Urinary tract infection

Commensal	Non-pathogenic colonising organism in healthy host
Pathogen	Organism with an ability to cause disease
Virulence	Degree of pathogenicity
Bacteriuria	Presence of bacteria in urine
UTI	Bacterial invasion of the urothelium resulting in inflammatory response
Opportunistic inf.	UTI caused by non-pathogens due to weakened host defences
Isolated inf.	First infection or separated from last infection by 6 months
Unresolved inf.	Denoted by failed resolution of UTI on culture despite ABx. Due to: Initial bacterial resistance Acquired bacterial resistance Multiple organisms – selective overgrowth of resistant strain Renal impairment – reduced urinary concentration Staghorn calculus Poor compliance
Recurrent inf.	UTI after confirmed resolution on culture Defined as 2 infections in 6 months or 3 in a year Divided into re-infection and persistence Reinfection - from outside UT (usually ascending) accounts for 95% all recurrent UTIs in females – typically different organisms, but not always. Persistence - from within UT more common in males and highlighted by rapid infection with same organism
Complicated inf.	UTI a/w higher likelihood of sepsis, tissue necrosis, organ dysfunction and death. Factors a/w complicated UTI: Functional/structural UT abnormality* Male sex Elderly Pregnant History of childhood UTI Febrile UTI Likely obstruction History of stone disease DM, immunosuppression, renal impairment Renal tract instrumentation Recent antibiotic therapy Duration of therapy longer than 7 days * Catheter in situ PVR > 100ml Neurogenic bladder Obstuctive uropathy VUR Urinary diversion

Pathogenesis

Clinical significance of UTI dependent on type of organism, bacterial virulence and host defence factors

A. Types of organism

- Community
  - E. Coli (85%)
  - Other enterobacteria (5-10%)
    - Klebsiella
    - Proteus*
    - Enterococcus faecalis
    - Pseudomonas
    - Providentia*
    - Citrobacter
    - Serratia
  - Staph. Saprophyticus (10-30% of young women)
  - * more common in men
- Hospital
  - E. Coli (50%)
  - Pseudomonas
  - Enterococcus
  - Citrobacter

B. Bacterial virulence factors

- Fimbrial adhesins
  - Type 1 pili
    - Commonest type
    - Mannose-sensitive haemagglutinin (addition of mannose can prevent/reverse haemagglutination)
    - Bind to uroplakins 1a and 1b
  - Type p pili
    - Less common
    - Type II found in ~80% pyelonephritis
    - Type III found in cystitis
    - (Type 1 in animals only)
    - mannose-insensitive haemagglutinin
    - binds to ‘p’ blood group antigens
- Non-fimbrial adhesins
  - ‘Glycocalyx’ (e.g. Dr adhesins on E Coli)
- Toxin production
  - Endotoxin produced from GNB [lipopolysaccharide secreted from outer membrane of bacterial cell wall: lipid component toxic; polysaccharide component immunogenic. Heat stable to boiling point]
- Haemolysins
- Enzyme secretion (protease, urease etc.)
- Swarming factor (P.mirabilis)
- Avoidance of phagocytosis
  - Intracellular growth
- Biofilm formation

C. Host defence
- Urinary flow
- Urinary acidity
- Urinary osmolality (high or very low)
- Tamm-Horsfall protein (uromodulin)
  - From AloH and DCT
  - Binds type 1/type S fimbriated bacteria
  - Activates phagocytosis
- Mucosal defense
  - lgA
  - Lysozyme
  - Lactoferrin
  - Bladder mucin
- Commensal bacteria
  - Lactobacillus acidophilus
  - Oestrogens – glycogen – metabolised by l.a. to lactic acid – pH drop inhibitory to pathogens
- General integrity of immune system
  - Innate
  - Acquired (Humoral and cell-mediated)
- Genetic susceptibility
  - HLA-A3 antigen a/w 4x risk of recurrent UTI (?why)
  - Non-secretor phenotype for Lewis blood group antigens

Diagnosis

<u>Urine dipstick testing</u>

Urinary nitrite and leukocyte esterase surrogates for bacteria and WBC respectively. Reference bacteruria > 10^5 orgs/ml

Early morning urine has increased sensitivity

Urinary Nitrite
- Dietary nitrates - urinary nitrates - nitrate reducing bacteria (enterobacteria) -urinary nitrites - react with amine-impregnated dipstix reagent - pink diazonium compound
- Sensitivity = 35-85%, Specificity = 92-100%
- False positives:
  - Contamination
- False negatives:
  - Non–enteric bacteria
  - Dilute urine/ frequent voiding
  - Vitamin C
  - High osmolality/ urinary H+
  - Urobilinogen

Urinary Leukocyte Esterase
- LE from neutrophil/ basophil granules reacts with reagent strip - indoxyl moeity produces colour changes by oxidation of diazonium salt
- Sensitivity = 72-97%, Specificity = 64-82%
- False positives
  - Specimen contamination
- False negatives

Old specimen (leucocyte lysis)
High osmolality/specific gravity
Vitamin C
Urobilinogen

When Nitrite and LE combined; Sensitivity = 70-100%, Specificity = 60-98%

Urine microscopy and culture

Clean catch MSU specimen
First voided morning specimen – examine within one hour
Centrifuged samples 5 mins at 3000rpm – resuspend
Examine at low power (100x) and high power (400x) 1 hpf = 1/20,000 ml
Routine examination for:

RBCs	
RBC casts	Glomerulonephritis
WBCs	> 10wbc/hpf = significant inflammation
WBC casts	Pyelonephritis
Bacteria	5/hpf = 100,000/ml*

* Significance controversial. Original studies by Kass (1950s). Found that only 15% women with <100,000 bacteria/ml had Hx UTI and usually commensals. >50% with counts over 100,000/ml had Hx UTI and organisms typically pathogenic. However well known that a subpopulation of women (up to 30%) can have symptomatic UTI with counts 10^3-10^5 orgs/ml (Finding of pyuria can be very helpful)

EAU significance criteria

- ≥ 10^3 cfu/ml in women with acute uncomplicated cystitis
- ≥ 10^4 cfu/ml in women with acute uncomplicated pyelonephritis
- ≥ 10^5 cfu/ml in women with complicated UTI
- ≥ 10^5 cfu/ml in asymptomatic bacteriuria in pregnancy
- ≥ 10^4 cfu/ml in men with complicated UTI

Asymptomatic bacteruria

Seldom associated with adverse outcomes except in following groups:

- Children
- Pregnant females
- Before urological procedures

Screening or treatment not of proven benefit in following groups:

- Pre-menopausal women
- Diabetic women
- Elderly patients
- Spinal cord injury
- Catheterised patients

Urosepsis

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response
Bacteraemia	Bacteria present in blood as confirmed by culture. May be transient
Systemic inflammatory response syndrome (SIRS)	Response to a wide variety of clinical insults, which can be infectious, as in sepsis but may be non-infectious in aetiology (e.g. burns, pancreatitis). This systemic response is manifested by two or more of the following conditions: Temperature > 38°C or < 36°C Heart rate > 90 beats min Respiratory rate > 20 breaths/min or $PaCO_2$ < 32mmHg (< 4.3kPa) WBC > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or ≥ 10% immature (band) forms
Sepsis	Activation of the inflammatory process due to infection
Hypotension	A systolic blood pressure of < 90mmHg or a reduction of > 40mmHg from baseline in the absence of other causes of hypotension
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute alteration of mental status
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured
Refractory septic shock	Septic shock that last for more than 1 hour and does not respond to fluid administration or pharmacological intervention

SIRS – remember acronym THReW

Severe sepsis and organ dysfunction:

Severe sepsis = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate greater than the upper limits of normal laboratory results
Urine output <0.5 mL/kg hr for >2 hrs, despite adequate fluid resuscitation
ALI with Pao_2/Fio_2 <250 in the absence of pneumonia as infection source
ALI with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dL (176.8 µmol/L)
Bilirubin >2 mg/dL (34.2 µmol/L)
Platelet count <100,000
Coagulopathy (INR >1.5)

ALI, acute lung injury; INR, international normalized ratio.

Severe sepsis and septic shock a/w mortality 20-40% (recently ~18%)
Urogenital tract a source in ~5%
Increased incidence and mortality in elderly, diabetics and immuno-compromised. TNF-a, IL-1, IL-6 and IL-8 commonly implicated cytokines
C-reactive peptide and particularly procalcitonin believed to be specific for bacterial vs. viral/other infections

Management

'Simultaneous investigation, resuscitation and treatment'
See **Surviving Sepsis Campaign** recommendations below
Establish IV access – 2 large bore cannulae antecubital fossae

Send blood for FBC, U+E, LFTs, CRP, serum lactate and clotting
Arterial blood gases
Blood cultures
    2 peripheral cultures + and line > 48 hours old
Urine culture and catheterisation
Fluid resuscitation
    20ml/kg crystalloid or equivalent
    1000ml or 330ml colloid over 30mins
    Slow fluids and refer for inotropes/CVP monitoring if refractory hypotension after 20ml/kg fluid challenge (~1500ml in 75kg man)
High-flow oxygen therapy
Broad spectrum antibiotics
Consider further adjunctive measures
    Relief of urinary obstruction
    Debridement of necrotic tissue
Early ITU opinion
    Central venous and arterial pressure and cardiac index measurement
    Inotrope administration (if MAP <= 65mmHg)
        Noradrenaline first choice peripheral support
        Dopamine first choice central support
        Dobutamine for cardiac dysfunction
    Steroid administration
        Only for refractory hypotension
        Hydrocortisone preferred (<= 300mg/day)
    Activated Protein C (dotrecogin alpha; bleeding risk)
        APACHE score >25
        Multiple organ failure

Table 3. Initial resuscitation and infection issues

Strength of recommendation and quality of evidence have been assessed using the GRADE criteria, presented in parentheses after each guideline
- ● Indicates a strong recommendation, or "we recommend"
- ○ Indicates a weak recommendation, or "we suggest"

Initial resuscitation (first 6 hrs)
- ● Begin resuscitation immediately in patients with hypotension or elevated serum lactate >4 mmol/L; do not delay pending ICU admission (1C)
- ● Resuscitation goals (1C)
  CVP 8–12 mm Hg[a]
  Mean arterial pressure ≥ 65 mm Hg
  Urine output ≥0.5 $mL \cdot kg^{-1} \cdot hr^{-1}$
  Central venous (superior vena cava) oxygen saturation ≥70% or mixed venous ≥65%
- ○ If venous oxygen saturation target is not achieved (2C)
  Consider further fluid
  Transfuse packed red blood cells if required to hematocrit of ≥30% and/or
  Start dobutamine infusion, maximum 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$

Diagnosis
- ● Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration (1C)
  Obtain two or more BCs
  One or more BCs should be percutaneous
  One BC from each vascular access device in place >48 hrs
  Culture other sites as clinically indicated
- ● Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so (1C)

Antibiotic therapy
- ● Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B)
- ● Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B)
- ● Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1C)
- ○ Consider combination therapy in *Pseudomonas* infections (2D)
- ○ Consider combination empiric therapy in neutropenic patients (2D)
- ○ Combination therapy ≤3–5 days and de-escalation following susceptibilities (2D)
- ● Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrainable foci of infection or immunologic deficiencies (1D)
- ● Stop antimicrobial therapy if cause is found to be noninfectious (1D)

Source identification and control
- ● A specific anatomic site of infection should be established as rapidly as possible (1C) and within first 6 hrs of presentation (1D)
- ● Formally evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage, tissue debridement) (1C)
- ● Implement source control measures as soon as possible following successful initial resuscitation (1C) (exception: infected pancreatic necrosis, where surgical intervention is best delayed) (2B)
- ● Choose source control measure with maximum efficacy and minimal physiologic upset (1D)
- ● Remove intravascular access devices if potentially infected (1C)

Table 4. Hemodynamic support and adjunctive therapy

Strength of recommendation and quality of evidence have been assessed using the GRADE criteria, presented in parentheses after each guideline.

- ● Indicates a strong recommendation, or "we recommend"
- ○ Indicates a weak recommendation, or "we suggest"

Fluid therapy

- ● Fluid-resuscitate using crystalloids or colloids (1B)
- ● Target a CVP of ≥8 mm Hg (≥12 mm Hg if mechanically ventilated) (1C)
- ● Use a fluid challenge technique while associated with a hemodynamic improvement (1D)
- ● Give fluid challenges of 1000 mL of crystalloids or 300–500 mL of colloids over 30 mins. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion (1D)
- ● Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement (1D)

Vasopressors

- ● Maintain MAP ≥65 mm Hg (1C)
- ● Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- ○ Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
- ○ Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- ● Do not use low-dose dopamine for renal protection (1A)
- ● In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

Inotropic therapy

- ● Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- ● Do not increase cardiac index to predetermined supranormal levels (1B)

Steroids

- ○ Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C)
- ○ ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B)
- ○ Hydrocortisone is preferred to dexamethasone (2B)
- ○ Fludrocortisone (50 μg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone if optional if hydrocortisone is used (2C)
- ○ Steroid therapy may be weaned once vasopressors are no longer required (2D)
- ● Hydrocortisone dose should be ≤300 mg/day (1A)
- ● Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it (1D)

Recombinant human activated protein C

- ○ Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥25 or multiple organ failure) if there are no contraindications (2B, 2C for postoperative patients).
- ● Adult patients with severe sepsis and low risk of death (typically, APACHE II <20 or one organ failure) should not receive rhAPC (1A)

Appendix

Human infective organisms (in descending size order):

- Arthropods
- Helminths
  - Nematodes, cestodes & trematodes (including schistosomiasis)
- Eukaryotes
  - Protazoa
  - Fungi
- Prokaryotes
  - Bacteria
  - Rickettsiae
  - Chlamydia
  - Mycoplasma
  - Spirochaetes
- Viruses
  - RNA (HIV, HAV, HCV)
  - DNA (Herpes, HPV, HBV)

EUKARYOTIC GENERA

PROTOZOA

Sporozoa: *Plasmodium, Isospora, Toxoplasma, Cryptosporidium*

Flagellates: *Giardia, Trichomonas, Trypanosoma, Leishmania*

Amoebae: *Entamoeba, Naegleria, Acanthamoeba*

Others: *Babesia, Balantidium, Pneumocystis*[a]

FUNGI

Mould-like: *Epidermophyton, Trichophyton, Microsporum, Aspergillus*

Yeast-like: *Candida*

Dimorphic: *Histoplasma, Blastomyces, Coccidioides*

True yeast: *Cryptococcus*

PROKARYOTIC GENERA

FILAMENTOUS BACTERIA

Actinomyces, Nocardia, Streptomyces, Mycobacterium

'TRUE BACTERIA'

Gram-positive bacilli: Aerobes — *Corynebacterium, Listeria, Bacillus*

Anaerobes — *Clostridium, Lactobacillus, Eubacterium*

Gram-positive cocci: *Staphylococcus, Streptococcus, Enterococcus*

Gram-negative cocci: Aerobes — *Neisseria*

Anaerobes — *Veillonella*

Gram-negative bacilli: Aerobes

Enterobacteria — *Escherichia, Klebsiella, Proteus, Salmonella, Shigella*

Pseudomonads — *Pseudomonas, Alcaligenes*

Parvobacteria — *Haemophilus, Bordetella, Brucella, Pasteurella, Yersinia*

Anaerobes — *Bacteroides, Fusobacterium*

Gram-negative vibrios: *Vibrio, Spirillum, Campylobacter, Helicobacter*

SPIROCHAETES

Borrelia, Treponema, Leptospira

MYCOPLASMAS

Mycoplasma, Ureaplasma

RICKETTSIAE AND CHLAMYDIAE

Rickettsia, Coxiella, Rochalimaea, Chlamydia

Parasites Arthropods, helminths and protozoa
Eukaryotes > 1 chromosome, double membrane intracellular structures
Prokaryotes 1 chromosome, no nuclear membrane, no mitochondria

	Gram +ve	Gram –ve
Cocci	Staphylococci Coagulase +ve S. aureus Coagulase –ve S. epidermidis Streptococci β-haemolytic Gp A S. pyogenes Gp B,C,D Neonatal infections α-haemolytic S. viridans, S. pneumoniae non-haemolytic S. bovis E. faecalis	Neisseria meningitidis Neisseria gonorrhoea
Rods	**Bacilli** Aerobic Bacillus anthracis Coynebacterium diphtheriae Listeria monocytogenes Nocardia Anaerobic Clostridia botulinum perfringens tetani difficile Actinomyces israelii	Enterobacteriaceae E. Coli Proteus mirabilis Klebsiella Salmonella Shigella eneterobacter Serratia Yersinia Haemophilus Influenzae Brucella Pseudomonas Legionella Helicobacter Pylori Bacteroides (anaerobic)

Beta haemolysis = clear zone of haemolysis on blood agar due to haemolysins O and S
Alpha haemolysis = partial clearing with green discoloration not due to haemolysins

<u>Gram staining</u>
Gram-positive bacteria have a thick mesh-like cell wall made of peptidoglycan (50-90% of cell wall), which stains purple while gram-negative bacteria have a thinner layer (10% of cell wall), which stains pink.
4 steps:

Crystal violet	both types stain purple
Iodine	CV trapped in cells

Ethanol wash	Degrades GN cell membrane and leaches CV from GNB. No effect on GPB
Safranin	Counterstain allows identification of translucent GNB

Multi-resistant organisms

ESBL

- Extended spectrum beta lactamase
- Tend to be carried in bowel – impossible to eradicate with antibiotics and promotes overgrowth and further resistance
- Resistant to third-generation cephalosporins and monobactams
- Retained sensitivity to cefomycins (e.g. cefotetan) carbapenems (e.g. imipenem)
- Also sensitive to beta-lactamase inhibitors like clavulanic acid but co-amoxyclav does not work clinically – too much beta lactamase produced to allow amoxycillin to be efficacious
- Plasmid mediated – explains cross-resistance among organisms and therefore reason for isolation

MRSA

- Methicillin-resistant staphylococcus aureus
- Resistant to all penicillins, including those with beta lactamase (due to the production of penicillin-binding protein PBP-2
- Vancomycin and teicoplanin always sensitive; fusidic acid, rifampicin usually, trimethoprim and doxycycline occasionally; cipro never
- MRSA prostatitis may be troublesome
  - IV vancomycin/teicoplanin
  - PO doxycycline, trimethoprim, rifampicin or if desperate linezolid
- Oral vancomycin does not get absorbed – only for CDT

VRE

- Low grade infections – generally not septic
- Spectrum narrow – IV or PO linezolid

Surviving sepsis resuscitation and management bundles

The goal is to perform all indicated tasks 100% of the time within the first 6 hours of identification of severe sepsis.

The tasks are:

1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotic, *within 3 hrs of ED admission and within 1 hour of non-ED admission*
4. In the event of hypotension and/or a serum lactate > 4 mmol/L
   a. Deliver an initial minimum of 20 ml/kg of crystalloid or an equivalent
   b. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L
   a. Achieve a central venous pressure (CVP) of ≥ 8 mm Hg
   b. Achieve a central venous oxygen saturation (ScvO2) ≥ 70 % or mixed venous oxygen saturation (SvO2) ≥ 65 %

Efforts to accomplish these goals should begin immediately, but these items may be completed within 24 hours of presentation for patients with severe sepsis or septic shock.

1. Administer low-dose steroids for septic shock in accordance with a standardized ICU policy. *If not administered*, document why the patient did not qualify for low-dose steroids based upon the standardized protocol.
2. Administer drotrecogin alfa (activated) in accordance with a standardized ICU policy. *If not administered*, document why the patient did not qualify for drotrecogin alfa (activated).
3. Maintain glucose control $\geq$ 70, but < 150 mg/dl
4. Maintain a median inspiratory plateau pressure (IPP)* < 30 cm H2O for mechanically ventilated patients