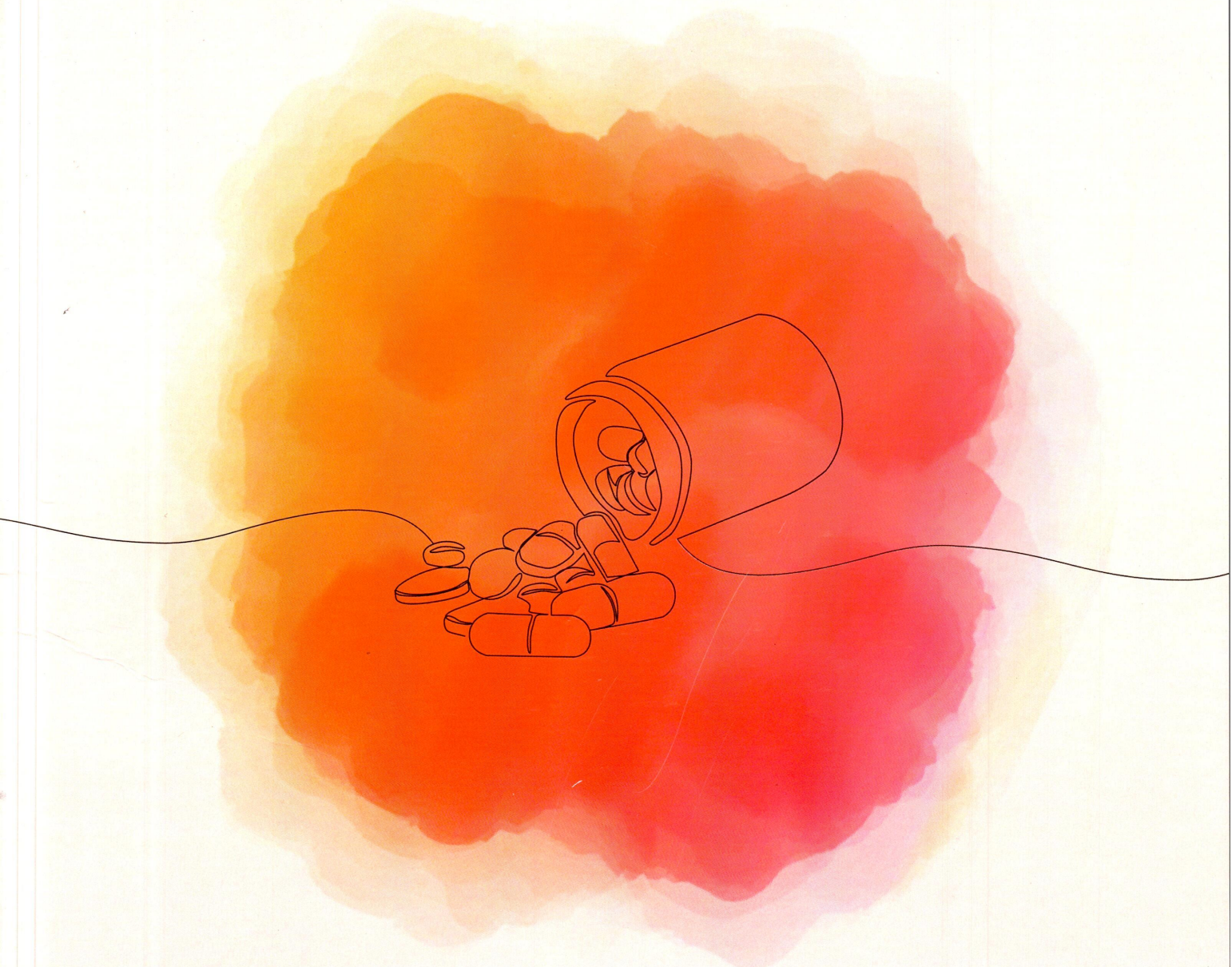
VOLUME-I

PrepLadder



MEDICINE

NEET SS VERSION 4.0

PREFACE

Dear Dreamer,

Pat your back and reward yourself, today you've taken an important step towards reaching your dream. Mark Twain said, "the secret of getting ahead is getting started". You have started in the right direction.

The next few months until your targeted exam or exams are crucial. Every moment counts and each step you take now, will help you reach your goal, your dream.

PrepLadder is your partner in this journey. We are in this together. So, don't worry, do not stress. Just focus on your preparation and stay positive. Set daily targets, achievable and realistic ones. If you pass the target, celebrate. However, if you miss a daily target, forgive yourself, move on and do better the next day.

Always remember that you are special and unique. Do not compare your preparation, your speed, your abilities with others. Believe us, it doesn't help.

Practice a lot. Solve the QBank. Take Grand Tests. Review your performance. But don't let ranks and results drag you down. Rather use them as a guiding light to know your strengths and weaknesses, to increase your speed and accuracy, and to get yourself ready for the exam day.

If you have a doubt or a question, ask us. We are here.

Lastly and most importantly. take care of yourself. You and your health are precious. So, keep up with exercise, eat healthy, get enough sleep and care for yourself.

We're behind you, cheering you on to the finish line. You might be feeling stressed, overwhelmed, and so tired, but you're nearly there. Give it everything you've got, and know that whatever happens next, you've got what it takes for the life you want. You are a Champion.

)wn Your Dream
eam PrepLadder

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INFECTIOUS DISEASE

1 URINARY TRACT INFECTIONS, PYELONEPHRITIS AND PROSTATITIS PART -1

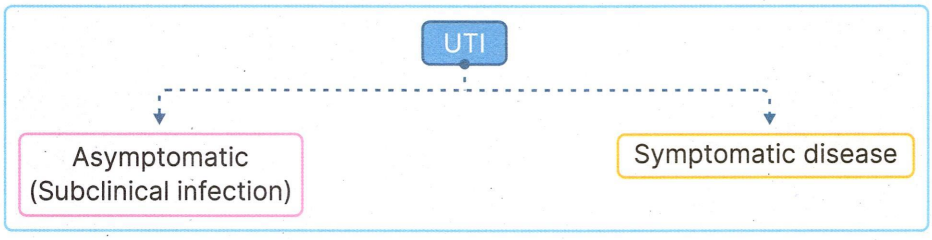
Introduction

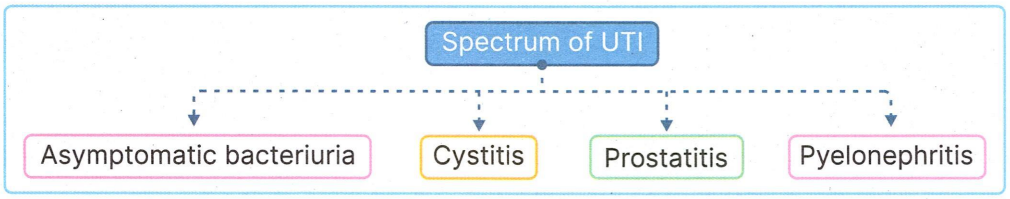
00:00:21

- UTI (Urinary tract infection) – Common & painful human illness rapidly responsive to antibiotic treatment
- Antibiotic preference depends upon the urinary pathogen
- In pre-antibiotic era, UTI caused significant morbidity
- First antibiotic introduced (in 1950) against UTI: Nitrofurantoin
- M/c manifestation: Acute cystitis
  - More common in females than in males

Definitions

00:02:13



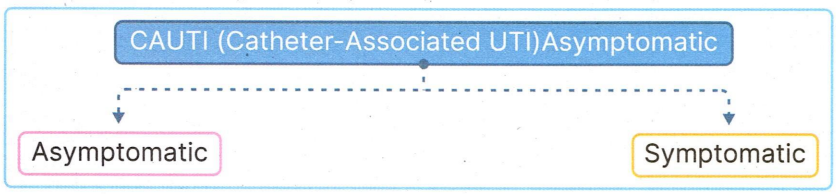


Asymptomatic bacteriuria

- Connote the presence of bacteria in urinary tract
- Urine: Presence of bacteria + WBCs + Inflammatory cytokines
- Do not require treatment

UTI

- Symptomatic disease
- Require antimicrobial therapy
- Cystitis: Symptomatic infection of bladder
- Pyelonephritis: Symptomatic infection of kidney (Renal parenchyma)
- Uncomplicated UTI/ Acute cystitis: Refers to infection confined to bladder
- Complicated UTI: Clinical features suggesting infection extending beyond the bladder
  - Symptoms
    → Fever
    → Signs & symptoms suggestive of systemic illness
- Catheter-associated bacteriuria

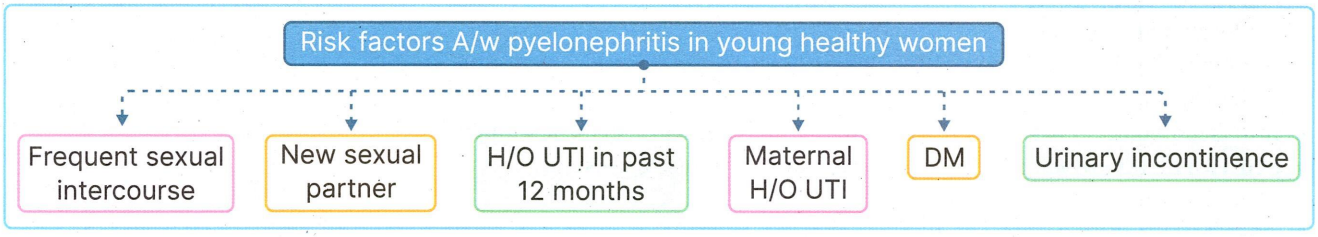


Epidemiology & Risk Factors

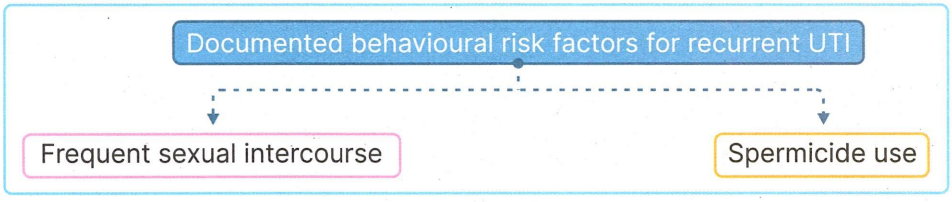
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- Gender variation between 1 year – 50 years of age: Females > Males

- In neonatal period: Males > Females
  - Male infants are more prone to congenital urinary tract anomalies → predispose to ↑ risk of UTI
- After 50 years of age
  - D/t benign prostatic hyperplasia, UTI is more common among males
- 50-80% of women in general population acquire 1 UTI during their lifetime
  - Mostly uncomplicated cystitis i.e., infection confined to urinary bladder
  - Risk factor for acute cystitis
    - → Recent use of diaphragm with spermicide
    - → Frequent sexual intercourse
    - → History of UTI
- In healthy postmenopausal women: Risk factors
  - DM: Also ↑ risk of pyelonephritis
  - Urinary incontinence
  - Sexual activity
- Many factors predisposing women to cystitis also ↑ risk of pyelonephritis



- 20-30% of women who have has 1 episode of UTI will have recurrent episodes of UTIs
- Early recurrence i.e., within 2 weeks → Regarded as relapse rather than reinfection
  - Indicate the need to evaluate patient for sequestered focus
  - Likelihood of recurrence decreases with increasing time since last infection
- **Case control study:** Premenopausal women with recurrent UTI
  - Identified frequent sexual intercourse
  - Use of spermicide
  - New sexual partner
  - First UTI before 15 years of age
  - Maternal history of UTI



In post-menopausal women

- Major risk factors for recurrent UTI
  - H/O UTI in premenopausal women
  - Anatomical factors affecting bladder emptying
    - → Presence of cystocele
    - → Urinary incontinence
    - → Presence of residual urine

In pregnant women

- Asymptomatic bacteriuria has clinical consequences
  - So, screening and treatment is required
  - Clinical consequences → Associated with Maternal pyelonephritis → In turn associated with preterm delivery

- Antibiotic t/t of ASB: Reduce
  → Risk of pyelonephritis
  → Preterm delivery
  → Development of low-birth-weight babies

In Men

- **Majority** of men with UTI have functional or anatomic abnormality in urinary tract
  - M/c – Urinary obstruction secondary to BPH (Benign Prostatic Hyperplasia)
  - Common in men of age group > 50 years
- Men are advised to undergo circumcision
  - E. coli – More likely to colonize in glans penis & prepuce → migrate to urinary tract of uncircumcised men

Women with diabetes

- 2-3-fold higher risk of ASB
- Duration of DM – Associated with risk of UTI
- Additional risk factors commonly found with DM which ↑ risk of UTI
  - Poor bladder function
  - Obstruction in urinary flow
  - Incomplete voiding
- In diabetic women → ↓ secretion of cytokine → ↑ Risk of UTI in diabetic women
- SGLT2 inhibitors (Sodium-Glucose Co-transporter 2): Cause glycosuria
  - Initial concern: ↑ risk of UTI
    → Not supported by recent data

Aetiology for development of UTI

00:31:49

- Uro-pathogen: M/c – Enteric Gram -ve rods like E. coli

Organism responsible for development of Acute uncomplicated cystitis	• E. Coli: 75-90% • Staphylococcus saprophyticus: 5-15% • Kliebseilla, Proteus, Enterococcus, & Citrobacter: 5-10%
Spectrum of agents causing uncomplicated pyelonephritis	• E. coli (predominant)

In Uncomplicated UTI (e.g., CAUTI)	• E. coli
	• Other aerobic gram-negative rods
	  ○ Pseudomonas aeruginosa
	  ○ Klebsiella
	  ○ Proteus
	  ○ Citrobacter
	  ○ Acinetobacter
	  ○ Morgonella species

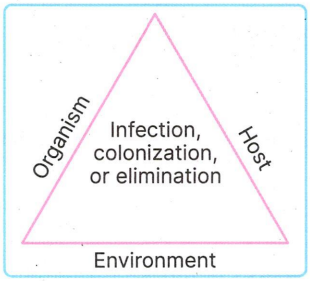
Pathogens in complicated UTI	• Gram-positive bacteria
	  ○ Enterococci
	  ○ S. aureus
	• Gram negative: E. coli > Pseudomonas, Klebsiella, Proteus, Citrobacter, Acinetobacter, Morganella species

Pathogenesis

00:35:34

- Urinary tract→ anatomical unit linked by a continuous column of urine extending from the urethra to the kidneys
- In majority of UTIs, Bacterial infections ascend from urethra to kidneys
- Integrity of host, pathogens, & environmental factors determines whether the tissue invasion & symptomatic infection will occur or not

Organism	Host factors	Environmental factors
• Type of organism • Presence of virulence factors • Expression of virulence factors	• Genetic background • Behavioural factors • Underlying diseases • Tissue-specific receptors	• Vaginal ecology • Anatomy/ urinary retention • Medical devices



- Bacteria often enter the bladder after sexual intercourse but women doing normal voiding & innate immunity will eliminate the organism from urinary tract
- Any foreign body in urinary tract such as urinary catheter or stones → provide an inert surface for bacterial colonization
- Abnormal micturition/ presence of significant residual urine volume → promote risk of infection
- Bacteria can gain access to urinary tract through blood stream also
  - Hematogenous spread: For < 2% of documented UTIs
  - Caused by highly virulent organisms like Salmonella & S. aureus
- Hematogenous infections may produce focal abscess or area of pyelonephritis in kidneys → +ve urine culture

Pathogenesis of Candiduria 00:42:44

- Hematogenous route for UTI is common
- Candida in urine of non-instrumented immunocompetent patient implies either genital contamination or potential widespread visceral dissemination

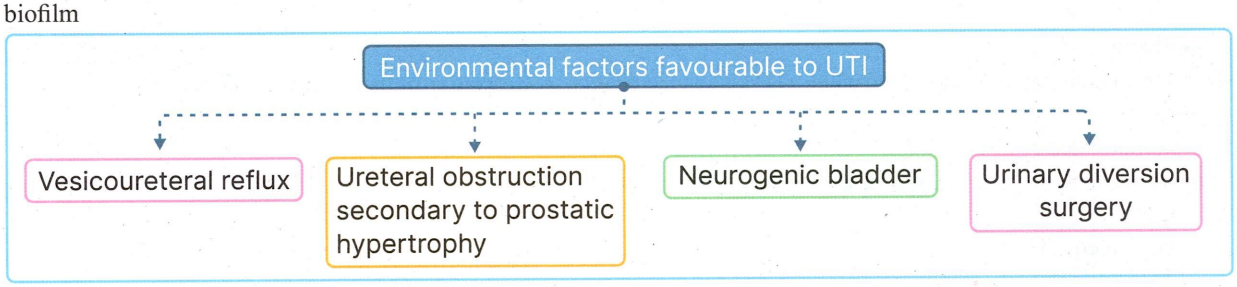
Environmental Factors 00:44:08

Vaginal ecology

- Important environmental factor increasing risk of UTI in females
- Colonization of vaginal introitus & periurethral area with intestinal flora from GIT like E. coli → Critical initial step in pathogenesis of UTI
- Sexual intercourse → Associated with ↑ risk of vaginal colonization with E. coli → ↑ risk of UTI
- Nooxynol-9 in spermicide → Toxic to normal vaginal lactobacilli → Associated with ↑ risk of vaginal colonization with E. coli & bacteriuria
- In postmenopausal women, the previously predominant vaginal lactobacilli → Replaced by gram -ve bacteria
  - Usage of topical oestrogens to prevent UTI → Controversial
  - Oral estrogen should not be used to prevent UTI

Anatomical & Functional abnormalities 00:47:48

- Any condition permitting urinary stasis/ obstruction → predispose individual to UTI
- Any foreign body such as urinary catheter or stones → provide an inert surface for bacterial colonization → form persistent biofilm



- In these conditions, E. coli strains lacking typical urinary virulence factors is often the cause of infection

Other environmental factors

Inhibition of ureteral peristalsis, deceased ureteral tone
↓
Lead to Vesicoureteral reflux
↓
Important in pathogenesis of pyelonephritis in pregnant women

Anatomical factors

- Specifically, distance of urethra from anus → Considered as primary reason for development of UTI
  - Females > Males

Host factors 00:51:37

- Genetic background of host influence individual susceptibility for recurrent UTI
- Genetic background: Familial predisposition to UTI
- Women with recurrent UTI have had 1st episode before 15 years of age
  - Have maternal history of UTI
- Component of underlying pathogenesis of Familial predisposition: H/O of persistent vaginal colonization of E. coli in mother → Women will have recurrent UTI
- Vaginal & periurethral cells from women with recurrent UTI → Have 3-fold more uropathogenic bacteria

Epithelial cells from women who are non-secretors of certain blood group antigens
↓
Possess specific receptors to which E. coli can bind
↓
Facilitate colonization & invasion

- Mutation in host innate immune genes coding for Toll-like receptor and IL-8 receptors → Linked to recurrent UTI & pyelonephritis

Microbial factors 00:56:33

- Anatomically normal urinary tract → Provide strong barrier to infectious organism
- Abnormal urinary tract → ↑ risk of UTI
  - E.g., Strains of E. coli express certain genetic virulence factors i.e., surface adhesins → mediates binding to specific receptors on surface of uroepithelial cells
  - Bet studied adhesin of E. coli: p-fimbriae
    → P-fimbriae: Hair-like protein structure that interacts with specific receptors on epithelial cells
    – Important in pathogenesis of pyelonephritis & subsequent blood stream invasion from kidney
  - Another adhesin: Type-1 pilus
    → Also, a fimbria which all E. coli strain possess but not all E. coli strains express
    → Thought to play key role in initiating E. coli bladder infection
    → Mediate binding to mannose on luminal surface of bladder uroepithelial cells
- Toxins, metal (iron) acquisition systems, biofilm formation & capsules → Contribute to ability of pathogenic E. coli to thrive in bladder

Approach to the Patient

Clinical syndromes 01:09:25

- Most important issue to be addressed when a UTI is suspected is characterization of the clinical syndrome
  - ASB
  - Uncomplicated cystitis
  - Pyelonephritis
  - Prostatitis
  - Complicated UTI

Asymptomatic Bacteriuria

- Diagnosis can be considered only when patient doesn't have local or systemic symptoms referable to urinary tract
- Clinical presentation: Bacteriuria
  - Detected incidentally from screening unrelated to urinary tract

Cystitis

- Typical symptoms
  - Dysuria
  - Increased urinary frequency
  - Urgency
- Other features
  - Nocturia
  - Hesitancy
  - Suprapubic discomfort
  - Gross haematuria

Uncomplicated Cystitis

- Infections confined to bladder, no upper urinary tract involvement
- U/L back/ flank pain – suggestive of upper urinary tract involvement
- Fever: Suggest invasion beyond the bladder
  - Can be in kidney, prostate, blood stream

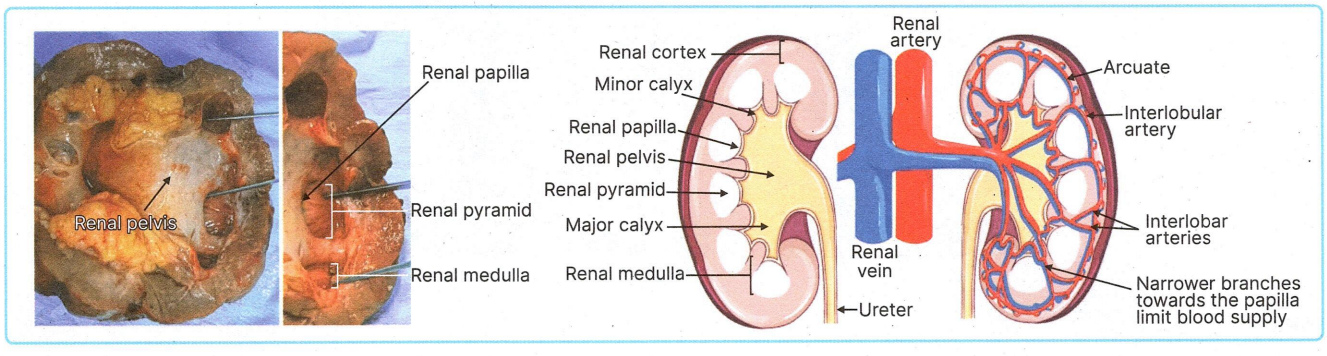
} Inconsistent with uncomplicated cystitis findings

Pyelonephritis 01:15:16

- Presentation in mild pyelonephritis: Low grade fever ± Low backpain/ costovertebral angle pain
- Severe pyelonephritis: High grade fever, rigors, nausea, vomiting, flak or loin pain
- Symptoms – Acute in onset
- Fever- Typically exhibits a high spiking picket fence pattern
  - Resolves over 72 hrs of therapy
  - Bacteraemia: Develops in 20-30% cases

Important Information

Fever: Important feature to distinguish between cystitis from pyelonephritis

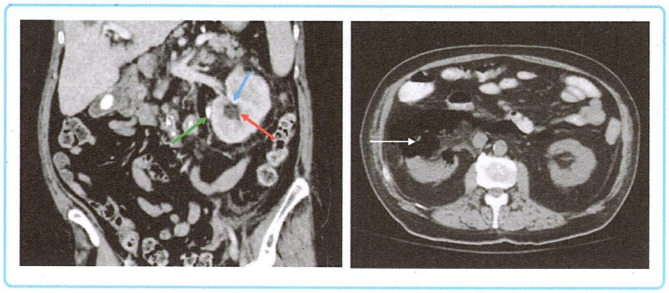


- Patient with diabetes may present with obstructive uropathy associated with acute papillary necrosis
- Sloughed papilla → Obstruction of ureter
- Papillary necrosis may also be evident in some cases of pyelonephritis
  - In sickle cell disease, analgesic nephropathy
- In rare cases of Bilateral papillary necrosis → Rapid rise in serum creatinine levels (1st indication)

Emphysematous pyelonephritis

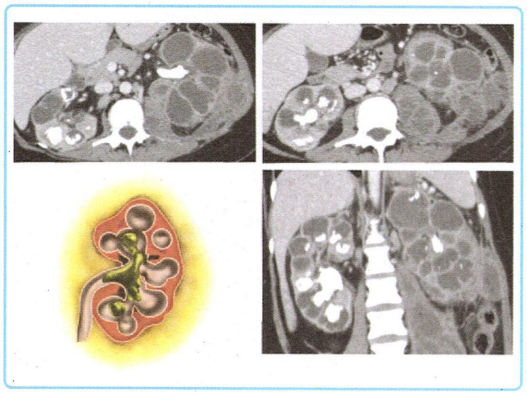
- Particularly severe form of disease associated with production of gas in renal parenchyma & perinephric tissue

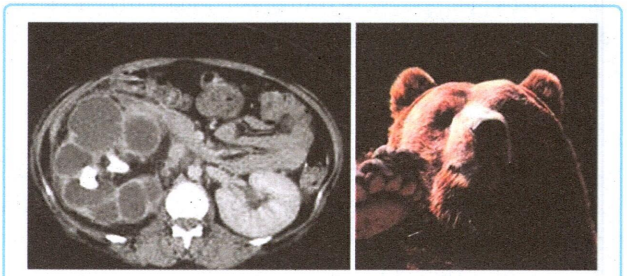
- Commonly seen in diabetic patients
- Organism: E. coli i.e., gas forming facultative anaerobic pathogen



Xanthogranulomatous pyelonephritis

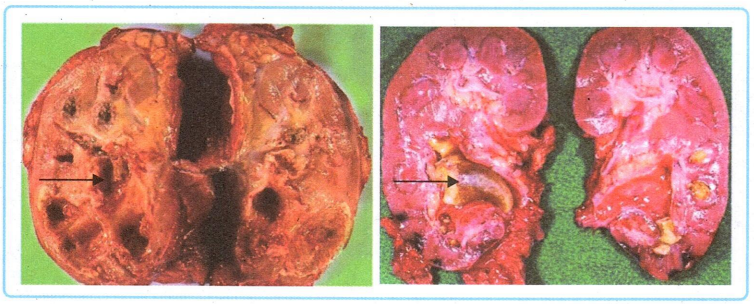
- Occurs d/t chronic urinary tract obstruction, often by Staghorn calculi
- Chronic obstruction by Staghorn calculi + chronic infection → Suppurative destruction of renal tissue i.e., Xanthogranulomatous pyelonephritis
- Pathological examination: Residual renal tissue has yellow coloration d/t infiltration by lipid laden macrophages





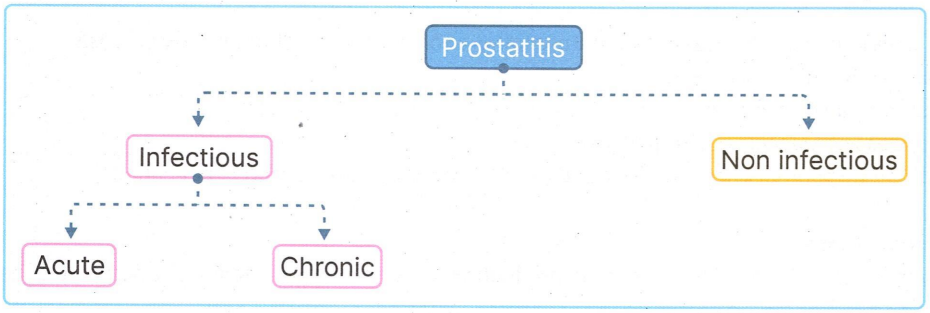
Bear claw sign

- Pyelonephritis can also be complicated by intraparenchymal abscess formation
  - Suspected when patient have continued fever not subsiding with antibiotic therapy
  - Mass effect of xanthogranulomatous pyelonephritis can mimic renal malignancy



Prostatitis

01:25:58



- Infections: Almost always bacterial in nature
  - Less common than non-infectious
- Acute bacterial prostatitis: Presentation
  - Dysuria
  - Increased frequency in urination
  - Pain in prostatic pelvic or perineal area
  - High grade fever with chills
  - Symptoms of bladder obstruction: Decreased/ Obstructed urinary flow
- Chronic bacterial prostatitis: Presentation
  - Recurrent cystitis
  - Pelvic and perineal pain
  - Men should be evaluated for prostatic focus & urinary retention

Complicated UTI 01:28:20

- Present as systemic illness with infectious focus in urinary tract and frequently occurs in patients with anatomical predisposition to infection
- Infection is beyond the bladder

2 URINARY TRACT INFECTIONS, PYELONEPHRITIS, AND PROSTATIS PART-2

Diagnostic tools

History

- Diagnosis of UTI syndromes or ASB begins with detailed history
- High predictive value in uncomplicated cystitis
- Metanalysis evaluating probability of acute UTI on basis of history and physical findings concluded that in women presenting with at least 1 symptom of UTI (dysuria, frequency, haematuria, or back pain) & without complicating factors, the probability of acute cystitis or pyelonephritis – 50%
- Vaginal discharge + No complicating factors → Risk of UTI: 90%
  - No laboratory investigation is required
- Combination of dysuria & urinary frequency in absence of vaginal discharge → Probability of UTI is 96%
  - Further laboratory evaluation with dipstick testing & urine culture – Not required before initiation of definitive therapy
- One significant concern: T/t of sexually transmitted disease by C. Trachomatis as Urinary tract infection
  - Particularly in females of age group 25 years
- D/D for dysuria in women

Cervicitis	Vaginitis
Causative organism: C. Trachomatis, N. Gonorrhoea	Causative organism: Candida albicans & Trichomonas vaginalis

- Other D/D: Herpetic urethritis / interstitial cystitis / non-infectious vaginal/vulvar irritation.
- Women with > 1 sexual partner & inconsistent use of condoms → High risk of UTI & STDs

Urine dipstick test, Urinalysis & Urine culture

00:07:31

- Useful diagnostic tools
- Urine dipstick test & urinalysis → Provide point of care information
- Urine culture: Retrospectively confirm previous diagnosis, organism & provide organism susceptibility

Urine dipstick test

Nitrite test	• Members of family Enterobacteriaceae
	  ○ Convert Nitrate to nitrite
	  ○ Enough nitrite must accumulate in urine to reach threshold of detection
	• Excess amount of fluid consumption & voiding make nitrite test (dipstick test) → Less likely to be positive

Leucocyte esterase test	• Detect leukocyte esterase in polymorphonuclear leucocytes in host urine whether the cells are intact or lysed • Presence of polymorphonuclear leucocytes in urine sample → Suggests urine infection

- Urine dipstick test: Confirm diagnosis of uncomplicated cystitis in patient with reasonably high test positivity of disease
- Blood in urine may also suggest diagnosis of UTI
- Negative dipstick test is not sufficiently sensitive to rule out bacteriuria, particularly in pregnant women

Urine microscopy

- Reveals pyuria (presence of WBCs) in all cases of cystitis & haematuria
- Efficacy: 30%

Automated system & Manual examination

- Most hospital laboratories use automated system over manual examination for urine microscopy
- Machine aspirates a sample of urine & then classifies the particles in urine by size, shape, contrast & volume of particle
- Automated systems are useful in counting numbers of dysmorphic RBCs, WBCs or Crystals

- Also count number of bacteria but less accurate

Urine culture

- To identify specific organisms
- Require 24 hours to identify specific organism
- Studies of women with symptoms of cystitis have found that a colony count threshold of $\geq 10^2$ bacteria/ml is more sensitive & specific than threshold of 10^5/ ml for diagnosis of acute cystitis in females
- In men, minimal level indicating infection – 10^3/ml
- Urine samples can get contaminated normal microbial flora present in
  - Distal part of urethra
  - Vagina
  - Skin
- Contaminants can grow to high numbers if collected urine is allowed to stand at room temperature
- In most instances, if culture yields mixed bacterial species → Indicates contaminated sample
- Except in setting of
  - Long term catheterization
  - Chronic UTI
  - Presence of fistula between Urinary tract & GIT/ Genital tract

Treatment

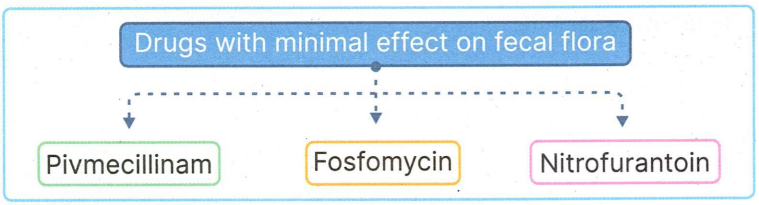
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- Accounts for major proportion of
  - Antimicrobial use in ambulatory care
  - Inpatient care
  - Long term care settings
- Choice of antimicrobial agent, dose & duration of therapy depends on
  - Site of infection
  - Presence/ absence of complicating conditions
- For each category of UTI variant, a different approach is required based on particular clinical syndrome
  - E. coli ST131 – predominant multilocus sequence worldwide
    → Cause of multidrug-resistant UTI
- Recommendation of treatment depends upon local resistance pattern in geographical area
  - E.g., Fosfomycin & pivmecillinam – Considered as 1st line option, but not available in all countries
    → Retain activity against majority of uropathogens
    → Produce extended-spectrum beta-lactamases
- Therapeutic choices depend on
  - Local resistance
  - Drug availability
  - Individual patient factors like recent travel & antimicrobial use

Treatment of Uncomplicated cystitis in women

00:27:08

- TMP-SMX (1999) – Considered as first line agents for uncomplicated UTI
- But later antibiotic resistance against TMP-SMX for uropathogens causing uncomplicated cystitis → Increased
- Collateral damage – adverse ecological effects of antimicrobial therapy
  - Killing of normal flora
  - So, selection of drug-resistant organisms was required
- Newer agents have been studied for killing of organism
- But now there is no longer a single best agent for treatment of uncomplicated cystitis
- The implication of collateral damage for UTI – Drug highly efficacious for treatment of UTI is not necessarily the optimal 1st line agent (Have profound secondary effects on flora)



- TMP-SMX, quinolones & ampicillin – affect normal fecal flora more significantly

1st line agents	2nd line agents
• TMP-SMX • Nitrofurantoin	• Beta lactams

- There is increasing experience with use of Fosfomycin in UTI, especially with complicated infections particularly for infections caused by multidrug-resistant E. coli
- According to advisory from the US food & Drug Administration (FDA), fluoroquinolone → not used for uncomplicated cystitis unless there is no alternative

Nitrofurantoin	• Resistance to nitrofurantoin (used for > 60yrs) → very low ○ As it requires several mutation steps • Highly effective against E. coli & most of the non-E. coli isolates • Proteus, pseudomonas, Serratia, Enterobacter & yeasts → Insistently resistant to nitrofurantoin • Traditionally been prescribed as 7 days regimen • Present day guidelines also recommend 5 days course as well • It does not reach significant levels in tissues; hence, it has no role in pyelonephritis

Fosfomycin	• Guidelines also recommend Fosfomycin as 1st line agents for acute uncomplicated cystitis
	• Oral Fosfomycin – Given as 3g dose sachet
	  ○ Dissolved in glass of water and swallowed
	• Interferes with cell wall formation
	• Bactericidal
	• Fosfomycin with
	  ○ E. coli – Susceptible
	  ○ Pseudomonas – Intrinsically resistant
	  ○ Against Klebsiella → Unreliable

Fluoroquinolones	• Mostly are highly effective as short course therapy for cystitis
	• Except moxifloxacin, as it does not reach adequate urinary levels
	• Drugs used
	  ○ Ciprofloxacin
	  ○ Levofloxacin
	• Concern
	  ○ Propagation of fluoroquinolone resistance
	  ○ Potential adverse effects
	• Adverse effect
	  ○ In > 60 yrs of age: ↑ risk of Achilles tendon rupture
	  ○ Irreversible neuropathy
	  ○ A/w Aortic dissection (noted by FDA & European Medicine agency)

Beta-lactams	• In case of acute cystitis – Not performed well in comparison to TMP-SMX or Fluoroquinolones • Pathogen eradication is low & relapse rate is high

Cephalosporins	• Due to rising resistance to TMP-SMX & the goal of avoiding fluoroquinolones, usage of oral cephalosporins is increased
	• Oral cephalosporins
	  ○ Cefpodoxime
	  ○ Cefixime

Urinary analgesics	• Appropriate in certain situations to speed resolution of bladder discomfort • Drug: Phenazopyridine • Adverse effect: Nausea • Combination analgesics containing urinary antiseptics: Methenamine, methylene blue • Urine acidifying agent: Sodium phosphate • Antispasmodic agent: Hyoscyamine

Treatment for pyelonephritis

00:49:00

- Since pyelonephritis is tissue invasive disease, it requires treatment regimen with very high likelihood of eradicating the causative organism
- These antibiotics should reach blood therapeutic levels quickly
- 1st line drug for acute uncomplicated pyelonephritis: Fluoroquinolones, orally or parenteral, depends upon patients' tolerance for oral intake
- TMP-SMX have high rate of resistance against E. coli
- Randomised trial demonstrated that 7 days trial with oral ciprofloxacin (500mg, BD) with or without initial IV dose – highly effective for initial treatment of pyelonephritis
- Oral TMP-SMX (one double-strength tablet twice daily for 14 days) – Effective for treatment of uncomplicated pyelonephritis if uropathogen is known to be susceptible
- If pathogen's susceptibility is not known & TMP-SMX is given, then preferred treatment is IV 1 gm ceftriaxone
- Oral beta lactams are less effective than fluoroquinolones
  - Should be used with caution & close follow-up
- Parenteral therapy for uncomplicated pyelonephritis
  - Fluroquinolones / Extended spectrum cephalosporins ± Aminoglycosides / Carbapenem
- Drugs given with complicated history
  - Combination of beta-lactam & beta lactam inhibitor like ampicillin-sulbactam, piperacillin-tazobactam

    Or
  - Carbapenem like Imipenem-cilastatin, ertapenem, meropenem
- Complicated histories include
  - Previous episode of pyelonephritis
  - Presence of antimicrobial resistance
  - Recent Urinary tract manipulations with catheters
- If patient respond clinically, IV therapy is replaced with oral therapy

UTI in pregnant women

00:59:55

- Relatively safe antibiotics in early pregnancy: Nitrofurantoin, ampicillin & cephalosporins
- Sulphonamide: Clearly avoided both in 1st trimester & near-term pregnancy as they are teratogenic
  - At near term there are chances of development of kernicterus
- Fluroquinolones – Avoided d/t adverse effect on Fetal cartilage development
- Ampicillin & cephalosporins – Used extensively in pregnancy
  - DOC for symptomatic as well as asymptomatic patients of UTI in pregnancy
- Pregnant women with ASB – Treated for 4-7 days in absence of evidence of supportive single-dose therapy
- Pregnant women with overt pyelonephritis – Require parenteral β-lactams ± Aminoglycosides

UTI in men

01:04:18

- Prostate is involved in majority cases of febrile UTI
- Goal – Eradication of prostatic & bladder infections
- Course of therapy: 7-14 days course of fluoroquinolones or TMP-SMX if uropathogen is susceptible
  - Clinical practice stands towards the shorter duration i.e., 7 days to reduce antibiotic exposure
- Acute bacterial prostatitis: Start antibiotics only after urine & blood is collected for culture
  - Therapy is tailored according to urine culture results & is constituted for 2-4 weeks
- Chronic bacterial prostatitis
  - Duration of antibiotic therapy: 4-6 weeks
  - For recurrence: Course of antibiotic therapy: 12 weeks

Complicated UTI

01:09:09

- Occurs in a heterogeneous group of patients, may with structural & functional abnormalities of the urinary tract & kidney
- Range of species & their susceptibility to antimicrobial agent → Heterogeneous
- As a consequence, therapy for complicated UTI infection must be individualized & guided by urine culture result

Xanthogranulomatous pyelonephritis

- Treated with nephrectomy
- Percutaneous drainage can be used as an initial therapy in case of emphysematous pyelonephritis
  - Followed by elective nephrectomy

Papillary necrosis with obstruction

01:11:32

- Requires intervention to relieve the obstruction & preserve renal function

Treatment of Asymptomatic Bacteriuria

01:12:20

- Doesn't decrease frequency of symptomatic infections or complications except in
  - Pregnant women
  - Persons undergoing urologic surgery
  - Neutropenic patients
  - Renal transplant patients

} T/t is guided by urine culture reports

Catheter associated UTI

01:13:59

- Multiple institutions have released guidelines for treatment of CAUTI defined by bacteriuria & symptoms in catheterized patients
- Majority cases of catheterized associated bacteriuria → Asymptomatic & do not require antimicrobial therapy
- In symptomatic patients, signs & symptoms are either localized to urinary tract or can include otherwise unexplained systemic infections such as fever
- Accepted threshold for bacteriuria to meet definition of CAUTI: $\geq 10^3$ CFU/ ml
- Threshold for bacteriuria to meet definition of ASB → $\geq 10^5$ CFU/ ml
- Typical signs & symptoms of UTI
  - Pain
  - Urgency
  - Dysuria
  - Fever
  - Periphery leucocytosis
  - Pyuria
- All these signs & symptoms have less predictive value for diagnosis of infection in catheterized patients
- Aetiology of CAUTI → Diverse & urine culture is essential to guide the treatment
- Goal of treatment of CAUTI: To remove biofilm-associated organisms
  - Biofilm serves as a nidus for reinfection
- Pathology studies revealed that many patients with long term catheters have occult pyelonephritis.

- A randomized trial in persons with spinal cord injury with intermittent catheterization found to have relapse more commonly after 3 days of therapy than after 14 days
- Duration of treatment: 7-14 days of antimicrobial therapy
- Best strategy for prevention of CAUTI: To avoid unnecessary catheterization or to remove catheters which are no longer necessary
- Antimicrobial catheters impregnated with silver or nitrofurazone → Have no significant clinical benefit
- No evidence for recommending suprapubic catheters & condom catheters
  - Not an alternative to indwelling urinary catheters
  - Cannot prevent bacteriuria
- Intermittent catheterization > Long-term indwelling urethral catheterization
  - To prevent both infectious & anatomical complications
- Intermittent catheterization → Preferred in spinal cord injuries

Candiduria

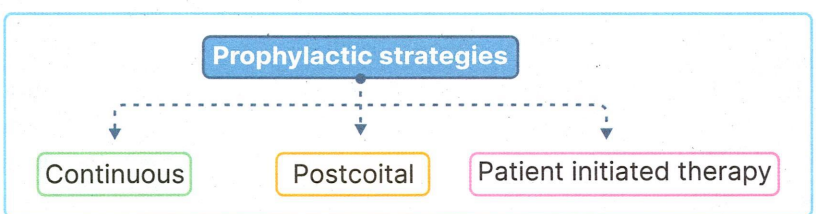
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- Increasingly common complication of indwelling catheterization, particularly in
  - Patients in ICU
  - Those who are taking broad-spectrum antimicrobial drugs
  - Those with underlying DM
- > 50% of urinary candida isolates are non-albicans species
- Clinical presentation – Varies from laboratory finding without symptoms to pyelonephritis to sepsis
- Removal of urethral catheter results in resolution of candiduria in > 1/3rd of asymptomatic patients
- Treatment of asymptomatic cases do not decrease frequency of recurrence of candiduria
- Therapy – Recommended for symptomatic cystitis or pyelonephritis or those with high risk of disseminated disease
- High risk patients include those with
  - Neutropenia
  - Urologic manipulation
  - Clinically unstable
  - Low birth weight infants
- Therapy: Fluconazole – 200-400mg/day x 7-14 days
  - Reaches high level in urine
  - 1st line regimen for candida infection in urinary tract
- Newer azoles & echinocandins are characterized by successful eradication of candiduria but by low level urinary excretion
  - Hence not recommended for candiduria
- Drugs recommended for candida isolates with high resistance to fluconazole: Oral flucytosine or parenteral amphotericin B
- Bladder irrigation with amphotericin B – Not recommended

Prevention of recurrent UTI in women

01:34:59

- Recurrence of uncomplicated cystitis – Very common in women of reproductive age group
- If recurrence is very common & interfere with patients lifestyle then preventive strategy is indicated
- Threshold of 2 or more symptomatic episodes/ year – Not absolute
- Decision regarding intervention should take patients preference into account



Continuous & postcoital prophylaxis	• Low doses of TMP-SMX or nitrofurantoin • These regimens are highly effective in period of active antibiotic intake • Duration of prophylactic regimen: 6 months then discontinued • If bothersome infection recurrence occurs, prophylaxis institution is reinstituted for longer periods • Selection of resistant strains in fecal flora – Documented in studies of women taking prophylactic antibiotics for 12 months
Patient initiated therapy	• Involves providing patient with materials for urine culture with a course of antibiotics for self-medication at 1st symptom of infection • Urine culture collected is refrigerated & delivered to physician's office for confirmation of diagnosis • Lactobacillus probiotics: Good for UTI infection prevention • Studies of cranberry products for UTI prevention – Mixed results ○ Varying dosing & product composition between studies & issue for providing the clinical guidance

Prognosis

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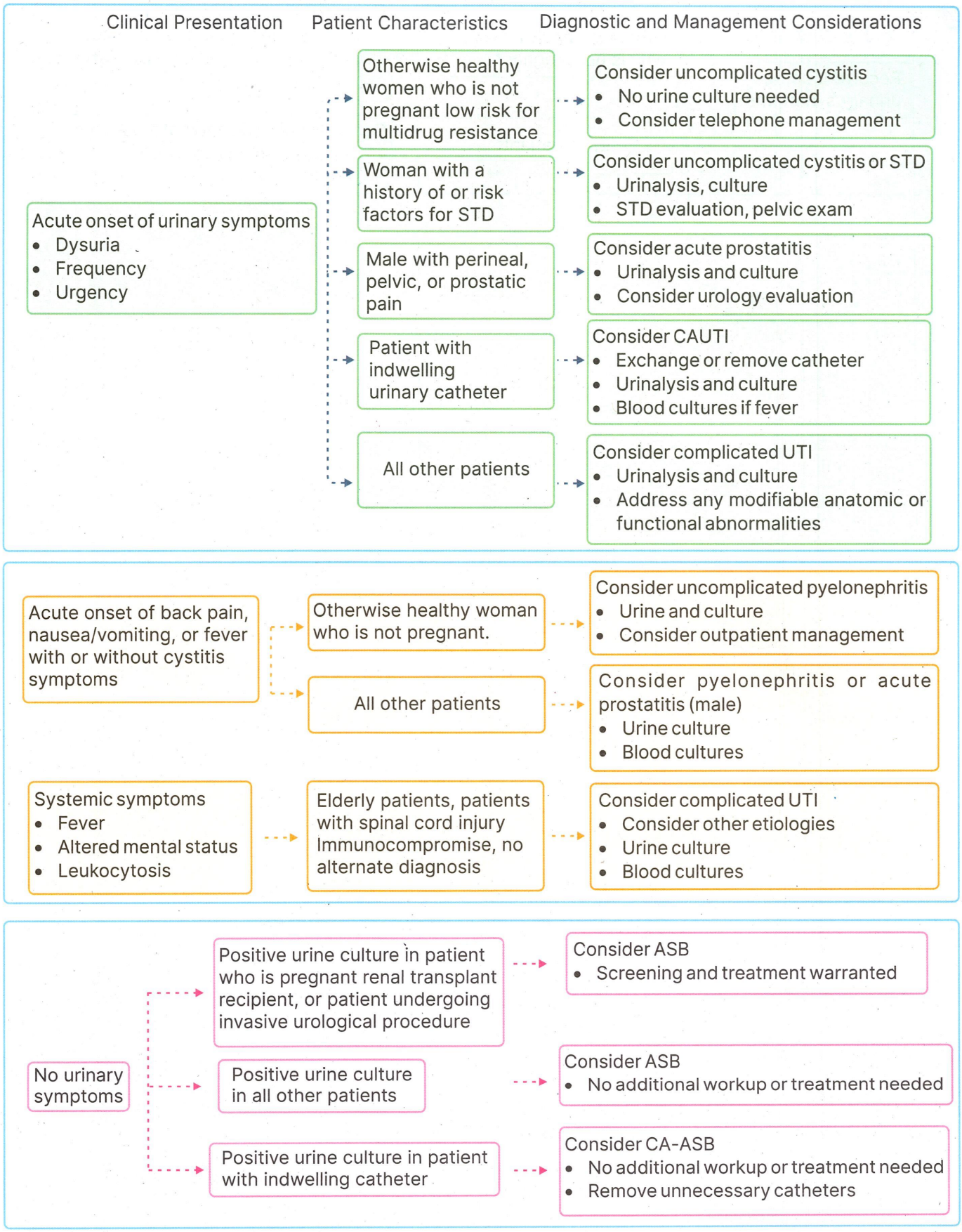
- Cystitis – Risk factor for recurrent cystitis & pyelonephritis
- ASB is common for older and catheterized patients but does not increase the risk of death in itself
- In absence of anatomic abnormalities like reflux, recurrent infection in children & adult doesn't lead to chronic pyelonephritis or renal failure
- Infection doesn't play a primary role in case of chronic interstitial nephritis
  - Primary etiological factor
    - → Analgesic abuse
    - → Obstruction
    - → Development of reflux
    - → Toxin exposure
- In presence of underlying renal abnormalities particularly stones, infection as secondary factor accelerate renal parenchymal damage

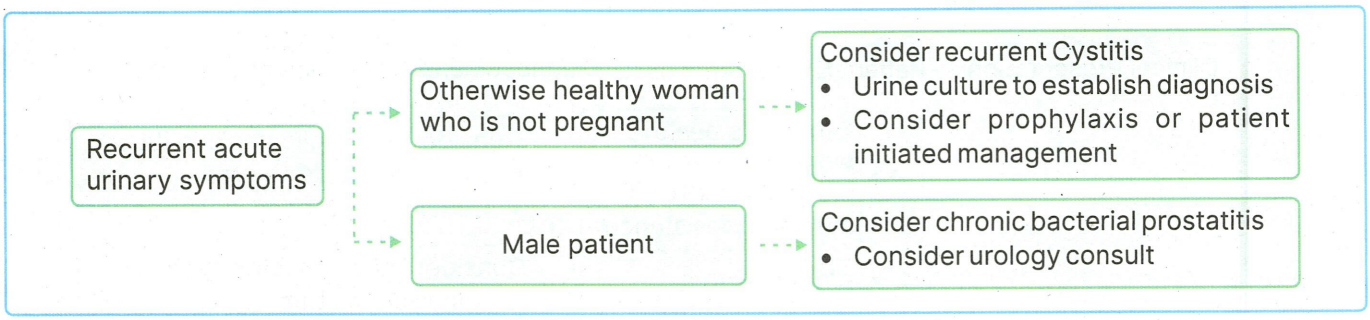
Pros & cons of specific agents

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Drug & dose	Estimated clinical efficacy (%)	Estimated bacterial efficacy (%)	Common side effects
Nitrofurantoin, 100mg, BSD x 5-7 days	87-95	82-92	Nausea, headache
TMP-SMX, 1 DS tablet bid x 3d	86-100	85-100	Rash, urticaria, nausea, vomiting, hematological abnormalities
Fosfomycin, 3g single dose sachet	83-95	78-98	Diarrhoea, nausea, headache
Pivmecillinam, 400mg bid x 3-7 days	55-82	74-84	Nausea, vomiting, diarrhoea
Fluoroquinolones, dose varies by agent; 3-d regimen	81-98	78-96	Nausea, vomiting, diarrhoea, headache, drowsiness, insomnia
Beta-lactams, dose varies by agent, 5-7 d regimen	79-98	74-98	Diarrhoea, nausea, vomiting, rash, urticaria

Summary


Clinical Presentation
Patient Characteristics
Diagnostic and Management Considerations
Acute onset of urinary symptoms
• Dysuria
• Frequency
• Urgency
Otherwise healthy women who is not pregnant low risk for multidrug resistance
Consider uncomplicated cystitis
• No urine culture needed
• Consider telephone management
Woman with a history of or risk factors for STD
Consider uncomplicated cystitis or STD
• Urinalysis, culture
• STD evaluation, pelvic exam
Male with perineal, pelvic, or prostatic pain
Consider acute prostatitis
• Urinalysis and culture
• Consider urology evaluation
Patient with indwelling urinary catheter
Consider CAUTI
• Exchange or remove catheter
• Urinalysis and culture
• Blood cultures if fever
All other patients
Consider complicated UTI
• Urinalysis and culture
• Address any modifiable anatomic or functional abnormalities
Acute onset of back pain, nausea/vomiting, or fever with or without cystitis symptoms
Otherwise healthy woman who is not pregnant.
Consider uncomplicated pyelonephritis
• Urine and culture
• Consider outpatient management
All other patients
Consider pyelonephritis or acute prostatitis (male)
• Urine culture
• Blood cultures
Systemic symptoms
• Fever
• Altered mental status
• Leukocytosis
Elderly patients, patients with spinal cord injury Immunocompromise, no alternate diagnosis
Consider complicated UTI
• Consider other etiologies
• Urine culture
• Blood cultures
No urinary symptoms
Positive urine culture in patient who is pregnant renal transplant recipient, or patient undergoing invasive urological procedure
Consider ASB
• Screening and treatment warranted
Positive urine culture in all other patients
Consider ASB
• No additional workup or treatment needed
Positive urine culture in patient with indwelling catheter
Consider CA-ASB
• No additional workup or treatment needed
• Remove unnecessary catheters


Recurrent acute urinary symptoms
Otherwise healthy woman who is not pregnant
Consider recurrent Cystitis
• Urine culture to establish diagnosis
• Consider prophylaxis or patient initiated management
Male patient
Consider chronic bacterial prostatitis
• Consider urology consult

3 SEPSIS PART-1

Introduction and Definitions

00:00:37

Sepsis

- Life-threatening organ dysfunction caused by dysregulated host response to infection
- **Systemic inflammatory response syndrome**
- Clinical features
  - Signs of infection
  - Organ dysfunction (hepatic, renal or haematological)
  - Altered mental status, tachypnoea, hypotension on examination
- **Criteria for sepsis**
  - Sepsis 1 criteria – 1991
  - Sepsis 2 criteria – 2003
  - Sepsis 3 criteria – 2016
    - → Suspected infection
    - → Acute increase in ≥ 2 sepsis related organ failure assessment (SOFA)

Severe sepsis

- Sepsis with acute organ dysfunction
- To clarify terminology and reflect the current understanding of the pathobiology of sepsis, the Sepsis definition task force in 2016 proposed the third International Consensus Definitions specifying that Sepsis is a dysregulated host response to infection, causing acute organ dysfunction

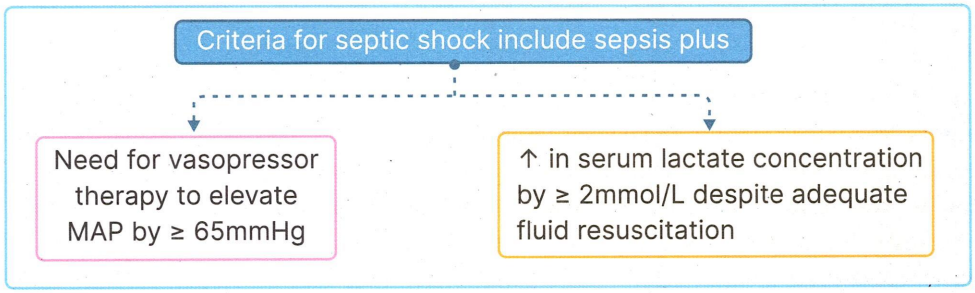
Important Information

- Difference between sepsis & severe sepsis
  - Sepsis – No organ dysfunction
  - Severe sepsis – Acute Organ dysfunction

Septic shock

00:05:02

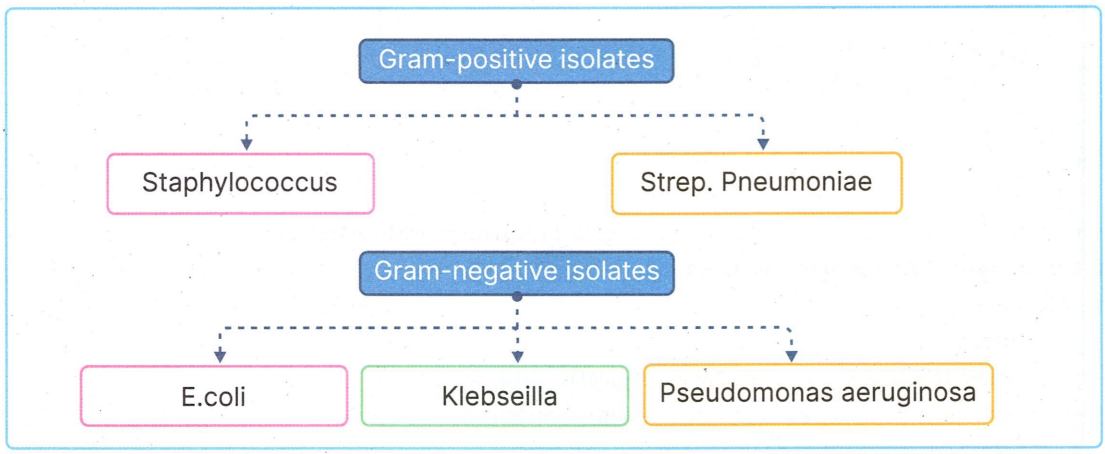
- Subset of patients with circulatory & cellular/ metabolic abnormalities leading to substantially ↑ risk of mortality
- Sepsis + hypotension despite adequate fluid resuscitation + perfusion abnormalities
- To aid clinicians in identifying sepsis & septic shock at the bedside, "Sepsis-3" clinical criteria include
  - Suspected infection
  - Acute organ dysfunction: Defined as ↑ by ≥ 2 points from baseline on the SOFA score



Aetiology

00:14:42

- Sepsis arises from both community-acquired as well as hospital-acquired infections
- Pneumonia contributes to ½ cases of sepsis
- Intrabdominal & genitourinary infections
- Blood culture: Positive in almost 1/3rd cases of sepsis but many cases are culture negative at all the sites



- In recent years: Gram-positive infection > Gram-negative infections
- 75-country point prevalence study of 14,000 patients on ICUs
  - 62% isolates - Gram-negative bacteria
  - 47% isolates – Gram-positive
  - 19% isolate – Fungi

Risk factors

00:18:32

- Common risk factors for increased risk of infection
  - Chronic disease: HIV, COPD, Cancer
  - Immunosuppression
- Risk factors for progression from infection to organ dysfunction (less well understood)
  - Underlying health status
  - Preexisting organ function
  - Timelines of treatment
- Age, gender, race/ ethnicity – Influence the incidence of sepsis
  - Highest at extremes of age
  - Males > females
  - Blacks > Whites (d/t genetic differences in susceptibility to infection)

Pathogenesis

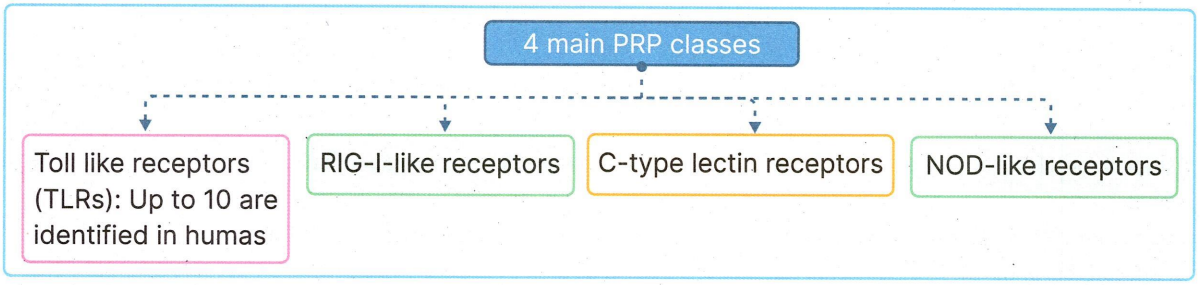
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- Excessive inflammatory host response (SIRS) – Was considered the reason for clinical features of sepsis for many years
- Recently, it has become apparent that infection triggers a much more complex, variable & prolonged host response than previously thought
- Specific response depends on
  - Pathogen load & virulence
  - Host factors: Genetic composition & co-morbidity
- **Pro-inflammatory reaction**: Directed at eliminating the pathogen
  - Responsible for collateral tissue damage i.e., damage to organisms & tissue of host
- **Anti-inflammatory responses**: Implicated in increased susceptibility to secondary infection
- These 2 mechanisms is characterized as an interplay between 2 "fitness costs"
  - Direct damage to organ by pathogen
  - Damage to organs from host immune response
- Host's ability to resist as well as tolerate both direct & immunopathologic damage – Decide whether uncomplicated infection becomes sepsis

Initiation of inflammation

00:28:05

- Host response to infection is initiated when pathogens are recognised & bound by innate immune cells (macrophages)
- 2 components
  - Pathogen recognition receptors (PRRs): Present on surface of immune cells
  - Pathogen associated molecular patterns (PAMPs): Binds with PRPs
    → Present on organism
- Interaction of PRRs with PAMPs result in
  - Upregulation of inflammatory gene transcription
  - Activation of innate immunity



- These 4 main PRR classes are known as Inflammasomes
- Activity of PRR: Responsible for initiation of inflammation

PAMPs

00:32:36

- Includes viral RNAs & flagellin
- Common PAMP: Lipid A moiety of LPS
  - Found in outer membrane of gram-negative bacteria

LPS first attaches to LPS-binding protein present on surface of monocytes/ macrophages/ neutrophils
↓
LPS then Transfers and signals via TLR4
↓
To produce & release proinflammatory cytokines like TNF & IL-1
↓
Grow & alert other cells & tissues

- Also sense endogenous molecules released from injured cells called as DAMPs (Damage Associated Molecular Patterns)
- DAMPs or alarmins – Nuclear, cytoplasmic or mitochondrial structures released from cells as a result of infection, tissue injury or cell necrosis.
  - E.g.,
    → High mobility group protein B-1
    → S-100 proteins
    → Extra-cellular DNA/RNA & histones
  - Recognised by PRRs on immune cells once released into the extracellular environment resulting in upregulation of proinflammatory cytokine production

Important Information

- Other cellular elements released during infection
  - Reactive oxygen species
  - Microparticles
  - Proteolytic enzymes
  - Neutrophil extracellular traps

} Influence inflammatory process

Activation of PMN

Along with microphage activation, polymorphonuclear leukocyte (PMN) surface receptors also bind microbial components

↓

Results in expression of surface adhesion molecules

↓

PMN aggregate & marginate to vascular endothelium

↓

Through multiple process of rolling, adhesion, diapedesis & chemotaxis, PMNs migrate to site of infection

↓

Release inflammatory mediators

↓

Responsible for local vasodilation, hyperaemia & ↑ microvascular permeability

- Sepsis occurs when these local proinflammatory immune processes become exacerbated → Result in generalized immune response
- Though it remains unclear why this malignant transition occurs, various theories implicated are
  - Direct effects of the invading microorganism
  - Overproduction of proinflammatory mediators
  - Activation of the complement system

Coagulation abnormalities

00:49:03

- Sepsis is commonly associated with coagulation disorders resulting in DIC
- Abnormalities in coagulation are thought to isolate invading microorganisms & prevent spread of infection & inflammation to other tissues & organs
- **Causes of clot formation**
  - Coagulation via tissue factor → Excess fibrin deposition
    - → Tissue factor: Transmembrane glycoprotein expressed buy various cell types
  - Impaired anticoagulant mechanisms including protein C system & antithrombin
  - Compromised fibrin removal d/t depression of fibrinolytic system
- **Coagulation (& other) proteases** further enhance inflammation via protease activated receptors
- In infections with endothelial predominance, these mechanism can be common & deadly

Organ dysfunction

00:53:02

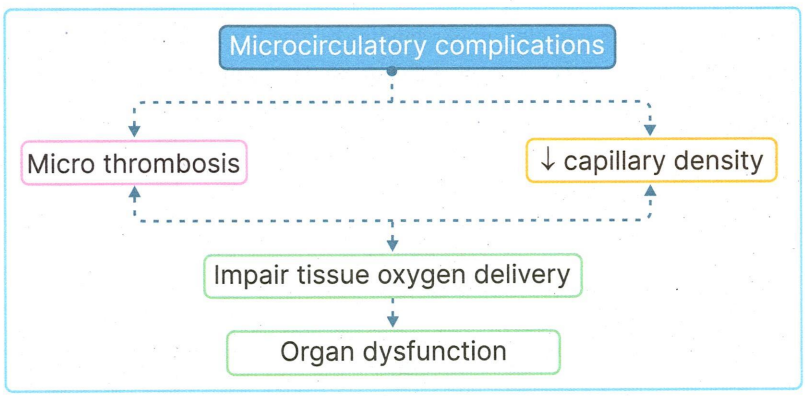
- Although the mechanism that underlie organ failure in sepsis are only partially known, both cellular & hemodynamic alterations play a key role

Key contributing factors

- Abnormal inflammatory response/ aberrant infection → causes cellular damage → ↑ risk of organ dysfunction
- Cellular alterations
  - Include
    - → Impaired cellular death pathways
    - → Mitochondrial dysfunction
    - → Intracellular handling of reactive oxygen species
  - E.g., Mitochondrial damage d/t oxidative stress & other mechanisms impair cellular oxygen utilization
  - Slowing of oxidative metabolism & ↓ oxygen delivery → reduce cellular oxygen extraction
  - Yet energy (ATP) still needed to support basal & vital cellular function
  - ATP is derived from glycolysis & fermentation → Yields H^+ & lactate
  - Deprived Oxygen delivery to tissues → Anaerobic glycolysis → Excessive lactate production
  - With severe & prolonged insult → ATP levels fall beneath a critical threshold → ensure bioenergetic failure, release of toxic

ROS & apoptosis → Irreversible cell death & organ failure

- Endothelial dysfunctions: Critical to pathogenesis of multiorgan failure common to sepsis
  - Cell to cell interactions in vascular endothelium are disrupted in sepsis resulting in loss of barrier integrity → Subcutaneous & body cavity edema
  - Endothelial glycocalyx disruption contribute to ↑ endothelial permeability & edema formation
- Circulatory abnormalities
  - Both at systemic & microcirculatory levels → common in sepsis → contribute to organ failure
- Uncontrolled release of nitric oxide from cellular damage cause
  - Vasomotor collapse in individual
  - Opening of AV shunt & pathological shunting of oxygenated blood from susceptible tissues



- Emerging evidence suggests that the gut also plays an independent role in development of sepsis associated organ dysfunction
- Proposed hypotheses include bacterial translocation through
  - Impaired mucosal integrity
  - Release of toxic mediators by injured gut mucosa
  - Alteration in gut microbiome d/t critical illness
- Generally, organs such as lung undergo extensive microscopic changes
- Some organs like kidney may lack significant structural damage but have significant tubular cell changes that impairs the function of organs

Anti-inflammatory Mechanism

01:13:22

- Immune system harbours humoral, cellular & neural mechanisms → may exacerbate potentially harmful effects of pro-inflammatory response
- Phagocytes can switch to an anti-inflammatory phenotype → promotes tissue repair
- Regulatory T cells & myeloid-derived suppressor cells → ↓ Inflammation
- Neuroinflammatory reflex
  - Sensory input – Relayed through afferent Vagus to brain stem → where efferent vagus nerve activates splenic nerve in celiac plexus with consequent norepinephrine release in spleen & Ach release by substrate of CD4 + T cells
  - Ach targets α-7 cholinergic receptors on macrophages, reducing proinflammatory cytokine release
- Disruption of this neural-based system by vagotomy causes more vulnerability to endotoxic shock
- Disruption of the neuroinflammatory reflex results in induction of sepsis

Immunosuppression

01:20:17

- A patient who survives early sepsis but remains dependent on intensive care occasionally demonstrates evidence of a suppressed immune system
  - May have ongoing infection foci despite antimicrobial therapy or
  - May experience reactivation of latent virus

- Multiple investigations have been documented reduce responsiveness of blood leucocytes to pathogens in patients with sepsis
- Enhanced apoptotic cell death especially B cell death, CD4 + T cells, and follicular dendritic cells
- In a cohort of > 1000 ICU admission for sepsis, secondary infections develop in 14% of patients, associated with genomic response at time of infection suggesting
  - Immune suppression is responsible for development of secondary infection
  - Impairment of glycolysis
  - Impairment of cellular gluconeogenesis
- M/c secondary infection
  - Catheter-related blood stream infections
  - Ventilator-associated pneumonia
  - Abdominal infections
- Dynamic nature of the immune response & unclear understanding of whether the dysfunctional immune system is driving organ dysfunction or whether the immune system is just another dysfunctional organ, remains challenging