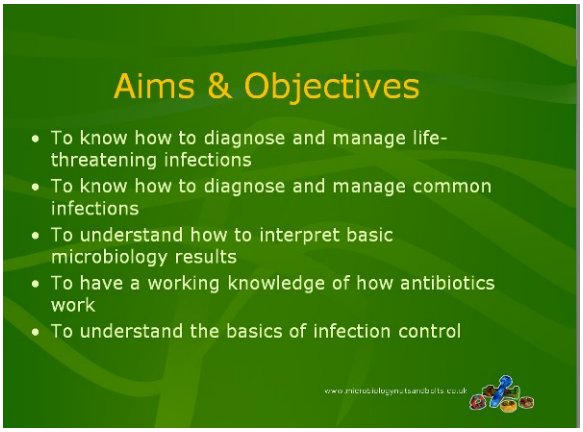
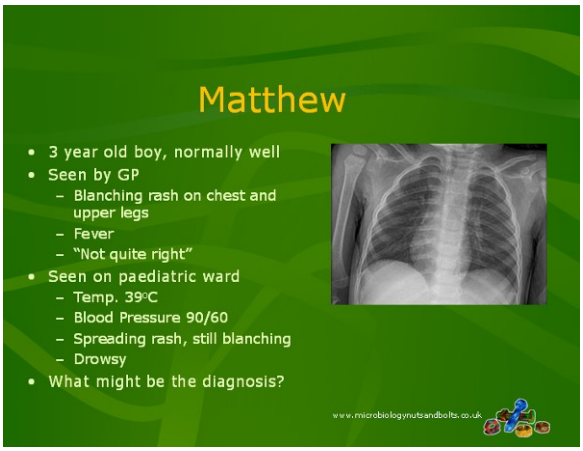
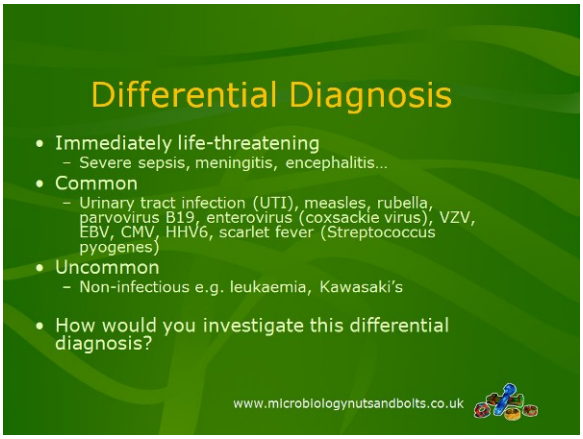
Microbiology Nuts & Bolts: Session 4: Central Nervous System Infections



- 30-40% of patients admitted to hospital will receive an antibiotic
- It is critical to pick out those with life-threatening conditions in order to manage them appropriately and correctly in order to give them the best chance of survival
- It is also important to know how to diagnose and manage common infections so that complications do not occur and patients get better as quickly as possible
- Knowing about antibiotics ensures the correct ones are used for the correct indications, prevents prescribing errors and keeps patients safe
- Everyone working in a healthcare setting has a responsibility to protect patients from harm including cross infection from other patients

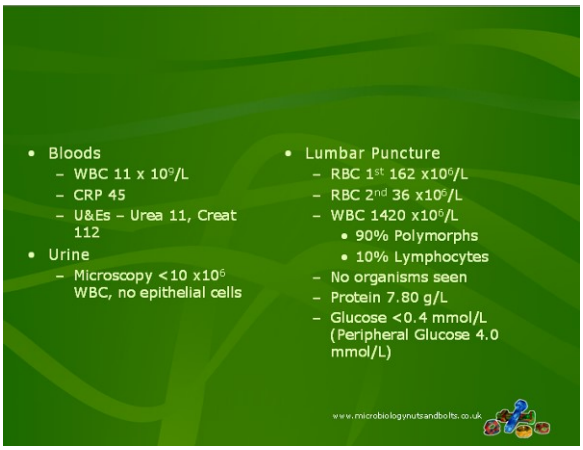


- It is important to take age in to account when assessing any child as the physiological parameters vary, and Matthews blood pressure is essentially normal for his age
- Parental concern and drowsiness should all ring alarm bells with the clinical team looking after Matthew, and indeed parental concern often scores a 2 on paediatric early warning score templates
- His blanching rash raises a host of potential infectious causes for his illness such as measles, rubella, enterovirus, but unfortunately it has become the case that many healthcare staff are falsely reassured by the blanching nature
  - Many healthcare professionals quote the "tumbler test" as a way of looking for a non-blanching rash by pressing a glass over the rash, but this is a lay-persons test
  - The rash of meningococcal sepsis begins a s a blanching rash as bacteria invade the blood vessels supplying the skin, it becomes non-blanching when this leads to bleeding in to and necrosis of the skin supplied by these blood vessels and is a late sign
  - If a child is septic then meningococcus should be consider in the differential diagnosis irrespective of the presence of a rash



- Formulating a differential diagnosis appears to be going out of fashion but it is essential if diagnoses are not to be missed
- A systems approach (e.g. respiratory, cardiac, Gastrointestinal, genitourinary, neurological, skin, bone, joint, etc) can be fitted to a template of life-threatening, common, uncommon in order to complete the differential but considering the life-threatening first ensures these are dealt with as early as possible
- It is not a static process but can change throughout a patients management as new information becomes available and their clinical condition changes
- The process does not just apply to infectious diseases, but to any potential clinical condition

- It is essential to know the normal values of all tests within your hospital
- Full blood count (FBC)
  - The total white blood cell count can go up or down in infection
  - The differential white blood cell count can help to point to the type of organism but nothing is 100% (neutrophils = bacteria/fungi, lymphocytes = viruses, eosinophils = parasites)
  - Platelets are an acute phase reactant and go up in infection (they can go down in severe infections when disseminated intravascular coagulation DIC develops)
- CRP (C reactive protein)
  - Produced in liver in response to inflammation, often goes up in bacterial infection
  - >200 usually significant, otherwise need to know what the trend is i.e. increasing, decreasing
  - Beware, patients in liver failure do not produce much CRP – use other markers of liver synthetic function to guide you e.g. INR, Albumin
- Urea & Electrolytes (U&Es)
  - Antibiotics can only be prescribed safely if the patients kidney function is known
- Urine point of care includes a dipstick test
  - There are different ways of taking urine samples from children and each has it's potential drawbacks
  - Clean Catch Urine (CCU) – the urine sample is caught in a clean container when a small child starts to micturate, the main drawback is the time taken to get the sample
  - Bag urine - a sterile collecting bag is stuck to the perineal skin around the genitalia and the child micturates into the back, these are convenient but because the urine is able to wash over the perineal skin they are prone to contamination, they have a use in disproving the diagnosis of a UTI but are popular with microbiologists
  - Suprapubic Aspirate – in many ways the gold standard way of collecting urine samples because the urine is collected directly from the bladder bypassing any potential contamination, unfortunately this is an invasive test and not popular with parents

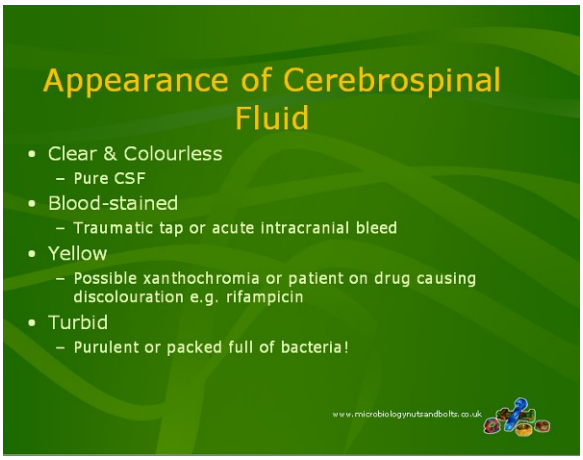


- Lumbar puncture is the procedure used to investigate an abnormality of the cerebrospinal fluid surrounding the brain and spinal cord
- For microbiological purposes it is taken to help diagnose meningitis and sometimes encephalitis
- A lumbar usually consists of taking 4 sterile universal sample, a fluoride oxalate sample of CSF and a peripheral blood glucose
- Samples 1 and 3 have a red blood cell count performed and compared, if a vertebral vessel is hit on the way in the blood will clear and the red blood cell count decrease in sample 3 compared to sample 1
- A white blood cell count is performed on sample 3, a normal white cell count is either < 4 x 10^6/ml, or a ratio of 1 WBC to 600 RBC (the same as in whole blood)
- The differential white blood cells count has the same implication as in peripheral blood with neutrophils

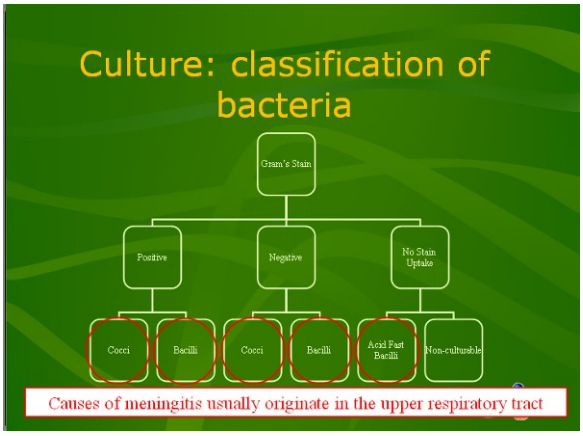
usually indicating a bacterial infection and lymphocytes indicating a viral infection

- There are 2 exceptions to this in that Mycobacterium tuberculosis and Listeria monocytogenes tend to be intracellular and so promote a lymphocyte response
- The normal value of protein is usually less than 0.4 g/L and it raises slightly in viral infections or is normal, whereas in bacterial it rises well above 1 g/L
- Glucose is normally >50% of serum glucose which is why you need to have a peripheral blood glucose to compare to
- If the peripheral blood glucose is forgotten a CSF value of <2mmol/L is significantly low anyway (because the lower limit of normal in blood is 4mmol/L)
- Bacteria utilise glucose as an energy source so the CSF glucose in bacterial meningitis is very low whereas in viral it is normal
- Whilst it can be difficult to distinguish Listeria or Tuberculosis based solely on the differential white cell count it can be done because in both these bacterial infections the protein will be high and the glucose low

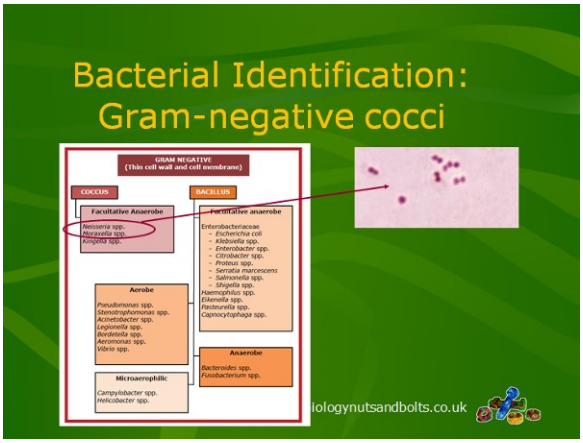
- As with other tests it is important to have a system for looking at microbiology results
  - CSF samples are first assessed to see if the patient actually has evidence of a non-microbiological problem based on the appearance
  - Microscopy will indicate the likelihood of infection as detailed above
  - Culture will indicate if one of the common bacterial causes of meningitis is present or whether there might be a virus or something more unusual



- The appearance can be very helpful for looking for an alternative diagnosis to meningitis such as a sub-arachnoid haemorrhage (SAH)

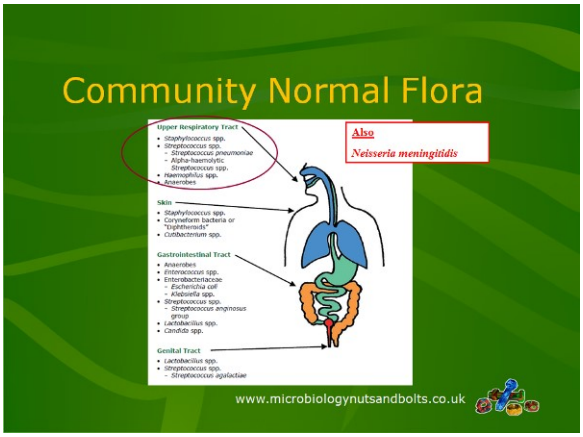


- The Gram film can be very informative if it is positive as there is really only one main organism in each type which causes meningitis
- Gram-positive coccus = Streptococcus pneumoniae
- Gram-positive bacillus = Listeria monocytogenes
- Gram-negative coccus = Neisseria meningitidis
- Gram-negative bacillus = Haemophilus influenzae
- Acid Fast Bacillus = Mycobacterium tuberculosis
- The common viruses are Enteroviruses, Herpes Simplex Virus and occasionally Herpes Varicella Zoster Virus



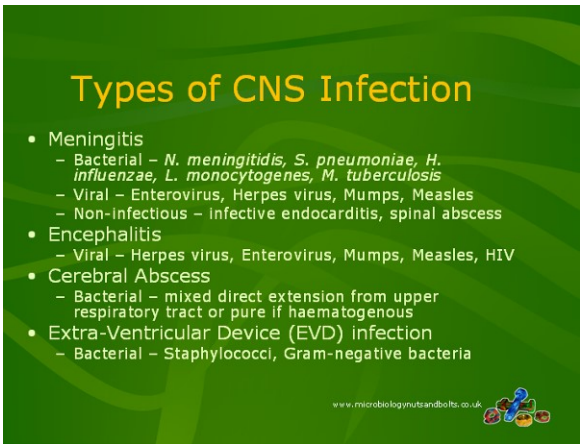
- There are very few common medically important Gram-negative cocci
- The two most important are both part of the Neisseria species:
- Neisseria meningitidis causes sepsis and meningitis
- Neisseria gonorrhoea cause the sexually transmitted infection gonorrhoea which can occasionally disseminate to cause sepsis and septic arthritis

- CSF is an urgent sample and the laboratory should be contacted as soon as the sample has been taken to let them know it is coming
- Delaying the processing of CSF leads to a reduced white blood cell count as the cells start to degrade, and a potential change in ratio of neutrophils to lymphocytes as they degrade at different speeds
- Ideally CSF should be processed within 2 hours of being taken
- Suspected meningitis should be treated before the results are available and the antibiotics reviewed at the time the results come back
- There is increasing use of PCR to identify the causes of meningitis. This is useful in that treatment can be started before the LP as PCR does not rely on the organisms being alive and PCR can also identify viruses. The main drawback is that PCR does not give antimicrobial sensitivities and so treatment often remains empirical

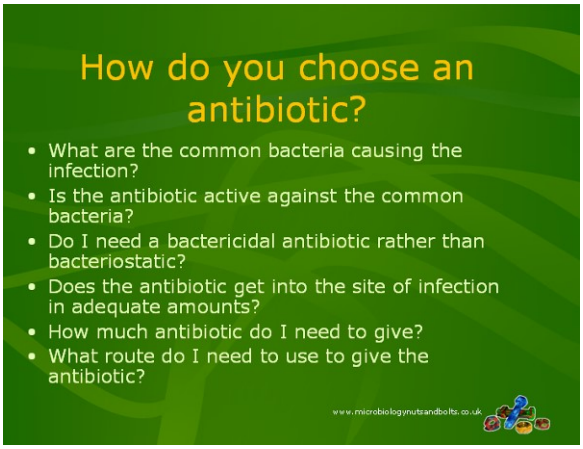


- The normal flora of a human body consists of 10^{14} bacteria (that's approximately 15,000 times the number of humans on the Earth!)
- Knowing the common bacteria that colonise the human body allows:
  - Prediction of the causes of infection from any body site because 85% of infections are caused by the patients own flora getting in to a site it should not be e.g. UTI caused by bacteria from the gastrointestinal tract
  - Prediction of the origin of an infection when a bacteria is found in a normally sterile site e.g. E. coli in blood cultures from either urine, bowel or Biliary tract
- The causes of meningitis usually colonise the upper respiratory tract shortly before they invade to cause infection

- Matthews rash has now become purpuric suggesting meningococcal sepsis as well as the earlier diagnosis of meningitis
- Patients can have either or both infections, they are different clinical entities caused by the same bacteria
- Capillary refill time is a measure of tissue perfusion and should be < 2 seconds
  - CRT is usually performed by pressing over the sternum for 5 seconds to remove the blood from the tissue and then counting how long the blood takes to come back after the pressure has been removed
- Once the diagnosis has been considered an EDTA blood should be sent for meningococcal PCR and a throat swab taking for culture
- These allow the type of meningococcus to be established as well as potential antibiotic sensitivities which aid in the use of vaccines and antibiotics to protect contacts

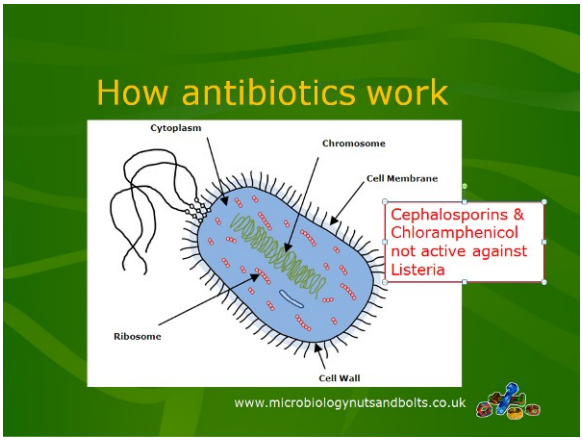


- There are many neurological tract related infections and distinguishing them in a patient who is already unwell and may not be able to give an accurate history can be difficult initially
- Meningitis tends to present with headache, fever, photophobia, neck stiffness
- Encephalitis often has symptoms such as reduced conscious level, altered behaviour, confusion, seizures and occasionally focal neurological signs (MRI is very helpful in the diagnosis of HSV encephalitis)
- The symptoms and signs of cerebral abscesses depend on how quickly they develop and are usually related to either focal neurological signs or raised intracranial pressure
- Extra-Ventricular Devices (EVDs) are put into the cerebral ventricles in order to drain CSF and control hydrocephalus for short periods of time; when infected the symptoms are usually those of meningitis

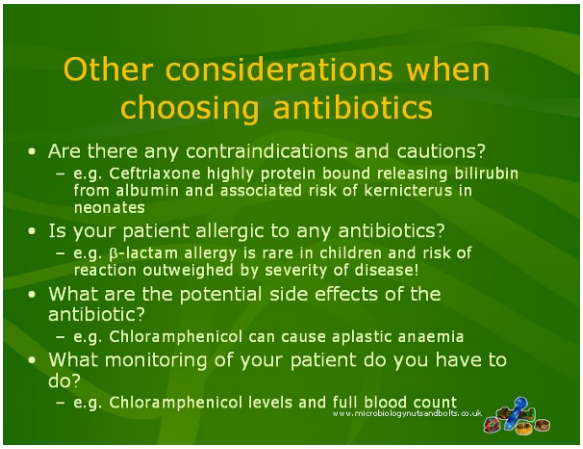


- Over treatment with antimicrobials is a common and serious problem
- There are a number of common reasons for this:
  - The patient does not have a bacterial infection
  - Clinical signs are over interpreted
  - Treatment is trying to target normal flora
- Many of these instances can be avoided by carefully considering the patient and their results before deciding to treat
- CNS infections are serious and life-threatening and so patients are often started on broad empirical therapy until the cause is known
- Bactericidal antibiotics are given in high doses intravenously as quickly as possible to try and save the patients life
- It is important to review these antibiotics when the cause becomes apparent or when other causes are excluded in order to start to narrow down the spectrum of the antibiotics being used in order to avoid side effects and complications of treatment

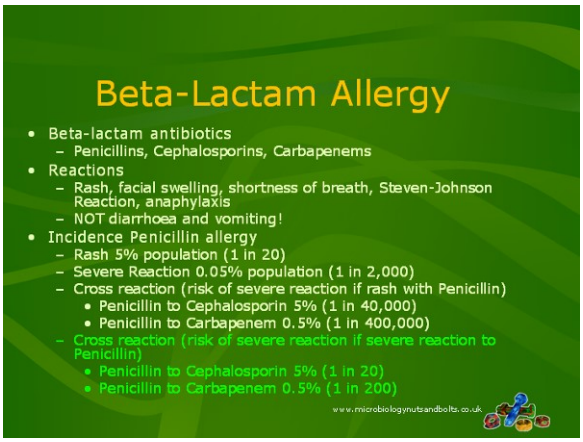
- CNS infections are life-threatening and should be treated urgently and aggressively
- Empirical guidelines allow doctors to start appropriate antibiotics as quickly as possible without having to contact someone else for advice
- Chloramphenicol is often used as an alternative to the Beta-lactams in severe penicillin allergy
- Remember if the penicillin allergy is only a rash then the cephalosporins can still be used
- Don't forget to start Dexamethasone within 12 hours of starting treatment to reduce long term sequelae



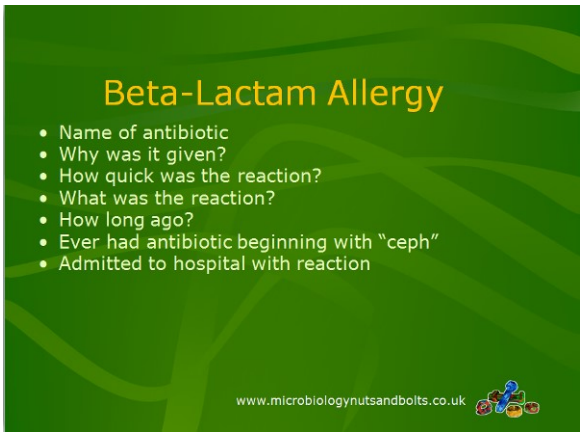
- Note: cephalosporins and Chloramphenicol are not active against Listeria monocytogenes and so when this is considered either Amoxicillin should be added or you should seek specialist advice
- It can helpful to split antibiotics into 3 groups based upon their mechanism of action as this makes it easier to remember them:
  - Mainly act on the cell wall
    - The Beta-lactams act primarily on the cell wall and are cidal to most bacteria within their spectrum of activity
  - Mainly act on the ribosome
    - Interfere with protein production therefore may not be cidal to some bacteria e.g. Chloramphenicol
  - Some other individual action
    - Aciclovir, as an antiviral, is used to treat HSV encephalitis
    - Aciclovir is a nucleoside analogue converted in to an active form by viral thymidine kinase in infected cells; it is therefore more effective when given early in the course of the infection



- Ceftriaxone is contra-indicated in neonates because of it's ability to precipitate kernicterus, a form of brain damage cause by high levels of bilirubin
- It always worth checking if a patient is allergic to whatever drug you are going to give them although be sure they are describing an allergy not just a recognised side-effect
- Some antibiotics have common or severe side effects and doctors should be familiar with these and warn patients about them, as part of the informed consent to treatment process
- Many antibiotics also require monitoring for these side effects and this should be checked in the BNF at the time of prescribing



- Beta-lactam allergy causes a lot of problems for doctors and pharmacists when it comes to prescribing antibiotics
- It is crucial to get as mush detail about a reported allergy as possible, if necessary contacting relatives and primary care physicians to get more information
- Many patients report side-effects as "allergies" and this can lead to patients being denied safer and more effective treatments incorrectly
- It is important that all healthcare staff are familiar with all of the names of Beta-lactams so that allergic patients are not accidentally given a Beta-lactam because the staff member did not recognise the risk
- Severe penicillin allergy is rare but is a contra-indication to all of the other Beta-lactams as well because the risk of having a SEVERE cross reaction are very high
- If the reaction is only mild then other Beta-lactams can still, be used because the risk of a SEVERE cross reaction is still very low (even if the risk of a mild cross reaction is actually high)
- It is a balance of risk between benefit and harm



- When taking a history of a drug allergy it is important to be thorough
- For a beta-lactam or Penicillin allergy history you need to answer a number of questions

Matthew

- Aggressive resuscitation
- IV Ceftriaxone 50mg/kg BD for 7 days
- Notified to Public Health
  - Family given antibiotic prophylaxis
- Matthew made a full recovery and was discharged home 2 weeks later.

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- Antibiotics are only a part of the management of meningococcal sepsis and meningitis, and it is the life supporting treatments that usually make the biggest difference to outcome
- These patients should be managed by the most senior and experienced staff available with early help from specialist intensive care units
- All cases of meningitis and encephalitis should be reported urgently to the public health medical team at Public Health England (PHE) so that they can manage contacts and potential outbreaks

Caution: *Prophylaxis & Infection Control*

- Organised and co-ordinated by Public Health
- Contact tracing household contacts
- Oropharyngeal decolonisation
  - Adults & Children – Ciprofloxacin
  - Pregnancy – IM Ceftriaxone
- Infection Control
  - Isolate patient
  - Personal Protective Equipment (PPE)
    - Gloves and aprons
    - Face mask if manipulating airway
  - If splashed in face consider antibiotics

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- Public Health England will coordinate the distribution of antibiotics to close contacts as well as the use of vaccines for vaccine preventable causes of infection
- Antibiotics are used to eliminate potential colonisation of the oropharynx of people who have had close contact with the case so that they either do not acquire the infection or do not pass the organism on to others

Conclusions

- Meningitis usually caused by bacteria from the upper respiratory tract
  - *S. pneumoniae*
  - *N. meningitis*
  - *H. influenzae*
- Meningitis and encephalitis are medical emergencies
- Antibiotics are chosen to treat the likely bacteria
- All of the microbiology report is important and helps with interpretation of the result
- Severe penicillin allergy is rare and cross reaction to other beta-lactams is even rarer

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- Meningitis is usually caused by bacteria which originally colonise the upper respiratory tract before invading
- Management should be regarded as an emergency and senior help requested at the earliest opportunity
- Severe penicillin allergy is rare, and cross reaction to other Beta-lactams is even rarer, a careful evaluation of the reaction and an assessment of risk:benefit should allow for safe prescribing