fluid** containing zinc, which has potent antimicrobial activity.
- Unobstructed urinary flow with the subsequent **washout of ascending bacteria** is essential in preventing UTI.
- Urinary retention, stasis, or reflux of urine into the upper urinary tract can promote bacterial growth and subsequent infection. Consequently, any **anatomic or functional abnormalities** of the urinary tract that impede urinary flow can increase the host's susceptibility to UTI.
- The **urine itself** has specific characteristics (its osmolality, urea concentration, organic acid concentration, and pH) that inhibit bacterial growth and colonization.
- **Uromodulin** (Tamm-Horsfall glycoprotein, THG) is present in an extraordinarily high concentration in the urine (>100 mg/mL), may play a defensive role by saturating all the mannose-binding sites of the type 1 pili, thus potentially blocking bacterial binding to the uroplakin receptors of the urothelium.
- The **epithelium lining** of the urinary tract not only provides a physical barrier to infection but also has the capacity to recognize bacteria in order to activate innate host defenses.

# Adherence and colonization

- **Bacterial adherence** to vaginal and urothelial epithelial cells is an essential step in the initiation of UTIs.
- A UTI typically starts with periurethral contamination by a uropathogen, followed by colonization of the urethra and subsequent migration of the pathogen to the bladder, an event that requires appendages such as **flagella** and **pili.**
- In the bladder, the consequences of **complex host–pathogen interactions** ultimately determine whether uropathogens are successful in colonization or eliminated.
- Multiple **bacterial adhesins** recognize receptors on the uroepithelium and mediate colonization.
- UPEC binds to **mannose-containing glycoprotein receptors** on superficial bladder urothelial cells via **FimH**, an adhesin located at the distal end of **type 1 pili**. Adherence to the urothelium protects the UPEC from being washed out of the urinary tract by countering urinary shear forces during bladder emptying. Once bound, the epithelial cells internalize UPEC with their own endocytotic pathway.
- Uropathogens survive by invading the bladder epithelium, producing **toxins** and **proteases** to release nutrients from the host cells, and synthesizing **siderophores** to obtain iron.
- This **internalization** allows the bacteria to enter the nutrient-rich intracellular environment where they are protected from antibiotics, neutrophil influx, and shear stress. Binding and internalization of UPEC activates host inflammatory and apoptotic cascades in the epithelium.

# Intracellular bacterial communities (IBCs)

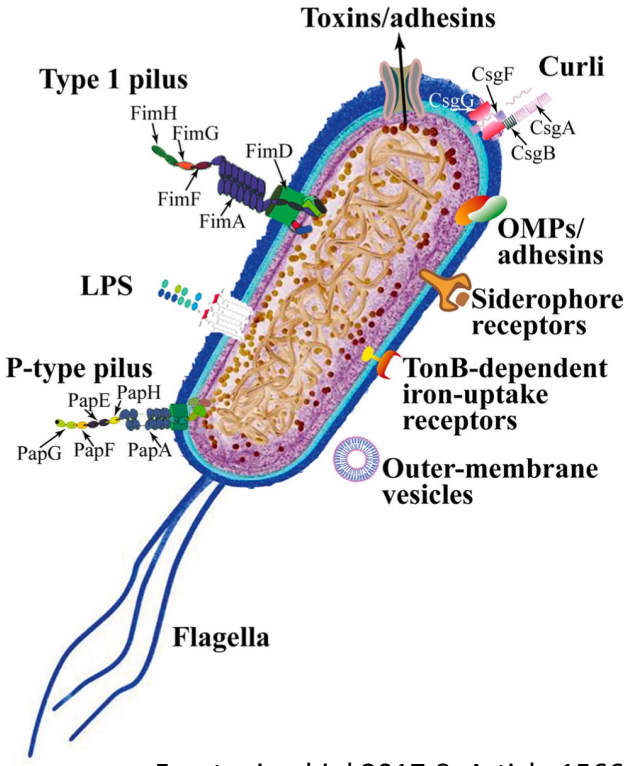



FEMS Microbiol Rev 2012;36:616

- Pathogenesis of infections caused by UPEC include invasion of urothelial cells lining the urinary bladder with formation of **intracellular bacterial communities (IBCs)**. In this **biofilm state**, IBCs may go undetected by standard urine cultures, evade host defense mechanisms, and persist despite antibiotic therapy.
- IBC formation starts when bacteria attach onto the apical transitional epithelium of the  bladder via type 1 pili. Theses 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.

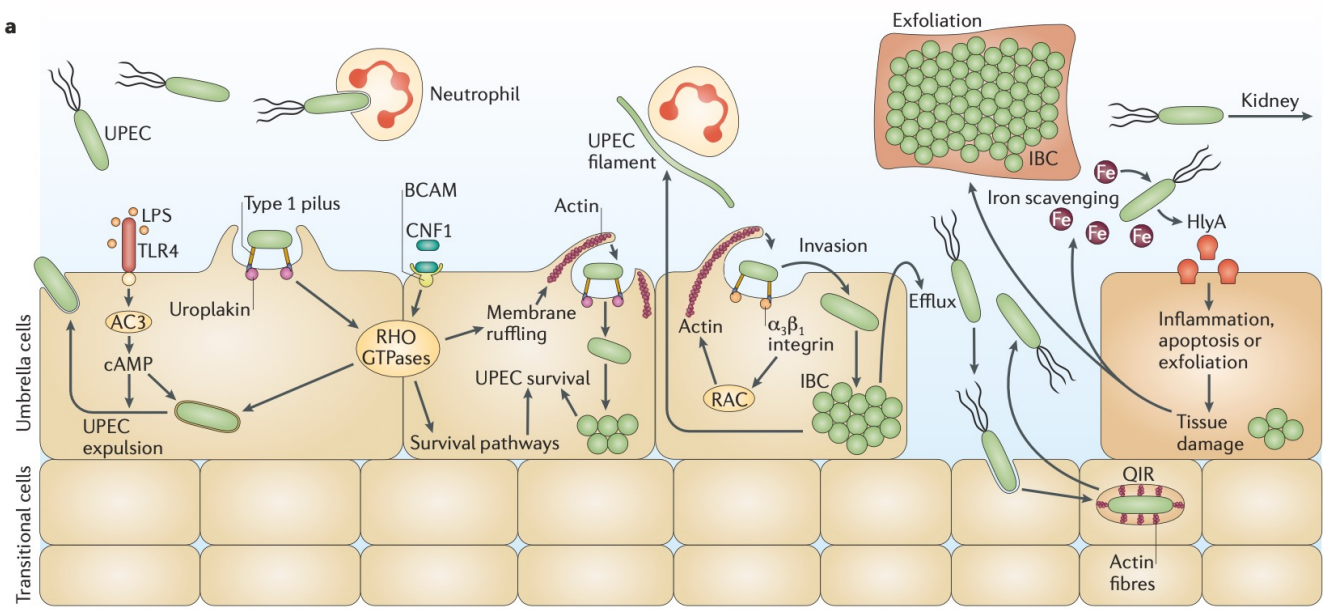
# Bacterial virulence factors

- Virulence characteristics play a role in determining both if an organism will invade the urinary tract and the subsequent level of infection within the urinary tract.
- The expression of virulence factors enable uropathogen to adhere to and colonize the perineum and urethra and migrate to the bladder where they establish an inflammatory response in the urothelium.
- UPEC expresses a number of **adhesins** that allow it to attach to urinary tract tissues. These adhesins are classified as either fimbrial or afimbrial, depending on whether the adhesin is displayed as part of a rigid fimbria or pilus. Pili are defined functionally by their ability to mediate hemagglutination of specific types of erythrocytes. The most well-described **pili** are **types 1, P, and S.**
- UPEC adherence to the urinary tract epithelium is primarily mediated by fimbriae assembled by the **chaperone-usher pathway**. **Type 1 fimbriae** bind to uroplakins via the tip-located **FimH adhesin**. Type 1 fimbriae enhance colonization and activation of host innate immune pathways, and promote biofilm formation and host cell invasion.
- To be able to grow in human urine, uropathogens utilize **siderophore systems** for **iron (Fe3+) scavenging**; these systems are composed of the siderophore assembly machinery, a siderophore responsible for binding iron and a membrane receptor that internalizes the iron bound to the siderophore.




Front microbiol 2017;8: Article 1566

# Virulence factors of UPEC that contribute to UTIs




Nat Rev Microbiol 2015;13:269

1. The type 1 pilus adhesin, FimH, binds mannosylated **uroplakins** and **integrins** that coat the surface of umbrella cells. Uroplakin binding by FimH induces actin rearrangement and bacterial internalization. **FimH–$\alpha_3\beta_1$ integrin interactions** induce actin rearrangement via activation of RHO-family GTPases, resulting in bacterial invasion. Inside the host cell, UPEC can subvert host defense and resist antibiotic treatment. However, **lipopolysaccharide (LPS)** released by UPEC is sensed by **Toll-like receptor 4** (TLR4), which induces cAMP production, resulting in **exocytosis** of vesicular UPEC across the apical plasma membrane.

2. UPEC subverts this innate defense mechanism by escaping into the cytoplasm, where it then multiplies to form intracellular bacterial communities **(IBCs)**. Maturation of IBCs causes bacterial dispersal and allows the invasion of other host cells, which enables UPEC to re-enter the IBC cycle. UPEC can also establish quiescent intracellular reservoirs (**QIRs**) in the underlying transitional cells.

3. UPEC survives within the harsh bladder environment by secreting several factors that are important for nutrient acquisition. The **toxin α-haemolysin (HlyA)** promotes host cell lysis through pore formation, facilitating iron release and nutrient acquisition. The **siderophores** expressed by UPEC allow the bacterium to scavenge iron and thus promote survival during a UTI. HlyA also triggers **epithelial exfoliation** to promote the spread of UPEC to other hosts following urine expulsion or to expose deeper layers of the uroepithelium for QIRs. **Cytotoxic necrotizing factor 1 (CNF1)** is also important for host cell remodeling and functions by binding to the receptor basal cell adhesion molecule (BCAM) on host cells resulting in actin cytoskeletal rearrangements and membrane ruffling.

# Virulence factors used by the main uropathogens

| Uropathogen | Virulence factors | | | | |
|---|---|---|---|---|---|
| | Adherence | Toxin | Immune evasion | Iron acquisition | Other |
| UPEC | • F1C pili<br>• P pili<br>• S pili<br>• Type 1 pili<br>• Dr adhesins | • HlyA<br>• CNF1 | • HlyA<br>• Capsular antigens<br>• CNF1<br>• Yersiniabactin | • Aerobactin<br>• Enterobactin<br>• Salmochelin<br>• Yersiniabactin | • Antigen43<br>• Flagella |
| *Klebsiella pneumoniae* | • Type 1 pili<br>• Type 3 pili | ND | Capsule | • Aerobactin<br>• Enterobactin | ND |
| *Proteus mirabilis* | • MR/P pili<br>• NAFs<br>• PMFs<br>• AipA adhesin<br>• TaaP adhesin | • Haemolysins (HpmA and HlyA)<br>• Pta | • Capsule<br>• ZapA | • Proteobactin<br>• Yersiniabactin-related | • Flagella<br>• Urease |
| *Pseudomonas aeruginosa* | • Extracellular DNA<br>• Exopolysaccharides (alginate, PEL and PSL) | ND | • Capsule<br>• Elastase<br>• ExoS<br>• Phospholipase<br>• Rhamnolipids | • Pyochelin<br>• Pyoverdin | Quorum sensing |
| *Staphylococcus saprophyticus* | • Aas adhesin<br>• SdrI adhesin<br>• Uaf adhesin | Aas | ND | ND | Urease |
| *Enterococcus faecalis* | • Ebp pili<br>• Ace adhesin<br>• Esp adhesin | ND | Epa | ND | • Sortase A<br>• SigV<br>• MsrA and MsrB |
| *Enterococcus faecium* | • Ebp pili<br>• Esp adhesin | ND | ND | ND | ND |

AipA, adhesion and invasion mediated by the *Proteus* autotransporter; CNF1, cytotoxic necrotizing factor 1; Ebp, endocarditis- and biofilm-associated; Epa, enterococcal polysaccharide antigen; Esp, enterococcal surface protein; ExoS, exoenzyme S; F1C pili, type 1-like immunological group C pili; HlyA, α-haemolysin; HpmA, haemolysin; MR/P, mannose-resistant *Proteus*-like; Msr, methionine sulfoxide reductase; NAF, non-agglutinating fimbria; ND, not determined; PMF, *P. mirabilis*-like fimbria; P pili, pyelonephritis-associated pili; Pta, *Proteus* toxic agglutinin; TaaP, trimeric autoagglutinin autotransporter of *Proteus*; UPEC, uropathogenic *Escherichia coli*.

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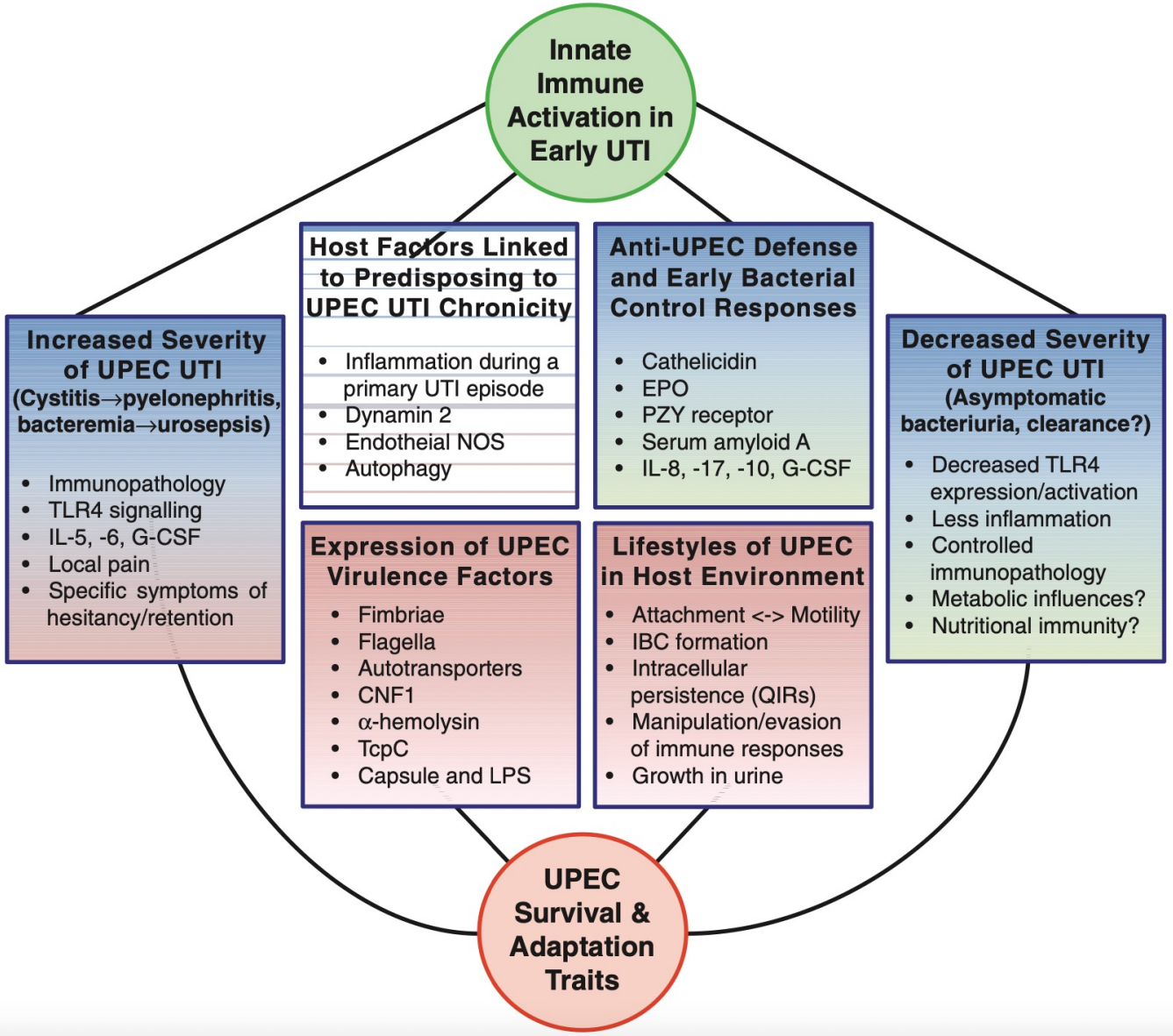
# Innate immune mechanisms

- The host recognition of the pathogen is mediated by a series of pathogen-associated molecular pattern receptors (**PAMPs**), such as **Toll-like receptors (TLRs)**, which provide the link between recognition of invading organisms and development of the innate immune response.
- TLRs recognize molecular patterns that are conserved among many species of pathogens, such as **lipopolysaccharide (LPS)** and **peptidoglycan (PG)**, and activate signaling pathways that initiate immune and inflammatory responses to kill pathogens.
- The innate immune response involves a variety of cell types, including **polymorphonuclear leukocytes, neutrophils, macrophages, eosinophils, natural killer cells, mast cells**, and **dendritic cells**.
- In addition, increased transcription of inducible nitric oxide synthase by polymorphonuclear leukocytes results in high levels of **nitric oxide** and related breakdown products that also have toxic effects on the bacteria.
- Adaptive immunity involves the specific recognition of pathogens by **T and B lymphocytes** and production of **high-affinity antibodies**, a process that occurs 7 to 10 days after infection.

# UPEC virulence factors and innate immune responses shape the pathogenesis and severity of UTI




- UPEC virulence factors directly influence the extent of innate immune responses and determine potential **lifestyles of the pathogen** within the host environment.
- UPEC enhances virulence by modulating inflammatory responses at the level of **TLR recognition**, thereby extending a “window of opportunity” to establish infection by evading innate surveillance mechanisms.

Curr Opin Microbiol 2013,16:100

# 4. Clinical Manifestations and Diagnosis

# Clinical manifestations

- Cystitis: **dysuria**, **frequency**, and/or **urgency**; suprapubic pain and hematuria are less common.
- Lower tract symptoms are usually predate the appearance of upper tract symptoms by several days.
- Pyelonephritis: classically associated with **fever**, **chills**, and **flank pain**; nausea and vomiting may be present.
- Renal or perirenal abscess: indolent fever and flank mass and tenderness.
- In the elderly, the symptoms may be much more subtle or asymptomatic.
- Patients with indwelling catheters often have asymptomatic bacteriuria, but fever associated with bacteremia may occur rapidly and become life threatening.

# Urine collection

- Presumptive diagnosis of UTI is made by direct or indirect **urinalysis** and is confirmed by **urine culture**. Occasionally, localization studies may be required to identify the source of the infection.
- The urine and the urinary tract are normally free of bacteria and inflammation.
- **False-negative** urinalysis and culture can occur in the presence of UTI, particularly early in an infection when the numbers of bacteria and WBCs are low or diluted by increased fluid intake and subsequent diuresis.
- **False-positive** urinalysis and culture are caused by contamination of the urine specimen with bacteria and WBCs during collection.
- Diagnostic accuracy can be improved by reducing bacterial contamination when the urine is collected.
- The first 10 mL of urine (representative of the urethra) and a midstream specimen (representative of the bladder) should be obtained.
- In women, the voided specimen is contaminated if it shows evidence of **vaginal epithelial cells** and **lactobacilli** on urinalysis, and a mid-catheterized specimen should be collected.
- **Suprapubic aspiration** is highly accurate, but because it carries some morbidity there is limited clinical usefulness except for a patient who cannot urinate on command, such as patients with spinal cord injuries and newborns.

# Urinalysis

- Urinalysis provides rapid identification of bacteria and WBCs and presumptive diagnosis of UTI.
- Microscopic examination of the urine for WBCs and bacteria is performed after centrifugation.
- **Microscopic bacteriuria** is found in more than 90% of infections with counts of **$10^5$** colony-forming units (CFU) per milliliter of urine or greater and is a highly specific finding.
- The validation of the midstream urine specimen can be questioned if numerous **squamous epithelial cells** (indicative of preputial, vaginal, or urethral contaminants) are present.
- **Pyuria** and **hematuria** are good indicators of an inflammatory response.
- The urine can be immediately evaluated for **leukocyte esterase**, a compound produced by the breakdown of white blood cells (WBCs) in the urine. Positive leukocyte esterase indicates the presence of 5–15 WBC/HPF.
- **Urinary nitrite** is produced by reduction of dietary nitrates by many Gram-negative bacteria.
- Combined positive nitrite and leukocyte esterase on urine dipstick analysis is **80–90% sensitive** and **60–98% specific** for UTI. Their main role is in **screening** asymptomatic patients.

# Urine culture

- Standard urine culture is the **gold standard** for identification the presence of bacteriuria, which supports  a diagnosis of UTI in the symptomatic patient.
- The urine should be collected in a sterile container and cultured immediately after collection. When this is not possible, the urine can be stored in the refrigerator for up to 24 hours.
- Historically, a colony count of at least $10^5$ CFU/ml of urine was used to diagnose a UTUI. However, many studies have demostrated that women with dysuria may have lower bacterial colony counts. Thus, in dysuric patients, an appropriate threshold value for defining significant bacteriuria is **$10^2$ CFU/mL** of a known pathogen.
- Modifying standard culture techniques would enable detection of bacteria that previously would have been missed, such as **expanded quantitative urine culture (EQUC)**.
- The EQUC specifically analyzed a larger volume of urine, which was subject to different atmospheric conditions and longer incubation times.
- With more sophisticated techniques available to detect microbes, clinical judgement is paramount to prevent overtreatment fb bacteriuria.

## Sensitivity and specificity of urinalysis

| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Esterase | 79 (73–84) | 87 (80–92) |
| Nitrite | 49 (41–57) | 98 (96–99) |
| Esterase+Nitrite | 45 (30–61) | 98 (96–99) |
| WBC | 74 (67–80) | 86 (82–90) |
| Bacteria | 88 (75–94) | 92 (83–96) |

## Probability of UTIs based on urine culture

| **Collection** | **CFU** | **Probability of infection (%)** |
|---|---|---|
| Suprapubic | Gram-negative any<br>Gram positive >1000 | >99 |
| Catheterization | $>10^5$<br>$10^{4–5}$<br>$10^{3–4}$<br>$<10^3$ | 95<br>Likely<br>Repeat<br>Unlikely |
| Clean catch | | |
| Male | $>10^4$ | Likely |
| Female | 3 specimens: $>10^5$<br>2 specimens: $>10^5$<br>1 specimen: $>10^5$<br>$5 \times 10^4–10^5$<br>$1–5 \times 10^4$ symptomatic<br>$1–5 \times 10^4$ nonsymptomatic<br>$<10^4$ | 95<br>90<br>80<br>Repeat<br>Repeat<br>Unlikely<br>Unlikely |

Smith & Tanagho's general urology, 2020, 19th Ed, Ch 14

# Imaging techniques

- Imaging studies are not required in most cases of UTI because clinical and laboratory findings alone are sufficient for correct diagnosis and adequate management of most patients.
- Infection in most men or a compromised host, febrile infections, signs or symptoms of urinary tract obstruction, failure to respond to appropriate therapy, and a pattern of recurrent infections suggesting **bacterial persistence** within the urinary tract warrant imaging for identification of **underlying abnormalities**.
- Indications for radiologic investigation in acute clinical pyelonephritis:

| | |
|---|---|
| **Potential ureteral obstruction** | stone, ureteral stricture, tumor |
| **History of calculi** | especially infection (struvite) stones |
| **Potential papillary necrosis** | sickle cell anemia, DM, analgesic abuse |
| **Genitourinary surgery that predisposes to obstruction** | ureteral reimplantation or ureteral diversion |
| **Poor response to appropriate antimicrobial agents** | |
| **Diabetes mellitus** | |
| **Polycystic kidneys with dialysis/severe renal insufficiency** | |
| **Neuropathic bladder** | |
| **Unusual infecting organisms** | tuberculosis, fungus, urea-splitting organisms |

# Asymptomatic bacteriuria

- The term asymptomatic bacteriuria is appropriately used when a person has no signs or symptoms of UTIs, yet bacteria are identified in a noncontaminated urine sample.
- In women, the term is used when the same bacteria is identified in quantitative counts ≥ $10^5$ CFUs in **two consecutive** voided sample. But in men, only **one clean-catch** voided sample that identified one bacterial species in quantitative counts ≥ $10^5$ CFUs is necessary.
- The prevalence of asymptomatic bacteriuria varies based on age, sex, and comorbid conditions. The prevalence increased with age. It also correlates with sexual activity and menopause.
- More recent work establishes that treating asymptomatic bacteriuria is potentially deleterious.
- Treatment of asymptomatic bacteriuria contributes to development of multidrug-resistant symptomatic UTIs.
- IDSA (Infectious Disease Society of America) guidelines in 2005: In the majority of patients, asymptomatic bacteriuria **should not be treated**.

| | |
|---|---|
| **Do not treat** | premenopausal, non-pregnant women, women with diabetes, older community dwellers, elderly institutionalized patients, patients with SCI, and patients with indwelling catheters, pyuria with asymptomatic bacteriuria |
| **Treat** | pregnant women, patients undergoing procedures in which transmucosal bleeding is anticipated |

# 5. Treatment

- The goal in treatment is to eradicate the infection by selecting the **appropriate antibiotics** that would target specific bacterial susceptibility.
- The general principles for selecting the appropriate antibiotics include consideration of the infecting pathogen, the patient, and the site of infection.
- Antimicrobial selection should be influenced by efficacy, safety, cost, and compliance.
- By utilizing the antibiogram available through >95% of hospitals and communities, **susceptibility patterns** can help guide empiric treatment.
- Resolution of infection is closely associated with the susceptibility of the bacteria to the **concentration** of the antimicrobial agent **achieved in the urine**.
- The concentration of the antimicrobial agent achieved in blood is not important in treatment of uncomplicated UTIs. However, blood levels are critical in patients with bacteremia and febrile urinary infections consistent with parenchymal involvement of the kidney and prostate.
- Because most antibiotics are cleared from the body by the liver or the kidney, certain antimicrobial agents need to be adjusted in the presence of liver or renal disease.
- Minimum inhibitory concentration (MIC) demonstrates the lowest amount of antibiotic necessary to exhibit antimicrobial activity against a certain pathogen. While it would seem straightforward to pick the antibiotic with the **lowest MIC** reported for antibiotic sensitivities, the pharmacokinetics of the drug must be considered.
- In the past several years, the frequency and spectrum of **antimicrobial-resistant UTIs** have increased in both the hospital and community.

# Mechanism of action of common antimicrobials used in the treatment of UTIs

| Drug or drug class | Mechanism of action | Mechanisms of drug resistance |
|---|---|---|
| β-Lactams (penicillins, cephalosporins, aztreonam) | Inhibition of bacterial cell wall synthesis | Production of β-lactamase<br>Alteration in binding site of penicillin-binding protein<br>Changes in cell wall porin size (decreased penetration) |
| Aminoglycosides | Inhibition of ribosomal protein synthesis | Downregulation of drug uptake into bacteria<br>Bacterial production of aminoglycoside-modifying enzymes |
| Quinolones | Inhibition of bacterial DNA gyrase | Mutation in DNA gyrase-binding site<br>Changes in cell wall porin size (decreased penetration)<br>Active efflux |
| Fosfomycin | Inhibition of bacterial cell wall synthesis | Novel amino acid substitutions or the loss of function of transporters |
| Nitrofurantoin | Inhibition of several bacterial enzyme systems | Not fully elucidated—develops slowly<br>With prolonged exposure |
| Trimethoprim-sulfamethoxazole | Antagonism of bacterial folate metabolism | Draws folate from environment (enterococci) |
| Vancomycin | Inhibition of bacterial cell wall synthesis (at β-lactams) | Enzymatic alteration of peptidoglycan at different point than target |

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

# Antibiotics that require dosage adjustments for liver and renal diseases

| | |
|---|---|
| **Renal disease** (CCr < 30ml/min) | Aminoglycosides<br>β-Lactams (Cefoxitin, ceftizoxime Cefonicid, ceftazidime Cefuroxime, cefepime Cefpirome, moxalactam)<br>Carbenicillin, ticarcillin, ticarcillin–clavulanate<br>Vancomycin<br>Tetracyclines (except doxycycline)<br>Sulfonamides |
| **Hepatic diseases** (with elevated bilirubin) | Chloramphenicol<br>Tetracyclines<br>Clindamycin<br>Rifampin<br>pefloxacin |
| **Renal–hepatic diseases** | Ceftriaxone<br>Cefoperazone<br>Carbenicillin<br>Ticarcillin<br>Azlocillin<br>Mezlocillin<br>Piperacillin |

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# Recommended antimicrobial agents for common genitourinary pathogens

| Bacteria | | Oral therapy | Parenteral therapy |
|---|---|---|---|
| **Gram(+) cocci** | Staphylococcus aureus | Nafcillin, nitrofurantoin, ciprofloxacin | Nafcillin, vancomycin |
| | Staphylococcus epidermidis | Ampicillin, nitrofurantoin, ciprofloxacin | Ampicillin, penicillin G |
| | Staphylococcus saprophyticus | Ampicillin, nitrofurantoin, ciprofloxacin | Ampicillin, penicillin G |
| | Streptococcus, group D<br>S. faecalis (enterococci)<br>S. bovis | <br>Ampicillin, nitrofurantoin<br>Penicillin G, ampicillin | <br>Ampicillin plus gentamicin<br>Ampicillin, vancomycin |
| | Streptococcus, group B | Ampicillin, cephalosporin | Ampicillin, cephalosporin |
| **Gram(-) cocci** | Neisseria gonorrhoeae | Ciprofloxacin plus doxycycline | Ceftriaxone |
| **Gram(-) rods** | Escherichia coli | TMP-SMX, ciprofloxacin, nitrofurantoin | Gentamicin |
| | Enterobacter spp. | TMP-SMX, ciprofloxacin, nitrofurantoin | Gentamicin plus piperacillin |
| | Gardnerella vaginalis | Metronidazole, ampicillin | Metronidazole |
| | Klebsiella spp. | TMP-SMX, ciprofloxacin | Gentamicin plus cephalosporin |
| | Proteus spp. | Ampicillin, TMP-SMX, ciprofloxacin | Ampicillin, gentamicin |
| | Pseudomonas aeruginosa | Carbenicillin, tetracycline, ciprofloxacin | Gentamicin plus piperacillin |
| | Serratia spp. | TMP-SMX, carbenicillin | TMP-SMX, amikacin |
| **Other pathogens** | Chlamydiae | Tetracycline, erythromycin | Tetracycline, erythromycin |
| | Mycoplasmas, ureaplasmas | Tetracycline, erythromycin | Tetracycline, erythromycin |
| | Obligate anaerobes | Metronidazole, clindamycin | Metronidazole, clindamycin |

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# Recommended antimicrobial agents and duration of therapy based upon the type of UTI for adults

| Diagnosis | Choice of antibiotics | Duration of therapy |
|---|---|---|
| **cystitis** | 1st: TMP-SMX<br>2nd: Fluoroquinolone | 1–3 days |
| **Pyelonephritis** | 1st: Fluoroquinolone<br>2nd: 2nd-generation cephalosporin<br>3rd: Aminopenicillin/BLI | 7–10 days |
| **Complicated UTI** | 1st: Fluoroquinolone<br>2nd: Aminopenicillin/BLI<br>3rd: 3rd-generation cephalosporin<br>Aminoglycosides | Afebrile: 2 weeks<br>Febrile: continue for additional 3–5 days after last fever (minimum 2 weeks) |
| **Prostatitis** | 1st: Fluoroquinolone<br>2nd: 2nd-generation cephalosporin<br>3rd: 3rd-generation cephalosporin | Acute: 2 weeks<br>Chronic: 4–6 weeks |
| **Epididymitis** | 1st: Fluoroquinolone<br>2nd: 2nd-generation cephalosporin<br>or<br>1st: Doxycycline<br>2nd: Macrolide | 14 days |
| **Urethritis** | 1st: IM ceftriaxone + azithromycin<br>2nd: Doxycycline | Single dose<br>7 days |

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# Recommended antimicrobial agents and duration of therapy based upon the type of UTI for children

| Diagnosis | Choice of antibiotics | Dose | Duration of therapy |
|---|---|---|---|
| **cystitis** | 1st: Cephalexin<br>2nd: Nitrofurantoin<br>3rd: TMP-SMX | 50–100 mg/kg in 4 doses<br>5 mg/kg in 2 doses<br>8–10 mg/kg of TMP in 2 doses | 7 days |
| **pyelonephritis** | 1st: Amoxicillin–clavulanic acid,<br>1st-line cephalosporin<br>2nd: 3rd- or 4th-generation cephalosporin<br>(Ceftriaxone) | 20–40 mg/kg in 3 doses<br><br>75 mg/kg in 1 dose | 7-14 days |

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1. Bacteriuria and WBCs provide a presumptive diagnosis of UTI. But bacteriuria and pyuria are not synonymous with a UTI. UTIs are classified based on their presumed site of origin. UTIs can be uncomplicated or complicated.
2. Most UTIs are caused by bacteria, usually originating from the bowel and skin flora.
3. UTI occurs when bacterial virulence increases and/or host defense mechanisms decrease. Bacterial virulence factors, including adhesin, play a role in determining which bacteria invade and the extent of infection.
4. Obstruction to urine flow is a key factor in increasing host susceptibility to UTIs.
5. Clinical presentation is critical in considering diagnosis; results of urine testing cannot be analyzed without knowledge of signs and symptoms.
6. Urine must be collected in a manner that minimizes contamination. Formal urinalysis is preferred over dipstick testing. Urine culture results provide information regarding bacterial sensitivities.
7. Imaging studies are not required in most women with UTIs. Men and compromised patients or those who do not respond to therapy require imaging to identify abnormalities.

# Take home message

8. Several guidelines recommend not screening for or treating asymptomatic bacteriuria except in specific patient populations. Treatment of asymptomatic bacteriuria contributes to development of multidrug-resistant symptomatic UTIs. Untreated asymptomatic bacteriuria is not associated with hypertension or renal insufficiency.
9. Asymptomatic bacteriuria should be screened for and treated in pregnant women and in patients who are undergoing urologic procedures.
10. Prophylactic antimicrobial therapy reduces morbidity and the time to recurrent bacteriuria, but the risk of recurrence remains the same.
11. Effective antimicrobial therapy must eliminate bacterial growth in the urinary tract. The majority of patients respond promptly to short courses of antimicrobial therapy. Antimicrobial resistance is increasing because of excessive use.
12. Antimicrobial selection should be influenced by efficacy, safety, cost and compliance. The choice of the agent as well as the duration of therapy are critical in preventing the perpetuation of antimicrobial resistance as well as adverse events related to treatment.

# Take home message

# Reference


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