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Bacterial, Fungal, and Parasitic Infectious Diseases of the Central Nervous System: Pathogenesis and Pathophysiology

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Abstract

Introduction: Bacterial, fungal, and parasitic pathogens pose a diverse and formidable threat to the central nervous system (CNS), exploiting unique strategies to breach the protective blood-brain barrier (BBB) and establish devastating infections. By deciphering diverse CNS pathogen vulnerabilities, we pave the way for rapid diagnosis and better treatment, boosting hope for improved outcomes.

Objective: To study that how diverse CNS pathogens (bacteria, fungi, parasites) breach brain defenses (BBB) and proposes rapid diagnosis tools to improve treatment and patient outcomes.

Methodology: A narrative approach was employed to explore the pathophysiology, risk factors, complications, and prognosis of infectious categories. Exclusion criteria were applied and a relevant timeline was established from 2007 to 2023.

Results: Trends were established amongst routes of inoculation, proteins being used to bypass the BBB, inflammatory processes, risk factors, and epidemiology present amongst CNS infections. Limitations include assessment of English-only papers and assessment of open-access publications only. Future research in applied biological and chemical sciences could include viral causes of CNS infection to provide a broader scope of disease and treatment.

Conclusion: Fast diagnosis of CNS infections saves lives, preserves function, and improves quality of life. Existing research is limited, so we explored detection and treatment methods to boost patient outcomes. We hope a deeper understanding of disease roots will benefit patients.

Keywords: bacterial; fungal; parasitic; meningitis; meningoencephalitis; neurocysticercosis; abscess; neurodegeneration; pathophysiology; treatment; complications

Introduction

Girolamo Fracastoro, an Italian physician, poet, and scholar, proposed that infections of the central nervous system (CNS) could be caused by microscopic organisms in 1546, more than 100 years before the first reported observation was made under a scientific lens [1]. Since then, advancements such as multiplex PCR have allowed for prompt and accurate identification of causal pathogens enhancing clinical decision-making and treatment. CNS infections can have irreversible harmful effects on patients so assessment must be fast and accurate. A barrier to our ability to prevent disease by these microscopic organisms is the incomplete understanding of the pathophysiology of their infectivity. Through this review, we aim to aid in this understanding by conducting a comprehensive analysis of CNS infections caused by bacteria, fungi, and parasites to assist in identifying potential future therapeutic targets. Current knowledge outlines the series of events leading to a CNS infection: (i) mucosal colonization by a pathogen; (ii) microbe interaction and crossing of the blood-brain or blood-choroid barrier; (iii) microbial survival and growth within the CNS; (iv) induction of CNS inflammation; (v) pathophysiologic alterations in the CNS; and (vi) the subsequent development of neuronal damage [2]. CNS infectious diseases included in the scope of this paper are meningitis, meningoencephalitis, brain abscesses, parasitic infections, and neurodegenerative disease. Each diseased state has one or more isolated causative pathogens, suggesting a potential trend in the pathophysiology of these microorganism's virulence.

Meningitis, the inflammation of the meninges of the brain, can occur as a result of bacterial or fungal infections. Bacterial meningitis has shifted in epidemiology over the previous decades, as successful vaccination campaigns have led to the eradication of Haemophilus influenza in the developed world. Pneumococcus is now the most common cause of bacterial

meningitis in the US and Europe. It has been successfully targeted by a conjugate vaccine in all regions of the world that have been able to adopt this approach [3]. Nonetheless, bacterial meningitis remains a significant healthcare burden in the developing world. The prognosis for bacterial meningitis is poor. Prompt recognition and accurate treatment are of utmost importance in the clinical setting. Broad-spectrum antimicrobial therapy is given in the presence of high clinical suspicion of bacterial meningitis without confirmation because it could lead to irreversible brain injury if not treated without delay [4]. Mortality rates remain high, despite advances in detection and therapies. Because of this, we must continue our efforts to optimize detection and treatment.

Meningoencephalitis is the inflammation of both brain tissue and the meninges. Cryptococcus neoformans, an opportunistic fungal infection found in bird droppings, causes cryptococcal meningoencephalitis (CM) [5]. This fungus accesses human hosts in the form of spore inhalation. Spores have shown a preference for dissemination to the lymph system, exploiting host immune cells to escape the lungs and gain access to other tissues, including the brain [6]. Specific cytokines have been seen to be key mediators in this spore signaling process and further research into these small proteins as therapeutic targets is suggested. Cryptococcus is known to traverse the BBB in a paracellular fashion and three potential therapeutic targets have already been identified for the management of CM patients [5].

Brain abscesses are focal areas of necrosis with surrounding membranes within the parenchyma and usually occur as a result of an infectious or traumatic process. They occur by hematogenous seeding to the brain from distant infections, often pulmonary and cardiovascular-related [7]. Both bacterial and fungal pathogens are responsible for the creation of brain abscesses. With an understanding of the chemical interplay of this infective process, we may be able to work towards evading known pathological components of it.

Neurocysticercosis and Toxoplasmosis are known parasitic infections of the CNS that can cause detrimental inflammatory responses. Toxoplasmosis is of particular importance due to its vertical transmission from mother to fetus and neurocysticercosis is relevant due to the health burden caused by the Taenia solium parasite in developing countries. While many current therapeutic approaches target how foreign organisms traverse the BBB, Toxoplasma gondii also crosses the placenta, and more research is needed to understand the pathophysiology of this organism's infectivity. There are no current vaccines for the prevention of parasitic CNS diseases, and the creation of such could be a powerful potential future goal. Neurocysticercosis remains a public health problem for impoverished countries and more effort needs to be directed towards global public health equity to properly address this.

Neurodegenerative disease occurs as a result of neuronal cell death and these processes have been linked to extensive inflammatory responses to both gram-positive (GP) and gram-negative (GN) bacteria. A component of gram-positive bacterial cell walls, LTA (lipoteichoic acid) has been associated with an increase in reactive oxygen species (ROS) further increasing oxidative stress, a key player in the pathogenesis of neuronal cell death [8]. However, lipopolysaccharides (LPS) in the outer membrane of gram-negative bacteria are what enable their penetration of the blood-brain barrier (BBB) through both mitochondrial dysfunction and the increase in the number of pro-inflammatory cytokines [9]. Multiple different pathogenic mechanisms leading to the same disease identify the need for multiple therapeutic targets. The virulence factors at hand are bacterial cell wall components, and cell wall modifying agents may also be explored.

The goal of this approach is to identify potential future therapeutic targets and to aid in the clinical decision-making of physicians with up-to-date knowledge of how these infectious CNS disease processes work. To do this, we will need to elaborate on the pathogenesis and pathophysiology of each organism's causal disease. With this elaboration, we aim to identify trends in virulence and manipulate these to work for us rather than against us, making the specific chemical mediators into future therapeutic targets. Immune surveillance is key, for those who are immunocompromised or struggle with comorbid diseases such as Diabetes, Alzheimer's, and Sickle Cell Disease and are at a high risk of infection and complications. Furthermore, a deeper understanding of these disease processes will make room for potential preventative strategies.

Materials and methods

This literature review adopts a narrative approach to explore bacterial, fungal, and parasitic infections affecting the central nervous system (CNS), emphasizing pathogenesis, pathophysiology, treatments, and complications. Articles were sourced from PubMed using specific keywords tailored to each infection category, such as "bacterial CNS infection," "fungal CNS infection," and "parasitic CNS infection."

The search strategy incorporated MeSH terms related to "infection diagnosis," "pathophysiology," "treatment," and "complications."

Inclusion criteria involved primary research publications, systematic reviews, and meta-analyses published in English, focusing on CNS infections from the timeline spanning from 2007 to November 2023.

Exclusion criteria filtered out non-English language publications, studies focusing solely on non-CNS infections, and those lacking relevance to the specified categories.

The titles and abstracts of retrieved articles underwent independent screening by six reviewers to determine their relevance to the research topic, resulting in a narrowed-down selection of 32 articles (Figure 1). Full-text articles were subsequently scrutinized to ensure alignment with the literature review's objectives. The review's outcomes aim to contribute to a deeper understanding of the intricate dynamics and mechanisms underlying infectious CNS diseases, shedding light on the pathogenesis, pathophysiology, and virulence trends of causative organisms.

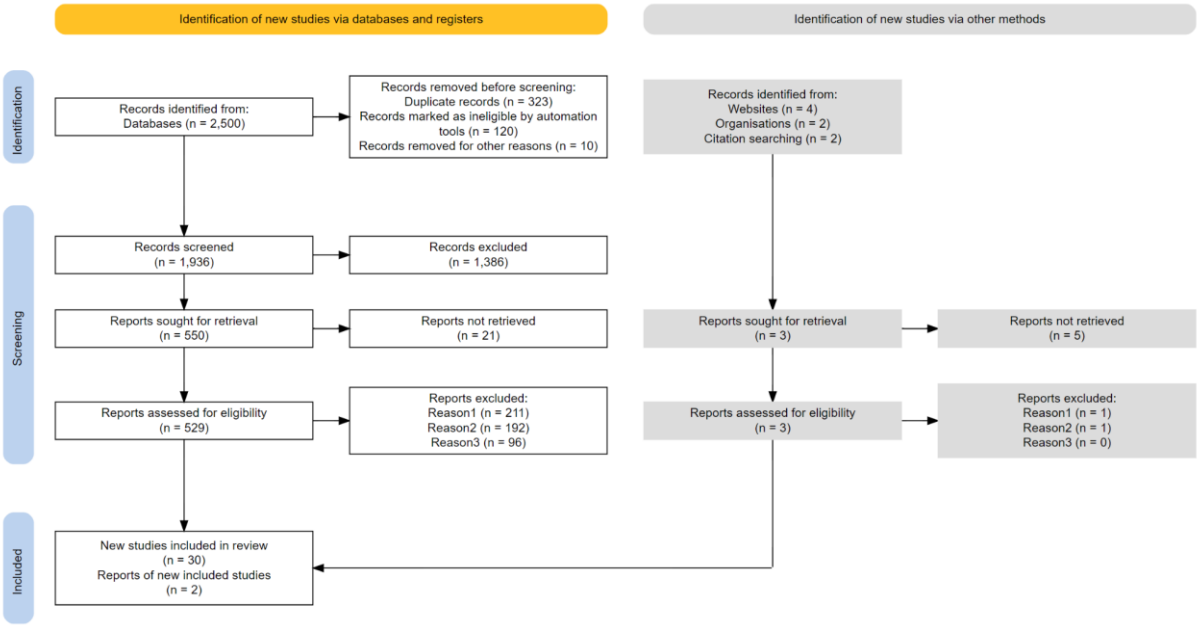

Figure 1: PRISMA Flowchart showing the selection of articles

Results

While the complete pathophysiology of CNS disease by infectious microorganisms remains elusive, these are the trends we established in our research.

Bacterial infections

Bacterial infections are the most common cause of CNS infections. There are a wide variety of organisms that cause these infections but for this paper, it was decided to focus on the most common causes. The likelihood of certain infections varies with age. In newborns, the most common causes of bacterial CNS infection are group B Streptococcus (GBS), *Escherichia coli*, and *Listeria monocytogenes*. Beyond the age of newborns, the predominant causes shift to either Neisseria meningitis or *Streptococcus pneumoniae*. Special cases of bacterial CNS infection include *Mycobacterium tuberculosis* and *Treponema pallidum* [10].

Pathogenesis: Bacteria can invade the CNS in several ways but the main two are direct inoculation or spread from an infection outside the CNS with an upper respiratory infection being the most common source and hematogenous spread being the most common route [10, 11]. Most bacteria that cause CNS infection have special proteins that allow them to bypass the blood-brain barrier (BBB). Specific examples of this would be Meningococci's PilC1 adhesin or Streptococci's CbpA protein [12]. Once the bacteria enter the CNS they multiply further and lyse which exacerbates the body's inflammatory process that is already in progress at the time of infection [12]. Several toxins from the bacteria can damage the surrounding tissue such as H2O2 and pneumolysin in *S. pneumoniae* [13]. These toxins and their route of spread can lead to exacerbation of cases.

Risk factors: Several factors can cause bacterial CNS infections including current infection, immunocompromised state, recent surgery, vaccination status, trauma, and contact with infected persons as bacterial meningitis is extremely contagious.

Clinical presentation: Parasitic CNS infections are unique in that they range in severity and have various presentations, making the diagnosis of etiology and eventual treatment more difficult. The triad for meningitis of neck stiffness, fever, and altered mental status occurs in only a small percentage of patients [10]. Most patients with early cases will present with general symptoms such as headache, nausea/vomiting, fever, and altered mental status/behavioral changes. Specific pathogens can have specific symptoms that make their diagnosis easier. For example, about 50-75% of Neisseria infections present with petechiae or a maculopapular skin rash [14].

Diagnostics: The main techniques used to diagnose bacterial CNS infections are CSF analysis and culture, MRI/CT, and physical examination. A combination of these tools is necessary to get an accurate diagnosis. Concerning CSF analysis, bacterial infections will typically have an elevated neutrophil count, low glucose, and high protein [15]. However, listeria and tuberculosis-induced meningitis will show values more familiar with viral infections with elevated T cells rather than neutrophils as they are intracellular organisms [15]. CSF fluid for bacterial infections should appear cloudy as well, but this is not confirmatory [15]. After the CSF culture is done, the samples can be amplified with PCR to determine species.

Treatments: The first line of defense is vaccination. In the United States, most children will receive a meningococcal meningitis vaccine around the age of 10-12 years with a booster given at 16-18 years. However, this vaccine only protects against meningococcal meningitis [10]. There is also a vaccine for *Haemophilus influenzae type b (Hib)* which was at one point a very common cause of bacterial meningitis [10]. A pneumococcal vaccine is also available for certain groups thus preventing meningitis induced by *S. pneumoniae* [10]. If an infection is acquired, systemic antibiotics are usually the go-to treatment along with

symptomatic management. Prophylactic drugs should also be given to those who came into contact with the patient or anyone at risk of developing an infection as a complication [10]. The most commonly used drugs for prophylaxis are Rifampin, Ciprofloxacin, and Ceftriaxone [10]. There isn't one agreed-upon empiric treatment for bacterial meningitis but a combination that comes up often is Vancomycin + ceftriaxone as they cover a broad spectrum of pathogens [16]. Once the specific pathogen is identified with lab results, the antibiotics can be adjusted.

Prognosis and Complications: These infections can progress from meningitis to meningoencephalitis or an abscess [10]. If an abscess develops and it is large enough, a surgeon will either have to drain it or remove it, smaller ones can usually resolve on their own with antibiotics [10]. Regardless of the size of the abscess they are all given antibiotics [10]. Up to 30% of survivors of bacterial meningitis suffer from some complications which can include seizures, sensory and motor deficits, cerebral palsy, learning disabilities, and possible blindness [10].

Fungal infections

Fungal infections of the CNS are rare and are typically only seen in immunologically compromised individuals. These infections are commonly caused by either *Cryptococcus neoformans*, *Histoplasma*, *Blastomyces*, *Candida*, and/or *Coccidioides* [17]. *Cryptococcus* is often found in bird droppings or the soil and of these infections, it is the most common fungal cause of CNS infection [10]. Patients who suffer from cryptococcal meningitis are usually HIV positive [10]. *Histoplasma* infections are commonly seen in the Midwest United States in the Mississippi and Ohio river valleys and are spread by birds and bats [18]. *Blastomyces* is found in the eastern and central United States [19]. *Coccidioides* are typically found in the dusty southwest United States [20].

Pathophysiology: Similarly, to bacterial infections, fungal infections of the CNS enter the brain either via direct inoculation of from or infection outside the CNS.

Risk factors: Location of residence, recent travel, contact with vehicles of infection, exposure to fungal spores, immunocompromised states, catheters, and recent surgery are all important risk factors for fungal infections of the CNS.

Clinical presentation: The clinical presentation of fungal infections in the CNS is very similar to bacterial infections of the CNS. Both have very general symptoms such as nausea, fever, headaches, and neck stiffness [10].

Diagnostics: These infections are primarily distinguishable from other forms of infection via CSF analysis. These patients will have CSF that is cloudy with varying sugar and protein levels [15]. WBC count is mildly elevated [15]. Once CSF is obtained cultures should be made and viewed under a microscope. From there the organism can be confirmed.

Treatments: There are currently no vaccinations available to prevent fungal CNS infections. The go-to drug of choice for fungal infection is IV amphotericin B., once the pathogen is determined the regimen can be modified to better for the pathogen[21]. If an abscess develops, they too are treated with antifungals and if large enough are either drained or resected surgically [10].

Prognosis and Complications: Cryptococcal Fungal infections of the CNS have about a 44% mortality rate and cause about 15% of HIV-related deaths [22]. Other complications are similar to bacterial infections.

Parasitic infections

Common neurological parasitic infections include neurocysticercosis (*Taenia solium*), toxoplasmosis (*Toxoplasma gondii*), and brain-eating amoeba (*Naegleria fowleri*) [23, 24, 25]. The important determining factor for infection here is contact.

Pathophysiology: The source of all of these infections stems from contaminated sources. Most commonly the parasite will enter the body through either ingestion or implantation. *Taenia solium*, which causes neurocysticercosis, and *Toxoplasma gondii* enter the body via fecal-oral transmission and from there migrate to the brain [23, 24]. However, *Toxoplasma gondii* can also move transplacentally, thus infecting newborns and causing congenital toxoplasmosis [23]. Toxoplasmosis is also one of the most common complications seen in HIV-positive patients [26]. *Naegleria fowleri*, on the other hand, enters through the nose [25]. Once it enters the nose it travels up through the sinus into the brain and causes primary amebic meningoencephalitis (PAM) [25]. Regardless of how they enter they all migrate through the host tissues into the CNS. Once there the pathogens branch off in their assault on tissue.

Risk factors: Contact with contaminated food or water, exposure to a carrier, immunocompromised state, fecal to oral contact with a patient.

Clinical presentation: Presentations can vary depending on the species but will mostly present with very general neurological symptoms and then each branching off as they progress further [10]. The main clinical symptoms of neurocysticercosis are seizures, headache, and focal neurological deficits depending on where the lesions are [24]. The main symptoms of toxoplasmosis are seizures, headache fever, confusion, focal deficits (depending on location), and visual alterations due to retinal toxoplasmosis [26]. However congenital toxoplasmosis can cause Intracranial calcifications, Hydrocephalus, Chorioretinitis, and Ring-enhancing lesions on MRI [26, 27]. The most common symptoms of PAM include headache, neck stiffness, chills, fever, seizures, photophobia, confusion, and possible coma [28]. Rare symptoms of PAM include myocardial necrosis, rhythm abnormalities, and myocardial necrosis [28]. CSF pressures of 600 mm H2O can be seen in PAM patients and are directly associated with death [28].

Diagnostics: Currently, the best ways to diagnose these infections are CSF analysis, PCR, and CT/MRI. These will of course depend upon what species is sought after. With any parasitic infection, the eosinophil levels should be monitored [15]. A stool culture can be used for *Taenia solium* [24]. On CT or MRI, neurocysticercosis will

appear as numerous highly attenuated parenchymal cysts of varying sizes [24,26]. With *Naegleria fowleri* the CT findings can be very non-specific. Toxoplasmosis on CT will appear as multiple hypodense regions predominantly in the basal ganglia and at the corticomedullary junction with ring-enhancing lesions [26]. Serological testing is used to diagnose toxoplasmosis primarily [26]. PAM may not have reliable CT/MRI results.

Treatments: Currently, there are no vaccines available for any major parasitic infection. Treatment is given upon discovery of the pathogen and many either will not receive treatment as they are unaware of any infection or it is too late for any treatment to be effective. In PAM, amphotericin B is the most widely prescribed treatment, but azithromycin, fluconazole, rifampin, miltefosine, and dexamethasone have also been used to attempt treatment based on success in the past [28]. With regards to neurocysticercosis, the condition is often treated with albendazole and/or praziquantel along with symptomatic treatment as the need arises [24]. For toxoplasmosis, the drug of choice is typically a combination of pyrimethamine and sulfadiazine [29]. Importantly both of these drugs can be used in pregnancy to prevent the spread of infection to the fetus [29]. On the chance that doesn't work and the baby develops congenital toxoplasmosis the same drug combination applies [29].

Prognosis and complications: Several factors will affect the prognosis however for parasitic infections, our research has shown the most important factor is time of discovery. The faster it is diagnosed and treatment begins the better the prognosis. When many of these cases are discovered, the parasites have done significant damage. *Naegleria fowleri* infection has at least a 90% chance of mortality, while a study by parenchymal neurocysticercosis has a mortality rate of around 5%[30, 31]. Many survivors of neurocysticercosis will suffer complications such as seizures/ acquired epilepsy, hydrocephalus, and/or dementia [24, 26]. In congenital toxoplasmosis, there is a 10% chance the pregnancy will end in a spontaneous abortion [32]. Usually, toxoplasmosis in adults has a low chance of mortality [23, 26].

Table 1: Similarities and differences between bacterial, fungal and parasitic infections of the CNS

	Bacteria	**Fungus**	**Parasite**
Species	Group B Streptococcus (GBS), *E. coli*, *L. monocytogenes*, N. Meningitidis, *S. Pneumoniae*, *M. Tuberculosis,* and *T. Pallidum*	*C. neoformans*, *Histoplasma*, *Blastomyces*, *Aspergillus*, *Candida*, and/or *Coccidioides*	*Taenia solium* *Toxoplasma gondii* *Naegleria fowleri*
Pathophysiology	Cell wall modifying proteins (LTA ; GN) (LPS; GP)	Hematologic spread to the CNS.	Hematologic and lymphatic spread to CNS.
Risk Factors	Exposure, recent infection, surgery, immunocompromised state, recent travel		
Clinical Presentation	Headache, fever, nausea/vomiting, neck stiffness, neurological deficits		
Diagnostics	CSF analysis and culture, CT/MRI, physical exam		
CSF results	Cloudy ↑ Neutrophils (except TB/Listeria d/t ↑lymphocytes). ↓ Glucose ↑ Proteins	Cloudy ↑ Lymphocyte Varying levels of glucose, proteins.	↑ Eosinophils ↑ Lymphocytes +/- Egg/Parasites ↓ Glucose ↑ Protein
Treatments	Vaccination, prophylaxis: Rifampin, Ciprofloxacin, Ceftriaxone	IV amphotericin B/ systemic antifungals	PAM: amphotericin B azithromycin, fluconazole, rifampin, miltefosine, and dexamethasone
	Treatment: Vancomycin + ceftriaxone		Neurocysticercosis:albendazole and/or praziquantel
			Toxoplasmosis: pyrimethamine + sulfadiazine

Discussion

CNS infections can have irreversible deleterious effects on patients. Because of this, immune surveillance is the primary goal alongside identification of those most at-risk for infection. Our results reflect an overwhelming commonality between the three domains (bacterial, fungal, and parasitic) of CNS infections covered in this paper - the requirement for the organism to bypass the blood-brain barrier (BBB) to lead to disease. The lack of understanding of this pathogenic process of BBB crossing, as well as the biochemical etiology of hematogenous spread, represents a hole in the approach for disease prevention as well as an exciting opportunity for novel research. For example, C. Neoformans, a fungal yeast, has been shown to penetrate the BBB by increasing the expression of the brain endothelial cell (BEC) junction proteins Claudin-5 (Cldn5) and WE-Cadherin to induce pathogenic remodeling of the cell barrier and gap formation [5]. These key proteins enhance the survival of the yeast in the blood and its crossing of the BBB, resulting in meningoencephalitis. Therapeutic management, rather than prevention, appears to be within closer reach than the elimination of disease altogether. A common complication of this disease is increased intracranial pressure due to an increase in cerebrospinal fluid and this is what pharmacological

agents are targeted towards reducing. The hypothesis for this increase in ICP includes an increase in vascular permeability and cerebral edema due to cytokine-induced inflammation plus the osmotic effects of the fungal component mannitol [5]. To challenge this hypothesis, acetazolamide (AZA), candesartan (CAN), and triciribine (TCBN) have been used in a preclinical trial based on their abilities to offer vascular protection, suppress inflammation, reduce brain lesions, minimize brain/lung injury but they each failed to demonstrate a significant reduction in ICP [5]. Current management of increased ICP in these patients includes serial lumbar punctures or ventriculostomy, both extremely invasive and painful. As with any invasive procedure, these open the door to opportunity for infection and other complications. Because of this, drug trials must continue.

We were able to identify various respects in which the three domains of CNS organisms and infections are either similar or different. Speaking first on their similarities, we start with the clearest example: pathogenesis. Generally speaking, each domain of organism infects primarily via direct inoculation or infectious spread. An example of these processes is seen in the spread of *Neisseria meningitides,* which requires a high-grade bacteremia before causing meningitis [3]. Preceding CNS seeding, bacteria concentrate in highly vascularized sites, dural defects, and the choroid plexus, and use their expressed adhesive proteins to invade the CNS [3]. These organisms then spread further into the CNS structures and cause inflammation, nonspecific symptoms, focal neurological deficits, as well as other symptoms [1]. This initial and continued host inflammatory response provides limited protection against the invading pathogen, and then ultimately becomes one of the main mediators of cerebral damage [1]. As the most common pathogenic routes, inoculation, and infectious spread deserve priority targeting for research into preventive medicine and novel therapeutics, like the type mentioned above. Currently, the novel combination of AZA, CAN, & TCBN offers insight into what types of drugs and what mechanisms of action might offer vascular protection and inflammation suppression of the type to confer resistance or protection against bacterial CNS invasion [5]. Another similarity between domains is the prevalence of CNS disease in immunocompromised individuals. Those who are immunocompromised may have neutropenia, immunoglobulin, or B/T-lymphocyte deficiency, maybe transplant patients, or may take drug treatments for certain disorders [22]. This population is particularly at risk for infection from some of the rare pathogens like *Aspergillus*, *Toxoplasma*, and *Rhizopus* causing Mucormycosis, *Cryptococcus*, *Listeria,* and *Nocardia* [11,18,22]. The diverse range of possible treatments for all organisms causative of CNS infections makes comprehensive prophylactic treatment impossible. This is due to the damaging long-term effects of many of the antibiotic, antifungal, and antiparasitic treatment options on the market today [16,21]. As a singular example, the antifungal drug Amphotericin B is known for its rapid nephrotoxicity, as well as its other side effects such as rigors, hypotension, hypoxia, and propensity for causing various electrolyte derangements [21]. Thus, it is ever more imperative to screen those who are immunocompromised regularly for symptoms and to take care in the prescription of immuno-modulating therapies. One more similarity between domains is the way they are diagnosed. Each infection in each domain is diagnosed with a mixture of methods including clinical presentation, CSF analysis, imaging, and PCR [15,24,26]. It is this method that likely holds the most promise for immediate innovation in the identification and treatment of CNS infections. Out of the commonly listed methods we use to diagnose these infections, none is evolving more rapidly than PCR. Although not yet a routine test, PCR currently plays a valuable part in the study of meningococcal disease and bacterial meningitis as a whole [3]. Although PCR sensitivity & specificity is currently inadequate for routine clinical use for the diagnosis of CNS infections, its historical use in rapid diagnosis of viral infections and current place in the study of bacteriology and parasitology holds promise for future clinical employment across all 3 domains of CNS infections [3,26]. Just as the development of PCR revolutionized the study of genomics, multiplex-PCR is revolutionizing our approach to diagnostic medicine. Future development of CNS infection primer kits could lead to rapid and inexpensive screening for CNS disease. Current empirical treatment research for the treatment of bacterial meningitis suggests the use of the highest tolerable dose of antibiotics like Cefotaxime or Ceftriaxone to lower the likelihood of clinical failures [16]. The rapid analysis of what pathogenic organism DNA is present in our blood or CSF would lead to equally rapid treatment, which as mentioned is the most important factor in CNS infection prognosis and minimization of complications. An earlier diagnosis due to rapid testing would mean avoiding complications of high-concentration antibiotic treatment as well as enabling the use of the most appropriate drug therapy in the patient, targeting the correct organism with the correct drug.

While the similarities between CNS infections of various types provide avenues for future innovation and treatment evolution, their differences make that innovation the challenge that it is. Very different compounds are used to treat the three domains of CNS infections. Bacterial infections are treated with antibiotics like Vancomycin and Ceftriaxone, or prophylactic measures like Rifampin, Ciprofloxacin, and Ceftriaxone [10,16]. Amphotericin B, as well as agents like Fluconazole, Itraconazole, and Voriconazole, are used preferentially against fungal infections [21,22]. Antiparasitic treatment involves a combination of these drugs as well as unique additions specific for certain organisms such as miltefosine, albendazole, praziquantel, pyrimethamine, sulfadiazine, and dexamethasone for inflammation [24,29]. In addition, there isn't a single antibiotic, or other category of drug, that can be applied to treat *all types* of infections. Combined with the ever-growing threat of drug resistance (whether that be to antibiotics, antifungals, or antiparasitics), treatment requires the very careful following of guidelines as well as careful deliberation in making the correct diagnosis. Another stark difference is the organism class of standouts like Mycobacterium, Treponema, Naegleria, and Rhizopus that go against the diagnostic or infectious patterns the rest of their groups set to make their treatment or diagnosis more difficult. Mycobacterium

may cause meningitis and space-occupying lesions, while Treponema may affect the vasculature, CSF, cranial nerves, brain, or spinal cord [10]. Both are rare among bacterial CNS infections and represent standouts due to their occurrence via either immunosuppression or vertical transmission [10]. Naegleria and Rhizopus represent a divergence from their categories because they can enter through the nose, present with nonspecific findings, and manifest a high lethality [24,25,30]. Despite the challenge represented by the distance between CNS infection categories, some differences between the domains make diagnosis an easier task. An example of this is the presence of an age discrepancy in bacterial CNS infections, which is not present in the other domains. As mentioned above, some bacteria cause meningitis mostly in younger individuals, and some only in older ones. Newborns are most at risk for infection with group B streptococcus; *E. coli*; and *Listeria monocytogenes,* while unlikely to ever present with *Neiserria meningitidis* or *Steptococcus pneumoniae* in their CNS [10]. Similarly present only in one category, the fungal domain has a unique etiological pattern based on location. Certain infections like Blastomycosis, Coccidioidomycosis, and Histoplasmosis are localized to specific regions of the United States and are rarely found outside their respective regions [18,19,20]. This enhances the certainty and speed of diagnosis, enhancing patient outcomes and limiting complications from continued infection or incorrect treatment.

We hope that knowledge of the similarities and differences between these domains of CNS infections, as well as understanding of the gaps in the study of CNS infection pathogenesis, can lead to novel evolutions in diagnostic and treatment modalities as well as provide avenues for further research. Attention is again brought to the need for the medical community to continually improve on the rapidity of diagnosis in order to further provide beneficial effects on patient prognosis.

Strengths and Limitations

Our narrative review employed an extensive search methodology, incorporating specific keywords and terms to amass pertinent literature, thereby enhancing the probability of encompassing a diverse array of studies. Stringent inclusion and exclusion criteria were explicitly delineated to ensure the alignment of selected articles with the research theme. Nonetheless, our scrutiny is not without limitations. The exclusion of non-English studies poses a potential constraint, introducing a language bias and potentially neglecting valuable research conducted in languages other than English. We utilized open-access literature to ensure accessibility without any financial constraints or requirements to review and analyze this literature. Despite involving multiple reviewers, our review remains susceptible to the inherent subjectivity of reviewers during the article screening process.

It is essential to acknowledge the potential for publication bias in this review, as there is a risk of unintentionally favoring positive or statistically significant findings, which could lead to the exclusion of studies with null or nonsignificant results. Noteworthy is the distinctive approach of this research, standing out among the limited studies addressing the etiology and treatments for CNS infections within a cohesive literature framework. The intentional exclusion of viral CNS infections is a strategic choice to maintain focus and depth, preventing unnecessary expansion of scope, simply due to the abundance of viruses in existence. In summary, this review contributes significantly by offering a thorough examination of central nervous system infections, encompassing the analysis of bacterial, fungal, and parasitic infections' pathophysiology. Its value lies in providing a clear and concise overview of a diverse range of CNS infections, facilitating other researchers in analyzing similarities and differences to advance the scientific field. The objective is to enhance comprehension of CNS issues within the medical domain and contribute to the advancements in the scientific realm.

Conclusion

Common trends have been established in the facilitation of these infectious agents to penetrate the CNS and cause disease, mainly revolving around the entry of the BBB. The prevalence of disease in immunocompromised individuals, as well as the shared need for pathogens to penetrate the blood-brain barrier, are among the similarities researchers can exploit to develop groundbreaking screening tools and treatments. With multiplex PCR being the most rapidly developing domain, screening and early detection of the causative organism may yield promising improvements in prognosis. Further enhancement of diagnostic testing is needed to identify causal pathogens more rapidly to speed up the time of treatment and to avoid debilitating CNS damage in these patients. Innovative diagnostic and treatment modalities will crucially improve the rapidity of diagnosis and treatment — producing an improvement in the prognosis of all patients with CNS infections.

Conflict of interest

The authors state no conflict of interest.

Author Contributions

All authors contributed equally in this study.

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