

Third edition

Notes & Notes

For MRCP part 1 & 2

By

Dr. Yousif Abdallah Hamad

Infectious diseases

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Leishmaniasis		
Leptospirosis		
Lyme disease		
Lymphadenopathy / Malaria		
Measles		
Rubella / Parotitis / Parotid swelling		
Orf / Pelvic inflammatory disease(PID)		
Psittacosis (ornithosis) / Pyogenic liver abscess		
Pyrexia of unknown origin / Q fever		
Rabies		
Scabies		
Helminths		
Schistosomiasis		
Strongyloides stercoralis / Tape worms		
Trypanosomiasis		
Nematodes		
Filariasis		
Loiasis		
Animal bites / Rocky Mountain spotted feve		
Histoplasmosis		
Actinomycosis / Malignant otitis externa		

Classification of bacteria

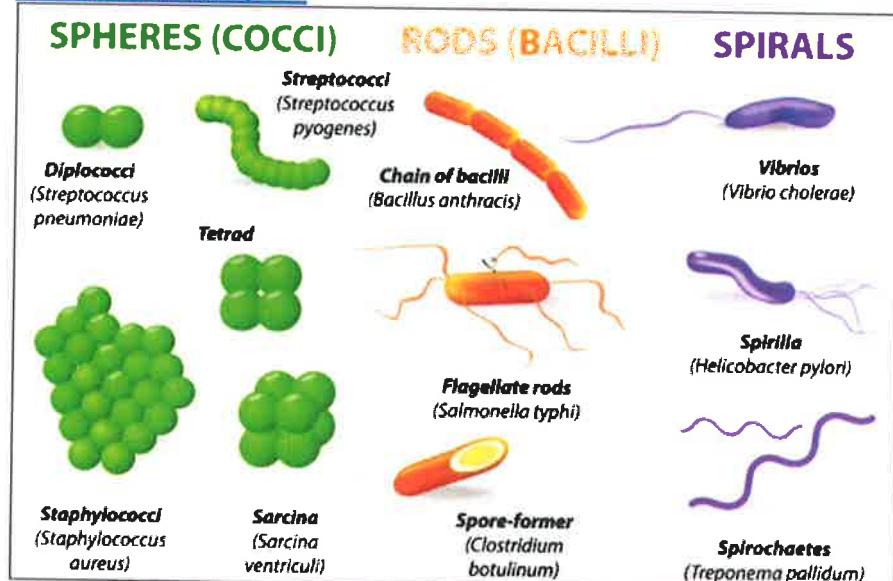
cocci

- Remember:
 - ⇒ Gram positive cocci = staphylococci + streptococci (including enterococci)
 - ⇒ **Gram negative cocci** = *Neisseria meningitidis* + *Neisseria gonorrhoeae*, also *Moraxella*

Rods (bacilli)

- only a small list of **Gram positive rods** (bacilli) need to be memorised to categorise all bacteria - mnemonic = ABCD L
 - ⇒ *Actinomyces*
 - ⇒ *Bacillus anthracis* (anthrax)
 - ⇒ *Clostridium*
 - ⇒ Diphtheria: *Corynebacterium diphtheriae*
 - ⇒ *Listeria monocytogenes*
- Remaining organisms are Gram negative rods

Bacterial shapes

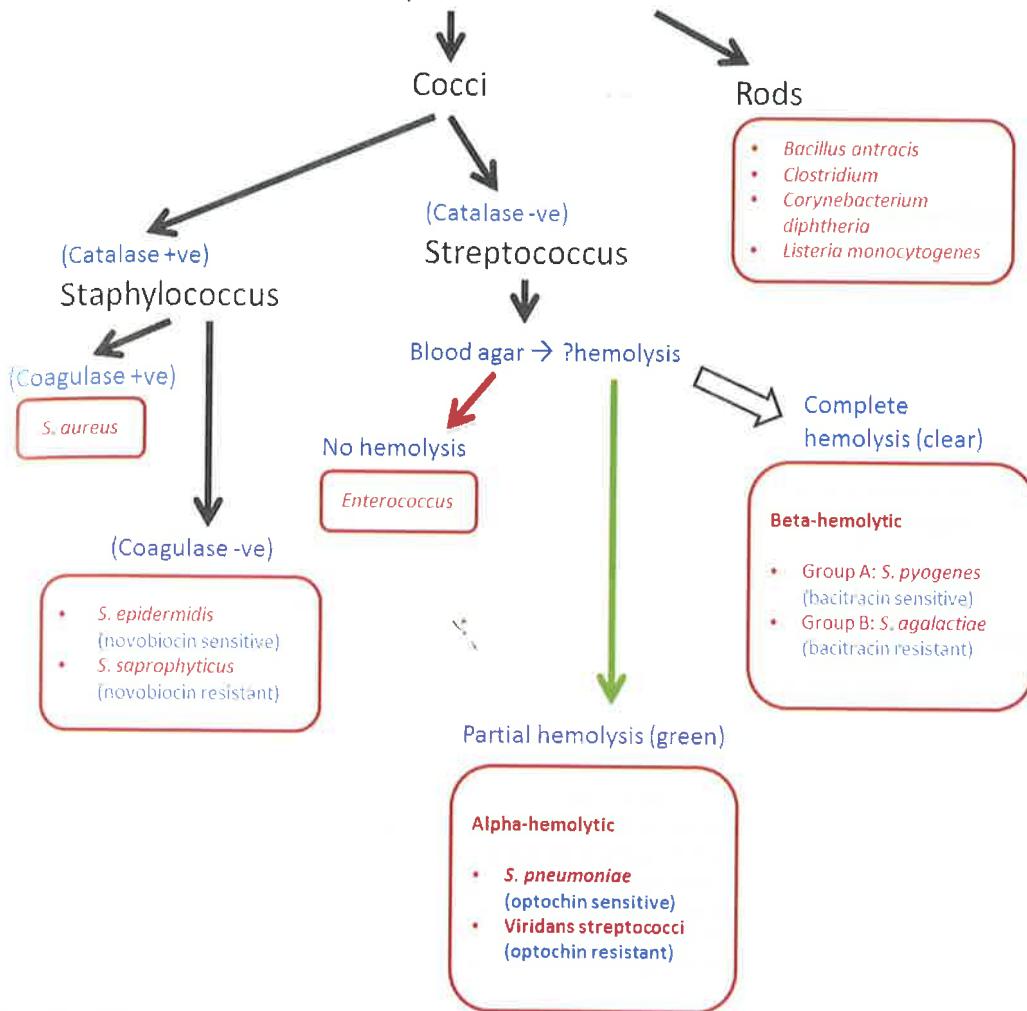


- *Staphylococcus aureus* appears as large Gram-positive cocci in clusters.

Identifying gram-positive bacteria

Gram positive bacteria will turn purple/blue following the gram staining. Microscopy will then reveal the shape, either cocci or rods.

Gram stain → Gram positive bacteria



Rods (bacilli)

- *Actinomyces*
- *Bacillus antracis*
- *Clostridium*
- *Corynebacterium diphtheriae*
- *Listeria monocytogenes*

Cocci

- makes catalase: **Staphylococci**
- does not make catalase: **Streptococci**

Staphylococci

- makes coagulase: *S. aureus*
- does not make coagulase: *S. epidermidis* (novobiocin sensitive), *S. saprophyticus* (novobiocin resistant)

Streptococci

- partial haemolysis (green colour on blood agar): **α -haemolytic**
 - ⇒ optochin sensitive: *S. pneumoniae*
 - ⇒ optochin resistant: Viridans streptococci
- complete haemolysis (clear): **β -haemolytic**
 - ⇒ bacitracin sensitive: Group A: *S. pyogenes*
 - ⇒ bacitracin resistant: Group B: *S. agalactiae*
- no haemolysis: γ -haemolytic

Staphylococci

Most common organism found in central line infections - *Staphylococcus epidermidis*

Staph aureus is a coagulase positive Staph

- Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease.
- **Staphylococci are skin organisms most commonly introduced during pacemaker insertion and such a discitis would present with back pain.**

Basic facts :

- Gram-positive cocci
- facultative anaerobes
- produce catalase

Coagulase test:

- used to differentiate between different *Staphylococcus* species
 - Coagulase-Positive Staph species:
 - **Staph aureus** is the most important of the coagulase positive *Staphylococcus* species and is highly pathogenic.
 - Coagulase-negative Staph species:
 - most likely to be skin commensal organisms of relatively low pathogenicity, such as *Staph epidermidis* or *Staph saprophyticus*, although some may still cause deeper infection or sepsis.

Types

- The two main types of Staphylococci you need to know about are *Staphylococcus aureus* and *Staphylococcus epidermidis*.

<i>Staphylococcus aureus</i>	<i>Staphylococcus epidermidis</i>
<ul style="list-style-type: none"> • Coagulase-positive • Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome 	<ul style="list-style-type: none"> • Coagulase-negative • Cause of central line infections and infective endocarditis

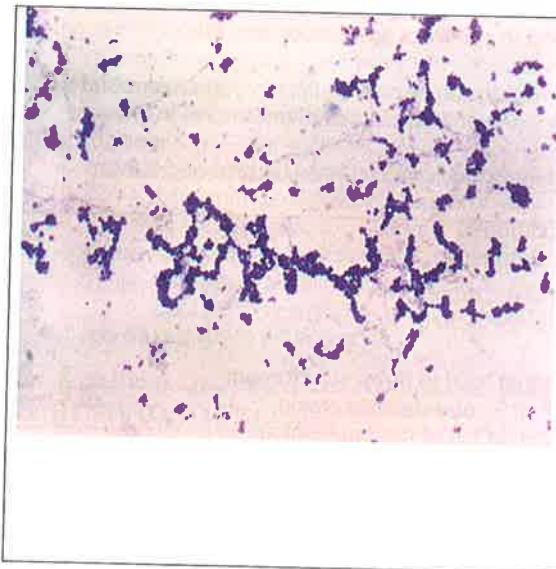
- Nasal swabs should be routinely checked in patients with recurrent staphylococcal abscesses
- Recurrent skin infections caused by **staphylococcus** often reflect **colonisation** that will require use of clearance procedures (body wash and topical nasal treatment) in order to prevent ongoing recurrences.
- This is particularly important in younger athletes in whom colonisation with resistant staphylococcal strains can occur.

Staphylococcus aureus

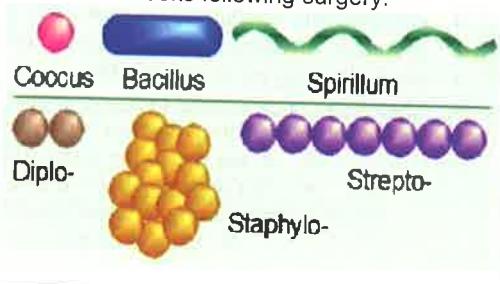
- catalase and coagulase positive, beta hemolytic organism.
- produces a yellow pigment ('Aureus' is Latin for 'gold'.)
- stained purple by gram staining.
- *Staphylococcus aureus* produce exotoxins that lead to three syndromes:
 1. food poisoning, caused by ingestion of *S. aureus* enterotoxin;
 - ***S. aureus*** is the most common cause of food poisoning.
 - The enterotoxin produced by *Staphylococcus aureus* (heat stable toxin) causes rapid-onset food poisoning.
 - ❖ Staph bacteria are killed by cooking, but the toxins are not destroyed
 2. scalded skin syndrome, caused by exfoliative toxin; (Exfoliatin A and B)
 3. toxic shock syndrome (TSS), caused by toxic shock syndrome toxin-1 (TSST-1)
- What is the mechanism by which methicillin-resistant *Staphylococcus aureus* gains resistance to penicillins?
 - Alterations in penicillin-binding proteins

Effective antibiotics:

- Staphylococcal and streptococcal organisms are effectively treated by **semisynthetic penicillins**, including oxacillin, nafcillin, dicloxacillin, and **cloxacillin**. Also, first- and second-generation cephalosporin
- Penicillin G, **ampicillin**, and **amoxicillin**: These agents are effective against streptococci, such as *S. pyogenes*, viridans group streptococci, and *S. pneumonia*, **but not against staphylococci**
- Ampicillin and amoxicillin are only effective against staph when ampicillin is combined with the **beta-lactamase inhibitor sulbactam** or when amoxicillin is combined with **clavulanate**.



- The Gram stain shows Gram positive cocci **growing in clusters, typical of *Staphylococcus aureus*.**
- This is the most likely organism to cause post-operative infection of prosthetic joints within the first one to four weeks following surgery.



Streptococci

- Streptococci are gram-positive cocci.
- divided into alpha and beta haemolytic types

Alpha haemolytic streptococci (partial haemolysis)

- The most important alpha haemolytic *Streptococcus* is *Streptococcus pneumoniae* (*pneumococcus*).
 - carried asymptotically in approximately 50% of people.
 - It can cause both non-invasive and invasive disease.
 - Non-invasive:**
 - includes otitis media, sinusitis, pneumonia and bronchitis.
 - Invasive pneumococcal disease (IPD)**
 - refers to disease in which the bacterium enters a sterile site such as blood, cerebrospinal fluid, pleural fluid or pericardial fluid.
 - If grow in blood cultures → IPD by definition.**
 - more common in HIV-infected patients** (20-30 times) compared to non-HIV infected patients.
 - offer HIV testing to all patients with IPD presenting to hospital.
 - Other immunodeficiency syndromes are associated with an increased risk of IPD, include:
 - X-linked (Bruton's) agammaglobulinaemia,
 - common variable immunodeficiency,
 - asplenia (anatomical or functional) and sickle cell disease.
 - the mechanism of resistance for penicillin resistant *Streptococcus pneumoniae***
 - Alteration of penicillin binding proteins (PBPs)**
 - Penicillin is a bactericidal antibiotic which acts by inhibiting cell wall synthesis.
 - Mutations in PBPs (enzymes required for cell wall synthesis) result in penicillin resistance.
 - Another clinical example is *Streptococcus viridans*

Beta haemolytic streptococci (complete haemolysis)

These can be subdivided into groups A-H. Only groups A, B & D are important in humans.

- **Group A**

- ⇒ most important organism is ***Streptococcus pyogenes***
- ⇒ responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis and pharyngitis/tonsillitis
- ⇒ immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis
- ⇒ erythrogenic toxins cause scarlet fever
- ⇒ **Penicillin is the antibiotic of choice for group A streptococcal infections. The BNF suggests stopping flucloxacillin if streptococcal infection is confirmed in patients with cellulitis, due to the high sensitivity.**

- **Group B**

- ⇒ *Streptococcus (GBS) agalactiae*
 - Maternal vaginal colonization with GBS, primarily *Streptococcus agalactiae*, is associated with serious and highly fatal neonatal infections, such as sepsis and meningitis.
 - **Lipoteichoic acid is the primary virulence factor of this organism**
 - A prerequisite to mucosal colonization or infection is bacterial adherence to the epithelium. Lipoteichoic acid, a cell wall glycolipid polymer, mediates attachment of GBS to the vaginal epithelial cells. Lipoteichoic acid is also involved in host cell adherence of other Gram-positive bacteria as well. Without this adhesion, it would not be possible to have infection.

- **Group D**

- ⇒ *Enterococcus*

Bacteria and growing media

Bacteria	Type	Growth media
Staphylococci	Gram-positive cocci in clusters	LB broth agar
Streptococcal species (hemolytic Streptococcal species such as <i>Streptococcus pyogenes</i>).	Gram-positive cocci in chains	Trypticase Soy Agar (TSA) supplemented with 5% Sheep Blood
<i>Streptococcus pneumoniae</i>	Gram-positive bullet-shaped diplococci	Todd Hewitt Broth
<i>E. coli</i> , <i>Klebsiella</i> , or <i>Enterobacter</i> .	Gram-negative lactose fermenting bacilli	Super Optimal Broth (SOB)
<i>Neisseria meningitidis</i>	gram-negative diplococcus	chocolate agar

Enterococcus

Classification

- Previously classified as group D streptococci
- In the 1980s, based on genetic differences, *enterococci* were removed from the genus *Streptococcus* and placed in their own genus, *Enterococcus*

Enterococcus species

- *E. faecalis*: **the predominant enterococcal species**, 80 to 90% of all clinical isolates,
- *E. faecium* : 5 to 15%
- Others: (*E. gallinarum*, *E. casseliflavus*, *E. durans*, *E. avium*, and *E. raffinosis*) less than 5%

Importance

- Enterococci are currently ascendant nosocomial pathogens (عدوى المستشفيات), due to their intrinsic resistance to several commonly used antibiotics
 - the second most common organisms recovered from nosocomial urinary tract and wound infections
 - the third most common cause of nosocomial bacteremia in the United States

Treatment

- Until recently, **vancomycin** was virtually the only drug that could be consistently relied on for the treatment of infections caused by multidrug-resistant enterococci.
 - Oral vancomycin, which is poorly absorbed, has been used extensively for the treatment of *Clostridium difficile* enterocolitis.
- Teicoplanin** is another glycopeptide antibiotic; Because of their activity against methicillin-resistant staphylococci and other gram-positive bacteria, these drugs have been widely used for therapy and prophylaxis against infections due to these organisms

Vancomycin-resistant enterococci

- Risk Factors**
 - patients in ICUs
 - prolonged hospitalization
 - patients with chronic renal failure, cancer, or organ transplant recipients,
 - Vancomycin use has been reported consistently as a risk factor for colonization and infection with VRE and may increase the possibility of the emergence of vancomycin-resistant *S. aureus* or *S. epidermidis*.
- Modes of Transmission**
 - Transmission of VRE by health care workers whose hands become transiently contaminated with the organism while caring for affected patients is probably the most common mode of nosocomial transmission.
- Clinical problems**
 - When they cause clinical problems, they are usually urinary tract infections (UTI), bacteraemia, wound infections, neonatal infections, endocarditis, etc.
- Sources**
 - May be found in healthy community volunteers not recently hospitalised**
 - Community reservoir in meat, poultry and perhaps cheese.
- Mechanism of resistance**
 - Vancomycin-resistant enterococci alter peptidoglycan precursors used to build cell walls. Vancomycin binds to D-ala-D-ala but the resistant enterococci have D-ala-D-lac or D-ala terminating precursors.
 - They acquire genes that produce enzymes to change the precursors.

Anthrax

Overview

- Anthrax is caused by *Bacillus anthracis*, a **Gram-positive rod**. aerobic, non-motile
- It is spread by infected carcasses
- It produces serious disease in the herbivore host and carnivores acquire the disease from either consuming the spores from the dead animal or by contact.
- It is also known as Wool-sorters' disease.
- Cutaneous disease is the commonest form of the infection in humans and is usually due to contact with infected animals or animal products.

Toxins

- *Bacillus anthracis* produces a tripartite (composed of 3 parts) protein toxin
 1. protective antigen
 2. **oedema factor**: a bacterial **adenylate cyclase** which **increases cAMP**
 3. lethal factor: toxic to macrophages

Features

- **painless** non-tender **black eschar** (cutaneous 'malignant pustule', but no pus)
 - ⇒ Following exposure, the skin lesion evolves over a period of ~2 weeks into a papule, pustule, vesicle and eventually forms an ulcer with a central black eschar.
 - ⇒ The surrounding skin is usually boggy and oedematous.
 - ⇒ Lesions are usually painless with tender regional lymph nodes.
- may cause marked oedema
 - ⇒ Edema factor toxin from *Bacillus anthracis* acts to mimic adenylate cyclase, thus increasing cAMP levels.
- anthrax can cause gastrointestinal bleeding

Investigations

- Inhalational anthrax is associated with a poor yield from sputum culture with the greatest yield from **blood culture**.

Management

- Lesions heal spontaneously in 80-90% of cases;
- 10-20% of patients progress and become bacteraemic - associated with a high mortality.
- Penicillin is effective in treating the infection.
- the current Health Protection Agency advice for the **initial management of cutaneous anthrax** is **ciprofloxacin**
- further treatment is based on microbiological investigations and expert advice

Prognosis

- Mortality from cutaneous disease is 20% if untreated whereas inhalational anthrax may have a mortality of 90% if untreated.



Cutaneous anthrax

Diphtheria

Overview

- caused by *Corynebacterium diphtheriae*,
- *Corynebacterium diphtheriae* is a **Gram positive**, non-spore-forming, pleomorphic bacteria that is also a facultative anaerobe.
- There are three recognised strains of *C.diphtheriae*: gravis, intermedium, and mitis.
 - ⇒ Intermedium is thought to be the one most associated with the exotoxin and is more virulent than the mitis strain.
- **Incubation period:** 2 - 5 days,
- patients may be infectious for 4 weeks.
- Diphtheria is spread by droplets, through contact with soiled articles (fomites), and, in areas of poor hygiene, from cutaneous spread.

Pathophysiology

- The inflammatory exudate forms a greyish membrane on the tonsils and respiratory tract which may cause respiratory obstruction.
- Diphtheria toxin inhibits elongation factor (EF-2)
- Diphtheria toxin commonly causes a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Attempts to remove the pseudomembrane result in bleeding. Systemic distribution may produce necrosis of myocardial, neural and renal tissue.
- Exotoxins produced by the organism may cause myocarditis or neurological defects.
- secretion of an exotoxin that interferes with cellular protein synthesis, resulting in tissue necrosis.
- The exotoxin is composed of two chains:
 1. **chain B** is responsible for entry into host cells,
 2. **chain A** inhibits protein synthesis and causes cell death

Feature

history of severe exudative pharyngitis in a person who has recently travelled to eastern Europe is highly suggestive of diphtheria.

- Typically, diphtheria attacks the respiratory system, but **may also affect the skin, conjunctiva, and external genitalia.**
 - ⇒ Cutaneous diphtheria presents with **non-healing ulcers covered with a grey membrane**, which can develop bacterial co-infection.
 - If isolated, the disease is indolent, but the ulcers can act as a reservoir which can subsequently lead to pharyngeal infection.
- **Pharyngeal diphtheria** presents with:
 - ⇒ fever
 - ⇒ sore throat
 - ⇒ cervical lymphadenopathy,
 - 'bulls neck' which results from cervical lymphadenopathy and mucosal swelling.
 - ⇒ adherent, grayish pharyngeal membrane.

- Neurological: cranial neuropathies, predominantly motor peripheral neuropathy (occasionally sensory neuropathy).
- Cardiac involvement is usually in the form of a cardiomyopathy and myositis, which is evident from the 10-14th day and may lead to arrhythmias. This accounts for 50% of deaths

Treatment

- isolation, securing a definitive airway, cardiac monitoring,
- antibiotic therapy and diphtheria antitoxin.
 - ⇒ benzylpenicillin: children: 2.4 to 4.8 g/day intravenously/intramuscularly given in divided doses every 6 hours for 14 days
 - ⇒ OR procaine benzylpenicillin 600,000 units intramuscularly once daily for 14 days
 - ⇒ OR Erythromycin 250-500 mg orally four times daily for 14 days
- Early administration of antitoxin is necessary to enable it to bind to and de-activate the free toxin in serum. **Antitoxin cannot de-activate toxin once it has entered cells**, which is signalled by the presence of mucocutaneous symptoms.
- Patients with respiratory diphtheria are placed in respiratory isolation (masks and standard measures such as hand-washing), and those with cutaneous diphtheria are placed in contact isolation (gloves and gowns), until cultures taken after cessation of therapy are negative.
- **close contacts of respiratory and cutaneous cases:**
 - ⇒ cultures taken immediately
 - ⇒ prophylactic antibiotic (Erythromycin 250 mg orally four times daily for 7-10 days Or benzathine benzylpenicillin 1.2 million units intramuscularly as a single dose.
 - ⇒ diphtheria toxoid immunisation.

Complications

- **The toxin affects the myocardium, nervous and adrenal tissues.**

Listeria

Listeria meningitis should always be considered in patients with meningitis associated with brain stem involvement, in elderly and in immunosuppressed patients. The treatment of choice is gentamicin and ampicillin.

- *Listeria monocytogenes* is a Gram positive bacillus
- has the unusual ability to multiply at low temperatures.
- It is typically spread via contaminated food, typically unpasteurised dairy products.
- infection is particularly dangerous to the unborn child where it can lead to miscarriage.
- Listeriosis is associated with the consumption of soft cheese.

Features - can present in a variety of ways

- diarrhoea,
- flu-like illness
- pneumonia ,
- meningoencephalitis
- ataxia and seizures

Investigations

- Suspected Listeria infection should be investigated by taking **blood cultures**.
- **CSF** may reveal a pleocytosis, with 'tumbling motility' on wet mounts

Management

- Listeria is sensitive to **amoxicillin/ampicillin** (cephalosporins usually inadequate)
- Listeria meningitis should be treated with IV amoxicillin/ampicillin and gentamicin

In pregnant women

- **pregnant women are almost 20 times more likely to develop listeriosis** compared with the rest of the population due to changes in the immune system
- fetal/neonatal infection can occur both transplacentally and vertically during child birth
- complications include miscarriage, premature labour, stillbirth and chorioamnionitis
- diagnosis can only be made from blood cultures
- treatment is with amoxicillin

Campylobacter

Overview

- Campylobacter is the commonest bacterial cause of infectious intestinal disease in the UK.
- The majority of cases are caused by the Gram-negative bacillus *Campylobacter jejuni*.
- It is spread by the faecal-oral route
- has an incubation period of 1-6 days.

Features

- prodrome: headache malaise
- diarrhoea: often bloody
- abdominal pain

Management

- usually self-limiting
- **the most appropriate therapy is IV fluids**. appropriate fluid replacement and anti-emetics are initially indicated - most units advocate no antibiotic treatment.
- the BNF advises treatment if **severe** or the patient is **immunocompromised**. Clinical Knowledge summaries also recommend antibiotics if severe symptoms (high fever, bloody diarrhoea, or more than eight stools per day) or symptoms have last more than one week
- the first-line antibiotic is **clarithromycin**

Complications

- Guillain-Barre syndrome may follow *Campylobacter jejuni* infections
- Reiter's syndrome
- septicaemia,
- endocarditis,
- arthritis

Shigella

Overview

- Shigella dysenteriae is a gram negative bacillus.
- Shigellosis is the bacillary dysentery caused by Shigella dysenteriae.
- causes bloody diarrhoea, abdo pain
- The most common signs of Shigella dysentery include colitis, malnutrition, reactive arthritis, and central nervous system problems.
- severity depends on type: S sonnei (e.g. from UK) may be mild, S flexneri or S dysenteriae from abroad may cause severe disease
- **treat with ciprofloxacin**

Escherichia coli

- *Escherichia coli* is a facultative anaerobic, lactose-fermenting, **Gram negative rod** which is a normal gut commensal.
- *E. coli* infections lead to a variety of diseases in humans including:
 - ⇒ diarrhoeal illnesses
 - ⇒ UTIs
 - ⇒ neonatal meningitis

Serotypes

E. coli may be classified according to the antigens which may trigger an immune response:

Antigen	Origin	Notes
O	Lipopolysaccharide layer	
K	Capsule	Neonatal meningitis secondary to <i>E. coli</i> is usually caused by a serotype that contains the capsular antigen K-1
H	Flagellin	

E. coli O157:H7 (enterohemorrhagic *E. coli*, EHEC):

- is a particular strain associated with severe, haemorrhagic, watery diarrhoea.
- It has a high mortality rate and can be complicated by haemolytic uraemic syndrome.
- It is often spread by contaminated ground beef.
- the diagnostic test is: Stool culture on sorbitol-MacConkey medium

multiple drug resistant *Escherichia coli* :

- **mechanism of resistance → Extended spectrum beta-lactamase (ESBL) production**
 - ⇒ Some *E. coli* isolates produce an Extended spectrum beta-lactamase (ESBL) that inactivates second and third generation cephalosporins.
- The class of drugs that will most reliably treat these infections are the carbapenems.
- Extended spectrum B-lactamase (ESBL) producing organisms are typically resistant to penicillins and cephalosporins and as such the **carbapenem class of antibiotics are typically first line** although nitrofurantoin or fosfomycin are also frequently effective.
- ESBL producers are most commonly *Escherichia coli* (*E. coli*) and *Klebsiella* species.

Which virulence factor contributes to the pathophysiology of the (*E. coli*) causing UTI?

→ P pilus

- Uropathogenic *E. coli* utilize a **P pilus** to bind to uroepithelial cells and colonize the urethra.

Incubation periods

Questions may either ask directly about incubation periods or they may be used to provide a clue in a differential diagnosis.

Less than 1 week	1 - 2 weeks	2 - 3 weeks	Longer than 3 weeks
<ul style="list-style-type: none"> meningococcus diphtheria influenza scarlet fever 	<ul style="list-style-type: none"> malaria dengue fever typhoid measles 	<ul style="list-style-type: none"> mumps rubella chickenpox 	<ul style="list-style-type: none"> infectious mononucleosis cytomegalovirus viral hepatitis HIV

Virulence factors

- Bacteria employ a large number of virulence factors which enable them to colonize the host and evade/suppress the immune response.
- The table below shows a select number of virulence factors which are important for the exam.

Virulence factor	Example organisms
IgA protease	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Neisseria gonorrhoeae</i>
M Protein	<i>Streptococcus pyogenes</i>
Polyribosyl ribitol phosphate capsule	<i>Haemophilus influenzae</i>
Bacteriophage	<i>Corynebacterium diphtheriae</i>
Spore formation	<i>Bacillus anthracis</i> <i>Clostridium perfringens</i> <i>Clostridium tetani</i>
Lecithinase alpha toxin	<i>Clostridium perfringens</i>
D-glutamate polypeptide capsule	<i>Bacillus anthracis</i>
Actin rockets	<i>Listeria monocytogenes</i>

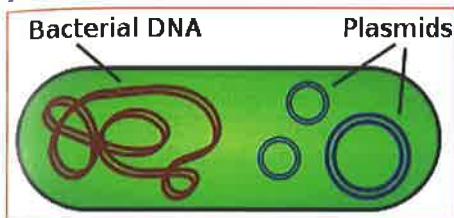
- New Delhi metallo-beta-lactamase 1**
 - is the mutation that leads to carbapenem resistance.
 - Typically found in *Klebsiella pneumoniae*, *Escherichia Coli* (E. Coli), *Enterobacter cloacae* and others.
 - First line of management is the old antibiotic **colistin** and second line may be **tigecycline**.

- **D-alanyl-D-lactate**
 - ⇒ **D-alanyl-D-lactate** variation leading to loss of affinity to antibiotics is the mechanism of VRE (vancomycin resistant enterococci).
 - ⇒ Vancomycin binds to D-ala-D-ala.

- **MexAB-OprM efflux pumps**
 - ⇒ The presence of **MexAB-OprM efflux pumps** is one of the mechanisms by which pseudomonas aeruginosa is resistant to -lactams, chloramphenicol, fluoroquinolones, macrolides, novobiocin, sulfonamides, tetracycline, and trimethoprim.

- **penicillin binding protein 2**
 - ⇒ Alteration to the **penicillin binding protein 2** is the mechanism behind methicillin-resistant staphylococcus aureus.
 - ⇒ **Mutations in the MEC gene** which codes the penicillin binding proteins give staphylococcus aureus its resistance.

Plasmids



- **Plasmid** is a small DNA molecule within a cell , separated from a chromosomal DNA and can replicate independently.
- Plasmids carry genes that may benefit the survival of the organism, for example antibiotic resistance.
- Bacteria develop resistance to antibiotics by gaining genes that encode for particular proteins that offer protection to the organism.
- Sometimes this is by mutation and at other times the gene may be acquired from another bacterial species.
- The genes are usually found in **plasmids - circular segments of DNA separate from the bacterial chromosome.**
- Plasmids can be used to clone genes by splicing a particular gene into a plasmid and then allowing the bacteria to multiply - this is then called recombinant plasmid DNA.
- Plasmids can easily spread from one bacteria to another - a sort of resistance package that bacteria can share.
- **Which best explains the loss of antibiotic resistance in bacterial strain?**
→ **Loss of a plasmid containing the resistance gene**

Antibiotic resistance mechanism

Antibiotic	Resistance mechanism
fluoroquinolones (eg: ciprofloxacin)	Change in the bacterial DNA gyrase due to genetic mutation
Macrolides (eg: Erythromycin)	Bacterial ribosomal methylation
Tetracycline	Bacterial efflux of antibiotic
chloramphenicol	Antibiotic inactivation by acetyltransferase
Penicillin	<p>Production of penicillinase by the bacteria is the most common mechanism of bacterial resistance to penicillin.</p> <p>However, penicillin resistance in streptococcus pneumonia is due to alteration in the penicillin-binding protein, not production of penicillinase.</p>
Vancomycin	D-ala-D-ala mutates to D-ala-D-lac

Tetanus

Definition

- Tetanus is a life-threatening neurological syndrome characterised by tonic muscle spasms and hyperreflexia, caused by the exotoxin of *Clostridium tetani*, a gram-positive spore-forming obligate anaerobe.

Incubation period: 3 - 21 days.

Pathophysiology

- C. tetani* spores contaminate a wound (especially with animal feces and soil) → production of the neurotoxins **tetanospasmin** and **tetanolysin**
- Tetanospasmin:** reaches the CNS **through retrograde axonal transport** → **cleaves a synaptobrevin protein** → prevention of inhibitory neurotransmitters (i.e., GABA and glycine) → tetanic spasms.
- Tetanolysin:** causes hemolysis and has cardiotoxic effects
- The wound is often unnoticed (the absence of a wound does not exclude tetanus).

Features

- Generalized tetanus: painful muscle spasms and rigidity
 - ⇒ **Trismus:** lockjaw due to spasms of jaw musculature
 - ⇒ **Risus sardonicus:** sustained facial muscle spasm that causes a characteristic, apparently sardonic grin and raised eyebrows
 - ⇒ **Opisthotonus:** backward arching of spine, neck, and head caused by spasms of the back muscles
 - ⇒ **Dysphagia**
- Life-threatening complications
 - ⇒ Laryngospasm and/or respiratory muscles spasms → respiratory failure

- ⇒ Autonomic dysfunction: manifest early as irritability, restlessness, sweating, and tachycardia.

Diagnosis

- clinical diagnosis based on muscle spasms and rigidity associated with an entry point for bacteria and an inadequate vaccination history.

Management

- **Supportive therapy:** e.g. ventilatory support, benzodiazepines and muscle relaxants
- **Immunization**
 - ⇒ Passive immunization → **Human tetanus immunoglobulin (HTIG)**
 - Should be given to:
 - ❖ patients **with contaminated wounds** who did not completed 3 doses of tetanus vaccine or unknown.
 - ❖ patient with **High-risk tetanus-prone wounds** who did completed 3 doses of tetanus vaccine, but last dose > 10 years ago.
 - Clean and minor wounds do not require HTIG.
 - ⇒ Active immunization → **Tetanus toxoid-containing vaccine (TT)**
 - For **ANY wound** if vaccination history is incomplete or unknown
 - For contaminated wounds **ONLY** if completed 3 doses of TT, but last dose > 10 years ago.
- **Wound cleaning and debridement**
- **Antibiotics :** **Metronidazole is now preferred to benzylpenicillin as the antibiotic of choice** (500 mg intravenously every six to eight hours for 7 to 10 days).

Post-exposure tetanus prophylaxis

Post-exposure tetanus prophylaxis			
Vaccination history & wound status	Clean wounds	Tetanus-prone wounds	High-risk tetanus-prone wounds
	Clean cuts	<ul style="list-style-type: none"> ▪ Contaminated puncture-type injuries ▪ wounds containing foreign bodies ▪ compound fractures ▪ wounds or burns with systemic sepsis ▪ certain animal bites and scratches 	<ul style="list-style-type: none"> ▪ heavy contamination with materials likely to contain tetanus spores e.g. soil, manure. ▪ wounds or burns that show extensive devitalised tissue ▪ wounds or burns that require surgery that is delayed > 6 hours.
Unknown or < 3 TT doses	TT vaccine	TT vaccine + HTIG	TT vaccine + HTIG
≥ 3 TT doses and last dose within 10 years	None required	None required	None required
≥ 3 TT doses, but last dose > 10 years ago	None required	TT vaccine	TT vaccine + HTIG

TT: Tetanus toxoid. HTIG: Human Tetanus Immuno-Globulin
 Reference: The green book, Guidance, From UK Health Security Agency January 2020
<https://www.gov.uk/government/publications/tetanus-the-green-book-chapter-30>

Tetanus vaccination

- Tetanus vaccine is currently given in the UK as 5 doses at: 2 months, 3 months, 4 months, 3-5 years and 13-18 years.
- Tetanus toxoid is only available in combination with other antigens such as diphtheria and pertussis.
 - ⇒ For age < 7, the **DTaP** (Diphtheria/Tetanus/acellular Pertussis vaccine) vaccine is given.
 - ⇒ After age 7, all tetanus vaccines are paired with a lower concentration of diphtheria as signified by the lower-case "d" in the vaccination names, **Tdap** (Tetanus/low-dose diphtheria/acellular pertussis vaccine) or **Td** (Tetanus/diphtheria) may be used for booster. **Td** is used when the pertussis vaccine component is contraindicated.
 - ⇒ For pregnant women, one dose of the **Tdap** vaccine should be administered during **each pregnancy** between 27 weeks and 36 weeks of gestation, regardless of when the last dose of **Td** or **Tdap** was given.
 - ⇒ If a tetanus booster is indicated for wound management during pregnancy, **Tdap** should be administered instead of **Td** if the woman has not received **Tdap** previously.

Patients with large or dirty wounds and an uncertain vaccination history should be offered tetanus toxoid containing vaccination as well as Human tetanus-specific immune globulin (HTIG).

If the patient with a clean non-tetanus-prone wound has a complete vaccination history and is less than 10 years since the last dose, no prophylaxis should be given.

MRCP-1- exam - January 2015: H/O 4 cm laceration to the dorsum of left hand after cutting using a Stanley knife. no sign of a foreign body. He has 'no idea' about his tetanus vaccination. What is the most appropriate action with respect to tetanus?

- Requires tetanus vaccine + complete vaccine course at a later date
 - (This wound is not high risk for tetanus)

Salmonella & Typhoid fever

Humans are the main reservoir for *Salmonella typhi*

Bacteriology

- Gram negative rods
- grow under both an **aerobic** and **anaerobic** conditions.
- not normally present as commensals in the gut.
- Incubation period
 - ⇒ 5–30 days (most commonly 7–14 days)
- **Transmission:**
 - ⇒ fecal-oral

Types

- *Salmonella typhi* causes Typhoid
- *Salmonella paratyphi* (types A, B & C) causes paratyphoid
 - ⇒ They are often termed enteric fevers.
 - ⇒ Blood and bone infections caused by non-typhi salmonella (NTS) are typically associated with malaria and homozygous sickle cell disease, especially in

children. The reason for this perceived susceptibility is not fully understood - but it may be in part due to the haemolysis and subsequent iron availability to the bacteria, which is 'siderophilic' in nature.

Pathophysiology

- **Lifecycle**

1. Oral uptake of pathogen
2. Distal ileum: migration into the Peyer patches
3. Infection of macrophages and reticuloendothelial system → nonspecific symptoms
4. Spread from macrophages to the bloodstream: septicemia → systemic disease
5. Migrates back to intestine → excretion in feces

Typhoid vaccines

- typhoid vaccines are currently available
 - ⇒ (Typhoid vaccine does not protect from paratyphoid infection)
- There are 3 types of typhoid vaccine:
 1. parenteral (Typh-I), → inactivated vaccine (i.e. killed)
 2. parenteral combined with hepatitis A (HA-Typh-I), and
 3. oral (Typh-O) → **Live-attenuated vaccine**
- These vaccines provide approximately **50% protection** against clinical disease.
- No vaccine is available against paratyphoid fever.
- Vaccinated individuals who develop the disease will **have a higher threshold** but the **same disease**.

Features

- initially systemic upset (headache, fever, arthralgia)
- relative bradycardia
- abdominal pain, distension
- diarrhoeal disease
 - ⇒ Yellow-green diarrhea, comparable to pea soup (caused by purulent, bloody necrosis of the Peyer patches)
- constipation:
 - ⇒ **although *Salmonella* is a recognised cause of diarrhoea, constipation is more common in typhoid**
 - ⇒ obstipation and ileus (as a result of swollen Peyer patches in the ileum)
- **Rose spots:**
 - ⇒ present on the trunk in 40% of patients,
 - (most commonly around the navel) حول السرة
 - ⇒ more common in paratyphoid
- Neurological symptoms (delirium, coma)
- Rarely causes sepsis, meningitis, myocarditis, and renal failure

Complication

- **Chronic *Salmonella* carrier**
 - ⇒ Definition:
 - positive stool cultures 12 months after overcoming the disease
 - ⇒ Incidence:
 - up to 6% of the patients become chronic carriers
 - ⇒ Presentation:
 - typically asymptomatic
 - ⇒ Treatment:
 - fluoroquinolones (e.g., ciprofloxacin) administered for at least 1 month
 - ⇒ Chronic carriers are not allowed to work in the food industry.
 - ⇒ Increased risk for cholangiocarcinoma (bile duct cancer)

Investigations

- normal or low leukocyte count with **eosinopenia**
- Blood culture,
 - ⇒ the most effective investigation for diagnosis
 - ⇒ (should be done prior to starting antibiotic)
- Bone marrow culture
 - ⇒ highly sensitive diagnostic test even in later stages of infection after antibiotic therapy has begun.
 - ⇒ indicated for all patients with prolonged pyrexia if routine investigations have not provided a diagnosis.
- **in chronic carriers**
 - ⇒ **Blood cultures** will be **negative** in chronic carriers because the organism resides mainly in the gallbladder.
 - ⇒ **Salmonella typhi can be cultured from intestinal secretions, faeces or urine**
- Widal's test
 - ⇒ Serological test
 - ⇒ poor sensitivity
 - ⇒ negative in early infection.
 - indicated only after 5 to 7 days of fever.
 - ⇒ not useful for detecting chronic carriage.
- Faecal culture
 - ⇒ positive in only 50% of cases during the first week of illness.

Complications

- osteomyelitis
 - ⇒ (especially in sickle cell disease where *Salmonella* is one of the most common pathogens)
- GI bleed/perforation
- meningitis
- cholecystitis
- chronic carriage (1%)
 - ⇒ **more likely if adult females**

Treatment

- best treated with quinolones, chloramphenicol or cotrimoxazole.
- However, with breast feeding chloramphenicol is relatively contraindicated as are quinolones due to potential risk even if small.
- Also, cotrimoxazole is safe in breast feeding except with infants less than 2 months due to possible risk of increased bilirubin.
- **In pregnancy or children, the drug of choice is parenteral ceftriaxone.**
- The gallbladder may act as a reservoir of infection and cause relapse in individuals treated with antibiotics. Cholecystectomy may be indicated.
- According to the NICE guidelines, anyone above the age of 50, immunocompromised or has cardiac valve disease/endovascular abnormalities should be treating empirically with ciprofloxacin 500mg BD when they have been diagnosed with non-typhoidal *Salmonella* gastroenteritis.

Meningitis

Causes

The most common cause of bacterial meningitis is ***Streptococcus pneumoniae*** (Gram positive diplococci), accounting for >50% cases.

Listeria is a less common Gram positive cause of meningitis.

0 - 3 months	3 months - 6 years	6 years - 60 years	> 60 years	Immunosuppressed
Group B <i>Streptococcus</i> (most common cause in neonates)	<i>Neisseria meningitidis</i>	<i>Neisseria meningitidis</i>	<i>Streptococcus pneumoniae</i>	<i>Listeria monocytogenes</i>
<i>E. coli</i>	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pneumoniae</i>	<i>Neisseria meningitidis</i>	
<i>Listeria monocytogenes</i>	<i>Haemophilus influenzae</i>		<i>Listeria monocytogenes</i>	

Coxsackie virus is the most common viral cause of meningitis.

Pneumococcal meningitis

- caused by the Gram positive coccus *Strep. pneumoniae*.
- the second commonest cause of bacterial meningitis (commonest in the elderly)
- associated with the highest mortality (20%) and highest morbidity, such as deafness which may occur in 50% (**Nerve deafness is a common complication**)
- Chronic adhesive arachnoiditis is a complication of pneumococcal meningitis characterized by fibrosis of the arachnoid granulations.
- Contacts do not require treatment
- there is no rash associated with pneumococcal meningitis.

In the context of septic meningitis, **the petechial rash is diagnostic for infection with *Neisseria meningitidis***

Listeria meningitis

- Risk factors for listeria meningitis include
 - ⇒ neonates
 - ⇒ Older age
 - ⇒ immunosuppression.
- It is typically associated with brainstem signs.

- **Beta-hemolysis** is the type of hemolysis exhibited by *Listeria monocytogenes*, an organism showing tumbling motility that causes meningitis in newborns.
- Cerebrospinal fluid shows:
 - ⇒ Neutrophilic pleocytosis
 - ⇒ Low glucose, and
 - ⇒ High protein.

Fungal meningitis

- Patients at risk for fungal **meningitis** include:
 - ⇒ those who are significantly immunocompromised,
 - ⇒ **those who have received intrathecal injections in the past.**
- Cerebrospinal fluid analysis
 - ⇒ elevated opening pressure
 - ⇒ detectable b-D-glucan
- **Testing for b-D-glucan has been an approved blood test to detect systemic fungal infection.**

Partially treated bacterial meningitis

Partial treatment of bacterial meningitis can result in **false negative CSF culture** and **Gram stain**, but **the CSF white cell count should be unaffected**.

- The assessment of children with suspected bacterial meningitis who have already received antibiotic therapy from their GP is a common diagnostic problem.
- Partial treatment may reduce the incidence of positive CSF Gram stains to less than 60%, and it also reduces the ability to grow the bacteria, particularly meningococcus.
 - Partial treatment may induce:
 - negative CSF culture
 - negative Gram stain
- CSF glucose, protein, neutrophils and bacterial antigen testing or polymerase chain reaction (PCR) should be completely unaffected.
- **A normal white cell count would make the diagnosis very unlikely.**
- In normal CSF the glucose is usually > 65% of blood glucose.

Meningitis: Investigations

- **Investigations suggested by NICE**
 - ⇒ full blood count
 - ⇒ CRP
 - ⇒ coagulation screen
 - ⇒ blood culture
 - ⇒ whole-blood PCR
 - ⇒ blood glucose
 - ⇒ blood gas
 - ⇒ Lumbar puncture if no signs of raised intracranial pressure

Meningitis: CSF analysis

Mumps meningitis is associated with a low CSF glucose

The table below summarises the characteristic cerebrospinal fluid (CSF) findings in meningitis:

	Bacterial	Viral	Tuberculous
Appearance	Cloudy	Clear/cloudy	Slight cloudy, fibrin web
Glucose	Low (< 1/2 plasma)	60-80% of plasma glucose*	Low (< 1/2 plasma)
Protein	High (> 1 g/l)	Normal/raised	High (> 1 g/l)
White cells	10 - 5,000 polymorphs/mm ³	15 - 1,000 lymphocytes/mm ³	10 - 1,000 lymphocytes/mm ³

*mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

- The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)
- **Bacterial culture of cerebrospinal fluid** is the **gold-standard** test for determining if a case of **meningitis** is bacterial in etiology

The CSF lymphocytosis combined with a glucose greater than half the serum level points towards a viral meningitis.

Management

In patients presenting with symptoms and signs of meningitis, treat empirically for bacterial meningitis while awaiting test results from the lumbar puncture.

- All patients should be transferred to hospital urgently.
- If patients are in a pre-hospital setting (for example a GP surgery) and meningococcal disease is suspected then intramuscular benzylpenicillin may be given, as long as this doesn't delay transit to hospital.
- **In bacterial meningitis, dexamethasone should also be given with the first dose of antibiotics.**

BNF recommendations on antibiotics

Scenario	BNF recommendation
Initial empirical therapy aged < 3 months	Intravenous cefotaxime + amoxicillin
Initial empirical therapy aged 3 months - 50 years	Intravenous cefotaxime
Initial empirical therapy aged > 50 years	Intravenous cefotaxime + amoxicillin
Meningococcal meningitis	Intravenous benzylpenicillin or cefotaxime
Pneumococcal meningitis	Intravenous cefotaxime
Meningitis caused by <i>Haemophilus influenzae</i>	Intravenous cefotaxime
Meningitis caused by Listeria	Intravenous amoxicillin + gentamicin

- If the patient has a history of immediate hypersensitivity reaction to penicillin or to cephalosporins the BNF recommends using chloramphenicol.
- Ceftriaxone does not cover *Listeria* well, and in the over 60s or immunosuppressed, amoxicillin should be added in to empirical meningitis management to cover this.

Management of contacts

- prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis
- oral ciprofloxacin or rifampicin may be used.
 - ⇒ The BNF recommends a twice a day dose of rifampicin for two days, based on the patients weight.
 - ⇒ The Health Protection Agency (HPA) guidelines now state that whilst either may be used **ciprofloxacin is the drug of choice as it is widely available and only requires one dose**
 - ⇒ **Rifampicin may reduce the efficacy of the oral contraceptive through liver enzyme induction. So not preferred in sexually active. Therefore ciprofloxacin would be the most appropriate agent as it does not induce cytochrome p450.**
- the risk is highest in the first 7 days but persists for at least 4 weeks
- meningococcal vaccination should be offered to close contacts when serotype results are available, including booster doses to those who had the vaccine in infancy
- **for pneumococcal meningitis no prophylaxis is generally needed.** There are however exceptions to this. If a cluster of cases of pneumococcal meningitis occur the HPA have a protocol for offering close contacts antibiotic prophylaxis.

September 2010 exam: A 57-year-old female presents with headache, fever, neck stiffness with a positive Kernig's sign. CSF culture: Gram positive bacilli. What is the most likely causative organism?

→ *Listeria monocytogenes*

MRCPUK-parat-1-January 2013 exam: A 47-year-old lady with Feature of fever, headache and nuchal rigidity. Lumbar puncture reveals: Appearance: Cloudy. Glucose:1.7 mmol/l. Protein:1.9 g/l. White cells: 900 / mm³ (90% polymorphs). What is the most likely infective agent?

→ *Streptococcus pneumoniae*

- (CSF → results bacterial meningitis (low glucose, high protein, high polymorphs)).
- In this age group *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common causes of bacterial meningitis)

MRCPUK-parat-1-May 2014 exam: A diagnosis of pneumococcal meningitis is made. There are no other reports of meningitis in the local area over the past 4 weeks. How should the close contacts of this boy be managed?

→ No action is needed (unless cluster of cases develop)

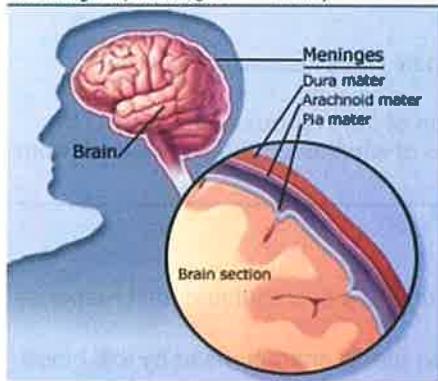
MRCPUK-parat-1-May 2009 exam: A 23-year-old man is admitted with purpuric rash, pyrexia and confusion. His GP had given him intramuscular benzylpenicillin. Which one of the following investigations is most likely to reveal the diagnosis?

→ Blood PCR for meningococcus

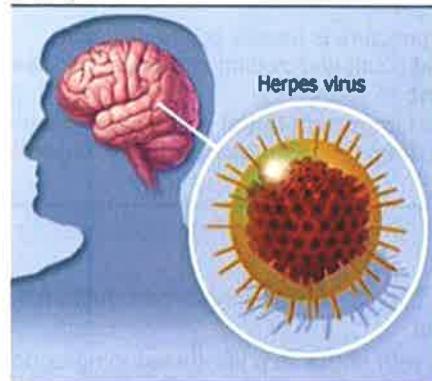
- (The blood cultures are likely to be negative as antibiotics have already been given, PCR has a sensitivity of over 90%)

Encephalitis

Meninges (Coverings of the Brain)



Encephalitis



Encephalitis usually presents with altered mental status, erratic behavior, etc (brain parenchyma involved).

Aetiology

- The most common cause is herpes simplex, usually type I (HSV-1).

Clinical Presentation

- Altered mental status with fever and headache is the primary clue to the diagnosis.
- Neck stiffness similar to that found in meningitis can occur, making it difficult to distinguish encephalitis from meningitis.
- Seizures may also occur.

Diagnosis

- Although CT or MRI scan of the head should be performed, it cannot give a specific diagnosis. HSV has a predilection for involvement of the temporal lobes, which can sometimes be seen on CT.
- A lumbar puncture is the key to the diagnosis.
- PCR (polymerase chain reaction) for HSV has a 98% sensitivity and >95% specificity, making it at least equal to the biopsy.

Treatment

- HSV encephalitis is best treated with IV acyclovir.
- Acyclovir-resistant herpes is treated with foscarnet

Meningococcal septicaemia

Overview

- It is associated with a high morbidity and mortality unless treated early
- meningococcal disease is the leading infectious cause of death in early childhood.
- A high index of suspicion is therefore needed.

Presentation of meningococcal disease:

- 15% - meningitis
- 25% - septicaemia
- 60% - a combination of meningitis and septicaemia

Investigations

- blood cultures
- blood PCR
- lumbar puncture is usually contraindicated
- full blood count and clotting to assess for disseminated intravascular coagulation

Management

- **the most important initial step → administration of intravenous antibiotics (cefotaxime) is the greatest priority, regardless of whether cultures have been sent.**

Sepsis

Overview

- Sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection.
- Sepsis with shock is a life-threatening condition that is characterised by low blood pressure despite adequate fluid replacement, and organ dysfunction or failure.

Definition

- The new definition attempts to draw upon up-to-date pathobiology and distinguish between sepsis and uncomplicated infection. A new tool has been developed for this purpose - the SOFA or qSOFA.
⇒ The qSOFA (Quick SOFA) criteria are:

- Respiratory rate > or equal to 22/min
- Altered GCS
- Systolic blood pressure < or equal to 100mmHg
- Septic shock is defined as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. This changes from the previous definition to recognise the importance of cellular abnormalities.
- Septic shock is defined by persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

Risk factors for sepsis

- Age (< 1 year and > 75 years)
- very frail people
- Immunocompromised
 - ⇒ impaired immune function (eg, DM, splenectomy, sickle cell disease)
 - ⇒ drugs(long-term steroids, chemotherapy, immunosuppressant)
- surgery, or other invasive procedures, in the past 6 weeks
- any breach of skin integrity (eg, cuts, burns, blisters or skin infections)
- misuse drugs intravenously
- indwelling lines or catheters

Risk stratification tool for adults, children and young people aged 12 years and over with suspected sepsis

High risk criteria	Moderate to high risk criteria
Objective evidence of new altered mental state	<ul style="list-style-type: none"> History from patient or relative of new onset of altered behaviour or mental state History of acute deterioration of functional ability Impaired immune system (illness or drugs including oral steroids) Trauma, surgery or invasive procedures in the last 6 weeks
<ul style="list-style-type: none"> respiratory rate: ≥ 25 breaths per minute New need for oxygen (more than 40% FiO_2) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease) 	Raised respiratory rate: 21–24 breaths per minute
Systolic blood pressure ≤ 90 mmHg or more than 40 mmHg below normal	Systolic blood pressure 91–100 mmHg
heart rate: > 130 beats per minute	heart rate: 91–130 beats per minute (for pregnant women 100–130 beats per minute) or new onset arrhythmia
Not passed urine in previous 18 hours. For catheterised patients, passed less than 0.5 ml/kg of urine per hour	Not passed urine in the past 12–18 hours For catheterised patients, passed 0.5–1 ml/kg of urine per hour
<ul style="list-style-type: none"> Mottled or ashen appearance Cyanosis of skin, lips or tongue Non-blanching rash of skin 	Tympanic temperature less than 36°C Signs of potential infection, including redness, swelling or discharge at surgical site or breakdown of wound.

Low risk criteria:

- Normal behavior
- No high risk or moderate to high risk criteria met

Temperature in suspected sepsis

- Do not rely on fever or hypothermia to rule sepsis either in or out.
- Some people with sepsis may not develop a raised temperature:
 - older or very frail
 - severely ill
 - people having treatment for cancer
 - young infants or children.
- a rise in temperature can be a physiological response (eg: after surgery or trauma).

Management

- 1 or more high risk criteria:
 - blood test for blood gas including glucose and lactate measurement, blood culture, full blood count, C-reactive protein, urea and electrolytes, creatinine, clotting screen.
 - Sepsis may be complicated by disseminated intravascular coagulation**

- ⇒ give a broad-spectrum antimicrobial at the maximum recommended dose without delay (within 1 hour)
- Any high risk criteria and lactate > 4 mmol/litre, or systolic BP < 90 mmHg:
 - ⇒ I.V fluid bolus without delay (within 1 hour)
 - ⇒ refer to critical care for review of management including need for central venous access , inotropes or vasopressors.
- Any high risk criteria and lactate between 2 and 4 mmol/litre: I.V fluid bolus without delay (within 1 hour)
- ⇒ Any high risk criteria and lactate < 2 mmol/litre: consider I.V fluid bolus
- Failure to respond within 1 hour of initial antibiotic and/or intravenous fluid resuscitation
 - ⇒ Failure to respond is indicated by any of:
 - systolic blood pressure persistently below 90 mmHg
 - reduced level of consciousness despite resuscitation
 - respiratory rate over 25 breaths per minute or a new need for mechanical ventilation
 - lactate not reduced by more than 20% of initial value within 1 hour.
- 2 or more moderate to high risk criteria
 - ⇒ blood test for blood gas including glucose and lactate measurement, blood culture, full blood count, C-reactive protein, urea and electrolytes, creatinine
 - ⇒ review the person's condition and venous lactate results within 1 hour
- 2 or more moderate to high risk criteria and lactate > 2 mmol/litre or evidence of acute kidney injury: treat as high risk
- 2 or more moderate to high risk criteria, have lactate < 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition cannot be identified:
 - ⇒ repeat structured assessment at least hourly
 - ⇒ review by a senior within 3 hours for consideration of antibiotics.
- 2 or more moderate to high risk criteria, have lactate < 2 mmol/litre, no evidence of acute kidney injury and in whom a definitive condition or infection can be identified and treated:
 - ⇒ manage the definitive condition
 - ⇒ if appropriate, discharge
- Intravenous fluids in people with suspected sepsis
 - ⇒ If patients over 16 years need intravenous fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/litre with a bolus of **500 ml over less than 15 minutes.**

Sepsis Resuscitation Bundle: Surviving Sepsis Campaign

- Should begin immediately, but must be accomplished within the first six hours of presentation.
 1. Serum lactate measured.
 - 2. Blood cultures obtained prior to antibiotic administration.**
 3. From the time of presentation, broad-spectrum antibiotics administered within three hours for ED admissions and one hour for non-ED ICU admissions.
 4. In the event of hypotension and/or lactate > 4 mmol/l (36 mg/dl):
 - Deliver an initial minimum of 30 ml/kg of crystalloid (or colloid equivalent).
 - 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 (36 mg/dl):
 - Achieve central venous pressure (CVP) of > 8 mm Hg.
 - Achieve central venous oxygen saturation (ScvO₂) of > 70%.

H/O sepsis secondary to pneumonia, treated with 4.5 L sodium chloride 0.9%, blood pressure was 82/40 mmHg. In attempting to restore the blood pressure, what is the most appropriate intravenous therapy?

→ noradrenaline (norepinephrine)

Ref: www.mrcuk.org/ Acute Medicine Specialty Certificate Examination/ sample questions

Tuberculosis (TB)**Definition**

- TB is an infection caused by *Mycobacterium tuberculosis* that most commonly affects the lungs.
- *Mycobacterium tuberculosis*:
 - ⇒ aerobic non-motile bacillus.
 - ⇒ classified as a Gram-positive organism

Pathophysiology**• Primary tuberculosis**

- Bacilli are transported via lymphatics early in the disease process to regional lymph nodes to cause marked lymphadenopathy.
- Process after exposure to mycobacterium tuberculosis:
 - 90 % of individuals with intact immunity control further replication of the bacilli, by either:
 - ❖ Clearance or
 - ❖ enter a "latent" phase (asymptomatic, but has the potential to become active at any time)
 - 10% → Progression to local pulmonary disease or dissemination
 - ❖ occurs more frequently in those with poor immune responses, such as:
 - ⇒ HIV
 - ⇒ chronic kidney failure,
 - ⇒ poorly controlled diabetes mellitus,

- ⇒ immunosuppressive medications (including transplant recipients),
- ⇒ young children (before the age of five),
- ⇒ older adults.
- **non-immune host** who is exposed to M. tuberculosis may develop primary infection of the lungs. A small lung lesion known as a **Ghon** focus develops. The Ghon focus is composed of tubercle-laden macrophages. The combination of a Ghon focus and hilar lymph nodes is known as a Ghon complex
- in **immunocompetent** people the initial lesion usually heals by fibrosis.
- **immunocompromised** peoples may develop disseminated disease (miliary tuberculosis).
 - ❖ ***Mycobacterium avium causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm³.***
- Pleural and pericardial infections (which can result in effusions) occur at or shortly after primary infection.
- **Secondary (post-primary) tuberculosis**
 - ⇒ Definition
 - Reactivation of the initial infection if the host becomes immunocompromised
 - ⇒ Site of reactivation:
 - Pulmonary: the most common site for secondary TB.
 - ❖ generally, occurs in the apex of the lungs and may spread locally or to more distant sites.
 - Extra-pulmonary:
 - ❖ CNS (tuberculous meningitis - the most serious complication)
 - ❖ Vertebral bodies (Pott's disease)
 - ❖ Cervical lymph nodes (Scrofuloderma)
 - ⇒ Scrofuloderma occurs when the skin becomes involved by direct extension from an underlying tuberculous infection (usually lymphadenitis).
 - ❖ Renal
 - ❖ GIT
 - ⇒ Causes of immunocompromise:
 - immunosuppressive drugs (e.g. Steroids)
 - HIV
 - malnutrition

Features

- Primary TB is usually asymptomatic
- cough >2 to 3 weeks' duration, lymphadenopathy, fevers, night sweats, weight loss
- Pulmonary complications of TB can include hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction, malignancy, and chronic pulmonary aspergillosis.
- **TB may be associated with an inflammatory polyarthritis that may follow a similar pattern to rheumatoid arthritis**

Transmission

- **Non-sputum producing patients are non-infectious**. Only untreated smear-positive pulmonary TB is likely to be infectious.

Screening

- **Mantoux test**
- Interferon-gamma blood test
 - ⇒ It is used in several specific situations such as:
 - the Mantoux test is positive or equivocal
 - people where a tuberculin test may be falsely negative (see below)

Patients should be routinely screened for TB exposure before treatment with Etanercept with the tuberculin skin test

Mantoux test (tuberculin test) (purified protein derivative (PPD) test)

- Mechanism:
 - ⇒ It is a **type IV**, (delayed) hypersensitivity reaction.
 - ⇒ **It is a cell mediated immune response** (measures the T cell-mediated immune response to TB antigen)
 - ⇒ **mediated by interferon- γ secreted by T_h1 cells** which in turn stimulates macrophage activity.
 - ⇒ **Memory TH1 cells previously formed against *M. tuberculosis* recognize peptide: MHC class II complexes on the surface of antigen presenting cells**
 - ⇒ **Positive tuberculin test occurs between three weeks and three months after primary infection.**
- Indication:
 - ⇒ the main technique used to screen for latent tuberculosis.
 - ⇒ **The most commonly used screening test for contacts of a patient with recently diagnosed TB**
- Method
 - ⇒ 0.1 ml of 1: 1,000 purified protein derivative (PPD) injected intradermally
 - ⇒ result read 2-3 days later
 - ⇒ The left forearm is typically used.
- Interpretation
 - ⇒ Only the induration, not surrounding erythema, is used in the measurement and the longest diameter is measured in millimeters:

Diameter of induration	Positivity	Interpretation
< 6mm	Negative - no significant hypersensitivity to tuberculin protein	Previously unvaccinated individuals may be given the BCG
6 - 15mm	Positive - hypersensitive to tuberculin protein	Should not be given BCG. May be due to previous TB infection or BCG or atypical mycobacteria. However, in other contexts (e.g. immigrant screening and contact tracing), further investigation and follow-up may be indicated.
> 15mm	Strongly positive - strongly hypersensitive to tuberculin protein	Suggests tuberculosis infection → do chest x-ray

- ⇒ **False negative tests may be caused by:** (→ ↓ reaction to tuberculin protein)
 - miliary TB
 - sarcoidosis
 - **immunosuppression (HIV, corticosteroids)**
 - lymphoma
 - very young age (e.g. < 6 months)
 - Viral infections,
 - live viral vaccines
 - poor nutrition.
- ⇒ Active disease may be indicated by grade III/IV response to tuberculin.
- ⇒ 8% of individuals with history of BCG vaccination have grade I/II response.

Which cytokines is most involved in the response of a Mantoux test?

- ⇒ **Interferon-γ**

BCG

- Definition
 - ⇒ a live attenuated vaccine derived from a strain of **Mycobacterium. bovis**.
- Benefits
 - ⇒ BCG is 70-80% effective against severe TB infection.
 - ⇒ Protection is thought to last for **10-15 years**, with greater efficacy in the under 16 years population.
 - ⇒ **it also has effects against leprosy (*Mycobacterium (M. leprae)*) (up to 80% protection)**
 - ⇒ BCG is currently used as a form of immunotherapy for treating bladder cancer; which can lead to disseminated *M. bovis* infection (systemic 'BCG-it is')
- Indications
 - ⇒ should be given to neonates in high risk groups.
 - ⇒ Previously unvaccinated individuals
 - A Mantoux should be documented before administration.

- It should not be given to children who have a strongly positive tuberculin test
- new entrants from high- incidence countries and are previously unvaccinated (that is, without adequate documentation or a BCG scar) and are aged:
 - ❖ younger than 16 years or
 - ❖ 16–35 years from sub- Saharan Africa or a country with a TB incidence of 500 per 100,000 or more.
- ⇒ healthcare workers
- ⇒ Mantoux- negative contacts of people with pulmonary and laryngeal TB if they:
 - have not been vaccinated previously **and** are aged
 - ❖ 35 years or younger **or**
 - ❖ are aged 36 years and older and a healthcare or laboratory worker who has contact with patients or clinical materials.
- Contraindications
 - ⇒ BCG is a live attenuated vaccine containing M bovis, it should therefore be avoided in the immunosuppressed population.
 - **In case of increased risk of HIV, NICE advises that an HIV test should be done prior to vaccination.**

Diagnosis

- **definitive diagnosis**
 - ⇒ isolation of *Mycobacterium tuberculosis* from a bodily secretion (eg, culture of sputum, bronchoalveolar lavage, or pleural fluid) or tissue (pleural biopsy or lung biopsy).
 - ⇒ Send multiple respiratory samples (3 deep cough sputum samples, preferably including 1 early morning sample) for TB microscopy and culture.
 - ⇒ If spontaneous sputum (by coughing) is difficult:
 - Sputum may be induced by inhalation of hypertonic saline generated by a nebulizer.
 - **If patient is unable to produce sputum, bronchoscopy with bronchial washings for microscopy staining and culture is the investigation of choice.**
 - In children who are unable to cough up sputum, the gold standard is gastric washings for M tuberculosis culture
 - ⇒ Tissue biopsy may establish a definitive diagnosis of TB when other diagnostic techniques are not diagnostic.
- **probable diagnosis:** can be based on:
 - ⇒ Typical clinical and chest X-ray findings, together with either
 - ⇒ sputum (or other specimens) positive for acid-fast bacilli,
 - stains very weakly on testing. When using the **Ziehl-Neelsen test** it stains **bright red** against a blue background.
 - ⇒ typical histopathological findings on biopsy material
- Smear-positive tuberculosis → **highly infectious (Patient needs treatment and isolation from casual contacts, his close contacts need screening)**
- **Culture-positive tuberculosis** means the immediate smear is negative, but prolonged culture has shown tuberculosis.

Management (NICE guidelines 2016)

- If there are clinical signs and symptoms consistent with a diagnosis of TB, start treatment without waiting for culture results.
 - ⇒ Consider completing the standard recommended regimen even if subsequent culture results are negative.
- Should only be carried out in hospitals with appropriate isolation facilities.
 - ⇒ Smear-positive tuberculosis means the patient is highly infectious to both **close contacts (more than 8 hours spent together per day)** and casual contacts, such as other patients on the ward and healthcare workers.
 - ⇒ He therefore needs to be isolated in a negative-pressure room,
 - ⇒ contacts should wear particulate masks until he has received anti-tuberculous therapy **for 2 weeks**. The sputum might remain positive after this time, but the organisms will be dead.
- **Length of treatment:**
 - ⇒ All forms of pulmonary TB may be treated equally except tuberculous pleural effusion which may require drainage (with large effusions causing breathlessness) and adjunct corticosteroids to delay reaccumulation.
 - ⇒ A 6-month course of treatment is adequate for all non-CNS disease.
 - ⇒ Length of treatment for other forms are:
 - **bone TB – 6 months**
 - ❖ Treatment for bone and joint tuberculosis is recommended to continue for 2 months with the initial phase consisting of quadruple therapy and the remaining 4 months of dual therapy.
 - ❖ It is recommended not to extend treatment for residual complications such as collapsed discs or bending of the spine, although there is some debate about this.
 - meningitis - 1 year
 - ❖ **Antituberculous treatment for 12 months is recommended for TB meningitis.**
 - drug resistance - 2 years.
 - ❖ Treatment must be continued for a minimum of 18 months, with **at least 9 months of treatment after the patient becomes culture-negative.**
- **TB with stridor:**
 - ⇒ If patient of **TB** presents with worsening breathlessness and stridor due to mediastinal lymph nodes compressing the carina, **the next step - after commencing steroid - is urgent (CT) scan**, first to confirm the degree of airway compression and second to assess the response to chemotherapy.
- **Patients on long term steroids with TB:**
 - ⇒ **Patients on long term steroids should have their dose of steroids increased when starting antituberculous therapy.**
 - The metabolism of corticosteroids is increased by rifampicin. (P450 inducer)
- **Failing regimen in the treatment of TB:**
 - ⇒ reactivation of (TB) infection during treatment course.
 - ⇒ Evidence of failing treatment:
 - worsening symptoms,
 - elevated C-reactive protein,
 - progression of chest X-ray changes
 - ⇒ **what is the most appropriate next treatment step?**
 - Most guidelines recommend **progression to five agents – rifampicin, pyrazinamide, isoniazid, ethambutol and streptomycin.**

TB Drug therapy

Treatment for active tuberculosis is:

- Initial phase - first 2 months (RIPE)
 1. Rifampicin
 2. Isoniazid
 3. Pyrazinamide
 4. Ethambutol
 - (the 2006 NICE guidelines now recommend giving a 'fourth drug' such as ethambutol routinely - previously this was only added if drug-resistant tuberculosis was suspected)
 - either ethambutol or streptomycin.
- Continuation phase - next 4 months
 1. Rifampicin
 2. Isoniazid
 - After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampicin are continued as daily or intermittent therapy for 4-or-more months.
 - Therapy must be extended if the patient has cavitary disease or remains culture positive after 2 months of treatment.

Treatment for latent tuberculosis

- isoniazid alone for 6 months

Treatment for meningeal tuberculosis

- treated for a prolonged period (at least **12 months**)
- 4 drugs for the first 2 months, followed by isoniazid and rifampicin 10 months.
- addition of **steroids** (equivalent to prednisolone 20-40 mg) is recommended for the first 2-3 weeks, then with gradual reduction.
 - ⇒ (use of steroids is recommended to ensure adequate brain penetration and to prevent cranial nerve compression by meningeal scarring.)

Directly observed therapy

- with a three times a week dosing regimen may be indicated in certain groups, including:
 - ⇒ homeless people with active tuberculosis
 - ⇒ patients who are likely to have poor concordance
 - ⇒ all prisoners with active or latent tuberculosis

Tuberculosis: drug side-effects and mechanism of action

- **Rifampicin**
 - ⇒ mechanism of action:
 - **inhibits** bacterial DNA dependent **RNA polymerase preventing transcription** of DNA into mRNA
 - ⇒ **mechanism of resistance for rifampicin resistant *Mycobacterium tuberculosis***
 - **Mutations in rpoB gene cause alterations in the bacterial DNA dependent RNA transcriptase, which prevents the binding of rifampicin.**
 - ⇒ In patients with HIV/TB co-infection:
 - Rifampicin is a potent inducer of liver enzymes (cytochrome P450). Furthermore, it up-regulates the expression of P-glycoprotein in the gastrointestinal tract.
 - Co-administration of a protease inhibitor with rifampicin therefore will often lead to sub-therapeutic levels of the protease inhibitor.

- the British HIV Association suggest the **substitution of rifampicin for an alternative rifamycin agent (rifabutin or rifapentine), which has less inducing action of cytochrome P450**
- ⇒ Side effects
 - potent liver enzyme inducer
 - hepatitis,
 - orange secretions (Red or orange discolouration of the urine and other body fluids)
 - flu-like symptoms
 - Rifampicin and isoniazid can cause a relative vitamin D deficiency
- **Isoniazid**
 - ⇒ mechanism of action:
 - Prevents cell wall synthesis by **inhibiting the synthesis of mycolic acid**
 - Bactericidal
 - ⇒ Side effects
 - **Hepatotoxicity**
 - ❖ INH is the most common drug associated with toxicity.
 - ❖ INH metabolites are responsible for INH hepatotoxicity
 - ❖ N-acetyltransferase 2 (NAT2) is the primary enzyme that contributes to INH metabolism.
 - ❖ NAT2 deficiency increases the risk of INH-induced liver injury.
 - ❖ slow acetylators are prone to develop more severe hepatotoxicity than rapid acetylators.
 - **Peripheral neuropathy:**
 - ❖ Isoniazid-related demyelinating peripheral neuropathy
 - ❖ relatively acute onset
 - ❖ typically presents with reduced sensation +/- absent reflexes in lower limbs.
 - ❖ prevented with low dose pyridoxine (Vitamin B6)
 - ❖ treated with high-dose Pyridoxine
 - agranulocytosis
 - Drug-induced lupus erythematosus
 - liver enzyme inhibitor
 - ⇒ **isoniazid toxicity**
 - Risk factors
 - ❖ alcoholism
 - ❖ diabetes
 - ❖ malnutrition,
 - ❖ HIV,
 - ❖ renal failure,
 - ❖ neurotoxic medications, and
 - ❖ pregnancy.
 - Treatment
 - ❖ **high-dose pyridoxine**, (low dose pyridoxine is used for prophylaxis).
 - ❖ stopping or reducing the dose of isoniazid
 - ❖ control of other risk factors (e.g. reduced alcohol intake, improved glycaemic control etc)

INH Injures Neurons and Hepatocytes

- Pyrazinamide

- ⇒ mechanism of action:
 - converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS)
 - Bactericidal
 - Streptomycin has high activity against extracellular organisms whilst **pyrazinamide have high activity against intracellular organisms.**
- ⇒ side effects
 - **hyperuricaemia causing gout**
 - arthralgia, myalgia
 - ❖ **the most common cause of arthralgia after starting antituberculous**
 - Hepatotoxicity

- Ethambutol

- ⇒ mechanism of action:
 - Prevents cell wall synthesis by **inhibiting arabinosyltransferase** (which polymerizes arabinose into arabinan)
 - **Bacteriostatic**
- ⇒ side effects
 - optic neuritis: **check visual acuity before and during treatment**
 - **Ocular side-effects of ethambutol**
 - ❖ Loss of acuity
 - ❖ Colour blindness
 - ❖ Restriction of visual fields
- ⇒ **dose needs adjusting in patients with renal impairment**
 - Ethambutol is **renally excreted** and therefore dose adjustment is necessary to minimise the risk of toxic effects (optic neuropathy). The remaining drugs are mainly metabolised in the liver and can be given in normal doses in renal failure.

- Anti-tuberculosis drug and LFTs :

- ⇒ **All tuberculosis patients should have pre-treatment LFTs.**
- ⇒ rifampicin/isoniazid/pyrazinamide all are associated with liver toxicity, **but isoniazid are most commonly implicated** (this fact are tested in MRCPI website -part 1, sample question)
- ⇒ Up to **20%** of the patients receiving **isoniazid** either in single or combination therapy develop **transient asymptomatic elevation in liver enzymes**, which settle with **continued use of the drug.**
 - while some patients (less than 1%–3%) develop severe liver injury and even liver failure
- ⇒ If there is no pre-existing liver disease, LFTs are only repeated (and treatment stopped) if fever, malaise, vomiting , jaundice or unexplained deterioration occurs during treatment.
- ⇒ Regular LFTs should be performed in patients with previously known chronic liver disease.
- ⇒ define hepatotoxicity → rifampicin/isoniazid/pyrazinamide **should be stopped**
 - If AST/ALT levels rise **by 5 times** upper limit of normal range **without symptoms**

- If ALT/AST levels rise **by 3 times** upper limit of normal range **with symptoms** (abdominal pain, nausea, vomiting, unexplained fatigue or jaundice)
- ⇒ If the patient is not unwell and/or has non-infectious TB, no treatment until LFT returns to normal.
- ⇒ If clinically unwell or sputum smear is positive within two weeks of starting treatment, consider **streptomycin and ethambutol until LFT returns to normal**.
- ⇒ Once LFT is back to normal, challenge dosages can be reintroduced sequentially in order of isoniazid, rifampicin and pyrazinamide with daily monitoring of patient's condition and LFT.
- ⇒ If there is a further reaction, the offending drug should be excluded and a suitable alternative regimen used.
- **Immune reconstitution disease**
 - ⇒ **Immune reconstitution inflammatory syndrome (IRIS)** (also known as **immune recovery syndrome**) is a condition seen in some cases of AIDS or immunosuppression, in which the immune system begins to recover, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse
 - ⇒ **occurs typically 3-6 weeks after starting treatment**
 - ⇒ **often presents with enlarging lymph nodes**

Latent tuberculosis infection (LTBI)

Definition

- screening tests indicating previous infection with *M. tuberculosis* are positive without any pathological findings on radiological imaging.

Epidemiology

- Approximately 30% of persons exposed to *Mycobacterium tuberculosis* will develop LTBI and, if untreated, approximately 5% to 10% of these persons will progress to active tuberculosis disease or reactivation of tuberculosis.

Risk for developing active tuberculosis

- The lifetime risk of reactivation TB for a person with LTBI is about 5–10%.
- **Risk factors for developing active tuberculosis** include:
 - ⇒ silicosis
 - ⇒ chronic renal failure
 - ⇒ HIV positive
 - ⇒ solid organ transplantation with immunosuppression
 - ⇒ intravenous drug use
 - ⇒ haematological malignancy
 - ⇒ anti-TNF treatment
 - ⇒ previous gastrectomy

Diagnosis

- **Mantoux tuberculin skin test (TST)**
 - ⇒ can be positive with both active and latent TB but can also be by a previous BCG vaccination.
 - ⇒ Recommended for close contacts of a person with TB.

- ⇒ If positive (**induration ≥ 5 mm, regardless of BCG history**) → assess for active TB
- **Interferon gamma release assay (IGRA)**
 - ⇒ Indications
 - Quantaferon testing (interferon gamma testing) is recommended as a second-line test for people whose Mantoux testing may be less reliable - for example, BCG-vaccinated people.
 - If the Mantoux test is positive + active TB is excluded, and evidence of infection is needed to decide on treatment. for example:
 - ❖ if the person needs enhanced case management or
 - ❖ if there could be adverse events from treatment.
 - **For immunocompromised**, (HIV and CD4 < 200 cells/mm³, or after transplant), → **Interferon- gamma release assay and a concurrent Mantoux test:**
 - ❖ If either test is positive → assess for active TB.
 - ❖ If assess for active TB is negative, → treatment for latent TB infection.
 - ⇒ Advantage
 - Quantaferon testing is not influenced by BCG vaccination status
 - **A positive test would, therefore, indicate prior exposure to M. tuberculosis (active or latent TB)**
 - ⇒ Disadvantage
 - The main disadvantage of the IGRA is its inability to distinguish between active and latent TB.
- **Chest x-ray**
 - ⇒ **NO** TB-related findings on chest x-ray (e.g., hilar lymphadenopathy, upper lobe opacification, or cavitation),

Treatment (NICE guidelines 2016)

- Treatment of LTBI can reduce the risk of development of disease by 90%
- For adults between the ages of 35 and 65 years, offer drug treatments only if hepatotoxicity is not a concern.
- test for hepatitis B, C and HIV before starting treatment for latent TB.
- NICE now give two choices for treating latent tuberculosis:
 - ⇒ **3 months of isoniazid (with pyridoxine) and rifampicin**
 - For people younger than 35 years if hepatotoxicity is a concern after an assessment of both liver function (including transaminase levels) and risk factors.
 - ⇒ **6 months of isoniazid (with pyridoxine)**
 - if interactions with rifampicin are a concern, for example, in people with HIV or who have had a transplant.

NICE advises that once a diagnosis of pulmonary TB has been made then **close contacts** should be managed as follow:

- If **asymptomatic and younger than 65 years**, then:
 - ⇒ test for latent TB.
 - If Mantoux-negative and unvaccinated then offer vaccination.
 - ❖ **If at risk of HIV then test for HIV first (HIV testing and if negative, then BCG vaccination).**
- If **asymptomatic and older than 65 years** then assess with a chest X-ray.

Miliary TB

Overview

- miliary TB most likely occur in young children.

Features

- presents with a gradual onset of vague ill health, loss of weight and then fever.
- TB meningitis
 - 15 - 20% of patients who have miliary TB also have TB meningitis at the time of presentation.
 - 33% of patient with TB meningitis have concomitant miliary TB.
- Hepatosplenomegaly is seen in advanced disease.
- Choroidal tubercles can be seen in the eyes.

Investigations

- tuberculin test is often negative.
 - negative in up to half of patients with severe disease
- chest x ray
 - may be normal in up to one third of patients.
 - The classic millet seed nodules are small measuring about 1-2 mm.
- Not all patients will be **sputum** positive and with evidence supporting a diagnosis of tuberculosis treatment should be commenced swiftly.
- Transbronchial biopsy – positive at an early stage.
- Biopsy of liver and bone marrow might be required.



Miliary TB

Non-tuberculous mycobacterial infections

Opportunistic mycobacteria

- *Mycobacterium kansasii*
- *Mycobacterium malmoense*
- *Mycobacterium xenopi*
- *Mycobacterium avium* intracellular (The presence of acid fast bacilli (AFB) and absence of TB (*Mycobacterium tuberculosis* negative on culture.) suggests an atypical AFB such as *M. avium*.)
 - ⇒ The presence of AFB yet absence of TB suggests an atypical AFB such as *M. avium*.
 - ⇒ *Mycobacterium avium* causes disseminated infection in patients with advanced HIV, typically when the CD4 count is less than 50 cells/mm³.

Mycobacterium malmoense

- is a non-tuberculous mycobacterium
- most commonly causes pulmonary infection in middle-aged and older adults with pre-existing lung disease or immunodeficiency and can also cause local invasion from a skin lesion.
- It causes nonspecific symptoms, such as malaise and weight loss, or chest symptoms that take an atypical course.

Pathophysiology

- they can colonise structurally abnormal lung, for example in patients with:
 - ⇒ Cavitary disease
 - ⇒ Bronchiectasis
 - ⇒ Chronic obstructive pulmonary disease
 - ⇒ Such patients might not always require treatment. However, if treatment is required, then it is usually for longer than the standard 6 months needed to treat pulmonary tuberculosis
- 'atypical' mycobacteria differ from *M. tuberculosis* in that they are ubiquitous organisms and have no person-to-person spread.
- ***Mycobacterium marinum*** infection
 - ⇒ It is an uncommon atypical mycobacterium infection
 - ⇒ The skin is the most common site of infection, where it usually produces a **solitary indolent granulomatous lesion - the 'fish tank granuloma'**.
 - ⇒ usually seen in **patients who handle fish** or swim in freshwater or saltwater.
 - ⇒ occurs when contaminated water is exposed to skin that has experienced open trauma.



'fish tank granuloma' caused by
Mycobacterium marinum

Diagnosis

- A single isolate from a non-sterile site might not be significant and can just represent contamination. **More than two isolates from a non-sterile site are required to establish disease.**
- Chest X-ray => (like other mycobacterium) upper-zone fibrosis and cavitation.

Treatment

- No need to isolate patients or notify public health authorities.

Multidrug-resistant tuberculosis (MDR-TB).

Definition

- Defined as resistance to rifampicin and isoniazid, with or without resistance to other anti-TB drugs.
- defined as **positive cultures after 4 months of therapy.**

Epidemiology

- Rare in previously untreated white patients born in the UK(< 2%).
- Higher levels of resistance occur in Indian subcontinent and black, with isoniazid resistance occurring in 4-6% of such patients.

Risk factors

- Poor compliance (the most common reason)
- Previous anti-TB treatment
- Contact with a known case of drug-resistant TB
- Birth in a foreign country, particularly high-incidence countries
- **HIV infection**
- Residence in London
- Age profile, with highest rates between ages 25 and 44
- Male gender
- Homelessness
- Intravenous drug use
- Infection acquired in institutions (eg prison)

Treatment

- **Directly observed therapy is recommended**
- should be treated with an injectable agent such as amikacin, kanamycin or capreomycin, in combination with a fluoroquinolone and at least three other agents. At least 5 drugs, one of which is a quinolone, is the recommended
- Ideally the **injectable agent is administered daily for the first 6-8 months**, forming an intensive phase of treatment, with other drugs then continued for a total of **18-24 months**.
- In practice, unwanted effects may lead to intravenous therapy being discontinued early.

Leprosy

Definition

- Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by *Mycobacterium leprae*.

Features

- patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
- sensory loss

Types

- The degree of cell mediated immunity determines the type of leprosy a patient will develop:
 - ⇒ Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')
 - extensive skin involvement
 - symmetrical nerve involvement
 - ⇒ High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')
 - limited skin disease
 - asymmetric nerve involvement

Management

- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine
- BNF advice:
 - ⇒ **multibacillary leprosy (>6 lesions) → rifampicin, dapsone and clofazimine for 12 months.**
 - ⇒ paucibacillary leprosy (5 or less lesions) → rifampicin and dapsone for 6 months.

Vaccinations

<p>Live attenuated vaccines</p> <ul style="list-style-type: none"> • BCG • measles, mumps, rubella (MMR) • oral polio • oral rotavirus • oral typhoid 	<ul style="list-style-type: none"> • influenza (intranasal) • yellow fever • Varicella <p>Live attenuated vaccines are contraindicated in all HIV positive and immunocompromised patients.</p>
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Inactivated preparations

- rabies
- influenza (intramuscular)

Detoxified exotoxins

- tetanus

Extracts of the organism/virus (sometimes termed fragment) (may also be produced using recombinant DNA technology)

- diphtheria
- pertussis ('acellular' vaccine)
- hepatitis B
- meningococcus, pneumococcus, haemophilus

Notes

- influenza:
 - ⇒ different types are available, including whole inactivated virus, split virion (virus particles disrupted by detergent treatment) and sub-unit (mainly haemagglutinin and neuraminidase)
- cholera:
 - ⇒ contains inactivated Inaba and Ogawa strains of Vibrio cholerae together with recombinant B-subunit of the cholera toxin
- hepatitis B:
 - ⇒ contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology

Contraindications to pertussis immunisation

- Acute illness - until recovered
- Previous reaction to pertussis:
 1. **Local:** an extensive area of redness and swelling which becomes indurated, involving most of the anterolateral surface of the thigh or a major part of the circumference of the upper arm
 2. **General:** **fever equal to or more than 39.5°C within 48 hours of vaccine,** anaphylaxis, bronchospasm, laryngeal oedema, generalised collapse, prolonged hyporesponsiveness, prolonged inconsolable or high-pitched screaming of more than four hours, convulsions or encephalopathy occurring within 72 hours.

Splenectomised patients

- Splenectomised patients are at **increased risk of infection with:**
 - ⇒ encapsulated bacteria
 - A popular mnemonic to remember most of the encapsulated bacteria is the **SHINE SKiS** bacteria (**S.** pneumo, **Hib**, **N.** meningitidis, **E.** Coli, **Salmonella**, **Klebsiella**, Group B **Strep**).
 - ⇒ infections that are filtered by the spleen (for example, malaria).
- When **elective splenectomy** is planned, vaccines to pneumococcus and meningococcus should be given **two weeks pre-surgery** to allow an antibody response to evolve.
- Patients who have **emergency splenectomies** should be vaccinated post-operatively (most effective if performed **at least 14 days after surgery**)

Prophylaxis in splenectomy

- Following a splenectomy patients are particularly at risk from pneumococcus, Haemophilus, meningococcus and (*Capnocytophaga canimorsus* infections usually from dog bites)
- **Vaccination**
 - ⇒ if elective, should be done 2 weeks prior to operation
 - ⇒ Hib, meningitis A & C
 - ⇒ annual influenza vaccination
 - ⇒ pneumococcal vaccine every 5 years
- **Antibiotic prophylaxis**
 - ⇒ penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

MRCPUK-part-1-January 2018 exam: H/O emergency splenectomy. Following this he takes penicillin V on a daily basis. He is unsure of his vaccination history. Which organism is he particularly susceptible to?

→ ***Haemophilus influenzae*** (Penicillin V would protect him against *Streptococcus pneumoniae* but not *Haemophilus influenzae* due to the production of beta-lactamases by the organism)

MRCPUK-part-1-September 2019 exam: A 12-year-old boy who had a splenectomy following RTA, he had his full immunisation course as a child and was given a repeat pneumococcal vaccination 5 days following surgery. What is the most appropriate ongoing management?

→ **Booster dose of Hib and MenC vaccine + annual influenza vaccination + lifelong penicillin V**

Post-exposure prophylaxis

Post-exposure prophylaxis for HIV: oral antiretroviral therapy for 4 weeks

Hepatitis A

- Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation

Hepatitis B

- HBsAg positive source:**
 - if the person exposed is a known responder to HBV vaccine then a booster dose should be given.
 - If they are in the process of being vaccinated or are a non-responder they need to have hepatitis B immune globulin (HBIG) and the vaccine
- unknown source:**
 - for known responders the green book advises considering a booster dose of HBV vaccine.
 - For known non-responders → HBIG + vaccine should be given
 - those in the process of being vaccinated should have an accelerated course of HBV vaccine.
 - accelerated course of HBV vaccine** → given at zero, one and two months. For those who are at continued risk, a fourth dose is recommended at 12 months.

Exposed person	Source person	
responder to HBV vaccine	HBsAg positive	unknown
non-responder	booster HBV vaccine (HBIG) + vaccine	booster HBV vaccine HBIG + vaccine
in the process of vaccination	(HBIG) + vaccine	accelerated course of HBV vaccine (given at zero, one and two months)

Hepatitis C

- Monthly PCR - if seroconversion then interferon +/- ribavirin

HIV

- **Three antiretroviral agents for 1 month**
 - ⇒ New guidelines in 2014 recommend three-agent PEP with **Truvada® (tenofovir and emtricitabine) and raltegravir**, which should both be taken for 1 month.
 - ⇒ (i.e. Within 1-2 hours, but may be started up to 72 hours following exposure) for 4 weeks
- Serological testing at 12 weeks following completion of post-exposure prophylaxis
- Reduces risk of transmission by 80%

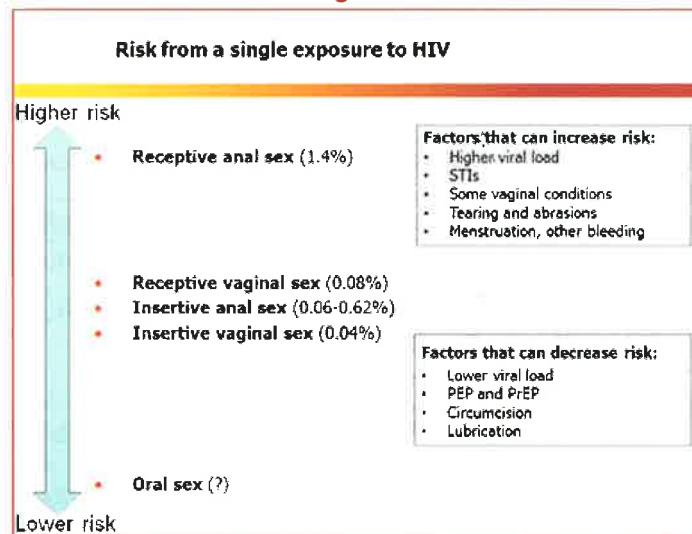
Varicella zoster

- VZIG for IgG negative pregnant women/immunosuppressed

Estimates of transmission risk for single needle stick injury

Hepatitis B	20-30%
Hepatitis C	0.5-2%
HIV	0.3%

First line management of needle stick injuries includes immediate washing of the affected area under running water.

**UK Guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure (PEPSE)**

- If the source is of unknown status: → establish the HIV status of the source.
- Source individual known to be HIV-positive: → determine the HIV viral load, resistance profile and treatment history.
- if the source is on antiretroviral therapy (ART) with a confirmed and sustained (>6 months) undetectable plasma HIV viral load → PEPSE is no longer recommended

- ⇒ However, if there are any doubts about the HIV viral load history or the source's adherence to ART → PEP should be given following unprotected receptive anal intercourse.
- ⇒ Initiation of PEPSE is recommended as soon as possible after exposure, preferably within 24 hours of exposure but can be offered up to 72 hours.
- ⇒ The first-line regimen is Truvada and raltegravir
 - Truvada → fixed-dose combination of two antiretroviral medications: tenofovir disoproxil and emtricitabine (both are Nucleoside analog reverse-transcriptase inhibitors (NRTIs))
 - Raltegravir (integrase inhibitors, a new class of HIV drugs) targets integrase, an HIV enzyme that integrates the viral genetic material into human chromosomes, a critical step in the pathogenesis of HIV.
- ⇒ PEPSE beyond 72 hours are not recommended
- ⇒ duration of PEPSE should be 28 days
- ⇒ follow-up HIV testing at 8-12 weeks after exposure
- ⇒ pregnancy should not alter the decision to start PEPSE. Women must be counselled that antiretroviral agents used for PEPSE are unlicensed in pregnancy and risks / benefits must be carefully discussed
- ⇒ In the event of a further high-risk sexual exposure in the last two days of the PEPSE course the PEP should be continued for 48 hours after the last high-risk exposure
- ⇒ If the recipient has missed more than 48 hours of PEPSE then the course should be discontinued.

Brucellosis

Overview

- Brucellosis is a zoonosis more common in the Middle East and in farmers.
- Gram negative bacilli
- It is considered a class B bioterrorist agent, is easily spread by aerosol, and is a significant hazard in microbiology laboratories.
- Four major species cause infection in humans: B melitensis (sheep), B abortus (cattle), B canis and B suis (pigs).
- incubation period 2 - 6 weeks
- Most cases of brucellosis in Northern Europe and North America are acquired overseas and/or from consuming unpasteurised milk products, including cheese.

Features

- non-specific:
 - ⇒ fever, (prolonged fever of unknown origin)
 - ⇒ malaise
- hepatosplenomegaly
- sacroiliitis: spinal tenderness may be seen. **Brucellosis is a recognised cause of spondylitis**
 - ⇒ associated rheumatic features in about 50% of cases.
- complications: osteomyelitis, infective endocarditis, meningoencephalitis, orchitis
- leukopenia is common

Diagnosis

- the Rose Bengal plate test can be used for screening but other tests are required to confirm the diagnosis
- **Brucella serology is the best test for diagnosis**
- blood and bone marrow cultures may be suitable in certain patients, but these tests are often negative

⇒ 75% have a positive blood culture (90% of bone marrow cultures will be positive).

Management

- doxycycline and streptomycin

Cat scratch disease (CSD)

Cat scratch disease - caused by *Bartonella henselae*

Definition: a benign, self-limiting infectious disease that is transmitted mainly by cats (via scratching, biting, or licking)

Pathogen: Gram negative rod *Bartonella henselae*

Features

- fever, headache, malaise
- history of a cat scratch
- regional lymphadenopathy**
- In immunocompromised individuals** (e.g., patients with HIV) → **Bacillary angiomatosis** (vascular proliferation, which leads to the development of solitary or multiple, red-purple papules that bleed easily).

Treatment

- Mild or moderate cases: azithromycin (5-day course) to decrease lymphadenopathy and the duration of illness
- In the case of persistent and/or disseminated disease (e.g., bacillary angiomatosis): erythromycin OR doxycycline
- In the case of CNS involvement or endocarditis: rifampicin PLUS either erythromycin OR doxycycline

Whooping cough (pertussis)

Bacteria

- caused by the bacterium *Bordetella pertussis*.
- gram-negative aerobic coccobacillus
 - ⇒ The virulence factors of *Bordetella pertussis* include its eponymous toxin and tracheal cytotoxin,
- grows best on Bordet-Gengou agar and Regan-Lowe medium (**Bordet** for **Bordetella**)

Epidemiology

- now more common in adolescents and adults than in children.

Mechanism

- The tracheal cytotoxin from *Bordetella pertussis* kills ciliated cells along the respiratory epithelium.
- Pertussis toxin inactivates Gi, an inhibitory protein. Gi normally inhibits activation of adenylate cyclase. Therefore, the pertussis toxin inhibits an inhibitor leading to increased activity of adenylate cyclase.**
 - ⇒ Pertussis toxin → ↓ Gi → ↑adenylate cyclase

Features

- Pertussis has three major phases: the catarrhal phase (like the common cold), the paroxysmal phase (bouts of coughing), and the convalescent phase (resolution).
- Lymphocytosis is typically found.
 - ⇒ it causes a profound leucocytosis by inhibiting chemokines that normally remove white cells from the blood stream.

Complications

- pneumonia, seizures, and encephalopathy
- **A rare complication is a hemiseizure-hemiplegia syndrome**, which is thought to be related to post-immunisation hyperthermia rather than direct neurological toxicity.

Treatment

- Treatment is largely supportive, but antibiotics can reduce the duration of symptoms.
- Erythromycin, clarithromycin and azithromycin are first choice

Prevention

- The pertussis vaccine is estimated to be 63% to 94% effective in the diphtheria-pertussis-tetanus (DPT) shot

Acute epiglottitis

Overview

- Acute epiglottitis is rare but serious infection caused by **Haemophilus influenzae type B**.
- Prompt recognition and treatment is essential as airway obstruction may develop.
- Epiglottitis was generally considered a disease of childhood but **in the UK it is now more common in adults due to the immunisation programme**.
- The incidence of epiglottitis has decreased since the introduction of the Hib vaccine

Features

- | | |
|---|---|
| <ul style="list-style-type: none"> • Rapid onset • High temperature, generally unwell | <ul style="list-style-type: none"> • Stridor • Drooling of saliva (the most specific sign) |
|---|---|

Diagnosis

- the preferred method of diagnosis → **direct visualization of the epiglottis** using nasopharyngoscopy/laryngoscopy → cherry-red epiglottis
 - ⇒ No attempt should be made to visualise the epiglottis until an **anaesthetist is present** as there is a high risk of causing acute airway obstruction by touching the inflamed tissue.
- Lateral neck soft-tissue radiography
 - ⇒ useful screening tool in suspected stable patient.
 - ⇒ Only 79% of epiglottitis cases are diagnosed by neck soft-tissue radiographs
 - ⇒ The classic findings are:
 - swollen epiglottis (ie, a thumb sign),
 - thickened aryepiglottic folds, and
 - obliteration of the vallecula (pre-epiglottic space). (vallecula sign).
 - ❖ The vallecula is the air pocket found at the level of the hyoid bone just anterior to the epiglottis.
- blood culture

Differential

- cough is specific for croup
- drooling is specific for epiglottitis
- laryngomalacia improves in the prone position

Treatment

- Unstable patients → immediate airway management. Early intubation is essential, especially in cases where there is respiratory distress.
- **Third generation cephalosporin is the treatment of choice.**
- **Close contacts** of patients in whom *Haemophilus influenzae* type b is isolated should receive **rifampin prophylaxis** (20 mg/kg; not to exceed 600 mg/d for 4 d).

- Recurrent episodes of acute epiglottitis in adults is unusual and, when present, warrants immune system investigation.

Haemophilus influenzae requires hemin (**factor X**) and NAD+ (**factor V**) for growth. Other *Haemophilus* species require only NAD+ and therefore grow on blood agar.

Haemophilus influenzae: culture requirements:

- Read Hemophilus as "HemoFive": · Needs Heme with Factors Five and Ten.

Cellulitis

Cellulitis

- Staphylococcus aureus and Streptococci are the commonest causative organisms.**
- Group B Streptococcus has a predilection for diabetic patients**

Definition

- inflammation of the skin and subcutaneous tissues,

Causes

- Staphylococcus aureus and Streptococci are the commonest causative organisms.**
- Group B Streptococcus has a predilection for diabetic patients and is the likeliest causative organism in diabetics**

Features

- commonly occurs on the shins
- erythema, pain, swelling
- systemic upset such as fever
- Cellulitis **does not** have sharp, well-defined borders, unlike an erysipelas infection.

Eron classification

NICE Clinical Knowledge Summaries recommend we use the Eron classification to guide how we manage patients with cellulitis:

Class	Features
I	There are no signs of systemic toxicity and the person has no uncontrolled co-morbidities
II	The person is either systemically unwell or systemically well but with a co-morbidity (for example peripheral arterial disease, chronic venous insufficiency, or morbid obesity) which may complicate or delay resolution of infection
III	The person has significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or unstable co-morbidities that may interfere with a response to treatment, or a limb-threatening infection due to vascular compromise
IV	The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis

Management

- Criteria for admission** for intravenous antibiotics
 - ⇒ **Eron Class III or Class IV cellulitis.**
 - ⇒ severe or rapidly deteriorating cellulitis (for example extensive areas of skin).
 - ⇒ very young (under 1 year of age) or frail.
 - ⇒ immunocompromised.
 - ⇒ significant lymphoedema.

- ⇒ facial cellulitis (unless very mild) or periorbital cellulitis.
- Management **Eron Class II cellulitis:**
 - Admission may not be necessary if the facilities and expertise are available in the community to give intravenous antibiotics and monitor the person.
 - Other patients can be treated with oral antibiotics.
- **Antibiotics**
 - ⇒ **mild/moderate cellulitis**
 - **First line** → **flucloxacillin** (BNF recommendation)
 - ❖ first choice to treat sensitive staphylococcal infections
 - ❖ MRSA is resistant to flucloxacillin
 - **in patients allergic to penicillin** → **Clarithromycin or clindamycin**
 - **in patients who have failed to respond to flucloxacillin** → **oral clindamycin**
 - ❖ **The most appropriate treatment is clindamycin and flucloxacillin**, which covers the majority of organisms responsible for cellulitis.
 - ⇒ **Flucloxacillin** is bactericidal for both *Staphylococcus* and *Streptococcus*, whereas *clindamycin* has an anti-toxin effect for both these groups of organisms (in addition to *Clostridium perfringens*). Their effect is therefore synergistic, and they should be used together where rapid control is required (e.g. in finger cellulitis) or in severe cases
 - ⇒ Although **clindamycin** is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of toxic shock syndrome (TSS).
 - If no significant improvement within 48 hours, the patient should be readmitted for intravenous antibiotics.
- ⇒ **Severe cellulitis**
 - should be treated with **intravenous benzylpenicillin + flucloxacillin**.
 - If there is any suspicion of tendon involvement (Intact joint movements make this less likely) → the plastics or orthopaedics team should be asked to review and **intravenous antibiotics** initiated.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Epidemiology

- In many hospitals, 40%-50% of the *S. aureus* isolates are resistant to methicillin

Mechanism of resistance

- **Penicillin binding proteins** are the characteristic mutated proteins in methicillin-resistant *Staphylococcus aureus*.
- The resistant organisms produce penicillin-binding proteins (PBPs) that have a low affinity for binding beta-lactamase antibiotics (**Modification of target penicillin-binding proteins**). Other organisms which do the same are *Pneumococci* and *Enterococci*.

Who should be screened for MRSA?

- all patients awaiting elective admissions
 - ⇒ exceptions include:
 - terminations of pregnancy
 - ophthalmic surgery
 - Patients admitted to mental health trusts.
- all emergency admissions.

Where is the site of most concern for staff carriage of MRSA?

- The nose is the area of carriage for MRSA which gives most area for concern with respect to carriage by staff.

How should a patient be screened for MRSA?

- nasal swab and skin lesions or wounds
 - the swab should be wiped around the inside rim of a patient's nose for 5 seconds
 - the microbiology form must be labelled 'MRSA screen'

Suppression of MRSA from a carrier once identified

- nose:
 - mupirocin 2% in white soft paraffin, TDS for 5 days
- skin:
 - chlorhexidine gluconate, OD for 5 days.
 - Apply all over but particularly to the axilla, groin and perineum

Treatment of MRSA infections

- Vancomycin → the first line**
- Teicoplanin**
- Linezolid
 - Linezolid is the only oral medication available against MRSA.
- Ceftaroline
 - fifth generation cephalosporin
 - Ceftaroline is the only cephalosporin to cover MRSA.
- Some strains may be sensitive to the antibiotics listed below but they **should not generally be used alone** because resistance may develop:
 - rifampicin
 - macrolides
 - tetracyclines
 - aminoglycosides
 - clindamycin
- Relatively new antibiotics such as **linezolid, quinupristin /dalfopristin combinations and tigecycline** have activity against MRSA but should be reserved for resistant cases

MRCPUK-part-1-January-2009: What is the most effective single step to reduce the incidence of MRSA?

→ Hand hygiene

MRCPI-part-1-jan-2017: What is the most appropriate antibiotic regimen for possible line sepsis from an indwelling permacath?

Vancomycin + Gentamicin

The antibiotic chosen should have both gram-positive and gram-negative cover, including MRSA. vancomycin and doxycycline are able to treat MRSA, but doxycycline has limited gram-negative cover, unlike gentamicin.

Necrotising fasciitis

Overview

- Necrotising fasciitis is a medical emergency that is difficult to recognise in the early stages.

Classification (according to the causative organism):

- Type 1** is caused by mixed anaerobes and aerobes (often occurs post-surgery in diabetics)
- Type 2** is caused by *Streptococcus pyogenes*
 - commonly caused by group A *Streptococci*

Features

- acute onset
- painful, erythematous lesions
- extremely tender over infected tissue

Management

- **urgent surgical referral debridement**
- intravenous antibiotics

⇒ **Clindamycin and Tazocin**

- Clindamycin
 - ❖ bacteriostatic
 - ❖ inhibits formation of peptides bonds at **50S ribosomal subunit**
 - ❖ It is also a potent suppressor of bacterial toxin synthesis.
- Group A *Streptococci* are usually very sensitive to benzylpenicillin so this is frequently added though this does not neutralises the toxin.

Toxic shock syndrome (TSS)

Staphylococcus aureus → Toxic shock syndrome toxin → binds to major histocompatibility complex II and T cell receptor → overwhelming release of cytokines → shock.

Causes

- *Staphylococcus aureus*, which releases enterotoxin type B (i.e. toxic shock syndrome toxin-1),
- *Streptococcus pyogenes*, which releases pyrogenic exotoxins.

Risk factors

- **Recent menstruation**
 - ⇒ Although the earliest described cases involved mostly menstruating women using highly absorbent tampons, only 55% of current cases are associated with menstruation.
- Recent use of barrier contraceptives such as diaphragms and **vaginal sponges**
- **Vaginal tampon** use (especially prolonged)
- Recent childbirth
- Recent surgery,
- Current *S. aureus* infection.

Features

- non-specific (e.g., fever, chills, myalgias, headache),
- toxicity occurs early, resulting in serious life-threatening disease
- **Staphylococcal scalded skin syndrome**
 - ⇒ **Diffuse erythema that desquamates as the patient recovers**
 - ⇒ Occur 10% of patients
 - ⇒ Exotoxin A is the causative toxin in staphylococcus scalded skin syndrome.
 - ⇒ most common in children but can be seen in immunocompromised adults.
 - ⇒ destroys keratinocyte attachments in the stratum granulosum, leading to a very superficial sloughing of the epidermis that heals completely.
 - ⇒ It is also known as Pemphigus neonatorum or Ritter disease.
- multi-organ system failure.

Types

- Streptococcal toxic shock syndrome (TSS) can occur with infection at any site but is more **commonly associated with an infected cutaneous site**.
- **Staphylococcal TSS** (menstrual or non-menstrual)
 - ⇒ severe systemic reaction to staphylococcal exotoxins.
 - ⇒ associated with extended tampon use, postpartum infections, and other sites of infection with the organism.

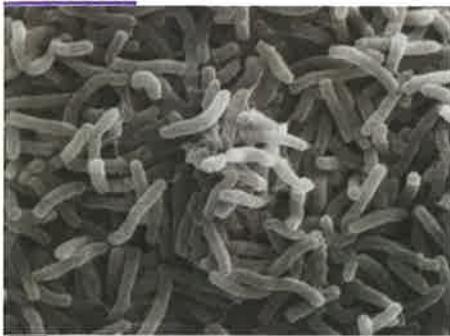
Diagnosis

- **Centers for Disease Control and Prevention diagnostic criteria**
 - ⇒ fever: temperature > 38.9 C
 - ⇒ hypotension: systolic blood pressure < 90 mmHg
 - ⇒ diffuse erythematous rash
 - ⇒ desquamation of rash, especially of the palms and soles
 - ⇒ involvement of three or more organ systems: e.g. gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. confusion)

Treatment

- supportive care in an ICU,
- early empirical antibiotic treatment, and further culture-sensitive antibiotic treatment.
 - ⇒ Although clindamycin is a bacteriostatic antibiotic, it acts by switching off protein synthesis within bacteria; this in turn will lead to decreased exotoxin expression, thereby removing the mediators of TSS.
- Surgical debridement may be needed for deep-seated streptococcal infections.

Cholera



electron microscope image of Vibrio cholerae bacteria

Overview

- caused by Vibrio cholerae - Gram negative bacteria
- Because the organism is not acid-resistant, it **depends on its large inoculum size** (infectious dose) to **withstand gastric acidity**.
 - ⇒ If ingested with water, a higher infectious dose is needed. When ingested with food, fewer organisms are required to produce disease.
 - ⇒ ↓ gastric acidity (anti-acid drugs, gastrectomy) → ↑ risk of cholera infection and severity

Mechanism by which cholera leads to fluid loss:

- Cholera toxin has two parts, A and B.

- ⇒ B subunits are responsible for binding to a ganglioside (monosialosyl ganglioside, **GM1 receptor**) located on the surface of the cells that line the intestinal mucosa.
- ⇒ B binds while A activates **G protein** → **activates adenylate cyclase** → ↑(cAMP) → unrestricted chloride secretion from villous crypts.

cholera toxin stimulates the generation of cyclic AMP as the second messenger

Features

- profuse 'rice water' diarrhoea
- dehydration
- hypoglycaemia
 - ⇒ After dehydration, hypoglycemia is the most common lethal complication of cholera in children.

Management

- oral rehydration therapy
- antibiotics: doxycycline, ciprofloxacin

Congenital infections

Congenital rubella

- sensorineural deafness
- congenital cataracts

The major congenital infections encountered in examinations are rubella, toxoplasmosis and cytomegalovirus

Cytomegalovirus is the most common congenital infection in the UK. Maternal infection is usually asymptomatic

	Rubella	Toxoplasmosis	Cytomegalovirus
Characteristic features	<ul style="list-style-type: none"> ⇒ Sensorineural deafness ⇒ Congenital cataracts ⇒ Congenital heart disease (e.g. patent ductus arteriosus) ⇒ Glaucoma 	<ul style="list-style-type: none"> ⇒ Cerebral calcification ⇒ Chorioretinitis ⇒ Hydrocephalus 	<ul style="list-style-type: none"> ⇒ Growth retardation ⇒ Purpuric skin lesions
Other features	<ul style="list-style-type: none"> ⇒ Growth retardation ⇒ Hepatosplenomegaly ⇒ Purpuric skin lesions ⇒ 'Salt and pepper' chorioretinitis ⇒ Microphthalmia ⇒ Cerebral palsy 	<ul style="list-style-type: none"> ⇒ Anaemia ⇒ Hepatosplenomegaly ⇒ Cerebral palsy 	<ul style="list-style-type: none"> ⇒ Sensorineural deafness ⇒ Encephalitis/seizures ⇒ Pneumonitis ⇒ Hepatosplenomegaly ⇒ Anaemia ⇒ Jaundice ⇒ Cerebral palsy

Chickenpox (Varicella-zoster virus)

Overview

- Chickenpox is caused by primary infection with varicella zoster virus.
- Shingles is reactivation of dormant virus in dorsal root ganglion
- Chickenpox is highly infectious (infection rate in household contacts of 90%).
- spread via the respiratory route
- can be caught from someone with shingles
- infectivity = 4 days before rash, until 5 days after the rash first appeared*
- incubation period = 10-21 days
- It is commonest in spring time
- **Causes congenital limb deformity**
- **HIV**
 - ⇒ **HIV-positive patients are more prone to herpes zoster regardless of their CD4 count.**
 - ⇒ In addition to the typical dermatomal distribution of the vesicular rash, HIV patients occasionally have vesicles scattered in adjacent dermatomes.
 - ⇒ In advanced HIV disease VZV can manifest as severe disseminated disease.

Clinical features (tend to be more severe in older children/adults)

- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular
- systemic upset is usually mild

Management

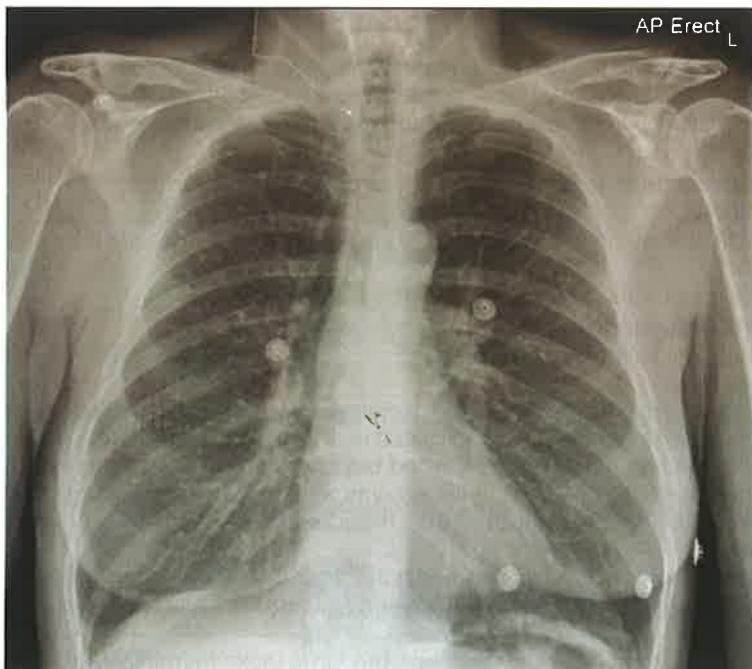
- is supportive
- keep cool, trim nails
 - calamine lotion
 - school exclusion: current HPA advice is 5 days from start of skin eruption. They also state 'Traditionally children have been excluded until all lesions are crusted. However, **transmission has never been reported beyond the fifth day of the rash.**'
 - immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered
 - ⇒ **Aciclovir** (also famciclovir, and ganciclovir) acts through **inhibition of viral (DNA) polymerase** but it is a **pro-drug** and first **requires phosphorylation by thymidine kinase**.
 - Resistance arises when the virus lacks thymidine kinase
 - ⇒ **For thymidine kinase-deficient varicella-zoster virus strain:**
 - **Cidofovir does not require activation by viral thymidine kinase; therefore, it would be best suited to treat the thymidine kinase-deficient varicella-zoster virus.**
 - adults chicken pox should be treated with acyclovir within 24 hours of the appearance of rash because it can lessen the occurrence of post herpetic neuralgia.

Complications

- Common complication is secondary bacterial infection of the lesions.
- Chicken pox in the first and second trimester can produce a syndrome of skin scarring, hypoplastic limbs, eye and central nervous system impairments.
- Rare complications include
 - ⇒ **Varicella pneumonia**
 - Varicella pneumonia occurs in up to 20% of adults with chickenpox,
 - uncommon in children

- The risk is higher in smokers and pregnancy.
- Features
 - ☞ appearing three to five days into the course of the illness.
 - ☞ **Symptoms include tachypnoea, cough, dyspnoea, and fever.**
 - ☞ Cyanosis, pleuritic chest pain and haemoptysis are common.
- Treatment → **Aciclovir**
- ⇒ Encephalitis (cerebellar involvement may be seen)
- ⇒ Disseminated haemorrhagic chickenpox
- ⇒ Arthritis, nephritis and pancreatitis may very rarely be seen

mechanism of acyclovir resistance → reduced production of viral thymidine kinase



Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

*it was traditionally taught that patients were infective until all lesions had scabbed over

Chickenpox exposure in pregnancy

Chickenpox exposure in pregnancy - first step is to check antibodies

- In pregnancy there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

Risks to the fetus and neonate relate to the time of infection:

- **Less than 20 weeks pregnancy:**

- ⇒ congenital varicella (limb hypoplasia, microcephaly, cataracts, growth retardation, skin scarring). High mortality.
- ⇒ The incidence of congenital varicella syndrome is about 2% in mothers who develop primary chickenpox in the first half of the pregnancy.
- **Second to third trimester:**
 - ⇒ herpes zoster in an otherwise healthy infant.
- **Minus seven days to plus seven days after delivery:**
 - ⇒ severe and even fatal disease (30% mortality).

Risks to the mother

- 5 times greater risk of pneumonitis

Fetal varicella syndrome (FVS)

- risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

Other risks to the fetus

- shingles in infancy: 1-2% risk if maternal exposure in the second or third trimester
- severe neonatal varicella: if mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases

Management of chickenpox exposure

- if there is any doubt about the mother previously having chickenpox maternal blood should be urgently **checked for varicella antibodies**
- if the pregnant women is not immune to varicella she should be given varicella zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest **VZIG is effective up to 10 days post exposure**
- consensus guidelines suggest oral aciclovir should be given if pregnant women with chickenpox present within 24 hours of onset of the rash

Varicella zoster immunoglobulin (VZIG)

- prepared from pooled plasma of UK blood donors with a history of recent chickenpox or herpes zoster.
- Donors are screened for HIV, hepatitis B and hepatitis C.
- VZIG prophylaxis is recommended for patients who fulfil all the following criteria:
 1. A clinical condition that increases the risk of severe varicella, (for example, immunosuppression, neonates, **pregnant women**)
 2. No antibodies to varicella zoster
 3. Significant exposure to chickenpox or herpes.
- VZIG prophylaxis is of no benefit if chickenpox has already developed.
- Severe or fatal varicella can occur despite VZIG prophylaxis. Active immunisation should therefore be used for susceptible immunosuppressed patients at long term risk.

Cytomegalovirus

Overview

- Cytomegalovirus (**CMV, HHV-5**), is one of the herpes viruses.
- **Herpesviridae** is the family of viruses to which cytomegalovirus belongs.
- **Double stranded DNA virus**.
- **Mononuclear cells** are the class of leukocytes in which cytomegalovirus **lies dormant**.
- It is thought that around 50% of people have been exposed to the CMV virus although it only usually causes disease in the immunocompromised, for example people with HIV or those on immunosuppressants following organ transplantation.

Diagnosis

- **infected cells have a 'Owl's eye' appearance due to intranuclear inclusion bodies**

Patterns of disease

- Congenital CMV infection
 - ⇒ features include growth retardation, pinpoint petechial 'blueberry muffin' skin lesions, microcephaly, sensorineural deafness, encephalitis (seizures) and hepatosplenomegaly
- **CMV mononucleosis**
 - ⇒ infectious mononucleosis-like illness
 - ⇒ may develop in immunocompetent individuals
- **CMV retinitis**
 - ⇒ common in HIV patients with a low CD4 count (< 50)
 - ⇒ presents with visual impairment e.g. 'blurred vision'. Fundoscopy shows retinal haemorrhages and necrosis, often called 'pizza' retina
 - ⇒ **IV ganciclovir is the treatment of choice**
 - **Valganciclovir is an oral pro-drug for ganciclovir, with similar bioavailability but without the need to deliver it IV, making it the preferred option here.**
 - The efficacy of valganciclovir is similar to ganciclovir without the need for IV administration, and this drives ganciclovir as the option where oral therapy isn't tolerated.
 - The toxicity profile for valganciclovir is the same as that for ganciclovir, with bone marrow suppression the main concern.
 - ⇒ **Foscarnet** is the drug of choice for **ganciclovir-resistant cytomegalovirus retinitis**.
- **CMV encephalopathy:** seen in patients with HIV who have low CD4 counts
- **CMV pneumonitis**
- **CMV colitis**
 - ⇒ HIV+ bloody diarrhea+ no abdominal pain +normal stool examination → Do Colonoscopy to diagnose CMV colitis
 - ⇒ Patients with inflammatory bowel disease are at increased risk of CMV colitis particularly those on immunosuppression.
 - ⇒ COLONOSCOPY finding → multiple ulcer and mucosal erosion
 - ⇒ **The most appropriate investigation is → Flexible sigmoidoscopy and biopsy**
 - in severe colitis endoscopy should be limited to flexible sigmoidoscopy only due to an increased risk of perforation.
 - Biopsy shows: cytomegalic cell+ intranuclear **inclusion body**

Dengue fever

Definition

- Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

Pathogen

- caused by Dengue virus , RNA virus of the genus Flavivirus
- Transmitted by the Aedes aegyti mosquito
- Incubation period **4-10 days**
 - ⇒ If symptoms appear more than 2 weeks after returning from a dengue-endemic region, it is very unlikely that dengue is the cause.

Epidemiology

- Distribution: tropical regions worldwide, particularly Asia (e.g., Thailand)
- Most common viral disease affecting tourists in tropical regions

Features

- headache (often retro-orbital)
- fever
- myalgia (severe musculoskeletal pain is a prominent feature) hence the name breakbone fever.
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash (confluent erythematous rash over the precordium)
 - ⇒ When the patient is near recovery there may develop a maculopapular rash beginning on the trunk and spreading to the extremities and the face.
- There is often adenopathy, palatal vesicles and sclera injection on the first day.
- Epistaxis and scattered petechiae may be observed.

Complication

- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

Laboratory tests

- Leukopenia
- Neutropenia
- Thrombocytopenia
- ↑ AST
- Hct significantly increased or decreased in DHF (due to plasma leakage)

Diagnosis

- diagnosed by dengue fever serology.

Treatment

- symptomatic e.g. fluid resuscitation, blood transfusion etc

Herpes simplex virus

Pathogen

- Herpes simplex virus is a DNA virus.
- There are two strains of the herpes simplex virus (HSV) in humans:
 1. **HSV-1 → most commonly cause orofacial disease**
 2. **HSV-2 → most commonly cause genital disease.**
- Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap
- Worldwide seroprevalence is high, with antibodies detectable in over 90% of the population.
 - ⇒ Of these cases, approx. 60% are caused by HSV-1.
- **Incubation period** → 2 days to 2 weeks.

Pathophysiology

- **Inoculation:** The virus enters the body through mucosal surfaces or small dermal lesions.
- **Neurovirulence:** The virus invades, spreads, and replicates in nerve cells.
- **Latency:** After primary infection, the virus remains dormant in the ganglion neurons.
 - ⇒ Trigeminal ganglion: HSV-1
 - ⇒ Sacral ganglion: HSV-2
- **Reactivation:** triggered by various factors (e.g., immunodeficiency, stress, trauma) → clinical manifestations
- **Dissemination**
 - ⇒ Infection spreads to unusual sites (e.g., lungs, gastrointestinal tract, eyes)
 - ⇒ May occur in pregnant patients or patients with severe immunodeficiency
- Recurrent attacks tend to be shorter and less severe.

Transmission

- Only from direct contact with mucosal tissue or secretions of another infected person
- Because the virus dies quickly outside of the body, it's nearly impossible to get the infection through contact with toilets, towels or other objects used by an infected person
- Infection with HSV-1 usually is acquired in childhood via saliva.
- HSV-2 is mostly spread through genital contact

Features

Herpes zoster usually has a prodrome pain before the vesicles appear. It usually follows a particular dermatome but in immune suppression the disease may affect more than one dermatome.

Herpes simplex II is the wrong answer. Herpes simplex II vesicles may appear, but they never follow a particular dermatome.

- Up to 80% of herpes simplex infections are **asymptomatic**.
- **Labial herpes (herpes labialis)**
 - ⇒ Pathogen → Mostly HSV-1
 - ⇒ Recurring, erythematous vesicles that turn into painful ulcerations, also known as cold sores; oral mucosa and lip borders
 - ⇒ In orofacial HSV infections, the **trigeminal ganglia** are most commonly involved
- **Herpetic gingivostomatitis**
 - ⇒ Mainly in children (~ 1–6 years), but also immunocompromised patients

- ⇒ Erythema and painful ulcerations on perioral skin and oral mucosa
- **Genital herpes (herpes genitalis)** → **painful genital ulceration**
 - ⇒ Pathogen → HSV-2
 - ⇒ Blistering and ulceration of the external genitalia or perianal region (cervix/rectum) → “punched-out” ulcer
 - ⇒ Painful lymphadenopathy in the groin area (tender inguinal lymphadenitis, usually bilateral.)
 - ⇒ In genital HSV infection, the **sacral nerve root ganglia (S2-S5)** are involved.
- **Eczema herpeticum**
 - ⇒ associated with preexisting skin conditions, most often atopic dermatitis
 - ⇒ Fever, malaise, lymphadenopathy
 - ⇒ Extensive disseminated and painful eruptions on the head and upper body; erythematous skin with multiple, round, umbilicated vesicles
- **Herpetic whitlow**
 - ⇒ **Pathogen** → HSV-1 in 60% of cases; HSV-2 in 40% of cases (in the adult population)
 - ⇒ **Aetiology** → Direct contact with infected secretions
 - ⇒ **Risk factors**
 - Children (via sucking of thumb/fingers (may have a history of labial herpes))
 - **Health care workers** exposed to oral secretions (e.g., **dentists**)
 - ⇒ Incubation period: 2–20 days
 - ⇒ Infection of the dermal and subcutaneous tissue
 - ⇒ **Grouped, non-purulent vesicles on an erythematous base**, may rupture or ulcerate, involved one or more fingers (**especially the thumb and index fingers**); mostly found on terminal phalanx.
 - ⇒ Axillary and epitrochlear **lymphadenopathy**
 - ⇒ Management → **oral acyclovir**

Investigations

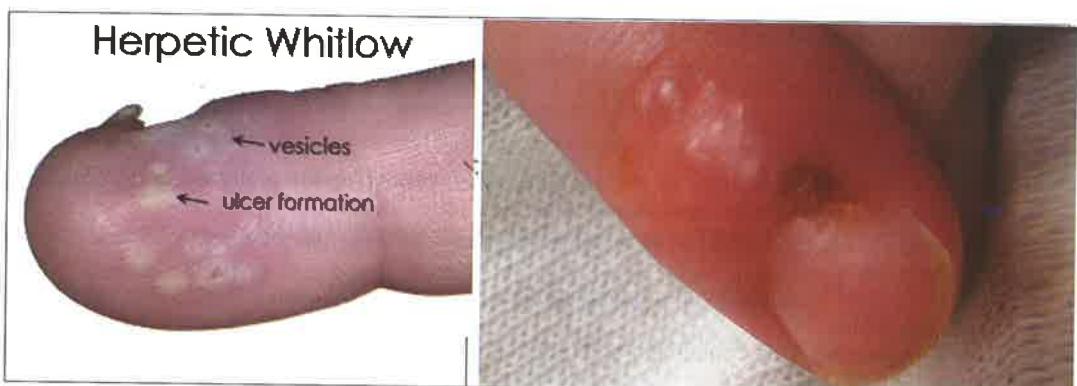
- **Nucleic acid amplification test (NAAT)** are recommended as the preferred diagnostic method for genital herpes, now regarded as **the test of choice**.
 - ⇒ **PCR** (a type of NAAT) : detects HSV RNA; identification of virus genotype
- **Western blot**
 - ⇒ the gold standard for the detection of **antibodies to HSV**, but it is not commercially available.
 - ⇒ expensive, time consuming and requires skilled interpretation.
 - ⇒ high sensitivity
 - ⇒ have ability to discriminate between HSV-1 and HSV-2 antibodies.
- **Viral culture**
 - ⇒ gold standard for definitive diagnosis; 100% specificity for HSV-1 or HSV-2
 - ⇒ The culture should be taken from a fresh vesicle, either from skin or genitals.
- **Light microscopy findings on a Tzanck smear**
 - ⇒ Detects **multinucleated giant cells (nonspecific)**
 - ⇒ Eosinophilic intranuclear Cowdry A inclusion bodies
 - ⇒ Unable to differentiate between HSV-1 and HSV-2, also commonly positive in VZV
 - ⇒ rarely used now for diagnosis.
 - ⇒ can be performed when an urgent result is needed and no alternative test is immediately available

Management

- Antiviral treatment reduces the severity of episodes but is not curative.
- gingivostomatitis: oral acyclovir, chlorhexidine mouthwash
- cold sores: topical acyclovir although the evidence base for this is modest

- **genital herpes: oral aciclovir.**
 - ⇒ Topical anaesthetic agents, e.g. 5% lidocaine (lignocaine) ointment
 - ⇒ Recommended regimens : Aciclovir 400 mg three times daily OR Valaciclovir 500 mg twice daily (for 5 days)
 - ⇒ Some patients with frequent exacerbations may benefit from longer term aciclovir
 - **more than six herpes episodes over the past 12 months → trial of suppressive therapy (aciclovir 400 mg BD for 12 months).**
 - ⇒ **Genital herpes in pregnant lady:**
 - Aciclovir is considered **safe and well tolerated.**
 - **If genital herpes is not recurrent** and healed after a course of aciclovir:
 - ❖ There is no need to continue suppressive therapy throughout the pregnancy.
 - ❖ **Restart acyclovir 400 mg TDS** suppressive dose **from week 36** to prevent active lesions being present at the time of delivery, where caesarean would definitely be needed.
 - **If there is a history of recurrent genital herpes** → she should continue taking acyclovir 400 mg TDS until the end of the pregnancy
 - **If there are active lesions or prodromal symptoms at the time of delivery**
 - A caesarean section should be considered

Early treatment of herpes infections is essential to prevent complications because antiviral drugs only inhibit the virus during its replication phase



Yellow fever

- Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola).

Aetiology

- Pathogen: yellow fever virus (genus Flavivirus)
- linear RNA virus
- spread by *Aedes* mosquitos (primarily *Aedes aegypti*)
- incubation period = 2 - 14 days

Epidemiology

- endemic in large parts of South America and Africa **but not in Asia.**

Features

- Most patients remain asymptomatic
- In symptomatic patients: classic progression in three stages
 1. Period of infection (3–4 days)

- Sudden onset of fever (up to 41°C)
- Headaches, chills
- Nausea, vomiting
- Bradycardia may develop
- 2. Period of remission (up to 2 days)
 - Easing of symptoms and decline in fever
- 3. Period of intoxication (only in ~ 15% of symptomatic patients)
 - Hemorrhage
 - Multiorgan dysfunction (e.g., acute kidney and liver failure)
 - ❖ Nausea, (bloody) vomiting, abdominal pain, severe jaundice
 - ❖ Zone 2 of the liver is most affected in Yellow fever.

Yellow fever is suggested by:

1. Travel to endemic area (West Africa and Central America)
2. Fever, with initial resolution
3. Progression to jaundice and renal failure

Investigations

- Leukopenia
- Thrombocytopenia, ↑ PTT
- Signs of organ failure (acute liver failure, acute renal failure)
- Virus detection
 - PCR: **the best test to rule out yellow fever infection is PCR**
 - ELISA
- Liver biopsy
 - Used for **definitive diagnosis** (e.g., postmortem)
 - Must not be done while the patient has an active yellow fever infection
 - May show Councilman bodies
 - **Councilman bodies (inclusion bodies) may be seen in the hepatocytes**
 - For exam purposes **Councilman bodies (eosinophilic inclusion in the liver on post mortem) are diagnostic** of yellow fever, although they can occasionally be seen in other Viral Haemorrhagic Fevers such as Crimean Congo Haemorrhagic Fever, (but this is nosocomially spread)

Treatment

- Symptomatic treatment
- No specific antiviral treatment is available

Prevention

- **Yellow fever vaccine**
 - **the vaccination is the only intervention which could prevent death .**
 - **a live, attenuated vaccine** that consists of the 17D strain of the virus, **grown in hens' eggs**.
 - Administration
 - A single dose provides life-long protection
 - administer at least 10 days before traveling to endemic area.
 - Its use is contraindicated in:
 - Under six months
 - With previous confirmed anaphylactic reaction to the vaccine
 - **previous confirmed anaphylactic reaction to egg**
 - thymus disorder
 - immunocompromised due to a congenital condition, disease process or treatment.

Human immunodeficiency virus (HIV)

Aetiology

- Consists of the two species :
 - ⇒ HIV-1: most common species worldwide
 - ⇒ HIV-2: restricted almost completely to West Africa

Pathophysiology

- HIV attaches to the CD4 receptor on host cells with its **gp120** glycoprotein (binding)
- For fusion, CD4 receptor and a coreceptor (CCR5 in macrophages, and CCR5 or CXCR4 in T-cells) must be present.
 - ⇒ Viral entry into macrophages via CCR5 mainly occurs during the early stages of infection, while entry via CXCR4 occurs in later stages.
 - ⇒ Individuals without CCR5 receptors appear to be resistant to HIV, those patients either have a homozygous CCR5 mutation (substantial resistance) or a heterozygous CCR5 mutation (slower course).
- **gp120** is the HIV glycoprotein that can **cross the placenta and infect the fetus**.
- The **lymph nodes** are the organs in which HIV replicates during the **latent phase**.

Associations

- Epstein-Barr virus reactivation, leading to B-cell lymphoma, typically occurs in AIDS patients with a CD4+ cell count less than 100/mm³.

Routes of transmission

- Sexual: responsible for ~ 80% of infections worldwide
- Parenteral transmission
- Needle sharing: → 0.67%
- Vertical transmission: from mother to child during childbirth (~ 5–15%)
-

Features

- In early HIV infection, patients are often asymptomatic.
- **Acute HIV infection** (acute retroviral syndrome) (ARS)
 - ⇒ Typically occurs 2-12 weeks after infection
 - ⇒ Fever, Fatigue, Myalgia and arthralgia
 - ⇒ Generalized nontender lymphadenopathy
 - ⇒ Generalized rash
 - ⇒ Gastrointestinal symptoms (nausea, diarrhea, weight loss)
 - ⇒ Oropharyngeal symptoms (sore throat, ulcerations, painful swallowing)
- **Clinical latency and AIDS**
 - ⇒ **Clinical latency:** Infected individuals may still be asymptomatic.
 - ⇒ **Non-AIDS-defining conditions** (common when CD4+ count is below 500 cells/mm³)
 - Generalized lymphadenopathy
 - Chronic diarrhea (> 1 month)
 - Localized opportunistic infections
 - ⇒ Oral candidiasis: creamy, white patches on the mucous membranes of the mouth that can be scraped off
 - ⇒ Oral hairy leukoplakia: lesions that cannot be scraped off located mainly on the lateral borders of the tongue; triggered by Epstein-Barr virus
 - ⇒ HPV-related: squamous cell carcinoma of the anus (common in men who have sex with men) or cervix
 - ⇒ molluscum contagiosum, warts; shingles
 - ⇒ **AIDS-defining conditions**
 - Kaposi sarcoma (typically occurs at CD4 count < 500)

- Mycobacterial infections (e.g, TB)
- Progressive multifocal leukoencephalopathy (typically occurs at CD4 count < 200)
- Disseminated or extrapulmonary coccidioidomycosis (occurs at CD4 count < 250)
- Pneumocystis pneumonia (occurs at CD4 count < 200)
- Disseminated or extrapulmonary histoplasmosis (occurs at CD4 count < 150)
- Conditions occurs at CD4 count < 100
 - ☞ Cerebral toxoplasmosis
 - ☞ Extrapulmonary cryptococcosis (especially cryptococcal meningitis)
 - ☞ Esophageal candidiasis or pulmonary candidiasis
 - ☞ Herpes simplex Esophagitis
 - ☞ Primary CNS lymphoma
- Conditions occurs at CD4 count < 50
 - ☞ Disseminated and/or extrapulmonary Mycobacterium avium complex
 - ☞ Cytomegalovirus infection

Unlike oral candidiasis, esophageal candidiasis is an AIDS-defining condition.

Man returns from trip abroad with maculopapular rash and flu-like illness - think HIV seroconversion

WHO (World Health Organization) classification

- **Primary HIV infection:** acute retroviral syndrome or asymptomatic
- **Clinical stage 1:** persistent generalized lymphadenopathy (PGL) or asymptomatic
- **Clinical stage 2:** e.g., unexplained moderate weight loss (< 10%), recurrent fungal/viral/bacterial infections
- **Clinical stage 3:** e.g., unexplained severe weight loss (> 10%), unexplained chronic diarrhea (> 1 month), unexplained persistent fever ($\geq 37.6^{\circ}\text{C}$ intermittent or constant > 1 month), persistent/severe fungal/viral/bacterial infections , unexplained anemia (< 8 g/dL) and/or neutropenia (< 500 cells/mm³) and/or chronic thrombocytopenia (< 50,000/ μL) for more than 1 month
- **Clinical stage 4:** AIDS-defining conditions (e.g., Kaposi sarcoma, Pneumocystis pneumonia)

Diagnosis

- **HIV-1/2 antigen/antibody combination immunoassay (Ag/Ab immunoassay) (ELISA)**
 - ⇒ Target of detection: IgM and IgG antibody **and** p24 antigen
 - ⇒ Approximate time to positivity: 15 to 20 days after event
 - ⇒ **If a very early infection is suspected (less than 2 weeks), advice for:**
 - Serial testing at 1 month and again at 3 months from the date of the possible exposure **OR**
 - HIV RNA viral load test
 - ⇒ p24 is the **capsid** protein of HIV, coded for by the *gag* gene.
 - ⇒ If negative → No further testing is required (exclude HIV)
 - ⇒ If positive → confirm by **HIV-1/2 differentiation immunoassay** (differentiates HIV-1 antibodies from HIV-2 antibodies)

- **HIV viral load test**
 - ⇒ Made by PCR of peripheral blood for HIV RNA
 - ⇒ Target of detection: RNA
 - ⇒ Approximate time to positivity: 5 – 15 days
 - ⇒ In acute HIV the viral load is very high.
- **HIV-1/2 differentiation immunoassay**
 - ⇒ Confirmatory test , indicated following a positive HIV-1/2 Ag/Ab immunoassay
 - ⇒ The differentiation assay is now the standard confirmatory test
 - ⇒ Determines whether it is HIV-1 or HIV-2 infection
 - ⇒ If both Ag/Ab immunoassay **and** differentiation immunoassay are positive → confirm diagnosis of HIV and determine as **positive** for HIV-1 antibodies, HIV-2 antibodies, or HIV antibodies, undifferentiated.
 - ⇒ If Ag/Ab immunoassay differentiation was positive but **differentiation immunoassay** is negative (non-reactive) → test for **HIV-1 nucleic acid test (NAT)**.
- **HIV-1 nucleic acid test (NAT)**
 - ⇒ A reactive HIV-1 NAT result and nonreactive HIV-1/HIV-2 antibody differentiation immunoassay result indicates laboratory evidence for **acute HIV-1 infection**.
 - ⇒ A negative HIV-1 NAT **and** nonreactive or indeterminate HIV-1/HIV-2 antibody differentiation immunoassay indicates a **false-positive result on the initial immunoassay**
- **Flow cytometry** is the lab technique used to **measure CD4 cell count**
 - ⇒ Used to determine the level of immune suppression once an infection is confirmed.
 - ⇒ **The most useful investigation in estimating the risk of developing an opportunistic infection**
 - ⇒ A count lower than $200/\text{mm}^3$ generally indicates progression to AIDS.
- The Centers for Disease Control (CDC) no longer recommends **Western blot** confirmatory testing for HIV.

Treatment

- Since late 2015, the World Health Organization (WHO) has recommended **starting ART in every HIV-positive individual, regardless of CD4 count**.
- In hepatitis B co-infection
 - ⇒ **Antiretrovirals that also have anti-HBV activity should be included in the regimen used to treat HIV.** These include:
 - Emtricitabine
 - **Lamivudine**
 - **Tenofovir**
 - ⇒ Discontinuation of drugs that have anti-HBV activity can lead to reactivation of HBV and cause serious hepatocellular damage.
- In patients with renal impairment → avoid **tenofovir** and consider avoiding atazanavir.

Initiation of ART should be delayed in the setting of TB meningitis and cryptococcal meningitis because of the high risk of immune reconstitution syndrome

Stopping NRTIs in patients with hepatitis B co-infection can lead to an acute worsening of their hepatitis!

HIV and pregnancy

Efavirenz is the only antiretroviral medication that is contraindicated in pregnancy (teratogenic)

Epidemiology

- In London the incidence may be as high as 0.4% of pregnant women.

Factors which reduce vertical transmission (from 25-30% to 2%)

- maternal antiretroviral therapy
- mode of delivery (caesarean section)
- neonatal antiretroviral therapy
- infant feeding (bottle feeding)

Screening

- NICE guidelines recommend offering HIV screening to all pregnant women

Treatment

- The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission.
- Antiretroviral therapy**
 - all pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously
 - if women are not currently taking antiretroviral therapy the RCOG recommend that it is commenced between 28 and 32 weeks of gestation and should be continued intrapartum. BHIVA recommend that antiretroviral therapy may be started at an earlier gestation depending upon the individual situation
 - No routine dose alterations are recommended for ARVs during pregnancy if used at adult licensed doses.
 - It is recommended that **women conceiving on an effective anti-retroviral (ART) regimen should continue this even if it contains efavirenz or does not contain zidovudine**. Exceptions are:
 - (1) Protease inhibitor (PI) monotherapy should be intensified to include (depending on tolerability, resistance and prior antiretroviral history) one or more agents that cross the placenta.
 - (2) The combination of stavudine and didanosine should not be prescribed in pregnancy.
- Mode of delivery**
 - vaginal delivery is recommended if viral load is less than 50 copies/ml** at 36 weeks, **otherwise caesarian section is recommended**
 - zidovudine infusion should be started four hours before beginning the caesarean section
- Neonatal antiretroviral therapy**
 - zidovudine is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise triple ART should be used. Therapy should be continued for 4-6 weeks.
- Infant feeding:** in the UK all women should be advised not to breast feed

HIV: anti-retrovirals

HIV drugs, rule of thumb:

- NRTIs end in 'ine'
- PIs: end in 'vir'
- NNRTIs: nevirapine, efavirenz

Anti-retroviral therapy for HIV is now started at the time of diagnosis, rather than waiting for the CD4 count to drop to a particular level

HIV: anti-retrovirals - P450 interaction

- nevirapine (a NNRTI): induces P450
- protease inhibitors: inhibits P450

Overview

- **Start HAART as soon as possible after diagnosis regardless** CD4 count.
- Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging
 ⇒ Atripla® (efavirenz, tenofovir, emtricitabine) is an acceptable choice.

Nucleoside analogue reverse transcriptase inhibitors (NRTI) (**ine** at the end)

Emtricitabine causes hyperpigmentation of skin including palmar creases in 8% of black patients.

- examples: zidovudine (AZT), lamivudine, stavudine, didanosine, zalcitabine
- general NRTI side-effects:
 - ⇒ Peripheral neuropathy
 - ⇒ **Mitochondrial toxicity → dilated cardiomyopathy**
 - NRTI → reduce vascular responsiveness to acetylcholine → endothelial dysfunction.
 - Mitochondrial dysfunction induced by HAART → decreased myocardial contractility. This is because cardiac myocytes can utilise energy less well, leading to decreased ejection fraction and dilative cardiomyopathy.
 - myocardial biopsy usually reveals mitochondria full of myelin, a sign of mitochondrial dysfunction.
 - Withdrawal of zidovudine and substitution with an agent associated with less mitochondrial toxicity, coupled with appropriate treatment for heart failure with diuretics and ACE inhibition, usually resolves the problem, although HIV itself is decreasingly recognised as a cause of cardiomyopathy.
- **zidovudine:** anaemia, myopathy, black nails
 - ⇒ **most frequently causes anaemia, usually by bone marrow suppression and patients can become transfusion-dependent in severe cases.**

- **Macrocytosis is a typical finding in patients on zidovudine and can be used as a parameter to monitor adherence to therapy.**
- ⇒ Other side-effects of zidovudine include:
 - **Myalgia, Myopathy, Myositis**
 - ❖ Elevated CK → a picture of rhabdomyolysis
 - Pancytopenia,
 - Lactic acidosis.
 - Blue or black discolouration of the nails is a rare side-effect. May be misdiagnosed as cyanosis and melanoma.
- Didanosine: pancreatitis (Didanosine and stavudine cause mitochondrial toxicity, hence peripheral neuropathy, pancreatitis and hyperlactataemia.)
- **NRTIs - in particular stavudine, didanosine and zidovudine - classically cause mitochondrial toxicity as an unwanted side effect. This can result in nausea, pancreatitis, lactic acidosis and lipotrophy**
- Truvada → combination of two (Nucleoside analog reverse-transcriptase inhibitors (NRTIs) : tenofovir disoproxil and emtricitabine
 - ⇒ tenofovir may cause:
 1. life-threatening liver damage
 2. lactic acidosis
 3. sudden worsen of hepatitis B after stopping tenofovir → lab tests regularly for several months after stop.
- **Abacavir:** (the only NARTI which is not ended by (ine))
 - ⇒ is a nucleoside reverse transcriptase inhibitor (NRTI).
 - ⇒ It is recommended by the British HIV Association (BHIVA) in association with lamivudine as an alternative to Truvada as part of a HAART regime.
 - ⇒ **Abacavir causes a hypersensitivity reaction** in patients who are HLA-B5701 positive.
 - However, this would occur within 1–2 months of starting treatment
 - in the UK all patients would be tested prior to initiation.
 - It is typified by nausea, vomiting, malaise and fever, with or without a rash.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (vir** in the middle)**

- Examples: nevirapine, delavirdine, efavirenz and etravirine.
- Side-effects:
 - ⇒ P450 enzyme interaction (nevirapine **induces**),
 - ⇒ Skin rashes
 - **Rashes are common on starting treatment with nevirapine, occurring in ~15% of patients.**
 - **Nevirapine can cause acute hepatitis and skin rash as a part of hypersensitive reaction**
 - ❖ this is the rationale for starting low-dose therapy with nevirapine in the first 2 weeks
 - Serious side effects are more common in patients with relatively well preserved immune function.
 - ⇒ **Acute hepatitis**
 - ⇒ **Efavirenz side effects**
 - more common → neuropsychiatry side effects.
 - less common → **Gynaecomastia**

Efavirenz is the most common HAART drug associated with gynecomastia.

Protease inhibitors (PI) (vir at the end)

- Examples: **indinavir**, **nelfinavir**, **ritonavir**, **saquinavir**
- Side-effects:
 - ⇒ diabetes,
 - ⇒ **hyperlipidaemia, Hypertriglyceridaemia**
 - ⇒ Buffalo hump, central obesity,
 - ⇒ P450 enzyme inhibition
 - ⇒ **Lipodystrophy**
 - ⇒ Indinavir: → **renal stones**, asymptomatic hyperbilirubinaemia
 - ⇒ Ritonavir:
 - Potent inhibitor of the P450 system (3A4 inhibitor)
 - **Produces very significant elevations in plasma fluticasone (even an inhaled preparation).**
 - ❖ so, it increases the levels of rifampin.
 - ❖ These levels are sufficient to suppress endogenous cortisol levels and produce **Cushing's syndrome**.

Co-trimoxazole prophylaxis for *Pneumocystis* (PCP) is not necessary unless the CD4 count is below 200

Patient who have high viral load despite treatment:

- Causes of treatment failure:
 - ⇒ poor adherence
 - ⇒ drug interactions or absorption issues
 - ⇒ primary resistance or superinfection with a new resistant strain.
- **All patients should have had a resistance test at baseline**
 - ⇒ The most appropriate course of action is to **arrange an urgent resistance test** and manage the antiretrovirals accordingly with this result.

Patient who have TB associated with HIV:

- Efavirenz is used in combination with an NRTIs because it has little effect on the plasma levels of rifampin which is being used to treat the pulmonary tuberculosis.

Preventing Opportunistic Infections in Patients With HIV

- **Initiation of Prophylaxis and Treatment**
 - ⇒ Patients not taking ART who present with disseminated *Mycobacterium avium* complex (MAC) infection should be treated for the infection without ART for 2 weeks, and then started as soon as possible on ART while monitored closely for symptoms of the immune reconstitution inflammatory syndrome (IRIS).
 - ⇒ Severe IRIS has also been reported after early ART in the management of **cryptococcal and tuberculous meningitis**, and it has been suggested that such patients **delay ART until 4-6 weeks after control of the opportunistic infection**.
 - ⇒ Patients with CD4 counts of less than 50 cells/ μ L at presentation should be considered for cryptococcal antigen testing,
 - ⇒ among those diagnosed with **cryptococcal meningitis**, **initial ART should be delayed at least 2 weeks** into cryptococcal therapy and as long as 10 weeks.
 - which must be treated initially with amphotericin and flucytosine.
- **CD4 counts are useful landmarks for initiation of antimicrobial prophylaxis:**
 - ⇒ Less than 250 cells/ μ L - Coccidioidomycosis prophylaxis if seropositive in high-risk area

- Patients with a new positive immunoglobulin M (IgM) or IgG serologic test result who live in endemic areas and have a CD4 count of less than 250 cells/ μ L should receive fluconazole 400 mg PO daily
- ⇒ **Less than 200 cells/ μ L - PCP prophylaxis**
 - The preferred regimen is trimethoprim-sulfamethoxazole 1 double-strength tablet orally daily or 1 double-strength tablet orally 3 times weekly.
- ⇒ Less than 150 cells/ μ L - Histoplasmosis prophylaxis if high-risk exposure
 - Patients with a CD4 count of less than 150 cells/ μ L at high risk for exposure or who live in a hyperendemic area should receive itraconazole 200 mg PO daily
- ⇒ Less than 100 cells/ μ L - Toxoplasmosis prophylaxis (if seropositive)
 - Trimethoprim-sulfamethoxazole, one double-strength tablet orally once daily is preferred
- ⇒ Less than 100 cells/ μ L - Penicilliosis prophylaxis if living in high-risk area
- ⇒ Less than 50 cells/ μ L - MAC infection prophylaxis
 - Patients with CD4 count of fewer than 50 cells/ μ L should be given **azithromycin** 1200 mg orally **weekly** after ruling out disseminated MAC infection on clinical assessment
 - Alternatives include clarithromycin 500 mg orally twice daily or rifabutin 300 mg orally daily
- **Clinical Landmarks for Terminating Primary Prophylaxis**
 - ⇒ ***Mycobacterium avium-intracellulare* (MAI) infection prophylaxis:**
 - should be continued with antiretroviral therapy (ART) until the CD4 count exceeds 100 cells/ μ L **for 3 months**.
 - ⇒ ***P carinii* pneumonia (PCP) and **toxoplasmosis** prophylaxis:**
 - should be continued until the CD4 count exceeds 200 cells/ μ L **for 3 months**.
 - ⇒ **Histoplasmosis prophylaxis:**
 - can be discontinued when the CD4 count has exceeded 150 cells/ μ L for 6 months,
 - ⇒ **coccidioidomycosis prophylaxis:**
 - can be discontinued when CD4 counts exceed 250 cells/ μ L for 6 months,
 - ⇒ **penicilliosis prophylaxis:**
 - can be discontinued when CD4 counts exceed 100 cells/ μ L for 6 months.

HIV lipodystrophy (Antiretroviral-related lipodystrophy)

- Lipodystrophy (loss of adipose tissue), lipoatrophy and alterations in serum lipid values have been observed in patients with human immunodeficiency virus (HIV) disease taking highly active antiretroviral therapy (HAART).
- **Consequences**
 - ⇒ ↑serum lipid levels → premature coronary artery disease.
 - ⇒ Hypertriglyceridaemia → central fat deposition and insulin resistance (**Antiretroviral insulin-resistance syndrome**)
 - there is some evidence that the insulin sensitizers (glitazones) may be effective in some patients

- Causes

- ⇒ Abnormalities of serum lipid levels are likely to be **multifactorial** in patients with HIV disease but appear **much commoner in patients taking protease inhibitors.**
- ⇒ Isolated **hypertriglyceridaemia** can occur in HIV disease in the absence of **protease inhibitors** but extremely high serum triglycerides have been documented in some patients treated with these drugs.

- Treatment

- ⇒ Mild to moderate hyperlipidaemia → 1st line dietary modification and exercise
- ⇒ Predominant **hypercholesterolaemia** or with a mixed picture → statin
 - Caution must be exercised since some **protease inhibitors** interact with some **statins** due to metabolism by CYP3A4 pathway.
 - Simvastatin is contraindicated in patients on protease inhibitors and plasma levels of atorvastatin are also greatly elevated in these patients.
 - For this reason, **pravastatin is usually the drug of choice.**
 - ❖ **Pravastatin is preferred because its metabolism is not as dependent on the CP450s** as other agents in this group.
- ⇒ **Hypertriglyceridaemia → fenofibrate**
- ⇒ Switching therapy might be an option, to non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- ⇒ In women with lipoatrophy syndromes, oral estrogens should be avoided as they can exacerbate the hypertriglyceridemia and result in acute pancreatitis.

Immune reconstitution syndrome

- Due to activation of the immune system following HIV therapy against persisting antigen.
- **Typically occurs a few weeks after commencing anti-retroviral therapy in a patient with underlying tuberculosis.**

HIV: biliary and pancreatic disease

- The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia
- **Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine)** or by opportunistic infections e.g. CMV

HIV: diarrhoea

Supportive therapy is the mainstay of treatment in Cryptosporidium diarrhoea

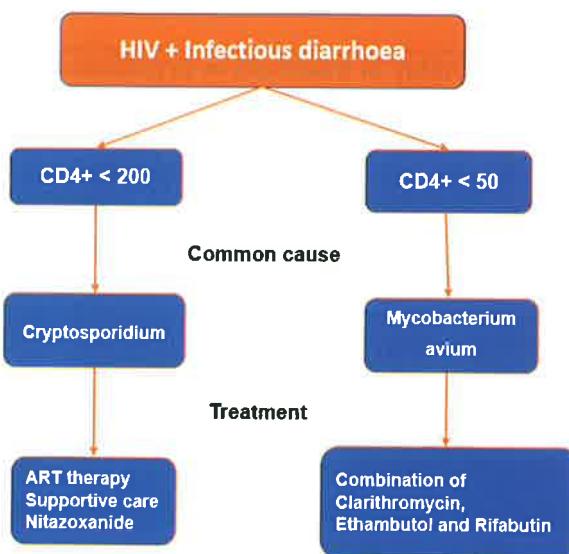
- Diarrhoea is common in patients with HIV.

Causes

- Infection, may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections (usually there are fever and wasting)
- Malignancy (infiltrative diseases, such as lymphoma or Kaposi's sarcoma.)
- Medications (e.g. antiretroviral therapy, particularly when diarrhea is the sole presenting symptom and there is a temporal association.)
 - Ritonavir-containing protease inhibitors (PIs) are the drugs most commonly associated with diarrhoea.

Infectious causes

- **Cryptosporidium** (**the most common cause of diarrhoea in HIV patients who their CD4+ > 50**)
 - ⇒ It is an intracellular protozoa and has an incubation period of 7 days.
 - ⇒ Presents as watery diarrhoea, often with severe abdominal pain, commonly lasting >7 days.
 - ⇒ Diagnosis: usually by detection of *Cryptosporidium* oocysts, antigens, or DNA in stools.
 - ⇒ Treatment:
 - **Supportive therapy is the mainstay of treatment**
 - If patient is not on antiretroviral therapy (ART) : initiation of ART is the primary intervention
 - Nitazoxanide may be used for treatment (Antiprotozoal)
- ***Mycobacterium avium intracellulare***
 - ⇒ is an atypical mycobacteria seen with the CD4 count is below 50.
 - ⇒ Presentation: fever, sweats, abdominal pain and diarrhoea. There may be hepatomegaly and deranged LFTs.
 - ⇒ Diagnosis is made by blood cultures and bone marrow examination.
 - ⇒ Management is with combination of clarithromycin, ethambutol and rifabutin



HIV nephropathy

Overview

- Accounts for up to 10% of end-stage renal failure cases in the United States.
- Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself.
- Protease inhibitors such as **indinavir** can precipitate intra-tubular crystal obstruction

Features

- Raised creatinine
- Nephrotic range proteinuria
- **Normal sized kidneys** on ultrasound scan,
- **Focal segmental glomerulosclerosis on renal biopsy.**
- Raised immunoglobulins
- Raised cholesterol
- **Normotension**

Cryptococcal disease in AIDS (Cryptococcosis)

Epidemiology

- The most common fungal infection of the CNS
- The most common fungal disease in HIV

Features

- **May present as:** space-occupying lesion, meningitis, or meningoencephalitis.
- **Symptoms are typically of gradual onset over one to two weeks.**

Risk factors

- usually develops only when CD4+ lymphocyte counts fall **below 100 cells/mL**.

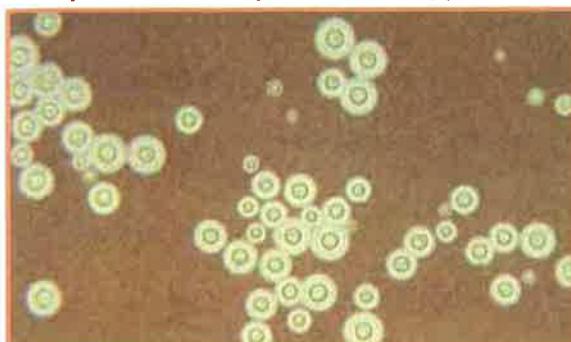
Diagnosis

- MRI, with and without contrast, is the preferred diagnostic imaging modality.

- The India ink test is used to diagnose cryptococcal meningitis,
- the raised opening pressure, turbid appearance to the CSF, raised protein and mixed lymphocytic/neutrophil picture are relatively typical of the diagnosis.

Treatment

- Treatment is with amphotericin B and flucytosine (5FC);
- patients then require lifetime suppression with fluconazole.



Microscopy of *Cryptococcus neoformans*.

Cryptococcus neoformans skin lesions

- Most often seen in T cell deficiency states and HIV-infected patients with CD4 counts of $<100/\text{mm}^3$.
- **Gomori's methanamine silver stain** shows budding yeasts.
- Serum cryptococcal antigen can also be used in diagnosis.
- Treatment is with an eight-week course of **fluconazole** 400 mg /day followed by 200 mg/day.

HIV: immunisation

The Department of Health 'Greenbook' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults

Vaccines that can be used in all HIV-infected adults	Vaccines that can be used if CD4 > 200	Contraindicated in HIV-infected adults
<ul style="list-style-type: none"> • Hepatitis A • Hepatitis B • <i>Haemophilus influenzae</i> B (Hib) • Influenza-parenteral • Japanese encephalitis • Meningococcus-MenC • Meningococcus-ACWY I • Pneumococcus-PPV23 • Poliomyelitis-parenteral (IPV) • Rabies • Tetanus-Diphtheria (Td) 	<ul style="list-style-type: none"> • Measles, Mumps, Rubella (MMR) • Varicella • Yellow Fever 	<ul style="list-style-type: none"> • Cholera CVD103-HgR • Influenza-intranasal • Poliomyelitis-oral (OPV) • Tuberculosis (BCG)

Routine vaccines

- People with HIV are at risk of Hep B, invasive pneumococcal disease and severe morbidity from influenza. These are all inactivated vaccines and can be given at any CD4 count.
- **Should be vaccinated against Hepatitis B, pneumococcus, and yearly against influenza**
 - Hepatitis B is given as a course of three injections at double dose and booster as required.
 - pneumococcal vaccine PPV23 is a single dose but could be boosted 5-10 years later.
 - influenza vaccine should be administered yearly.

Other vaccines

- **Men C vaccine** → only recommended in people under 25.
- **polio vaccine**
 - ⇒ the oral polio vaccine is not recommended in HIV as it is a live vaccine.
 - ⇒ However, the parenteral polio vaccine is acceptable.
- **MMR vaccine**
 - ⇒ It is a live vaccine that is contraindicated in patients with a CD4 count of less than 200 cells/ μL but could be safely administered in patient with CD4 count above 200 cells/ μL .
- ***Haemophilus influenzae B vaccine***
 - ⇒ is an inactivated vaccine that can be given to patients at any CD4 count.
 - ⇒ Although *Haemophilus influenzae* is an issue in people with HIV it is the pneumococcal vaccine that is recommended for all HIV patients.
 - ⇒ it is only recommended for those who have:
 - splenic dysfunction,
 - recurrent pulmonary infections
 - previous *Haemophilus influenzae* disease with risk of recurrence.
- **shingles vaccine**
 - ⇒ thought to be safe and immunogenic even in those who have recently had shingles.
 - ⇒ However, it must be used with caution in any immunocompromised state
 - ⇒ should not be used in patients with a CD4 count of less than 200 cells/ μL .

HIV: Kaposi's sarcoma

Kaposi's sarcoma - caused by HHV-8 (human herpes virus 8)

Overview

- Kaposi sarcoma is a **neoplasm of endothelial cells** (vascular tumor) that is **caused by human herpes virus 8 (HHV-8)**
- most commonly seen in patients with HIV and **transplant** patients.
 - ⇒ can be seen in HIV patients with a CD4+ cell count of less than 500/mm³.
- Human herpes virus 8, which causes Kaposi sarcoma in HIV patients, is **transmitted by sexual contact**.
- Aside from affecting the skin, Kaposi sarcoma can also affect the **gastrointestinal tract** and lungs.

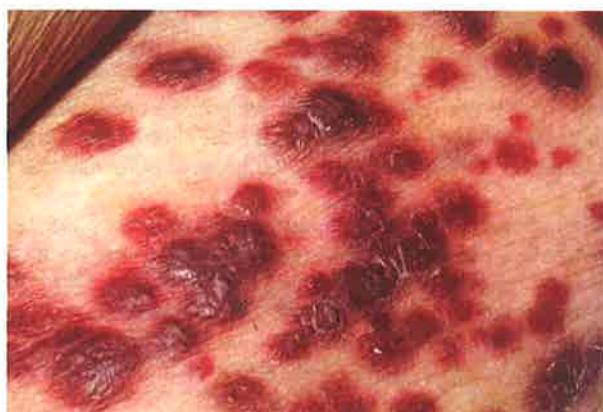
Feature

- presents as purple papules or plaques on the skin or **mucosa** (e.g. gastrointestinal and respiratory tract)
- lesions occur most commonly on the face

- skin lesions may later ulcerate
- respiratory involvement may cause massive haemoptysis and pleural effusion, Chest x ray may show pulmonary nodules.
- Histopathology classically show
 - ⇒ **lymphocytic inflammation**.
 - ⇒ proliferation of endothelial cells (**spindle cells**)

Treatment

- Radiotherapy + resection
 - ⇒ Radiotherapy may be used to treat painful or highly visible lesions.
- AIDS-related Kaposi's sarcoma becomes smaller as immune function improves such as with treatment with highly active antiretroviral therapy (HAART).
- In some circumstances chemotherapy may be added to HAART.
- **Human herpes virus 8** is also associated with:
 - ⇒ primary effusion lymphoma (a rare lymphoma of serous cavities)
 - ⇒ Castleman's disease.



Kaposi's sarcoma in a patient with HIV

HIV: Dermatologic conditions (Eosinophilic folliculitis) (EF)

Overview

- Dermatologic conditions are very common in HIV/AIDS infection; knowing the common infections and their treatment is important.

Types

- There are three main variants of Eosinophilic folliculitis (EF):
 - Classic EF immunosuppression-related EF (mostly HIV-associated) and Infancy-associated EF.
 - **The most common type of EF is the immunosuppression-related (HIV-associated) form.**
 - The clinical presentations of EF vary slightly, but histologically the forms are identical.
- **Classic EF**
 - ⇒ also known as Ofuji disease (eosinophilic pustular folliculitis)
 - ⇒ more common in individuals of Japanese descent, although anyone can be affected.

- **Immunosuppression-EF**

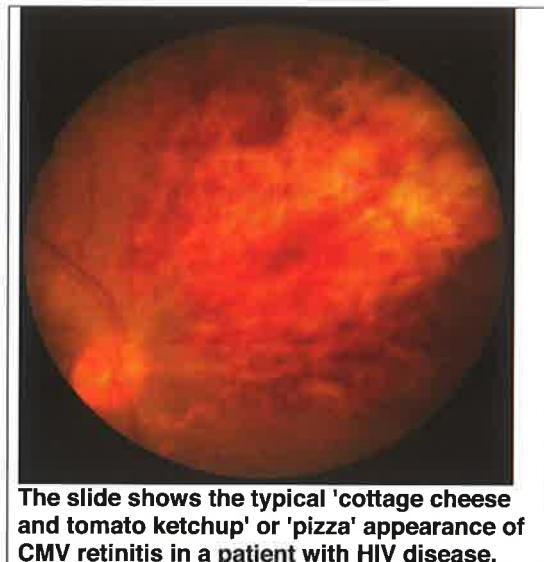
- ⇒ Differs from the classical form in that the eruption is exquisitely **pruritic**. It also tends to present with erythematous, almost oedematous, papules with few pustules (whereas the classic form tends to have clusters of pustules).
- ⇒ Because the eruption is so pruritic the lesions are often **excoriated** on presentation, making identification of a primary lesion difficult.
- ⇒ The lesions are found primarily on the face and upper trunk (from the waist up).
- ⇒ **Histologic examination** of a papule shows an acute and chronic infiltrate of eosinophils and lymphocytes focused at the level of the follicular isthmus that can rarely progress to complete follicular destruction.
- ⇒ Men more commonly affected than women.
- ⇒ may worsen 3 - 6 months after initiation of antiretroviral therapy as part of the immune restoration syndrome and even after the CD4+ cell count rises above 200/ μ L.

HIV: abnormal vaginal bleeding

- **Abnormal bleeding can be a sign of cervical dyskaryosis.**
- Advanced HIV with HPV co-infection is a very strong risk factor for developing cervical dyskaryosis and currently the British HIV association recommend that **patients with HIV should have yearly smears.**
- The US guidelines recommend that HIV positive females under the age of 26 and MSM should be immunised as the HPV vaccine is safe and immunogenic at all CD4 counts.
- The risk of HPV infection already present is too great in patients older than 26 for cost effectiveness.
- In Britain the national programme now immunises all females aged 12-13 years.
- If cervical dyskaryosis is detected it is treated in the same way as in HIV negative patients.
- **HIV patients should have a yearly smear as per the current BHIVA guidelines.** This may change as more information is gathered about cervical disease in patients who are stable on ARVs.
- Cervical dyskaryosis is invisible to the naked eye and so a normal speculum examination does not rule out cervical disease.

CMV retinitis in a patient with HIV

- AIDS retinitis is typically caused by cytomegalovirus.



Vaginal discharge

Vaginal discharge is a common presenting symptom and is not always pathological

Common causes	Less common causes
<ul style="list-style-type: none"> physiological <i>Candida</i> <i>Trichomonas vaginalis</i> bacterial vaginosis 	<ul style="list-style-type: none"> Gonorrhoea <i>Chlamydia</i> can cause a vaginal discharge although this is rarely the presenting symptoms ectropion foreign body cervical cancer

• Black women report higher incidence of candidiasis infections compared with white women.

Key features of the common causes are listed below

Condition	Key features
<i>Candida</i>	<ul style="list-style-type: none"> • 'Cottage cheese' discharge • Vulvitis • Itch
<i>Trichomonas vaginalis</i>	<ul style="list-style-type: none"> • Offensive, yellow/green, frothy discharge • Vulvovaginitis • Strawberry cervix
Bacterial vaginosis	<ul style="list-style-type: none"> • Offensive, thin, white/grey, 'fishy' discharge

Bacterial vaginosis (BV)

Bacterial vaginosis - overgrowth of predominately *Gardnerella vaginalis*

Pathogen

- Bacterial vaginosis (BV) describes an overgrowth of predominately anaerobic organisms such as *Gardnerella vaginalis*.

Epidemiology

- **BV is the commonest cause of abnormal vaginal discharge** in women of childbearing age. It is twice as common as vaginal candidiasis.

Risk factors

- intrauterine coil device,
- vaginal douching
- number of sexual partners.
- Whilst BV is not a sexually transmitted infection it is seen almost exclusively in sexually active women.

Features

- vaginal discharge: 'fishy', offensive , Gray, thin, and homogeneous
- asymptomatic in 50%
- This leads to a consequent fall in lactic acid producing aerobic lactobacilli resulting in a raised vaginal pH.

Diagnosis

Epithelial cells with a stippled border (Clue cells**) are the hallmark microscopic findings of bacterial vaginosis**

- **Amsel's criteria for diagnosis of BV** - 3 of the following 4 points should be present
 1. thin, white homogenous discharge
 2. **clue cells** on microscopy: **stippled vaginal epithelial cells**
 3. **vaginal pH > 4.5**
 4. positive whiff test (addition of potassium hydroxide results in fishy odour)

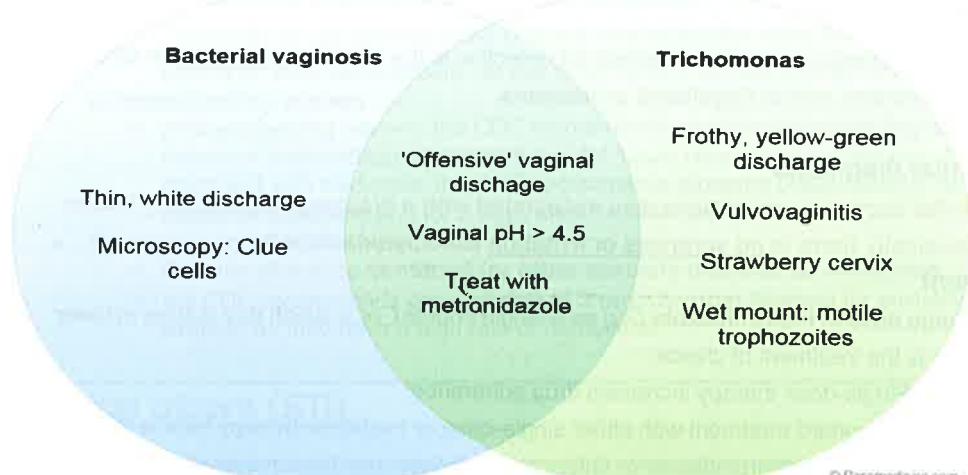
Management

Bacterial vaginosis treatment → oral metronidazole

- Infection resolves spontaneously in one-third of cases
- oral metronidazole (400 mg twice daily given for 5-7 days)
 - ⇒ initial cure rate → 70-80%
 - ⇒ relapse rate > 50% within 3 months
- the BNF suggests topical metronidazole or topical clindamycin as alternatives

Bacterial vaginosis in pregnancy

- complications
 - ⇒ results in an increased risk of preterm labour, low birth weight and chorioamnionitis, late miscarriage
- treatment
 - ⇒ it was previously taught that oral metronidazole should be avoided in the first trimester and **topical clindamycin** used instead. **Recent guidelines however recommend that oral metronidazole is used throughout pregnancy.** The BNF still advises against the use of high dose metronidazole regimes



Comparison of bacterial vaginosis and *Trichomonas vaginalis*

MRCPUK-part-1-January 2020 exam: H/O offensive vaginal discharge. Diagnosed as bacterial vaginosis. What is the most appropriate initial management?

→ Oral metronidazole

Trichomonas vaginalis

Overview

- anaerobic flagellated protozoan, which thrive in more **alkaline** conditions.
- incubation period is 5 to 28 days.
- transmitted directly, for example, through sexual transmission.

Feature

- asymptomatic (in most men and 50% of women)
- yellow-green, frothy vaginal discharge
- vulvar pruritus
- dysuria, dyspareunia, and lower abdominal pain.
- Punctuate hemorrhages on the cervix, i.e. "**strawberry cervix**", or along the vaginal wall are less common signs, but are highly suggestive of infection with *Trichomonas vaginalis*.
- The **pH** of the discharge is **greater than 4.5**

Diagnosis

- The most rapid and practical method for detection is the use of a **wet mount** in clinic, which demonstrates **motile flagellated protozoans**.

Differential diagnosis

- Whilst bacterial vaginosis is also associated with a discharge with a fishy odour, classically there is no soreness or irritation associated with it.**

Treatment

- A large dose of **metronidazole** (2 g as a single course), or a seven day course at lower dose is the treatment of choice.
 - ⇒ Single-dose therapy increases drug adherence.
 - ⇒ If standard treatment with either single-dose or multidose therapy fails, a regimen of 2 g of oral metronidazole or tinidazole for 5 days may be considered
 - ⇒ Patients should not consume alcohol during the course of treatment or during the 24 hours after the completion of the medication.
 - ⇒ Patients on tinidazole therapy should not consume alcohol during therapy or for 72 hours after completion of the medication.
 - ❖ Drinking alcohol while taking tinidazole causes **disulfiram-like reaction**, which includes (nausea, vomiting, headache, ↑BP, flushing, and shortness of breath).
 - ⇒ Tinidazole has a longer half-life (12-14 h) than metronidazole (6-7 h).
 - ⇒ metronidazole and tinidazole are equally effective
 - ⇒
- Partner**
 - ⇒ **Partners** should be identified and also screened for infection as men rarely exhibit symptoms of a *T. vaginalis* infection.

- ❖ The epithelial damage caused by *T. vaginalis* increases susceptibility to HIV virus infection and transmission.
- ⇒ Both patient and partner should abstain from sex until pharmacological treatment has been completed and they have no symptoms.
- **HIV-positive women with Trichomoniasis.**
 - ⇒ the CDC recommends considering the **multidose treatment in HIV-positive women with Trichomoniasis.**
 - (metronidazole 500 mg twice daily for 7 days) are more effective in treating *T. vaginalis* in HIV-positive women than a single-dose treatment (metronidazole 2 g single dose).
- **In pregnant women**
 - ⇒ The CDC recommends that infected **symptomatic** pregnant women be considered for treatment, as metronidazole has not been definitively shown to be harmful during pregnancy and may prevent transmission to the newborn.
 - ⇒ Infected **asymptomatic** pregnant women may wish to defer treatment to after 37 weeks' gestation.
 - ⇒ Pregnant women should be treated with 2 g metronidazole in a single dose, according to the CDC.
 - ⇒ The safety of tinidazole in pregnancy is not known.
 - ⇒ Tinidazole is a pregnancy class C agent; animal studies have demonstrated adverse effects on fetal development. Its use is not recommended in pregnant women.
- **In breastfeeding women**
 - ⇒ In breastfeeding women, the CDC recommends stopping breastfeeding during the course of metronidazole treatment and for 12-24 hours after the last day. For treatment with tinidazole, the CDC recommends stopping breastfeeding for the course of treatment and for 3 days after the last dose.
- **Screening and Rescreening**
 - ⇒ Patients should be **screened for other sexually transmitted infections.**
 - ⇒ the CDC recommends **rescreening at 3 months post therapy** for sexually active women, as they have a high rate of reinfection.

Genital ulcers (STI)

Genital ulcers:

- **Painful:** herpes much more common than chancroid
- **Painless:** syphilis more common than lymphogranuloma venereum + granuloma inguinale

Other causes of genital ulcers

- Behcet's disease
- carcinoma
- granuloma inguinale: *Klebsiella granulomatis* (previously called *Calymmatobacterium granulomatis*)

Genital herpes

- Causes:
 - ⇒ most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1).
- Features:
 - ⇒ **Multiple painful penile vesicles and ulcers are characteristic.**
 - ⇒ Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site.
- Diagnosis:
 - ⇒ Tzanck smear for lesions suspicious of HSV
- Treatment:
 - ⇒ **Oral Acyclovir is the treatment of choice.**
- Prognosis:
 - The lesions generally heal within 2 weeks.
 - Recurrence of painful genital lesions is a characteristic.

Chancroid

- Causes:
 - *Haemophilus ducreyi*.
- Features: (Remember the saying: "You do cry with *ducreyi*".)
 - ⇒ **painful genital ulcers**
 - The ulcers typically have a sharply defined, ragged, undermined border, which readily bleeds on contact.
 - ⇒ unilateral, **painful inguinal lymph node** enlargement.
- Diagnosis
 - ⇒ definitive diagnosis based on isolation of *H ducreyi* on special media
 - ⇒ polymerase chain reaction (PCR) = rapid detection of *H ducreyi*
 - ⇒ test for the other common STDs (syphilis, HSV, gonorrhea, chlamydia) and HIV.
- Treatment:
 - ⇒ Antibiotic treatment: single dose oral azithromycin or IM ceftriaxone
 - ⇒ Examine and treat sexual partner(s).

Lymphogranuloma venereum (LGV)

- Causes:
 - ⇒ (L1, L2 or L3 serovars of) ***Chlamydia trachomatis***.
- Spread:
 - ⇒ The bacterium gains entry through breaches in the epithelial/mucous membranes, travelling through the lymphatics via macrophages to local nodes.
- Stages: three stages:
 - ⇒ **stage 1:** small painless pustule which later forms an ulcer at the site of inoculation 3-12 days later.
 - ⇒ **stage 2:** painful inguinal lymphadenopathy (Presents 1-6 months later).
 - Enlarged lymph nodes are known as buboes, they are often painful and can lead to thinning of the overlying skin causing abscesses.

- Groove sign is separation inguinal nodes by the inguinal ligament and is characteristic of the disease.
- ⇒ **stage 3:** proctocolitis (if rectally, then tenesmus, proctocolitis, strictures and fistulas can ensue. Cervicitis and urethritis are also common features.)
- **Diagnosis:**
 - ⇒ enzyme linked immunoassays or polymerase chain reaction of infected sample areas/pus.
 - Acute and convalescent sera can be used, but requires two samples 2 weeks apart.
 - ⇒ Inclusion bodies in the cytoplasm of scraped tissue cells are identified by iodine staining.
- **Treatment:**
 - ⇒ Antibiotics either doxycycline or macrolides (azithromycin or erythromycin)
 - **the most appropriate intervention → Doxycycline for 21 days**
 - In patients where this is unsuitable, azithromycin is also thought to be effective.
 - ⇒ surgical drainage/aspiration of the buboes or abscesses.
- **Complications:**
 - ⇒ genital elephantiasis,
 - ⇒ hepatitis,
 - ⇒ infertility,
 - ⇒ pelvic inflammatory disease,
 - ⇒ arthritis
 - ⇒ fitz hugh curtis syndrome (Perihepatic adhesions).

Syphilis

Aetiology

- Syphilis is a sexually transmitted infection caused by the spirochaete ***Treponema pallidum***.
- **Risk and chance of infection after sexual contact:**
 - ⇒ Approximately one-third of sexual contacts of infectious syphilis will develop the disease.
- **The incubation period** is between 9-90 days

Stages

- **Primary syphilis**
 - ⇒ occurs 14 days to three months post exposure
 - ⇒ **chancres - painless ulcer at the site of sexual contact**
 - ⇒ local non-tender lymphadenopathy
 - ⇒ often not seen in women (the lesion may be on the cervix)



primary chancre associated with syphilis

- **Secondary syphilis**

- ⇒ occurs one to six months following the primary infection.
- ⇒ caused by dissemination of the bacteria from the chancre, leading to systemic symptoms
- ⇒ systemic symptoms: fevers, malaise, lymphadenopathy
- ⇒ rash on trunk, palms and soles
- ⇒ buccal 'snail track' ulcers (30%)
- ⇒ condylomata lata
- ⇒ Iritis
- ⇒ Hepatitis
- ⇒ Early neurosyphilis:
 - **Meningovascular syphilis**
 - ❖ is a form of early neurosyphilis involving the small and medium sized intracranial vessels,
 - ❖ most commonly presents as a stroke involving the middle cerebral artery.



Classical palm lesions of secondary syphilis



More generalised rash of secondary syphilis

- **Tertiary syphilis**

- ⇒ occurs in one-third of untreated patients around 15–30 years after initial infection.
- ⇒ It is divided into:
 - Gummatous syphilis (granulomatous lesions of the skin and bones) most common (15% of patients)
 - Cardiovascular syphilis, ascending aortic aneurysms
 - **Late neurosyphilis.**
 - ☞ **general paralysis of the insane**
 - ⇒ Gradual onset confusion
 - ⇒ Hallucinations
 - ⇒ Tremors
 - ⇒ Fits
 - ⇒ Cognitive impairment
 - ⇒ Hyperreflexia,
 - ⇒ Argyll-Robertson pupils
 - ☞ **tabes dorsalis**

Features of congenital syphilis

- blunted upper incisor teeth (Hutchinson's teeth), 'mulberry' molars
- rhagades (linear scars at the angle of the mouth)
- keratitis
- saber shins
- **saddle nose**
- deafness

Investigation

- The diagnosis usually based on clinical features, serology and microscopic examination of infected tissue
- Both VDRL and TPHA are often positive in gummatous syphilis. However, **in cardiovascular and neurosyphilis, TPHA is positive and VDRL is often negative.**
- **Serological tests** can be divided into
 - ⇒ **cardiolipin tests** (not treponeme specific)

- syphilis infection leads to the production of non-specific antibodies that react to cardiolipin
- examples include VDRL (Venereal Disease Research Laboratory) & RPR (rapid plasma reagent)
- insensitive in late syphilis
- not specific
- becomes negative after treatment
- **Causes of false positive cardiolipin tests**
 - ❖ pregnancy
 - ❖ SLE, anti-phospholipid syndrome
 - ❖ TB
 - ❖ leprosy
 - ❖ malaria
 - ❖ HIV

⇒ **Treponemal specific antibody tests**

- example: TPHA (*Treponema pallidum* Haem Agglutination test)
- more specific
- **remains positive after treatment**

Management

- **Benzylpenicillin**
 - ❖ First line treatment
 - ❖ benzathine penicillin 2.4 million units given intramuscularly. This is administered either as a single dose or two doses given one week apart.
- Alternatives: doxycycline or erythromycin
 - ❖ may be given in patients with allergies to penicillins.
 - ❖ **In case of severe penicillin allergy, a single dose of (2 g) azithromycin is the preferred option because it is effective and doesn't raise compliance issues.**
- **Jarisch-Herxheimer reaction**
 - ❖ **This is an acute febrile illness with headache, myalgia, chills and rigors starting within 12 hours of the first dose of treatment and resolving within 24 hours**
 - ❖ It is thought to be due to the release of endotoxins following bacterial death
 - ❖ It is usually not important in early syphilis unless there is neurological or ophthalmic involvement or in pregnancy when it may cause fetal distress and premature labour.
 - ❖ It occurs in ~50% of patients with primary syphilis, **90% with secondary syphilis** and 25% with early latent syphilis.
 - ❖ also occurs in **Lyme disease** and **Q fever**.
 - ❖ Patients should be counselled about the reaction prior to receiving therapy for syphilis.
 - ❖ **the appropriate management → reassurance** and paracetamol for symptom control

UK national guidelines on the management of syphilis 2015

- **General advice**
 - ⇒ Infected patient should be advised to abstain from sex until any lesions (if any) have resolved or until two weeks after treatment completion
- **First-line:**
 - ⇒ Benzathine penicillin dose: 2.4 Mega units IM weekly for up to 3 weeks
 - ⇒ alternative : Procaine dose: 1.8–2.4 mega units IM daily for 14 days.
 - * Only if benzathine penicillin is not available (due to the pain and multiple injections associated)
 - second-line → oral azithromycin single dose.
- **Treatment during pregnancy:**
 - ⇒ first and second trimesters → give single dose benzathine penicillin;

- ⇒ third trimester → two doses of benzathine penicillin one week apart.
- **Neurosyphilis:**
 - ⇒ Procaine penicillin 1.8-2.4 units once daily (IM, for 14 days) with oral probenecid 500 mg four times a day.
 - ⇒ Tests for monitoring the effect of treatment → RPR/VDRL test
 - ⇒ Treponemal enzyme immunoassay (EIA)/chemiluminescent assay (CLIA), preferably detecting both IgM and IgG is the screening test of choice.

Genital warts

Genital warts - 90% are caused by HPV 6 & 11

Genital wart treatment

- multiple, non-keratinised warts: topical podophyllum
- solitary, keratinised warts: cryotherapy

Overview

- Genital warts (also known as condylomata accuminata) are a common cause of attendance at genitourinary clinics.
- They are caused by the many varieties of the human papilloma virus HPV, especially types 6 & 11.
- It is now well established that HPV (primarily types 16, 18 & 33) predisposes to cervical cancer.
- **HPV 16 is an oncogenic virus** and causes squamous cell carcinomas in the oral cavity, cervix, anus and penis.

Features

- small (2 - 5 mm) fleshy protuberances which are slightly pigmented
- may bleed or itch

Management

- **first-line** → topical podophyllum or cryotherapy, depending on the location and type of lesion.
 - ⇒ Multiple, non-keratinised warts → best treated with topical agents
 - ⇒ solitary, keratinised warts → respond better to cryotherapy
- **second line** → **topical imiquimod**
- genital warts are often resistant to treatment and recurrence is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years

Chlamydia genitourinary infections

Pathogenesis: *Chlamydia trachomatis*, is an obligate intracellular pathogen.

Incubation period: 7-21 days

Epidemiology

- *Chlamydia* is the most prevalent sexually transmitted infection in the UK. Approximately 1 in 10 young women in the UK have *Chlamydia*.

Features

- Asymptomatic in the majority of the patient

- Women: cervicitis (Muco-purulent discharge, postcoital bleeding), dysuria, dyspareunia → pelvic inflammatory disease, increased incidence of ectopic pregnancies, infertility and perihepatitis (Fitz-Hugh-Curtis syndrome)
- Men: urethral discharge, dysuria

Diagnosis

- Nuclear acid amplification tests (NAATs) is the investigation of choice

Management (2018 UK national guideline for the management of infection with Chlamydia trachomatis, published by: British Association for Sexual Health and HIV).

- 1st line: Doxycycline 100mg bd for 7 days is now recommended as first line treatment for uncomplicated urogenital, pharyngeal and rectal chlamydia infections.
- 2nd line: Azithromycin (1 g as a single dose), for those who cannot take doxycycline. It is also the preferred option for pregnant individuals.
- Patients are advised to avoid sexual contact for 7 from starting medication
- partner notification
 - ⇒ all individuals who had sexual contact with the patient within the 60 days prior to infection or the most recent sex partner if the last contact was more than 60 days prior.
 - ⇒ Contacts of confirmed *Chlamydia* cases should be offered treatment prior to the results of their investigations being known (treat then test)

Chlamydia – Doxycycline is the first line of treatment.

September 2008 exam: A swab taken in the clinic showed a Gram-negative diplococcus and treatment with IM ceftriaxone was given. his symptoms have not resolved. What is the most likely explanation?

- Co-existent *Chlamydia* infection (Co-existent infection with *Chlamydia* is extremely common in patients with gonorrhoea).

Gonorrhoea

Epidemiology

- Gonorrhoea is the second most common bacterial STI in the UK after chlamydia.

Pathogen

- *Neisseria gonorrhoeae* (*N. gonorrhoeae*, gonococcus)
- Gram-negative, intracellular, aerobic, diplococci

Transmission

- Sexual (oral, genital, or anal)
- Perinatal

Incubation period: 2-5 days

Risk factors: multiple sexual partners in recent months, known partner with gonorrhoea, drug use, prior STI, and men who have sex with men.

Features

- Primary infection is symptomatic in 90-95% of men, but only 50% of women.
- **Urogenital features**
 - ⇒ males: urethral discharge, dysuria
 - ⇒ females: cervicitis e.g. leading to vaginal discharge
 - ⇒ rectal and pharyngeal infection is usually asymptomatic
- **Gonorrhoeae can cause invasive infections such as pelvic inflammatory disease and Fitz-Hugh-Curtis syndrome in women and epididymitis and prostatitis in men.**
 - ⇒ Fitz-Hugh-Curtis syndrome or perihepatitis. This inflammation of the Glisson capsule surrounding the liver can cause sharp pleuritic right upper quadrant pain with nausea, vomiting, and fever.
- **Disseminated gonococcal infection (DGI)** (haematogenous spread from mucosal infection)
 - ⇒ **Arthritis-dermatitis syndrome:** a triad of:
 - 1) **Polyarthralgias:** migratory, asymmetric arthritis that may become purulent
 - 2) **Tenosynovitis:** simultaneous inflammation of several tendons
 - 3) **Dermatitis:** vesicular, pustular, or maculopapular lesions
 - ⇒ **Purulent gonococcal arthritis (without skin lesions)**
 - Abrupt inflammation in up to 4 joints (commonly knees, ankles, and wrists)
 - ⇒ Not to be confused with reactive arthritis

Diagnosis

- Test of choice: nucleic acid amplification testing (NAAT)
- **Culture:** All individuals with gonorrhoea diagnosed by NAAT should have cultures taken for susceptibility testing prior to treatment.

Complications

- **Increased risk of acquiring HIV infection.** Individuals diagnosed with gonorrhoea should be tested for all sexually transmitted infections including HIV
- **local complications:** urethral strictures, epididymitis and salpingitis (hence may lead to infertility). Gonococcal infection being the **most common cause of septic arthritis in young adults.**
- **Disseminated gonococcal infection (DGI),** septic arthritis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome).

Management (British Society for Sexual Health and HIV (BASHH) guidelines- 2018)

- **First line empirical treatment is now monotherapy with ceftriaxone 1 g intramuscularly**
 - ⇒ Use Ciprofloxacin 500 mg orally as a single dose as a first line when infection is known to be susceptible
 - ⇒ in penicillin-allergic patients ceftriaxone and cefixime are suitable treatment options, unless there is a history of severe hypersensitivity (e.g. anaphylactic reaction) to any beta-lactam antibacterial agent (penicillins, cephalosporins, monobactams and carbapenems)
 - **Cefixime** 400 mg orally as a single dose **plus azithromycin** 2 g orally.
- A test of cure (TOC) is recommended in all cases.
 - ⇒ if symptomatic → Culture, performed at least 72 hours after completion of therapy
 - ⇒ if asymptomatic → NAAT, performed 14 days after completion of therapy followed by culture if NAAT-positive.

- Sexual partners must be treated simultaneously to avoid reinfections.
 - ⇒ Who partners should be notified?
 - Male patients with **symptomatic urethral infection**: All partners within the preceding two weeks, or the last partner if longer than two weeks ago.
 - Patients with **infection at other sites or asymptomatic infection**: All partners within the preceding three months
 - ⇒ Who should be treated?
 - For those presenting after 14 days of exposure → treat only following a positive test for gonorrhoea
 - For those presenting within 14 days of exposure:
 - ❖ epidemiological treatment based on a clinical risk assessment
 - ❖ In asymptomatic individuals, it may be appropriate to not give epidemiological treatment, and to repeat testing 2 weeks after exposure.
- **DGI** → **IV ceftriaxone 1 g OD for 7 days.** (May be switched to oral 2 days → Cefixime 400 mg or Ciprofloxacin 500 mg twice daily)

Cephalosporins are now the treatment of choice for Gonorrhoea

Acute monoarthritis, a pustular rash and synovial fluid analysis suggestive of joint sepsis in a young woman make gonococcal arthritis the most likely diagnosis.

More commonly patients present with co-infection with *Chlamydia trachomatis*.

May 2014 exam: H/O a purulent urethral discharge. A sample of the discharge is shown to be a Gram-negative diplococcus. What is the most appropriate antimicrobial therapy?

→ **Intramuscular ceftriaxone stat dose + oral azithromycin stat dose**

January 2016 exam: What is the most likely complication from repeated *Neisseria gonorrhoea* infection?

→ **Infertility**

▪ (Infertility secondary to pelvic inflammatory disease (PID) is the most common complication of gonorrhoea)

Toxoplasmosis

Congenital toxoplasmosis

- cerebral calcification
- chorioretinitis

Overview

- Toxoplasma gondii is an obligate intracellular protozoa which infects the body via the GI tract, lung or broken skin.
- It's oocysts release trophozoites which migrate widely around the body including to the eye, brain and muscle.

Transmission (fecal-oral route)

- Toxoplasmosis can be contracted through:
 1. cysts in meat, (**from undercooked meat**)
 - The usual animal reservoir is the cat, although other animals such as rats carry the disease.
 - Kittens are the primary host (mature cats are less likely to secrete toxoplasma)
 - sheep and cattle eat food contaminated with soil contaminated by kitten faeces; and humans ingest the organisms in poorly cooked meat.
 - Oocysts excreted with cat faeces can remain in soil for months.
 2. oocysts in cat feces,
 - ingestion of fresh food contaminated by toxoplasma excreted in cats' faeces.
 3. transplacental → **Congenital toxoplasmosis**.

Epidemiology

- 30% risk of **reactivation** in immunocompromised (especially CD4+ count < 100 cells/ μ L)
 - ⇒ in those not receiving prophylaxis or antiretroviral therapy
- ~ 30% of the worldwide population is infected

Risk factors

- HIV patients when the CD4+ count is less than 100 cells/microL
 - ⇒ Toxoplasmosis is the most common central nervous system protozoal infection that presents with brain abscesses in patients with HIV.

Pathophysiology

- HIV is associated with **reactivation** of the disease.

Feature

- Most infections are asymptomatic.
- often **features resembling infectious mononucleosis** (fever, malaise, lymphadenopathy).
 - ⇒ Highly characteristic of toxoplasmosis is **asymmetrical lymphadenopathy** limited to an isolated lymph node group.
- Other less common manifestations include meningio-encephalitis and myocarditis.
- **Can present with fits in patients with AIDS**
 - ⇒ **Most common infection of the central nervous system in patients with AIDS**
 - **ring-enhancing lesion on head imaging**
 - ❖ **MRI is more sensitive and preferred**
 - CD4+ count < 100 cells/ μ L
- Eye manifestations include:

- ⇒ Focal choroido-retinitis
- ⇒ Granulomatous uveitis
- ⇒ Optic atrophy
- ⇒ Retinal detachment
- ⇒ Cataract
- ⇒ Posterior uveitis
- ⇒ Glaucoma.

- **Congenital toxoplasmosis** presents with a classic triad of:
 1. **chorioretinitis**,
 2. hydrocephalus and
 3. **intracranial calcifications**.

Investigation

- antibody test: **Serology testing** for anti-toxoplasma IgM and IgG antibodies via **ELISA**
 - ⇒ The serologic diagnosis of toxoplasmosis in immunocompromised patients is based on the presence of **IgG** antibodies.
- Sabin-Feldman dye test
- Congenital toxoplasmosis is associated with elevated platelet count.
- HIV patients usually presents with multiple ring-enhancing lesions on brain MRI.

Treatment

- Symptomatic patients usually have a self-limiting infection,
- Treatment usually reserved for those with severe infections or patients who are immunosuppressed
 - ⇒ **pyrimethamine plus sulphadiazine for at least 6 weeks**
 - Folinic acid, (also known as leucovorin), should be added to prevent pyrimethamine- associated hematologic toxicity

Prevention

- Trimethoprim-sulfamethoxazole is the therapy of choice for prophylaxis against toxoplasmosis reactivation.
- pregnant women
 - ⇒ Since the protozoal infection is commonly contracted through the handling of cat feces, pregnant women should be advised to avoid contact with cat litter to reduce their fetus's risk for congenital infection.
- for infected **pregnant** to prevent maternal-fetal transmission → **spiramycin**,
 - ⇒ Risk of fetopathy is reduced by more than 50% if spiramycin, which can prevent maternal-fetal transmission, is given to mothers

Pyrimethamine

- MOA → Dihydrofolate Reductase (DHFR) Inhibitor (competitive inhibitor)
 - ⇒ DHFR is a key enzyme for production of tetrahydrofolate, a cofactor that is required for the synthesis of DNA and proteins.
- Indications: used as an antimalarial or with a sulfonamide to treat toxoplasmosis.

Sulfadiazine

- Bacteriostatic, inhibits bacterial folic acid synthesis by competing with para amino benzoic acid.

Spiramycin

- Macrolide antibiotics inhibit bacterial growth by targeting the 50S ribosomal subunit
- Resistance to spiramycin is commonly attributed to mutations in 50S rRNA

January 2018 exam: HIV positive man is admitted with right-sided hemiplegia. CT scan shows multiple ring enhancing lesions. A diagnosis of cerebral toxoplasmosis is suspected. What is the most suitable management?

→ Pyrimethamine and sulphadiazine

At which CD4 count should prophylaxis against toxoplasmosis begin?

→ <100 cells/ μ L (with trimethoprim-sulfamethoxazole).

⇒ although prophylaxis for toxoplasmosis is not required until the CD4 count is <100 cells/microL, the patient will be covered at a CD4 count <200 cells/microL when prophylaxis against *P. jiroveci* is instituted.

What is risk of transmission of HIV to a health care worker after percutaneous exposure?

⇒ 0.3% with no prophylaxis.

* the risk is reduced by ~80% when post exposure prophylaxis is administered.

HIV- white lesion in oral mucosa

- **Oral hairy leukoplakia** are white oral lesions **caused by the Epstein-Barr virus**.
- a condition seen in HIV-infected patients with a CD4 count between 200 and 500/mm³.
- Unlike oral candidiasis (thrush), these lesions **cannot be scraped off** the tongue and buccal mucosa.

H1N1 influenza pandemic

Overview

- The H1N1 virus is a subtype of the influenza A virus
- **the most common cause of flu in humans.**
- Only influenza type A viruses are known to have caused **pandemics**.
- Influenza A and B viruses circulate and cause outbreaks and **epidemics**.
- The 2009 pandemic was caused by a new strain of the H1N1 virus.
- incubation period is about 2 days.
- In temperate climates, seasonal epidemics occur mainly during winter, while in tropical regions, influenza may occur throughout the year, causing outbreaks more irregularly.

The following groups are particularly at risk:

- patients with chronic illnesses and those on immunosuppressants
- pregnant women
- young children under 5 years old

Features: The majority of symptoms are typical of those seen in a flu-like illness:

- | | |
|---------------------------|--------------------------|
| • fever greater than 38°C | • rhinitis |
| • myalgia | • sore throat |
| • lethargy | • cough |
| • headache | • diarrhoea and vomiting |

A minority of patients may go on to develop an acute respiratory distress syndrome which may require ventilatory support.

Treatment

There is evidence to support the use of oseltamivir as a prophylactic agent against influenza

- There are two main treatments currently available:

Oseltamivir (Tamiflu)

- **action**
 - ⇒ **neuraminidase inhibitor** which prevents new viral particles from being released by infected cells. thus, slowing viral replication down rather than directly killing the virus particle.
 - This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus.
- **Administration**
 - ⇒ **oral medication**
- **Indications**
 - ⇒ **For critically ill patients with confirmed or suspected H1N1,**
 - **oseltamivir 150 mg bd for ten days is the recommended treatment.**
 - ⇒ **1st line for influenza B**
 - ⇒ **prophylaxis against influenza.**
 - NICE guidance recommends prophylaxis with oseltamivir **within 48 hours of close contact** with a patient infected with influenza for high risk patients.
 - ❖ Zanamivir can be used **within 36 hours of contact** with an infected individual.
 - ❖ zanamivir is associated with idiopathic bronchial hypersensitivity, as such it is largely considered a second line agent for treatment of influenza.
 - **may be used in the prophylactic treatment of healthcare workers during flu epidemics.**
 - However, viral replication is rapid and to be effective the drug must be given as early as possible after the development of symptoms of flu and **preferably within 48 hours.**
- **side-effects**
 - ⇒ common side-effects include nausea, vomiting, diarrhoea and headaches.
 - Gastrointestinal symptoms are the most common side-effects of oseltamivir (Tamiflu).**

Zanamivir (Relenza)

- **action**
 - ⇒ also, a neuraminidase inhibitor
- **administration**
 - ⇒ **inhaled** medication
 - ⇒ intravenous preparations are available for patients who are acutely unwell
 - The only parenteral alternative is zanamivir (**300 mg IV for 10 days**).
 - can be safely given using peripheral venous access.
 - For **hospitalized influenza patients** with suspected or known gastric stasis, **gastric malabsorption**, gastrointestinal bleeding, or for patients suspected or confirmed with oseltamivir-resistant influenza virus infection, intravenous zanamivir should be considered.
- **Indications**
 - ⇒ Zanamivir is a second line therapy for Influenza B, but first line for Influenza A.
- **Side effects**
 - ⇒ may induce bronchospasm in asthmatics

Intensive Care Management of Pandemic (H1N1) Influenza

- Ideally patients should be nursed in a negative pressure room.
- **NIV**
 - ⇒ Whilst there is no evidence that NIV prevents invasive ventilation in H1N1 patients, it is commonly used as bridging therapy.

- ⇒ It is important to remember that these are open circuits and **still require personal protection for staff.**
- ⇒ **NIV should be started after the mask is secured to the face**
 - Ensuring that a well-fitting mask is in place before airflow starts can reduce the amount of aerosol production.
- ⇒ Experience with helmet devices is limited but increasing, and it has been successful in patients who are unable to tolerate the nasal or orofacial devices. The advantage is that it may provide a tighter seal than nasal or orofacial devices.
- avoiding water humidification and use of a closed hood is also advised.

Influenza treatment

- Oseltamivir (tamiflu) is the first line treatment recommended for patients with suspected or confirmed Influenza A.
- Zanamivir is useful in patients with poor swallow or in those with suspected or confirmed exposure to oseltamivir-resistant influenza.

Infectious mononucleosis & (Epstein-Barr virus)

Atypical lymphocytes - ?glandular fever

Aetiology

- Infectious mononucleosis (glandular fever) is caused by the **Epstein-Barr virus** (also known as human herpesvirus 4, HHV-4).
- The incubation period of EBV infectious mononucleosis is 1-2 months.

Epidemiology

- most common in adolescents and young adults.

Pathophysiology

- The **CD8+ T-cell response** caused by infectious mononucleosis, leads to generalized lymphadenopathy, splenomegaly, and high WBC count with atypical lymphocytes.

Features

EBV infectious mononucleosis → triad of fever, pharyngitis, and lymphadenopathy.

- sore throat
- lymphadenopathy
 - ⇒ Bilateral posterior cervical adenopathy is most highly suggestive of EBV infectious mononucleosis.
- Pyrexia, malaise, anorexia, headache
- palatal petechiae
 - ⇒ Palatal petechiae of the posterior oropharynx distinguish infectious mononucleosis from other causes of viral pharyngitis but do not distinguish it from group A streptococcal pharyngitis, in which palatal petechiae may occur.
- Uvular edema is an uncommon, but, if present, it is a helpful sign in distinguishing EBV infectious mononucleosis from other causes of viral pharyngitis or from group A streptococcal pharyngitis.
- splenomegaly - occurs in around 50% of patients and may rarely predispose to splenic rupture
- hepatitis

- **haemolytic anaemia secondary to cold agglutins (IgM)**
- a maculopapular, pruritic rash develops in around 99% of patients **who take ampicillin/amoxicillin** whilst they have infectious mononucleosis
 - ⇒ Drug-induced rash is usually pruritic and is prolonged, in contrast to the viral rash of EBV infectious mononucleosis.
 - ⇒ Early infectious mononucleosis may present with a maculopapular generalized rash. It is nonpruritic and rapidly disappears.
- Because **leukocytosis** is the rule in infectious mononucleosis, the presence of a **normal or decreased WBC count should suggest an alternative diagnosis.**
- Lymphocytosis
 - ⇒ Relative lymphocytosis ($\geq 60\%$) plus atypical lymphocytosis ($\geq 10\%$) are the characteristic findings of EBV infectious mononucleosis.
- presence of 50% lymphocytes with at least 10% **atypical lymphocytes**
 - ⇒ **Atypical lymphocytes**
 - **most commonly** seen in patients who have **infectious mononucleosis.**
 - Other causes
 - ❖ drug reactions (phenytoin),
 - ❖ stress,
 - ❖ **viral** or bacterial **infections,**
 - ❖ allergies,
 - ❖ autoimmune diseases, thyroid problems
 - ❖ malignancy.
- ESR is most useful in differentiating group A streptococcal pharyngitis from EBV infectious mononucleosis.
 - ⇒ (ESR elevated with EBV infectious mononucleosis, not elevated in group A streptococcal pharyngitis).

atypical lymphocytosis point towards a viral illness

Diagnosis

- **heterophile antibody test (Monospot test)** (immunoglobulin IgM to EBV)
 - ⇒ **the initial screening test**
 - ⇒ sensitivity 85% and specificity 100%.
 - ⇒ Cytomegalovirus is a herpesvirus that causes **infectious mononucleosis with a negative monospot test.**
- EBV serological tests
 - ⇒ **Definitive diagnosis**
 - ⇒ should be obtained in patients with a mononucleosis-like illness and a negative finding on the Monospot test.

Management

- is supportive and includes:
- rest during the early stages, drink plenty of fluid, avoid alcohol
 - simple analgesia for any aches or pains
 - consensus guidance in the UK is to **avoid playing contact sports for 8 weeks after having glandular fever to reduce the risk of splenic rupture**
 - unfortunately on clinical appearances it is not possible to distinguish bacterial from viral or throat infections with any degree of reliability.

- If the child has EBV infection, then the administration of Amoxicillin will give an erythematous rash. Non-vomiting patients can be treated with oral penicillin-v.'
- Patients with EBV infectious mononucleosis who have positive throat cultures for group A streptococci should not be treated because this represents colonization rather than infection
- complicated EBV infectious mononucleosis :
 - ⇒ Short courses of corticosteroids are indicated for EBV infectious mononucleosis with:
 - hemolytic anemia,
 - thrombocytopenia,
 - CNS involvement, or
 - extreme tonsillar enlargement (impending airway obstruction).

EBV: associated malignancies:

- Burkitt's lymphoma
- Hodgkin's lymphoma
- nasopharyngeal carcinoma

In which structure is the immune response most likely localized? → Paracortex

- immune response to the virus takes place through T-cell mediated immune responses, which take place in the **lymphocyte-rich areas of the lymph node, namely the paracortex.**
- A biopsy of the lymph node of this patient would show reactive hyperplasia due to increased activity of the paracortex.

Parvovirus B19

Pathogen: Parvovirus B19 is a single-strand DNA virus.

Transmission: particularly via airborne infection

Pathology

- Primarily infects progenitor cells of erythrocytes in bone marrow and endothelial cells
- Attaches to P antigen on RBCs and endothelial cells → cell destruction

Diseases

- **erythema infectiosum**
 - ⇒ The most widely known clinical manifestation of parvovirus B19 is erythema infectiosum ('slapped cheek syndrome'), a mild viral illness of childhood characterised by a classic exanthema in which both cheeks appear bright red as though they had been slapped.
- **Aplastic crisis** in patients with hemolytic anemias (e.g. sickle cell disease, thalassemias)
- **Parvovirus B19-associated arthritis**
 - ⇒ most commonly in adults, particularly in women
 - ⇒ affect the small joints of the hands and feet. Knees or elbows are rarely involved.
 - ⇒ may mimic rheumatoid arthritis. Unlike rheumatoid arthritis, the post-infectious arthritis associated with parvovirus B19 does not cause permanent damage to bones or joints.

- **Pure red blood cell aplasia**
- The virus has a tropism for rapidly dividing erythrocyte precursors which they infect and destroy. Thus, no reticulocytes (immature erythrocytes) are available to replace aging or damaged erythrocytes as they are cleared by the reticuloendothelial system. This may not have any significant impact on otherwise healthy individuals, but can trigger an aplastic crisis - particularly in patients with haemoglobinopathies.

Leishmaniasis

Mucocutaneous ulceration following travel? - *Leishmania brasiliensis*

- Leishmaniasis is caused by the intracellular protozoa *Leishmania*, (intra-macrophage protozoa)
- transmitted to humans by phlebotomine sand flies.
- There are four main clinical syndromes: cutaneous, muco-cutaneous, visceral (also known as kala-azar) and post kala-azar dermal leishmaniasis.

Cutaneous leishmaniasis

- caused by *Leishmania tropica* or *Leishmania mexicana*
- crusted lesion at site of bite
- present with ulcers or nodules.
- usually heal spontaneously, but slowly, in immunocompetent individuals with resultant disfiguring scars.

Mucocutaneous leishmaniasis

- caused by *Leishmania braziliensis*
- skin lesions may spread to involve mucosae of nose, pharynx etc
- characterised by progressively destructive ulcerations of the mucosa extending from the nose and mouth to the pharynx and larynx,
- are not self-healing.

Visceral leishmaniasis (kala-azar)

- mostly caused by *Leishmania donovani*
- caused by the *Leishmania donovani* complex
 - (*L. donovani* sensu stricto in East Africa and India,
 - *L. infantum* in Europe, North Africa and Latin America).
- incubation period of 2-6 months
- patients present with persistent systemic infection (fever, sweating, rigor, malaise, loss of appetite and weight loss) (*occasionally patients may report increased appetite with paradoxical weight loss)
- parasitic infection of the blood and reticulo-endothelial system → lymphadenopathy, massive splenomegaly and hepatomegaly
- grey skin - 'kala-azar' means black sickness
- **investigations**
 - pancytopenia secondary to hypersplenism
 - There is also often marked polyclonal hypergammaglobulinaemia.
 - **Visualisation of the parasite (amastigote form) from lymph nodes, bone marrow or spleen is used as a confirmatory test.**
 - PCR can be used to detect the parasite in the blood.

- Anti-leishmanial antibodies can be detected, but they remain positive up to several years after cure and therefore cannot be used to detect relapse.
- **Treatment**
 - First line antimonials are sodium stibogluconate and meglumine antimoniate. Adverse effects include cardiac arrhythmias and acute pancreatitis.
 - Amphotericin B is increasingly being used.

Post kala-azar dermal leishmaniasis

- a complication of visceral leishmaniasis
- characterised by a macular, maculo-papular or nodular rash
- frequently observed after treatment. It can also occur in immunosuppressed individuals.
- highly infectious.

Leptospirosis (Also known as **Weil's disease*)**

Leptospirosis - give penicillin or doxycycline

- *the term Weil's disease is sometimes reserved for the most severe form
 - If the infection causes jaundice, kidney failure and bleeding, it is then known as **Weil's disease**.
 - If it affects the lung and causes pulmonary haemorrhage, then it is known as **severe pulmonary haemorrhage syndrome**.
- leptospirosis is commonly seen in questions referring to sewage workers, **farmers**, vets or people who work in abattoir.
- It is caused by the spirochaete *Leptospira interrogans* (serogroup L icterohaemorrhagiae),
- classically being spread by contact with infected rat urine.
- Weil's disease should always be considered in high-risk patients with **hepato-renal failure**

Features

- fever
- flu-like symptoms
- **renal failure (seen in 50% of patients)**
- **jaundice**
- headache, may herald the onset of meningitis
- subconjunctival haemorrhage
- Haemorrhagic tendencies with purpura or petechiae
- Enlargement of liver and spleen.
- Presentation with heart failure is uncommon but has been described in severe leptospirosis.

Management

- high-dose benzylpenicillin or doxycycline
- other options: cefotaxime or ceftriaxone.

Lyme disease

Aetiology

- Lyme disease is caused by the spirochaete ***Borrelia burgdorferi*** and is spread by ticks of the **genus Ixodes**
 - ⇒ ***Ixodes ricinus*** is predominantly responsible for its transmission in Europe.
 - ⇒ ***Ixodes pacificus*** and ***Ixodes scapularis*** are the ticks responsible for transmission in the USA.

Features

Bilateral facial weakness can occur with Lyme disease, myasthenia gravis, sarcoidosis and bilateral Bell's palsy.

Early features

- **erythema chronicum migrans** (small papule often at site of the tick bite which develops into a larger annular lesion with central clearing, 'bulls-eye'. Occurs in 70% of patients)
 - ⇒ **Erythema migrans is often the presenting sign of Lyme disease**
- systemic symptoms: malaise, fever, arthralgia

Later features

- CVS: heart block, myocarditis
- neurological: (**Neuroborreliosis**): cranial nerve palsies, meningitis
- polyarthritis

Investigation

- serology: antibodies to *Borrelia burgdorferi* (**ELISA test for antibodies to Borrelia burgdorferi**)
 - Serological tests are the most appropriate first line investigation for diagnosing Lyme disease.
 - ELISA tests are preferred to Western blots as they are more sensitive.

Management

- Early disease:
 - doxycycline is the drug of choice for 2 – 3 weeks
 - Amoxicillin is an alternative if doxycycline is contraindicated (e.g. pregnancy)
- Disseminated disease:
 - **ceftriaxone if disseminated disease**
- Jarisch-Herxheimer reaction is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease)

MRCPUK-part-1-September 2013 exam: H/O returning from a camping holiday in the New Forest. C/O lethargy, arthralgia, rash consistent with erythema chronicum migrans. What is the most appropriate test to perform given the likely diagnosis?

→ **ELISA test for antibodies to *Borrelia burgdorferi***

Lymphadenopathy

There are many causes of generalised lymphadenopathy

Infective

- infectious mononucleosis
- HIV, including seroconversion illness
- eczema with secondary infection
- rubella
- toxoplasmosis
- CMV
- tuberculosis
- roseola infantum

Neoplastic

- leukaemia
- lymphoma

Others

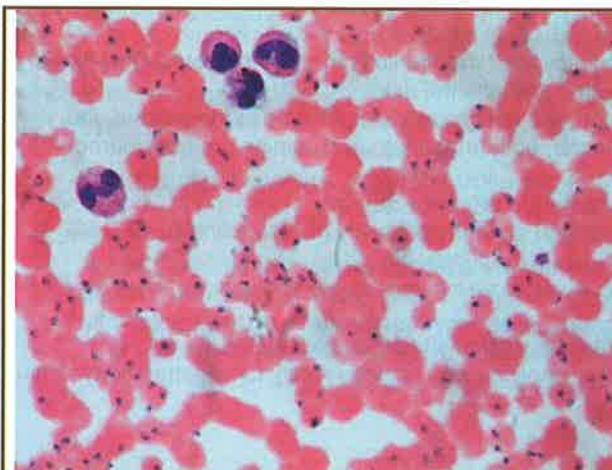
- autoimmune conditions: SLE, rheumatoid arthritis
- graft versus host disease
- sarcoidosis
- **drugs: phenytoin and to a lesser extent allopurinol, isoniazid**

Malaria

Malaria: Falciparum

Severe falciparum malaria - intravenous artesunate

- *P. falciparum* typically presents **within the first three months** of return from an endemic area.



In the slide shown, the blood film shows ring forms within erythrocytes; some erythrocytes contain two to three parasites per cell - **typical of falciparum**; other forms of malaria seldom have more than one parasite per red cell.

Feature of severe malaria

- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 C
- severe anaemia
- complications as below
- **Complications**
 - cerebral malaria: seizures, coma
 - acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
 - acute respiratory distress syndrome (ARDS) → (**Respiratory rate 30 per minute**)
 - hypoglycaemia
 - disseminated intravascular coagulation (DIC)

Uncomplicated falciparum malaria

- strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

Severe falciparum malaria

- a parasite counts of more than **2%** will usually need parenteral treatment irrespective of clinical state
- **Hyperparasitemia**, where **more than 5%** of the red blood cells are infected by malaria parasites
 - In 2010, WHO defined hyperparasitemia as >2%/100 000/ μ L in low intensity transmission areas or >5% or 250 000/ μ L in areas of high stable malaria transmission intensity.
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
 - I.V quinine is reserved for severe or cerebral malaria (most deaths from *M. falciparum* occur in first 96 hours of starting treatment).
 - The initial dose should NOT be reduced in those severely ill with renal/hepatic impairment.
 - High doses of quinine in pregnancy are teratogenic in the first trimester. However in malaria, the benefit of treatment outweighs the risk.
 - **WHO Guidelines (2006)** recommend artemisinins are first line in the second and third trimester. In the first trimester, both artesunate and quinine are considered treatment options.
 - **Hypoglycaemia is an important side effect of quinine**
 - Quinine → ↑ insulin secretion and the sensitivity of cells to insulin → hypoglycaemia
 - Malaria itself can cause hypoglycaemia too, so blood glucose should be monitored every 2 h.
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse

Malaria: non-falciparum

Non-falciparum malarias are almost always chloroquine sensitive

- **P. vivax:**
 - The **most common cause of non-falciparum malaria is *Plasmodium vivax***, with *Plasmodium ovale* and *Plasmodium malariae* accounting for the other cases.
 - The **incubation period of P. vivax can go up to six months or more** with malaria being caused by hypnozoites.
 - *P. falciparum* incubation is normally around six days though it can go till 14 days or more.
 - **The Duffy antigen on RBCs acts as a receptor for P. vivax.** → facilitate the entry of *P. vivax* in to RBCs.
 - Duffy negative individuals are therefore resistant to this strain
 - West Africans lack the Duffy blood group and therefore *P. ovale* replaces *P. vivax* in this region.
- **P. ovale:**
 - it is quite rare
 - The incubation period is similar to that of *P. vivax* but on the thick film the parasites are more compact and smaller. On the thin film the red blood cells appear oval with ragged ends.
- **P. malariae:**
 - it is rare.
 - Its incubation could go up to 14 days like *P. falciparum*.
 - The thick film will show a few compact rings or small neat schizonts or small round gametocytes with yellow-brown pigment. The thin film will show red blood cells in band forms.
- *Plasmodium vivax* is often found in Central America and the Indian Subcontinent whilst *Plasmodium ovale* typically comes from Africa
- Both *P. vivax* and *P. ovale* have a liver hypnozoite stage which can cause repeated relapses.
 - May present **six months** after return from an endemic area

Features

- fever,
 - *Plasmodium vivax/ovale*: cyclical fever every 48 hours.
 - *Plasmodium malariae*: cyclical fever every 72 hours
- headache,
- splenomegaly

Investigations

- ***Plasmodium ovale*,**
 - **all stages of the parasite and not just trophozoites and gametocytes are visible in the peripheral blood.**
- In *P. falciparum* malaria, only trophozoite-ring forms and gametocytes are usually seen.

Treatment

- non-falciparum malarias are almost always chloroquine sensitive
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse.
 - all individuals should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency, as primaquine may cause haemolysis in those without the enzyme.

fast-acting	intermediate-acting	slow-acting
high-efficacy blood schizonticides that may be effective as monotherapy Artemesinin Mepacrine	Quinine Mefloquine	low-efficacy schizonticides that normally need to be administered in combination. Pyrimethamine Doxycycline is also a very slow-acting antimalarial.

Pyrimethamine

- used in the treatment of uncomplicated malaria, particularly for chloroquine-resistant *P. falciparum*.
- It acts on both the erythrocytic and hepatic phases of infection.
- It inhibits dihydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, and thereby halting the processes of DNA replication, cell division and reproduction.
- It is normally used alongside a sulfonamide.

Malaria: prophylaxis

- around 75% of malaria in patients returning from endemic countries are caused by the potentially fatal *Plasmodium falciparum* protozoa.
- The majority of patients who develop malaria did not take prophylaxis.
- It should also be remembered that UK citizens who originate from malaria endemic areas quickly lose their innate immunity.

Drug	Side-effects + notes	Time to begin before travel	Time to end after travel
Atovaquone + proguanil (Malarone)	GI upset	1 - 2 days	7 days
Chloroquine	Headache Contraindicated in epilepsy Taken weekly	1 week	4 weeks
Doxycycline	Photosensitivity Oesophagitis	1 - 2 days	4 weeks
Mefloquine (Lariam)	Dizziness Neuropsychiatric disturbance Contraindicated in epilepsy and mental illnesses Taken weekly	2 - 3 weeks	4 weeks
Proguanil (Paludrine)		1 week	4 weeks
Proguanil + chloroquine	See above	1 week	4 weeks

- Which drug?

- In certain parts of South-East Asia there is widespread chloroquine resistance. Chemoprophylaxis using atovaquone + proguanil (Malarone), mefloquine (Lariam) or doxycycline is therefore recommended.
- Doxycycline prophylaxis is the safest option with less resistance in many parts of the world compared to the other options available.
- Atovaquone and proguanil are used for prophylaxis especially where there are high levels of resistance against most of the other drugs.
- Proguanil should not be used alone as malaria could develop resistance to it.

- Pregnant women

- Pregnant women should be advised to avoid travelling to regions where malaria is endemic. Diagnosis can also be difficult as parasites may not be detectable in the blood film due to placental sequestration. However, if travel cannot be avoided:
 - chloroquine can be taken
 - proguanil: folate supplementation (5mg od) should be given
 - Malarone (atovaquone + proguanil): the BNF advises to avoid these drugs unless essential. If taken then folate supplementation should be given
 - mefloquine: caution advised
 - doxycycline is contraindicated

- Children

- It is again advisable to avoid travel to malaria endemic regions with children if avoidable. However, if travel is essential then children should take malarial prophylaxis as they are more at risk of serious complications.
 - diethyltoluamide (DEET) 20-50% can be used in children over 2 months of age
 - doxycycline is only licensed in the UK for children over the age of 12 years

MRCPUK-part-1-May 2013 exam: H/O vivax malaria treated initially with chloroquine then later given primaquine. What is the benefit of the primaquine?

→ Destroy liver hypnozoites and prevent relapse

MRCPUK-part-1-May 2014 exam: A 25-year-old man with a history of epilepsy presents for advice regarding malarial prophylaxis. Next month he plans to travel to Vietnam. What is the most appropriate medication to prevent him developing malaria?

→ Atovaquone + proguanil

Measles

Overview

- RNA paramyxovirus
- spread by droplets
- infective from prodrome until 4 days after rash starts
- incubation period = 10-14 days

Features

- prodrome: irritable, conjunctivitis, fever
 - Patients present with the three C's: cough, coryza, and conjunctivitis.
 - Rash usually develops on the head and torso, typically sparing the wrists and hands.
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa
 - Koplik's spots are small, irregular, bright red spots with blue-white centres, occurring on the inside of the cheek next to the premolars. Seen only in measles, they are diagnostic.

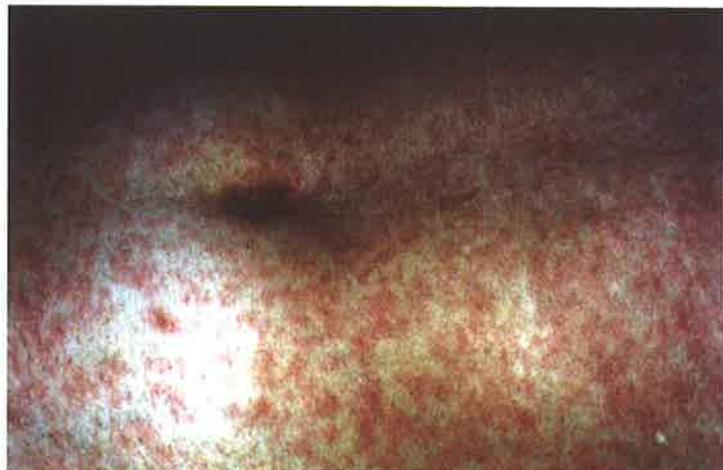
- The spots usually occur briefly after the fever begins and a couple of days before the generalised rash appears.
- Not infrequently, the spots disappear as the eruption develops.
- rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent



Koplik spots

Complications

- encephalitis: typically occurs 1-2 weeks following the onset of the illness)
- subacute sclerosing panencephalitis: very rare, may present 5-10 years following the illness
- febrile convulsions
- giant cell pneumonia
- keratoconjunctivitis, corneal ulceration
- diarrhoea
- increased incidence of appendicitis
- myocarditis



The rash typically starts behind the ears and then spreads to the whole body

Management of contacts

- if a child not immunized against measles comes into contact with measles then MMR should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection)
- this should be given within 72 hours

Rubella

- also known as german measles.
- RNA virus , part of the togavirus family
 - **rubella** has **positive single-stranded RNA**.
 - **rubeola virus (measles)** contains **negative** single-stranded RNA
- affects unimmunized children and presents with a rash that begins at the head and moves down with postauricular lymphadenopathy.
- **A positive rubella haemagglutination inhibition (HAI) combined with a negative rubella IgM** is consistent with:
 1. Early acute infection with rubella
 - The IgM may take several days to rise and **the test should be repeated one to two weeks later.**
 2. Previous vaccination, or
 3. Previous rubella infection.

Parotitis

Causes

- **Bacterial parotitis**
 - Commonly unilateral
 - more common in older patients.
 - The most common bacterial cause of parotitis is **Staphylococcus aureus**.
 - The risk is increased by agents that have an atropine-like action, including medications prescribed to reduce excess respiratory secretions.
 - A ductal stone, with consequent pooling of infected secretions, should be excluded, and ultrasound is an appropriate investigation to perform for this.
 - Antibiotics should be selected that cover typical mouth flora.
- **Viral parotitis**
 - Mumps parotitis is usually bilateral
 - Parotitis, orchitis, aseptic meningitis, and pancreatitis are symptoms of **mumps** virus infection.
- autoimmune disease, **Sjogren's syndrome**.
- **Bulimia nervosa**

Parotid swelling

- causes of bilateral parotid swelling include:
 - ⇒ Infection with viruses, including mumps, parainfluenza virus type 3, Coxsackie viruses and influenza A virus
 - ⇒ Metabolic diseases, such as:
 - diabetes mellitus
 - uraemia

- ⇒ Drugs, such as:
 - phenylbutazone
 - **thiouracil**
- Other conditions associated with **chronic parotid swelling** include:
 - ⇒ Alcoholic liver disease
 - ⇒ Sarcoidosis
 - ⇒ Sjögren syndrome
 - ⇒ Lymphoma
 - ⇒ Infection with HIV

Orf

Orf is generally a condition found in sheep and goats although it can be transmitted to humans. It is caused by the **parapox virus**.

In animals

- 'scabby' lesions around the mouth and nose

In humans

- generally affects the hands and arms
- initially small, raised, red-blue papules
- later may increase in size to 2-3 cm and become flat-topped and haemorrhagic

Pelvic inflammatory disease (PID)

Definition

- infection and inflammation of the female pelvic organs including the uterus, fallopian tubes, ovaries and the surrounding peritoneum.
- It is usually the result of ascending infection from the endocervix

Causative organisms

- *Chlamydia trachomatis* - the most common cause
- *Neisseria gonorrhoeae*
- *Mycoplasma genitalium*
- *Mycoplasma hominis*
 - ⇒ one of the most frequently isolated mycoplasma in the genital tract.
 - ⇒ It is an opportunistic pathogen which may cause pelvic inflammatory disease in immunocompromised patients.
 - ⇒ Clindamycin is used in the treatment

Features

- lower abdominal pain
- fever
- deep dyspareunia
- dysuria and menstrual irregularities may occur
- vaginal or cervical discharge
- cervical excitation

Investigation

- screen for Chlamydia and Gonorrhoea

Management

- due to the difficulty in making an accurate diagnosis, and the potential complications of untreated PID, consensus guidelines recommend having a low threshold for treatment
- Consensus guidelines recommend treatment once a diagnosis of pelvic inflammatory disease is suspected, rather than waiting for the results of swabs
- oral **ofloxacin + oral metronidazole** or intramuscular ceftriaxone + oral doxycycline + oral metronidazole
- RCOG guidelines suggest that in mild cases of PID intrauterine contraceptive devices may be left in. The more recent BASHH guidelines suggest that the evidence is limited but that '*Removal of the IUD should be considered and may be associated with better short term clinical outcomes'*

Complications

- infertility - the risk may be as high as 10-20% after a single episode
- chronic pelvic pain
- ectopic pregnancy
- **Fitz-Hugh-Curtis syndrome**
 - ⇒ is a rare complication of pelvic inflammatory disease, resulting in liver capsule inflammation.
 - ⇒ It is most often caused by untreated sexually transmitted infections including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.
 - ⇒ a patient may present with septic shock secondary to the untreated liver capsule infection.

Psittacosis (ornithosis)

- *Chlamydia psittaci* is endemic in birds including psittacine birds, canaries, finches, pigeons and poultry.
- Pet owners, vets and zoo keepers are most at risk. It is rare in children.
- **Person to person transmission occurs** especially in a hospital environment.
- Sputum Gram stain reveals a few leucocytes and no predominant bacteria.
- There are few signs and few laboratory/x ray findings.
- Positive serology is with complement-fixing antibodies.
- It is treated with tetracycline.

Pyogenic liver abscess

- The most common organisms found in pyogenic liver abscesses are *Staphylococcus aureus* in children and ***Escherichia coli* in adults**.

Management

- **amoxicillin + ciprofloxacin + metronidazole**
- if penicillin allergic: ciprofloxacin + clindamycin

January 2018 exam: What is the most appropriate antibiotic therapy to accompany drainage of liver abscess?

→ **Amoxicillin + ciprofloxacin + metronidazole**

Pyrexia of unknown origin

Indium labelled leukocyte study:

- **useful for detecting occult abscesses** in patients with pyrexia of unknown origin where conventional scans have failed to detect a source of infection.

Definition

- Defined as a prolonged fever of > 3 weeks which resists diagnosis after a week in hospital

Neoplasia

- lymphoma
- hypernephroma
- preleukaemia
- atrial myxoma

Infections

- abscess
- TB

Connective tissue disorders

Q fever

Q fever - *Coxiella burnetii*

Overview

- Q fever is a zoonotic disease caused by ***Coxiella burnetii*** an obligate gram-negative intracellular bacterium.
- The organism is very resistant to drying:
- does not grow on standard culture media.

Transmission

- **The organism is usually inhaled from infected dust** (animal products)
- acquired through contact with animals.
⇒ Cattle, sheep and goats are the primary reservoirs of *C. burnetii*.
- drinking unpasteurised milk from infected cows.

Risk factors

- It is not notifiable, but can occur in outbreaks in **farming communities** and in abattoirs. and therefore an occupational history is very important.

Features:

- high fevers, chills, sweats
- severe headache, (typically retrobulbar)
- general malaise, myalgia,
- confusion,
- sore throat, ,
- non-productive cough,
- nausea, vomiting, diarrhoea, abdominal pain
- chest pain.
- Between 30% and 50% of patients with a symptomatic infection will develop pneumonia.
- may be complicated by immune complex-mediated glomerulonephritis

- Chronic infection can manifest as hepatitis, osteomyelitis or endocarditis.
- In **Q fever endocarditis**:
 - ⇒ the aortic valve is involved in over 80% of cases.
 - ⇒ A murmur is not always present, but augmentation of an existing murmur may occur.
 - ⇒ **Low-grade fever (or no fever)**,
 - ⇒ signs of heart failure,
 - ⇒ hepatosplenomegaly,
 - ⇒ clubbing,
 - ⇒ arterial emboli,
 - ⇒ **leukocytoclastic vasculitic rash**.

Diagnosis:

- Confirmed by **serological testing** for *C. burnetii*.
 - ⇒ phase I antibody titre to *Coxiella burnetti* (IgG and/or IgA) greater than 1:200 is virtually diagnostic of Q fever.
- chest X-ray might show multilobar consolidation.
- Anaemia
- Thrombocytopenia
- Elevated ESR
- Hypergammaglobulinaemia
- liver function tests
 - ⇒ abnormal in the majority of patients and some will develop hepatitis.
- Microscopic haematuria may be present.

Treatment :

- Most patients will recover within a few months with no treatment.
- **Doxycycline** is the treatment of choice for acute Q fever. OR prolonged courses of tetracyclines.

Prognosis

- Only 1–2% of people with acute Q fever die of the disease.
- Chronic Q fever
 - Endocarditis with **negative culture findings and seropositivity** is the main clinical presentation of **chronic Q fever**,
 - usually occurring in patients with preexisting cardiac disease including valve defects, rheumatic heart disease, and prosthetic valves.

Rabies

Rabies - following possible exposure give immunoglobulin + vaccination

Overview

- Rabies is a viral disease that causes an acute encephalitis.
- The rabies virus is classed as a RNA rhabdovirus and has a bullet shaped capsid.
- It is commonly transmitted by bat, raccoon and skunk bites.
- Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Features

- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries.

Following an animal bite in at risk countries:

- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination
- Lyssaviruses such as rabies **cannot cross intact skin** and humans are regarded as an end-host (outside of transplantation-associated transmission). **Therefore, only standard infection-prevention precautions such as gloves and gowns are required.**

Scabies

Scabies should be suspected in any sexually active young person who presents with generalised pruritus without any specific signs.

Overview

- Scabies is **caused by** the mite *Sarcoptes scabiei* and is **spread by** prolonged skin contact.
- It typically affects children and young adults.

Pathophysiology

- The scabies mite burrows into the skin, laying its eggs in the stratum corneum.
- The intense pruritus associated with scabies is due to a delayed type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.

Features

- widespread pruritus
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
⇒ The tiny erythematous burrows in the web spaces of the fingers are almost **pathognomonic**
- in infants the face and scalp may also be affected
- secondary features are seen due to scratching: excoriation, infection

Investigation

- Skin scrapings** → demonstrate *Sarcoptes scabiei*

Management

- first-line is → permethrin 5%
- second-line is → malathion 0.5%
- Application should be repeated seven days after initial treatment to kill any mites hatched from eggs in that time
- give appropriate guidance on use (see below)
- pruritus persists for up to 4-6 weeks post eradication

Patient guidance on treatment (from Clinical Knowledge Summaries)

- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic

⇒ **Re-infection most likely means → Other household members were not treated**

- launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

Patients should be given the following instructions:

- The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation.
- apply the insecticide cream or liquid to cool, dry skin
- pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- allow to dry and **leave on the skin for 8-12 hours for permethrin, or for 24 hours for malathion**, before washing off
- reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- repeat treatment 7 days later

Crusted (Norwegian) scabies

- **Crusted scabies** is seen in patients with **suppressed immunity, especially HIV**.
- The crusted skin will be teeming with hundreds of thousands of organisms.
- **Ivermectin** is the treatment of choice and isolation is essential



Helminths

Nematodes (roundworms)

Worm	Notes	Treatment
<i>Strongyloides stercoralis</i>	Larvae are present in soil and gain access to the body by penetrating the skin Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered	Ivermectin and - bendazoles are used
<i>Enterobius vermicularis</i> (pinworm)	asymptomatic in 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms Diagnosis may be made by applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs	-bendazoles
<i>Ancylostoma duodenale</i> , <i>Ne cator americanus</i> (hookworms)	Larvae penetrate skin of feet; gastrointestinal infection → anaemia Thin-shelled ova	-bendazoles
<i>Loa loa</i>	Transmission by deer fly and mango fly Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae	Diethylcarbamazine
<i>Trichinella spiralis</i>	Typically develops after eating raw pork . Features include fever, periorbital oedema and myositis (larvae encyst in muscle)	-bendazoles
<i>Onchocerca volvulus</i>	Causes 'river blindness'. Spread by female blackflies Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria	Ivermectin rIVERblindness = IVERmectin
<i>Wuchereria bancrofti</i>	Transmission by female mosquito Causes blockage of lymphatics → elephantiasis	Diethylcarbamazine
<i>Toxocara canis</i> (dog roundworm)	Transmitted through ingestion of infective eggs. Features include visceral larva migrans and retinal granulomas VISCious dogs → blindness	Diethylcarbamazine

Worm	Notes	Treatment
<i>Ascaris lumbricoides</i> (giant roundworm)	<ul style="list-style-type: none"> the most common nematode parasite of humans. Eggs are visible in faeces large roundworm, growing up to 35 cm in length result of pneumonitis caused by the worm's migration through the lungs May cause intestinal obstruction and occasional migrate to lung (Loffler's syndrome) biliary/pancreatic duct obstruction. 	-bendazoles Piperazine is the treatment of choice in patients presenting with bowel obstruction; mebendazole may be used to treat other infections.

Cestodes (tapeworms)

Worm	Notes	Treatment
<i>Echinococcus granulosus</i>	<ul style="list-style-type: none"> Responsible for hydatid disease Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers. Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal) the most appropriate next step in diagnosis? → ELISA testing for Echinococcus 	<ul style="list-style-type: none"> bendazoles alone (For smaller cysts) albendazole combined with surgical excision. (for larger cysts)
<i>Taenia solium</i>	Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance'	-bendazoles
<i>Fasciola hepatica</i> (the liver fluke)	May cause biliary obstruction	Triclabendazole

Trematodes (flukes)

Worm	Notes	Treatment
<i>Schistosoma haematobium</i>	Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer	Praziquantel
<i>Paragonimus westermani</i>	Caused by undercooked crabmeat, results in secondary bacterial infection of lungs	Praziquantel
<i>Clonorchis sinensis</i>	Caused by undercooked fish Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma	Praziquantel

Schistosomiasis

Schistosoma haematobium causes haematuria

Schistosomiasis, or bilharzia, is a parasitic flatworm infection.

Types

- Schistosoma mansoni and Schistosoma intercalatum: intestinal schistosomiasis
- **Schistosoma haematobium:** urinary schistosomiasis
 - ⇒ This typically presents as a 'swimmer's itch' in patients who have recently returned from Africa. Schistosoma haematobium is a risk factor for squamous cell bladder cancer

Features

- frequency
- haematuria
- bladder calcification

Management

- single oral dose of praziquantel
- Praziquantel is the treatment of choice for all Schistosoma species.
- CNS involvement
 - ⇒ ***S. japonicum***
 - **Praziquantel 60 mg/kg per day for 6 days and prednisolone 1 mg/kg per day**
 - Praziquantel 60 mg/kg per day for six days is recommended for *S. japonicum* with a maximum dose of 5 grams per day with prednisolone 1 mg/kg.
 - ⇒ *S. mansoni* and *S. haematobium*.
 - Praziquantel 40 mg/kg per day for three days is recommended for *S. mansoni* and *S. haematobium*.
 - ⇒ Since some of the pathology in neuroschistosomiasis is secondary to hypersensitivity reactions there is need to use a steroid, in this case prednisolone 1 mg/kg per day. There is no consensus about when it should be started or stopped.

Complications:

- ***S. mansoni*** Eggs can migrate to liver through the portal venous system where they can elicit a granulomatous fibrosing reaction → venous blockade → Portal venous hypertension → varices and upper GIT bleeding.
- ***S. haematobium*** leads to granulomatous inflammation, ulceration of the vesicle and ureteral walls. Subsequent fibrosis can cause bladder neck obstruction, hydrourerter and hydronephrosis. These changes can cause a chronic renal impairment and predispose to secondary bacterial infection as well as squamous cell carcinoma.
- **all schistosome species** can result in immune complex deposition in the kidneys leading to a proteinuria and nephrotic syndrome.
- ***S. japonicum*:**
 - ⇒ is prevalent in China, Indonesia, Thailand and the Philippines mainly.
 - ⇒ **It is the commonest cause of Schistosoma encephalitis.**
 - ⇒ Its eggs are smaller unlike those of *S. mansoni* and *S. haematobium* which are more likely to cause spinal cord schistosomiasis because of their larger size and spikes which do not enable them to get to the brain hence the infection in the spinal cord.

Strongyloides stercoralis

- *Strongyloides stercoralis* is a human parasitic nematode worm. The larvae are present in soil and gain access to the body by penetrating the skin. Infection with *Strongyloides stercoralis* causes strongyloidiasis.

Features

- diarrhoea
- abdominal pain/bloating
- papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks
- larva currens: pruritic, linear, urticarial rash
- if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered

Treatment

- ivermectin and albendazole are used

Tape worms

- Tape worms are made up of repeated segments called proglottids. These are often present in faeces and are useful diagnostically

Cysticercosis

- caused by *Taenia solium* (from pork) and *Taenia saginata* (from beef)
- These may affect any tissue in the body but are commonest in subcutaneous tissues and (CNS) → patient with a palpable nodule who has an epileptic seizure
- management: niclosamide

Hydatid disease

- caused by the dog tapeworm *Echinococcus granulosus*
- life-cycle involves dogs ingesting hydatid cysts from sheep liver
- often seen in farmers
- may cause liver cysts
- management: albendazole

Trypanosomiasis

- Two main forms of this protozoal disease are recognised:
 1. African trypanosomiasis (sleeping sickness) and
 2. American trypanosomiasis (Chagas' disease)

1. African trypanosomiasis, or sleeping sickness

- Two forms of African trypanosomiasis, or sleeping sickness, are seen:
 - 1) *Trypanosoma brucei gambiense* in West Africa
 - West African trypanosomiasis has a slower course. Symptoms start several weeks or even months after the tsetse fly bite.
 - 2) *Trypanosoma brucei rhodesiense* in East Africa.
 - *Trypanosoma rhodesiense* tends to follow a more acute course.
 - progression is more rapid - starting within days of infection. Death may occur within weeks or months.
 - Rash is a more prominent feature and lymphadenopathy is less frequently present.
- Both types are spread by the tsetse fly.
- Clinical features include:
 - Trypanosoma chancre - painless subcutaneous nodule at site of infection

- intermittent fever
- enlargement of posterior cervical lymph nodes
- later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis
- The reversal of the sleep wake cycle is typical and can be accompanied by behavioural changes.

➤ **Stages**

- The **first stage** of disease is haematolymphatic spread and is accompanied by fever, and lymphadenopathy (discrete, rubbery, non-tender nodes). A rash sometimes occurs and mild hepatosplenomegaly may develop.
- The **second stage** is the meningoencephalitic stage. This occurs months or years after the acquisition of infection. Manifestations include personality change and progressive indifference with daytime somnolence. Extrapiramidal signs and ataxia are common.

⇒ **Management**

- early disease: IV pentamidine or **suramin**
- later disease or central nervous system involvement: IV **melarsoprol**

2. American trypanosomiasis, or Chagas' disease

- caused by the protozoan *Trypanosoma cruzi*.
- Transmitted by triatomine bug bite.

➤ **Features:**

- acute phase:
 - ❖ asymptomatic (95%)
 - ❖ chagoma (an erythematous nodule at site of infection)
 - ❖ periorbital oedema
- Chronic Chagas' disease mainly affects the heart, gastrointestinal tract and CNS.
 - ❖ Cardiac feature → myocarditis may lead to dilated cardiomyopathy (with apical atrophy) and arrhythmias.
→ **Cardiac involvement is the leading cause of death in patients with Chagas' disease**
 - ❖ GIT feature:
 - Mega-oesophagus (causing dysphagia)
 - Mega-colon (causing constipation)
 - ❖ CNS feature → meningoencephalitis

➤ **Management**

- treatment is most effective in the acute phase using azole or nitroderivatives such as **benznidazole** or nifurtimox
- chronic disease management involves treating the complications e.g., heart failure.

Nematodes

- most common cause of cutaneous larva migrans → *Ancylostoma braziliense*
- commonest cause of visceral larva migrans → *Toxocara canis*

Ancylostoma braziliense

- most common cause of cutaneous larva migrans
- common in Central and Southern America
- The infection is acquired by direct contact with dog or cat faeces - often acquired when sunbathing on contaminated sand, etc. The larvae burrow in the dermo-epidermal junction.
- **Symptoms** include pruritus and a raised, serpiginous erythematous rash that migrates at a rate of up to 1 cm/day.
- **Treatment i**
 - ⇒ The disease is self-limiting but the duration of disease varies considerably
 - ⇒ **Oral ivermectin** in a single dose of 200 µg/kg body weight is the main treatment.
 - ⇒ Other treatment options include oral albendazole or topical thiabendazole.

Strongyloides stercoralis

- acquired percutaneously (e.g. walking barefoot)
- causes pruritus and larva currens - this has a similar appearance to cutaneous larva migrans but moves through the skin at a far greater rate
- abdo pain, diarrhoea, pneumonitis
- may cause Gram negative septicaemia due carrying of bacteria into bloodstream
- eosinophilia sometimes seen
- management: thiabendazole, albendazole. Ivermectin also used, particularly in chronic infections

Toxocara canis

- commonly acquired by ingesting eggs from soil contaminated by dog faeces
- commonest cause of visceral larva migrans
- other features: eye granulomas, liver/lung involvement



cutaneous larva migrans



cutaneous larva migrans

Filariasis

- Manifestations of filariasis

⇒ Remember 3 L's:

- Lymphatic filariasis (caused by *Wuchereria bancrofti* and *Brugia malayi*)
- Loiasis (caused by *Loa loa*)
- Light (light, sight, blindness - river blindness caused by *Onchocerca volvulus*)

⇒ Tropical eosinophilia:

- Tropical eosinophilia is an allergic reaction to microfilaria of *Wuchereria bancrofti*.
- Characteristic features include:
 - ❖ myalgia; fatigue;
 - ❖ weight loss;
 - ❖ cough and dyspnoea with wheeze;
 - ❖ fever;
 - ❖ current or previous residence in an area endemic for filariasis (southern Asia, Africa, India, South America);
 - ❖ lymphadenopathy;
 - ❖ marked peripheral blood eosinophilia
 - ❖ high titres of anti-filarial antibodies.
- The chest x ray shows bilateral reticulonodular shadowing.
- This condition is commonly accompanied by false positive serological tests for syphilis and high titres of cold agglutinins.
- There is typically a rapid response to treatment with diethylcarbamazine.

- Diagnosis

⇒ finger prick test

- identifying microfilariae on Giemsa stained, thin and thick blood film smears,

⇒ "Filariasis fills the blood at night."

⇒ To remember that Microfilaria can be demonstrated in peripheral smear only at night.

- *W. bancrofti*, whose vector is a mosquito; night is the preferred time for blood collection.

- *Loa loa*'s vector is the deer fly; daytime collection is preferred.

- Which immune mechanisms does the body employ against the live filarial worms ?

→ Antibody-dependent cell-mediated cytotoxicity

Loiasis

- Loiasis is a filarial infection caused by *Loa Loa*.
- It is transmitted by the Chrysops deerfly and tends to occur in rainforest regions of Western and Central Africa.
- It has less pathological features than other the microfilarial infections Onchocerciasis and Lymphatic Filariasis.

Clinical features

- pruritus
- urticaria
- Calabar swellings: transient, non-erythematous, hot swelling of soft-tissue around joints
- 'eye worm' - the dramatic presentation of subconjunctival migration of the adult worm.

Treatment

- Ivermectin is currently the drug of choice for control of both Onchocerciasis and Lymphatic Filariasis in Africa.
- **high loa loa microfilaraemia is associated with encephalopathy following treatment with either Ivermectin or DEC.** This occurs due to the death of vast numbers of blood microfilaria. Both of these drugs are contraindicated if loa loa microfilaraemia exceeds 2500 mf/ml.



Adult *Loa loa* parasite. *Loa loa* is the filarial nematode (roundworm) species that causes loa loa filariasis. It is commonly known as the 'eye worm.' Its geographic distribution includes Africa and India. Credit: NIAID

Animal bites

Animal bite - co-amoxiclav

- The majority of bites seen in everyday practice involve dogs and cats.
- Dog bites become infected in 10% of cases.
- the most common isolated organism is *Pasteurella multocida*.**

Management

- cleanse wound
- current BNF recommendation is co-amoxiclav
- if penicillin-allergic then doxycycline + metronidazole is recommended



Previous exams

MRCPUK-part-1-January- 2019: H/O a dog bite to right hand. What is the most appropriate antibiotic therapy? **Co-amoxiclav**

MRCPUK-part-1-January- 2018: A patient has been bitten by his dog that morning. the wound looks clean as he has washed it well. He is penicillin allergic. Which antibiotic therapy is suitable?

→ Metronidazole and **doxycycline** in combination

Rocky Mountain spotted fever

- Rocky Mountain spotted fever (RMSF) is a systemic vasculitis **caused by infection with *Rickettsia rickettsii***, a tick-borne, gram-negative, intracellular bacterium, that primarily infects vascular endothelial cells.
- It is the most common fatal tick-borne infection in the USA
- Transmitted by bites of the dog or wood tick, which predominantly occur in spring and summer throughout much of the United States.

Feature

- Fever, headache, myalgia, rash, vomiting, and history of tick bite are commonly reported; however, the absence of any of these does not exclude diagnosis. A history of tick bite may not be elicited in up to 45% of cases.
- The rash usually sparing the face and may involve palms and soles.
- Signs and symptoms may be difficult to distinguish from those of common viral illnesses, leading to delayed diagnosis.
- Diagnosis should be considered in any person with a compatible clinical presentation and recent outdoor exposure.
- Late-stage manifestations, such as noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]) and cerebral edema, are consequences of microvascular leakage.

Investigation

- PCR (polymerase chain reaction) is the most appropriate test

Treatment

- Doxycycline is the drug of choice** for adults and children and is almost always curative, especially if given in the first 5 days of illness.
 - ⇒ Tetracyclines acts on 30S ribosomes to prevent protein synthesis in the infecting organism.

- ⇒ **Aluminium hydroxide can complex with this antibiotic in the gastrointestinal tract, preventing absorption.** Dairy products ingested at the same time can also cause this.
- ⇒ **Aluminium hydroxide medication should be stopped till the antibiotic course is finished**
- Because the risk of death rises if appropriate therapy is not started before the fifth day of illness, doxycycline should be prescribed for suspected Rocky Mountain spotted fever before confirmatory diagnostic test results are available.

Typhus (Rickettsial infection)

- caused by Rickettsia typhi (endemic typhus) or Rickettsia prowazekii (epidemic typhus). T
- **Rickettsia prowazekii (epidemic typhus)** is transmitted via human-to-human contact through body lice.
- Arthropod vectors transmit the etiologic agents to humans.
- Presented with fever and rash
- Both forms of typhus consist of a **rash that classically begins centrally, and spreads outwardly sparing the palms and soles** (unlike Rocky Mountain spotted fever)
- Rocky Mountain Spotted Fever can be distinguished from typhus because its rash begins peripherally, and spreads centrally to the palms, soles, and trunk.
- Doxycycline is the drug of choice for treatment in patients of all ages.

Histoplasmosis

Overview

- Histoplasmosis is one of the most common systemic fungal infections in the United States. It is endemic to the Ohio and Mississippi river valleys
- often associated with spelunkers (**cave divers**) or patients recently exposed to bird and bat droppings.

Feature

- The majority are asymptomatic.
- can closely mimic tuberculosis in symptomatology and imaging.
 - ⇒ dry cough, shortness of breath, fatigue, and fever
- **Disseminated infection causes bilateral adrenal enlargement in 80% of cases** and it can result in adrenal insufficiency.
 - ⇒ **Diagnosis: Adrenal biopsy or FNA with Grocott stain (Grocott-stained adrenal biopsy).**

Investigation

- Chest X-ray often reveals a solitary lung lesion.
- Disseminated histoplasmosis can cause systemic granulomatous inflammation and cavitation, which may be fatal.
- The organisms can be visualized using methenamine silver or periodic acid-Schiff staining.
- **On histology → Macrophages containing yeast**
 - ⇒ *Histoplasma capsulatum* is a small intracellular yeast that is phagocytosed by alveolar macrophages.

Treatment

- Itraconazole for 3-6 months

Actinomycosis

Predisposing conditions include:

- tooth extractions,
- fractures of the jaw,
- periodontal abscesses,
- foreign bodies penetrating the mucosal barrier (bone splinters, fish bones) or
- suppurating tonsillar crypts.
- impaired immunity

Features

- cervicofacial actinomycosis
 - ⇒ the most common manifestation of infection with *Actinomyces* spp.
- Initially, cervicofacial actinomycosis presents either as an acute, usually odontogenic, abscess or cellulitis of the floor of the mouth, or as a slowly developing hard, painless, reddish or livid swelling.
- Small, acute actinomycotic abscesses may heal after surgical drainage alone. More often, however, the acute initial stage is followed by a subacute to chronic course if no specific antimicrobial treatment is administered.
- Chronic disease is characterised by regression of central suppurative foci while the infection progresses peripherally; it can spread to involve other parts of the head and neck, including the meninges.
- A quick and comparatively reliable diagnosis is possible microscopically, when sulphur granules are present; this is not conclusive, however, as nocardiosis may present similarly and has a similar appearance on microscopy.
- One way to differentiate *Actinomyces* spp. from *Nocardia* spp. is through culture: the former grow in anaerobic conditions and the latter do not.

Malignant otitis externa

Causes

- Malignant otitis externa is a necrotizing infection of the ear that is **commonly caused by *Pseudomonas aeruginosa*.**
 - ⇒ *Pseudomonas* species are often found swimming pools and hot tubs, and can also cause "hot tub folliculitis".

Risk factors

- Susceptible individuals include diabetics and other immunosuppressed patients.

Feature

- Physical exam may reveal discharge from the ear
- severe pain, out of proportion to physical findings, on manipulation of the ear.
- The disease can affect surrounding bony architecture and cause cranial nerve palsies. Such involvement suggests poor prognosis.

Treatment

- Treatment for suspected *Pseudomonas* infections → anti-**pseudomonal penicillin such as piperacillin-tazobactam**, which is a penicillin paired with a beta-lactamase inhibitor.