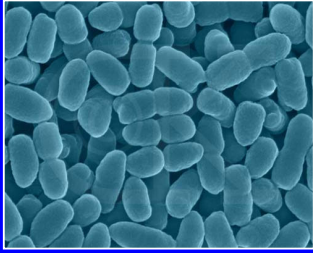


UTI = urinary tract infections



Prof Peter O'Donoghue

1

Learning Objectives

Lecture: Overview of bacterial structure and function

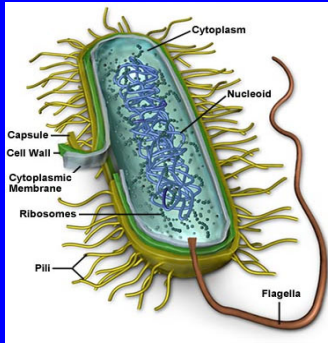
- review prokaryotic (bacterial) structure
- identify major virulence factors
- appreciate growth potential and mutability

Lecture: Case study – UTI (urinary tract infections)

- differentiate urethritis, cystitis, pyelonephritis
- compare community and hospital acquired UTIs
- examine treatment options

2

Typical bacterium (prokaryote)



Important structures:

- wall
- cytoplasmic membrane
- peptidoglycan cell wall
- capsule
- flagella
- pili/fimbriae
- cytoplasm
- organelles
- no endomembranes
- nucleoid (DNA)

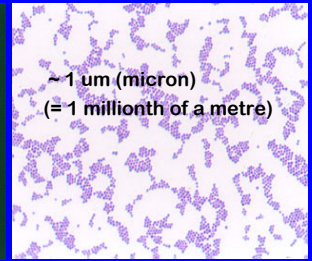
3

Distinguishing features of bacteria

- Morphology (size, shape, staining)



agar plates



~ 1 μm (micron)
(= 1 millionth of a metre)

smears

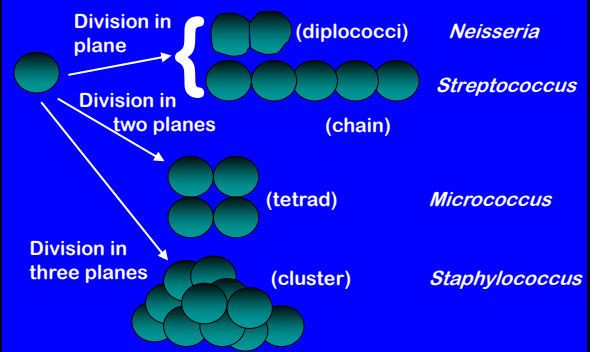
4

Bacterial morphology

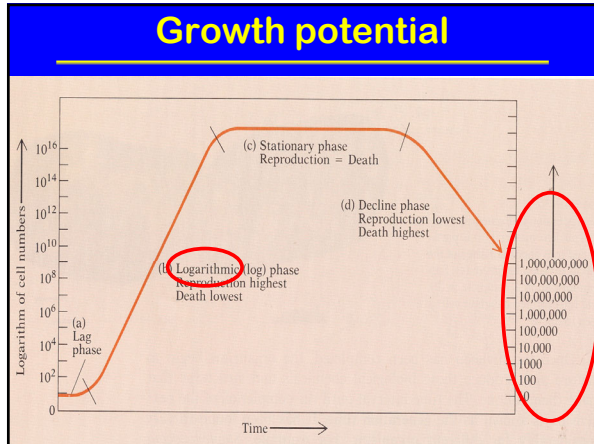
	Straight rod (bacillus)	eg. <i>Escherichia</i>
	Club-shaped rod	eg. <i>Corynebacterium</i>
	Branching rod	eg. <i>Actinomyces</i>
	Comma forms	eg. <i>Vibrio</i>
	Spore-forming rod	eg. <i>Clostridia</i>
	Spiral forms	eg. <i>Spirochaeta</i>
	Coccus	eg. <i>Staphylococcus</i>

5

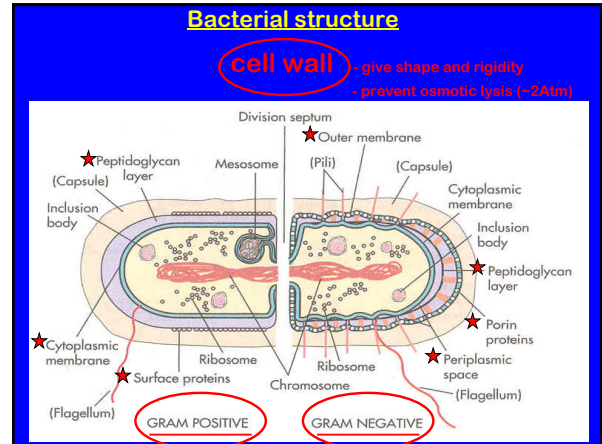
Bacterial cell division



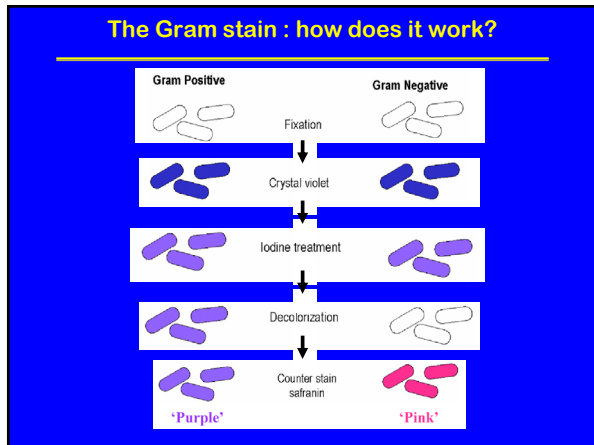
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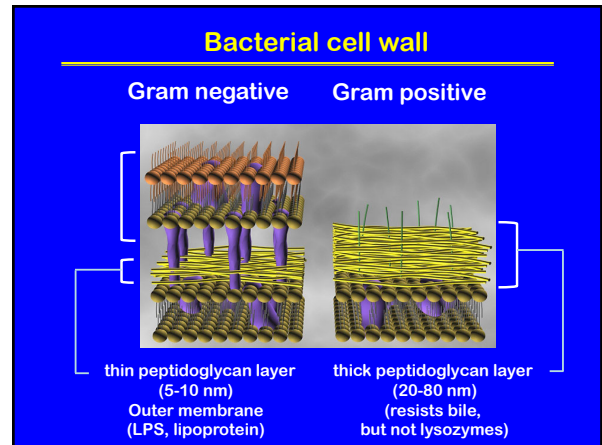
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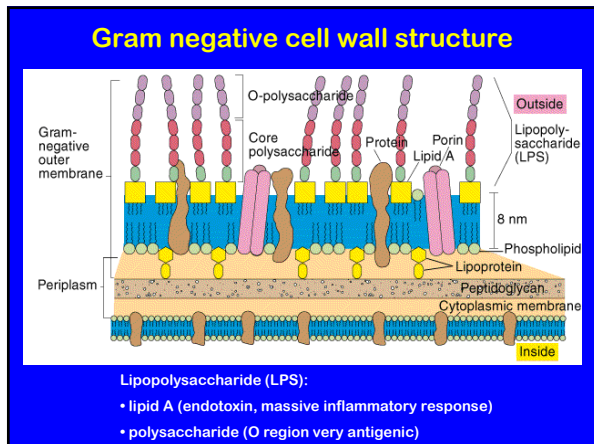
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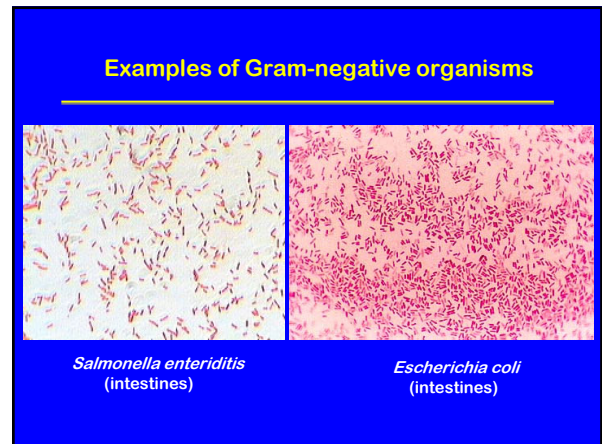
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Gram positive cell wall structure

Antigenic and involved in pathogenicity: peptidoglycan, surface proteins (adhesins, invasins) and teichoic acids recognized by defense cells of the body

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Examples of Gram-positive organisms

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Cell wall characteristics of G+ and G- bacteria

Characteristic	Gram negative	Gram positive
Outer membrane	Yes	No
Peptidoglycan layer	Thinner	Thicker
LPS	Yes	No
Endotoxin	Yes	No
Teichoic acid	Absent	Often present
Capsule	Sometimes present	Sometimes present
Lysozyme	Resistant	Sensitive
Penicillin sensitivity	More resistant	More susceptible

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Why should we examine Gram-stained smears?

Presumptive diagnosis:

- bacterial meningitis
- bacterial pneumonia
- bacteriuria
- gonorrhoea
- acute pyogenic infections (e.g. *Staphylococcus aureus* infections)

Suitable specimens: sputum, urine, cerebrospinal fluid, or material from wounds or abscesses

Unsuitable specimens - throat and stool

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Clinical examples

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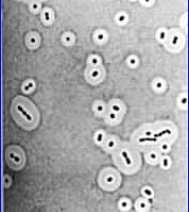
Bacterial structure

Capsule - protection

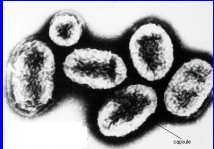
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Capsules

- help bacteria avoid phagocytosis
- protects cell drying, traps nutrients, etc.
- biofilms



Streptococcus mutans




Brucella


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Examples of pathogens where capsules play a crucial role in pathogenicity

Streptococcus mutans
(tooth decay)
Capsule is primary constituent of dental plaque



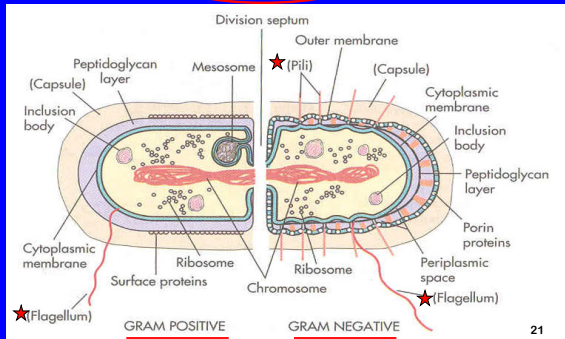
Streptococcus pneumoniae
(major cause of pneumonia, most common cause of death from infection in developed world)
Capsule is major virulence factor (avoid phagocytosis)
More than 90 serotypes exist



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Bacterial structure

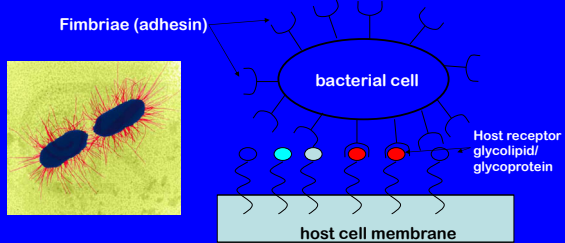
Appendages - attachment, motion



GRAM POSITIVE GRAM NEGATIVE

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Fimbriae (Pili)



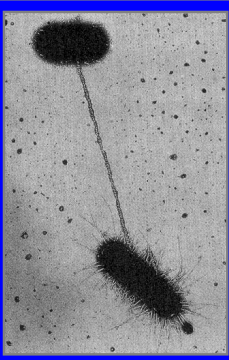
bacterial cell host cell membrane

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Bacterial conjugation

Two cells make contact:

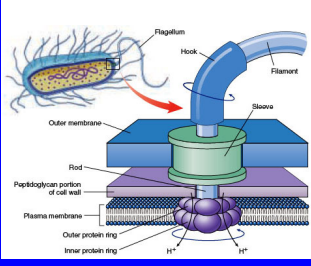
F⁺ gives F plasmid to F⁻ cell via pilus

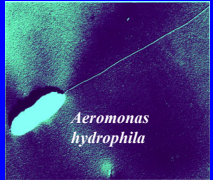


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Bacterial flagella

organelles of locomotion
rotary axis (unlike eukaryotes)



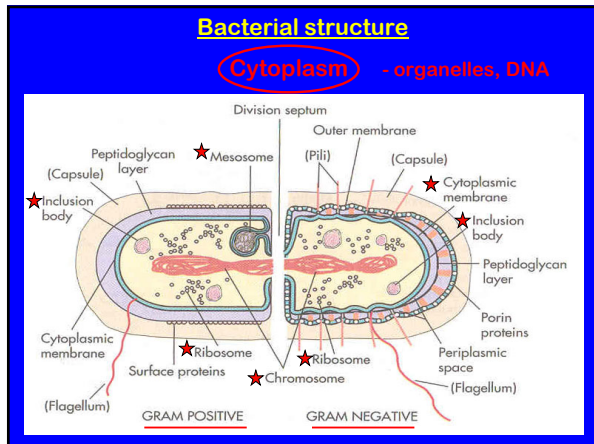


Aeromonas hydrophila

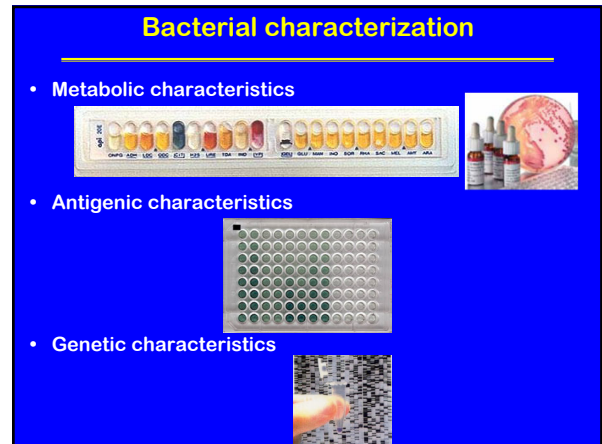


Salmonella typhimurium

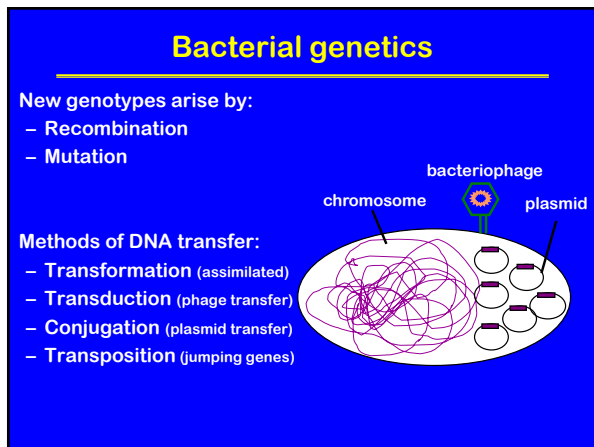
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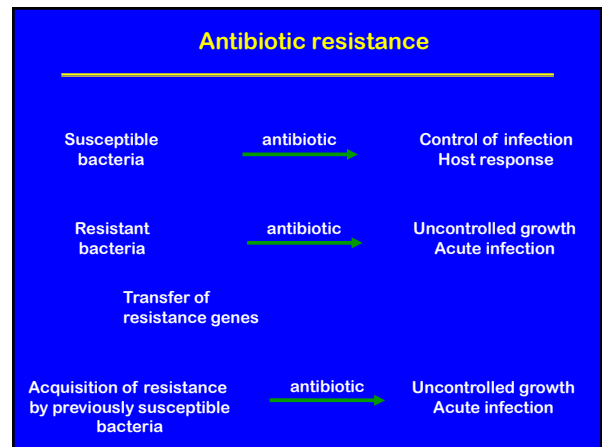
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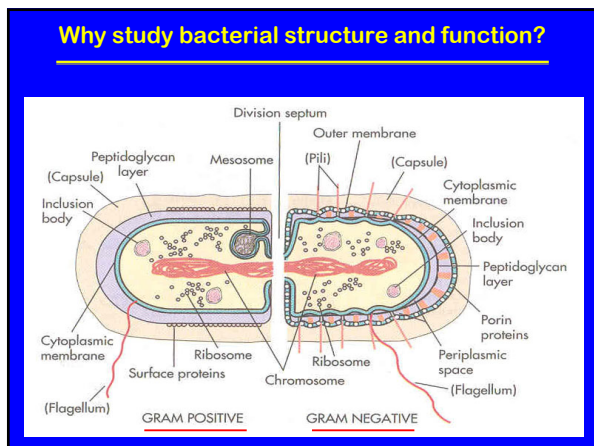
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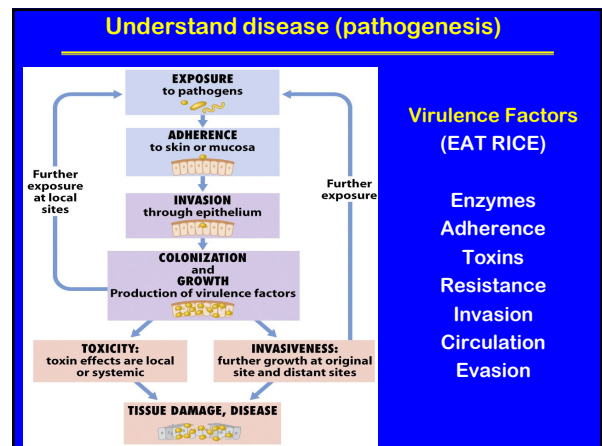
27



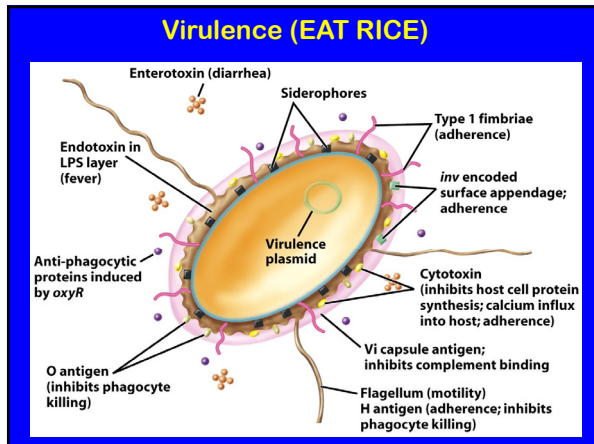
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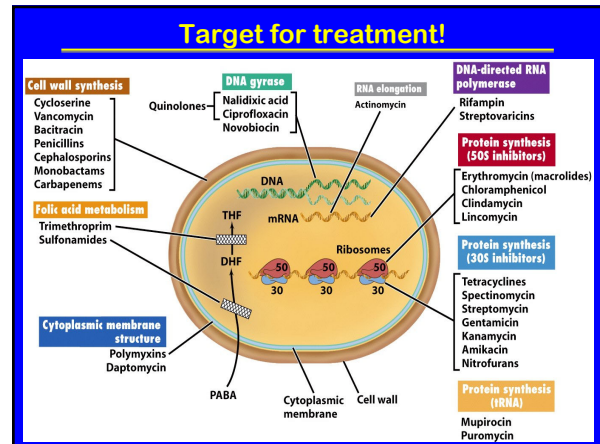
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UTI

- take a comfort break first!

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Urinary tract

- eliminates nitrogenous wastes from body
- regulates water, electrolyte and acid-base balance
- chemically hostile place!

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Disease: urinary tract infection (UTI)

- causes inflammation of urethra/bladder/kidney
- very common, esp. women and elderly
- 50% of all women will experience a UTI
- USA: UTI account for:
 - 9.6 million doctor visits per year
 - A\$1.6 billion in expenses per year
- multi-drug resistant organisms becoming more common

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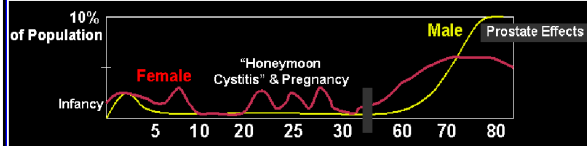
Infections

- urethritis (infection of urethra)
- cystitis (infection of urinary bladder)
- pyelonephritis (infection of kidney)
- most infections ascending & luminal
- sometimes systemic (from blood) & septicaemic

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Age and gender distribution of UTI

Most occur in females. Age is an important factor.



- Community acquired UTIs almost always ascending infections
- Reservoirs:
 - most uropathogenic strains harboured in colon
 - gain access to urethral opening (toilet habits/sexual activity)
 - vaginal tract easily colonised, acts as additional reservoir

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Recurrent UTI

UTI often recur, due to:

Reinfection

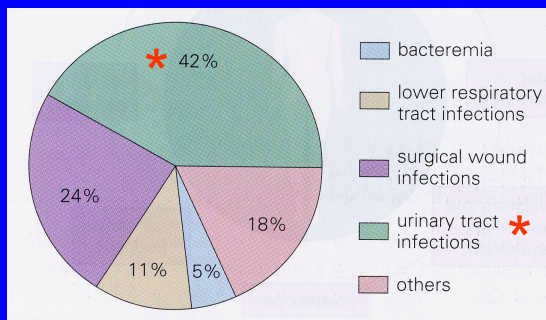
- ~ 80% re-infection rate
- new/same infecting organism
- can occur anytime (does not suggest anatomic abnormality)
- usually originates from faecal matter in rectal region

Relapse

- reappearance of original infection post-treatment
- persistence of infecting organism
- often occurs in pyelonephritis or associated with obstructions (e.g. kidney stones) and structural abnormalities

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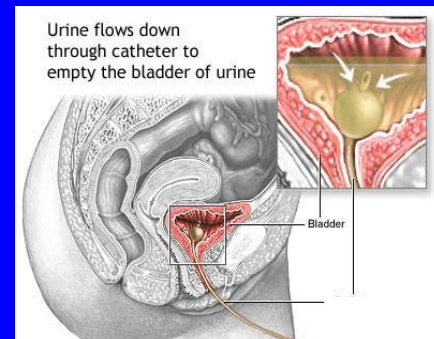
Nosocomial infections



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Hospital acquired UTI

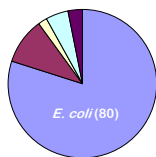
Catheter-associated infections



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Causative agents

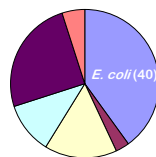
Community acquired UTI



- | | |
|---|---|
| ■ <i>Escherichia coli</i> | ■ <i>Proteus mirabilis</i> |
| ■ Coagulase -ve Staph (<i>Staphylococcus saprophyticus</i>) | ■ Other G-ves (<i>Klebsiella species</i> , <i>Enterobacter species</i> , <i>Serratia species</i> , <i>Pseudomonas aeruginosa</i>) |
| ■ Other G+ves (<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Enterococcus faecalis</i>) | ■ <i>Candida albicans</i> |

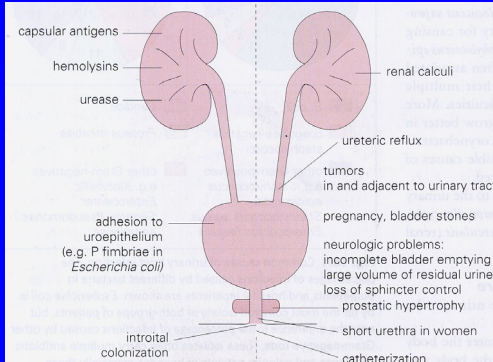
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Hospital acquired UTI



Pathogenesis

- bacterial virulence
- host susceptibility



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Clinical features

Lower UTI (bladder)

- asymptomatic
- dysuria (pain), urgency/frequency
- cloudy urine (pyuria/haematuria/bacteriuria)
- systemic signs (fever/aches (lower back))

Upper UTI (ureter ± kidney)

- all of above (plus nausea & vomiting)
- hypertension (loss of renal function)
- obstruction (abscess/stone formation)
- septicaemia (systemic infection)

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Please provide a urine sample!

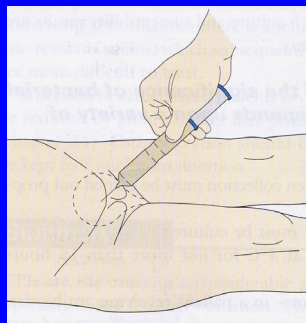
- What! From over here!
- I can't stop!
- Got a bigger bottle!
- I just went!
- Don't look!
- Ouch!
- Whoops!
- Got some tissues!
- That doesn't look right!



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Diagnostic samples

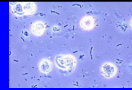
- collect urine
- minimize potential contamination by commensal organisms (peri-urethral or faecal)
- urine
 - mid-stream
 - early morning
 - catheter
 - suprapubic aspirate



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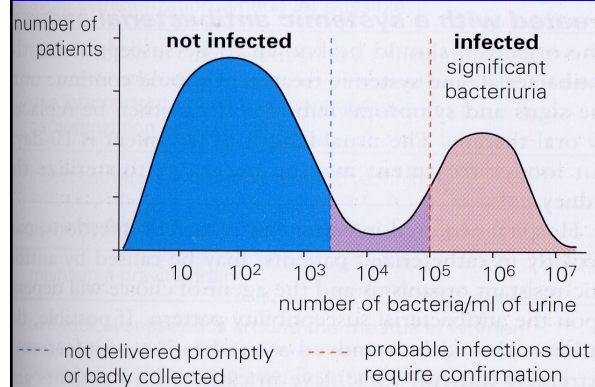
Diagnostic examination

- Macroscopic: cloudiness an indicator of infection
- Microscopic: WBC, RBC, epithelial cells, crystals, bacteria. presence of WBC > 10/mm³ (pyuria) evidence of infection WHEN accompanied with bacteriuria
- Culture: BA/Mac/CLED media; 18h/37°C/air >10⁵ CFU/mL of a SINGLE organism differentiates infection from contamination (<10⁵ CFU/mL) Sensitivity testing: antibiotic resistance.
- Biochemistry: Dipstick: glucose undetectable. nitrates leucocytes (WBC).
- imaging X-ray, ultrasound, CT



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Quantitation (>10⁵)



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Treatment

- uncomplicated UTI (cystitis)
 - oral antibiotic (1-3 day course)
 - differential diagnosis & follow-up
 - drink large volumes of water
- complicated UTI (pyelonephritis)
 - systemic antibiotic (10 day course)
 - differential diagnosis & follow-up
 - drink large volumes of water

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Antibiotics (UTI)

- inhibit cell wall synthesis
 - β-lactams (penicillins, cephalosporins)
 - glycopeptides
- inhibit protein synthesis
 - aminoglycosides
 - tetracyclines
 - chloramphenicol
 - macrolides
 - lincosamides
 - fusidic acid
- inhibit nucleic acid synthesis
 - sulphonamides
 - trimethoprim
 - quinolones
 - rifampicin
- other action
 - nitroimidazoles (toxic radicals)
 - polymyxins (membrane disruption)

ampicillin amoxicillin
augmentin
cephalexin
trimethoprim cotrimoxazole
nalidixic acid ciprofloxacin
+ nitrofurantoin urinary antiseptic

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Virulence (EAT RICE)

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Uropathogenic *Escherichia coli*

- UPEC cause >80% of all UTI
- Major virulence factors:
 - Adherence factors (Type 1 fimbriae, P fimbriae)
 - Aggregation factors
 - Toxins
 - Iron uptake systems
 - LPS (O Antigen)
 - Capsule

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Type 1 fimbriae mediate attachment to and invasion of uroepithelial cells

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Aggregation factors

- bacteria persist
- antigen 43 promotes bacterial clumping

- Ag43

+ Ag43

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Toxins

- Hemolysin
 - secreted protein lyses RBC (and others)
 - creates pores in eukaryotic cell membranes
 - stimulates cytokine production
- Cytotoxic necrotizing factor 1 (CNF-1)
 - kills epithelial cells
 - role in UTI remains to be determined

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Other virulence factors

- Iron acquisition systems
 - multiple systems
 - enterobactin, aerobactin, yersiniabactin
- LPS (O Antigen)
 - certain types associated with UTI strains (e.g. O1, O4, O6, O18)
 - may be linked to serum resistance
- Capsule
 - certain types associated with UTI strains (e.g. K1)
 - may be linked to serum resistance

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Vaccines

UPEC Type 1 fimbriae: FimH

- *In vitro*:
 - anti-FimH antibodies block bacterial adhesion
- *In vivo*:
 - immunization of mice reduces colonization by >99%
 - immunization of monkeys results in protection
- Future
 - human trials (in progress)
 - But, who should get the vaccine?
 - How effective will it be?
 - [most *E. coli* produce type 1 fimbriae. Normal flora?]

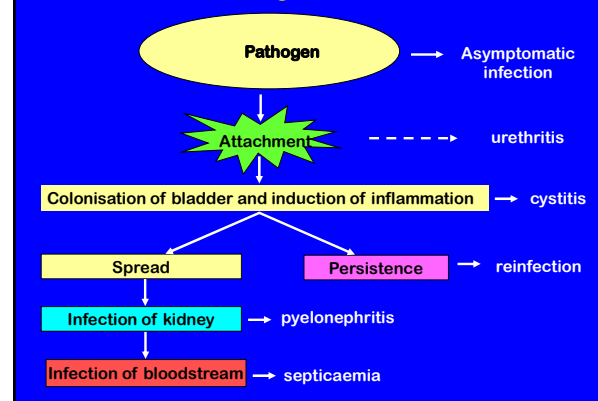
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Probiotics

- Asymptomatic bacteriuria
- Trials in Sweden with *E. coli* 83972
- Inhibits catheter colonisation by other pathogens
- Prevents UTI in patients with dysfunctional bladder
- Future
 - Why do some strains cause asymptomatic infections?
 - Virulence factors?
 - Host responses?
 - Who could/should receive such treatment?
 - Human trials?

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Summary of UTI



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gotta go!



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