Infant fever differential diagnostics and infant meningitis management

1 Fever in small children – causes

This lesson is targeted to childhood meningitis, but for context it is necessary to know the differential diagnostics. So we offer some typical causes of fever in small children.

Urinary tract infection (UTI) and pyelonephritis are the most common cause of so called severe bacterial infections (SBI). This reason accounts for 3–8% of uncharacterized fevers. It is more common in girls and more common in uncircumcised than circumcised children. Blood count and examination of urine (POCT strip test, biochemical analysis, microbiology testing) may be helpful.

Pneumonia and sinusitis may be another reason. Sinusitis is uncommon in children youngen than 3 years (sinuses not yet formed). Pneumonia can be detected by physical examination combined with chest X-rays, the findings may include grunting, tachypnoea, hypoxemia.

Meningitis. To set this diagnosis, "The Bacterial Meningitis Score", a clinical decision rule developed by Nigrovic et al, can be used. It is composed of positive CSF Gram stain (can be replaced by any other proof of presence of bacteria in the CSF); CSF absolute neutrophil count of 1000/μl or higher; CSF protein level of 80 mg/dl or higher; peripheral blood absolute neutrophil count of 10,000/μl or higher; history of seizure before or at the time of presentation. More details will be provided later.

2 Fever in small children – clinical reasoning

Fever in small children is typically characterised by seizure (particularly complex febrile seizure)

Diagnosis is different according to the age group.

In children younger than 3 months we consider physical exam findings:

- Tachypnoea, hypoxemia → lower respiratory tract (LRT) infection
- Irritability, inconsolability, bulging anterior fontanelle → meningitis
- Vomiting/diarrhoea → non-specific, the cause may be gastroenteritis (GE), acute otitis media (AOM), UTI, meningitis

We should also look at the history. Recent immunization means increased risk of SBI (usually UTI) 24–72h after immunization. Confirmed bronchiolitis (viral), that is specific for this age group are also associated with SBI. They are usually caused by enteroviruses or virus of parainfluenza.

In children older than 3 months, but younger than 36 months we also use to consider physical exam findings:

- vomiting, diarrhoea, rhinorrhoea, cough, rash; still playful and responsive → viral infections, such as upper respiratory tract infection or gastroenteritidis
- fever, foul-smelling urine, crying when urinating → likely UTI
- irritability with handling, vomiting, bulging anterior fontanelle, complex febrile seizures → likelihood of meningitis

In children older than 36 months the presentation of physical exam findings is more adult-like. Apart from other causes, we have to watch for: Group A streptococcal pharyngitis (caused by *Streptococcus pyogenes*), infectious mononucleosis (caused by EB virus) and also Kawasaki disease.

Kawasaki disease is a form of vasculitis – it is characterized by inflammation of the blood vessels, which can restrict blood flow and damage vital organs and tissues. Kawasaki disease primarily occurs in children from 6 months to 5 years. The symptoms include fever over 39 °C lasting more than 5 days, and at least four of following symptoms:

- A rash on the main part of the body or in the genital area.
- An enlarged lymph node in the neck.
- Very red eyes without a thick discharge.
- Red, dry, cracked lips and a red, swollen tongue.
- Swollen, red skin on the palms of the hands and the soles of the feet. Later the skin on fingers and toes peels.

The symptoms might not happen at the same time. Other symptoms might include belly pain, diarrhoea, fussiness or joint pain.

3 Acute meningitis – basic facts

Acute meningitis remains a devastating disease. Clinicians need a low threshold for suspecting meningitis, to undertake appropriate investigations and provide treatment in a timely manner, to minimise the risk of poor outcome in bacterial disease, while limiting unnecessary treatment in viral meningitis.

Viral meningitis is the most common form of meningitis in many countries, but bacterial meningitis continues to be important, with a high mortality. Clinical features are poor discriminators for meningitis, so urgent investigations, starting with lumbar puncture, are key.

Most patients do not need brain imaging before lumbar puncture. Patients exhibiting clinical features of brain shift warrant urgent CT. Otherwise, imaging can cause delays in commencing antibiotics, which can lead to increased mortality.

It is necessary to take 10 ml of CSF during lumbar punction (LP). Larger volumes may be needed to diagnose tuberculous meningitis, and enable additional aliquots to be available for further diagnostic testing. Of course, in very small children smaller amounts of CSF are usually taken, and they are usually sufficient, as the bacterial load in these children is usually higher than in older children or adults.

Prompt testing of CSF and blood by PCR can hasten pathogen diagnosis and improve patient management.

Purulent meningitis in children and adults may have only non-specific symptoms, characteristic symptoms may be absent. If purulent meningitis is suspected, it is recommended to examine the cerebrospinal fluid, if there are no contraindications to lumbar puncture. Diagnostic scoring systems can be helpful in establishing the diagnosis of meningitis and/or distinguishing between purulent and serous meningitis in individual cases, but the physician's clinical judgment is of fundamental importance in the decision to initiate treatment for purulent meningitis.

3.1 Definitions

Meningitis is inflammation of the meninges covering the brain. It is a pathological definition. The cerebrospinal fluid (CSF) typically exhibits an elevated number of leucocytes (or a pleocytosis). In adults, >5 leucocytes/µl is defined as elevated. Bacterial or viral meningitis is confirmed by the detection of a

pathogen in the CSF. Bacterial meningitis may also be suggested by symptoms of meningism and appropriate bacteria in the blood.

The incidence of bacterial meningitis in infants and children has decreased since the routine use of conjugated vaccines targeting *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Also, the ratio between particular pathogens changed, as the vaccine against Haemophilus influenzae type b is a part of regular vaccination scheme, while that against *Streptococcus pneumoniae* and *Neisseria meningitidis* are just recommended ones. However, this infection continues to be associated with considerable mortality and morbidity if not treated effectively with empirical antimicrobial therapy. Diagnosis still rests on clinical signs and symptoms, and cerebrospinal fluid analysis. In we do not have information concerning the causative agent, the current recommendations for empirical therapy usually include a third-generation cephalosporin (mostly for Gram-negative causative agents) and in some countries also vancomycin (for Gram-positive ones). The recommendations may change according to the recent situation in the given country and given moment.

Besides typical community meningitis, we have to see also special cases. These may include meningitis associated with cerebrospinal fluid (CSF) shunts or meningitis (often hospital acquired) caused by organisms such as *Escherichia coli* and other Enterobacterales. Viral meningoencephalitis caused by herpes simplex although need special approach, it is obvious that in this case we need antivirotics rather than antibiotics for treatment. Importantly, meningitis caused by *Mycobacterium tuberculosis* (TB) can present with symptoms that are similar to other forms of bacterial meningitis, especially in areas with high TB rates.

3.2 Causative agents and current epidemiology

The epidemiology of meningitis has been influenced dramatically by universal immunization programs delivering conjugate vaccines for *Haemophilus influenzae* type b (Hib), that dramatically decreased the number of cases (prior to vaccination, this organism had been the leading causative agent in age group of toddlers), but also available vaccines against Neisseria meningitidis and Streptococcus pneumoniae. Viruses account for up to half of cases in meningitis. Enterovirus is the commonest, with herpes simplex and varicella zoster the next most frequent. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the commonest bacteria, together accounting for approximately one-quarter of cases.

In case of the *Streptococcus pneumoniae* meningitis (and also other invasive diseases, such as pneumonia), the epidemiology is influenced by the type of vaccine. Conjugated vaccines may include 7–13 serotypes. Polysaccharide vaccine available in many countries, including Czechia, gives protection against 23 serotypes, but it gives less protection to people with underdeveloped immunity, such as small babies. That is why it is only recommended for children older than two years and its main purpose is protection of seniors, especially in case of hospitalisation.

The incidence of *Neisseria meningitidis* meningitis in children and adults has decreased significantly since the introduction of routine meningococcal serogroup C immunization programs. Later the quadrivalent conjugated A, C, Y, and W meningococcal vaccine started to be used, what brings a benefit firstly because people travel to regions with different serogroups, and also the prevalence of particular serogroups in many countries is changing. Two vaccines that target serogroup B (Bexsero, Trumemba) are now available in many countries, but first date speak about possible lower immunogenicity of that vaccine in comparison to that against A, C, Y and W types. This is connected with the antigenic difference between these serogroups.

Meningitis caused by *Streptococcus agalactiae* (SAG, also known as group B streptococcus – GBS, especially in USA and Canada) remains an important cause of meningitis in infants up to 90 days old.

Although *Listeria monocytogenes* is an uncommon cause of meningitis beyond the neonatal period, it should be considered when specific host risk factors, such as immunosuppression, are present, or if brain stem infection is the initial presentation.

Other causes such as *Haemophilus influenzae*, *Listeria monocytogenes*, *Mycobacterium tuberculosis* and fungi (typically cryptococci) are less frequently detected, together representing <10% of cases. Currently, many adults with meningitis have no pathogen detected.

3.3 Antimicrobial susceptibility

Streptococcus pneumoniae. Meningitis susceptibility breakpoints should always be applied in the setting of presumed or confirmed meningitis, given the requirement for adequate drug levels in the central nervous system (CNS). S pneumoniae breakpoints have been specifically designed for interpretation in the context of meningitis. Although penicillin or aminopenicillins are drugs available for treatment, with regards of the access to CSF, ceftriaxone is usually recommended for treatment.

Neisseria meningitidis. In the past several years, many countries have reported increasing prevalence (ranging from 30 % to 80 %) of *N. meningitidis* with reduced susceptibility to penicillin. In some countries, ciprofloxacin is used for treatment, but ciprofloxacin-resistant *N. meningitidis* has also emerged in some countries such as USA. Ceftriaxone is recommended for treatment also for this pathogen.

Haemophilus influenzae. While Hib is now an uncommon cause of meningitis in children, it as well as other *H. influenzae* serotypes should still be considered in a child who is not fully immunized or unimmunized. Ceftriaxone or cefotaxime should be used as empiric therapy, pending susceptibility testing. Ampicillin might have effect, but also here the number of resistant strains is increasing.

Streptococcus agalactiae. Penicillin or aminopenicillins are currently recommended drugs of choice for infection caused by this pathogen. However, empirical coverage with cefotaxime or ceftriaxone in infants would be reasonable until culture results are available.

Current susceptibility data reaffirm the empiric management of suspected meningitis with ceftriaxone or cefotaxime and vancomycin until susceptibility results are available.

3.4 Diagnostic procedures in meningitis

3.4.1 Basic facts

In patients with suspected purulent meningitis, it is necessary to examine the number and type of leukocytes, protein and glucose concentration, culture and microscopy in the cerebrospinal fluid. In order to evaluate the real decrease in glycorachia, it is necessary to simultaneously examine the glycemia and calculate the glucose quotient (G_{CSF}/G_{blood} ratio). Before administering the first dose of ATB, it is also necessary to take blood for a blood culture examination. Depending on availability, it is advisable to perform an immunochromatographic examination of the cerebrospinal fluid for the presence of pneumococcal antigen. PCR examination of the cerebrospinal fluid is recommended to be performed at the same time as the culture or additionally in the case of a negative cerebrospinal fluid culture after 24 hours using a sample of cerebrospinal fluid from the entrance puncture kept in the refrigerator.

3.4.2 Clinical features

Clinical features alone cannot confirm the diagnosis of meningitis. A lumbar puncture (LP) is essential to confirm the diagnosis of meningitis and establish the cause.

In one study, 95 % of bacterial meningitis patients had at least two symptoms of headache, neck stiffness, fever and altered consciousness. The latter three features were present together in only 44 % of cases. Neurological deficits are found in around one-third of patients. Similar findings are reported by other studies.

A rash in suspected meningitis makes *N. meningitidis* more likely. However, 37 % of meningococcal meningitis patients have no rash. Varicella and enterovirus can also be associated with a rash.

Risk factors for *Listeria* meningitis include overt or relative immune compromise, the latter including chronic illness, diabetes, alcohol dependency, malignancy or old age. *Listeria* meningitidis is rarely seen in immunocompetent adults under 60 years of age. Travel history, symptoms of otitis media / sinusitis, contact with another person with meningitis, sepsis or tuberculosis are other useful diagnostic clues.

3.4.3 Clinical findings

In infants typical signs are fever, hypothermia, bulging fontanel, lethargy, irritability, seizures, respiratory distress, poor feeding, vomiting. In older children if can be fever again, and headache, photophobia, meningism, nausea/vomiting, confusion, lethargy, irritability.

3.4.4 Investigations

Lumbar puncture is the key investigation. It enables rapid confirmation of meningitis and type of infecting organism. Diagnostic yield of LP can be diminished by collecting small CSF volumes. At least 10 ml can be safely removed. LP serves for different particular purposes.

Cerebrospinal fluid cytology remains one of the most rapidly informative tests. Pleocytosis indicates meningeal inflammation, of which infection is the most common cause. Van de Beek and colleagues reported that >90% of adults with bacterial meningitis had a CSF leukocyte count > 100 cells/µl. Absence of pleocytosis makes meningitis much less likely, but does not completely rule it out. Approximately 1–2 % of patients with bacterial meningitis will have a normal CSF leukocyte count. Positive pathogen detection and an absence of pleocytosis more frequently occurs among children, the immunocompromised, those pretreated with antibiotics or with mycobacteria tuberculosis infection.

Cerebrospinal fluid leukocyte differential can help predict which type of pathogen is causing infection. Lymphocyte predominance suggests viral, while neutrophil predominance suggests bacterial infection. There are several exceptions to this general guide, including CSF neutrophil predominance observed in association with tuberculous meningitis.

Cerebrospinal fluid biochemistry. Cerebrospinal fluid glucose is normally approximately two-thirds the blood (plasma) concentration. It is often lower in bacterial and tuberculous meningitis. As CSF glucose is influenced by the plasma glucose, it is essential to measure blood glucose at LP, to obtain an accurate CSF : blood glucose ratio. A CSF : blood glucose ratio < 0.36 is an accurate marker for distinguishing bacterial from viral meningitis. Cerebrospinal fluid protein is normally < 0.4 g/l. Elevated protein suggests inflammation. A CSF protein < 0.6 g/l largely rules out bacterial infection.

Cerebrospinal fluid microbiology. Cerebrospinal fluid is obviously also sent to microbiology examination. Quick tests are preferred, so that we can get the results in range of tens of minutes rather than days. One of them is usually Gram stain, that is combined with one more test. Antigenic analysis

of CSF is a traditional way of examining CSF in a microbiology laboratory, but recently it is widely replaced by multiplex PCR test. Its advantage is that if the test is well chosen, it may cover also viral and not only bacterial causative agents. Be prepared that the laboratory may have a different request for classical bacteriology (Gram stain, antigenic analysis, and also culture, that would have its results later, but is needed for exact bacterium identification and also its antimicrobial susceptibility testing) and different for PCR tests.

3.4.5 Diagnosis

Infants with meningitis often present with nonspecific findings of fever, poor feeding, lethargy (or decreased interaction with caregivers), vomiting, and irritability. They sometimes have a rash. Inconsolable crying, prolonged or worsening irritability, or progressive lethargy are also important clinical features that may indicate a CNS focus such as meningitis. Nuchal rigidity is uncommon in infants. Older children are more likely to have specific symptoms related to meningitis, such as headache, nuchal pain or rigidity, and impaired consciousness, as well as other nonspecific symptoms. Patients should undergo a full examination, including respiratory status and detailed neurological examinations, to detect focal neurological signs, posturing, cranial nerve abnormalities, and assessment of level of consciousness.

A lumbar puncture (LP) for CSF analysis (cell count, glucose and protein levels, microbiological laboratory testing) is basic for setting the appropriate diagnostic. An LP should always be attempted unless there are contraindications, such as coagulopathy, cutaneous lesions at the proposed puncture site, signs of herniation, or an unstable clinical status such as shock. If papilledema, new onset seizures, focal neurological deficits, or decreased level of consciousness or coma are present, an LP should be deferred until imaging (a contrast-enhanced computed tomography and/or magnetic resonance imaging of the head) is performed, and the risk of potential herniation is ruled out. Although there are no specific studies involving children, herniation following an LP in meningitis is rare in the absence of focal CNS lesions.

Other investigations, such as urine culture, pharyngeal culture, or chest radiograph, should be performed as clinically indicated.

3.4.6 Evaluation

Initial laboratory testing represents the clinical reasoning in the unsure moment when the origin of the problem is not clear. It should include blood culture, blood count with differential and platelet count, inflammatory markers (CRP, procalcitonin), serum electrolytes, urea, creatinine, glucose, blood coagulation markers: prothrombin time (PT) with interational normalized ratio (INR) and activated partial thromboplastin time (aPTT).

Lumbar puncture (LP) should be performed in all children with suspected meningitis, unless there is a specific contraindication to LP. Contraindications to LP include: cardiopulmonary compromise, clinical signs of increased intracranial pressure, papilledema, focal neurologic signs, and skin infection over the site for LP. If there is a contraindication to or inability to perform an LP, or if the LP is delayed by the need for cranial imaging, antimicrobial therapy should not be delayed. Blood cultures should be obtained and empiric antibiotics administered as soon as is possible. CSF should be sent for cell count and differential, glucose and protein concentration, and microbiology examination.

Brain CT is recommended to be performed before lumbar puncture if any of the following criteria are present: focal neurological findings (except for cranial nerve palsy), new seizures (< 7 days), severe impairment of consciousness (GCS < 10), significant immunodeficiency (HIV+, transplant recipients). In patients with the absence of these criteria, CT before LP is not recommended. Other criteria

recommended in many countries are a known history of an intracranial focal process and papilledema on the fundus (if the examination was performed; examination of the fundus is not necessary in patients without focal findings). It is recommended to start antibiotic treatment of purulent meningitis as soon as possible, within 1 hour at the latest. When LP is delayed, empirical treatment must be initiated based on clinical suspicion.

Blood cultures should always be taken on admission and are helpful when antibiotics are started before LP. Blood cultures are positive in 50–80 % of bacterial meningitis cases.

Blood PCR is increasingly important, especially as PCR detects bacteria several days after antibiotic initiation.

Throat, nasopharyngeal, and stool swabs are useful for detecting enteroviruses if the CSF PCR is negative.

Brain imaging is neither obligatory in the management of meningitis, nor a prerequisite to LP. Performing neuroimaging before LP is associated with delays in commencing antibiotics, which in turn can lead to an increase in mortality.

Indications for brain imaging before lumbar puncture (LP) in suspected meningitis are focal neurological signs, presence of papilloedema, continuous or uncontrolled seizures.

3.5 Treatment, prognosis and complications

3.5.1 Treatment

If a patient exhibits signs of airway, breathing or circulatory difficulties (eg. in coexisting sepsis), management should initially focus on stabilisation of these systems.

All patients should be reviewed by a senior clinician. The Glasgow coma score (GCS) should be recorded for its prognostic value, and to enable changes to be monitored. Presence of a rash and use of preadmission antibiotics should also be recorded. If the patient presents with sepsis, they should be managed according to the sepsis guidelines. If the infective focus of sepsis is meningitis, then the antibiotic treatment should follow the guidelines for meningitis. For example, piperacillin/tazobactam is not recommended for use in sepsis secondary to meningitis, because of its poor penetration of the blood brain barrier. A recent large open-label trial showed no benefit of prehospital antibiotics in sepsis.

Treatment for bacterial meningitis is antibiotics, with or without steroids. The choice of antibiotics is a three stage process: an initial empirical decision based on clinical suspicion, review following microscopy results, and review again when culture or PCR results are available.

In Czechia (and similarly also other European countries; in USA and Canada situation may be different) momentary guidelines include

Empiric therapy:

- For newborns: ampicillin or penicillin + cefotaxime, or ampicillin + an aminoglycoside
- For children other than newborns and for adults: cefotaxime or ceftriaxone
- (For adults over 50 years or having risk of listeria infection addition of ampicillin or penicillin is recommended)
- Meropenem or chloramphenicole for people allergic to drug of choice.

If causative agent is known:

- *S. pneumoniae* or *N. meningitidis* susceptible to penicillin: penicillin or ampicillin

- *S. pneumoniae* or *N. meningitidis* resistant to penicillin: ceftriaxone or cefotaxime, vancomycine + rifampicine if resistant to cephalosporines.
- *L. monocytogenes* or *S. agalactiae*: ampicillin or penicillin
- *H. influenzae*: ampicillin if susceptible, otherwise ceftriaxone, cefotaxime and others

In suspected bacterial meningitis, dexamethasone should be started either shortly before or simultaneously with antibiotics at 10 mg intravenously (i. v.) 6-hourly. Up until 12 hours after antibiotic initiation, dexamethasone can still be started, but the impact of this on mortality has not been studied. If pneumococcal meningitis is probable, dexamethasone should continue for 4 days. In suspected tuberculous meningitis, dexamethasone provision should follow the recommended guidelines. Once another cause of meningitis is probable, dexamethasone should be stopped.

There is no specific treatment for viral meningitis. Treatment with aciclovir has only been of proven benefit in herpes encephalitis, not meningitis. Only if the patient has encephalitic features, such as impairment of consciousness, focal neurological signs, inflammation of brain parenchyma in the region of the temporal lobe on cranial imaging, should aciclovir be considered.

Because the prognosis of meningitis depends on treating infection before clinically severe disease ensues, the timely administration of empirical antimicrobial therapy is critical. Antimicrobials should be administered without delay when meningitis is suspected or confirmed. Also, the careful, ongoing assessment and appropriate management of hemodynamic status is required. An LP should be performed to support the diagnosis, but if an LP is not possible, antimicrobials should be given empirically irrespective of the delay in obtaining an LP, and the patient should be transferred to a facility where an LP can be performed.

Steroids as adjuvant therapy. In adults, multiple studies and meta-analysis have determined that adjuvant empiric steroids offered clinical benefit resulting in slightly lower mortality rates and reduction in hearing losses. Dexamethasone should be considered for infants and children with meningitis with suspicion for *S. pneumoniae* or *H. influenzae* origin. The recommended dose of dexamethasone is 0.6 mg/kg/day in four divided doses administered every 6 h immediately before, concomitant with, or within 4 h of administering the first dose of antimicrobials. Clinical benefit is probably greater when steroids are received earlier within this 4 h window.

Duration of the therapy. Recommended length of therapy for uncomplicated meningitis due to *Streptococcus pneumoniae* is 10 to 14 days; due to *Haemophilus influenzae*, 7 to 10 days; and due to *Neisseria meningitidis*, 5 to 7 days. Recommended therapy for uncomplicated *Streptococcus agalactiae* meningitis is 14 to 21 days, and may be longer if cerebritis or ventriculitis is present.

Audiology assessment. Formal audiology assessment should be performed as soon as possible after diagnosis of meningitis for all children affected (and always before discharge from hospital) to optimize management in the event of hearing loss.

3.6 Acute management

- Ensure adequate oxygenation, ventilation, and circulation.
- Obtain venous access and initiate cardiorespiratory monitoring while obtaining laboratory studies.
- Keep the head of bed elevated at 15 to 20°.
- Treat hypoglycaemia, acidosis, and coagulopathy, if present.
- Antimicrobial therapy should be initiated immediately following the LP if the clinical suspicion for meningitis is high. Administer first doses of empiric antibiotic therapy (age related)
- Consider dexamethasone therapy* (0.15 mg/kg i. v.) in patients with certain risk factors (unimmunized patients, children in age ≥ 6 weeks to ≤ 5 years, children with sickle cell disease,

asplenic patients) or if there is known or suspected Haemophilus influenzae infection. If dexamethasone is given, it should be administered before, or immediately after, the first dose of antibiotic therapy.

Prognosis. Mortality occurs almost exclusively in bacterial meningitis. Up to 57 % in meningococcal sepsis, 30 % of pneumococcal and 7 % of meningococcal meningitis without sepsis cases die. Morbidity is common in bacterial meningitis.

Complication. According to Czech guidelines, following possible complications may occur in purulent meningitis. They require following examinations; and treatment.

- Convulsions – brain CT or MR, EEG; anticonvulsives
- Ischaemia – brain CT or MR; no specific treatment
- Bleeding, subdural effusion, empyema, brain abscess – brain CT or MR; neurosurgical consultation and/or operation needed
- Cerebral Venous Sinus Thrombosis (CVST) – brain CT or MR; no specific treatment
- Hydrocephalus – brain CT or MR; neurosurgical consultation and/or operation needed
- Hearing problems – otoacustic emissions, audiometry; cochlear implant
- Disorder of natrium and water metabolism – biochemical markers; treatment according to findings

Resources and futher materials for study

1) Pediatric fever, available on https://ddxof.com/pediatric-fever/ visited 2024-03-29

2) Management of acute meningitis, Clin Med (Lond). 2018 Apr; 18(2): 164–169., available on:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6303447/ visited 2024-03-29

3) Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than 2 months of age, posted: Oct 19, 2020, available on: https://cps.ca/en/documents/position/management-of-bacterial-meningitis visited 2024-03-29

4) https://www.uptodate.com/contents/image?imageKey=PEDS%2F74865&topicKey=EM%2F85767&source=see_link , visited 2024-03-29

5) https://www.vakciny.net/doporucene_ockovani/penumo.html (Czech language), visited 2024-03-29

6) https://infektologie.cz/DoporMenPur17.htm (Czech language), visited 2024-03-29

7) https://emedicine.medscape.com/article/961497-workup?form=fpf visited 2024-03-29