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КАФЕДРА ДЕТСКИХ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ С КУРСОМ
ПОВЫШЕНИЯ КВАЛИФИКАЦИИ И ПЕРЕПОДГОТОВКИ

О. Ф. Романовская, Р. Н. Манкевич

ИНФЕКЦИИ ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ У ДЕТЕЙ

CENTRAL NERVOUS SYSTEM INFECTIONS IN CHILDREN

Учебно-методическое пособие

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Романовская Ольга Фадеевна
Манкевич Римма Николаевна

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ABBREVIATIONS

CNS — central nervous system
CBC — complete blood count
CSF — cerebrospinal fluid
CT — computed tomography
CMV — Cytomegalovirus
CXCL — C-X-C chemokine
e.g. — exempli gratia (from Latin) that means for example
etc. — et cetera
EBV — Epstein-Barr virus
E.coli — Escherichia coli
EEG — electroencephalography
ESR — erythrocyte sedimentation rate
GBS — Group B Streptococcus
GCS — Glasgow coma score
HHV 6 — Human Herpes virus 6
HHV 7 — Human Herpes virus 7
Hib — Haemophilus influenzae type b
HIV — Human Immunodeficiency virus
HSV — Herpes Simplex virus
i.e. — id est (from Latin) that is to say
IMD — invasive meningococcal disease
IVIG — intravenous immune globulin
LP — lumbar puncture
MD — Meningococcal disease
MRI — magnetic resonance imaging
PCR — polymerase chain reaction
TB — tuberculosis
VZV — Varicella Zoster virus

MOTIVATIONAL CHARACTERISTICS OF TOPIC

Total in-class hours: 7.

The central nervous system infections are life-threatening conditions, especially in young children, associated with significant morbidity and mortality. CNS infections are caused by a wide variety of pathogens, which some of them are endemic, others sporadic and yet others cause epidemics. Epidemiological considerations, appreciation of the presenting clinical syndrome (acute bacterial

meningitis, acute aseptic meningitis, chronic meningitis or space-occupying lesions) and CSF analysis facilitates diagnosis.

Despite the availability of potent newer etiotropic agents, the mortality rate and long-term neurological sequelae due to the CNS infections remain significantly high. Consequently, early recognition and initiation of treatment are key to the management of CNS infections and improve outcomes.

The objective of the lesson. The purpose of teaching and learning consists in the formation of obtaining and getting to the student contemporary scientific knowledge about CNS infections in children, taking into account the features of the clinical course of the disease, depending on the child's age and the character of a pathogen.

Class tasks. *The students should know:*

– aetiology, epidemiology, pathogenesis of the most common CNS infections in children and adolescents;

– the clinical presentations and syndromes of the CNS infections;

– the features of clinical course of the CNS infections in young children;

– the differential diagnosis of infections of the CNS;

– clinical symptoms and special characteristics of emergency conditions in the CNS infections, the diagnosis and administering immediate care in life-threatening conditions;

– the major diagnostic methods of infections of the CNS;

– the major complications and outcomes of the CNS infections;

– the principles of treatment of these diseases in children;

– prevention of the CNS infections in children;

– anti-epidemic measures at the outbreak site.

The students should be able to:

– perform the clinical examination of a child with suspected infection of the CNS, make the plan of examination, and identify the necessity of hospitalisation;

– evaluate the results of examination of patients with the CNS infection; make a clinical diagnosis;

– fill in medical reports in case of the CNS infection;

– organise preventive measures at the outbreak site.

The students should master:

– the methods of epidemiological analysis of development of infectious disease of the CNS;

– the methods of identifying the clinical symptoms, atypical, severe and complicated forms of the CNS infections;

– the contemporary methods of clinical, instrumental and laboratory examination;

– the methods of inpatient and outpatient giving first medical aid in life-threatening conditions;

– the methods and forms of health education of the population.

Requirements for the initial level of knowledge. Revise:

– Normal Anatomy: anatomical and morphological structure of the brain and spinal cord;

– Microbiology, Virology, Immunology: mechanisms of the development of immune response in the different CNS infections; characteristic features of the most common causative agents of CNS infections;

– Pathologic Anatomy: general patterns and mechanisms of development of pathological processes in CNS infections;

– Biological Chemistry: molecular basis of development of pathological processes, basic principles of biochemical diagnostic methods;

– Propedeutics of Internal Diseases: examination approaches, clinical and laboratory parameters evaluation;

– Paediatrics: clinical manifestations of non-infectious CNS disorders in children;

– Neurology and Neurosurgery: neurological examination of patients (meningeal signs, symptoms of cranial nerve damage, physiological and pathological reflexes); cerebrospinal fluid analysis; lumbar puncture technique; neuroimaging techniques (electroencephalography, magnetic resonance imaging);

– Pharmacology: pharmacological properties of antibiotics, antiviral agents, corticosteroids, antipyretics and the basis of their clinical application, directions for the use.

Questions for self-control from related disciplines:

1. What pathogens cause the CNS infections in children? Give the characteristic of pathogens.
2. What clinical syndromes of CNS infections do you know? Give their description.
3. Describe the methods of laboratory diagnosis of CNS infections.
4. Name the pathological changes observed in the brain and spinal cord in CNS infections.

Test questions on the topic of the lesson:

1. Aetiology of CNS infections in children depending on age. Describe the relevant pathogens.
2. Make the differential diagnosis of infectious and non-infectious CNS disorders in children.
3. Bacterial meningitis: common causative agents, epidemiology, pathogenesis, clinical manifestations, diagnosis, and management.
4. Aseptic meningitis: common causative agents, epidemiology, pathogenesis, clinical manifestations, diagnosis, and management.
5. Encephalitis: common causative agents, epidemiology, pathogenesis, clinical manifestations, diagnosis, and management.

6. Myelitis: common causative agents, epidemiology, pathogenesis, clinical manifestations, diagnosis, and management.

7. Diagnostic approach to a patient with suspected CNS infection.

INTRODUCTION

Central nervous system infections — infections involving the brain (cerebrum and cerebellum), spinal cord, optic nerves, and their covering membranes — are medical emergencies that are associated with substantial morbidity, mortality, or long-term sequelae that may have catastrophic implications for the quality of life of affected individuals. Children with immature immune defenses and blood-brain barrier are more vulnerable to CNS infections than adults are. The aetiological spectrum of CNS infections is constantly expanding. As a result, recent decades have witnessed the emergence and re-emergence of numerous medically important viruses affecting CNS in children, such as Zika, West Nile, and enterovirus/parechovirus. Viral infections outnumber bacterial, fungal, and protozoal infections. However, in many regions bacterial CNS infections still remain a major public-health challenge owing to low vaccination coverage and the emergence of mutant strains with multidrug resistance.

Acute CNS infections generally result from blood-borne spread of the respective microorganisms. Other causes of CNS infections include head trauma resulting in fractures at the base of the skull or the cribriform plate that can lead to an opening between the CNS and the sinuses, mastoid, the middle ear, or the nasopharynx. Extrinsic contamination of the CNS can occur intraoperatively during neurosurgical procedures. In addition, implanted medical devices or adjunct hardware (e.g., shunts, ventriculostomies, or external drainage tubes) and congenital malformations (e.g., spina bifida or sinus tracts) can become colonized and serve as sources or foci of infection.

CNS infection is a medical emergency condition requiring immediate hospitalisation and urgent actions to clarify the diagnosis and initiate empirical etiotropic therapy.

Herein, we review the most common CNS diseases in children featuring meningitis, encephalitis, meningoencephalitis, and myelitis, diagnosis, differential diagnosis, and treatment.

GLOSSARY

Jolt accentuation of headache — a clinical sign for early diagnosis of meningitis, which assesses meningeal irritation. Checking for this sign, the patient is asked to turn his head horizontally with frequency of 2–3 times in a second,

and it is considered positive if the patient's basic headache accentuated with this maneuver.

Brudzinski sign consists of spontaneous flection of the lower extremities after passive flexion of the neck when meningeal irritation is present. Any flexion of the hips and knees while passively flexing the patient's neck is a positive Brudzinski sign.

Kernig sign: position the patients is supine, flex the patient's leg to 90° at both the hip and knee, and then slowly extend the leg and straighten the knee. Pain and increased resistance to extension of the knee indicate a positive Kernig sign. If Kernig sign is positive bilaterally, suspect meningeal irritation. Kernig's sign: position the patients is supine with their hips flexed to 90°. This test is positive if there is pain along spinal cord, and/or resistance to knee extension on passive extension of the knee.

Meningitis is a clinical syndrome characterised by inflammation of the meninges in response to penetration of pathogens.

Meningism (i.e., meningismus) — a condition characterised by neck stiffness, headache, and other symptoms suggestive of meningeal irritation, but without actual inflammation of the meninges. Spinal fluid pressure may be elevated but spinal fluid is normal.

Nuchal rigidity (or neck stiffness): with the patient in the supine position, place your hand behind the patient's head and passively flex the neck forward until the patient's chin touches their chest, if possible. The neck should be supple, and the patient should not have problems bending the head and neck forward. This test is positive if there is palpable resistance to flexion or stiffness.

Pleocytosis is an abnormal increase in the number of cells in CSF (> 5 cells/μL in adolescents and adults, while in younger children — when cells exceed the age norm).

Invasive pneumococcal (or meningococcal, etc.) disease is defined as all clinical phenotypes in which pathogen is isolated from blood, cerebrospinal fluid, pleural fluid, or any other normally sterile site by culture, antigen testing, or molecular assays.

The red flag combination in bacterial meningitis is symptoms and signs associated with this disease. Bacterial meningitis should be strongly suspected in babies, children and adults with the red flag combination, which consists of fever, headache, neck stiffness, and altered level of consciousness or cognition (including confusion or delirium).

AETIOLOGY OF CNS INFECTIONS IN CHILDREN

Infectious diseases of the CNS include a wide spectrum of infections caused by various pathogens selectively affecting certain components of the nervous system. Viral infections outnumber bacterial, fungal, and protozoal infections. Among viral aetiology the most common are *Enteroviruses, Parechoviruses, Herpes simplex virus type 1, 2,* and *Arboviruses*. Less common organisms causing CNS infections are other herpes family viruses (*Epstein-Barr virus, Cytomegalovirus, Varicella-Zoster virus, Human herpes virus type 6*), *Influenza A and B viruses, Lymphocytic choriomeningitis virus, Mumps virus, Measles virus, Human immunodeficiency virus,* etc.

Viral agents are followed by bacteria. The older a patient gets, the higher proportion of bacterial agents is observed in CNS infections. The specific aetiology depends on factors such as age, immune function, immunisation status, genetics and geographical location.

Children under 3 months of age. Premature infants, neonates and infants less than 2 months of age represent the highest risk groups for bacterial meningitis in children. Group B Streptococcus (*Streptococcus agalactiae*) and *Escherichia coli* remain the leading causes of bacterial meningitis in neonates with little change in incidence rates over time. Although, *Listeria monocytogenes* currently is an uncommon cause, it should be considered in patients at this age.

The aetiology and incidence of bacterial CNS infections are closely related to whether the children have received routine immunisation with the meningococcal vaccine, the Haemophilus influenzae type b vaccine, and the Streptococcus pneumoniae vaccine.

In infants over 3 months of age who have not received routine immunisation, the most common causes of bacterial meningitis include:

– *Streptococcus pneumoniae* (many serotypes; particularly in infants with no record of S. pneumoniae conjugate vaccination);

– *Neisseria meningitidis* (especially serogroup B, but occasionally groups A, C, Y, or W135);

– *Haemophilus influenzae type b* (particularly in infants with no record of H. influenzae type b conjugate vaccination).

Conjugate vaccines against the three most common causative pathogens (Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae) have reduced the incidence of disease, but with the replacement by non-vaccine pneumococcal serotypes and the emergence of bacterial strains with reduced susceptibility to antimicrobial treatment. Hib has essentially disappeared in countries where the conjugate vaccine is routinely used.

Other aetiologies of bacterial meningitis **in infants and children > 3 months of age** have been reported but are very rare. *Staphylococcus aureus,* coagulase-negative staphylococci, streptococci, and gram-negative enteric bacilli,

especially *Escherichia coli, Klebsiella spp.,* and *Pseudomonas aeruginosa* may cause meningitis in infants who have had trauma or neurologic surgery. Use of respiratory equipment in the nursery increases the risk of infection caused by *Serratia marcescens, Pseudomonas aeruginosa,* and *Proteus* species. Invasive devices predispose infants and young children to the infections caused by *Staphylococcus epidermidis* and *Pseudomonas, Citrobacter,* and *Bacteroides* species.

Fungal infections of the CNS are relatively rare and associated with *HIV*, immunosuppressive therapies, and organ transplants. *Cryptococcus neoformans* meningoencephalitis is the most common of these infections and usually affects patients with uncontrolled HIV infection. Predisposing factors for *Candida* infections of CNS in children may be prematurity, low birth weight, neurosurgery, abdominal surgery, intravenous catheter use, parenteral nutrition, hyperalimentation, and feeding intolerance. Other possible causative agents include *Aspergillus*, mucormycetes, *Histoplasma, Blastomyces* и *Coccidioides*, etc.

Another rare cause of CNS infection in children may be a protozoan *Toxoplasma gondii*. It can affect individuals with weakened immune systems, such as those with acquired immunodeficiency syndrome (AIDS), leukemia patients, and newborns. Congenital toxoplasmosis is one the most serious manifestation of infection, resulting from the vertical transmission of *T. gondii* during antenatal period.

COMMUNITY-ACQUIRED BACTERIAL MENINGITIS IN CHILDREN

Bacterial meningitis is the inflammation of the meninges and subarachnoid space caused by bacteria, which most commonly affects young children (especially those under 3 months). Meningitis is a severe life-threatening condition with a high case fatality rate, which can lead to serious long-term sequelae.

Aetiology of community-acquired bacterial meningitis

The most common pathogens of bacterial meningitis vary according to the age of a child (table 1).

Male infants have a higher incidence of gram-negative neonatal meningitis. Female infants are more susceptible to *Listeria monocytogenes* infection. *Streptococcus agalactiae* affects both sexes equally.

A recent systematic analysis estimated that *Neisseria meningitidis* comprised 17.3 % (16.5–18) of global all-age meningitis cases in 2019, ranging from 8.5 % in Australasia to 21.4 % in Central Sub-Saharan Africa, while *Streptococcus pneumoniae* comprised 13 % (12.4–13.6) of global all-age meningitis cases in the same year, ranging from 10.4 % in Eastern Europe to 14.7 % in Tropical Latin America.

Table 1

Aetiology of community-acquired bacterial meningitis in children

Age group		Bacterial pathogen
Neonates	**Early onset** **< 1 week**	Streptococcus agalactiae Escherichia coli Listeria monocytogenes
	Late onset **> 1 week and < 6 weeks**	Escherichia coli Klebsiella pneumoniae Streptococcus agalactiae Staphylococcus aureus Pseudomonas aeruginosa Enterobacter species Listeria monocytogenes
Infants, 1–3 months		Escherichia coli Haemophilus influenza Streptococcus pneumoniae Neisseria meningitidis Listeria monocytogenes
Children, 3 months — 5 years old		Haemophilus influenza Streptococcus pneumoniae Neisseria meningitidis
Children > 5 years old		Streptococcus pneumoniae Neisseria meningitidis

In the neonatal period, early-onset meningitis (during the first week of life) is primarily a result of vertical transmission from colonized mothers to neonates during pregnancy or birth. Late-onset meningitis is generally contracted as nosocomial or community infection.

Infectious agents can reach the CNS via haematogenous routes, transneurally thereby avoiding the blood-brain barrier, and across mucosal or skin surfaces. Pathogens can attack the CNS via direct action on host cells or overactivation of the host's immune response creating a cascade of neural injury by an overactive inflammatory process. Further immune dysregulation in the wake of an acute infection can lead to subsequent neural damage not only secondary to direct effect of the pathogen but also due to autoantibody responses triggered by that pathogen. The presence of bacteria in the subarachnoid space leads to activation of the immune response, resulting in bacterial lysis. The presence of bacterial particles triggers a further inflammatory response with on-going migration of neutrophils across the blood–brain barrier and continuous cytokine and chemokine release (including IL-1B or CXCL 1, 2, 5). A persistent inflammatory state subsequently leads to decreased cerebral perfusion, cerebral oedema, raised intracranial pressure, metabolic disturbances, and vasculitis, all contributing to neuronal injury and ischaemia.

Bacterial meningitis classically presents with fever, severe headache, signs of meningeal irritation, and altered level of consciousness or cognition including confusion or delirium (so called red flag combination). However, these symptoms and signs may be hard to detect or absent in some cases, especially in neonates and infants.

High fever with acute onset and intense, expanding headache, diffuse or localized in the frontotemporal regions, not relieved by taking painkillers are typical for bacterial meningitis. Nevertheless, children with meningitis may be afebrile at the time of initial presentation, or not complain of a headache due to their altered condition. Within a few hours after the onset of the disease, nausea and/or vomiting appear. Vomiting is repeated, not associated with food intake, especially in the morning or at night. Sometimes dizziness may be noticed. General hyperesthesia (muscular, tactile, optic, and auditory) is characteristic.

Physical signs of meningeal irritation include jolt accentuation of headache, nuchal rigidity (neck stiffness), Kernig sign, and Brudzinski signs. On examination, meningeal irritation in children usually manifests as neck stiffness. The Kernig sign and Brudzinski signs have lower sensitivity. When seen in meningitis, these signs are usually present acutely within 24 hours of symptom onset. There is no correlation between meningeal signs and the severity of meningeal inflammation. Irrespective of disease severity, these meningeal signs may be absent in infants, in immunocompromised or comatose patients. Moreover, meningeal signs may result from non-infectious causes of nerve root irritation (e.g., subarachnoid hemorrhages from trauma or from vascular malformation, meningeal reaction to radiotherapy or intrathecal drugs for tumors).

The clinical picture of bacterial meningitis may manifest seizures. The incidence rate of seizures varies from 25 to 50 %. It can either be short-term febrile convulsions at the beginning of illness or be repeated generalised seizures with comatose status indicating the development of brain oedema.

The presence of a rash is not directly related to meningitis, but may be associated with development of sepsis. Generally, it is non-blanching petechial or purpuric rash mainly occurred in invasive meningococcal disease (meningococcemia) with or without meningococcal meningitis, less often in Haemophilus influenza sepsis or pneumococcal sepsis.

Children younger than 3 months may have very non-specific symptoms, including hyperthermia or hypothermia, change in sleeping or eating habits (trouble waking from sleep, not waking to eat), irritability or lethargy, vomiting, constant or high-pitched cry, and seizures. Meningism and a bulging fontanel may be observed but are not needed for diagnosis. Infants with meningitis may be quiet at rest but cry when moved or comforted (paradoxical irritability). Temperature instability with fever or hypothermia is common but not always present. Seizures occur in 15 % to 34 % of infants. Neck stiffness is uncommon.

After the age of 3 months, children may more often display characteristic symptoms of bacterial meningitis (fever, vomiting, irritability, lethargy, or any behavior change). After 2–3 years, children may complain of headaches, stiff neck, and photophobia.

The onset of illness, generally is acute, but may be peracute, fulminant with rapid progression to severe disease. The fulminant course is more often associated with meningococcal infection.

Neurological complications of bacterial meningitis include cerebral infarction, cerebral abscess, subdural empyema, cerebritis, and intracerebral bleeding, and these can lead to long-term sequelae such as focal neurological deficits, hearing loss, cognitive impairment, and epilepsy. Intellectual and behavioral deficits, particularly speech or language problems, are the most common sequelae following meningitis. Children under 24 months of age developed neurological sequela more commonly than older children did. Early identification and intervention may help to minimize long-term impact of these problems.

Diagnosis of community-acquired bacterial meningitis

Collecting medical history, examining complaints and physical examination are decisive for a diagnosis of meningitis. History should include questioning about any recent neurosurgical procedures, immunisation status, living arrangements, and travelling. Pronounced headache, persistent nausea, vomiting, which is not associated with food intake, febrile fever, and signs of meningeal irritation with or without altered mental status require the exclusion of meningitis. However, none of the signs and symptoms mentioned above presents in 100 % of cases in meningitis, and no clinical feature is diagnostic in isolation or pathognomic of meningitis. It should also be taken into account that meningeal signs may be negative at the time of physical examination. It can be observed in the beginning of meningitis, in patients having coma or with immunosuppression, therefore the absence of meningeal signs does not exclude bacterial meningitis and require a lumbar puncture.

Laboratory testing of a patient with suspected meningitis includes:

1. CBC with differential and platelet count.
2. Blood culture.
3. Biochemical blood test (serum electrolytes, blood urea nitrogen, creatinine, glucose, CRP).
4. Procalcitonin test.
5. Evaluation of haemostasis (prothrombin time, international normalized ratio, activated partial thromboplastin time).
6. Blood gas analysis (including measurement of lactate level).
7. CSF evaluation.

Lumbar puncture should be performed in all children with suspected meningitis, unless there is a specific contraindication to LP.

Contraindications to lumbar puncture. Absolute contraindications are a space-occupying intracranial lesion or diffuse brain oedema, which both cause a substantial brain shift, results in an increased risk of cerebral herniation when a LP is performed. Other (relative) contraindications for immediate LP are severe coagulation disorders, septic shock, respiratory failure, and infection at the site for LP. In critically unwell or shocked children LP may be delayed until the patient is haemodynamically stabilised, but sampling should be completed as soon as feasible.

In patients with a history of CNS lesions, new-onset seizures, focal neurological deficits, an immunocompromised state or a moderate-to-severe impairment of consciousness preliminary cranial imaging (by CT scan or MRI) is required.

CSF analysis is the gold standard for defining the presence of meningitis and helps determine the type and cause of the disease.

Mandatory CSF evaluation is following:

– CSF cell count and differential;
– CSF glucose and protein concentration;
– CSF lactate concentration;
– Gram stain;
– CSF culture.

CSF should be collected as soon as possible after admission, preferably before antibiotic therapy is started, and referred to the laboratory immediately.

Typical abnormalities of the CSF in bacterial meningitis are characterised by elevated opening pressure, the CSF WBC count greater than 1,000 cells/μL (10^6/L/cells) mainly of polymorphic leukocytes, low glucose concentration (CSF/ blood glucose ratio < 0.4), and increased protein level (usually exceeding more than 1g/ L).

A measurement of CSF lactate concentration can be useful in differentiating bacterial from viral meningitis. It was estimated that a CSF-lactate ≥ 4 mmol/L is regarded as a strong indicator of a non-viral meningitis with a diagnostic sensitivity and specificity of up to 93–99 % and 88–94 %, respectively. An increased CSF lactate is found earlier than a reduced glucose in bacterial infection. In viral meningitis, lactate levels remain normal, even when neutrophils are present in the CSF. We should nevertheless draw attention to other reasons for raised level of CSF lactate. It may occur in patients with severe cerebral hypoxia or genetic lactic acidosis, intracranial haemorrhage, and epilepsy.

The probability of visualizing bacteria depends on the concentration of bacteria in CSF. Bacteria are identifiable in 60–90 % of all cases of acute bacterial meningitis, particularly in cases where more than 10^5 colony-forming units/mL

are present. The specificity of a positive Gram stain for bacterial meningitis is approximately 95 %. Severely immunocompromised patients can develop bacterial meningitis, but might present with only a minimal pleocytosis. In these patients, CSF Gram stain might be especially important. However, Gram staining does not provide a definitive identification of the bacteria and information concerning antibiotic sensitivities. Oral or intravenous pretreatment with antibiotics may disable the identification of organisms.

Bacterial culture is the first priority for confirmation and isolation of the pathogen. Culture is considered as a gold standard but has low sensitivity due to potential antibiotic use by the patient before sample collection. CSF cultures should ideally be combined with simultaneous blood cultures, as meningitis caused by bacterial pathogens is usually associated with the onset of bacteraemia. When the CSF punctate is collected (under aseptic conditions) into numbered tubes, the first tube should not be used for culture due to a higher probability of skin contaminants and tube number 3 is frequently reserved for culture.

The pathogen can be identified by blood cultures in 50–80 % of cases, making blood cultures a valuable, readily available alternative diagnostic tool.

Additional supporting studies are CSF latex agglutination test and CSF PCR. Latex agglutination test allows rapid detection of bacterial antigens in the CSF. Sensitivity varies greatly between bacteria. The results may be negative in early meningitis. This technique does not replace Gram stain and CSF culture. PCR assays can improve clinical outcomes through providing earlier results compare to CSF culture. PCR is especially useful in patients who started antibiotic treatment before the LP, as in these individuals, CSF and blood cultures are often negative. Currently, multiplex PCR detecting 14 of the most common bacterial, viral, and fungal causes of infectious meningoencephalitis is available (Meningitis/ Encephalitis Panel). The time of testing is only 3 hours.

The CSF definition of meningitis includes a combination of CSF culture positivity or CSF pleocytosis along with either blood culture positivity or CSF PCR / CSF latex agglutination positivity.

Neuroimaging. Apart from severely depressed mental status (coma) and focal neurologic deficit, indications for neuroimaging before LP include: papilloedema, history of hydrocephalus and/or presence of a CSF shunt, recent history of CNS trauma or neurosurgery.

CT scan is highly sensitive to acute intracranial hemorrhages (parenchymal or extra-axial), calcified lesions or bone deformities. MR imaging is much more sensitive for detecting early changes of CNS infections and depicting various imaging findings during each disease process, due to its high anatomy resolution, superb soft tissue differentiation, multiplanar acquisition, and versatile sequences of delineating different characters of pathological processes of CNS infections. Administration of intravenous contrast in MRI increase the sensitivity and

specificity of the MRI technique, helping further delineate the pathology, exclude most non-infectious aetiologies, narrow down the differential diagnoses.

Electroencephalography is a useful adjunct to clinical neurological examination but is not required for the clinical diagnosis of coma or encephalitis. EEG can be helpful for monitoring cerebral function, distinguishing organic from non-organic disorders, assessing a liability to concurrent symptomatic seizures in patients with CNS infections.

Clinical manifestations of community-acquired bacterial meningitis

Pneumococcal meningitis. *Streptococcus pneumoniae (pneumococcus)* is one of the most common cause of bacterial meningitis in children and adults worldwide. Pneumococcus is a Gram-positive diplococci, facultative, anaerobic bacterium, which appears as lanceolate diplococci, single cocci and/or in short chains under microscopy. More than 90 serotypes have been identified depending on the unique polysaccharide capsules.

The epidemiology of pneumococcal meningitis has changed significantly with the implementation of vaccination in the last two decades. Although the introduction of the pneumococcal conjugate vaccine has greatly reduced the global burden of invasive pneumococcal disease including meningitis, pneumococcal meningitis remains more frequently associated with worse outcomes than meningococcal meningitis, with a mortality rate of 35 % and neuropsychological sequelae in 25 % of those who survive.

Currently, nearly all pneumococcal infections in children in areas covered vaccination are caused by non-vaccine pneumococcal serotypes. Pneumococcal meningitis occurs more commonly during the winter.

The human nasopharynx is the main reservoir for S. pneumoniae. Transmission occurs through respiratory droplets or saliva. In most of cases, the bacteria are dormant. Carriage rates of S. pneumoniae are highest among young children (37 %) and may rise to up to 58 % in crowded situations such as day care centers. Pneumococcal carriage is also frequent in children with siblings attending day care center. Pneumococcal meningitis is not considered to be contagious. Therefore, there is little chance of a second related case occurring.

There are underlying conditions, which predispose to invasive infection or meningitis such as asplenia (anatomic or functional), antibody deficiency state, cerebrospinal fluid leak, and otic fistula (e.g., cochlear implant). Boys appear to be more commonly affected in a near 2 : 1 ratio.

The clinical symptoms, CSF profile, and neurologic complications of pneumococcal meningitis are similar to other forms of purulent bacterial meningitis. CSF microscopy often reveals typical lancet-shaped, Gram-positive cocci in

pairs; CSF analysis identifies neutrophilic pleocytosis, a low CSF-blood glucose ratio (< 0.6), and a high CSF protein concentration (usually > 1 g/L). Clinical presentation of pneumococcal meningitis in typical cases is characterised by the presence of symptoms and signs in the red flag combination (any combination of fever, headache, neck stiffness, altered level of consciousness or cognition including confusion or delirium), but may vary depending on the age of the child and duration of illness. An antecedent upper respiratory tract infection may be reported in the history.

Invasive pneumococcal disease in children is not often accompanied by rash which is more typical for meningococcal sepsis. Bacteraemia is quite common in young children. Bacteraemia might occur in conjunction with meningitis, pneumonia, or septic arthritis, and also occur concurrently with a localized disease such as acute otitis media or without any focal lesions. Symptoms are non-specific, including less activity, poor feeding and irritability, fever with chills, clammy skin, confusion, difficulty in breathing, and severe body ache.

Meningococcal meningitis. *Neisseria meningitidis* is an anaerobic Gram-negative diplococcus, the obligate human commensal/pathogen that resides in the pharyngeal mucosa and responsible for invasive meningococcal disease.

The most common clinical manifestations of IMD are meningitis and septicemia, although in some cases both clinical pictures are present. Globally, the incidence of IMD is 500,000 cases every year, although the incidence varies from < 1 per 100,000 per year in North America and Europe to 10–1,000 per 100,000 per year in the "meningitis belt" of sub-Saharan Africa.

The meningitis belt consists of 26 countries in Africa spanning from Senegal to Ethiopia. This region has historically reported epidemics of *Neisseria meningitidis* serogroup A. To reduce the incidence rate of meningitis, 24 of the 26 countries in the meningitis belt had introduced meningococcal serogroup A conjugate vaccine (MACV [MenAfriVac]) campaigns by the end of 2021.

Globally, 53 countries have meningococcal conjugate vaccines in their routine immunisation schedule, including 27 countries with quadrivalent meningococcal ACYW vaccines and 9 countries with meningococcal serogroup B vaccines. At the end of 2023, the U.S. Food and Drug Administration (FDA) has approved the first and only pentavalent vaccine (Penbraya) that provides coverage against the five most common serogroups (A, B, C, W and Y) in adolescents and young adults 10 through 25 years of age.

Although the burden of meningococcal meningitis is greatest in the meningitis belt of sub-Saharan Africa, meningitis is a threat in all countries of the world. Death occurs in 6–10 % of cases and sequelae in 4.3–11.2 % of cases.

All age groups are at risk for IMD, but infants and adolescents are particularly vulnerable. Crowded living conditions including some settings, such as schools, university dormitories, and military barracks result in increased transmission of

N. meningitides. Moreover, low socioeconomic status, minority ethnicity, immune deficiencies and asplenia predispose individuals to meningococcal infection.

The clinical manifestations of IMD may be more insidious in young children accompanied by non-specific signs. A high-grade fever, drowsiness, nausea/vomiting, irritability and poor feeding are present within 4–6 hours from the onset of the disease. In general, infants exhibit a more rapid progression of the disease compared to older children. When meningococcal meningitis develops, the red flag symptoms are observed (listed above). Neck stiffness is rare in children younger than 2 years of age. Bulging anterior fontanelle may occur in infants < 18 months age. In older children the most common symptoms are fever, nausea/vomiting, photophobia, headache, agitation, decreased level of consciousness, and neck stiffness. However, seizure and focal neurological signs are less common. Meningitis can develop simultaneously with meningococcemia but more often on the 2–3 day of the disease.

In case of meningococcal septicaemia (i.e., meningococcemia), rash appears 2–12 hours after the onset of fever. The rash may manifest on the 3–5th day from the disease onset, which is typical for adolescents. The most characteristic skin lesions are star-shaped non-blanching haemorrhagic elements 2–5 mm in size with an infiltrated dense base raised compared to the skin surface. The size of the haemorrhagic rash can vary from petechia to purpura and ecchymosis. The typical places of the rash are the chest, abdomen, shoulders, buttocks, outer surfaces of the thighs, shins, cheeks, and forehead. The haemorrhagic rash usually starts on the lower extremities, although mucous membranes and sclera may be involved. Skin lesions may include roseolas, macules, maculopapules, and urticariae with single haemorrhagic elements. The purpuric rash may progress to purpura fulminans, a cutaneous manifestation of disseminated intravascular coagulation. These cases are often associated with septic shock and skin necrosis, ischemia, or infarction of digits or limbs that usually require amputation. Three clinical signs of early sepsis have been identified in children and adolescents: leg pain, cold hands and feet, and abnormal skin color. Equally important is determination of altered behavior or mental state.

Chronic or recurrent meningococcemia may occur consisted of recurrent attacks of fever, arthralgia and/or arthritis associated with a rash and headache. The risk factor for recurrent meningococcal disease is primary or secondary immunodeficiency, including HIV, congenital complement deficiency or acquired inhibition, reduced or absent spleen function.

The diagnosis of IMD should be suspected when a child develops a haemorrhagic rash and/or signs of meningeal irritation and altered level of consciousness or cognition against the background of an acute onset of a high-grade fever and toxic appearance. A CBC test reveals leukocytosis, neutrophilia with a shift to the left, lymphopenia, and acceleration of the ESR. In meningococcal

meningitis, the CSF WBC count, CSF protein concentration and inflammatory markers (C-reactive protein, procalcitonin) typically are elevated; neutrophilic pleocytosis and low CSF glucose level are observed in the same way as in bacterial meningitis of other aetiologies. CSF microscopy often shows Gram-negative diplococci.

Neurological sequelae are relatively rare in meningococcal meningitis compare to meningitis caused by H. influenzae or S. pneumoniae. The most common sequelae are hearing loss (rate of occurrence 2 % to 15 % of cases in various studies), epilepsy, learning disabilities, headache and visual defects/loss of vision.

Haemophilus influenzae meningitis. *Haemophilus influenzae* is a facultatively anaerobic, pleomorphic, Gram-negative coccobacillus of the family Pasteurellaceae. H. influenzae is divided into encapsulated and non-encapsulated types (i.e., non-typeable). Encapsulated strains express six antigenically distinct capsular polysaccharides, which are classified as serotype a through f. Before the introduction of widespread immunisation, H. influenza type b was the most common cause of bacterial meningitis in children, and remains the leading cause of meningitis morbidity and mortality in unimmunised populations around the world. The pick incidence of invasive Hib in unimmunised populations is in the 6–24 months age group. H. influenzae non-type b strains can cause invasive disease clinically similar to type Hib disease (pneumonia, bacteraemia, meningitis, epiglottitis, septic arthritis, cellulitis, or purulent pericarditis). Non-typeable strains can also cause invasive disease but more commonly cause localised respiratory tract infections in children.

Medical underlying conditions predisposing to invasive Hib disease include sickle cell disease, functional asplenia, HIV infection, IgG2 subclass deficiency, chemotherapy for malignancies, bone marrow transplantation.

H. influenza, along with S. pneumoniae and N. meningitidis are carried asymptomatically in the human nasopharynx and transmission occurs through respiratory droplets or saliva. Symptoms typically occur within 3–7 days after transmission. The clinical picture of H. influenza meningitis has classic manifestations of bacterial meningitis and characterised by the presence of the red flag symptoms (see above). Infants usually show non-specific symptoms such as irritability, drowsiness, poor feeding, and vomiting in addition to the classic symptoms. Antecedent symptoms of an upper respiratory tract infection are common. Occasionally, the course is fulminant, with rapid neurologic deterioration leading to respiratory arrest. Septic shock is present in 20 % of cases of meningitis and can be associated with coagulopathy and purpura. In a number of cases, the course of meningitis is complicated by the development of subdural effusion or empyema, ischemic or haemorrhagic cortical infarction, cerebritis, ventriculitis, intracerebral abscess, and hydrocephalus. Hib meningitis case fatality ratios in industrialised countries are around 5 % but may be as high as 40 % in developing

countries. H. influenza meningitis/meningoencephalitis in 10–15 % of survivors results in severe permanent neurologic sequelae that include bilateral sensorineural deafness, blindness, hydrocephalus, epilepsy, and cerebral palsy. A further 15–20 % will have less severe long-term sequelae such as partial hearing loss, cognitive or developmental delay.

The typical laboratory finding in Hib meningitis is polymorphonuclear pleocytosis, as is the case in most other forms of purulent bacterial meningitis. CSF White Blood Cell counts in Hib meningitis are greater than 100/μL in more than 90 % of cases and greater than 1,000 in 65–70 % of cases. Low CSF-to-serum glucose ratios and increased CSF protein concentration are also characteristic.

In the setting of bacterial meningitis, CSF lactate is frequently elevated. Elevation of CSF lactate in Hib meningitis may be due to cerebral oedema or changes in cell membranes or cellular energy metabolism leading to anaerobic glycolysis. CSF lactate may remain elevated for a fairly long time after effective antimicrobial therapy has resulted in amelioration of brain oedema and restoration of intracranial pressure to the reference range. Gram staining of the CSF may reveal the Hib pleomorphic Gram-negative coccobacilli.

Streptococcus agalactiae meningitis. *Streptococcus agalactiae,* commonly referred to as group B Streptococcus, remains the most common bacterial cause of meningitis in the neonatal period. S. agalactiae is a beta-hemolytic, Gram-positive, encapsulated bacterium that commonly colonizes the gastrointestinal and genital tracts of more than 50 % of adult individuals. GBS is a commensal organism of the normal vaginal and intestinal microbiome of healthy adults. However, due to its opportunistic nature, GBS can transition to a highly invasive pathogen under certain conditions. This bacterium can lead to severe disease in neonates and, occasionally, in postpartum women and individuals with an impaired immune system or underlying medical condition.

There are three types of the disease in infants, depending on the age of presentation:

1. *Early-onset disease* is defined as the onset of infection in the first six days of life, with symptoms usually within the first 12 h after birth and almost always clinically apparent in the first 24 to 48 h. Early-onset disease usually presents as bloodstream infection without a focus (80–85 %), with shock in about 25 % of cases, pneumonia (10–15 %), and meningitis (5–10 %).

2. *Late-onset disease* defined as GBS infection from day 7 to day 89 of life (median 37 days), has a similar clinical presentation to early-onset disease but with another frequency of occurrence of clinical syndromes. Although bloodstream infections remain the most common presentation of late-onset disease (in 65 %), meningitis occurs in 25–35 % of cases. Late-onset disease may also present with other less common sites of infections, such as pneumoniae, osteomyelitis, pyogenic arthritis, and cellulitis-adenitis syndrome.

3. *Very late-onset disease* is defined as GBS infection in infants 3 months of age or older. Most cases occur in premature infants or those with very low birth weights whose corrected prepatellar age is younger than 3 months. In full-term infants, very late-onset disease can be associated with HIV infection or immunodeficiency. The clinical manifestations in these older infants are similar to those in patients with typical late-onset infection; bacteraemia without a focus and meningitis are the most common clinical features.

The absence of specific symptoms, together with a high incidence of negative blood cultures, makes the diagnosis of meningitis more difficult in newborns than in any other age groups. Clinical presentation of neonates with meningitis is often subtle and non-specific, and is absent in more than 30 % of cases. It includes fever, lethargy, listlessness, high-pitched crying, irritability, feeding difficulties and refusal, vomiting, diarrhea, respiratory distress, bulging fontanelle, and seizures. Nuchal rigidity occurs in less than 25 % of affected neonates and is often a late finding of the illness, being associated with poor prognosis.

Laboratory data of CSF in S. agalactiae meningitis generally characterised by polymorphonuclear pleocytosis, low CSF-blood glucose ratio, and elevated CSF protein concentration. Nevertheless, for neonates with bacterial meningitis caused by GBS, CSF white blood cell counts are often inconclusive, and a normal CSF study does not exclude meningitis. CSF Gram staining can help in the identification of GBS with a sensitivity ranging between 80 and 90 %. CSF microscopy reveals Gram-positive cocci in pairs (diplococci) and chains.

The main risk factor for early-onset disease is maternal rectovaginal colonization with GBS at the end of the pregnancy; additional established risk factors include prolonged rupture of membranes before delivery (> 18 h), intrapartum fever (≥ 38 °C), GBS bacteriuria during the current pregnancy, a previous infant with GBS disease, and preterm delivery at less than 37 weeks of gestation. Risk factors and the transmission route for late-onset disease are less well established; the GBS may be acquired from the mother or from environmental sources.

The outcome of GBS disease is related to the severity and site of infection. The overall mortality rate of GBS remains substantial at 3 % to 10 % for early-onset disease and 1 % to 6 % for late-onset disease. Premature infants born before 37 weeks gestation with early-onset disease have the highest mortality rate, approximately 20 %. There is not much information available on the long-term outcome of patients with GBS sepsis without meningitis. In infants with septic shock, the development of periventricular leukomalacia correlated with neurodevelopmental sequelae.

Despite advances in prevention, detection, and care for patients with GBS meningitis, the neurologic outcome of patients remains the same. Approximately 20 % to 30 % of infants with early- or late-onset meningitis will have permanent severe neurologic impairments such as cortical blindness, bilateral sensorineural

hearing loss, cerebral palsy, or severe motor deficits. Another 25 % of patients will have mild to moderate impairments such as hydrocephalus requiring a ventriculoperitoneal shunt, seizures, or mild developmental and learning delays. Only 51 % of patients demonstrated normal age-appropriate development.

Listeria monocytogenes meningitis. *Listeria monocytogenes* is a Gram-positive facultative anaerobic intracellular bacillus widely distributed in the environment, which can grow at low temperatures (4 °C to 10 °C) and withstand low pH and high salt concentrations. It is generally transmitted to humans through ingestion of contaminated food (ready-to-eat food, deli meats and soft cheeses). The primary bacteraemia, after ingestion, is followed by dissemination in the CNS, endocardium and for pregnant women, invasion of the placenta and fetus. Newborns, elderly people, and immunocompromised people are particularly susceptible to L. monocytogenes infection (listeriosis). L. monocytogenes causes about 4 % of community-acquired bacterial meningitis in patients over 16 years and about 1.5 % of bacterial meningitis in newborns. Compared to other meningitis-causing bacterial pathogens, such as S. pneumoniae, N. meningitidis, and H. influenzae, L. monocytogenes has a higher propensity to invade the CNS. More than 90 % of infected newborns develop meningitis. Non-neonatal children have lower L. monocytogenes meningitis incidence compared to neonates.

Neonates can present with early-onset and late-onset syndromes similar to those of group B streptococcal infections. Preterm birth, pneumonia, and septicaemia are common in early-onset disease (within the first 7 days of life), with fatality rates of 14 % to 56 %. Early-onset listeriosis is usually acquired through transplacental transmission. The most common signs and symptoms of invasive neonatal listeriosis are respiratory distress, fever, neurological abnormalities (lethargy, altered consciousness, or seizures), maculopapular or papulovesicular rash, and jaundice. Less common is infantisepticum granulomatosis (an erythematous rash with small, pale papules characterised histologically by granulomas). Late-onset infection occurs at 8 to 90 days following term deliveries and usually result in meningitis with fatality rates of approximately 25 %. Late-onset listeriosis occurs due to vertical or nosocomial transmission. Most listeriosis feature elevated peripheral blood leukocyte count, C-reactive protein, and procalcitonin levels, and increased erythrocyte sedimentation rate.

L. monocytogenes also can cause rhombencephalitis (brain stem encephalitis) in otherwise healthy adolescents and young adults.

The laboratory parameters of CSF in L. monocytogenes meningitis (cell count, protein level, glucose level) are similar to that of other bacterial meningitis. However, a half of the patients with L. monocytogenes meningitis may have normal CSF glucose levels, and a one third may have a mononuclear cell predominance. It should be considered that the organisms can be gram-variable and can resemble diphtheroids, cocci, or diplococci in a Gram stain.

Management of community-acquired bacterial meningitis

Antimicrobial therapy. When bacterial meningitis is suspected, antimicrobial therapy should be initiated immediately following the LP, and maintained until CSF culture results are negative. In the acute phase, minimisation of delays in antibiotic therapy is the primary goal. Several studies have demonstrated increased risk of mortality and adverse outcome with delays in antibiotics greater than 4–6 hours compared to less than 2 hours from presentation.

The choice of the initial empirical antibiotics should be based on age, local epidemiological patterns of microbial resistance and the need to add ampicillin against L. monocytogenes. For suspected bacterial meningitis when the causative organism has not been identified ceftriaxone is recommended. If ceftriaxone is contraindicated, cefotaxime is a first-line antibiotic.

Contraindications to administration of ceftriaxone include: documented hypersensitivity to ceftriaxone; premature neonates up to an age of 41 weeks (gestational age + chronological age); neonates (≤ 28 days) if they receive calcium-containing IV products, or hyperbilirubinemic neonates due to ability to displace bilirubin from its binding to serum albumin, which leads to risk of bilirubin encephalopathy.

Meningococcal meningitis patients with significant hypersensitivity to β-lactam antimicrobial agents can be treated with chloramphenicol. H. influenza and S. pneumoniae are also highly susceptible to chloramphenicol.

Treatment for neonatal bacterial meningitis should cover Escherichia coli, Streptococcus agalactiae, and Listeria monocytogenes. It cannot be overemphasised that Listeria spp. are resistant to cephalosporins; thus, ampicillin should be given to newborns and all immunosuppressed patients with suspected L. monocytogenes meningitis, including pregnant women or elderly people. Ampicillin or amoxicillin is also a drug of choice for S. agalactiae meningitis. For neonates and infants with suspected E.coli meningitis ampicillin should be combined with an aminoglycoside (e.g., gentamicin, tobramycin, and amikacin). If S. pneumoniae is suspected, vancomycin should be added. First-line and alternative antibiotic therapies for bacterial meningitis in neonates and infants are presented in table 2.

Once the causative pathogen and its specific antimicrobial susceptibility have been determined, the antibiotic therapy must be optimised for targeted treatment.

Antibiotic therapy should be administered IV to achieve adequate serum and CSF levels. An intraosseous route is acceptable if venous access is not an option. There is no role of oral antibiotics in children with suspected meningitis excepting trimethoprim-sulfamethoxazole.

Successful treatment of meningitis requires *administration of the highest recommended doses of antimicrobials*. Dosages and dosing intervals for intravenous antimicrobials in infants and children with bacterial meningitis are shown in annex.

Table 2

Etiotropic therapy for bacterial meningitis in neonates and infants, 1–3 months

Bacterial pathogen	First-line antibiotic therapy	Alternative antibiotic therapy	Duration
Streptococcus agalactiae	Ampicillin or penicillin G	Cefotaxime, ceftriaxone (if not contraindicated) or vancomycin	14–21 days
Escherichia coli	Ampicillin plus an aminoglycoside	Cefotaxime, ceftriaxone (if not contraindicated) or vancomycin	At least 21 days
Listeria monocytogenes	Ampicillin or penicillin G	Trimethoprim-sulfamethoxazole	At least 21 days

For beta-lactams, in vitro and animal studies have demonstrated that the best predictor of bacterial killing is the time duration which the free drug concentration exceeds the minimum inhibitory concentration of the organism. Therefore, it is important to follow the correct dosage regimen. When prescribing meropenem, it should be taken into account that extended infusion of this medicine provides more benefits compared to standard infusion. A high-dose extended infusion of meropenem should start from bolus containing a single dose (over 30 minutes), following the next dose 8 hours after infusion lasting 3–4 hours.

The standard recommendations for antibiotic therapy duration in bacterial meningitis in children are based predominantly on expert consensus. In the patient who has an uncomplicated course, experts recommend 7 days for meningococcal meningitis, 10 to 14 days for pneumococcal meningitis, and 7 to 10 days for meningitis resulting from Hib. For the neonate and younger infant, minimum 14 days of antibiotics are recommended for treatment of meningitis resulting from GBS. The recommended duration of antibiotic administration for treating meningitis resulting from Gram-negative enteric bacteria in the neonate and younger infant is at least 3 weeks or 2 weeks beyond the first sterile repeat CSF culture, whichever is longer.

If the CSF results suggest bacterial meningitis, but the aetiology has not been established antibiotic therapy should be continued for 10–14 days.

In neonates with gram-negative bacillary meningitis, examination of CSF during treatment is necessary to verify that cultures are sterile. Reexamination of CSF for chemistries and culture should be performed 48–72 hours after treatment initiation; further specimens are obtained if CSF sterilisation is not demonstrated or clinical response is not apparent.

The decision to end antimicrobial therapy for bacterial meningitis should be based on the following points:

– clinical improvement (resolution of fever, headache, disappearance of meningeal irritation);

– CSF findings including a decrease in protein levels, normalisation of glucose and lactate concentrations, reducing the severity of pleocytosis with a predominance of lymphocytes;

– CSF culture and Gram stain test should be negative.

A longer course of therapy is required for children with meningitis whose course is complicated. Prolonged treatment, sometimes for as long as eight weeks, may be required for infants with ventriculitis, abscesses, or multiple areas of infarction or haemorrhage with resulting encephalomalacia.

Adjunctive therapy. The goal of adjunctive therapies is to reduce inflammation-related neuronal death and brain damage. *Dexamethasone* is the only adjunctive therapy that has been advocated by the IDSA and ESCMID guidelines. Available evidence suggests that, in high-income countries, dexamethasone treatment should be started with or 10–20 minutes before the first dose of antibiotic and continued for 4 days in both children and adults. Dexamethasone is recommended in children > 3 months old with bacterial meningitis especially if H. influenza or S. pneumoniae is suspected in a dose of 0.15 mg/kg/dose IV 6 hourly not exceeding an adult dose (10 mg 6 hourly). The course of dexamethasone should be cancelled simultaneously. If dexamethasone has not been started, it can still be administered up to 4 hours after the first dose of antibiotic has been given.

Anticonvulsants should be administered for immediate treatment of seizures at the following dosages:

– Diazepam (0.1–0.2 mg/kg/dose IV);

– Lorazepam (0.05–0.2 mg/kg/dose IV).

Supportive care and pathogenetic therapy preventing or reducing brain swelling include following:

1. Keeping the neck straight and elevated to allow the brain to drain with ease.

2. Closely monitoring *blood gas levels* to ensure adequate oxygenation and metabolic stability.

3. Careful fluid therapy, avoiding both hypo- and hypervolemia.

4. Minimising the use of PEEP.

5. Inducing coma with barbiturates (protective sedation).

6. Use of hyperosmolar therapy: mannitol (bolus dosing 0.5 to 1.5 mg/kg following intermittent dosing 0.25 to 0.5 mg/kg), three per cent hypertonic saline (i.e., 3 % NaCl) as a 3–5 ml/kg bolus (over 10–20 minutes), monitoring serum sodium levels closely. It is considered relatively safe while serum sodium is less than 140–160 mEq/dL. Three ml/kg of 3 % NaCl will increase plasma sodium by approximately 2–3 mmol/L.

7. Use of loop diuretics for venodilation and diuresis without causing an increase in intracranial blood volume (furosemide in a dose of 1.0 mg/kg/dose IV, max 40 mg).

8. Administration of corticosteroids (dexamethasone in a dose of 0.15 mg/kg/dose IV 6 hourly).

9. A decompressive craniectomy allowing the brain to sell without causing compression. It is usually considered as a last resort when all other intracranial pressure-lowering measures have failed.

All patients suffering from meningitis should have an audiologic evaluation upon completion of therapy. All recovering newborns should undergo auditory evoked potential studies to screen for hearing impairment.

ASEPTIC MENINGITIS IN CHILDREN

Aseptic meningitis is the inflammation of the brain meninges caused by various factors (non-purulent) other than the pathogens of classic purulent bacterial meningitis (S. pneumoniae, N. meningitidis, H. influenza, etc.).

Viruses are the most common cause, and enteroviruses are the most frequently detected viruses. However, we highlight that aseptic and viral meningitis are not interchangeable because aseptic meningitis can also be triggered by diverse factors, including infections caused by mycobacteria, spirochetes, fungi, systemic diseases (e.g., sarcoidosis, Kawasaki disease, systemic lupus erythematosus, etc.), medications (e.g., non-steroidal anti-inflammatory drugs, sulfamides, penicillins, lamotrigine, monoclonal antibodies, etc.), and malignancy (metastasis from solid cancers or lymphoma, and leukaemia).

Aseptic meningitis of viral aetiology

Viral meningitis is the most prevalent, and is usually benign and self-limiting. The most common causes associated with aseptic meningitis in children include *Enteroviruses, Parechoviruses, Tick-borne encephalitis virus, Arboviruses, Herpes simplex virus.* Other uncommon viral pathogens are *Mumps virus, Lymphocytic choriomeningitis virus, HIV, Epstein-Barr virus,* and *Cytomegalovirus.* Rarely aseptic meningitis could stem from *Varicella zoster virus, Influenza viruses, Parainfluenza viruses, Human herpesvirus type 6, Measles virus, Rotavirus, Coronavirus,* and *Primate Erythroparvovirus 1.*

Viral meningitis most commonly occurs in young children, with the incidence decreasing with age. Clinical picture of viral meningitis varies according to their age, immune status, and aetiologic agents. Viral meningitis typically manifests similar symptoms as bacterial meningitis (acute onset of fever, headache, photophobia, neck stiffness, and nausea/vomiting) but is less severe.

Mumps was previously a common cause of viral meningitis in children but has sharply decreased recently due to the widespread immunisation, and was supplanted by *Enteroviruses.* Mumps meningitis occurs in approximately 5–10 % of mumps cases. Varicella zoster virus can also cause viral meningitis, more commonly with reactivation than in primary infection. Varicella meningitis can occur without cutaneous lesions.

Aseptic meningitis can be caused by HSV infection (especially HSV type 2) and manifests as mild, self-limited illness, or as life-threatening meningoencephalitis.

Meningitis due to enterovirus and parechovirus infection. *Enterovirus* and *parechovirus* infections are a major cause of aseptic meningitis in children, especially in neonates and young infants. Enteroviruses and Parechoviruses are the small RNA non-enveloped viruses, which belong to the *Picornaviridae* family, genus *Enterovirus* and *Parechovirus,* respectively.

The incidence of parechovirus infection has been underestimated, but data shows that Parechoviruses are at least as prevalent as Enteroviruses. Parechovirus infections are rare in older children and adults, while enterovirus infections are regularly seen in older children and adults. The majority of cases of CNS infections are caused by Coxsackievirus A and B, Enterovirus B69, A71, B73, and Parechovirus type 3, which is the most pathogenic parechovirus type. The enterovirus D68 was also reported as a common cause of viral meningitis, with severe and fatal complications.

Transmission of infection occurs through the fecal-oral and transplacental routes, and by respiratory droplets. The primary replication sites of Enteroviruses and Parechoviruses are the epithelial cells of the oropharyngeal and intestinal mucosa. Although some replication may occur in the nasopharynx with spread to upper respiratory tract lymphatics, most of the viruses are swallowed and transferred to the stomach and lower gastrointestinal tract. There, Enteroviruses presumably bind to specific receptors on enterocytes. The virus crosses the intestinal lining cells reaches the Peyer's patches, where significant viral replication occurs. This is followed by a viremia that may lead to a secondary site of tissue infection including the CNS resulting in meningitis or encephalitis.

The seasonality of Enteroviruses and Parechoviruses (types 1 and 3) is notably not uniform. Parechoviruses types 3 infections peak in the spring and summer months *Enterovirus* infections have seasonal peaks in summer and fall, whereas Parechoviruses types 1 cases have been recorded year-round with a low incidence in the summer months.

The clinical picture of parechovirus and enteroviral CNS infections is similar and represented by non-specific symptoms, including fever, headache, vomiting, irritability, neck stiffness, malaise, and poor feeding. Many clinical cases may be accompanied by macular or maculopapular rash and gastrointestinal symptoms.

The CSF analysis reveals mild to moderate pleocytosis (usually not exceeded 1000 cells/μL) with lymphocytic predominance, but early in the course of aseptic meningitis polymorphonuclear cells can be predominant. CSF glucose level typically is normal. Protein level is usually normal to mildly elevated. The elevated values may correlate with the presence of encephalitis. Normal lactate concentration is seen. It should be noted that lack of pleocytosis in parechovirus and enteroviral CNS infections is possible in newborns and young infants.

Molecular detection of pathogen in CNS is definitive for the aetiological diagnosis of viral meningitis. The gold standard for diagnosing enterovirus and parechovirus infection is Reverse-transcriptase real-time quantitative PCR. CSF along with blood and feces has the highest sensitivity for identifying an Enterovirus or Parechovirus. Detection of viral nucleic acid in CSF confirms CNS infection. The BIOFIRE FILMARRAY Meningitis/Encephalitis Panel for these purposes can be used, which becoming increasingly popular nowadays. This diagnostic panel simultaneously tests 14 of the most common bacterial, viral, and fungal pathogens that attack the nervous system, including Enteroviruses and Parechoviruses.

Treatment is supportive; no antivirals are available. However, when the patient seems significantly ill or the CSF characteristics are ambiguous it is appropriate to initiate antibiotic therapy, then discontinue as soon as the diagnosis of viral infection is confirmed.

Tick-borne encephalitis. Tick-borne encephalitis virus is an RNA virus of the genus Flavivirus. Five subtypes of the virus, i.e., European, Siberian, Far Eastern, Baikalian, and Himalayan have been described. Tick-borne encephalitis virus can be transmitted to humans through the bite of an infected Ixodes spp. tick or by consuming infected raw milk and dairy products (mainly raw goat or sheep milk, rarely cow's milk). Direct person-to-person spread of tick-borne encephalitis virus does not occur except rarely through blood transfusion or breastfeeding. Most cases are occur from April to November, with the peak appearing during the summer months. Although tick-borne encephalitis virus and B. burgdorferi share the same vector, coinfection in children is rarely reported.

While tick-borne encephalitis can affect children of any age, the mean age is around nine years, and the incidence rate increases with age. The case-fatality rate associated with the European and Siberian subtypes is 1 % to 3 %. The Far Eastern subtype typically causes a more severe monophasic illness with a case fatality rate of about 20 % and neurologic sequelae in up to 80 % of survivors.

The majority of tick-borne encephalitis virus infections is asymptomatic. Children often show mild clinical presentation with favorable outcomes compared to adults, and deaths in paediatrics are rare. However, severe forms have been reported among children, including infants and newborns. Several studies have found a tendency toward greater severity of tick-borne encephalitis with increasing age, with a more severe form in children more than 8 years of age. The median

incubation time is about 8 days (range, 2–28 days). In the event of foodborne infection, this interval is generally shorter, only 3–4 days. Tick-borne encephalitis virus (European) infection in 58 % to 100 % of the cases has a biphasic course, beginning with flu-like symptoms (fever, tiredness, headache, nausea/vomiting, malaise, and myalgia). The first phase usually continues about 1 week (range, 1–14 days). Following a symptom-free interval lasting about 1 week, the second phase develops in 5 to 30 % of children, starting with the reappearance of fever, asthenia, and headache, the occurrence of meningeal signs, associated or not with additional focal neurologic deficits leading to altered mental status. Fever in the second phase of illness lasts from two to 14 days. In a pediatric population, meningitis is the most frequent form; meningoencephalitis occurs less often, and meningoencephalomyelitis is only rarely diagnosed.

During the first phase of tick-borne encephalitis, complete blood count examination often reveals leukopenia and thrombocytopenia, in the second phase — leukocytosis with normal distribution or an elevated neutrophil count. Serum C-reactive protein concentration can be elevated.

CSF analysis typically shows moderate pleocytosis with lymphocytic predominance, but early in the course, polymorphonuclear cells can be predominant. Protein level is usually within the normal range, and elevated values correlate with the presence of encephalitis. Normal glucose and lactate concentration is seen.

Diagnostic criteria for a confirmed case of tick-borne encephalitis include:

– CNS inflammation symptoms (e.g., meningitis, meningoencephalitis, encephalomyelitis, encephaloradiculitis)

and at least one of the following laboratory criteria:

– presence of specific IgM and IgG antibodies in serum;

– presence of specific IgM antibodies in CSF;

– seroconversion or fourfold increase of tick-borne encephalitis virus-specific antibodies in paired serum samples;

– detection of tick-borne encephalitis-viral nucleic acid in a clinical specimen, or isolation of the virus from clinical specimen.

During tick-borne encephalitis infection, the viremic phase is very short. Therefore, tick-borne encephalitis viral RNA is rarely detected in blood and/or CSF samples, and PCR in blood contributes to the diagnosis only in the initial phase, and has no diagnostic value in the second phase.

IgM and IgG antibodies may be detectable from two to three weeks after the supposed contamination and could persist up to 10 months after acute infection for IgM and over a lifetime for IgG.

Treatment consists of supportive care; no antivirals are available.

Aseptic meningitis of non-viral aetiology

Aseptic meningitis may be caused by non-pyogenic pathogens such as *Borrelia burgdorferi, Mycobacterium tuberculosis, Leptospira,* fungies, and rarely, by *Toxoplasma gondii, Mycoplasma* and *Chlamydia pneumoniae, Richettsia, Treponema,* and *Brucella species.*

Fungal meningitis may occur in immunocompromised patients under immunosuppressant agents or living with HIV, children with cancer, previous neurosurgery, or cranial trauma, or premature infants with low birth weights. The most common causative organism of fungal meningitis is *Cryptococcus spp.,* which is ubiquitous and significantly associated with the HIV pandemic.

Lyme neuroborreliosis. *Borrelia burgdorferi sensu lato complex* are fastidious, microaerophilic spirochetes transmitted through the tick bite of the Ixodes spp. and causing a multisystem inflammatory disease. Borrelia pathogens show the ability to spread easily, affect various tissues in the body, activating the host's immune defense, and causing the diverse presentation of the disease. A neurological manifestation occurs in 3–15 % of infections and can manifest as aseptic meningitis, polyradiculitis, and rarely encephalomyelitis.

Lyme neuroborreliosis is the early disseminated disease, which occurs 3–10 weeks after tick bite and mainly caused by *Borrelia garinii* genospecies. Lyme meningitis is characterised by intermittent fluctuating headaches without fever, nausea and vomiting, and uncertain or absent meningeal signs. Meningitis in children can be easily overlooked due to very mild symptoms. Neuroborreliosis should be considered even in the absence of signs of meningeal irritation in patients having daily headaches which have developed subacutely.

In patients suffering from neuroborreliosis, combined involvement of the central and peripheral nervous systems is possible. The triad of painful radiculopathy, cranial neuropathy, and lymphocytic pleocytosis in CSF has been described as Bannwarth syndrome (i.e., lymphocytic meningoradiculitis). Although Bannwarth syndrome is very common among adults, it occurs only in 3.6 % of neuroborreliosis in children. Presence of Lyme antibodies in CSF confirms the diagnosis, which can be supported by neuroimaging and neurophysiological studies.

Very rarely, Lyme neuroborreliosis can present with a normal neurological examination (showing no abnormalities in mental status; skull, spine and meninges; cranial nerves; motor examination; sensory examination; coordination; reflexes; and gait and station), which can also lead to misdiagnosis and delay in proper treatment implementation.

Lyme meningitis is characterised by the following abnormalities in the CSF: pleocytosis with the lymphocytes predominance, elevated protein levels, while glucose is within the normal range. Lactate level in the CSF is only slightly

elevated in the patients with Lyme neuroborreliosis. Do not rule out the possibility of Lyme meningitis in people with symptoms but no clear history of tick exposure. According to The European Federation of Neurologic Societies guidelines, the diagnosis of definite Lyme neuroborreliosis must be based on the fulfillment of three criteria, and two of them for possible Lyme neuroborreliosis: neurological symptoms, CSF pleocytosis, and Borrelia burgdorferi-specific antibodies produced intrathecally.

PCR may be used for detection of the Borrelia genome in CFS in recent neuroborreliosis with a short duration of neurological symptoms. However, due to the small number of copies of the spirochete in CSF samples even in early stage, the sensitivity of the PCR-based test is low. Therefore, a negative PCR result does not exclude Lyme neuroborreliosis.

CSF culture in diagnosis of neuroborreliosis is not recommended and not widely used as a routine procedure, due to many culturing requirements and a time-consuming (2–3 months) process.

The antibiotic treatment should be initiated in all patients with Lyme neuroborreliosis. Third generation cephalosporins are the drugs of choice. Intravenous ceftriaxone should be used as a first line:

– for children under 12 years (under 50 kg) in a dose of 80 mg/kg (up to 4 g) once per day for 21 days;

– for adults and young people (aged 12 and over) 2 g twice per day or 4 g once per day for 21 days.

Oral doxycycline may be alternative medicine in neuroboreliosis:

– for children aged 9–12 years (under 45 kg) use in a dose of 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days;

– for adults and young people (over 50 kg) use in a dose of 200 mg twice per day or 400 mg once per day for 21 days.

The dose of oral doxycycline for severe infections should be up to 5 mg/kg daily in children aged 9–12 years (under 45 kg).

Tuberculous meningitis. About one quarter of the world's population is infected with tuberculosis bacteria. Globally, an estimated 1.2 million children develop tuberculosis each year. In 2022, an estimated 214,000 children and young adolescents (< 15 years) died from TB. Ninety six per cent of deaths occur in children and young adolescents who did not access TB treatment. Therefore, early detection of the disease and initiation of etiotropic treatment is extremely important. Although TB meningitis constitutes a small proportion of the total reported TB cases (around 1 %), it is the most devastating form of the disease.

Haematogenous spread to the CNS may occur after a short bacteremia when M. tuberculosis is filtered into the local draining lymph nodes during primary TB infection, before granuloma formation; or the latent infection stage may

progress to active TB disease due to a lapse or decrease in the immune response. Tuberculosis bacilli may migrate across the blood-brain barrier and blood-CSF barrier via infected macrophages and neutrophils, or bacillary invasion of brain endothelium. In the brain, the TB bacilli initiate the development of tuberculous lesions in the meninges or the subpial or subependymal surface. Poor outcomes in TB meningitis are due to host inflammatory responses, which result in the formation of a thick exudate at the base of the brain. The dense basal exudate blocks the basal subarachnoid cisterns by the formation of adhesions, obstructing CSF flow, and resulting in hydrocephalus and raised intracranial pressure. Further extension of the exudate results in obliterative vasculitis of small proliferating blood vessels, leading to the development of focal and diffuse ischemic brain changes, whereas blockage of larger arteries results in infarction; and perineuritis, resulting in cranial nerve palsies; and in severe cases direct parenchymal involvement.

The peak incidence of TB meningitis in children is between 2 and 4 years of age. Boys are affected more than girls are. The onset takes less than 12 months from the time of primary infection in 75 % of children. TB meningitis typically presents as a subacute disease with many days or weeks (an average of 5 to 30 days) of non-specific symptoms such as malaise, low-grade fever, dizziness, vomiting without nausea, headache, personality changes, weight loss, and symptoms related to pulmonary TB and/or flu-like illness. However, the clinical onset of TB meningitis may be acute also. Patients with advanced disease may present with more severe headache, signs of meningeal irritation, altered mental status, and focal neurological signs. The various cranial nerve palsies are observed, including second, third, sixth and seventh cranial nerve palsies.

TB meningitis is classified into three grades of severity according to the British Medical Research Council TB meningitis grade. Grade 1 TB meningitis is defined as a Glasgow coma score of 15 with no focal neurology, Grade 2 as a GCS of 15 with a focal neurological deficit, or a GCS of 11–14 and Grade 3 is defined as a GCS of ≤ 10 indicating severe brain injury. The clinical stage on presentation is the strongest predictor of clinical outcome, with a high mortality risk for patients presenting with stage 3 disease. Death is invariably inevitable if TB meningitis is not treated.

CSF findings in TB meningitis include a mild pleocytosis (the median white count generally runs between 100 and 200 cells/μL) with lymphocyte predominance of > 50 per cent, protein elevation (usually > 1 g/L) and decrease in CSF glucose concentration which is reflected as either decreased glucose in CSF or CSF to plasma glucose ratio. The glucose level tends to become progressively lower and the protein progressively higher as the duration of illness progresses without appropriate therapy. Although any one of these CSF parameters may be completely normal, it is extremely unusual for all three parameters (pleocytosis, glucose and protein concentration) to be completely normal in a patient with true

TB meningitis. When the CSF is left to stand undisturbed, a fine clot resembling cobwebs may form due to the presence of very high level of protein.

In children suspected with TB meningitis, apart from standard CSF analysis, acid-fast smear microscopy, CSF culture for mycobacteria, and growth-based drug susceptibility testing should done. WHO recommends the use of Xpert MTB/RIF Ultra as the initial diagnostic test for CSF testing TB meningitis. The Ultra cartridge showed better performance compare to Xpert MTB/RIF for the detection of M. tuberculosis in smear-negative culture-positive specimens, paediatric specimens, and CSF.

In children who develop TB meningitis on the heels of primary tuberculosis infection, chest radiographic evidence of M .tuberculosis infection has been observed in 50–80 % of cases.

Most survivors of childhood TB meningitis suffer from long-term complications of neurocognitive and functional impairment. Early diagnosis and treatment of TB meningitis has long been recognised as the single most important factor determining outcome.

Treatment of TB meningitis is discussed in the discipline of phthisiopulmonology.

Cryptococcal meningitis. Cryptococcosis is an opportunistic infection represents a danger to those with CD4 cell counts indicating severe immunosuppression. Cryptococcal meningitis remains a major cause of HIV-related mortality worldwide. Among more than 50 existing species of *Cryptococcus, C. neoformans* and *C. gattii* cause the majority of infections.

Cryptococcal meningitis usually presents with subtle and non-specific such as a headache, fever, nausea, vomiting, altered mental status, and signs of meningeal irritation. The disease typically evolves over days to weeks. Early diagnosis and treatment of cryptococcal meningitis is key to reducing mortality from cryptococcal disease.

CSF usually presents low glucose and high protein levels. White cell count can be normal or higher than 20 cells/μL with a lymphocyte predominance. Nevertheless, CSF can be normal in CNS cryptococcal infection (especially in HIV-positive patients who do not have an adequate inflammatory response). In addition to standard laboratory testing patients with suspected meningitis (as set forth above in section diagnosis of community-acquired bacterial meningitis), a CSF rapid cryptococcal antigen assay is the preferred diagnostic approach. If a cryptococcal antigen assay is not available and/or rapid results are not available, lumbar puncture with CSF India ink test examination is the preferred diagnostic technique. When lumbar puncture is clinically contraindicated rapid serum, plasma or whole-blood cryptococcal antigen assays are the preferred diagnostic ways. CSF cryptococcal culture is also recommended in parallel with cryptococcal antigen testing if this is feasible.

The approved antifungal therapy for cryptococcal meningitis includes a combination of liposomal amphotericin B, flucytosine, and fluconazole.

ENCEPHALITIS IN CHILDREN

Encephalitis is inflammation of the brain parenchyma that produces neurologic dysfunction (e.g., altered mental status, behavior, or personality; motor or sensory deficits; speech or movement disorders; hemiparesis; and paresthesias).

Despite the similar clinical presentation, it is necessary to distinguish between encephalitis and encephalopathy. Encephalopathy is a group of conditions that cause brain dysfunction. Encephalopathy refers to permanent or temporary brain damage, disorder, or disease resulted from the impact of various damaging factors such as trauma, toxins, hypoxia, infections, metabolic disorders, high blood pressure, etc. These factors do not lead to inflammatory changes in the brain. Whereas, encephalitis refers to inflammation in the brain.

Aetiology and pathology of encephalitis

Encephalitis is caused by direct CNS infection or mediated by the immune system. More than 100 different aetiologies can lead to encephalitis in children; but the majority (50–70 %) of patients lack an identified aetiology. The most common causes of encephalitis are viruses. Viral encephalitis is responsible for high rates of morbidity, permanent neurologic sequelae, and according to the virus, may have high mortality rates. The most prevailing viral encephalitis agents are *Herpes simplex virus* type 1, 2, non-polio *Enteroviruses, Parechoviruses,* and arboviruses such as *Dengue virus, Japanese encephalitis virus, Tick-borne encephalitis virus, West Nile virus, Chikungunya virus, Eastern* and *Western equine encephalitis virus.* Other relevant aetiologies are *Influenza virus, Varicella-Zoster virus, Cytomegalovirus, Epstein-Barr virus,* and *Human herpesvirus type 6.*

CNS invasion can occur two main routes: pathogen spread across the blood-brain barrier following a viraemia in primary infection (this occurs for enteroviruses and arboviruses) or virus reactivation from latency in the nerve ganglia (e.g., in HSV infection) and travelling centripetally along the cranial nerves to the brain. In viral encephalitis, the pathogenesis often consists of a mixture of direct viral cytopathology and a para-infectious or post-infectious inflamatory or immune-mediated response. For most viruses, the brain parenchyma and neuronal cells are primarily infected, but for some, the blood vessels can be attacked, giving a strong vasculitic component. Demyelination following infection can also contribute. For example, HSV primarily, but not exclusively, targets the brain parenchyma in the temporal lobes, sometimes with frontal or parietal involvement. Mumps virus can cause an acute viral encephalitis, or an immune mediated delayed-onset encephalitis. Measles virus causes a post-infectious encephalitis, which may have a severe haemorrhagic component (acute haemorrhagic leukoencephalitis). For influenza A virus, a diffuse cerebral oedema can be a major feature in the pathogenesis, while for VZV, vasculitis is a major pathogenic process.

Clinical manifestations of encephalitis

Typical clinical features of encephalitis include altered mental status (decreased level of consciousness, lethargy, personality change, unusual behavior) lasting at least 24 hours, seizures, and/or focal neurologic signs, often accompanied by fever, headache, nausea, and vomiting. A minority of patients may have more subtle presentations. These patients may not be febrile or only have a low-grade fever at presentation; seizures can be subtle including tonic eye deviation, nystagmus, or subtle clonic movements of the face or limbs or any paroxysmal alteration in heart rate or other observations. Such individuals may present with behavioural changes or speech and language disturbances but then become more obviously encephalopathic or experience a seizure. Children, who are immunocompromised, may have a more subacute presentation.

Herpes simplex virus encephalitis is the leading cause of sporadic fatal encephalitis with a global incidence of 1 in 250 000 to 1 in 500 000 per year. One fifth of HSV encephalitis cases occur in the paediatric age group. HSV encephalitis accounts for approximately 10 % to 20 % of viral encephalitis cases in developed countries. Without treatment, HSV encephalitis has a mortality rate of 70 %, which is reduced to 10–25 % with aciclovir. Despite optimal therapy, around half of all survivors are left with significant neurological disability such as recurrent convulsions, motor disabilities, visual impairment, and mental disability.

In neonates, HSV encephalitis is most often due to disseminated HSV type 2 infection acquired during the birth process. Infants with neuroinfection usually present with illness between the second and third weeks of life. Generally, fever and lethargy appear followed by the onset of seizures, which can be focal and difficult to control; skin lesions exist in about 35 % to 40 % of cases at the time of presentation. Some infants have only non-specific signs and symptoms early in the course of disease.

CSF examination usually reveals a mild pleocytosis (50–400 cells/μL), predominantly mononuclear, a slightly decreased glucose level, and a modestly to markedly elevated protein concentration (500–1000 mg/dL). The EEG typically is abnormal diffusely. Temporal lobe involvement on MRI is typical, but diffuse infection can occur in neonates.

Beyond the neonatal period, HSV type 1 is the most common cause of encephalitis in children. It may occur in all age groups. Encephalitis can occur as a result of primary (~25–33 % of cases) or recurrent infection (~67–75 % of cases). Encephalitis commonly has an acute onset with a fulminant course, leading to coma and death in untreated patients. Typically, clinical manifestations of acute HSV encephalitis are severe and include brief prodromal symptoms followed by persistent fevers, headache, nausea, vomiting, altered consciousness, and personality/behavioural changes. They may also have meningism, seizures and focal neurological signs.

The CSF findings usually are characterised by the presence of a few hundred white blood cells/μL, with a lymphocyte predominance (75 % to 100 %). However, pleocytosis varies from a few to more than 1000 white blood cells/μL, and occasionally neutrophils predominate; protein concentration is normal in about one half of CSF specimens obtained during the first week of illness, but thereafter, concentrations as high as 500 to 1200 mg/dL are observed. Patients with HSV encephalitis may also have an increased number of RBCs in CSF.

Production of HSV-specific antibody in the CNS occurs by the second week of illness. PCR testing is considered the gold standard for the laboratory diagnosis of HSV encephalitis. However, CSF obtained before the third day of illness can be falsely negative by PCR. If the index of suspicion remains high for HSV encephalitis, a repeat lumbar puncture for CSF analysis by PCR should be performed. EEG typically reveals focal spike and slow wave abnormalities early in the course of HSV encephalitis. A characteristic finding is paroxysmal lateralizing epileptiform discharges. MRI can be normal at the onset of illness, followed within days by development of oedema associated with focal infection or haemorrhagic necrosis classically in the temporal lobe.

Diagnosis of encephalitis

In 2013, the International Encephalitis Consortium has recommended for case definitions of encephalitis and encephalopathy of presumed infectious or autoimmune aetiology the following criteria:

Major criterion (required). Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥ 24 h with no alternative cause identified.

Minor criteria (two required for possible encephalitis; three or more required for probable or confirmed encephalitis):

1. Documented fever ≥ 38 °C (100.4 °F) within the 72 h before or after presentation.
2. Generalized or partial seizures not fully attributable to a pre-existing seizure disorder.
3. New onset of focal neurologic findings.
4. CSF leukocyte count ≥ 5 mm³.
5. Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset.
6. Abnormality on EEG consistent with encephalitis and not attributable to another cause.

Confirmed encephalitis requires one of the following:

1. Pathologic confirmation of brain inflammation consistent with encephalitis.

2. Defined pathologic, microbiologic, or serologic evidence of acute infection with a microorganism strongly associated with encephalitis from an appropriate clinical specimen.

3. Laboratory evidence of an autoimmune condition strongly associated with encephalitis.

It should be noted, that the absence of CSF pleocytosis does not exclude encephalitis. In particular, it is recognised that the CSF may be devoid of cells in immunocompromised patients or early in the course of infection.

Lumbar puncture should be performed in all patients with suspected encephalitis, unless there is a specific contraindication to LP (as mentioned above).

Laboratory testing of a patient with suspected encephalitis includes:

1. CSF leukocyte count with differential, proteins, lactate, and glucose.
2. CSF PCR to identify viruses: HSV 1 and 2, VZV, enterovirus, parechovirus, CMV, EBV, HHV 6 and 7, and others if indicated (e.g., tick-borne encephalitis virus).
3. Serology for infectious aetiologies: HSV CSF IgG and IgM; EBV CSF VCA IgG and IgM and EBNA IgG; VZV CSF IgG and IgM.
4. CSF culture.
5. CSF Gram stain.
6. CBC with differential and platelet count.
7. Blood culture.
8. Biochemical blood test (serum electrolytes, blood urea nitrogen, creatinine, glucose, CRP).
9. Procalcitonin test.
10. Blood gas analysis (including measurement of lactate level).
11. HIV serology (is required for children over the age of 15).
12. Neuroimaging (MRI preferred to CT).
13. EEG.
14. When clinical features of extra-CNS involvement are present, additional testing may be recommended (e.g., biopsy of skin lesions, bronchoalveolar lavage and/or endobronchial biopsy in those with pneumonia/pulmonary lesions, throat swab PCR/culture in those with upper respiratory illness; stool culture in those with diarrhea).

Management of encephalitis

Supportive measures include the treatment of immediate complications such as reduced consciousness, seizures and raised intracranial pressure, and circulatory support.

There is a lack of etiotropic therapy in the majority of encephalitis cases. However, aciclovir should be started in all patients with clinical features

suggestive of encephalitis as soon as possible, pending the results of diagnostic studies. The diagnosis of HSV encephalitis should be considered in any patient with a progressively deteriorating level of consciousness with fever, focal seizures or focal neurological abnormalities in the absence of any other cause. Patients with HSV encephalitis should be treated for 21 days with intravenous aciclovir.

If there is no ongoing clinical suspicion of HSV encephalitis (a definitive alternative diagnosis becomes apparent, or it seems very unlikely that the patient has viral encephalitis), aciclovir therapy should be stopped. Aciclovir may also be stopped if a negative CSF HSV PCR is obtained at > 72 h following onset of neurological symptoms **and** there is a low clinical suspicion of HSV encephalitis (e.g., a clinical recovery and normal level of consciousness, normal neuroimaging and less than 5 cells/μL in CSF).

Aciclovir should not be stopped if CSF HSV PCR is negative but other features consistent with HSV encephalitis (particularly if CSF and MRI findings are abnormal and consistent with the diagnosis).

Neonates and infants under 3 months: the dosage of acyclovir is 60 mg/kg per day in three divided doses (20 mg/kg/dose every 8 hours), administered intravenously for a minimum of 21 days in CNS disease. All infants with CNS involvement should have a repeat LP performed near the end of therapy to document that the CSF is negative for HSV DNA on PCR assay. In the unlikely event that the PCR result remains positive near the end of a 21-day treatment course, intravenous aciclovir should be administered for another week, with repeat CSF PCR assay performed near the end of the extended treatment period and another week of parenteral therapy if it remains positive. Parenteral antiviral therapy should not be stopped until the CSF PCR result for HSV DNA is negative.

The landmark placebo-controlled study demonstrated that 6 months of viral suppressive therapy following completion of parenteral therapy in neonatal HSV disease including encephalitis improved neurodevelopmental outcomes. Infants surviving neonatal HSV CNS disease should receive oral aciclovir suppression at 300 mg/m²/dose (300 mg per square meter of body surface area per dose), administered 3 times daily for 6 months after the completion of parenteral therapy for acute disease; the dose should be adjusted monthly to account for growth. Absolute neutrophil counts should be assessed at 2 and 4 weeks after initiating suppressive aciclovir therapy and then monthly during the treatment period.

Infants beyond 3 months and children under 12 years of age with known or suspected HSV encephalitis should be given aciclovir in doses of 500 mg/m²/dose every 8 hours for 21 days.

Children 12 years of age and older and adults should be given aciclovir in doses of 30 mg/kg per day in three divided doses (10 mg/kg/dose every 8 hours) for 21 days.

The required dose of aciclovir in patients at any age should be administered by slow intravenous infusion over 1 hour. Patients with impaired renal function require an appropriately modified dose, according to the degree of impairment.

Completion of the intravenous aciclovir therapy should be based on a negative HSV DNA result on PCR assay in CSF analysis repeated near the end of a 21-day treatment course. If the CSF is still positive, aciclovir should continue intravenously, with weekly PCR until it is negative.

Use of concomitant corticosteroids has not been adequately studied in patients with HSV encephalitis and is not routinely recommended.

No specific treatment is recommended for enterovirus encephalitis; in patients with severe disease pleconaril (if available) or IVIG may be worth considering. No specific treatment is needed for VZV cerebellitis owing to immune-mediated reactions underlying this condition. For VZV encephalitis, whether due to primary infection or reactivation, intravenous aciclovir is recommended for up to 14 days, especially if it can be started within a few days of symptom onset. Antiviral therapy can be administered with or without a short course of corticosteroids. If there is a vasculitic component, there is a stronger case for using corticosteroids.

MYELITIS IN CHILDREN

Myelitis is a rare inflammatory syndrome of the spinal cord, causing weakness, bladder dysfunction, flaccid paralysis, and reduced or absent reflexes. There are several types of myelitis. Transverse myelitis is a demyelinating disorder longitudinally involving the spinal cord (a segment of the spinal cord), causing bilateral deficiencies while partial myelitis manifests by asymmetric symptoms. The localisation of spinal cord injuries in myelitis may be associated with a certain causative factor. For instance, anterior myelitis (anterior horns lesion) is typical for poliomyelitis and other non-polio enterovirus infections.

Myelitis is more common among adults; children comprise 20 % of total cases with bimodal age distribution primarily affected children under five and older than 10 years of age.

Aetiology of myelitis

There are many different causes of myelitis, including infectious, post-vaccination, systemic inflammation, and multifocal CNS diseases. The most common cause of myelitis is idiopathic, when no causative factor is found.

Infections leading to transverse myelitis include but are not limited to the following:

– viral infections: herpes viruses (*Herpes simplex, Varicella zoster, CMV, EBV, Human herpes virus 6 and 7*), enteroviruses, parechoviruses, polioviruses;

flaviviruses such as *West Nile, Dengue* and *Zika, Japanese encephalitis virus, Tick-borne encephalitis virus,* and *Hepatitis C virus; influenza, mumps, measles, rubella, HIV, Human T-cell lymphotropic virus;*

– bacterial infections such as diphtheria, tuberculosis, syphilis, mycoplasma pneumoniae infection, tetanus, campylobacteriosis, pertussis, and Lyme borreliosis;

– fungal infections such as aspergillus, blastomyces, coccidioides, and Cryptococcus;

– parasites including toxoplasmosis, cysticercosis, shistosomiasis, and angtiostrongyloides.

It is unclear whether direct effect of a pathogenic microorganism or a post-infectious response causes inflammation of the spinal cord.

Myelitis may be a very rare complication after vaccination. Correlation between Covid-19 vaccination, Japanese encephalitis vaccination, use of tetanus toxoid vaccines, vaccination against influenza, hepatitis B, measles–mumps–rubella vaccination and inflammation of the spinal cord have been described.

Myelitis can be the first symptom of an autoimmune or immune-mediated diseases such as multiple sclerosis, neuromyelitis optica spectrum disorder, acute disseminated encephalomyelitis or systemic lupus erythematosus.

Systemic inflammatory autoimmune disorders such as ankylosing spondylitis, antiphospholipid syndrome, Behçet disease, mixed connective tissue disease, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren syndrome, and paraneoplastic syndromes also have been reported to have an association with transverse myelitis.

Clinical manifestations of myelitis

The duration of this disease may be as little as 3 to 6 months or may become permanently debilitating. Myelitis may be either acute (developing over minutes to several days) or subacute (usually developing over one to four weeks). Subacute or chronic myelitis is associated with retroviruses (e.g., Human T-cell lymphotropic virus type 1).

Clinical presentation of transverse myelitis is characterised by classic features:

– initial symptom is usually lower back pain or sharp, shooting pain that radiates down the legs or arms or around the person's torso;

– weakness of the legs and arms depending on the affected area that worsens rapidly;

– sensory alteration including numbness, tingling, coldness, or burning of the skin; sensory symptoms generally affect the level of the lesion or one of the levels above or below the lesion;

– bowel/bladder dysfunction can present as increased urgency to urinate or defecate, or as incontinence, difficulty voiding, or constipation.

Other symptoms may include muscle spasms, a general feeling of discomfort, and loss of appetite.

Acute flaccid myelitis manifests as rapidly progressive asymmetric limb weakness accompanied by low muscle tone, developing within hours to a few days. A distinctive feature is keeping intact sensation. A prodromal period (typically febrile with respiratory symptoms) a few days prior to the onset of flaccid paralysis is common. Children also frequently report pain in the affected limb at the time of weakness onset.

Diagnosis of myelitis

Diagnosis of myelitis. When suspecting transverse myelitis, it is recommended the following diagnostic tools be performed:

– MRI of the entire spine and brain with contrast (whereas, transverse myelitis is a diagnosis of exclusion, a compressive cord lesion must be excluded first);

– CSF analysis, including cell count with differential, protein, glucose analysis, oligoclonal bands, IgG index;

– serum laboratory testing for anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies;

– viral and bacterial pathogen testing for agent isolation and specific antibodies to exclude possible infections (enterovirus, parechovirus, HSV, VZV, EBV, CMV, West Nile virus, HIV, Mycoplasma pneumoniae, Borrelia burgdorferi, Treponema pallidum, and etc.).

Transverse myelitis typically manifests as abnormal T2/fluid-attenuated inversion recovery hyperintensities affecting one or more cord segments. The CSF findings are abnormal in about 50 % of cases, often with lymphocytic pleocytosis, elevated protein, but normal glucose level. Positive oligoclonal bands and increased IgG in CSF suggest autoimmune myelitis. Evaluation for metabolic myelopathies with testing of vitamin B12, copper, and vitamin E should be considered in children at risk for gastrointestinal and metabolic comorbidities.

Diagnostic criterion for acute transverse myelitis includes:

– bilateral sensory, motor, and autonomic dysfunction localised to one OR more spinal segment;

– no evidence of compressive cord lesion;

– enhancing lesion on MRI;

– pleocytosis or elevated IgG index.

However, it should be taken into consideration that young children may not reliably report a sensory level.

Management of myelitis

No randomized controlled trials in paediatric population were conducted. Current treatment is based on adult data, case series, and expert opinion. Standard first-line therapy in idiopathic acute transverse myelitis is intravenous high dose corticosteroids that are prescribed as 30 mg/kg/day (maximum 1 gr/d) of methylprednisolone for 3–7 days. Plasma exchange, or IVIG also sometimes is used. For myelitis related to systemic inflammatory and connective tissue disorders Cyclophosphamide can be used.

If infectious myelitis is established, etiotropic therapy is indicated when it is available. Thus, myelitis related to herpes simplex or varicella zoster infection should be administered intravenous aciclovir for 14–21 days in combination with corticosteroids.

Approximately 33 % of patients recover with little to no lasting deficits, 33 % have a moderate degree of permanent disability, and 33 % are permanently disabled. In general, children have more favorable outcome, as almost 50 % of children obtain recovery after two years. However, younger age, longer time to diagnosis, and larger extent of lesions are associated with poorer prognosis.

SELF-CONTROL TASK

1. A 1-month-old term infant was admitted to the inpatient department with a two-day history of lethargy and fever of 38 °C. The lumbar puncture was performed on the second day of disease onset.

CSF analysis shown:

Opening pressure — increased
Color — light yellow
Transparency — cloudy
White cell count — 980 × 10^6/L (cells/μL)
Neutrophils — 98 %
Lymphocytes — 2 %
Protein — 1.62 g/l
Glucose — 1.19 mmol/L
Chlorides — 117 mmol/L.

Answer the following questions:

1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect most?

2. A 6-year-old female was admitted to the inpatient department owing to appearance of rapidly progressive, symmetric muscle weakness in the lower extremities having a preceding upper respiratory tract infection one week prior.

CSF analysis shown:
Opening pressure — normal
Color — colorless
Transparency — transparent
White cell count — 1×10^6/L (cells/μL)
Neutrophils — 0 %
Lymphocytes — 100 %
Protein — 0.67 g/L
Glucose — 4.2 mmol/L
Chlorides — 117 mmol/L
Lactate — 1.7 mmol/L (normal range, 1.1–2.8 mmol/L)
Answer the following questions:
1. Evaluate the CSF.
2. Assume possible causes of this condition.

3. A previously healthy 14-year-old male presented to the hospital with a 4-day history of fever. Since this morning, he has been inhibiting, suffering significant muscle weakness, and he has experienced one episode of loss of consciousness, accompanied by jerking extremity movements from the left side.

CSF analysis shown:
Opening pressure — increased
Color —— colorless
Transparency — transparent
White cell count — 488×10^6/L (cells/μL)
Neutrophils — 18 %
Lymphocytes — 82 %
Protein — 0.95 g/L (normal range, 0.1–0.45 g/L)
Glucose — 3.6 mmol/L
Chlorides — 121 mmol/L
Lactate — 1.8 mmol/L (normal range, 1.1–2.8 mmol/L)
Answer the following questions:
1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

4. A 1-year old male presented with high-grade fever, altered level of consciousness, repeated vomiting, and neck stiffness. On the second day of disease onset, he was brought to the emergency department and undergone a lumbar puncture.

CSF analysis shown:
Opening pressure — increased
Color — colorless
Transparency — cloudy
White cell count — 3258 × 10^6/L (cells/μL)
Neutrophils — 100 %
Lymphocytes — 0 %
Protein — 4.04 g/L (normal range, 0.1–0.38 g/L)
Glucose — 0.2 mmol/L
Chlorides — 114 mmol/L
Lactate — 7.3 mmol/L (normal range, 1.1–2.8 mmol/L)
Answer the following questions:
1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

5. A 16-year-old female was brought to the emergency department because of fever, photophobia, weakness, and headache. The physical examination revealed pale skin, no rash, 2-second capillary refill time, the heart rate — 112 beats per minute, the respiratory rate — 24 breaths per minute, and her blood pressure was normal for age. Owing to, positive neck stiffness and Kernig sign, she was given a lumbar puncture.

CSF analysis demonstrated:
Opening pressure — increased
Color — whitish
Transparency — cloudy
White cell count — 5330 × 10^6/L (cells/μL)
Neutrophils — 100 %
Lymphocytes — 0 %
Protein — 3.12 g/L (normal range, 0.1–0.45 g/L)
Glucose — 0.2 mmol/L (normal range, 2.5–3.89 mmol/L)
Chlorides — 110 mmol/L
Lactate — 8.7 mmol/L (normal range, 1.1–2.8 mmol/L)
CSF microscopy — Gram-negative diplococci were observed.
Answer the following questions:
1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

6. A previously healthy 4-year-old boy had a 2-day history of low-grade fever, headache, a single vomiting, and reduced appetite. He was brought to the emergency department due to constant severe headache. On physical examination, jolt accentuation of headache was revealed; he was performed a lumbar puncture.

CSF analysis shown:

Opening pressure — increased
Color — colorless
Transparency — transparent
White cell count — 147 × 10^6/L (cells/μL)
Neutrophils — 90 %
Lymphocytes — 10 %
Protein — 0.2 g/L
Glucose — 3.8 mmol/L
Chlorides — 120 mmol/L
Lactate — 2.1 mmol/L (normal range, 1.1–2.8 mmol/L)
CSF microscopy — negative
Thick-blood film — negative

Answer the following questions:

1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

7. A 6-month-old male arrived to the emergency department with the complaints of fever, irritability, and continuous cry. The physical examination revealed bulging fontanelle, pale, mottled skin, non-blanching rash, 4-second capillary refill time, cool extremities. His heart rate was 190 beats per minute, the respiratory rate — 45 breaths per minute, and the blood pressure was normal for age. A 6-month-old male arrived to the emergency department with the complaints of fever, irritability, and continuous cry. He was given a lumbar puncture.

CSF analysis demonstrated:

Opening pressure — increased
Color — colorless
Transparency — cloudy
White cell count — 1824 × 10^6/L (cells/μL)
Neutrophils — 96 %
Lymphocytes — 4 %
Protein — 0.45 g/L
Glucose — 4.5 mmol/L (normal range, 2.5–3.89 mmol/L)
Chlorides — 129 mmol/L

Lactate — 3.6 mmol/L (normal range, 1.1–2.8 mmol/L)
CSF microscopy — Gram-negative diplococci were observed
Answer the following questions:
1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

8. A 1-year-old male was admitted to the inpatient department with the complaints of sustained febrile fever, emesis, lethargy, and lack of appetite. On the second day of the disease onset, his physical examination revealed positive neck stiffness and Kernig sign, no focal neurological deficit. He was given a lumbar puncture.

Prior medical history: the child suffered from chronic sensorineural hearing loss, and he underwent cochlear implantation a week ago.

CSF analysis shown:
Opening pressure — increased
Color — colorless
Transparency — transparent
White cell count — 1066 × 10^6/L (cells/μL)
Neutrophils — 100 %
Lymphocytes — 0 %
Protein — 0.6 g/L (normal range, 0.1–0.38 g/L)
Glucose — 2 mmol/L
Chlorides — 127 mmol/L
Lactate — 4 mmol/L (normal range, 1.1–2.8 mmol/L)
CSF microscopy — extracellular gram-positive diplococci were revealed
Answer the following questions:
1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

9. A 17-year-old female arrived with the complaint of fever, headache, lethargy, and altered consciousness. Owing to, positive neck stiffness she was given a lumbar puncture.

CSF analysis shown:
Opening pressure — increased
Color — pink
Transparency — cloudy
White cell count — 1224 × 10^6/L (cells/μL)
Neutrophils — 100 %
Lymphocytes — 0 %

Protein — 0.82 g/L (normal range, 0.1–0.45 g/L)
Glucose — 1.3 mmol/L
Chlorides — 126 mmol/L
Lactate — 4.2 mmol/L (normal range, 1.1–2.4 mmol/L)
CSF microscopy — Gram-negative diplococci were revealed
Answer the following questions:
1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

10. A previously healthy 8-year-old male presented to the hospital with a 10-day history of fever. Despite the administration of cefuroxime axetil, fever had continued up to 39.2 °C, weakness and repeated vomiting appeared. He refused to eat and drink. The lumbar puncture was performed on the day of admission on account of positive neck stiffness.

CSF analysis shown:
Opening pressure — increased
Color — colorless
Transparency — transparent
White cell count — 212 × 10^6/L (cells/μL)
Neutrophils — 7 %
Lymphocytes — 93 %
Protein — 0.7 g/L
Glucose — 1.51 mmol/L
Chlorides — 107 mmol/L
Answer the following questions:
1. Evaluate the CSF.
2. Make a diagnosis.
3. What aetiology do you suspect?

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RECOMMENDED ANTIMICROBIAL TREATMENT FOR BACTERIAL MENINGITIS IN CHILDREN

Antimicrobial agent	Dosage, route	Treatment frequency
Ampicillin	Neonates 0–7 days, gestational age up to 34 weeks: 100 mg/kg/day IV	In two divided doses (12 hourly)
	Neonates 8–28 days, gestational age up to 34 weeks: 150 mg/kg/day IV	In two divided doses (12 hourly)
	Neonates 0–28 days, gestational age greater than 34 weeks: 150 mg/kg/day IV	In three divided doses (8 hourly)
	Children 150–200 mg/kg/day IV	In six divided doses (4 hourly)
	Adults 12 g/day IV	In six divided doses (4 hourly)
Ceftriaxone	Children 15 days to 12 years of age (< 50 kg): 100 mg/kg/day (max 4 g) IV	In two divided doses (12 hourly)
	Adults and children over 12 years of age (≥ 50 kg): 4 g per day IV	
Cefotaxime	Neonates 0–7 days: 100 mg/kg/day IV	In two divided doses (12 hourly)
	Children 7 days to 1 month: 150 mg/kg/day IV	In three divided doses (8 hourly)
	Children 1 month to 12 years of age (< 50 kg): 200 mg/kg/day (max 12 g) IV	In four divided doses (6 hourly)
	Adults and children over 12 years of age (≥ 50 kg): 12 g per day IV	In four divided doses (6 hourly)
Vancomycin	Children 1 month to 12 years of age: 60 mg/kg/day (max 2–4 g per day) IV	In four divided doses (6 hourly)
	Adults and children over 12 years of age: 15–20 mg/kg (max 2 g per dose) IV; a loading dose of 25–30 mg/kg IV can be used to facilitate rapid attainment of target trough serum vancomycin concentration	Every 8 hours
Meropenem	Children 3 months to 12 years of age (< 50 kg): 40 mg/kg IV(max 2 g per dose)	Every 8 hours
	Adults and children over 12 years of age (≥ 50 kg): 2 g IV	
Trimethoprim-sulfamethoxazole	Adults and children over 2 months: 10–20 mg/kg/day (trimethoprim component) IV	In two to four divided doses (6 to 12 hourly)

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