Urogenital System

Dr Noluthando Nematswerani
Department of Pharmacology

Urogenital Disorders

- Urinary tract infections
- Urinary frequency, urgency and incontinence
- Erectile dysfunction
- Benign prostatic hypertrophy
- Drugs that alter PH of urine
- Oxytocic therapy
- Tocolytics
- Sexually Transmitted Infections

Urinary Tract Infections (UTI)

- Cystitis
- Pyelonephritis
- Urethritis
- Prostatitis

Acute cystitis

- Urinary tract infections are the most common bacterial infections in women, with 50% of all women experiencing at least one UTI in their lifetime.
- Most UTIs in women are acute uncomplicated cystitis caused by *Escherichia coli* (86%), *Klebsiella* (3%), *Proteus* (3%), *Enterobacter* (1.4%), *Staphylococcus sacrophyticus* (4%), *Pseudomonas*

Presentation & Diagnosis

- Lower urinary tract symptoms:
  - Dysuria
  - Frequency of micturition
  - Urinary urgency
  - Haematuria (sometimes)
  - Suprapubic dyscomfort (less common)
- Urine dipstix for diagnosis (convenient and cost-effective), appropriate alternative to urinalysis and urine microscopy
  - Midstream , clean-catch urine specimen

Treatment

- First-line
  - Nitrofurantoin 100mg BD x 5 days
  - Trimethoprim / sulfamethoxazole 960mg (DS) BD
- Second line
  - Fluoroquinolones (Ofloxacin, ciprofloxacin,levofloxacin)
  - Beta-lactam antibiotics (amoxy/clav, cefaclor, cefpodoxime)

Choice of antibiotic

- Beta-lactam not recommended as first line because of widespread *E.coli* resistance rates >20%.
- Fluoroquinolones are also not recommended as 1st line to preserve their effectiveness.
- Cystitis in pregnancy
  - Penicillins, cephalosporins

Table 1. Characteristics of Patients with Uncomplicated and Complicated Urinary Tract Infections

Uncomplicated
Immunocompetent
No comorbidities
No known urologic abnormalities
Nonpregnant
Premenopausal
Complicated*
History of childhood urinary tract infections
Immunocompromised
Preadolescent or postmenopausal
Pregnant
Underlying metabolic disorder (e.g., diabetes mellitus)
Urologic abnormalities (e.g., stones, stents, indwelling catheters, neurogenic bladder, polycystic kidney disease)

**—Urinary tract infections in men are usually complicated.*

Information from reference 5.

Pyelonephritis

- Common bacterial infection of the renal pelvis and kidney most often seen in young adult women

Presentation

- Fever
- Flank Pain

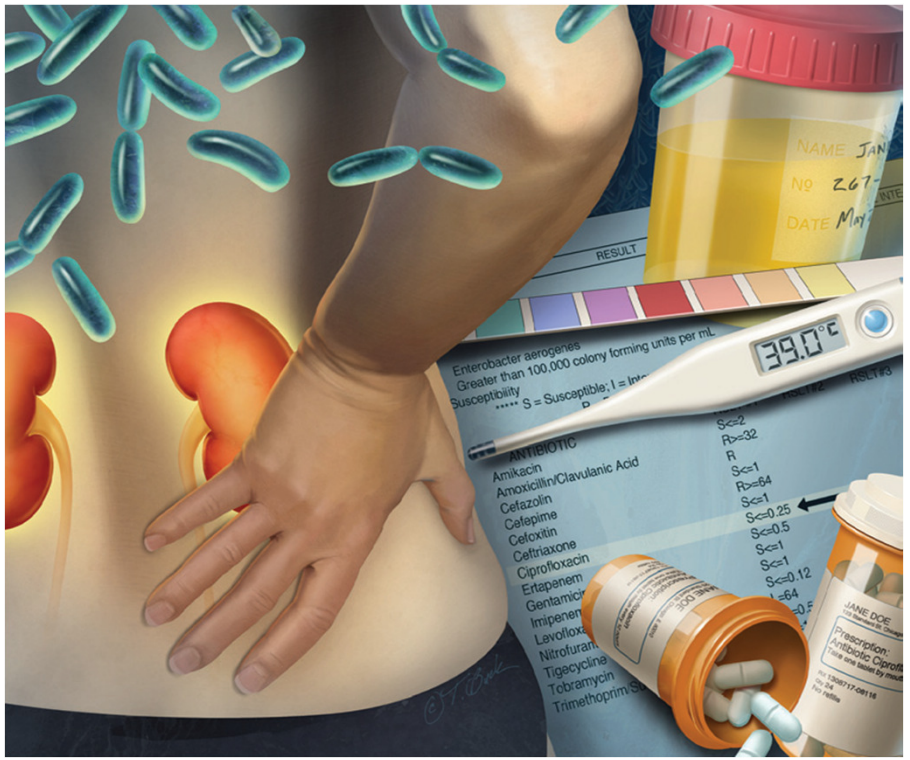

Table 1. Causative Organisms in Acute Pyelonephritis

Organism	*Prevalence (%)*
Escherichia coli	82 (women) 73 (men)
Klebsiella pneumoniae	2.7 (women) 6.2 (men)
Staphylococcus saprophyticus	< 3 (women)
Candida species	Rare
Enterococcus species	Rare
Other Enterobacteriaceae (e.g., *Proteus* species, *Enterobacter* species)	Rare
Pseudomonas aeruginosa	Rare
Ureaplasma species	Rare

Information from reference 4.

Risk factors for Acute Pyelonephritis

- In non-pregnant women
  - sexual intercourse three or more times per week during the previous 30 days,
  - UTIs in the previous 12 months,
  - diabetes,
  - stress incontinence in the previous 30 days,
  - a new sex partner in the previous year,
  - recent spermicide use,
  - and a history of UTIs in the patient's mother

Table 2. Clinical and Laboratory Findings in Patients with Acute Pyelonephritis

Category	*Findings*
History	Lower urinary tract symptoms (e.g., frequency, urgency, dysuria)
	Upper urinary tract symptoms (e.g., flank pain)
	Constitutional symptoms (e.g., fever, chills, malaise)
	Gastrointestinal symptoms (e.g., nausea, vomiting, anorexia, abdominal pain)
Physical examination	Fever (temperature > 100.4°F [38.0°C]), tachycardia, hypotension
	Costovertebral angle tenderness
	Possible abdominal or suprapubic tenderness
Laboratory tests	Urinalysis showing positive leukocyte esterase test, microscopic pyuria or hematuria, or white blood cell casts
	Peripheral blood smear showing leukocytosis, with or without left shift
	Positive blood culture in 15 to 30 percent of cases
	Urine culture growing ≥ 10^5 colony-forming units per mL of urine

Information from reference 12.

Table 5. Considerations for Hospitalization in Patients with Acute Pyelonephritis

Comorbid conditions (e.g., renal dysfunction, urologic disorders, diabetes mellitus, advanced liver or cardiac disease)
Hemodynamic instability*
Male sex
Metabolic derangement (e.g., renal dysfunction, acidosis)
Pregnancy
Severe flank or abdominal pain
Toxic appearance
Unable to take liquids by mouth
Very high fever (> 103°F [39.4°C])

*—*Physicians must be alert for the presence of severe sepsis and septic shock, which require urgent specialized management that is beyond the scope of this review.*

Information from reference 14.

Table 6. Outpatient Treatment Options for Nonpregnant Women with Acute Pyelonephritis

Drug class	*Antibiotic*	*Dosage*
Fluoroquinolones*	Ciprofloxacin† (Cipro)	500 mg orally, twice per day for seven days
	Ciprofloxacin, extended-release‡	1,000 mg orally, once per day for seven days
	Levofloxacin‡ (Levaquin)	750 mg orally, once per day for five days
Folate inhibitors§	Trimethoprim/sulfamethoxazole† (Bactrim, Septra)	160 mg/800 mg orally, twice per day for 14 days

Table 7. Initial and Step-Down Inpatient Treatment Options for Nonpregnant Women with Acute Pyelonephritis

Phase of therapy	*Antibiotic**	*Dosage*
Initial	Ciprofloxacin (Cipro)	400 mg IV, twice per day†
	Levofloxacin (Levaquin)	250 to 500 mg IV, once per day†
	Ceftriaxone (Rocephin)	1,000 mg IV, once per day†
	Aminoglycoside‡	5 mg per kg§ IV, once per day†
	Imipenem/cilastatin (Primaxin)	500 mg IV every six hours†‖
Step-down	Ciprofloxacin¶	500 mg orally, twice per day for seven days
	Ciprofloxacin, extended-release¶	1,000 mg orally, once per day for seven days
	Levofloxacin¶	750 mg orally, once per day for five days
	Trimethoprim/sulfamethoxazole** (Bactrim, Septra)	160 mg/800 mg orally, twice per day for 14 days

Nitrofurantoin

- It inactivates or alters bacterial ribosomal proteins and other macromolecules that may interfere with metabolism and cell wall synthesis.
- Bioavalability increased with food
- Susceptible strains *E.coli , Klebsiella, Enterobacter , Staphylococcus sacrophyticus and aureus*

Quinolones -mechanism of action

- Inhibits bacterial DNA gyrase
- Responsible for cutting and supercoiling DNA
- Post AB effect against gram negative and positive organisms

Quinolones -Pharmacokinetics

- 80% systemic available after oral dose
- Bioavailability decreased by antacids
- Large volume of distribution: including eye, lungs, prostatic fluid, CSF, bone and cartilage
- Entero-hepatic cycle: AB in urine 5 days after stopping Rx
- t½=4 hours. Rx less often than t½ (post AB effect)
- Removed by glomerular filtration and tubular secretion
- Less active in acidic urine

Quinolones –side effects

- GIT
- CNS
- Hypersensitivity
- QT prolongation/ torsades de pointes
- Liver and renal damage
- Reversible arthralgia
- Tendonitis/ tendon rupture
- Drug interactions

Quinolones -dosages

- **Ciprofloxacin:** 250-500 mg bd p.o
  200-400mg IVI 8-12 hourly

- **Norfloxacin:** 400 mg bd for 7-10 days
  (3 days Rx if uncomplicated)

- **Ofloxacin**: 100 mg bd 3-7 days
  Pyelonephritis : 200 mg bd

Co-trimoxazole

Sulfamethoxazole + Trimethoprim

- Inhibits production of folic acid
- Hypersensitivity reaction
- Steven Johnson’s
- Aplastic/ hemolytic anaemia
- CI: newborn, porphyria, G6PD deficiency

Urinary frequency, urgency and incontinence

- History
- Examination
- **Exclude:** infection, drugs, organic bladder pathology and diabetes
- **Urge incontinence**: infection or detrusor overactivity
- **Stress incontinence:** anatomical abnormality
- Refer for further investigation

Management

- Non-pharmacological: physiotherapy, behaviour therapy
- Pharmacologic:
  - Oestrogen creams/ HRT
  - Anticholinergics
  - Antidepressants
  - Desmopressin

Oestrogen creams/HRT

- Limited use
- Use in post menopausal women
- Irritative bladder symptoms

Anticholinergics

- Non specific muscarinic receptor antagonists
- Compete with Ach by binding to muscarinic receptors
- Reduce frequency and intensity of involuntary detrusor contractions
- Increase functional bladder capacity

Anticholinergics

Examples

- Oxybutynin
- Tolterodine
- Flavoxate
- Propiverine
- Darifenacin

Anticholinergic side effects

- Dry mouth
- Constipation
- Palpitations
- Blurry vision
- Confusion
- Arrhythmias
- Dry flushed skin

Contra-indications

- Closed angle glaucoma
- Myasthenia Gravis
- Paralytic ileus
- BPH
- Pyloric stenosis

Antidepressants

- Imipramine
- Amitriptyline

Mechanism of action

- Tricyclic antidepressants
- Closely related in structure to phenothiazines
- Block uptake of NA and 5HT from central adrenergic synapse
- Multipotent blocker

Pharmacokinetics

- Rapidly absorbed
- Highly plasma protein bound
- Large volume of distribution
- Narrow therapeutic index
- Converted to active metabolites
- Long t½
- Metabolized in liver
- Low rate of elimination

Side effects

- Atropine like SE
- Sedation, confusion, motor incoordination
- Postural hypotension
- Ventricular dysrrhythmias
- Allergic reaction
- Bone marrow suppression
- Drug interactions

Contra-indications

- Epilepsy
- MI
- Heart block
- Porphyria
- Glaucoma
- BPH

Desmopressin

- Synthetic analogue of Vasopressin
- Antidiuretic hormone
- Longer acting
- Minimal vasoconstrictor effects
- Diagnosis and treatment of Diabetes Insipidus
- Rx of primary nocturnal enuresis in a patient with normal ability to concentrate urine

Erectile dysfunction

- **Erection:** Vasorelaxation in arteries/arterioles supplying erectile tissue
- Penile blood flow leads to sinusoidal filling, which compresses venules, reducing venous outflow
- Autonomic and somatic innervation
- Nitric oxide is main mediator of erection. Released from nitrergic nerves and endothelium

Causes

- Drugs
- Psychiatric disorders
- Vascular disease
- Hypogonadism
- Hyperprolactinaemia
- Arterial disease
- Neuropathy

Treatment

- **AIM:** smooth muscle relaxation within corpora cavernosa
- Oral administration of vasoactive drugs
- Intracarvernosal injection

Oral drugs

- Phosphodiesterase type 5 (PDE5) inhibitors
  - Sildenafil (Viagra®)
  - Tadalafil (Cialis®)
  - Vardenafil (Levitra®)
- Do not use these drugs together !!!

Mechanism of action

- NO activates guanylyl cyclase
- ↑ cGMP → vasodilatation
- PDE5 inactivates cGMP
- PDE5 inhibitors cGMP during erotic stimulation

Kinetics

- Peak concentration 30-120 minutes after oral intake
- 53% of men will have erection within 25 min
- Absorption delayed if taken with fatty meal
- Metabolized by CYP3A4
- Drug interactions
- Tadalafil: longer acting (up to 36 hours)
- Vardenafil: quickest acting, more selective for PDE5

Side effects

- Hypotension
- Flushing
- Headache
- Visual disturbances (Sildenafil – PDE VI in retina)
- Sudden hearing loss (Sildenafil)
- Corporeal fibrosis in case of prolonged erection

DO NOT USE IF PT IS TAKING NITRATES !!!!!!

Dosage

- Sildenafil: 50 mg before anticipated activity
- Tadalafil: 20 mg
- Vardenafil: 10 mg
- Be careful in pt with hepatic/renal impairment

Intracavernosal injections

- Papaverine
- Alprostadil

Prostatitis

- Acute bacterial
  - Broad spectrum penicillin
  - 3rd generation cephalosporins with or without aminoglycosides
  - Flouroquinolones
- Chronic bacterial
  - Fluoroquinolones (relief in 50% of patients)
  - Supportive measures: analgesiaa, alpha-blocking-agents

Benign prostate hypertrophy

- Stromal / glandular hyperplasia of prostate gland
- Rx:
  - α 1 Blockers
  - Testosterone 5α reductase inhibitors

Alpha 1 blockers

- Uroselective
  - Alfuzosin
  - Tamsulosin
- Doxazosin
- Terazosin

- All 4 agents have equal clinical effectiveness. The choice of agent should depend on the patient's comorbidities, side effect profiles and tolerance.

Mechanism of action

- α1 Stimulation →contraction of smooth muscle of prostrate / bladder neck
- 40 % of bladder outlet resistance
- α1 Blockers – block α1 receptors

Side effects

- Postural hypotension
- Dizziness
- Sedation

Dosage

- Titrate dose, start at night
- Once daily due to long half life
- Effects and side effects are dose related
- Monitor blood pressure
- Alfuzosin and Terazosin safe if used in combination with PDE5 inhibitors

Testosterone 5α reductase inhibitors

- Finasteride
- Dutasteride

Mechanism of action

- Testosterone converted to dihydrotestosterone by 5α reductase
- These drugs inhibit conversion to more active compound, dihydrotesterone in prostate gland
- Leads to prostate shrinkage
- Reduces symptoms
- Combination with blockers improves symptoms

Side effects

- Reduced libido
- Gynaecomastia
- Erectile dysfunction
- PSA levels are halved – careful with interpretation
- Shrinkage of prostate not permanent, regrowth occurs after drug is withdrawn
- Do not expose females to drug

Uterus

- Uterine muscle contracts rhythmically both in vitro/in vivo, originating in muscle itself
- Regulated by sex hormones
- Nerve supply – excitatory and inhibitory sympathetic components

Oxytocic therapy

- Induce or augment labour
- Induce abortion
- Control uterine bleeding

Examples

- Oxytocin
- Ergometrine
- Prostaglandins

Oxytocin

- Release stimulated by cervical dilatation and suckling
- Action limited to smooth muscle of uterus, especially end of pregnancy
- Oestrogen-mediated increase in oxytocin receptors
- Induction of labour
- Management of PPH
- Expression of milk
- Weak antidiuretic action
- Slight vasodilator action

Kinetics

- Hydrolysed quickly – give as infusion IVI
- t½ =2-10 minutes
- IMI
- Can be administered intranasally – promotes milk ejection
- Monitor mother and baby carefully

Side effects

- N+V
- Cardiac arrhythmias
- Hypotension
- Water retention and hyponatraemia
- Cerebral oedema and convulsions

high doses

- Uterine rupture
- Fetal distress

Ergometrine

- Ergot alkaloid
- Ergot- fungus growing on rye
- Stimulate smooth muscle
- Contracts uterus, does not relax completely
- Reduces blood loss from uterus after delivery
- Used for treatment of PPH
- Give only once baby is born!!! (Careful if undiagnosed twins)
- DO NOT use to induce labour !!!

Kinetics

- Oral
- IMI
- IVI – avoid due to risk of adverse effects
- Onset of action within 5-15 minutes
- Effect for 3 hours

Side effects

- Hypertension
- Angina
- N+V
- Headache
- Blurry vision
- Convulsions

Prostaglandins

- **Dinoprostone (PGE2) registered**
- **Dinoprost (PGF2a)**
- **Misoprostol (PGE 1 analogue)**
  - Contracts pregnant and non-pregnant uterus
  - Increases uterine tone
  - Ripens cervix
  - Induction of labour
  - Therapeutic abortions

Routes of administration

- Intravaginal as gel or tablet
- Intracervical
- Oral
- Rectal
- IVI not used due to SE
- SE: N+V, Diarrhea, cramps

Cautions

- Avoid if pt has acute infection of genital tract
- Careful if previous scar present
- Careful if used in combination with oxytocin
- Careful in asthmatics, COPD, hypertension, thyrotoxicosis, renal or hepatic disease

Tocolytics

- Inhibit premature labour
- Atosiban: oxytocin receptor antagonist
- Nifedipine: calcium channel blocker
- Salbutamol: β2 agonist
- NSAIDs: be careful

Prolactin inhibitors

- Bromocriptine: ergot alkaloid, dopamine agonist
- Cabergoline: ergoline derivative
- Quinagolide: non-ergot dopamine agonist

Vaginal discharges

- *Candida albicans*
- *Trichomonas vaginalis*
- *Gardnerella vaginalis*
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*

Vaginal candidiasis

- Nystatin
- Imidazole derivative – Miconazole, Clotrimazole
- Pessary or vaginal cream
- Oral
  - Fluconazole
  - Itraconazole
  - Ketoconazole

Mechanism of action of Azoles

- Inhibit fungal cytochrome p450 enzyme, 14-L-demethylase
- Enzyme in pathway that synthesizes ergosterol from squalene
- Disrupts cell membrane

Candidiasis

Exclude the following if recurrent infections:

- Diabetes
- Steroid use
- HIV
- Pregnancy
- AB use

Bacterial Vaginosis

- It is the most prevalent cause of vaginal discharge or malodor
- It is associated with:
  - having multiple male or female partners,
  - a new sex partner,
  - douching,
  - lack of condom use,
  - and lack of vaginal lactobacilli;
  - women who have never been sexually active can also be affected.

Bacterial vaginosis

- High concentrations of anaerobic bacteria (e.g., *Prevotella sp. and Mobiluncus sp.), G. vaginalis, Ureaplasma, Mycoplasma, and numerous fastidious or uncultivated anaerobes*

Recommended Regimens
Metronidazole 500 mg orally twice a day for 7 days*
OR
Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days
OR
Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days†

Pelvic Inflammatory Disease

- A spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.
- Pathogens
  - *N. gonorrhoeae and C. trachomatis,*
  - *G. vaginalis, Haemophilus influenzae, enteric Gram-negative rods, and Streptococcus agalactiae*

Oral Treatment

Recommended Regimen
Ceftriaxone 250 mg IM in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Cefoxitin 2 g IM in a single dose and **Probenecid**, 1 g orally administered concurrently in a single dose
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days
OR
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
PLUS
Doxycycline 100 mg orally twice a day for 14 days
WITH or WITHOUT
Metronidazole 500 mg orally twice a day for 14 days

Parenteral Treatment

Recommended Parenteral Regimen A

Cefotetan 2 g IV every 12 hours

OR

Cefoxitin 2 g IV every 6 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

Urethritis

- Urethral inflammation, can result from infectious and noninfectious conditions.
- Symptoms:
  - discharge of mucopurulent or purulent material, dysuria, or urethral pruritis.
  - Asymptomatic infections are common.
  - Common pathogens: *N. gonorrhoeae* and *C. trachomatis*
  - *Mycoplasma genitalium* has also been associated with urethritis

Non-gonococcal urethritis

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Levofloxacin 500 mg orally once daily for 7 days

OR

Ofloxacin 300 mg orally twice a day for 7 days

Recurrent & Persistent Urethritis

- Persistent urethritis after doxycycline treatment might be caused by doxycycline-resistant *U. urealyticum, M. genitalium or T. vaginalis*

Recommended Regimens
Metronidazole 2 g orally in a single dose
OR
Tinidazole 2 g orally in a single dose
PLUS
Azithromycin 1 g orally in a single dose (if not used for initial episode)

Genital Ulcer Disease

- Syphilis
- Chancroid
- Herpes Simplex
- Lymphogranuloma venereum

Syndromic Management

- Mixed infection
- Triple therapy
- Cefixime: 400mg p.o. single dose
- or Ceftriaxone: 250 mg IMI
- Metronidazole: 2g p.o. single dose
- Doxycycline: 100mg p.o. bd (Amoxicillin if pregnant) for 7 days