

# Infections of the CNS Represent a Significant Source of Morbidity and Mortality throughout the World

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## Abstract

Infections of the brain often also involve other parts of the central nervous system, including the spinal cord. The brain and spinal cord are usually protected from infection, but when they become infected, the consequences are often very serious. Infections can cause inflammation of the brain (encephalitis). Viruses are the most common causes of encephalitis. Infections can also cause inflammation of the layers of tissue (meninges) that cover the brain and spinal cord—called meningitis. Often, bacterial meningitis spreads to the brain itself, causing encephalitis. Similarly, viral infections that cause encephalitis often also cause meningitis. Technically, when both the brain and the meninges are infected, the disorder is called meningoenkephalitis. However, infection that affects mainly the meninges is usually called meningitis, and infection that affects mainly the brain is usually called encephalitis.

**Keywords:** Brain infections; Pathogens; Cerebrospinal fluid

## Introduction

Infections of the central nervous system (CNS) are among the most devastating infectious diseases worldwide and often result in medical emergencies that require prompt management. Pathogens may access the CNS by crossing the blood–brain barrier (BBB), which normally protects the CNS from microbial invasion, or via Trans neuronal routes that bypass the BBB. A broad array of infectious agents can cause CNS infections in the meningeal or parenchymal compartments [1]. Infection of the cerebrospinal fluid (CSF) and its surrounding meninges, termed meningitis, is accompanied with the acute onset of fever, headache, and neck stiffness. Infection of the CNS parenchyma leads to encephalitis, which clinically involves fever, neuropsychological impairment, and seizures. By contrast, CNS infection confined to small areas of focal lesions or abscesses are more likely to occur in immunocompromised individuals [2]. Here, we summarize the etiologies of these potentially vaccine-preventable infections, their transmission routes, and the recent advances in understanding the mechanisms of CNS invasion by different neurotropic pathogens.

We conducted a prospective cohort study in Cipto Mangunkusumo Hospital, a government university hospital that serves the local community and acts as a tertiary referral hospital for Indonesia. From January 2015 to April 2016, all consecutive patients over 16 years of age with clinically suspected CNS infection (according to clinical judgement of the attending neurologists) were included. Systematic history taking, physical and neurologic examination, CSF and blood examinations, and reading of brain CT and chest X-ray were done. CSF and blood samples were archived for further testing. All patients with a confirmed or presumptive diagnosis of CNS infection were followed prospectively for 6 months [3].

## Meningoencephalitis

The clinical picture is one of neurological signs and symptoms (cognitive disorders or behavioural disorders, focal signs, seizures), associated with a fever with clear liquid in the lumbar puncture. This is a serious disease (10 to 12% mortality) and is relatively common (incidence in the world: 3.5 to 7.4/100,000 inhabitants per year). The problem is a diagnostic one, with an identified aetiology for these clinical pictures in only 52 to 63% of cases [4]. There are many causative microorganisms. In a recent multicentric study in 253 non-HIV infected

patients with infectious encephalitis, the aetiology was identified in 52% of cases, with viral (69%) and bacterial (30%) aetiologies.

## Meningitis

Meningitis can be caused by a virus or bacteria. Bacterial meningitis is a serious condition and needs to be treated immediately. Rarely, meningitis can also be caused by a fungus or parasite.

Several types of bacteria can first cause an upper respiratory tract infection and then travel through the bloodstream to the brain. Bacterial meningitis can also occur when certain bacteria invade the meninges directly [5].

The classic signs of meningitis include a sudden fever, severe headache, stiff neck, photophobia, and nausea and vomiting. Being unable to bend your chin down to your chest is a sign of meningitis. While the symptoms may start out resembling those of a cold or upper respiratory infection, they can quickly become more severe.

## Encephalitis

Encephalitis is usually caused by a virus, such as the herpes simplex virus types 1 and 2, or arboviruses, in the United States [6]. Arboviruses are spread from animals to humans and causes mosquito-borne disease. An example is the West Nile virus.

Symptoms may start out as mild flu-like symptoms and headaches, quickly followed by behavioral changes, hallucinations, and confusion.

Empiric antibiotic treatment for suspected bacterial meningitis centres on the treatment for meningococcal meningitis, owing to the severity of this infection, and consists of intravenous administration of a

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third-generation cephalosporin, such as ceftriaxone or cefotaxime with good CNS penetration [7]. Duration of treatment for meningococcus tends to be shorter than that for other bacterial meningitis infections, averaging around 7 days.

*Streptococcus pneumoniae* Streptococcal meningitis from the causative organism *S. pneumoniae* is the leading cause of meningitis in the elderly, and one of the leading causes of bacterial meningitis in all adults and children older than 2 months. The illness is usually not as rapid and fulminant as that caused by meningococcal meningitis, but nonetheless can present with similar symptoms [8]. Workup is similar to those patients suspected of having meningococcal meningitis, with LP preceding empiric treatment with a third-generation cephalosporin. LP should return gram-positive diplococci. In cases where resistance to cephalosporin is suspected, vancomycin should be added for additional coverage. Out of the several species of bacterial meningitis, clinical trials to date have provided the greatest benefits for adjuvant dexamethasone therapy for pneumococcal meningitis [9–10]. An estimated 1 in 12 cases of streptococcal meningitis is fatal, with 1 in 3–4 survivors suffering neurologic sequelae, including deafness, persistent seizures, and mental retardation in children. Since the advent of the heptavalent pneumococcal vaccine in 2000, pneumococcal meningitis has decreased significantly in children, estimated by the Center for Disease Control (CDC) to be around 77% lower than immediately before vaccine introduction, while diminishing in adults as well due to herd immunity [11].

*Haemophilus influenzae* *Haemophilus influenzae*, particularly serotype B (HiB), is a frequent cause of meningitis in children under the age of 5 years [12]. This organism is a gram-negative rod and a frequent inhabitant of the sinuses, inner and middle ear, respiratory tract, and bloodstream; it commonly causes meningitis via a combination of both direct sinus and hematogenous spread. The frequency of HiB strain in the United States has decreased dramatically, however, in the past couple of years since the advent of the HiB vaccine, and is now a distant third behind streptococcus and meningococcus in childhood meningitis [13]. It continues, however, to be a major cause of childhood meningitis worldwide, with 386,000 deaths per year being attributed to the combination of HiB meningitis and pneumonia [14]. Furthermore, 15%–35% of all survivors of HiB meningitis are left with permanent neurologic sequelae, including deafness and mental retardation [15]. Timely administration of corticosteroids has been shown to help decrease the risk of subsequent neurologic deficits. Expanding vaccine coverage into developing countries has the potential to reduce these numbers.

## Conclusion

Infections of the CNS represent a significant source of morbidity and mortality throughout the world, and demand that physicians in a variety of specialties are familiar enough with their presenting signs and symptoms and can formulate a diagnosis in time before further damage arises. Despite advances in vaccinations, meningitis arising from *N. meningitidis* and *S. pneumoniae* species in adults and children and from Group B *Streptococcus*, *E. coli*, and *Listeria* species in neonates remain common reasons for presentation to the emergency room.

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