

Wound Healing Process, Phases of Wound Healing and Risk Factors: A Review

Parul Nigam*, Shubham Goyal

ACME Research Solutions

Abstract: Meningitis is a serious infection of the meninges, the thin layers of tissue that surround and protect the brain and spinal cord. Although most cases of meningitis are caused by viruses, bacteria can also cause this potentially life-threatening condition. Streptococcus pneumonia is a type of bacteria that is a common cause of meningitis, particularly in young children and adults over age 65. This bacterium can also cause other serious infections, such as pneumonia and blood poisoning (sepsis). Symptoms of meningitis can include headache, stiff neck, fever, confusion, and seizures. Meningitis is most often caused by infections with viruses or bacteria, but can also be caused by other things like cancer or certain drugs. Treatment for meningitis generally includes antibiotics or antiviral drugs, depending on the cause.

Keywords: Meningitis, Meningitis Causes, Meningitis Symptoms, Streptococcus Pneumonia

Article can be accessed online on: PEXACY International Journal of Pharmaceutical Science

DOI: 10.5281/zenodo.7013456

Update: Received on 18 August, 2022; Accepted, 20 August, 2022; Published on 21 August, 2022,
Consolidated December 2022 Issue on [02 December, 2022]

INTRODUCTION

When an object pierces the skin, it creates a wound. The depth of the wound depends on the object that caused it. A shallow wound may only damage the outer layer of skin, while a deep wound can penetrate all the way to the bone. A wound can have a significant impact on

a person's life, depending on its severity. A minor wound may heal quickly and cause little inconvenience, while a more serious one may take weeks or months to recover from and may require hospitalization. In some cases, a wound can lead to permanent disability or even death.

Wound healing is a natural process wherein the skin or any other injured part of the body repairs itself. It is a complex process that involves various steps like inflammation, formation of new tissue, etc. The process of wound healing can be divided into three phases: inflammatory, proliferative, and maturation. The inflammatory phase occurs immediately after injury and is characterized by the release of cytokines, growth factors, and enzymes that promote tissue repair. The proliferative phase is characterized by cell proliferation and extracellular matrix synthesis. This phase lasts for approximately 2-3 weeks following injury. The final stage of wound healing, maturation is characterized by remodeling of the extracellular matrix and collagen.

Types of Wound

There are four types of wounds: incised, lacerated, punctured, and avulsion. Incised wounds are caused by a clean, sharp-edged object like a knife or razor. Lacerations are ragged tears in the skin caused by a blunt force. Punctures are small, deep holes caused by something sharp, like a nail or needle. Avulsions

occur when part of the body is torn away from the rest, usually by trauma. [13].

Incised wound

Incised wound is caused by a sharp object, like a knife, slicing through the skin. It's a clean cut with well-defined edges. Incised wounds are deep cuts that go through all the layers of the skin.

Lacerated Wound

A lacerated wound is a deep cut or tearing of the skin. Lacerations can occur from sharp objects, such as knives or glass, or from blunt trauma, such as a punch or fall. Depending on the depth and location of the laceration, they can be quite painful and may require stitches or other medical treatment

Punctured Wound

Punctured wound is a deep cut that penetrates the skin and underlying tissues. It is caused by a sharp object, such as a nail or knife. The most common type of punctured wound is a

stab wound, which is usually inflicted with a sharp object, such as a knife.

Avulsion Wound

An avulsion wound is a type of traumatic injury that occurs when an external force tears a body part away

Stages of Wound

Stages of wound healing are haemostasis, inflammation, proliferation and remodeling. Each stage is characterized by different events which lead to successful healing. Haemostasis occurs immediately after injury where blood vessels constrict to stop bleeding. Inflammation follows where repair cells and antibodies are attracted to the site of injury.

Proliferation is when new tissue starts to form and remodeling is the final stage where tissues heal and scarring may occur. Stages of wound healing are haemostasis, inflammation, proliferation and remodeling. Each stage is characterized by different events which lead to successful healing. Haemostasis occurs immediately after injury where blood vessels constrict to stop bleeding. Inflammation follows where repair cells and antibodies are attracted to the site of injury. Proliferation is when new

from the rest of the body. This can occur when a limb is severed by an accident or when clothing or jewelry gets caught on something and pulls off the skin. Avulsion wounds are usually very painful and can result in significant blood loss.

tissue starts to form and remodeling is the final stage where tissues heal and scarring may occur.

Diagnosis

Meningitis is diagnosed through a spinal tap to look for increased white blood cells and inflammation in the cerebrospinal fluid [22]. A lumbar puncture is performed by numbing the lower back and inserting a needle between the vertebrae into the spinal canal. A small amount of cerebrospinal fluid is removed and sent to a laboratory for analysis. The procedure is also called a spinal tap [23].

A lumbar puncture, also known as a spinal tap, is a diagnostic procedure used to collect cerebrospinal fluid (CSF) for testing. CSF surrounds and cushions the brain and spinal cord and helps to remove waste products from these organs [24]. During a lumbar puncture, a thin needle is inserted into the lower back, between the

spine's bones, and into the CSF-filled space around the brain and spinal cord. A small amount of CSF is then withdrawn for testing [25].

Pathogenesis of Meningitis

Streptococcus pneumoniae is spread through contact with respiratory secretions, such as saliva, mucus, or cough droplets from an infected person [26]. The bacteria can also be spread through contact with objects or surfaces contaminated with respiratory secretions. Once inside the body, *Streptococcus pneumoniae* colonizes the upper respiratory tract and begins to multiply. In some cases, the bacteria invade more profound into the lungs, where they can cause pneumococcal pneumonia, a severe lung infection [27].

In other cases, *S. pneumoniae* invades the bloodstream and spreads to other body parts, including the meninges (the protective membranes covering the brain and spinal cord) [28]. This invasion of Meningitis is an infection of the meninges, the protective layer surrounding the brain and spinal cord. Meningitis caused by *Streptococcus pneumoniae* is the most common type of meningitis [26].

Streptococcus pneumoniae is a bacterium that can cause several different infections,

including meningitis [29]. When *Streptococcus pneumoniae* infects someone's lungs, it can spread to their bloodstream and other body parts. This is how *Streptococcus pneumoniae* can cause meningitis in people with other health conditions, such as diabetes or HIV/AIDs. People usually get strep throat (a throat infection caused by *Streptococcus pneumoniae*) around the time they are exposed to other people [30].

Etiology of Meningitis

Wound etiology is important to consider when treating a patient with an ulcer. Ischemia, venous disease, and arterial insufficiency are the most common etiologies of wounds. The practitioner must also be aware of other potential causes, such as diabetes, trauma, infection, and neoplasm. Treatment will vary depending on the underlying cause of the wound. For example, a wound caused by ischemia will require revascularization while a wound caused by infection will require antibiotics. The practitioner must also take into account the patient's comorbidities and individual circumstances when formulating a treatment plan."The importance of considering wound etiology cannot be understated. When treating patients with

ulcers, it is crucial to first identify the underlying cause of the wound. Ischemia, venous disease, and arterial insufficiency are the most common etiologies of wounds; however, other potential causes such as diabetes, trauma, infection, and neoplasm must also.

Phases of Meningitis

Adhesion

Pneumococcal meningitis is the presence of *S. pneumoniae* bacteria in the nasopharynx. These bacteria can colonize the nasopharynx by binding to epithelial cells via adhesion [39]. Once these bacteria have colonized the nasopharynx, they can invade the bloodstream and cause meningitis. The symptoms of pneumococcal meningitis include headache, stiff neck, and fever. If left untreated, this disease can lead to death [40].

Invasion

The second step in initiating pneumococcal meningitis is the invasion of bacteria into the bloodstream [41]. This step is facilitated by several virulence factors possessed by the bacteria. Pneumococci can attach to and invade various host cells, including endothelial and epithelial cells.

The interaction between the bacterial surface proteins and receptors on host cells allows for the entry of the bacteria into the host cell. Once inside the host cell, *Streptococcus pneumoniae* can multiply and spread to other nearby cells [42].

CNS invasion

CNS invasion by tumour cells is a hallmark of high-grade brain tumour and the main reason these tumour are so difficult to treat. The blood-brain barrier (BBB) protects the CNS from foreign invaders, but cancer cells can exploit this barrier and invade the brain. Once inside the brain, tumour cells can grow and spread quickly, leading to serious neurological problems and death [43]. There are currently no effective treatments for CNS invasion by tumour cells, which is why preventing this tumour from developing in the first place is essential.

CNS invasion in meningitis can lead to cerebral abscesses, and pus-filled lesions that form in the brain. These abscesses can cause a range of symptoms, including headaches, seizures, and changes in mental status. If not treated promptly, cerebral abscesses can be fatal [44].

Neuronal Injury

Neuronal injury in meningitis results from the release of pro-inflammatory cytokines and chemokine, which recruit and activate leukocytes, resulting in direct injury to neurons. Cytotoxic T cells are also activated in meningitis and can damage neurons directly. The death of neurons leads to cerebral edema and increased intracranial pressure, which can further damage brain tissue [45].

Treatment

Meningitis is a serious, life-threatening illness. Early diagnosis and treatment is essential. Treatment usually involves hospitalization and antibiotics [46]. In some cases, corticosteroids may also be used to reduce inflammation. If meningitis is caused by a bacterial infection, the patient will usually be given intravenous (IV) antibiotics [47].

If the patient has a viral infection, they will usually be treated with supportive care to help relieve symptoms [48]. Meningitis is a serious condition that can lead to death if not treated early. The mainstay of treatment for meningitis is antibiotics, which must be

given intravenously if the patient has a bacterial infection. Corticosteroids may also be used in some cases to reduce inflammation around the brain and spinal cord. Patients with meningitis caused by a viral infection will typically receive supportive care to help manage their symptoms [49].

Bactericidal therapy targeting Gram-positive bacteria is the mainstay of treatment for serious *S. aureus* infections, with Vancomycin being the agent most commonly used. However, the emergence of Vancomycin-resistant strains of *S. aureus* (VRSA) has limited the usefulness of this drug [50]. Linezolid is an alternative bactericidal therapy with activity against Gram-positive bacteria, including VRSA. This agent inhibits protein synthesis by binding to bacterial ribosomes. Clinical studies have demonstrated that linezolid is effective in the treatment of various types of infections caused by Gram-positive bacteria, including VRSA infections [51].

Ampicillin plus Broad-spectrum Cephalosporin

Ampicillin and cephalosporin mechanism of action are very similar and used in the treatment of *S. agalactiae*, *E. coli*, or *L.*

monocytogenes [52]. Both drugs are beta-lactam antibiotics that work by inhibiting bacterial cell wall synthesis. This ultimately leads to cell death. Both bind to and inhibit bacterial penicillin-binding proteins (PBPs) [53].

PBPs are enzymes involved in the final stages of peptidoglycan synthesis, which is an important component of the bacterial cell wall. By inhibiting PBPs, ampicillin and Cephalosporins prevent the cross-linking of peptidoglycans, leading to cell lysis [54]. The main difference between the two drugs is their spectrum of activity. Ampicillin has a narrower spectrum of activity than cephalosporin and is effective against gram-positive bacteria while cephalosporin has a broader spectrum of activity and is effective against both gram-positive and gram-negative bacteria [54].

Ampicillin plus Broad-spectrum Cephalosporin

Ceftazidime is a third generation cephalosporin antibiotic. It is active against most gram-negative bacteria including *Pseudomonas aeruginosa*, *S. pneumoniae*, *L. monocytogenes*, or

Gram-negative bacilli [51]. Ceftazidime has good activity against many Gram-

positive bacteria, with the exception of methicillin-resistant *Staphylococcus aureus* (MRSA). The bactericidal action of Ceftazidime results from interference with bacterial cell wall synthesis [55].

Vancomycin plus Ceftazidime

Vancomycin inhibits bacterial cell-wall synthesis by binding to one or more of the components (peptidoglycan precursors) required for peptidoglycan assembly [55]. This action leads to lethal wall distortion and eventual osmotic lysis of the bacteria. Vancomycin has little activity against Gram-positive bacteria (*Staphylococci*, gram-negative bacilli, or *S. pneumoniae*) that have already acquired a thick peptidoglycan layer [56].

Both Vancomycin and Ceftazidime work by inhibiting bacterial cell wall synthesis. Vancomycin does this by binding to the peptidoglycan component of the cell wall, while Ceftazidime inhibits the activity of enzymes involved in cell wall synthesis. This action leads to the death of the bacteria [57].

Broad-spectrum Cephalosporin

Cephalosporin mechanism of action is similar to that of penicillin and work

against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae*. They are bactericidal agents that work by inhibiting bacterial cell wall synthesis [58]. More specifically, they bind to and inhibit enzymes (penicillin-binding proteins) required for the cross-linking of peptidoglycans in the bacterial cell wall. This leads to the weakening of the cell wall, which causes it to rupture and lyse [59].

Cephalosporins are classified into four generations based on their spectrum of activity. The first-generation Cephalosporins have a limited spectrum of activity and are mostly active against Gram-positive bacteria, with some activity against Gram-negative bacteria [57]. The second-generation Cephalosporins have a broader spectrum of activity and are more active against Gram-negative bacteria than

first-generation Cephalosporins. The third-generation Cephalosporins have an even broader spectrum of activity and are also active against some species of *Enterobacteriaceae* [60].

Conclusion

Meningitis is a severe infection of the brain and spinal cord. It can occur in people of any age but is most common in infants and young children. Early diagnosis and treatment are essential to avoid permanent damage or death. Meningitis can be caused by several different bacteria, viruses, and other organisms. The most common cause in the developed world is viral meningitis, which usually resolves without lasting effects. Bacterial meningitis is much more severe, often resulting in death or permanent disability if not treated promptly with antibiotics.

References

1. Tattevin, P., Tchamgoué, S., Belem, A., Bénézit, F., Pronier, C., & Revest, M. (2019). Aseptic meningitis. *Revue neurologique*, 175(7-8), 475-480.
2. Seddon, J. A., Tugume, L., Solomons, R., Prasad, K., Bahr, N. C., & Tuberculous Meningitis International Research Consortium. (2019). The current global situation for tuberculous meningitis: epidemiology, diagnostics, treatment and outcomes. *Wellcome open research*, 4.
3. Moriguchi, T., Harii, N., Goto, J., Harada, D., Sugawara, H.,

- Takamino, J., ... & Shimada, S. (2020). A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *International journal of infectious diseases*, 94, 55-58.
4. Wilson, M. R., Sample, H. A., Zorn, K. C., Arevalo, S., Yu, G., Neuhaus, J., ... & Chiu, C. Y. (2019). Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. *New England Journal of Medicine*, 380(24), 2327-2340.
 5. Jarvis, J. N., Lawrence, D. S., Meya, D. B., Kagimu, E., Kasibante, J., Mpoza, E., ... & Harrison, T. S. (2022). Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. *New England Journal of Medicine*, 386(12), 1109-1120.
 6. Soeters, H. M., Diallo, A. O., Bicaba, B. W., Kadadé, G., Dembélé, A. Y., Acyl, M. A., ... & MenAfriNet Consortium. (2019). Bacterial meningitis epidemiology in five countries in the meningitis belt of sub-Saharan Africa, 2015–2017. *The Journal of infectious diseases*, 220(Supplement_4), S165-S174.
 7. Young, N., & Thomas, M. (2018). Meningitis in adults: diagnosis and management. *Internal medicine journal*, 48(11), 1294-1307.
 8. McGill, F., Griffiths, M. J., Bonnett, L. J., Geretti, A. M., Michael, B. D., Beeching, N. J., ... & Martin, W. (2018). Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *The Lancet Infectious Diseases*, 18(9), 992-1003.
 9. Naz, S., Hanif, M., Haider, M. A., Ali, M. J., Ahmed, M. U., & Saleem, S. (2020). Meningitis as an initial presentation of COVID-19: a case report. *Frontiers in Public Health*, 8, 474.
 10. Alamarat, Z., & Hasbun, R. (2020). Management of acute bacterial meningitis in children. *Infection and Drug Resistance*, 13, 4077.
 11. Donovan, J., Figaji, A., Imran, D., Phu, N. H., Rohlwick, U., & Thwaites, G. E. (2019). The

- neurocritical care of tuberculous meningitis. *The Lancet Neurology*, 18(8), 771-783.
12. Davis, A. G., Rohlwick, U. K., Proust, A., Figaji, A. A., & Wilkinson, R. J. (2019). The pathogenesis of tuberculous meningitis. *Journal of leukocyte biology*, 105(2), 267-280.
13. Rajasingham, R., Wake, R. M., Beyene, T., Katende, A., Letang, E., & Boulware, D. R. (2019). Cryptococcal meningitis diagnostics and screening in the era of point-of-care laboratory testing. *Journal of clinical microbiology*, 57(1), e01238-18.
14. Méchaï, F., & Bouchaud, O. (2019). Tuberculous meningitis: challenges in diagnosis and management. *Revue neurologique*, 175(7-8), 451-457.
15. Molloy, S. F., Kanyama, C., Heyderman, R. S., Loyse, A., Kouanfack, C., Chanda, D., ... & Harrison, T. S. (2018). Antifungal combinations for treatment of cryptococcal meningitis in Africa. *New England Journal of Medicine*, 378(11), 1004-1017.
16. Novak, R. T., Ronveaux, O., Bitá, A. F., Aké, H. F., Lessa, F. C., Wang, X., ... & Fox, L. M. (2019). Future directions for meningitis surveillance and vaccine evaluation in the meningitis belt of sub-Saharan Africa. *The Journal of infectious diseases*, 220(Supplement_4), S279-S285.
17. Patel, J. C., Soeters, H. M., Diallo, A. O., Bicaba, B. W., Kadadé, G., Dembélé, A. Y., ... & MenAfriNet Consortium. (2019). MenAfriNet: a network supporting case-based meningitis surveillance and vaccine evaluation in the meningitis belt of Africa. *The Journal of infectious diseases*, 220(Supplement_4), S148-S154.
18. Palacios, C. F., & Saleeb, P. G. (2020). Challenges in the diagnosis of tuberculous meningitis. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 20, 100164.
19. Mohanty, T., Fisher, J., Bakochi, A., Neumann, A., Cardoso, J. F. P., Karlsson, C. A., ... & Linder, A. (2019). Neutrophil extracellular traps in the central nervous system hinder

- bacterial clearance during pneumococcal meningitis. *Nature communications*, 10(1), 1-13.
20. Donovan, J., Cresswell, F. V., Thuong, N. T. T., Boulware, D. R., Thwaites, G. E., & Bahr, N. C. (2020). Xpert MTB/RIF ultra for the diagnosis of tuberculous meningitis: a small step forward. *Clinical Infectious Diseases*, 71(8), 2002-2005.
21. Tenforde, M. W., Gertz, A. M., Lawrence, D. S., Wills, N. K., Guthrie, B. L., Farquhar, C., & Jarvis, J. N. (2020). Mortality from HIV-associated meningitis in sub-Saharan Africa: a systematic review and meta-analysis. *Journal of the International AIDS Society*, 23(1), e25416.
22. Wilson, M. R., O'Donovan, B. D., Gelfand, J. M., Sample, H. A., Chow, F. C., Betjemann, J. P., ... & DeRisi, J. L. (2018). Chronic meningitis investigated via metagenomic next-generation sequencing. *JAMA neurology*, 75(8), 947-955.
23. Ellis, J., Bangdiwala, A. S., Cresswell, F. V., Rhein, J., Nuwagira, E., Ssebambulidde, K., ... & Boulware, D. R. (2019, October). The changing epidemiology of HIV-associated adult meningitis, Uganda 2015–2017. In *Open forum infectious diseases* (Vol. 6, No. 10, p. ofz419). US: Oxford University Press.
24. Ribeiro, M. H. D. M., Mariani, V. C., & dos Santos Coelho, L. (2020). Multi-step ahead meningitis case forecasting based on decomposition and multi-objective optimization methods. *Journal of Biomedical Informatics*, 111, 103575.
25. Xu, M., Hu, L., Huang, H., Wang, L., Tan, J., Zhang, Y., ... & Huang, L. (2019). Etiology and clinical features of full-term neonatal bacterial meningitis: a multicenter retrospective cohort study. *Frontiers in pediatrics*, 7, 31.
26. Lee, S. H., Chen, S. Y., Chien, J. Y., Lee, T. F., Chen, J. M., & Hsueh, P. R. (2019). Usefulness of the FilmArray meningitis/encephalitis (M/E) panel for the diagnosis of

- infectious meningitis and encephalitis in Taiwan. *Journal of Microbiology, Immunology and Infection*, 52(5), 760-768.
27. Boudet, A., Pantel, A., Carles, M. J., Boclé, H., Charachon, S., Enault, C., ... & Marchandin, H. (2019). A review of a 13-month period of FilmArray Meningitis/Encephalitis panel implementation as a first-line diagnosis tool at a university hospital. *PLoS One*, 14(10), e0223887.
28. Gudina, E. K., Tesfaye, M., Wieser, A., Pfister, H. W., & Klein, M. (2018). Outcome of patients with acute bacterial meningitis in a teaching hospital in Ethiopia: a prospective study. *PLoS One*, 13(7), e0200067.
29. Hlebowicz, M., Jakubowski, P., & Smiatacz, T. (2019). Streptococcus suis meningitis: epidemiology, clinical presentation and treatment. *Vector-Borne and Zoonotic Diseases*, 19(8), 557-562.
30. Susilawathi, N. M., Tarini, N. M. A., Fatmawati, N. N. D., Mayura, P. I., Suryapraba, A. A. A., Subrata, M., ... & Mahardika, G. N. (2019). Streptococcus suis-associated meningitis, Bali, Indonesia, 2014–2017. *Emerging Infectious Diseases*, 25(12), 2235.
31. Liesman, R. M., Strasburg, A. P., Heitman, A. K., Theel, E. S., Patel, R., & Binnicker, M. J. (2018). Evaluation of a commercial multiplex molecular panel for diagnosis of infectious meningitis and encephalitis. *Journal of clinical microbiology*, 56(4), e01927-17.
32. Fernandez, K., Lingani, C., Aderinola, O. M., Goumbi, K., Bicaba, B., Edea, Z. A., ... & Ronveaux, O. (2019). Meningococcal meningitis outbreaks in the African meningitis belt after meningococcal serogroup A conjugate vaccine introduction, 2011–2017. *The Journal of infectious diseases*, 220(Supplement_4), S225-S232.
33. Bodilsen, J., Storgaard, M., Larsen, L., Wiese, L., Helweg-Larsen, J., Lebech, A. M., ... & DASGIB Study Group. (2018). Infectious meningitis and encephalitis in adults in

- Denmark: a prospective nationwide observational cohort study (DASGIB). *Clinical Microbiology and Infection*, 24(10), 1102-e1.
34. Assegu Fenta, D., Lemma, K., Tadele, H., Tadesse, B. T., & Derese, B. (2020). Antimicrobial sensitivity profile and bacterial isolates among suspected pyogenic meningitis patients attending at Hawassa University Hospital: Cross-sectional study. *BMC microbiology*, 20(1), 1-10.
35. Green, D. A., Pereira, M., Miko, B., Radmard, S., Whittier, S., & Thakur, K. (2018). Clinical significance of human herpesvirus 6 positivity on the FilmArray meningitis/encephalitis panel. *Clinical Infectious Diseases*, 67(7), 1125-1128.
36. Tucker, E. W., Pieterse, L., Zimmerman, M. D., Udawadia, Z. F., Peloquin, C. A., Gler, M. T., ... & Dooley, K. E. (2019). Delamanid central nervous system pharmacokinetics in tuberculous meningitis in rabbits and humans. *Antimicrobial agents and chemotherapy*, 63(10), e00913-19.
37. Poley, M., Koubek, R., Walsh, L., & McGillen, B. (2019). Cryptococcal meningitis in an apparent immunocompetent patient. *Journal of Investigative Medicine High Impact Case Reports*, 7, 2324709619834578.
38. Tugume, L., Rhein, J., Hullsiek, K. H., Mpoza, E., Kiggundu, R., Ssebambulidde, K., ... & Boulware, D. R. (2019). HIV-associated cryptococcal meningitis occurring at relatively higher CD4 counts. *The Journal of infectious diseases*, 219(6), 877-883.
39. Ramalho, E., Sousa Jr, I., Burlandy, F., Costa, E., Dias, A., Serrano, R., ... & da Silva, E. E. (2019). Identification and phylogenetic characterization of human enteroviruses isolated from cases of aseptic meningitis in Brazil, 2013–2017. *Viruses*, 11(8), 690.
40. Tubiana, S., Varon, E., Biron, C., Ploy, M. C., Mourvillier, B., Taha, M. K., ... & Martin-Blondel, G. (2020). Community-acquired

- bacterial meningitis in adults: in-hospital prognosis, long-term disability and determinants of outcome in a multicentre prospective cohort. *Clinical Microbiology and Infection*, 26(9), 1192-1200.
41. Dien Bard, J., & Alby, K. (2018). Point-counterpoint: meningitis/encephalitis syndromic testing in the clinical laboratory. *Journal of Clinical Microbiology*, 56(4), e00018-18.
42. Kawamoto, M., Murakami, Y., Kinoshita, T., & Kohara, N. (2018). Recurrent aseptic meningitis with PIGT mutations: a novel pathogenesis of recurrent meningitis successfully treated by eculizumab. *Case Reports*, 2018, bcr-2018.
43. Davis, A., Meintjes, G., & Wilkinson, R. J. (2018). Treatment of tuberculous meningitis and its complications in adults. *Current treatment options in neurology*, 20(3), 1-15.
44. Molloy, S. F., Kanyama, C., Heyderman, R. S., Loyse, A., Kouanfack, C., Chanda, D., ... & Harrison, T. S. (2018). Antifungal combinations for treatment of cryptococcal meningitis in Africa. *New England Journal of Medicine*, 378(11), 1004-1017.
45. Thee, S., Basu Roy, R., Blázquez-Gamero, D., Falcón-Neyra, L., Neth, O., Noguera-Julian, A., ... & ptbnet TB Meningitis Study Group. (2021). Treatment and Outcome in Children With Tuberculous Meningitis: A Multicenter Pediatric Tuberculosis Network European Trials Group Study. *Clinical Infectious Diseases*.
46. Tenforde, M. W., Shapiro, A. E., Rouse, B., Jarvis, J. N., Li, T., Eshun-Wilson, I., & Ford, N. (2018). Treatment for HIV-associated cryptococcal meningitis. *Cochrane Database of Systematic Reviews*, (7).
47. Liu, Z. Y., Wang, G. Q., Zhu, L. P., Lyu, X. J., Zhang, Q. Q., Yu, Y. S., ... & Li, T. S. (2018). Expert consensus on the diagnosis and treatment of cryptococcal meningitis. *Zhonghua nei ke za zhi*, 57(5), 317-323.
48. Pavan, C., LR Xavier, A., Ramos, M., Fisher, J., Kritsilis, M., Linder, A., ... & Lundgaard, I. (2021).

- DNase treatment prevents cerebrospinal fluid block in early experimental pneumococcal meningitis. *Annals of Neurology*, 90(4), 653-669.
49. Hlebowicz, M., Jakubowski, P., & Smiatacz, T. (2019). Streptococcus suis meningitis: epidemiology, clinical presentation and treatment. *Vector-Borne and Zoonotic Diseases*, 19(8), 557-562.
50. Cresswell, F. V., Meya, D. B., Kagimu, E., Grint, D., Te Brake, L., Kasibante, J., ... & Elliott, A. M. (2021). High-dose oral and intravenous rifampicin for the treatment of tuberculous meningitis in predominantly human immunodeficiency virus (HIV)-positive Ugandan adults: A phase ii open-label randomized controlled trial. *Clinical Infectious Diseases*, 73(5), 876-884.
51. Luo, M., Wang, W., Zeng, Q., Luo, Y., Yang, H., & Yang, X. (2018). Tuberculous meningitis diagnosis and treatment in adults: A series of 189 suspected cases. *Experimental and therapeutic medicine*, 16(3), 2770-2776.
52. Mashau, R. C., Meiring, S. T., Quan, V. C., Nel, J., Greene, G. S., Garcia, A., ... & Ngubane, W. (2022). Outcomes of flucytosine-containing combination treatment for cryptococcal meningitis in a South African national access programme: a cross-sectional observational study. *The Lancet Infectious Diseases*.
53. Hope, W., Stone, N. R., Johnson, A., McEntee, L., Farrington, N., Santoro-Castelazo, A., ... & Bicanic, T. (2019). Fluconazole monotherapy is a suboptimal option for initial treatment of cryptococcal meningitis because of emergence of resistance. *MBio*, 10(6), e02575-19.
54. Lewin, J. J., Cook, A. M., Gonzales, C., Merola, D., Neyens, R., Peppard, W. J., ... & Ziai, W. C. (2019). Current practices of intraventricular antibiotic therapy in the treatment of meningitis and ventriculitis: results from a multicenter retrospective cohort study. *Neurocritical care*, 30(3), 609-616.

55. Smilnak, G. J., Charalambous, L. T., Cutshaw, D., Premji, A. M., Giamberardino, C. D., Ballard, C. G., ... & Lad, S. P. (2018). Novel treatment of cryptococcal meningitis via neurapheresis therapy. *The Journal of infectious diseases*, 218(7), 1147-1154.
56. Cresswell, F. V., Te Brake, L., Atherton, R., Ruslami, R., Dooley, K. E., Aarnoutse, R., & Van Crevel, R. (2019). Intensified antibiotic treatment of tuberculosis meningitis. *Expert review of clinical pharmacology*, 12(3), 267-288.
57. Griffiths, M. J., McGill, F., & Solomon, T. (2018). Management of acute meningitis. *Clinical Medicine*, 18(2), 164.
58. Rogers, T., Sok, K., Erickson, T., Aguilera, E., Wootton, S. H., Murray, K. O., & Hasbun, R. (2019, March). Impact of Antibiotic Therapy in the Microbiological Yield of Healthcare-Associated Ventriculitis and Meningitis. In *Open Forum Infectious Diseases* (Vol. 6, No. 3, p. ofz050). US: Oxford University Press.
59. Bårnes, G. K., Gudina, E. K., Berhane, M., Abdissa, A., Tesfaw, G., Abebe, G., ... & Jørgensen, H. J. (2018). New molecular tools for meningitis diagnostics in Ethiopia—a necessary step towards improving antimicrobial prescription. *BMC infectious diseases*, 18(1), 1-14.
60. Gudina, E. K., Tesfaye, M., Wieser, A., Pfister, H. W., & Klein, M. (2018). Outcome of patients with acute bacterial meningitis in a teaching hospital in Ethiopia: a prospective study. *PLoS One*, 13(7), e0200067.