INTRODUCTION TO INFECTIOUS DISEASES

Principles of Diagnosis and Treatment of Infectious Disease

Infectious diseases are the manifestations of a complex interaction between the infected host and the infecting organisms(s) – treatment with an antimicrobial introduces another interaction.

1. Patient – immunity, pharmacology
2. Organism – pathogenesis, resistance
3. Antimicrobial – inhibition/killing, toxicity

Important aspects of infectious disease pathogenesis are:

1. Exposure to organism – endogenous Vs environmental flora
2. Adherence to host tissues
3. Local tissue destruction e.g. Staphylococcus aureus
4. Local toxin effects e.g. Vibrio cholera
5. Systemic toxin effects e.g. Clostridium tetani, Corynebacterium diphtheria
6. Systemic effects of sepsis e.g. fever, catabolism

Stage in the management of infectious diseases:

1. Recognise clinical syndrome
2. Consider likely pathogens
3. Collect appropriate specimens
4. Provide general and supportive care
5. Institute antimicrobial therapy in an appropriate dose, route, duration
6. Monitor progress and alter treatment as necessary
7. Public health measures

<table>
<thead>
<tr>
<th>Component</th>
<th>Impairment or absence</th>
<th>Common organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact skin</td>
<td>Burns</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Ciliary transport of mucus</td>
<td>Cystic fibrosis</td>
<td>P. aeruginosa, S. aureus</td>
</tr>
<tr>
<td>Gastric acid</td>
<td>Achlorhydia</td>
<td>Salmonellae</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>A/hypogammaglobulinaemia</td>
<td>Streptococcus pneumoniaiae, S. aureus, rotavirus, Giardia</td>
</tr>
<tr>
<td>Complement</td>
<td>Complement deficiency (C7/8/9)</td>
<td>S. pneumoniae, Neisseria meningitidis, N. gonorrhoea</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Chemotherapy, chronic granulomatous disease</td>
<td>Varied</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>Steroids and immunosuppressive therapy</td>
<td>Opportunistic infections e.g. Candida albicans, Pneumocystis carinii</td>
</tr>
<tr>
<td></td>
<td>HIV infection</td>
<td>Herpes viruses, Cryptococcus neoformans, Toxoplasma gondii</td>
</tr>
<tr>
<td>Splenic filtration</td>
<td>Asplenia 2° to surgery, sickle cell disease</td>
<td>S. pneumoniae, salmonellae</td>
</tr>
</tbody>
</table>

Use of the Microbiology laboratory

Identification of an infecting organism depends on requesting the appropriate test and collection of appropriate specimens. Diagnosis occurs by microscopy, antigen or toxin detection, culture, nucleic acid detection and/or serology; in light of clinical findings. Diseases fall into three groups:

1. Identification very likely, therapy based on laboratory results – e.g. infective endocarditis, bacterial meningitis, urinary tract infection, malaria
2. Identification unlikely, therapy based on studies of other patients with the same condition – e.g. otitis media, sinusitis, pelvis inflammatory disease
3. Identification in a variable proportion of patients – e.g. pneumonia, pharyngitis

The microbiology lab also provides information about the antimicrobial agents most likely to be effective in the treatment of a variety of organisms. Note that results from susceptibility testing of recent isolates (published annually) can be used as a guide for empiric therapy before tests return.

1. Minimum inhibitory concentration – the lowest concentration at which growth is inhibited
2. Minimum bactericidal concentration – the lowest concentration at which the organism is killed
3. Serum bacteriostatic/bactericidal titres – reflect susceptibility and serum antibiotic levels
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<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Specimen</th>
<th>Diagnostic yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood stream</td>
<td>Venous blood into an aerobic and anaerobic bottle (10mL each), at least 2 sets at least 30 minutes apart</td>
<td>98% bacteraemia detected</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Mid-stream urine containing &lt;10 epithelial cells per high power field</td>
<td>80% probability of infection if &gt;10^8 bacteria/L</td>
</tr>
<tr>
<td>Lung</td>
<td>Purulent sputum containing &lt;10 epithelial cells and &gt;25 polymorphs per high power field</td>
<td>&lt;30% detection of pathogen on microscopy or culture</td>
</tr>
<tr>
<td>Large bowel</td>
<td>Liquid faeces</td>
<td>&lt;50% detection of pathogen on microscopy or culture</td>
</tr>
</tbody>
</table>

ANTIBIOTICS

- **Antimicrobial Therapy**

Antimicrobials need selective toxicity for microbes (e.g. bacteria, fungi, protozoae, viruses) and minimal toxicity for human cells (i.e. attack microbe-specific targets).

1. **Antibiotic modes of action:**
   a. Cell wall synthesis – beta lactams, vancomycin
   b. Protein synthesis – aminoglycosides, macrolides, tetracyclines
   c. Intermediate (folate) synthesis – sulphonamides, trimethoprim
   d. DNA or RNA synthesis – quinolones, nitroimidazoles, rifampicin

2. Antibiotics may also be classified as bactericidal (kill the organism – penicillins, quinolones, aminoglycosides) or bacteriostatic (stop growth – macrolides, tetracyclines, sulphonamides)
   a. Bactericidals are useful in difficult-to-treat infections (e.g. CSF, endocarditis), in an immunocompromised patient, or in rapidly progressive disease (e.g. faecal peritonitis)
   b. Bacteriostatics are useful when the organism is easy to treat

3. Note that bacteria differ in terms of sensitivity to antimicrobials – it is also important to know the concentrations of antimicrobials associated with different routes of administration
   a. Minimum inhibitory concentration required to kill bacteria varies with resistance
   b. Levels of antimicrobials achieved varies by compartment and route (IV > oral)

**Efficacy of antimicrobial treatment** depends on:

1. Host defences – by far the most important in most infections
2. Organism susceptibility to antimicrobial
3. Antimicrobial levels at site of infection
4. Duration of treatment
5. Development of resistance during treatment – rarely (occasionally in TB monotherapy)

**Resistance to antimicrobials** is an increasingly important problem and a significant cause of treatment failure. Primary treatment failure due to resistance is unlikely if sensitivities are performed, but incomplete treatment means that resistant organisms are selected for leading to resistance.

1. Some rare or serious diseases respond well to antibiotics, and this leads to a population belief that antibiotics are effective or appropriate for common conditions
2. Most antibiotics are prescribed to common conditions (otitis media, pharyngitis, bronchitis, gastroenteritis) with minimal effects except for a constant selection pressure for resistance.
3. Antibiotics should only been used when the benefit exceeds the risk for the patient and the community – the patient’s normal bacterial flora should be cherished and conserved

- **Resistance to Antimicrobial Agents**

**General principles:**

1. **Mechanisms of resistance:**
   a. Prevent entry of drug into cell
   b. Pump drug out of cell
   c. Enzymatic inactivation of drug
   d. Modification of drug target
   e. Production of excessive drug target

2. **Sources of antimicrobial resistance**
   a. Pre-existing genetic variant
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b. Mutation of gene:
   i. Within target organism
   ii. Within another organism (treated endogenous microflora/acquired microflora)

3. Spread of antimicrobial resistance
   a. Transfer of resistant microbes or genes for resistance to others
   b. Acquisition of genetic material for resistance trait (via transformation, conjugation, or transduction) or mutation of genes previously conferring sensitivity
   c. Exposure to environmental conditions favouring survival of resistant clones and death of sensitive clones (e.g. treatment with antibiotic)
   d. Expansion of resistant clones and death of sensitive clones

Notes:
1. Genes conferring resistance were present in many species prior to use of antibiotics
2. If resistance only requires mutations altering one or two amino acids of the target protein, then resistance is likely to develop relatively quickly after exposure to the antimicrobial
3. “Cassettes” with genes coding for resistance to many different classes of antimicrobials may be clustered in a transposon and exchanged between plasmids and bacterial chromosome
4. Microbial species have inherent variability – strains of the same species isolated from different patients (or even from a single culture) may vary greatly in susceptibility
5. Risk of a resistant mutant being present at the start of treatment is greatly increased when very large numbers of a microbial species are present (e.g. cavitating pulmonary TB)

Excessive antimicrobial use is associated with increasing resistance. Resistance bad!

- Penicillins and Cephalosporins

  β-lactam antimicrobials (penicillins and cephalosporins) block synthesis of peptidoglycan (bacterial cell wall) by irreversibly binding bacterial transpeptidase-type enzymes
  1. β-lactamase resistant penicillins are a major advance (e.g. resistant Staphylococcus aureus)
  2. 1st, 2nd and 3rd generation cephalosporins have increased activity against Gram-negative and decreased activity against Gram-positive (no effect against enterococci)

Bottom line – cheap, relatively safe drugs (toxicity rare, generally not life-threatening)

<table>
<thead>
<tr>
<th>Name</th>
<th>Route</th>
<th>Spectrum</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl penicillin</td>
<td>IV/IM</td>
<td>Narrow – G+c, G-c but not G-b or enterococci; many anaerobes but not B. fragilis</td>
<td>Original penicillin 24hr duration 3-4wk duration</td>
</tr>
<tr>
<td>Procaine penicillin</td>
<td>IM</td>
<td></td>
<td>Commonly used for staphylococci</td>
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<tr>
<td>Benzathine penicillin</td>
<td>IM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram +ve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>IV/IM/O</td>
<td>As for benzyl penicillin but also G-b and enterococci (though ↑ E. coli resistance)</td>
<td>Still useful for bacterial respiratory tract infection</td>
</tr>
<tr>
<td>Dicloxacillin</td>
<td>IV/IM/O</td>
<td>As above, plus resistant G-b and benzyl penicillin resistant staphylococci</td>
<td>Most widely used antibiotic in NZ</td>
</tr>
<tr>
<td>Gram –ve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>IV/IM/O</td>
<td>As above but broader G-b spectrum (P. aeruginosa)</td>
<td>Rarely used for neutropenic patients</td>
</tr>
<tr>
<td>Amoxicillin plus clavulanate</td>
<td>IV/IM/O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>IV</td>
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<td></td>
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</tbody>
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<thead>
<tr>
<th>Name</th>
<th>Route</th>
<th>Spectrum</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>IV/IM</td>
<td>Broad – G+c, G-b; many anaerobes but not B. fragilis</td>
<td>Orthopaedic prophylaxis if penicillin contraindicated</td>
</tr>
<tr>
<td>Cephradine</td>
<td>IV/IM/O</td>
<td></td>
<td></td>
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<tr>
<td>Cephalexin</td>
<td>O</td>
<td></td>
<td></td>
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<tr>
<td>2nd generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>IV/IM</td>
<td>Better activity for G-b; cefoxitin for B. fragilis</td>
<td>Intra-abdominal sepsis, bacterial chest disease</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>IV/IM/O</td>
<td></td>
<td></td>
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<tr>
<td>3rd generation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>IV/IM</td>
<td>Broader spectrum; ceftazidime for P. aeruginosa</td>
<td>Minimise use unless absolutely necessary</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>IV</td>
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**Aminoglycosides**

- 1944 streptomycin for tuberculosis
- 1949 neomycin for gut "sterilisation", eye and ear infections
- 1963 gentamicin
- 1968 tobramycin for severe gram-negative infections
- 1972 amikacin

Penicillins and cephalosporins – time dependent killing with no post-antibiotic effect

Gentamicin – concentration dependent killing with prolonged post-antibiotic effect

**Aminoglycosides** interfere with protein synthesis by binding irreversibly to the 30S and 50S subunits of the bacterial ribosome. Note that they are not active against anaerobes and are often used with another agent such as metronidazole

1. Widely used for treatment of serious infections suspected or proven to be due to gram-negative bacilli (including *Pseudomonas aeruginosa*).
2. Have a narrow therapeutic margin – levels required for antimicrobial action are very close to those responsible for toxic effects (major dose adjustments needed for renal failure)
   a. Otoxicity (destroys hair cells in perilymph) → permanent deafness, vertigo, ataxia
   b. Nephrotoxicity (accumulate in proximal renal tubular cells) → reversible impairment
   c. Risk factors – renal impairment, old age, shock, high trough levels, prolonged therapy
3. Must be given parenterally – e.g. for gentamicin in a patient with normal renal function:
   a. Normal daily dose 4mg/kg per 24 hours
   b. Aim to have trough levels <1.0mg/L
   c. Protein binding <30%, well distributed but low levels in CSF, bile, bronchial secretions
4. Indications:
   a. Intra-abdominal sepsis
   b. Other infections where gram-negative enteric bacilli are likely
   c. In combination with penicillin vs Viridans streptococci
   d. In combination with flucloxacillin vs *Staphylococcus aureus*

**Quinolone Antimicrobials**

- 1965 nalidixic acid
- 1985 norfloxacin, ciprofloxacin
- 2002 moxifloxacin

**Quinolones** inhibit the activity of DNA gyrase (a topo-isomerase) which cuts bacterial DNA, introduces a superhelical twist and then rejoins the DNA. Resistance develops rapidly with nalidixic acid, but slowly with the new quinolones except some organisms (MRSA, *Campylobacter*)

1. Activity:
   a. Good against enteric gram-negative bacilli, *Neisseria, Haemophilus influenzae*
   b. Poor against Streptococci, *Staphylococci*, anaerobes
2. Usually given orally, 80% absorbed
   a. Variable distribution – ciprofloxacin good, norfloxacin poor
   b. Variable liver metabolism with active metabolites, increases serum theophylline level
   c. Excreted in urine (dose reduction required in renal failure)
3. Indications:
   a. Widely used for treatment of urinary tract infections
   b. Increasing use for treatment of gonorrhoea
   c. Only effective oral anti-pseudomonal agents (especially ciprofloxacin) in CF patients
   d. Newer agents (moxifloxacin, gatifloxacin) for treatment of chest infections

Bottom line – good oral antibiotics but should be restricted (not generally done) in order to reduce development of resistance (e.g. ciprofloxacin at APH needs approval from infectious diseases)

**Sulphonamides and Trimethoprim**

**Sulphonamides** and trimethoprim inhibit the synthesis of folate by the bacterial cell. Examples include sulphamethoxazole + trimethoprim (1-2 tablets bd, though trimethoprim alone may also work alone at 200-400mg/day) and sulphapyridine plus salicylic acid (sulphasalazine)

1. Broad spectrum of activity:
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a. Bacteria – Staphylococci, Streptococci, *Haemophilus influenzae*, Enterobacteriaceae (not effective against *E. faecalis, P. aeruginosa*)
b. Protozoa – *Toxoplasma gondii*, *Plasmodium falciparum*, *Pneumocystis carinii*

2. Given orally, well absorbed from the GI tract
   a. Lipid soluble and well-distributed throughout the body
   b. Variable renal excretion
   c. Adverse effects – allergic rash, Stevens-Johnson syndrome (erythema multiforme with mucous ulceration of eye, mouth, urethra), leucopaenia, aplastic anaemia

3. Indications – urinary tract infections, otitis media, acute bronchitis

**Tetracyclines, Macrolides, Lincosamides and Chloramphenicol**

<table>
<thead>
<tr>
<th>Year</th>
<th>Compound</th>
</tr>
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<tbody>
<tr>
<td>1947</td>
<td>chloramphenicol</td>
</tr>
<tr>
<td>1948</td>
<td>tetracycline</td>
</tr>
<tr>
<td>1952</td>
<td>erythromycin</td>
</tr>
<tr>
<td>1962</td>
<td>lincomycin</td>
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</tbody>
</table>

Chloramphenicol, macrolides and lincosamides bind to the 50s subunit of the ribosome, while tetracyclines bind to the 30s subunit. They were the first “broad spectrum” antibiotics to be discovered, with only penicillin and streptomycin (both iv only) available prior.

1. Tetracyclines and chloramphenicol are active against Gram-positive and Gram-negative, aerobic and anaerobic bacteria, spirochaetes, mycoplasmas, rickettsiae and chlamydiae
   a. Tetracyclines have additional activity against some protozoa
2. Erythromycin and lincomycin were initially regarded as useful second line agents against Gram-positive agents (particularly staphylococci and streptococci) and were not regarded as “broad spectrum” as the common aerobic Gram-negative bacilli were resistant
   a. Erythromycin has been subsequently shown to be active against several fastidious Gram-negative bacilli (*Legionella pneumophila, Bordetella pertussis, Campylobacter jejuni*) as well as spirochaetes, *Mycoplasma pneumoniae*, chlamydia and ureaplasma
   b. Lincomycin has also been found to have excellent anti-anaerobic activity and its 7 chlor-derivative clindamycin is used primarily as an anti-anaerobic

Tetracyclines enter bacteria through an energy-dependent process and bind primarily to the 30s ribosomal subunit where they block the binding of tRNA to prevent amino acids from being linked together in a peptide chain.

1. Most popular agent is doxycycline – well absorbed (even with food), has a long half-life (can be given once daily), and can be used safely in usual doses in renal failure
2. Adverse effects – photosensitivity, hypersensitivity, darkening of developing teeth, depression of skeletal growth in premature infants, GI side effects (10-20%), hepatic necrosis in pregnant women, renal failure, vertigo (30-70% on minocycline), benign intracranial hypertension
3. Indications – drug of choice for venereal infection by chlamydia and ureaplasma

Erythromycin is the most common macrolide prescribed, with activity against most Gram-positive organisms, some Gram-negative bacilli and many anaerobes (not *B. fragilis*). It is particularly useful in treatment of *Legionella pneumophila, Campylobacter jejuni, Bordetella pertussis* and some *Haemophilus influenzae*.

1. Variety of preparations available, usually given orally (sometimes IV) at 0.5-2g q6h in adults, 30-50mg/kg/day in children and smaller doses divided 12 hourly in infants
   a. Relatively poor CSF penetration
   b. Mostly inactivated in the body but some is excreted in urine and bile
   c. Dosage is essentially unchanged in renal insufficiency
2. Toxicity – GI side effects, cholestatic jaundice with estolate preparation
3. Indications:
   a. Legionellosis, diphtheria, pertussis, campylobacteriosis, mycoplasma infections
   b. Alternative to tetracycline for chlamydia/ureaplasma infections in infants/pregnancy
   c. Alternative to penicillin for streptococcal (except enterococcal) and staphylococcal infections, syphilis, gas gangrene, actinomycosis, prophylaxis of rheumatic fever and endocarditis (but not treatment of endocarditis)

Clindamycin is structurally similar to erythromycin (but is not a true macrolide), with similar activity but with more activity against anaerobes including *B. fragilis* (but less to *M. pneumoniae* and ureaplasma)
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1. Given 150-600mg q6h in adults, 1-30mg/kg/day in 4 divided doses in children
   a. Well distributed except eye, CNS – peak serum levels 2-10mg/L, 2-5x higher in bile
   b. Half-life is 3 hours, prolonged by hepatic but not renal failure
2. Toxicity – pseudomembranous colitis (0.01-10%), allergic rash (3-5%)
3. Indications:
   a. Alternative to metronidazole or chloramphenicol for anaerobic infections
   b. Superior to penicillin in anaerobic pleuro-pulmonary disease
   c. Alternative to cloxacillin in staphylococcal infections
   d. Should NOT be used in CNS infections

Chloramphenicol inhibits protein synthesis by binding to the 50s ribosomal subunit preventing attachment of tRNA. Although primarily bacteriostatic, it is also bactericidal against most strains of *H. influenzae*, *S. pneumoniae* and *N. meningitidis* and has exceptional activity against anaerobes.

1. Resistance mediated bacteria becoming impermeable or by production of the enzyme acetyl transferase → inactive diacetyl derivative. Resistance may be R-factor mediated, accounting for the widespread resistance of Enterobacteriaceae in third-world countries where it is OTC
2. Given 50-100mg/kg/day in divided doses every 6 hours, less in children and neonates. Well absorbed but bitter (except palmitate → hydrolysed in intestine). Succinate ester (hydrolysed in the tissues) may be given iv, im (slow/erratic absorption) or sc but levels are less than po
   a. Widely distributed, good penetrance into CSF, low levels in bile and urine
   b. Inactivated by conjugation/reduction in the liver prior to renal excretion
   c. Clearance delayed in neonates and those with impaired liver function
3. Indications – previously used for brain abscess, meningitis, typhoid fever, salmonellosis, rickettsial infections; but now superseded by other agents (except in third-world countries)

• Metronidazole

Metronidazole inhibits generation of H2 during bacterial energy production and also binds to bacterial DNA leading to loss of helical structure and strand breakage.

1. Active against all clinically important anaerobes – given a typical serum level of 10-20μg/mL;
   a. *Bacteroides fragilis* – MBC 0.5-8.0μg/mL
   b. *Clostridium perfringens* – MBC 0.5-8.0μg/mL
   c. *Gardnerella vaginalis* – MBC 4.0-16.0μg/mL
   d. *Peptostreptococcus* – MBC 0.1-8.0μg/mL
2. 90-95% absorption from the GI tract (not affected by food)
   a. Distribution to all body tissues including CSF (levels ~50% serum)
   b. Extensively metabolised by liver (needs dose reduction in liver failure)
   c. Parent drug and metabolites excreted in urine
3. Indications:
   a. Anaerobic infections – NO ACTIVITY against aerobes, so must be used in combination for mixed infection (intraabdominal, pelvis, pulmonary, CNS abscesses)
   b. Surgical prophylaxis of gastrointestinal or pelvic surgery
   c. Useful for antibiotic-associated pseudomembranous colitis (*Clostridium difficile*)
   d. Protozoal infections – vaginal trichomoniasis, GI/hepatic amoebiasis, GI giardiasis

• Septicaemia

Septicaemia was first defined in 1914 by Schottmueller as “a state of microbial invasion from a portal of entry into the blood stream which causes signs of illness”. It is notable that less than 50% of patients with sepsis have positive blood cultures, and not all patients with bacteraemia have signs of sepsis – it has not been until the last few decades that the sepsis was recognised as the result of excessive activation of host defence mechanisms rather than the direct effect of micro-organisms.

1. Systemic inflammatory response syndrome (SIRS) – the response to a wide variety of severe clinical insults manifests clinically with two or more of the following conditions:
   a. Temperature greater than 38°C or less than 36°C
   b. Heart rate greater than 90BPM
   c. Respiratory rate greater than 20/minute or PaCO2 less than 32mmHg
   d. White blood cell count >12x10⁹/L or <4x10⁹/L or >10% immature forms
2. Sepsis – systemic inflammatory response to a documented infection that meets the criteria for SIRS with as at least one of the following indications of inadequate organ function/perfusion:
   a. Alteration in mental state
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b. Hypoxaemia (PaO₂ <72mmHg at FiO₂ 0.21 not due to pulmonary disease)
c. Elevated plasma lactate level
d. Oliguria (urine output <30mL or 0.5mL/kg for at least 1 hour)

3. Severe sepsis – systemic inflammatory response to documented infection that meets criteria for sepsis and hypotension (systolic BP <90mmHg or reduction >40mmHg from baseline)
   a. Septic shock is a subset of patients with severe sepsis who develop hypotension despite adequate fluid resuscitation
   b. Multiple organ dysfunction syndrome – altered organ function in a patient who is acutely ill and in whom homeostasis cannot be maintained without intervention

Pathogenesis is complicated.

1. Mediator-induced injury – bacterial components (lipopolysaccharide in Gram-negative bacilli and lipoteichoic acid in Gram-positive cocci) → inflammatory mediators
   a. Macrophages release TNF, which activates lymphocytes (interleukins – IL6 associated with increased mortality) and triggers the coagulation cascade
   b. Complement is also activated, and this contributes to tissue damage by bradykinin generation and nitric oxide induction via neutrophil-endothelial cell interactions:
      i. Adhesion, margination, chemotaxis, phagocytosis
      ii. → arachidonic acid, lysosome, superoxide
      iii. → vasodilation, platelet aggregation, capillary leak
   c. Lipid mediators (eicosanoids), platelet activating factor and phospholipase A2 are also generated during sepsis, but their contribution to the sepsis syndrome is unclear

2. Abnormalities of coagulation and fibrinolysis homeostasis – leading to disseminated intravascular coagulopathy and microvascular thrombosis → organ dysfunction and death
   a. Damage to the vascular endothelium releases tissue factor and triggers the extrinsic coagulation cascade, eventually leading to intravascular thrombosis
   b. Endotoxins also increase the activity of inhibitors of fibrinolysis (plasminogen activator inhibitor, thrombin activatable fibrinolysis inhibitor)
   c. Levels of protein C and endogenous activated protein C are also decreased in sepsis

3. Circulatory and metabolic pathophysiology
   a. Arterial vasodilation → loss of peripheral resistance → hypotension and shock if not compensated by increased cardiac output
   b. Despite increased CO, the arterial-mixed venous oxygen difference is usually narrow and blood lactate is elevated – suggesting low global tissue oxygen extraction
   c. Peripheral shunting of oxygen → diminished oxygen extraction and uptake, pathological supply dependency of oxygen and lactic acidaemia in septic shock

Clinical features:

1. Aetiology:
   a. Organisms include *E. coli*, *S. aureus*, other Enterobacteriaceae, other Streptococci, *Enterococcus* spp, *P. aeruginosa*, anaerobes, *N. meningitis* and *Candida albicans*
   b. Respiratory and urinary tract infections are most common, then abdominal and soft tissue infections (intravascular devices most commonly cause iatrogenic sepsis)
      i. A focus may not be found in immunocompromised patients with neutropenia
      ii. Multiple sites of infections may be found in 6-15% of patients

2. Signs and symptoms:
   a. Patients present with non-specific symptoms including fever, chills, fatigue, malaise, anxiety or confusion (may be absent in serious infections, particular in the elderly).
   b. Untreated sepsis may progress to oliguria, hypotension, hypothermia, septic shock, multi-organ dysfunction and death.
   c. Factors that correlate with severity include abnormal host response, site/type of infection, timing/type of antimicrobial therapy, the organism, development of shock, underlying disease, the patient’s long-term health and location at the time of shock

Management:

1. Investigations:
   a. Bloods – FBC, U+E, LFTs, ABG, coagulation studies
   b. Microbiology – gram stain and culture, 2x blood cultures before starting antimicrobials
   c. Radiology – CXR, ultrasound if biliary tract focus, CT scan if abdominal focus
   d. Procedures – lumbar puncture, urinary catheter, Swan-Ganz catheterisation

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Infectious Diseases

2. **Acute Treatment:**
   a. General supportive care – maintenance of respiratory/circulatory function, supplemental oxygen, mechanical ventilation and volume infusion
   b. Haemodynamic support - monitoring, intravascular volume resuscitation, vasopressor support therapy (dopamine, noradrenaline, adrenaline, phenylephrine)
   c. Empirical antimicrobial therapy – based on probably source of infection, gram stained smears, immune status of patient and local patterns of bacterial resistance

3. **Complications** include ARDS (18% of patients), acute renal failure (40-50% of patients), disseminated intravascular coagulation (40% of patients) and death (40-50% of patients)

### Pneumonia

**Aetiology:**
1. *Streptococcus pneumoniae* is responsible for more than 75% of cases of community-acquired pneumonia. It can be seen in large numbers in gram-stained sputum in 50% of patients, but is grown in only 10-20% of patients.
2. CAP – *S. pneumoniae* (50+%), *M. pneumoniae* (6-30%), *H. influenzae* (3-15%), *Legionella sp* (2-30%), *Chlamydia sp* (1-5%), *S. aureus* (1-5%), Gram -ve bacilli (1-5%), viruses (1-5%)
3. Hospital acquired pneumonia – Gram negative bacilli (60%), *S. aureus* (13-40%), *S. pneumoniae* (3-20%), Anaerobes (5%)

**Management:**
1. **Investigations:**
   a. CXR (PA and Lateral)
   b. FBC, U&Es, glucose
   c. Sputum gram stain/culture (must be <10 epithelial cells, and >25 PMN/LPF)
   d. Blood culture – 1-16% positive in CAP
   e. Others – pleural tap, cold agglutinins, *Mycoplasma* and respiratory virus serology
2. **Criteria for hospital admission:**
   a. Increased mortality (10x) with any 2: confusion, RR >30/min, diastolic BP <60mmHg
   b. Other factors associated with increased mortality include:
      i. Age >60, pre-existing illness, cyanosis, new onset AF
      ii. $P_{O2} < 6.6 kPa$, urea >7mmol/L, WBC <10x10^9/L, lymphocytes <1x10^9/L
      iii. Multilobed or spreading shadows on CXR
3. **Treatment:**
   a. Acute lobar pneumonia – benzyl penicillin 1MU q4h iv or amoxycillin 500mg qid po for 3-5 days (erythromycin 500mg qid po if allergic to penicillin)
   b. Unusual presentations:
      i. Atypicals – erythromycin for *M. pneumoniae*, doxycline for *C. psittaci*, erythromycin plus rifampicin or *L. pneumophila*
      ii. Chronic bronchitis – Augmentin 1.2g q6h or cefuroxime 750mg q8h
      iii. Aspiration – clindamycin 600mg q8h or Augmentin 1.2g q6h
      iv. Post-influenza – Augmentin 1.2g q6h or cefuroxime 1.5g q8h
   c. Supportive – oral/iv fluids, analgesia, physiotherapy, O₂ therapy, assisted ventilation
4. **Follow-up:**
   a. Poor response may occur despite appropriate therapy, consider unusual organisms, underlying disease, alternative diagnoses
   b. Follow-up radiology – 50% normal by 6 weeks, 75% by 12 weeks.

### Meningitis

Meningitis is usually an acute illness with variable onset (hours to days). The cardinal symptoms are fever and headache; drowsiness, photophobia and nausea are also common. A non-blanching petechial or purpuric rash is strongly suggestive of infection due to *Neisseria meningitidis*.

1. **Enteroviruses** – coxsackieviruses, echoviruses, enteroviruses
   a. Faecal-oral spread, highly infectious, incubation period 3-5 days
   b. Asymptomatic, mild non-specific febrile illness, pharyngitis, gastroenteritis, meningitis
2. **Neisseria meningitidis**
   a. Winter epidemics, rate of 1/200 in Pacific children aged <1 year
   b. May be isolated meningitis or meningitis with bacteraemia
3. **Streptococcus pneumoniae**
   a. Associated with pneumonia, bacteraemia, head injury (CSF leak)
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b. Possibility of penicillin resistance

CSF interpretation – note that the most helpful initial result is if organisms are seen in the CSF, as there is a lack of a sharply demarcated threshold for the interpretation of CSF protein, glucose, WBC or polymorphonuclear leucocyte count. However, the following is a rough estimation:

<table>
<thead>
<tr>
<th>Protein</th>
<th>Viral</th>
<th>Bacterial</th>
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<tr>
<td>&lt;1.5 g/L</td>
<td>&gt;1.5 g/L</td>
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<tr>
<td>Glucose</td>
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<td>&lt;2.5 mmol/L</td>
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<tr>
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<td>&gt;500 x 10⁶/L</td>
</tr>
<tr>
<td>PMN</td>
<td>&lt;500 x 10⁶/L</td>
<td>&gt;500 x 10⁶/L</td>
</tr>
</tbody>
</table>

Treatment of meningitis:

1. General principles: S. pneumoniae is penicillin sensitive, except in CSF and middle ear
   a. High-dose IV penicillin gives serum levels high enough to kill resistant strains
      i. CSF concentrations are relatively low – high enough to kill some strains, but not enough to kill resistant strains
      ii. Ceftriaxone in CSF gets to higher levels, but again it may not be high enough to kill resistant strains
   b. Bottom line – gram positive cocci in CSF or supporting history (head injury) is an indication for vancomycin (plus penicillin or ceftriaxone – better for sensitive strains)
      i. Sensitive strains are very sensitive “scattering it around the North Shore will treat a patient at Auckland”
      ii. Stop vancomycin if lab demonstrates sensitivity to penicillin/ceftriaxone

2. Guidelines:
   a. Initial empiric treatment:
      i. Penicillin (or ceftriaxone or cefotaxime) alone
      ii. Add vancomycin if risk of S. pneumoniae or Gram positive cocci seen in CSF
   b. Definitive treatment (adult doses):
      i. N. meningitidis – benzyl penicillin 2mU iv q4h for 3 days
      ii. S. pneumoniae:
         1. Penicillin sensitive – benzyl penicillin 2mU iv q4h for 7 days
         2. Penicillin resistant – ceftriaxone 2g iv q4h for >7 days and/or vancomycin 500mg q6h iv for >7 days

3. Notes:
   a. Dexamethasone is useful before the initial antibiotic for meningitis due to H. influenzae, but that’s rare as rocking horse shit with the advent of the HIB vaccine
   b. Other issues – SIADH, convulsions, hearing impairment
   c. 2° cases can be reduced by eradication of N. meningitidis from the nasopharynx of the index patient and close contacts (rifampicin orally for 2 days)

Nosocomial Infections

General principles:

1. Factors promoting infection:
   a. Inadequate or non-existent hand hygiene
   b. Impaired patient immunity – extremes of age, chronic disease, immunosuppression
   c. Foreign bodies, medical devices (especially IV lines), wounds
   d. Antibiotic treatment

2. Sources of infection:
   a. Endogenous flora – skin, mouth, bowel
   b. Exogenous flora – hands, fomites, water, solutions

3. Prevention of infection:
   a. Hand hygiene after contact with each patient
   b. Review the need for continuing an IV line
   c. Minimise susceptibility (avoid immunosuppression, foreign bodies, antibiotics)
   d. Follow procedures in the infection control manual.

Bottom line: hand washing is good, Sterigel is better.
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**Antibiotic Prophylaxis in Surgery**
With appropriate agents, a significant reduction in the incidence of post-operative wound infection and reductions in post-operative respiratory and urinary infections can be achieved:

1. Post-operative infection doubles length of stay and cost relating to surgical/patient factors:
   a. Risk increased by degree of contamination, virulence/resistance, extent/duration of injury to wound and tissues, foreign material and infection at other sites
   b. Risk decreased by effective local/general host defences, prompt/skilful surgery of minimum duration in a sterile setting, and timely administration of antibiotics

2. One major determinant is the category of the procedure (classification by contamination):
   a. **Clean procedures** – primarily closed, elective procedures with no acute inflammation, no break in technique and no entry through mucosal surfaces
      i. Infection rates <2%, prophylaxis only if prosthetic device involved
      ii. Airborne, exogenous micro-organisms usually involved
   b. **Clean-contaminated procedures** – colonised viscus is entered, but no inflammation or significant spillage/contamination (e.g. appendectomy, cholecystectomy)
      i. Infection rates 5-25%, reduced to <2% with prophylaxis
      ii. Endogenous flora commonly involved
   c. **Contaminated procedures** – non-purulent inflammation, major spillage from a colonised viscus or a major breach in aseptic technique (including trauma <4hrs)
      i. Infection rates 15-40%, halved with treatment (not prophylaxis!)
   d. **Dirty procedures** – established infection (abscess, perforated viscus, devitalised tissue, traumatic wounds >4 hours old
      i. Infection rates >40%
      ii. Empirical antibiotic treatment usually required to cure the infection

**Basic principles:**

1. **Prophylactic antibiotics:**
   a. Peak concentration should be just when the knife hits the skin:
      i. Infection rate increases if given earlier, often with resistant organisms
      ii. Infection rate also increases if given after the start of the procedure
   b. For most procedures lasting <2hrs, a single dose is sufficient – for procedures lasting >2hrs or where there is massive blood loss, 1-2 further doses may be required
   c. Antibiotics should cover the organisms most likely to cause infection – broad spectrum agents not recommended (particularly 3rd generation cephalosporins, vancomycin)

2. **Other factors** – surgical technique, duration of surgery, shaving the operative site (depilatory creams bad, shaving less bad), repeat surgical procedures, obesity, immune compromise and a variety of host factors. Post-operative O2 may halve incidence of infections, oddly enough.

**Examples:**

1. **Clean procedures** – usually S. aureus and coagulase negative staphylococci (Gram-negative cover less important, anaerobic cover unnecessary), single dose cefazolin or cefuroxime; vancomycin if MRSA rife or patient allergic to cephalosporins
2. **Clean-contaminated procedures:**
   a. Upper GI – Gram-positive and –negative cover; 1st or 2nd generation cephalosporin
   b. Lower GI – Gram-negative and anaerobic cover; cephaparin (cefoxitin or cefotetan) or combination of an aminoglycoside (gentamicin) plus metronidazole

**PAEDIATRIC INFECTIOUS DISEASES**

**The Febrile Child**

Fever is the end result of activated endogenous pyrogens resulting in vasoconstriction, increased metabolic rate and heat production. It is unclear whether this is a productive/adaptive response, particularly as fever >40°C (hyperpyrexia) can be life-threatening. Common causes include:

1. **Infections (95%)** – viral and bacterial
   a. Viral (70%) – URTI, bronchiolitis, pneumonia, exanthem, gastroenteritis
   b. Otitis media (13%)
   c. **Bacterial pneumonia (9%)**
   d. Urinary tract infection (7%)
   e. Others – soft tissue infection, bone/joint infection, meningitis, septicaemia
2. **Other** – drugs and toxins, connective tissue disease, neoplasms, metabolic, CNS, miscellaneous e.g. immunisation
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Primary bacteraemia – usually occurs in relation to invasive disease, but can be occult in 3-36 months with no obvious focus of infection. Most commonly *S. pneumonia*, *(H. influenzae)*, *N. meningitidis* and *S. aureus*. Risk of subsequent invasive disease is 3-5%.

Clinical assessment:

1. History:
   a. Symptoms – fever, coryza, cough, diarrhoea and/or vomiting, lethargy and malaise, poor feeding, irritability, rash, headache
   b. Age (if >2yrs may be hypermetabolic), recent immunisation/exposure, ethnicity
   c. Past history – immunodeficiency or recurrent infection, chronic disease, medications

2. Examination is this child well or unwell?
   a. Vital signs, hydration, skin rash, level of consciousness
   b. Specific signs:
      i. Otitis media, tonsillitis/pharyngitis
      ii. Increased RR, retraction, crackles or wheeze
      iii. Meningism (unreliable) – neck stiffness, photophobia, Kernig’s sign
      iv. Joint/bony tenderness
      v. Abdominal tenderness

3. Temperature – normal 36.2-38°C in children >3 months old (varies diurnally)
   a. Rectal temperature (2-3 min) – closest to core temperature (not used if neutropenic)
   b. Oral (1 min) – useful after age 5-6, about 0.5° cooler than rectal
   c. Axillary (3-5 min) – 1-2° cooler than rectal
   d. Tympanic – pretty damned unreliable, but often the only one practical

Management:

1. <1 month – high risk of bacterial infection (~10%)
   a. Full septic screen – blood, CSF, urine cultures, CXR
   b. Directed tests if site identified – wound swab, limb X-Ray, joint aspirate
   c. Admit, treat with antibiotics

2. 1-3 months – high risk of bacterial infection (7% if T>39°C, 30% if T>40°C)
   a. Full septic screen including lumbar puncture
   b. Directed tests if site identified
   c. Admit (almost always), treat with antibiotics (usually)

3. 3-36 months:
   a. Specific treatment if site obvious (UTI, otitis media if well, pneumonia, meningitis)
   b. No focus and T >39°C:
      i. Septic screen ± CSF
      ii. Treatment depends on if focus found, infant well/unwell, other risk factors

4. >2 years – signs and symptoms are similar to adults (fontanelle closed), may → convulsions
   a. Lumbar puncture indicated

Treatment:

1. Fever is good, so we don’t necessarily want to treat it unless there are complications
2. Antipyretics – paracetamol, aspirin
   a. Avoid if T <39°C – use fluid replacement instead
   b. Avoid aspirin with chickenpox or influenza

Management of Otitis Media (See ORL notes for definitions, aetiology, etc)

Guidelines:

1. Conservative management:
   a. 70-90% spontaneously resolve in 7-14 days
   b. 6 out of 7 resolve spontaneously without complications
   c. Delayed treatment may be acceptable in some cases
   d. Avoid antimicrobial prophylaxis for recurrent otitis media

2. Medical management – 35% *S. pneumoniae*, 23% *H. influenzae*, 14% *M. catarrhalis*
   a. Antibiotics are good, because they reduce symptoms and development of complications, but there is reasonable evidence they are unnecessary. A delayed prescription may be useful – start antibiotics if it is not improving in three days
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b. Amoxycillin 80-90mg/kg/day tds for 5 days covers S. pneumoniae and H. influenzae – doesn’t cover M. catarrhalis but this has no significant sequelae, so who cares?
  i. Amoxycillin + clavulanate may be better if not resolving
  ii. Cotrimoxazole is useless as a first-line agent (30% resistance)
  iii. Cefaclor is yummy, but expensive.

c. Indications for changing antibiotic – initial treatment failure, persistent infection at 10-14 days, culture-positive resistant organism, prior treatment failure, compliance failure

3. Surgical management:
   a. Tympanostomy tubes for recurrent or persistent (bilaterally for 2-3/12, unilaterally for 4-6/12) acute otitis media rather than long-term antibiotic prophylaxis
   b. Tympanocentesis is indicated in immune deficient children, neonates, severe illness, excessive otalgia or the severely toxic child, poor response to medical therapy, and confirmed or potential suppurative or severe complications

Paediatric Meningitis

Meningitis is inflammation of the meninges that may be bacterial, aseptic (viral, partially treated bacterial, others – TB, fungi, parasitic) or non-infectious. It is rare, but is a medical emergency as it has devastating consequences if not treated appropriately – death, severe disability and deafness.

1. Aetiology varies by age:
   a. Bacterial:
      i. Neonate – Group B streptococcus, Listeria, Gram negative bacilli, enterococci
      ii. Older – Neisseria meningitidis, Streptococcus pneumonia, (Haemophilus influenza B
   b. Viral – entroviruses (80%), mumps, EBV, influenza, CMV, HSV, HIV

2. Differential diagnosis:
   a. Infant – other infection, metabolic disease, intracerebral bleeding (IVH, NAI)
   b. Children – influenza, referred pain (‘meningismus’) – tonsillitis, apical pneumonia, cervical sepsis

Assessment and management:

1. Clinical features
   a. Neonates usually non-specific
   b. Children – fever, vomiting, headache, neck stiffness, altered LOC (may look well)
   c. Others – seizures, papilloedema, purpuric rash, septicemia shock (N. meningitidis)

2. Investigations:
   a. Diagnosis by CSF examination (i.e. lumbar puncture)
      i. Contraindicated in coma, focal neurological signs or signs of increased ICP, and cardiorespiratory instability
      ii. Treatment must not be delayed if lumbar puncture has to be deferred
   b. Other tests – FBC, coags, blood cultures, chemistry (SIADH, hypoglycaemia), CT if focal signs or decreased level of consciousness to exclude other diagnoses

<table>
<thead>
<tr>
<th></th>
<th>WCC</th>
<th>Glucose</th>
<th>Protein</th>
<th>Gram stain</th>
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<td>↑PMN</td>
<td>↑↑</td>
<td>Positive</td>
</tr>
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<td>↑PMN</td>
<td>N</td>
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<td>Negative</td>
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<tr>
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<td>↑lymphocytes</td>
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<td>Negative</td>
</tr>
<tr>
<td>Partially treated bacterial</td>
<td>↑PMN</td>
<td>↓or N</td>
<td>↑or N</td>
<td>Negative</td>
</tr>
</tbody>
</table>
| b. Other tests – FBC, coags, blood cultures, chemistry (SIADH, hypoglycaemia), CT if focal signs or decreased level of consciousness to exclude other diagnoses

3. Treatment:
   a. Pre-hospital – parenteral antibiotics
   b. Hospital:
      i. Supportive – airway, ventilation, fluid resuscitation, inotropes, control seizures, maintain normal biochemistry, treat increased ICP
      ii. High dose antibiotics:
         1. Neonates – aminoglycosides
         2. Older – 3rd generation cephalosporins (cefotaxime or ceftriaxone)
            a. Add vancomycin for pneumococcus
            b. Add amoxycillin if <3 months old
         3. Duration – 10 days in pneumococcus, 4-7 for meningococcus
      iii. Dexamethasone prior to antibiotics and for 48 hours after
   c. Prophylaxis to eradicate carriage – household and day-care contacts:
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**Rifampicin** 10mg/kg q12h for 4 doses
**OR** single dose ceftriaxone

4. **Prognosis** – worst in neonates
   a. Overall mortality 5-10%
   b. 30% long-term sequelae – deafness, learning difficulties, developmental delay, seizures, cerebral palsy.

**SEXUALLY TRANSMITTED INFECTIONS**

*Urethritis and Cervicitis*

**Gonorrhoea**

1. Non-cornified epithelium infection by *N. gonorrhoea* (G-ve diplococci – only humans)
   a. Strain differentiation – auxotypes (growth media), serotypes (Ab)
   b. Defence mechanisms – antigenic variation, adherence mechanisms
   c. Antibiotic resistance – chromosomal or plasmid mediated
      i. Penicillin widespread, quinolone (ciprofloxacin) increasing, tetracycline unevenly spread (mainly SE Asia)
      ii. 3rd generation cephalosporins slowly increasing

2. **Clinical features**:
   a. Epidemiology – overall incidence dropped in last 20 years, now rising
      i. Incidence 42 per 100,000, district variation (higher South Auckland)
      ii. Transmitted by sexual contact (peno-vaginal, peno-anal, oro-genital), efficiency determined by sites infected and/or exposed
      iii. Infection acquired overseas often multi-resistant
   b. Males – urethral infection usually symptomatic (discharge, dysuria)
      i. Incubation period 1-14 days (commonly 2-5 days)
      ii. 95% of untreated cases ➔ asymptomatic after 6 months
      iii. Rectal infection (± symptoms – not a reliable indication of unsafe anal sex), pharyngeal infection (asymptomatic)
   c. Females – endocervical/urethral infections usually asymptomatic
      i. Incubation period less certain than males (symptoms within 10 days – vaginal discharge, dysuria, intermenstrual bleeding or menorrhagia)
      ii. Rectal infection (35-50%, asymptomatic), pharyngeal infection

3. **Treatment** of uncomplicated cases:
   a. Ceftriaxone 50mg IM stat (safe in pregnancy or breastfeeding)
   b. If allergic, consider azithromycin 2gm
   c. Concurrent anti-chlamydial therapy as co-infection is common

4. **Complications**:
   a. Males – epididymitis, lymphangitis, urethral stricture
   b. Females – acute salpingitis, pelvic inflammatory disease (10-20%)
   c. Disseminated gonococcal infection in 0.5-3% of cases (F>M), commonly with dermatitis-arthitis syndrome ➔ penicillin

**Chlamydia**

1. *Chlamydia trachomatis* serovars B, D-K ➔ non-specific anogenital disease, conjunctivitis, neonatal pneumonia, Reiter’s syndrome (squamocolumnar cells)
   a. Initial infection mild and self-limited – short-term immunity ➔ latent infection
   b. Recurrent infection ➔ severe inflammation with exaggerated host response, cross-reacting heat shock protein, chlamydial Ag, tissue damage/scarring

2. **Clinical features**:
   a. Epidemiology – most common cause of preventable infertility, rarely fatal
      i. Hallmark of the serially monogamous rather than the promiscuous
      ii. Incidence 480 per 100,000, higher in female ➔ 20-24yrs (3000 per 100,000)
         1. Female-to-male ratio 3:1
         2. Reduced from 24 to 7% of all STIs since 1980s
   b. Investigations – PCR, sDNA have high sensitivity (detects <log 1 organisms, old tests log 2-7) and better specificity over EIA
      i. Men – first-catch urine (better patient acceptability)
      ii. Woman – endocervical swab best, otherwise first-catch urine

3. **Treatment**:
   a. Medical – note poor adherence ➔ transient suppression

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i. Azithromycin 1g stat (as effective as doxycycline)
ii. OR Doxycycline 100mg bd 7-10 days (97-100% efficacy)
iii. OR erythromycin 800mg qid 10 days (test of cure 4/52 later)
iv. OR Amoxycillin 500mg qid for 10 days (if pregnant, TOC)

b. Related issues (reduce re-infection risk) – contact tracing (past 60 days, last partner), treat partners, protected sex during treatment

4. Complications:
   a. Females – PID, Fitz-Hugh-Curtis syndrome (perihepatic pain)
   b. Males – persistent/recurrent urethritis, epididymitis, infertility
   c. Reiter’s syndrome (M>F) – arthritis, uveitis, balanitis/vulvitis
   d. Paediatric disease – conjunctivitis, pneumonia, otitis media

Non-specific urethritis (cervicitis) – inflammation of unknown cause, usually symptomatic
1. Aetiology – genital Mycoplasma, Trichomonas vaginalis, Candida, viruses (HSV, respiratory viruses), other bacteria (e.g. N. meningitidis), other
2. Genital Mycoplasma (Ureaplasma urealyticum, M. genitalium, M. hominis in women) is common in the sexually active, respond to anti-chlamydial therapy (treat contacts)

   • Vaginal infection – usually related to disruption of vaginal lactobacilli (commensal)

Bacterial vaginosis
1. Overgrowth of facultative anaerobic bacteria (→ H₂O₂) → low pH, increased amines
   a. Homogenous greyish white thin watery adherent discharge
   b. Anaerobes (Prevotella sp, Mobiluncus sp), M. hominis, Gardnerella vaginalis
2. Clinical features:
   a. Epidemiology – 20-25% of women, sexually associated, recurrence common
      i. Change in male partner a risk, some association with NGU, more common in sexually active lesbian woman
   b. Diagnosis – Amsel’s criteria (3 of the following):
      i. Homogenous white adherent discharge
      ii. Elevated pH >4.5
      iii. Fishy malodour (10% KOH)
      iv. Microscopy – clue cells (may be present in asymptomatic women)
3. Treatment only if symptomatic, pregnant, pre-TOP, other gynaecologic surgery
   a. Nitroimidazole e.g. ornidazole 500mg bd for 5 days or 1.5g stat
   b. Vaginal clindamycin, metronidazole gel, condom use
   c. Maintenance regimes and contact treatment is not recommended
4. Complications – pregnancy (premature rupture of membranes, preterm labour, chorioamnionitis), gynaecology (post-TOP PID, wound infections)

Candidiasis (not an STD!)
1. Yeast overgrowth (90% C. albicans), present in ~20% asymptomatic healthy women
2. Clinical features:
   a. Epidemiology – 75% of women have at least one episode, 40-45% two or more, up to 5% have multiple episodes
   b. Pruritis, erythema ± discharge (white, thick, lumpy), vulval rash (satellite lesions), ↓pH
   c. Diagnosis – bench tests (wet mount, KOH mount), yeast culture
3. Treatment:
   a. Intravaginal topical azole therapy (80-90% effective)
   b. Oral therapy – mycological cure with small doses (itraconazole 400-600mg)
   c. Recurrent – episodic prophylaxis (itraconazole 200mg first day of menses)
   d. Male partners only need treatment if symptomatic (balanitis)

Trichomonas
1. Protozoal disease uncommon in NZ
   a. Men – rarely symptomatic (see NSU)
   b. Women – 50% symptomatic (purulent vaginal discharge, frothy, green, malodour, vaginal inflammation, perineal/inguinal/strawberry rash)
2. Treatment with oral nitroimidazoles (urethra and perivaginal glands infected)
   a. Women – stat dose cures 82-88%, course 95%
   b. Men – stat dose cure 60%
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- Genital skin/ulcer disease:

Anogenital warts
1. Caused by mucosotropic HPV types (site and species specific), associated with anogenital neoplasia – transformation/immortalisation of keratinocytes
   a. Fluctuating course – lesions, latency, recurrence/persistence/regression
   b. Majority sexually transmitted
2. Clinical features:
   a. Epidemiology:
      i. Visible warts common (about 1% sexually active population – decreases with age), HPV infection more so (10-30% prevalence)
      ii. Transmission:
         1. Sexual by microabrasion (virus → basal germ cell layer)
            a. Risks include # and sexual behaviour of lifetime sex partners, immunosuppression, lack of condom use
         2. Others – birth (laryngeal papillomatosis), fomites, auto/heteroinoculation, perinatal (laryngeal, conjunctival)
   b. Exophytic warts:
      i. Men – penile > anal > oral
      ii. Women – vulval > cervical > anal > oral
   c. Differential – Molluscum contagiosum, penile/vestibular papillosis, Fordyce spots
3. Treatment – control rather than cure, most similar efficacy (~70%) and relapse (1:3)
   a. Physical ablation (e.g. cryotherapy)
   b. Cytotoxics (e.g. podophyllotoxin)
   c. Immune (e.g. imiquimod in women)
   d. Vaccine – prophylactic and therapeutic (CIN)
4. Complications:
   a. Intraepithelial neoplasia (HPV 16 and 18 high risk, 6 and 11 low risk) – high grade dysplasia (cervical cancer – 100% has HPV), anogenital cancer
   b. Others – negative body image, stigma, transmission fears, side-effects

Genital herpes
1. Caused by herpes simplex viruses types 1 and 2 (cytopathic)
2. Clinical features:
   a. Epidemiology – incidence ~0.275%, prevalence ~11%, ~40% asymptomatic
      i. Risk of infection include ethnicity, prior STD (males), number of partners (females), cohabitation
      ii. Risk of recurrent include virus type (HSV-2 95%, HSV-1 50%), gender (M>F), stress has weak/indirect effects
   b. Transmission primarily by asymptomatic shedding:
      i. Women – 1-8% of days by culture, 28% by PCR
         1. 11.7 symptomatic and 5.5 asymptomatic days/year
            a. Risks – before/after recurrence, first year of infection
         2. Men – 2.2%
            a. Urethra, urine, semen, normal appearing penile skin
            b. Commonly before/after symptomatic shedding
      3. Acyclovir reduces asymptomatic shedding
   c. First episode varies from asymptomatic to severe mucocutaneous and systemic disease, generally worse in women
      i. Vesicular lesions, regional adenitis, systemic symptoms, neuralgia
      ii. Rarely – urinary retention (sacral autonomic radiculopathy)
   d. Diagnosis confounded by low patient awareness, poor swabbing technique
      i. PCR ($$$) – more sensitive than culture, can be type-specific
      ii. Type-specific serology ($) – sensitivity affected by antibody levels so time-dependent, high specificity, doesn’t determine site
3. Treatment by antiviral therapy (Acyclovir – note topical is not effective)
   a. Inhibits thymidine kinase, selective for HSV-infected cells
   b. Bioavailability 15-30%, renal toxicity at high doses (used for anorectal)
   c. Acute vs episodic vs suppressive therapy
Infectious Diseases

Molluscum contagiosum
1. Pox virus that causes a benign condition transmitted by skin contact (sexual, non-sexual, auto-inoculation) that may persist for 18 months to 2 years without treatment
   a. Incubation (3/12) ⇒ flesh-coloured papules, central umbilication (~5mm, up to 15mm)
2. Treatment – none, cryotherapy, removal of corse and application of phenol
3. Complications – bacterial superinfection, recurrence (15-35%)

Syphilis
1. Spirochaete (Treponema pallidum) that evades immune responses (immunologically privileged sites, intracellular sites, surface immunologically inert, ineffective Ab)
   a. CMI critical to maintenance of latency and control of proliferation
   b. Clinical disease due to immune response (vasculitis, destruction, fibrosis)
   c. Others – Yaws, Pinta (South America), Bejel (Middle east), endemic syphilis
2. Clinical features:
   a. Epidemiology – infectious cases uncommon (most ‘imported’ or from contact with ‘imported cases’), latent syphilis overdiagnosed (Yaws in Pacific Islands)
   b. Manifestations:
      i. Early manifestations (9-90 days after exposure) – genital ulceration, rash, ocular lesions, neurological signs (CN III, VI, VII, VIII)
      ii. 1° syphilis (14-21 days after exposure) – papular then ulceration (chancre), rubbery inguinal nodes, diagnosis by dark field microscopy
      iii. 2° syphilis (4-10 weeks after 1° lesion) – haematogenous spread ⇒ rash (macular, papular, papulosquamous)
      iv. Later manifestations – asymptomatic, aortic disease, optic atrophy, long tract or pyramidal signs, cognitive change
   c. Investigations – predictive value poor in low-prevalence settings
      i. VDRL – non-specific antiphospholipid antibody test, positive 3-5/52
         1. Highly specific in healthy patients and in CSF (low sensitivity)
         2. False positive – fever, immunisation, pregnancy, chronic disease, autoimmune disease, age
      ii. TPHA – specific test (haemagglutination test), positive 8-10/52
         1. False positive – SLE, infectious mononucleosis, leprosy
      iii. FTA – indirect immunofluorescent treponemal Ab test, positive 3-4/52
      iv. Lumbar puncture if neurological signs, treatment failure, serum VDRL >1:16, evidence of active disease, non-penicillin therapy, HIV positive
3. Treatment:
   a. Early infection:
      i. Benzathine penicillin G 2.4 MU im stat
      ii. OR Procaine penicillin 1.5 MU im od 10/7 with probenecid 500mg qid
      iii. OR Doxycycline 100mg bd 14/7
      iv. Follow-up – serology at 1/2/3/6/9/12/24 months post therapy
   b. Late infection:
      i. Benzathine penicillin G 2.4 MU im weekly for 3/52
      ii. OR Procaine penicillin 1.5 MU im od 2/52 with probenecid 500mg qid
      iii. OR Doxycycline 100mg bd for 4/52
      iv. Follow-up – serology at 3/6/12/24 months post therapy
   c. Adverse reactions:
      i. Anaphylaxis
      ii. Procaine reaction – acute psychosis, acute cardiorespiratory crisis
      iii. Jarisch-Herxheimer reaction – acute febrile (headache, myalgia)
   d. Contact tracing – offer treatment, follow-up serology in 3/12
      i. Primary – all contacts last 3 months
      ii. Secondary – all contacts past year
      iii. Early latent – all contacts last two years
      iv. Late – all long-term partners (and children of female index cases)