The Overview of Meningitis and its Treatment

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The Overview of Meningitis and its Treatment

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Abstract

Meningitis is generally an infection involving the inflammation of the meninges which is becoming an increasingly common non-infectious disease. Patients with meningitis must be given treatment within a rapid period of time as delay in treatment causes various serious complications. Studies have shown that meningitis has a high mortality rate in most countries and therefore, in our research paper, we aim to discover and explore more about the causative agents of meningitis, both classic signs and uncommon symptoms of meningitis, ways to diagnose infection of meningitis, risk factors for meningitis and also the therapies available to combat meningitis. In order to achieve the objectives above, we took several approaches to gain answers and explanations to our questions. First of all, we derived many research journals from the internet that were related to the field of our study. We analyzed the findings of these medical journals and focused on the selected topics we were assigned to. Also, we searched for related information from other published medical books. Upon completion of all the procedures, we found that meningitis could be classified into several groups based on their causative microorganisms. We also discovered that the empiric therapy for most meningitis cases were mostly third generation antibiotics as they could penetrate the CSF. Lumbar puncture may also be conducted to discover the causative agent of meningitis in a patient. Also, there were many drugs in the market available for the treatment of meningitis. This discovery enables us to determine the drugs for empirical therapy of meningitis and the specific drugs used after the causative agent of meningitis has been identified. In conclusion, this research study has increased our understanding of meningitis.

Introduction

Meningitis is a life-threatening infection of the brain, especially on the protective membranes that cover the brain and spinal cord. These membranes are known as the meninges. They consist of 3 connective tissue layers which are the pia mater, the arachnoid and the dura mater. In the brain, three of them cooperate to support the blood vessels and contain the cerebrospinal fluid. The brain may be infected by bacteria, fungus or virus which will cause the inflammation of the meninges. Patients need to receive the treatment within a very short time because it is can be lethal. Meningitis can be classified further into three main groups based on the causative agents --bacterial meningitis, nonbacterial meningitis, and viral meningitis. Bacterial meningitis is usually caused by Pneumococcal species, Haemophilus influenzae, Staphylococcal species, and meningococcal species. For nonbacterial meningitis, it is related to fungal and parasites that is frequently linked to etiologic agents like Cryptococcal species and Histoplasma species. In the aspect of viral meningitis, it can be Enterovirus meningitis or Herpes simplex virus meningitis. The bacteria causing meningitis is transmitted through water droplets from person to person. These can be promoted through intimate and prolonged contact, for instance, kissing, sneezing or coughing on another person and staying very close to the infected person.

The incidence rate of meningitis in developing countries such as Africa and India is higher than that in the developed countries by ten times since the access to preventive measures of the disease is still not well developed. Every year, there will be 8000 cases of meningitis and a total number of 2000 deaths occur that mark this disease as high morbidity and mortality. Between 1998 and 2003, there is a decline in the cases from 1.9 to 1.5 per 100,000 for the overall incidence of bacterial meningitis. The decrease in the figure was partly contributed by the promoted use of the vaccination especially in many developed countries. In 1986, the median age for persons having infected by bacterial meningitis was 15 months, while in 1998, the median age has been changed to 25 years. This reveals that the disease has a higher frequency in adults than in children even though patients younger than 5 years old are at high risk to get the disease. For the adults, the incidences of bacterial meningitis are 1.7 to 7.2 cases per 100,000 every year and the mean annual incidence is 3.8 cases per 100,000. There is a famous meningitis outbreak which is related to the meningococcal meningitis at the meningitis belt. The meningitis belt is an area of sub-Saharan Africa characterized by the dust winds and cold nights. Since meningococcal meningitis has seasonal variation, the
dry season holds responsibility for large epidemics that occur in the meningitis belt. [3]

There are a few common symptoms of meningitis, for instance, neck stiffness, altered mental status, fever and headache. However, the classic triad of fever, neck stiffness and an altered mental status remains low among adults with community-acquired bacterial meningitis. [4] Patients who are suspected to have meningitis should seek for examination and treatment as soon as possible. Any delay of treatment will lead to high mortality and ineffective of therapy.

The causative agents of meningitis

Bacteria

When bacteria invade the cerebrospinal fluid (CSF), the bacteria can multiply freely in CSF, and there they release poisons, causing inflammation and swelling in the meninges and the brain tissue itself [5, 6]. This will increase the pressure inside the brain, producing symptoms of meningitis such as headache, stiff neck and dislike of bright lights. Babies become irritable, may have a high-pitched or moaning cry, be stiff or floppy, and develop a bulging soft spot on their head [5, 6]. In both children and adult, there may be a rash which can occur anywhere on the body. This is a sign of blood poisoning (septicaemia) which sometimes happens because of meningococcal strains [7].

As the disease progresses the patient becomes drowsy, confused, and delirious. They may have seizures and eventually lose consciousness [5, 6]. If inflammation and damage to the brain cannot be successfully stopped with antibiotics and other treatments, the infection can be fatal. Usually the most common bacteria that cause meningitis are Streptococcus pneumoniae and Neisseria meningitidis [6].

Streptococcus pneumoniae usually causes pneumococcal meningitis. There are over 80 subtypes that cause the illness [7, 8]. Streptococcus pneumoniae can be found in the throat and usually people don’t get sick from them. The people who are at risk getting pneumococcal meningitis or pneumonia are those with weak immune systems or people who are very young and very old. People who get direct contact with someone who have pneumonia meningitis do not have to take antibiotics [8]. Pneumococcus can be fatal because of permanent loss of neurons due to apoptosis in the hippocampus [9]. Furthermore, the bacteria can block the invasion of leukocyte into the CSF. The pneumococci release toxins to induce apoptosis which damage the mitochondria results in the release of apoptosis-inducing factor (AF1).

Pneumococcus produces a potentially toxic factor that could contribute to this apoptosis, including cell wall components and surface-associated secreted toxins. Important pathogenicity factors unique to Streptococcus pneumoniae include the exotoxins, H2O2 and the pore-forming molecule pneumolysin. Pneumococcus is unusual because it is the only invasive human pathogen that lacks catalase, and the release of H2O2 is important for pneumococcal pneumonia. Pneumolysin is a thiol-activated pore-forming molecule that has potent cytotoxic activity and pneumolysin also plays an important pathogenic role in pneumococcal-induced pneumonia and otitis media. The two secreted toxin, pneumolysin and H2O2 help in inducing apoptosis of the neurons cells [9].

Neisseria meningitidis cause meningococcal meningitis. There are 5 subtypes that cause serious illness or blood infection [7, 8]. Approximately 15% of people carry these bacteria in their throats without getting sick. However, in rare cases, the bacteria can pass through the throat lining into the blood and it can pass through the blood brain barrier in the brain and infect the meninges. These bacteria are very contagious and can spread through the saliva during kissing, sharing of food, sneezing and coughing [8]. If the people have come in direct contact with the saliva of a person with Neisseria meningitidis, they need to take antibiotics for protection [8].

Meningococcal is a fast moving disease and can cause death in 24 to 48 hours starting from the start of the symptoms [10]. It can cause two types of infection, meningococcal meningitis which cause meninges and the other one is meningocemia or known as septicemia [9]. Septicaemia is blood poisoning caused by bacteria in the bloodstream [5]. The bacteria give off poisons which attack the blood vessels so that they leak. As a result, there is a smaller volume of blood being transported around the body to the vital organs. Reduced blood supply means that oxygen carried by the blood is not reaching the tissues and organs of the body where it is needed. In order to maintain sufficient oxygen supply to the vital organs the circulatory system reduces blood supply to the hands, feet and skin surface. This is how symptoms of septicaemia such as cold hands and feet, pale skin and rapid breathing develop. If treatment is not successful, septicaemia can ultimately lead to severe damage to vital organs, including heart failure, collapse, and death [5].

Virus

The first few signs of infection by viral and bacterial meningitis are both characterised by rapid onset of
fever, headache, nausea and throwing up. Therefore, it is rather difficult to diagnose whether the acute meningitis is caused by bacteria or viruses. Usually, evaluations will be made to determine presence for other symptoms like possible encephalitis, seizures, reduced Glasgow coma score, or focal neurological signs. For bacterial infection cases, patients who are left untreated will display retardation of mental status while virally infected meningitis patients will recover on their own after some time.

The most common agents that cause viral meningitis are Enteroviruses. Infections by these viruses are mainly without symptoms, but they cause systemic infections and may attack the brain neurons and cause aseptic meningitis, meningocehalitis and paralytic polyomylitis. Sudden retardation in mental status or occurrence seizures may be due to the progression from meningitis to meningocehalitis. It may also have other accompanied signs such as herpangina; hand-foot-mouth disease and generalised maculopapular rash. Enteroviruses include Coxsackie A and B viruses, echovirus, polioviruses, Human immunodeficiency virus and Epstein Barr Virus. Newborns and toddlers whose immune system is not completely developed will be very vulnerable to infections by enteroviruses.

Herpes simplex virus is another causative agent of meningitis. It is actually a complication from a primary genital herpes infection. Non-primary genital herpes infection seldom leads to the incidence of meningitis. The viral meningitis caused by herpes simplex virus might recur and lead to a relapse. [11] The first drugs or treatment used for patients with meningitis include chloramphenicol, penicillin and sulphonamides. In certain regions of Africa, some meningococcus strains have evolved to become resistant against the widely-used sulphonamides. Infections by these species, symptoms like brain abscesses will appear. Coma might follow suit after occurrence seizures may be due to the progression from meningitis to meningocehalitis. It may also have other accompanied signs such as herpangina; hand-foot-mouth disease and generalised maculopapular rash. Enteroviruses include Coxsackie A and B viruses, echovirus, polioviruses, Human immunodeficiency virus and Epstein Barr Virus. Newborns and toddlers whose immune system is not completely developed will be very vulnerable to infections by enteroviruses.

Chloramphenicol does not need a long course of medication therefore reduces the cost of the treatment. It is also taken orally and this increases the patient’s acceptance. Although it may cause aplastic anaemia in some patients, the incidence of this happening is low; therefore it serves as a good choice for treatment of meningitis. [12] In other cases, vancomycin and rifampicin can be used synergistically if there is observed resistance to penicillin. [13] Some drugs have been found to induce the infection of meningitis. A patient was found diagnosed with meningitis after being treated with amoxicillin due to treatment for a pretibial injury. Therefore, it can be said that meningitis may also be caused by hypersensitivity mechanisms and immunological reactions. [14] Zygomycetes are found mostly in earth, soil, faeces and bio-waste. Meningal infections in immunocompromised patients may be caused by zygomycosis due to its opportunistic nature of infection. A case report showed that a patient was infected by zygomycetes due to his immune system being altered by too frequent use of multiple antibiotic and steroids. In response to the patient’s condition, antibiotic and steroids were eliminated from his list of therapeutic drugs and continued with Amphotericin B. The dose of the drug must be adjusted and given accordingly to patients based on their conditions; in this case, 75mg infusions were given every day at first and then to every alternate day after improvements were seen. [15] Meningitis infections may be found in several areas of the brain, for example cyst-filled regions along the blood vessels. Symptoms of meningitis caused by Cryptococcus include significant increase of intracranial pressure and protein levels and a decrease in sugar and chloride levels. A patient may also experience headaches more often than not if he is having meningitis. Amphotericin A has been proved to be another potent and effective drug to treat meningitis caused by these bacteria.

Meningitis may also be caused by actinomycetes. In infections by these species, symptoms like brain abscesses will appear. Coma might follow suit after signs of extreme headache and dizziness. Sulfadiazine, sulfamerazine and streptomycin are the drugs of choice used in these cases. However, antibiotic therapy and chemotherapy can also act as substitutes for the sulphonamide family. [16] In Figure 1, a flow chart of how meningitis can affect a healthy person is shown.

**Empiric Therapy**

**Pre-treatment evaluation**

Pre-treatment evaluation may be needed in suspected patients with bacterial meningitis. The history requirements of the disease include any serious drug allergies and recent exposure to someone with meningitis, infection, or even the use of certain antibiotics. A history of injection drug use, otorrhea or rhinorrhea, HIV infection and other risk factors or other immunocompromising conditions may also be taken into consideration. Diagnostic tests then are carried out. Initial blood test is positive in 50 to 90 percent of adults with bacterial meningitis. [18] The positive blood cultures related to meningococcal infection has the
Lumbar puncture is one of the procedures which are popular to detect any meningitis infection. Fluid extracted from spinal cord can be analysed to determine the next step necessary in treatment. However, this treatment has many contraindicative measures because it is not suitable to those who had suffered from brain herniation that is related to intracranial pressure. We can proceed by using CT scan or magnetic resonance imaging (MRI) scan. The main goal is to eliminate any possible non-meningitis problems. Since almost half of the cases involved adults are due to meningitis, it is better to eliminate any non-meningitis possibilities. If lumbar puncture is difficult to be carried out, direct treatment with antibiotic is better rather than any delay which can cause high fatality. In this aspect, before lumbar puncture is performed on patients, we need to measure the opening pressure. If the pressure is higher than normal, we can suspect the presence of bacterial meningitis. If the observed fluid is cloudy, it can indicate that there is infection within brain part but we need to do more appropriate analysis for better results. [21]

From spinal fluid, we can measure the level of protein, white and red blood cells and glucose. Gram staining helps to determine which kind of bacteria in the fluid. Likewise, this measure can be replaced by microbiological culture. Other test, for instance, the limulus lysate test (determined by the presence of endotoxin), polymerase chain reaction (for indication of bacteria DNA or viral DNA) and latex agglutination can be done. [21]

There are a few types of assessment that can be obtained from the fluid of patients even though indirectly. They need to be sent for further tests such as microscopic test and then being centrifuged. All of these have to be done immediately because red blood cell (RBC) will undergo haemolysis within a few hours. Cytologic assessment will indicate the total amount of white blood cell (WBC) present in the fluid. If the total number of WBC is larger than that of a normal person, there might be an infection or in some rare cases, it could turn out to be leukemic infiltration. This will also indicate that the condition is preponderance of polymorphonuclear leukocytes (PMN) which has a similar indication as viral meningitis. In addition, cases like inflammation also can increase the total number of WBC. [22]

Protein assessment level can be a clue of any unsuspected neurologic disease. The high level of protein especially in post infectious diseases can be informative. Glucose assessment will indicate for diseases which are associated to any bacterial infection if there is a low level of glucose. This finding also can be seen in tumour infiltration and may be the one of the characteristic of meningeal carcinomatosis if cytologic assessment is negative. For the cases of high glucose concentration in CSF, no specific indications can be made. [22]

Xanthochromia of CSF is a yellow substance useful in distinguishing RBCs that is related to intracranial bleeding. We can observe the colour by naked eyes but to be more accurate, it is necessary to identify and quantify the substance in a laboratory. This will be the evidence of the blood present in subarachnoid space. This procedure has a better diagnostic sensitivity than CT scan of the head. Furthermore, CSF colour can diagnose pseudomonal meningitis by its bright green colour. [22] Before the lumbar puncture is done, anaesthetics should be given to the patients. [23]

Computer tomography scanner CT scan is always the first step to remove any contraindications for lumbar puncture. However, it cannot provide sufficient evidence for normal intracranial meningitis patient. Nevertheless, it is important especially when the complications involve neurosurgical intervention or detecting complications like venous thrombosis, infarction, and ventriculitis (a common meningitis complication which happens in neonates). The problem of this technique is that it is excluded from acute meningitis cases. This technique is effective in finding the causes of meningeal infection. [21] The common thing is that these technologies are harmless to the patients yet CT scan is only suitable for clinical needs, not for screening purpose. [24]

Magnetic resonance imaging is good technique for infectious meningitis detection and characterization for different aetiology. [25] It is a more sensitive instrument because the presence of inflammation in the brain can be detected. [26]
Reverse transcriptase polymerase chain reaction test (RT-PCR). (RT-PCR) is a complex assay important for clinical diagnosis. This is used if ribonucleic acid (RNA) cannot serve as the template for PCR, reverse transcription of the RNA template into cDNA is carried out and this is followed by its amplification. The common reverse transcriptases that have been used are avian myeloblastosis virus reverse transcriptase (AMV-RT) and Moloney murine leukemia virus reverse transcriptase (MLMC-RT). [27] This method can be very useful for detection of enteroviruses in cerebrospinal fluid CSF since the PCR test is highly sensitive. This will help to detect a variety of enteroviruses serotypes and epidemiologically unrelated isolates in CSF with aseptic meningitis. The results obtained will be in a shorter period of time. [28]

Choices of Empiric Therapy

**Choices of empiric treatment**

N.meningitidis and S. Pneumoniae are among the most common causative organism of community-acquired bacterial meningitis in immunocompetent adults, and are increasingly resistant to penicillin and cephalosporins. Thus, empirical therapy should be based on the possibility of the resistance involved. [29] Some selected third generation of cephalosporins (cefotaxime or ceftriaxone) have excellent penetration into CSF. This makes them the drugs of choice in the treatment of bacterial meningitis. Both have potent activity against major pathogens of bacterial meningitis except for Listeria monocytogenes and some penicillin-resistant strains of S. Pneumoniae. Due to dramatic increase in incidence of penicillin-nonsusceptible pneumococci-some of which have also exhibited decreased susceptibility to third generation cephalosporins-empirc vancomycin should be added until culture results are available. [30] Cefepime is safe to patients and can be used as an alternative to cefotaxime or ceftriaxone when broad spectrum activity against both pneumococcus and gram negative bacteria is necessary. [18]

Different combinations and doses of drugs have been given to treat different patients. The examples are patients who have unknown immune deficiency, impaired cellular immunity, nosocomial meningitis and those with severe beta-lactam allergies. [18, 31] The drug spectrum must be directed against Listeria monocytogenes and gram-negative bacilli (including Pseudomonas aeruginosa) as well as Streptococcus pneumoniae for patients with impaired cellular immunity whereas those with nosocomial meningitis must cover gram-positive and gram-negative (such as Klebsiella pneumoniae and Pseudomonas aeruginosa) nosocomial pathogens. Appropriate regimens and drug administration are compulsory, depending on the renal function, the age and the host factors. [18]

**Antibiotic regimen**

It is very important to remember that empiric therapeutic regimens for bacterial meningitis are provided according to the patient age and presentation. Classic empiric treatment of neonatal meningitis consists of ampicillin and an aminoglycoside. Third-generation of cephalosporins (cefotaxime) has changed the empiric approach nowadays as they cover most pathogens in neonatal meningitis with the exceptions of the enterococci and Listeria monocytogenes. [32] Ineffective penetration of aminoglycosides into the cerebrospinal fluid will cause high morbidity and mortality in neonatal meningitis. Even though intrathecal and intraventricular administration of aminoglycosides have been performed, it fails to enhance the expected therapeutic results [33]. Ampicillin and chloramphenicol have been used for initial empiric therapy of childhood meningitis since the mid-1970s. Problems associated with these drugs include the possibility of chloramphenicol-associated aplastic anemia and the existence of Hemophilus influenzae type b resistance to both ampicillin and chloramphenicol. The uses of third-generation cephalosporins have been proven to be as effective as ampicillin and chloramphenicol in the treatment of childhood meningitis. [35]

In the empiric therapy for community acquired bacterial meningitis, especially among infants and children, it is important to cover Streptococcus Pneumoniae and Neisseria Meningitidis. Thus, third or fourth generation of cephalosporins (ceftriaxone or cefotaxime or ceftazidime) must be given with the combination of vancomycin. [36] Third-generation cephalosporins are effective against ampicillin- or chloramphenicol-resistant Haemophilus strains as well as many gram-negative bacteria in the Enterobacteriaceae group. [37] However, cefuroxime should be avoided because there has reports of delayed sterilization of CSF cultures associated with hearing loss in children. [36] Children of more than three months, adults of less than 50-year-old and those who have unknown immune deficiency should be treated empirically with cefotaxime or ceftriaxone in combination with vancomycin. The empiric treatment in community acquired bacterial meningitis in adults should cover...
S. pneumoniae and N. meningitidis. Corticosteroids will be used in the treatment as adjunctive therapy by administering intravenous dexamethasone. [18, 36] A study done by Sáez-Llorens and O’Ryan (2001) shows that cefepime is an important therapeutic option for the empiric treatment of bacterial meningitis in children due to its good clinical response and bacteriologic eradication rates observed. [38] Empiric therapy for community acquired bacterial meningitis in adults aged 50 years and above should be handled carefully. Such patients with normal renal function should be treated empirically with ceftriaxone or cefotaxime in combination with vancomycin and ampicillin. [36] A third-generation cephalosporin should be given even though in vitro tests show some degree of susceptibility or resistance to cephalosporins. This is because they may exert synergistic effects when given together with vancomycin. [39]

For post-neurosurgical patients, the antimicrobial spectrum must be focused on gram negative bacilli such as Pseudomonas aeruginosa and Staphylococcus aureus. The intravenous administration of cephalosporins should be third and fourth generations only because they have the coverage of gram negative bacilli meningitis. Cefazidime however is the only cephalosporin with good activity against P. aeruginosa in central nervous system. In addition, meropenem is useful for gram negative bacilli that produce extended-spectrum B-lactamases such as enterobacter species. Vancomycin is included in the therapy until the infection with staphylococci is completely treated. [36] For patients with impaired cellular immunity, the drug spectrum must be directed against Listeria monocytogenes, gram-negative bacilli as well as Streptococcus pneumonia. On the other hand, for patients with nosocomial meningitis, the drug spectrum must cover both gram-positive and gram-negative nosocomial pathogens. Appropriate regimens in patients with normal renal function, depending on the culture results and susceptibility testing, include vancomycin and ampicillin with combination of cefazidime, cefepime or meropenem. [18, 36]

**Antibiotic regimen for viral and fungal meningitis**

For meningitis involving virus, enteroviruses is one of the the most notorious group. For empiric treatment, the uses of the Acyclovir can be useful in disrupting the viral replication. It is because virus uses the active form of acyclovir to make its DNA. Acyclovir has high selectivity against such virus and increased antiviral activity. [40] Cryptococcal meningitis is the problem which can caused danger complication. In this case, lumbar puncture culture will provide a negative result and CT scan will provide bad prognosis. This type of meningitis will not induce a fever response. Hence, Amphotericin B and 5-fluorocytosine can be given for fungal infection as the first step. [41] Amphotericin B is capable of destroying fungal membrane by changing the osmotic pressure of the fungi. It has broad anti-fungal activity including Candida spp., Cryptococcus, Histoplasma, Blastomyces, Coccidioides, and Aspergillus speciess. Nevertheless, this drug can cause severe side effects, for instance, fever, chills, muscle spasm, headache, hypotension, hypokalaemia, and thrombophlebitis. This drug is adiministered by intravenous infusion. [42]

In some cases where the patient infected by Cryptococcus neoformans is suffering from slight azotaemia, intial treatment is not accompanied with Amphotericin B. Instead, fluconazole, itraconazole, miconazole and flucytosine are given to the patient. During the later phase, the Amphotericin B is given to improve the patient's clinical symptoms. [43] For 5-Flucytosine, it interrupts DNA synthesis therefore inhibiting fungal replication and protein synthesis. It is effective against Cryptococcus and some species of Candida. To increase the efficacy, it is used in combination with Amphotericin. This drug may have side effects like gastrointestinal upset, anæmias, nephrotoxicity, ataxia, and paraesthesias. [42] For 5-Flucytosine, it interrupts DNA synthesis therefore inhibiting fungal replication and protein synthesis. It is effective against Cryptococcus and some species of Candida. To increase the efficacy, it is used in combination with Amphotericin. This drug may have side effects like gastrointestinal upset, anæmias, nephrotoxicity, ataxia, and paraesthesias. [42]

**Properties of Antibiotic regimen**

Antibiotics used in this regimen must be able to enter CSF, possess bactericidal effect within CSF and retain its optimal pharmacodynamics properties. Poor outcomes have been observed clinically in patients receiving bacteriostatic therapy. Due to the limitation in CSF penetration, intravenous antibiotics have been used widely. The administration via oral route is avoided as the dose and tissue concentration is lower than the desired amount. However there is an exception for Rifampin as it gives synergism for treatment of meningitis caused by beta-lactam-resistant S. pneumoniae or coagulase-negative Staphylococcus. [44] Drug penetration depends on status of blood-brain barrier. Beta-lactams have poor penetration through the blood-brain barrier unless there is meningeval...
inflammation. The inflammation leads to the separation of intercellular tight junctions, increasing the number of pinocytotic vesicles in cerebral microvascular endothelial cells, enhancing the CSF penetration. As inflammation subsides, antibiotic entry will consequently decrease. Specific dosing is therefore recommended to maintain maximal concentrations in the CSF. [45]

For antibiotics that exhibit time-dependent antimicrobial activity (such as Beta-lactams, Vancomycin), the bactericidal activity will depend on the time that the agent is above the minimal inhibitory concentration (MIC). This will be a proportion of the dosing interval. [18] For agents that exhibit concentration-dependent antimicrobial activity (such as Aminoglycosides), it exhibits bactericidal property over a wide range of antimicrobial concentrations and there is a prolonged recovery period (such as the post-antibiotic effect) after drug concentrations fall below the MIC. [46]

**Adjunctive therapy**

Adjunctive therapy begins with the early intravenous administration of glucocorticoids, especially the dexamethasone. [18] The anti-inflammatory agent is used to reduce mortality and neurological sequel in bacterial meningitis. This makes it possible to reduce local inflammatory reactions that are responsible for cerebral oedema and therefore, reducing the morbidity and mortality in purulent meningitis. Most cases have significant improvement of outcomes in children and adults with acute bacterial meningitis regardless of the causative organism. [47, 48] It should be given immediately before or at the same time with the first dose of antibiotics. [18]

The most important aspect is to avoid delays in administering antibiotics therapy and the choice of drug. Any delay in the administration of antibiotics will cause high case fatality. Indeed, greater delays results in higher case fatality rates. [48] In a study, it shows that a delay in antibiotic treatment of more than three hours after hospital admission will ultimately result in high mortality. Furthermore, delayed therapy is a greater risk factor than the isolation of a penicillin-resistant strain or a higher disease severity. [18]

**Mechanisms of Drug Action**

Ampicillin/ amoxicillin – Ampicillin and amoxicillin are aminopenicillins under the group of Penicillin. In comparison with ampicillin, amoxicillin is absorbed better and has higher bioavailability. Amoxicillin is useful in the infection of meningitis caused by streptococcus bacteria.

Penicillin G – The cross-linking of peptidoglycans, also known as Stage 3 in bacterial cell wall synthesis is inhibited by penicillins. Penicillins will bind to the penicillin-binding protein and will block its active site. Cross-linking usually takes place with the help of transpeptidase but when penicillin is given, transpeptidation step of peptidoglycan cannot take place.

Cefotaxime – Third-generation cephalosporins (I and ii) bind to penicillin binding proteins, which lead to cell lysis.[49]

Ceftriaxone – It is useful to treat community-acquired bacterial meningitis which is caused by streptococcus pneumonia. It kills the growth of bacterial meningitis by inhibiting bacterial cell wall synthesis. Thus, the cell wall becomes weakened and bursts. [50]

Gentamicin – Gentamicin is useful for meningitis caused by G-ve bacteria. It is classified under Aminoglycosides, where there are two mechanisms of action. First, they bind to the 30S subunit of the ribosome and interfere with protein biosynthesis by interrupting amino acid polymerization and elongation. When incorrect amino acids are produced, the original DNA sequence will be altered and results in nonsensical proteins. Nonsensical proteins will disrupt the vital cell functions and result in cell death. Gentamicin is used together with penicillin to treat bacterial meningitis caused by Streptococcus pneumoniae.

Vancomycin -Vancomycin is a Stage II inhibitor of cell wall synthesis of bacteria. Vancomycin is large glycoprotein molecule and therefore cannot enter the cell membrane of Gram negative bacteria. Therefore, Vancomycin can only treat meningitis caused by Gram positive streptomycyes species. It is a last resort where all other drugs do not induce any response due to antibiotic resistance. [49]

Rifampin – Rifampin is effective against Mycobacterium species including M. tuberculosis, M. kansasii and gram negative bacteria for example N. Meningitidis. Rifampin is usually given in combination therapy with other antibacterial drugs. They inhibit DNA-dependent bacterial RNA polymerase to prevent RNA synthesis in susceptible bacteria. Rifampin usually attacks the b-subunit of the enzyme, which is the main target for action. [51]

Tetracyclines- The tetracyclines target is the 30S ribosome of the bacteria where binding of aminoacyl-t-RNA to the acceptor site on the mRNA is inhibited. Tetracyclines enter cells by the mode of active transport.

Chloramphenicol - These antimicrobials bind to the 50S ribosome and inhibit peptidyl transferase activity by preventing amino-acyl-transfer RNA from attaching to the binding site. Thus, the peptide bond formation is inhibited. As a result, protein synthesis is inhibited. It
inhibits bacteria protein synthesis but not inhibit nucleic acid synthesis. [52] 

Trimethoprim-sulfamethoxazole (TMP, SMX) – The combination of these two drugs act on the bacteria by inhibiting the enzyme system in tetrahydrofollic (THF) acid synthesis in the bacteria. SMX inhibit hydrofolic acid synthesis, an intermediate for the THF formation. TMP prevent the formation of THF by binding to bacterial dihydrofotolate reductase. [53, 54, 55]

Amphotericin B – It acts on the fungal cell membrane by disturbing the cell membrane that lead to leakage of ions and small molecules which can kill or damage the fungal cells. [56]

Common settings people acquired Meningitis

The common settings in meningitis-infections are the hospital setting, community setting and by road accidents. Meningitis can be acquired based on different agent of infection whether bacteria, fungal or viral.

There is a high risk for acquiring meningitis in community setting. For instance, the risk for those getting infected is higher living in the same home or stay in day-care centre. The risk also increases with direct contact of oral secretions of an infected person. [57] For viral meningitis caused by Enteroviruses usually spread via faecal contamination and respiratory secretions. People can be infected via fecal contamination due to improper hand washing after changing a diaper or using the washroom. Besides that, viral meningitis can also spread via direct and indirect contact with respiratory secretions such as saliva, sputum or mucus. [57] There are nosocomial organisms present in the upper respiratory tract which can cause viral infection. This virus such as Haemophilus influenza can invade into the bloodstream and thus penetrate blood-brain barrier to reach subarachnoid space. If there is an infection in the paranasal or middle ear, bacteria can spread the infection to the meninges and cause meningitis. [62] For example, when an infected person sneezes or coughs within a certain distance near us, we might get infected. In other hand, fungal meningitis caused by Cryptococcus transmitted via inhaling bird droppings-contaminated soil. Most of meningitis-related fungus is transmitted through soil which is rich in decaying organic matter. The fungal spores can be spread and inhale once the soil environment containing these funguses is interrupted. [57]

Another meningitis-acquired common setting is hospital setting. The infection can occur during surgery operation or prolong exposure to the hospital environment. Usually the organism involved in infections in hospital setting is Candida sp.[57] Thus, the different health statuses of patients in the same hospital lead to a higher tendency of spreading of meningitis. [62] The usage of not 100% sterile equipments may carry the meningitis causative agents. The incidence of postcraniotomy (after surgery of opening skulls) infection was 4% and the most common infection is meningitis in the latest study in France. [58] Transmission of meningitis is usually by direct close contact from one patient to other patients in the hospital as well as by droplet. Besides that, patients who have a weak immune system have a high risk to get infected by bacterial meningitis in the hospital. [63]

Meningitis also happens resulting from a physical head injury due to a road accident. Subsequently, it leads to damaging the meninges or adjacent structures due to skull fracture. Commonly, Staphylococci pneumonia which is present in the external environment can cause this meningitis following a severe of cranial and intracranial injuries. [62] For example, an opening can be formed between the nasal sinuses and the subarachnoid space due to a serious skull fracture. The subarachnoid space release proinflammatory mediators which causes central nervous system inflammation. Thus, the intracranial pressure increases and thus the bacteria can penetrate the blood-brain barrier and infect the meninges easily. [61] Since there is no immediate surgery or action towards the open fracture, the meninges gets infected and contaminated easily. Even though meningitis is an infectious disease, it still can be prevented by several precautions. One of them is through vaccination. Currently, there are three types of vaccination available which are meningococcal group C conjugate vaccine, H influenzae type B conjugate vaccine, and pneumococcal conjugate vaccines. However, these three vaccines must be combined together to be effective against causative agent of meningitis. [59] On the other hand, detection of risk factors possessed by the patient in every surgery operation in hospital setting can allow respective adoption of prophylactic and therapeutic interventions to reduce of surgery site infections. [60] There are some precautions such as ensuring the private room of patient is closed every time to prevent the transmission of bacteria to other area. Besides that, patients who are infected by the similar meningitis disease may share same room since the numbers of private rooms are insufficient. The spreading of meningitis through nosocomial and droplet
transmission can be prevented by wearing a safety mask. Other precautions include limiting the area for movement or transport of meningitis patient. [63]

Conclusion
In a nutshell, meningitis is caused by bacteria, non-bacteria organisms and also viruses. Therefore, it is essential to determine the causative agent of meningitis before the administration of any medication in order to prevent multi-drug resistant strains. The public should also increase awareness regarding the signs and symptoms of meningitis so that treatment can be given in the fastest way possible to prevent any delays. It is hoped that with the knowledge and discovery of these studies, others may understand meningitis further and will be aware that meningitis can be treated within the right time and right medication so that patients infected with meningitis will no longer have a high mortality rate.

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Illustrations

Illustration 1

Figure 1

The bacteria live naturally in the back of our noses and throats and do not live long outside the body.

The bacteria spread through the sharing saliva (kissing, sharing of drinks).

The bacteria travel into the bloodstream.

The bacteria can diffuse across blood brain barrier and diffuse into the cerebrospinal fluid (CSF).

The bacteria will attack brain tissue or meninges. Specific bacteria will induce apoptosis in the neuronal fibers.

The meninges become swollen, the pressure increases in the skull blocks the flow of blood in the brain thus decreasing the nutrients needed by the brain.

Signs and symptoms: emerged such as fever, severe headache, neck stiff, and neck pain. Other symptoms includes photophobia, nausea and vomiting. Furthermore they may experience lethargy, confusion and delusion.

Need to seek medical treatment immediately because it can caused death in 24 hours.

Figure 1: The path of meningitis affects a healthy person. It is a viral disease and can cause high mortality.
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