055 - Chapter 8

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055

Chapter 8

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 8

Rheumatology

Ledderhose disease is involvement of the plantar fascia by a similar process of nodule and cord formation leading to contraction of the toes.

Baker cyst Look for a patient with osteoarthritis or rheumatoid arthritis with a swollen calf. A ruptured Baker's cyst is a "pseudophlebitis." Unruptured cysts can be palpated. Overview • A Baker's cyst (popliteal cyst) is a posterior herniation of the synovium of the knee. • A Baker cyst is the most common mass in the popliteal fossa. • Since the cyst is an extension from the knee joint, it is lined by synovium. Causes • the most common cause osteoarthritis Investigations • Ultrasonography is the imaging technique of choice in the evaluation of a popliteal mass, but using this technique it may be difficult to show a true connection with the joint space to establish a definitive diagnosis of popliteal cyst.

Third edition Notes & Notes For MRCP part 1 & 2 By Dr. Yousif Abdallah Hamad Infectious diseases Updated

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases 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 diphtheria Listeria monocytogenes • Remaining organisms are Gram negative rods Bacterial shapes • Staphylococcus aureus appears as large Gram-positive cocci in clusters.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

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. Rods (bacilli) • Actinomyces • Bacillus antracis • Clostridium • Corynebacterium diphtheriae • Listeria monocytogenes Cocci • makes catalase: Staphylococci • does not make catalase: Streptococci

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases

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

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Staphylococci • 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. Staphylococcus aureus Staphylococcus epidermidis • Coagulase-positive • Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome • Coagulase-negative • Cause of central line infections and infective endocarditis Staph aureus is a coagulase positive Staph

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• 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 streptococcalorganisms 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 onlyeffective against staph when ampicillin is combined with the beta-lactamase inhibitor sulbactam or when amoxicillin is combined with clavulanate.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases

• 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 asymptomatically 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 nonHIV 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

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Bacteria and growing media Bacteria Type Growth media Staphylococci Gram-positive cocci in clusters Streptococcal species (hemolytic Streptococcal species such as Streptococcus pyogenes). Gram-positive cocci in chains Trypticase Soy Agar (TSA) supplemented with 5% Sheep Blood Streptococcus pneumoniae Gram-positive bulletshaped diplococci E. coli, Klebsiella, or Enterobacter. Gram-negative lactose fermenting bacilli Neisseria meningitidis gram-negative diplococcus

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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% Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

LB broth agar Todd Hewitt Broth Super Optimal Broth (SOB) chocolate agar

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases

Importance • Enterococci are currently ascendant nosocomial (عودی الا تایفشتسملا)pathogens, 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 methicillinresistant staphylococci and other gram-positive bacteria, these drugs have been widely used for therapy and prophylaxis against infections due to these organisms

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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.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

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

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases

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.diphtheria: gravis, intermedius, and mitis. Intermedius 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 elogation 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

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases 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

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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

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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

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

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 E. coli 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.

Chapter 9

Infectious diseases

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 • meningococcus • malaria • dengue fever • typhoid • measles • diphtheria • influenza • scarlet fever

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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 Streptococcus pneumoniae Haemophilus influenzae Neisseria gonorrhoeae M Protein Streptococcus pyogenes Polyribosyl ribitol phosphate capsule Haemophilus influenzae Bacteriophage Corynebacterium diphtheriae Spore formation Bacillus anthracis Clostridium perfringens Clostridium tetani Lecithinase alpha toxin Clostridium perfringens D-glutamate polypeptide capsule Bacillus anthracis Actin rockets Listeria monocytogenes • 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. Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

• mumps • infectious mononucleosis • rubella • chickenpox • cytomegalovirus • viral hepatitis • HIV

• 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 methicillinresistant 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

Infectious diseases

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 Production of penicillinase by the bacteria is the most common mechanism of bacterial resistance to penicillin. However, penicillin resistance in streptococcus pneumonia is due to alteration in the penicillin-binding protein, not production of penicillinase. Vancomycin D-ala-D-ala mutates to D-ala-D-lac

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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 sporeforming 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 Contaminated puncture-type injuries wounds containing foreign bodies compound fractures wounds or burns with systemic sepsis certain animal bites and scratches 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

Infectious diseases

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:
6. parenteral (Typh-I), inactivated vaccine (i.e. killed)
7. parenteral combined with hepatitis A (HA-Typh-I), and
8. 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) لوحلا قرسلا 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)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 9

Infectious diseases

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 nontyphoidal 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 Group B Streptococcus (most common cause in neonates) Neisseria meningitides Neisseria meningitides E. coli Streptococcus pneumoniae Streptococcus pneumoniae Listeria monocytogenes Haemophilus influenzae 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. Notes & Notes for MRCP
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> 60 years Immunosuppres sed Streptococcus pneumoniae Listeria monocytogenes Neisseria meningitides Listeria monocytogenes

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• 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

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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/mm³ 15 - 1,000 lymphocytes/mm³ 10 - 1,000 lymphocytes/mm³ *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.

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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 Pneuomococcal meningitis Intravenous cefotaxime Meningitis caused by Haemophilus influenzae 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.