



**MEDICAL UNIVERSITY - PLEVEN
FACULTY OF MEDICINE**

DISTANCE LEARNING CENTRE

**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,
PARASITOLOGY AND TROPICAL MEDICINE**

**PRACTICAL EXERCISE № 4 –
BACTERIAL INFECTIONS OF THE CENTRAL NERVOUS
SYSTEM – CLINICAL FEATURES, DIAGNOSIS,
DIFFERENTIAL DIAGNOSIS, TREATMENT
THESIS**

**FOR E- LEARNING IN INFECTIOUS DISEASES
ENGLISH MEDIUM COURSE OF TRAINING**

SPECIALTY OF MEDICINE

ACADEMIC DEGREE: MASTER

PROFESSIONAL QUALIFICATION: DOCTOR OF MEDICINE

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PRACTICAL EXERCISES – THESES

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I. Aim of the practical exercise – after completed exercise, the students must be able to take informative history and physical examination of patients with central nervous system (CNS) infectious diseases, to group symptoms in syndromes, to prepare plan for diagnosis (and differential diagnosis), to be familiar with major principles of etiological and supportive treatment of CNS infectious diseases.

II. Tasks for achievement of mentioned above aim:

1. Repetition of microbiological characteristics of *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenza* type B.
2. Discussion on specific features of history in CNS infectious diseases emphasizing on specific features of CNS infectious diseases with bacterial etiology.
3. Importance of epidemiological part of history of mentioned above bacterial agents.
4. Information about past history and comorbidity.
5. Taking of physical examination of a patient with CNS infectious disease.
6. Discussion about syndromes in bacterial CNS infectious diseases and their diagnostic value.
7. Discussion about major principles of etiological and supportive treatment of bacterial CNS infectious diseases.

III. Theoretical part of the exercise:

INTRODUCTION

Numerous infectious agents affect the nervous system. Some organisms release neurotoxins or cause degenerative lesions of poorly understood pathogenesis. Other agents directly infect the nervous system, including the meninges or the brain.

A. Meningitis is inflammation of the meninges.

1. Bacterial meningitis is defined as meningitis with evidence of pathogenic bacteria in the cerebrospinal fluid (CSF).

2. Aseptic meningitis is defined as meningitis without the usual evidence of pathogenic bacteria in the CSF.

B. Encephalitis is inflammation of the parenchyma of the brain.

C. Meningoencephalitis is inflammation of the brain and meninges.

BACTERIAL MENINGITIS is an acute, life-threatening infection. The mortality rate is approximately 10-15% (depending on the bacteria involved), even with appropriate antimicrobial therapy. The incidence of the disease decreases with age. The prevalence of a particular etiologic agent is also related to the patient's age.

A. ETIOLOGY

Bacteria most commonly associated with meningitis are encapsulated and have high affinity for specific receptors in the chorioid plexus or the meninges.

1. More than 80% of cases of bacterial meningitis beyond the neonatal period are caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenza* type B.

a. Eighteen of the more than 80 recognized serotypes of *S. pneumoniae* are responsible for 90% of cases of pneumococcal meningitis.

b. Four serogroups (A, B, C, and Y) of *N. meningitidis* cause most cases of meningococcal meningitis, which can affect both children and young adults. *N. meningitidis* can

cause epidemic outbreak, particularly in overcrowded conditions (e.g., in military barracks, day care centers).

c. The frequency of meningitis caused by *H. influenzae* type B has decreased considerably since the introduction of the *H. influenzae* type B conjugate vaccines.

2. The remaining 20% of cases are caused by various pathogenic and opportunistic bacteria, including *Listeria monocytogenes*, Gram-negative enteric rods, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Staphylococcus epidermidis*, and *Mycobacterium tuberculosis*.

B. EPIDEMIOLOGY

1. Age dependence

a. **Meningitis in children.** *Table 1* lists the bacteria that most often cause bacterial meningitis in children of different ages.

Table 1. Bacteria Involved in Childhood Meningitis in Different ages

Neonatal (< 1 month)	Infant (1 month – 2 years)	Preschool Age (2 – 5 years)	School Age (5 – 12 years)	Adolescent (12 – 18 years)
<i>Escherichia coli</i> *	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
Group B <i>Streptococcus</i>	<i>N. meningitidis</i>	<i>N. meningitidis</i>	<i>N. meningitidis</i>	<i>N. meningitidis</i>
<i>Klebsiella</i> species	<i>Haemophilus influenzae</i> type B	<i>Haemophilus influenzae</i> type B	<i>Haemophilus influenzae</i> type B	
<i>Listeria monocytogenes</i>				
Group D streptococci				

* Strains with K1 capsular antigen are most common.

b. **Meningitis in older children, adolescents, and adults** is considerably less common and is most often caused by *N. meningitidis* or *S. pneumoniae*.

c. **Meningitis in the elderly** is most often caused by *S. pneumoniae*.

2. **Predisposing factors** include those related to the organism and those related to the host.

a. Bacterial factors

1) Organisms with **polysaccharide capsules** resist phagocytosis and are poorly immunogenic in children younger than 2 years.

2) Bacteria with **surface antigens** (e.g., the K1 antigen of *Escherichia coli*) that are tropic for the meninges.

b. Host factors

1) **Gender.** For unknown reasons, meningitis is more prevalent in men than in women (1.7:1 ratio).

2) **Prematurity, prolonged or difficult delivery, and maternal infection** contribute to meningitis in the neonate. Immaturity of the immune system in the neonate and increased opportunity for exposure to pathogenic bacteria play a role.

3) **Age.** The risk of contracting bacterial meningitis is greatest between birth and 5 years of age, with peak incidence in the first month of life.

4) **Congenital immunodeficiencies** predispose to meningitis.

a) Agammaglobulinemia and functional asplenia (e.g., sickle cell disease) increase the susceptibility to encapsulated bacteria.

b) Complement deficiencies (particularly of the terminal components C5 – C9) predispose to *N. meningitidis* meningitis.

c) Cell-mediated or combined immunodeficiencies predispose to *L. monocytogenes* meningitis.

5) Acquired immunodeficiencies increase the susceptibility to opportunistic organisms (e.g., in AIDS patients) and to encapsulated bacteria (e.g., in patients who have undergone splenectomy).

6) Poor sanitation, lack of access to preventive care, and overcrowding are predisposing factors.

7) Exposure of the cranial vault or spine (e.g., congenital, post-traumatic, or surgical) facilitates direct penetration of bacteria into the meningeal space.

C. PATHOGENESIS

1. Bacterial access to the meninges or subarachnoid space

a. **Bacteremic spread** of organisms from the nasopharynx or other foci of infection accounts for most cases of bacterial meningitis.

b. Direct invasion

1) Bacteria may directly invade the meningeal space from a contiguous focus of infection (e.g., sinusitis, mastoiditis, skull and vertebral osteomyelitis, possibly otitis media).

2) Interrupting the integrity of the CSF space allows ascending invasion by pathogenic bacteria. Loss of CSF integrity may be congenital (e.g., dermoid sinuses, meningocele), traumatic (e.g., penetrating injury or basilar skull fracture), or surgical (e.g., CSF shunt).

2. Release of bacterial products

Once infection is established, bacteria replicate and release toxic compounds (e.g., endotoxin, teichoic acids, and peptidoglycan).

a. These bacterial products cause changes in vascular permeability and perfusion both directly and through activation of leucocytes. Activated leucocytes release a variety of proteases and inflammatory mediators [e.g., tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin-8 (IL-8), and platelet activating factor (PAF)].

b. Complement split products, generated by leucocyte and bacterial proteases, and certain cytokines (e.g., IL-8) are chemotactic for neutrophils and other granulocytes, and cause massive influx of these cells into the meningeal space.

c. The cumulative effects of toxic and vasoactive compounds released by bacteria and leucocytes include interstitial edema, increased intracranial pressure, decreased cerebral blood flow, and subsequent damage to the brain. In addition, systemic effects of the same compounds may develop.

D. CLINICAL MANIFESTATIONS vary considerably depending on the virulence of the organism and the age of the patient.

1. In **neonates**, the signs of meningeal irritation (nuchal rigidity, and Brudzinski's and Kernig's signs) are infrequent and are often minimal when found. Early signs include temperature instability, irritability, poor feeding, and vomiting.

2. In **children 1 – 18 months of age**, signs and symptoms are often nonspecific and include fever, irritability, drowsiness, vomiting, poor feeding, crying when handled, bulging fontanel (due to increased intravascular pressure), and febrile seizures.

3. In **older children and adults**, the severity of the symptoms varies.

- a. Nearly all patients have fever, headache, and nuchal rigidity.
- b. The most common finding is a stiff neck characterized by pain and resistance on flexion.
- c. Neurologic findings may include Brudzinski's and Kernig's signs.
- d. Seizures, vomiting, lethargy, drowsiness, and irritability on movement are common signs. Confusion, agitated delirium, and stupor occur less frequently.
- e. Coma, when it develops, is a poor prognostic sign.

E. DIAGNOSIS

1. **Lumbar puncture.** A rapid and thorough examination of the CSF is important to confirm diagnosis of meningitis.

a. A lumbar puncture is not without risk in a patient with suspected meningitis because of the elevated intracranial pressure. Rapid withdrawal of CSF when the pressure is elevated can cause herniation of the cerebellar amygdala and death.

b. Lumbar puncture is contraindicated when signs of significantly increased intracranial pressure (retinal changes, altered pupillary responses, and hypertension with bradycardia) are present. A computerized tomography (CT) scan can be obtained to better evaluate the risks.

2. CSF findings (Table 2)

Table 2. Characteristics of Cerebrospinal Fluid in Different Types of Meningitis

Type of Meningitis	Leucocytes x 10 ⁶ /L (Range)	Predominant Cell Type	Protein Levels	Glucose concentration	Microbiological Tests
Bacterial	0 – 60 000	Neutrophils	Elevated	Very low	Positive*
Viral	0 – 1 000	Mononuclear cells**	Normal to slightly elevated	Normal	Negative
Tuberculous	25 – 500	Mononuclear cells	Elevated	Low	Negative
Fungal	0 – 1 000	Mononuclear cells	Elevated	Low	Negative***

* Uncluding Gram stain, culture, and rapid diagnostic tests for bacterial antigens.

** Neutrophils may predominate in early stages.

*** India ink tests, fungal cultures, and agglutination tests for fungal antigens may be positive.

a. The **leucocytes count** is elevated (typically 500 – 10 000 x 10⁶/L), with a predominance of neutrophils and other granulocytes. However, these findings may be absent early in the disease.

b. **Protein levels** are high, but it needs to be considered that normal levels vary considerably with age (1.2 – 1.5 g/L in premature babies, 0.1 – 1.2 g/L in term infants, and < 0.45 g/L after 3 months).

c. **Glucose levels** are low (typically < 4 mmol/L, less than half of the level of serum glucose).

d. A positive **Gram stain** or positive results in **latex agglutination tests** for *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* can allow a rapid diagnosis.

e. Cultures

1) **Bacterial cultures** should always be requested. One-quarter to one-half of children with bacterial meningitis have received antibiotics prior to admission, which may cause sterile CSF cultures. However, **it is very rare for all CSF parameters to be normalized by prior treatment.**

2) **Viral cultures** may also be indicated during the peak enterovirus season (late summer to early fall), or during an epidemic of viral meningitis.

3. **Other findings.** The **complete blood count** usually shows leukocytosis and neutrophilia. Other findings may reflect concomitant sepsis or involvement of other organs.

F. TREATMENT

1. Antibiotic therapy

a. **Empiric therapy.** Early treatment is of paramount importance. Because different bacteria are involved in different age groups, the recommendations for initial empiric treatment vary (**Table 3**).

b. **Definitive antibacterial therapy** is based on the results of antibiotic susceptibility tests. In neonates, the lumbar puncture should be repeated until the CSF is sterile, and again at the end of therapy. In older infants and children, repeated lumbar punctures are not necessary.

2. Adjunctive (supportive) therapy includes:

a. **Dexamethasone** for children older than 2 months, to reduce inflammatory component of meningitis

b. **General supportive care** (maintenance of ventilation, oxygenation, perfusion, and hydration, and nutritional support).

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