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2018 update of the 17th consensus conference (2008) on anti-infective agents

Management of acute community-acquired bacterial meningitis (excluding newborns). Long version with arguments☆

Prise en charge des méningites bactériennes aiguës communautaires (à l'exclusion du nouveau-né)

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- SFMU (Société française de médecine d'urgence);
- SFN (Société française de neurologie);
- SFORL (Société française d'ORL);
- SFP (Société française de pédiatrie);
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- SRLF (Société de réanimation de langue française);
- SFR (Société française de radiologie).

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10. Introduction

The latest consensus conference on the management of acute community-acquired bacterial meningitis was held in 2008. At that time a reduced incidence of *Streptococcus pneumoniae* strains with reduced susceptibility to penicillin was being observed, the national antibiotic plan had been launched in 2002, and the first 7-valent pneumococcal conjugate vaccine (Prévenar) had been commercialized in 2003. These 2008 guidelines no longer recommended the use of vancomycin for the treatment of suspected or microbiologically documented *S. pneumoniae*

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meningitis, and rather recommended using very high doses of third-generation cephalosporins (3GC) and corticosteroids. However, pediatricians wanted to keep using vancomycin for the empirical treatment of this infection because of the substantial serotype replacement observed with serotype 19A pneumococcal strains (carrying resistance to beta-lactams). However, they reconsidered their position in 2014 considering the strong impact of the second-generation pneumococcal conjugate vaccine (13-valent vaccine, Prévenar 13) and the substantial decrease in serotype 19A carriage and invasive infections in infants and young children.

Practice surveys performed as part of the French cohort study of adult bacterial meningitis (COMBAT study) in 2014–2015, revealed the high compliance of health professionals with these guidelines, thus highlighting their applicability. The 2008 jury board also recommended the close epidemiological surveillance of the disease and of the antibiotic susceptibility of its causative agents, as well as regular guidelines updates. With the help of many experts, the organizing committee of the 2018 update of the 2008 consensus conference began working on this matter.

As the 2008 guidelines were quite intelligible and considering that we just wanted to update them, we decided to take the 2008 guidelines as the basis of our work and to provide updated answers to the questions asked to the jury board in 2008. We performed a thorough literature analysis to compile these 2018 guidelines. They were then drafted by the organizing committee and closely reviewed by an independent ad hoc committee. We hope that the hard work of each partner has helped in providing straightforward and precise guidelines.

11. Question 1 – What is the initial diagnostic management of patients presenting with a suspicion of bacterial meningitis?

11.1. When should meningitis diagnosis be considered?

Early identification of signs and symptoms indicative of meningitis is essential to reduce the time between symptom onset and treatment initiation for bacterial meningitis, which is required to improve the prognosis.

11.1.1. Children

The clinical presentation depends on the child's age. The younger the child, the fewer and more atypical the clinical signs and symptoms [1].

Questions asked to parents aim to identify the recent onset of signs and symptoms. Some may be observed very early on: digestive signs are common and often misleading (vomiting, diarrhea); one third of infants present with behavioral disorders (recent change in behavior, fearful child or inconsolable crying, lower consciousness, difficulties in bottle feeding); focal or generalized seizures are observed in 20–30% of infants, sometimes with status epilepticus [2]. Fever may not be observed in young infants [3].

Meningococcal infections with progressive onset other than purpura fulminans are observed. Such infections have been reported by a British study, which provided the first accurate chronological description of clinical outcome of pediatric meningococcal infections before admission to hospital [4]. Fever was the first symptom in children aged below 5 years. Irrespective of age, the first truly specific clinical signs were signs of sepsis: abnormal skin coloration, cold extremities, muscle pain in the legs. These early warning signs and symptoms require particular parental and medical attention as urgent hospital admission is needed to adequately assess them. The first clinical sign indicative of meningococcal infection was often a non-specific skin rash. Within a few hours, petechiae were observed followed by an extensive hemorrhagic rash approximately 12 hours after symptom onset. Median time to onset of early meningitis typical signs (neck stiffness, photophobia, and bulging fontanelle — anterior when still open — [usually before 6 months of age]) was 12–15 hours. Median time to onset of late signs (consciousness disorders, seizures) was 15 hours in infants aged below one year and approximately 24 hours in older infants. Wide dissemination of information aimed at raising the physicians' and family's awareness on early signs of sepsis in children is recommended.

The most specific signs of severe bacterial infection should be detected at the medical examination. The authors of a prospective study [2] of 3066 infants aged below 3 months presenting with fever and managed at a community pediatrician office in the United States, identified the most specific signs of severe sepsis and pointed out three factors: the child's general presentation (change in skin color, deterioration of general status), behavioral changes (responsiveness and interactivity disorders, loss of smile), and fever > 39.5 °C. The physician's clinical judgment was in this study the most decisive factor.

Hospital surveillance is recommended when one of these signs is observed in infants aged below 3 months. A lumbar puncture should be performed in infants aged below 3 months if one of the following signs is observed:

- unusual behavior (plaintive crying, moaning, inconsolable crying, hyporeactivity, irritability, pain, cutaneous hyperesthesia);
- tachycardia with normal blood pressure, time to skin recoloration > 3 seconds, cyanosis;
- neurological abnormalities (bulging fontanelle, neck hypotonia, general hypotonia) — Kernig's and Brudzinski's signs are usually not observed;
- seizures;
- purpura.

Typical clinical symptoms (vomiting, bulging fontanelle, neck stiffness, photophobia, consciousness disorders) are most common in infants aged between 3 months and 2 years, although they can be absent. A lumbar puncture is required when seizures are observed in feverish children aged below 6 months and should be discussed in feverish children aged between 6 and 12 months. The authors of a retrospective and multicentric French study of 205 patients who experienced initial febrile seizure, reported that the risk of complications was very low between 6 and 11 months of age (no reported case, 95% CI: 0–2.2) [5]. Besides, the authors of a meta-analysis reported the low

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incidence of bacterial meningitis in children presenting with complex febrile seizure (0.6%; 95% CI: 0.2–1.4) [6]. The benefit of a systematic lumbar puncture to identify central nervous system infections requiring urgent treatment in children presenting with initial febrile seizure is therefore low, as the number of patients needed to treat (NNT) is 1109 in case of uncomplicated initial febrile seizure and 180 in case of initial complex febrile seizure.

Older children present with signs and symptoms more similar to those observed in adults: fever, chills, vomiting, photophobia, severe cephalgia. Several signs are associated with more specific etiologies: purpura and joint disorders are indicative of *Neisseria meningitidis* infection; otorrhea or otitis and a history of brain injury are indicative of a breach in the meninges and of pneumococcal infection. Signs and symptoms may first be observed on an occasional basis with recurrent seizures in patients presenting with fever, consciousness disorder, coma, and status epilepticus.

To sum up, in infants aged between 3 months and 2 years:

- the diagnostic strategy first relies on the identification of clinical signs indicative of severe bacterial infection (septic signs, behavioral disorders, fever), and then on the identification of signs and symptoms requiring lumbar puncture (behavioral disorders, hemodynamic disorders, neurological abnormalities, purpura);
- indications for lumbar puncture should remain broad. A lumbar puncture is mandatory in patients presenting with typical signs and symptoms (vomiting, bulging fontanelle, neck stiffness or hypotonia, photophobia, consciousness disorders). A lumbar puncture is also mandatory when seizures are observed in feverish children aged below 6 months, and should be discussed in feverish children aged between 6 and 11 months.

11.1.2. Adults

The authors of a meta-analysis of articles published between 1966 and 1997 assessing clinical signs of meningitis and including 733 patients (90% of bacterial meningitis cases), reported 46% sensitivity for the triad "fever, neck stiffness, and altered state of consciousness (or cephalgia)". However, 95% of patients presented with at least two of these symptoms and 100% with at least one. The meningitis diagnosis could therefore be ruled out in patients who did not present with any of these three signs [7]. Recent cohort studies of bacterial meningitis confirmed that fever was observed in 77–97% of cases, cephalgia in 58–87% of cases, neck stiffness in 65–83% of cases, and consciousness disorders in 30–69% of cases. The triad of fever, consciousness disorder, and neck stiffness was observed in 41–51% of cases [8–12].

Several studies reported the poor sensitivity of Kernig's and Brudzinski's signs and of neck stiffness [13,14]. A Japanese study suggested a new clinical sign: jolt accentuation. The aim is to identify exacerbation of cephalgia with rapid rotations of the head in the horizontal axis (2 to 3 per second) [15]. Sensitivity of jolt accentuation is 97%, its specificity 60%, its positive predictive value 81%, and its negative predictive value 92%. The authors of a more recent study reported 82% specificity for this sign, but lower sensitivity (21%) [14].

The largest prospective study conducted with adults [12] included 696 episodes of community-acquired bacterial meningitis (51% due to *S. pneumoniae* and 37% due to *N. meningitidis*). The triad of "fever, neck stiffness, and altered state of consciousness" was associated with 44% sensitivity. However, 95% of patients presented with at least two signs among cephalgia (87%), fever (77%), neck stiffness (83%), and altered state of consciousness (Glasgow score < 14 in 69% of patients, including coma in 14%). Focal neurological signs were observed in 33% of patients and seizures in 5% of patients. The usual triad of symptoms was more commonly observed in patients presenting with pneumococcal meningitis than in those presenting with meningococcal meningitis (58% *versus* 27%, $P < 0.001$). Cutaneous signs, mainly purpura, were observed in 26% of episodes (meningococcal meningitis: 95% of cases; otherwise pneumococcal meningitis).

To sum up, in children aged over 2 years and in adults:

- meningitis is highly probable when patients present with fever, neck stiffness, and either cephalgia or consciousness disorders;
- meningitis is highly probable when patients present with fever and purpura, even more so when cephalgia is also observed;
- meningitis should be considered in patients presenting with fever and localized neurological signs or seizures;
- the meningitis diagnosis should always be kept in mind in patients presenting with cephalgia and fever, without consciousness disorder nor neck stiffness or neurological disorders. When no other diagnosis is considered, a lumbar puncture should be discussed especially when an inflammation indicative of bacterial infection is observed (elevated CRP and/or procalcitonin levels);
- particular attention should be paid to patients with risk factors for meningitis such as those with chronic excessive alcohol consumption, psychiatric disorders, and homeless people. The meningitis diagnosis can be extremely difficult to establish in these patients on the sole basis of clinical presentation.

11.2. Which biological examinations should be performed to determine the bacterial etiology?

The positive and etiological diagnosis of bacterial meningitis relies on the microbiological examination of the cerebrospinal fluid (CSF). Bacterial identification in culture media remains the gold standard.

Clinical suspicion of bacterial meningitis requires a lumbar puncture to be performed as soon as possible:

- to initiate the empirical antibiotic therapy as soon as the lumbar puncture is performed;
- to document the positive and bacteriological diagnosis of meningitis, and to adjust the antibiotic therapy;
- to rule out differential diagnoses.

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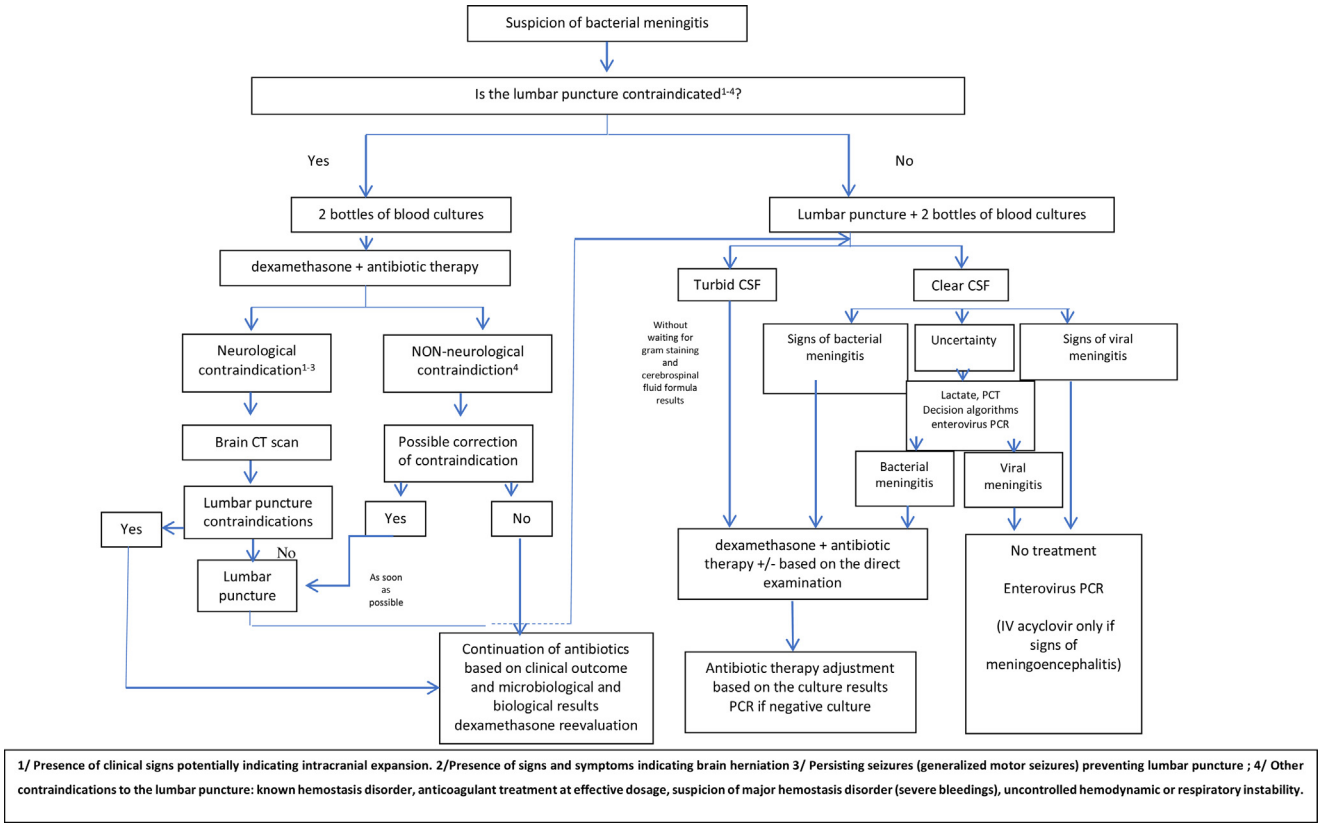

Fig. 1. Management diagram for bacterial meningitis suspicions. 1/Presence of clinical signs potentially indicating intracranial expansion. 2/Presence of signs and symptoms indicating brain herniation. 3/Persisting seizures (generalized motor seizures) preventing lumbar puncture. 4/Other contraindications to the lumbar puncture: known hemostasis disorder, anticoagulant treatment at effective dosage, suspicion of major hemostasis disorder (severe bleedings), uncontrolled hemodynamic or respiratory instability.
Logigramme de prise en charge des suspicions de méningites bactériennes.

The lumbar puncture should be performed within one hour following admission to the emergency department, unless contraindicated or provided an imaging test is required beforehand.

When the lumbar puncture cannot be immediately performed, an empirical antibiotic therapy should be initiated, dexamethasone should be administered, and at least two blood cultures should be performed beforehand (Fig. 1).

11.2.1. Contraindications to the lumbar puncture

There are two types of contraindications:

- neurological contraindications: clinical suspicion of intracranial expansion at neurological examination or neurological state incompatible with lumbar puncture (see below, indications for imaging test before lumbar puncture);
- non-neurological contraindications:
  - cutaneous infection localized to the lumbar puncture site,
  - uncontrolled hemodynamic or respiratory disorder,
  - known hemostasis disorders (hemophilia, other coagulopathy, platelet count < 50,000/mm^3); OR anticoagulant treatment (effective doses of vitamin K antagonists; unfractionated or fractionated heparin or direct oral anticoagulants, irrespective of the dose); OR spontaneous bleedings indicative of disseminated intravascular coagulation (DIC) [16] (Table 1).

An antiplatelet treatment does not contraindicate the lumbar puncture [17,18].

Fig. 1 details the required management strategies when the lumbar puncture is contraindicated.

The CSF should be collected into four sterile tubes for biochemical, microbiological, and cytological analysis purposes and for bacterial identification using molecular biology techniques. The first tube should not be used for these analyses to prevent any risk of contamination. The overall quantity of CSF required is 2 to 5 ml in adults (40–100 drops), ideally 2 ml (approximately 40 drops) in children, and approximately 0.5 ml (10 drops) for the molecular biology analysis. Bacterial detection and isolation depend on the volume used for analysis, but also on compliance with transport conditions and time requirements. The tube for molecular biology should be kept in frozen conditions (−20 °C or −80 °C) if transport to the laboratory is delayed.

Clinical data should imperatively be passed on to the bacteriologist. Results of the cytological and biochemical analyses, Gram staining and, if relevant, antigen detection by immunochromatographic assay should be communicated to the

Table 1
Contraindications to an immediate lumbar puncture.
Contre-indications à une ponction lombaire immédiate.

Non-neurological contraindications	Neurological contraindications (= clinical suspicion of intracranial expansion at neurological examination or impossibility to perform lumbar puncture due to other neurological abnormalities)
The lumbar puncture is contraindicated	1. Presence of clinical signs potentially indicating intracranial expansion
In case of a cutaneous infection spreading to the lumbar puncture site	- Signs of localization:
In case of uncontrolled hemodynamic or respiratory instability (the lumbar puncture should be delayed until stabilization) or in case of known hemostasis disorders (hemophilia, another coagulopathy, platelet count < 50,000/mm^3)	Motor deficit: central facial palsy; oculomotor palsy; upper limb and/or lower limb impairment Hemi-body sensitive deficit Homonymous hemianopsia (visual field testing using fingers or blink reflex) Cerebellar syndrome Aphasia
In case of anticoagulant treatment at an effective dosage, irrespective of the agent (unfractionated or fractionated heparin, oral vitamin K antagonists, or direct oral anticoagulants)	
In case of spontaneous bleedings indicative of disseminated intravascular coagulation (DIC)	
An antiplatelet treatment does not contraindicate the lumbar puncture	- Focal AND recent seizures
	2. Signs of brain herniation Consciousness disorders AND One or more of the following signs: pupillary abnormalities (fixed unilateral or bilateral mydriasis); dysautonomia (blood pressure and bradycardia, respiratory rate abnormalities); cerebellar tonic seizures; no reaction to stimuli; decortication or decerebration symptoms
	3. Persisting seizures (generalized motor seizures) preventing lumbar puncture
Management strategy. At least one pair of blood cultures, corticosteroids, and antibiotic therapy	
Correction of abnormalities	Emergency brain CT scan
Lumbar puncture if abnormalities have been corrected	Lumbar puncture as soon as possible if the CT scan results do not contraindicate the lumbar puncture

patient's medical team within the hour following lumbar puncture.

11.2.2. Cytobacteriological examination of CSF

Normal CSF is crystal clear. Turbid CSF is due to hyperleukocytosis. The detection threshold for turbid CSF is approximately 200 leukocytes/mm^3. CSF culture should be systematically performed as soon as possible.

11.2.2.1. Cytological examination. The first step consists in counting the number of leukocytes and red blood cells (RBC) in CSF. Normal CSF is devoid of cells (< 5 cells/mm^3). Bacteria may be detected during microscopic examination, in the absence of cellular reaction, even though very rarely. This test may only be performed with a minimum of 10 leukocytes/mm^3. In case of traumatic lumbar puncture, it is impossible to rely on the cytological analysis. The meningitis diagnosis is unlikely when the leukocytes/RBC ratio is < 1/700. In the absence of a dedicated tube and if the total CSF volume is sufficient, 500 μL (10 drops) should be stocked by the laboratory at −20 °C before performing any test, for potential microbiological test using gene amplification (PCR).

Turbid CSF usually indicates cellular reaction of at least 200 leukocytes/mm^3 with a predominance of more or less altered neutrophils. Even after antibiotic administration, bacterial meningitis is associated with a leukocyte count > 1000 cells/mm^3 in 87% of patients and > 100 cells/mm^3 in 99% of patients. Patients presenting with viral meningitis usually have < 100 cells/mm^3.

There is a correlation between the number of neutrophils and bacterial inoculum: 67% of CSF samples with high cellularity have a bacterial inoculum > 10^3 CFU/ml ($P < 0.01$) [19].

Generally speaking, the sole CSF cytological analysis is not enough to confirm the viral or bacterial etiology of meningitis. Results should be put into perspective with the other clinical, biological (CSF and serum), and microbiological results. This approach is complicated by the various clinical situations, especially when the lumbar puncture or antibiotic therapy has been performed or initiated early on:

- the cytological analysis of CSF may be normal if the lumbar puncture is performed early on. A mixed count or even lymphocytic predominance may be observed if the lumbar puncture is performed very early on, especially in case of *N. meningitidis* [20,21];
- viral meningitis is usually associated with lymphocytic predominance. However, polymorphonuclear leukocyte predominance or a mixed count may be observed in case of enteroviral meningitis when the lumbar puncture is performed early on.

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11.2.2.2. Direct microbiological examination following Gram staining. This is a simple and rapid examination. Its sensitivity is improved when the CSF is concentrated using centrifugation. Its sensitivity ranges from 60 to 97% for a specificity close to 100% in the absence of antibiotic therapy [22]. It depends on the causative agent and on transportation time to the laboratory, but also on the health professional's experience in collecting samples.

Its sensitivity rapidly drops to 40–60% — or even lower — when antibiotics are initiated before lumbar puncture [23]. A minimum inoculum of 10^5 bacteria/ml is required to be detected by Gram staining. Gram staining sensitivity is 25% when the inoculum is $< 10^3$ bacteria/ml, 60% when the inoculum is between 10^3 and 10^4 bacteria/ml, and 97% when the inoculum is $> 10^5$ bacteria/ml [19]. Gram staining is always performed, irrespective of the cytological and biochemical results.

The following is recommended:

- when the Gram staining direct examination is positive, an antimicrobial susceptibility test should be performed to determine the minimum inhibitory concentrations (MIC) (Etest® method) directly from the samples if the remaining volume of CSF is sufficient and if the quantity of bacteria observed at direct examination indicates sufficient inoculum;
- in case of *S. pneumoniae* suspicion, Etest® assays should be performed (MIC determination) at least for cefotaxime or ceftriaxone. When the MIC of the tested cephalosporin is > 0.5 mg/l, the MIC of the second cephalosporin should be subsequently determined.

11.2.2.3. Soluble antigen detection. The conventional latex agglutination test should be distinguished from the more recent immunochromatographic test.

11.2.2.3.1. Latex agglutination test. Latex agglutination tests are no longer recommended.

11.2.2.3.2. Immunochromatographic test (BINAX Now Streptococcus pneumoniae® test). This rapid (15 minutes) and simple test detects the C-polysaccharide molecules present in the wall of all *S. pneumoniae* strains, irrespective of the serotypes. On the basis of studies including more than 2000 patients (more than half being children), of whom 156 presented with pneumococcal meningitis, the specificity of the immunochromatographic test was 100% and its sensitivity 95–99%. These figures are higher than those of the latex agglutination test [24–27]. However, cross-reactivity has been reported especially with *Streptococcus mitis* and *Streptococcus oralis*. The immunochromatographic test has the advantage of not being impacted by prior antibiotic therapy administration. This test cannot be used to monitor the outcome of pneumococcal meningitis because of the prolonged persistence of C-polysaccharide in the CSF (for several weeks).

A CSF immunochromatographic test is recommended to detect pneumococcal soluble antigens when the clinical signs and symptoms are highly indicative of bacterial meningitis even when the direct examination is negative.

11.2.3. Culture

A positive culture confirms the diagnosis, identifies the causative agent, and determines its susceptibility to antibiotics.

This examination may be faulted because of:

- antibiotic intake before lumbar puncture performance;
- the conditions and time required for transporting the sample to the laboratory, which may not be compatible with the survival of particularly fragile bacteria;
- a very low bacterial inoculum.

Selected culture media should favor the growth of the most frequently isolated bacteria in community-acquired meningitis, irrespective of the associated requirements.

11.2.4. Assessment of antibiotic susceptibility

Following isolation of a bacterium from a pure culture, its susceptibility to antibiotics may be assessed as per the guidelines of the French microbiology society (French acronym CA-SFM) [28].

For *S. pneumoniae*, the CA-SFM recommends the routine use of the 1-μg oxacillin disk to detect reduced susceptibility to beta-lactams [28]. Accurate determination of MICs is required for amoxicillin and for one of the two 3GCs (cefotaxime or ceftriaxone). The use of strips impregnated with a predefined concentration gradient of antibiotics is recommended (Etest®). In case of positive direct examination, MICs determined on the first day from the CSF samples should be controlled in culture media using a standardized inoculum. The Etest® method may be used for other bacterial species isolated from CSF (mainly *N. meningitidis*), depending on laboratory practices.

Ceftriaxone MICs should be determined in case of reduced susceptibility to cefotaxime, or cefotaxime MICs should be determined in case of reduced susceptibility to ceftriaxone because the MICs of both of these molecules are sometimes different.

11.2.5. Bacterial detection using direct gene amplification

Tests targeting a specific bacterial or viral agent should be distinguished from those aiming at detecting the presence of any bacterial DNA (universal PCR) from a biological specimen.

Two amplification techniques have been developed and validated for the main microorganisms responsible for meningitis (multiplex PCR and real-time PCR). Several kits for simultaneously performing several multiplex PCR tests according to a syndrome-based approach (infectious agents responsible for bacterial and viral meningitis and meningoencephalitis) are available or will be available in the years to come. Their role in the diagnosis of bacterial meningitis will need to be defined.

When bacterial meningitis is highly suspected and when the direct examination is negative, physicians should perform the following before culture result availability — whenever possible:

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- meningococcal PCR, pneumococcal PCR, and *Listeria* PCR (when patients have risk factors for the latter infection);
- or universal PCR.

When the direct examination is positive and the culture is negative at 24 hours, these PCR tests are also recommended.

When the suspicion of a bacterial etiology is low, a PCR test is recommended in infants and children to detect an enterovirus (Genexpert® test). Considering the high sensitivity (86–100%) and specificity (92–100%) of this test, the high prevalence of enteroviruses in pediatric acute meningitis, and the rapid time to results (two hours), a positive enterovirus PCR test rules out the need for a bacterial PCR and allows for discontinuing the antibiotic therapy if initiated [28]. However, several epidemic enteroviruses in infants such as parechoviruses, cannot be identified with this technique and a specific PCR test should be performed.

Meningococcal blood PCR performed on EDTA and/or skin biopsy of purpuric lesions in case of purpura fulminans suspicion, allows for confirming the diagnosis when meningococcemia is suspected. Blood PCR is, however, useless when performed more than 24 hours after treatment initiation.

11.2.6. Other bacteriological examinations

11.2.6.1. Blood cultures. At least one pair of blood culture bottles should be inoculated. A second blood culture may be performed in adults just before initiating the antibiotic therapy. Blood cultures are positive in 50–75% of cases even when the CSF culture is negative. An association between CSF bacterial load and blood inoculum has been demonstrated. Several experts suggest collecting two pairs of blood culture bottles at the same time, but this has not been assessed in bacterial meningitis.

11.2.6.2. Skin biopsy. Patients presenting with purpura skin lesions should have a skin biopsy performed, even more so when the antibiotic therapy has already been initiated or when the CSF direct examination is negative or has not been performed. The causative agent may be isolated from culture of this type of sample in 60 to 80% of cases (most frequently *N. meningitidis*). *N. meningitidis* persists in skin lesions for at least 24 hours after antibiotic therapy initiation [29].

11.2.7. Biochemical examinations

11.2.7.1. In CSF.

11.2.7.1.1. CSF glucose levels. CSF glucose levels should be interpreted according to blood glucose levels, which samples should be taken at the same time. Normal CSF glucose levels are usually two thirds (66%) of those of blood glucose. CSF glucose levels of patients presenting with bacterial meningitis are < 40% of those of blood glucose (sensitivity 80%, specificity 98% [30]).

11.2.7.1.2. CSF protein level. High CSF protein levels are significantly associated with bacterial meningitis. The CSF protein level threshold associated with bacterial meningitis ranges from 0.5 to 1.2 g/l.

11.2.7.1.3. CSF lactate levels. The 2008 consensus conference recommended routine measurement of CSF lactate levels for differentiating bacterial from viral meningitis using the 3.5 mmol/l threshold; CSF lactate levels above that threshold are indicative of bacterial meningitis in adults.

Since 2008, two meta-analyses of 25 and 33 studies have been published on that topic in 2010 and 2011, respectively (22 studies similar to both meta-analyses) [31,32]. They demonstrated the excellent diagnostic performance of this biochemical marker, with a threshold ranging from 3.7 to 4 mmol/l to distinguish bacterial from viral meningitis. Two recent studies [33,34], including one of meningitis episodes with negative CSF direct examination [34], confirmed the excellent diagnostic performance of lactate level measurement in CSF with 3.8 mmol/l as the best discriminatory value (sensitivity 0.94, NPP 0.99, and AUCROC 1 for the diagnosis of bacterial meningitis in De Viallon et al.'s study) [34]. The lowest CSF lactate level for bacterial meningitis was 3.2 mmol/l and the highest CSF lactate level for viral meningitis was 3.7 mmol/l [34]. Lactate levels should always be interpreted alongside the CSF cytological and biochemical results. Lactate level measurement is only useful when the direct examination is negative and when the other CSF parameters do not point to a bacterial origin.

11.2.7.2. In blood.

11.2.7.2.1. Procalcitonin (PCT). In 2008 the jury recommended performing serum measurement of PCT levels to help diagnose bacterial meningitis, using 0.5 ng/ml as the discriminatory value.

Several studies [35–37] and one meta-analysis of nine studies (725 patients) [38] have since confirmed the effectiveness of this marker in discriminating bacterial and viral meningitis, with thresholds ranging between 0.5 and 1 ng/ml. The diagnostic effectiveness of serum PCT level measurement seems to be even better with the new version of the BRAHMS/Thermofisher diagnostic kit (Kryptor®), and the discriminatory value is lower (close to 0.25 ng/ml) [34]. PCT level measurement is only useful when the direct examination is negative and when the other CSF parameters do not indicate a bacterial origin. When sepsis is observed in infants, PCT levels may be normal the first six hours; thus, the bacterial origin cannot be officially ruled out at that stage.

11.2.8. Combining parameters: decision algorithms

Eight clinical decision algorithms aiming at differentiating bacterial from viral meningitis have been suggested [24,39–45]. Among those validated by independent evaluations, physicians are advised to use one of the following three:

- Hoen's algorithm [43] combines the number of blood leukocytes, blood glucose levels, CSF protein levels, and the number of neutrophils in CSF in adults and children;
- the Bacterial Meningitis Score (BMS) is based on the presence of seizures, the number of blood neutrophils ($\geq 10{,}000/mm^3$), CSF protein levels (≥ 0.8 g/l), the number of neutrophils in CSF ($\geq 1000/mm^3$), and on a positive direct examination using CSF Gram staining [46] in children;

- the Meningitest®, an improved version of BMS, is based on the presence of purpura, severe presentation in children (irritability, lethargy, prolonged time to skin recoloration), seizures, positive direct examination using CSF Gram staining, CSF protein levels ≥ 0.5 g/l, or PCT levels ≥ 0.5 ng/ml [42] in children.

No new decision algorithm has since been published.

The effectiveness of the BMS in children has been confirmed by a meta-analysis of eight studies including 4896 children [47], and more recently by a retrospective study of 494 children presenting with acute meningitis in Brazil [48]. The BMS and the Meningitest® have been reassessed in a European prospective and multicentric study of 198 children presenting with acute meningitis. They were both associated with 100% sensitivity and 100% negative predictive value; the specificity of the BMS was better than that of the Meningitest® [49].

11.3. Which patients should undergo a CT scan before lumbar puncture?

In France and in other countries, brain imaging test — usually a CT-scan — is too often performed before lumbar puncture when confronted with meningitis suspicion [50].

Arguments for our recommendations are as follows:

- a lumbar puncture is essential for diagnosing meningitis, identifying the bacterium, and assessing its susceptibility;
- the prognosis of bacterial meningitis depends on the rapidity of antibiotic therapy initiation;
- the CSF culture rapidly becomes negative when the antibiotic therapy is initiated, especially in case of meningococcal meningitis. Empirical antibiotic therapy initiation followed by CT scan and lumbar puncture may lead to a negative CSF culture because of the additional time required to perform the CT scan;
- the theoretical risk of lumbar puncture is brain herniation;
- brain herniation results from pressure disorders due to CSF discharge impairment and cerebral lesions (mass effect). Intracranial hypertension, commonly observed in severe meningitis, is not a contraindication to lumbar puncture per se.

An observational study demonstrated that a shorter time to lumbar puncture — by reducing the number of indications for imaging tests performed beforehand and by removing the "consciousness disorder" contraindication (only in the absence of brain herniation signs) — was associated with a substantial improvement in case fatality and sequelae rates, as compared with a historical cohort. This improvement was due to the increased number of patients receiving an antibiotic therapy within the first hour [51].

Removing consciousness disorders, recent seizures, and immunodeficiency (even severe) from the list of scenarios requiring brain CT scan to be performed before the lumbar puncture (besides those associated with brain herniation signs) led to performing the lumbar puncture earlier on and to better prognosis (case fatality and severity of sequelae) [52].

Recent and current international guidelines (ESCMID, EFNS, SPILF, IDSA, UKJSS) include "immunodeficiency, history of neurological disease, recent seizure, papillary edema, consciousness disorders, focal neurological deficit" as indications for CT scan before the lumbar puncture [30,53–56]. Several studies demonstrated that these recommendations were associated with a longer time to antibiotic therapy initiation in patients presenting with bacterial meningitis [50,57,58]. This increased time to antibiotic therapy initiation is due to a more frequent use of imaging tests before lumbar puncture. More than half of these imaging tests are not justified by contraindications. The contribution and compliance with indications for imaging tests before lumbar puncture recommended by the IDSA [30] in case of community-acquired bacterial meningitis suspicion were assessed in eight hospitals of Houston (Texas, United States) and its region between 2005 and 2010 [59]. A total of 614 cases of meningitis were included in this assessment. Imaging tests were performed in 549/614 cases (89%). They were not recommended in two-thirds of cases and only led to identifying two cases of minor abnormalities in this population. An imaging test was indicated in 193 cases and revealed major abnormalities requiring a change in clinical management in only 15 cases. Indication was based on isolated consciousness disorders in 17% of cases (5.8% overall). Two-thirds of the 119 patients presenting with consciousness disorders had a second contraindication to lumbar puncture. Median times to lumbar puncture observed in this study were respectively 5.5 hours and 8.25 hours in patients who did not undergo or who underwent an imaging test before the lumbar puncture. This is not compatible with adequate management of bacterial meningitis, which only accounted for 46 of 614 cases (7.4%).

The 2009 Swedish guidelines [50] removed the three criteria that were not supported by a sufficient level of scientific evidence (consciousness disorders except in the presence of brain herniation signs, recent seizures, and immunodeficiency) and assessed the impact of this removal using a national register [51,60]. The retrospective comparison of two periods (2005–2009 [former guidelines] and 2010–2012 [new guidelines]) using groups of more than 300 patients each, highlighted the substantial reduction in time to antibiotic therapy initiation (by 1.12 hours on the whole cohort, and by 1.6 hours in case of immediate lumbar puncture), the increased number of patients treated within one hour and within two hours following hospital admission, and the decreased case fatality (38% vs 49%) and sequelae rates (6.9% vs 11.7%) [51,60].

A recent North American study assessing the IDSA guidelines reported a median time to antibiotic therapy initiation of 8.25 hours in patients who underwent a CT scan before lumbar puncture. This study also confirmed that the likelihood of a significant brain tumor was very low in patients presenting with signs of acute meningitis who only had consciousness disorders as potential contraindications to the lumbar puncture [59].

However, some factors may lead physicians to consider the likelihood of brain herniation such as the following

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contraindications to lumbar puncture without prior brain imaging: sus- and infratentorial focal neurological signs (with or without consciousness disorders or even direct signs of brain herniation) are absolute contraindications to the lumbar puncture; however, in case of brain herniation signs, normal imaging results do not allow the lumbar puncture to be performed.

However, the risks of brain herniation following lumbar puncture are very low even when performed in the presence of intracranial lesions with a mass effect. The authors of a study of 94 brain abscesses [61] reported that 55 patients (59%) had a lumbar puncture performed while — besides the abscess — mass effect had been observed at CT scan in 65% of them. Only one of these patients died from brain herniation within six hours following the lumbar puncture, but the authors could not establish the causative role of the lumbar puncture in the patient's death. This figure is similar to those reported in brain abscesses. Recent seizures may be manifestations of intracranial expansion; the lumbar puncture is in that case dangerous. A Dutch study of adult patients presenting with bacterial meningitis reported that 5% of the 666 patients experienced one or more seizures before hospital admission. Seventy per cent of these patients had a brain imaging performed before lumbar puncture, with focal lesions observed in 32% of them [62]. Post-critical state may hide neurological abnormalities indicative of focal neurological lesions because of the associated hypotonia and confusion. The neurological examination is not contributory in case of status epilepticus and is a cause of intracranial hypertension. Children aged below 5 years often present with generalized seizures in case of fever, irrespective of the origin. They are therefore not considered contraindications to the lumbar puncture, except for unilateral seizures, which should be considered a sign of localization. Consciousness disorders associated with brain herniation (pupillary abnormalities [fixed unilateral or bilateral mydriasis], dysautonomia [blood pressure and bradycardia, respiratory rate abnormalities], cerebellar tonic seizures, no reaction to stimuli, decortication or decerebration symptoms) are absolute contraindications to lumbar puncture without prior imaging test.

11.3.1. Recommendations

When bacterial meningitis is suspected, brain imaging should be performed BEFORE lumbar puncture in the following situations only (neurological contraindications to the lumbar puncture):

- presence of clinical signs potentially indicating intracranial expansion:
  - signs of localization (Table 1),
  - focal AND recent seizures (< 4 days);
- signs of brain herniation: consciousness disorders AND one or more of the following signs:
  - pupillary abnormalities (fixed unilateral or bilateral mydriasis),
  - dysautonomia (blood pressure and bradycardia, respiratory rate abnormalities),
  - cerebellar tonic seizures,
  - no reaction to stimuli,
  - decortication or decerebration symptoms;
- persisting seizures (i.e., generalized motor seizures) preventing lumbar puncture.

Isolated consciousness disorders are not considered contraindications to an immediate lumbar puncture.

12. Question 2 – What is the initial antibiotic therapy for patients presenting with a suspicion of bacterial meningitis?

12.1. Should the antibiotic therapy be urgently prescribed to patients presenting with a suspicion of bacterial meningitis?

The antibiotic therapy should be urgently initiated in patients presenting with bacterial meningitis. The immediate and mid-term prognoses depend on how early the antibiotic therapy is initiated [63]. However, defining the optimal time to initiation is difficult because of the observational nature of available studies.

Several studies demonstrated the statistically significant association between time to antibiotic administration and bacterial meningitis prognosis in adults. Proulx et al. studied prognostic factors in 123 patients [64]. The median time between arrival at the emergency department and antibiotic therapy initiation was 3.8 hours (IQR 1.4–6.1 hours). The multivariate analysis revealed that more than 6 hours between admission and administration of the first dose of antibiotics were significantly associated with a higher rate of deaths, with an adjusted odds ratio (OR) of 8.4 (95% CI 1.6–40.9, $P < 0.01$). Auburtin et al. assessed risk factors for poor prognosis in 156 adult patients presenting with *S. pneumoniae* meningitis hospitalized in the intensive care unit (ICU) [65]. Median time between clinical sign onset and antibiotic therapy initiation was 15 hours (IQR 7–36 hours), while the median time between hospital admission and antibiotic therapy initiation was 3 hours (IQR 1–6 hours). The multivariate analysis revealed that more than 3 hours between admission and administration of the first dose of antibiotics were significantly associated with a risk of death at 3 months, with an adjusted OR of 14.12 (95% CI 3.93–50.9, $P < 10^{-4}$) and with an increased risk of neurological sequelae in surviving patients [30]. Another study assessed the impact of a delayed antibiotic therapy initiation in 176 patients aged above 16 years and hospitalized for bacterial meningitis, including 40% caused by *S. pneumoniae*. Although the time between admission and antibiotic therapy initiation was short (median of 1 hour, mean of 1.2 ± 0.9 hours) and was not considered a risk factor for poor prognosis, the multivariate analysis revealed that a time interval > 24 hours between symptom onset and treatment initiation was associated with a higher risk of poor outcome (OR 2.8; 95% CI 1.13–7, $P = 0.026$) [66]. A prospective cohort study conducted in the Czech Republic between 1996 and 2006 included 279 adult patients to assess predictive factors of mortality and sequelae. Pneumococcal (29%) and meningococcal (27%) meningitis cases were the most frequent. This study focused on time to antibiotic therapy initiation after symptom

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onset and not after hospital admission as usually done in most studies. The multivariate analysis revealed that time to antibiotic therapy initiation > 48 hours following symptom onset was independently associated with poor outcome, defined by a score between 1 and 4 on the Glasgow outcome scale (sequelae or death) (OR: 2.468; 95% CI: 1.036–5.882, $P = 0.041$) [67]. The authors of a retrospective study assessed case fatality in the ICU according to four time periods between admission and administration of the first dose of antibiotics. The case fatality was 8% between 0 and 2 hours, 17% between 2 and 4 hours, 22% between 4 and 6 hours, and 25% between 6 and 12 hours. However, the multivariate analysis revealed that time to administration below 2 hours was not significantly associated with reduced case fatality (OR: 0.3, 95% CI 0.0–1.6, $P = 0.155$) [68]. A study published in 2016 including 173 adult patients presenting with bacterial meningitis in Denmark (poor outcome: 45%, case fatality: 19%) reported similar results. The median time between admission and antibiotic therapy initiation reported in this retrospective study was 2 hours (IQR: 1.0–5.5). The adjusted risk ratio for poor outcome (death or sequelae) was 1.5 (95% CI 1.0–2.2) when the antibiotic therapy was administered more than 6 hours after admission versus within two hours of admission. It was 1.1 (95% CI 0.8–1.5) for each additional hour of delay [69].

The most convincing recent study was published by a Swedish team who assessed the impact of the modifications of the 2009 national guidelines. The main change was the removal of consciousness disorders and recent seizures from the list of contraindications to lumbar puncture without prior brain CT scan [51]. Using the data from the national Swedish register, the authors retrospectively compared two periods: one before the introduction of modifications (2005–2009) and the other after (2010–2012). A total of 712 files were analyzed. The number of files analyzed during the two periods were comparable (394 and 318 patients, respectively) and *S. pneumoniae* was the causative agent in half of cases. Approximately three-quarters of patients had received high doses of corticosteroids. Among all patients for whom the data was available, 31.5% had received an appropriate antibiotic therapy within the hour following hospital admission and 51.2% within two hours. Mean time to antibiotic therapy administration was on average shorter by 1.18 hours during the second period (95% CI 0.46–1.90 hours, $P < 0.01$). After adjustment based on age, sex, consciousness disorders, use of corticosteroids, and antibiotic choice, odds ratios for antibiotic administration within one or two hours following admission were respectively 1.82 (95% CI 1.15–2.89, $P < 0.05$) and 2.07 (95% CI 1.34–3.20, $P < 0.01$) during the second period. The authors also reported a decreased case fatality between both periods, from 11.7% to 6.9% ($P < 0.05$), but the difference was not statistically significant after adjustment based on the above-mentioned criteria. The risk of neurological or hearing sequelae was lower during the second period, including after adjustment. One of the key findings of this study was that time to treatment administration was significantly associated with the risk of death, with a relative increase of 12.6% (95% CI 3.1–23.1%, $P < 0.01$) per delayed hour of administration of the first dose of antibiotics.

Recommendations: The antibiotic therapy (and the administration of dexamethasone when indicated) should ideally be initiated within the hour following hospital admission, irrespective of the presumed time since meningitis onset. Any delay in antibiotic therapy initiation is associated with a poorer prognosis.

12.2. Which patients should receive an antibiotic therapy before lumbar puncture?

The lumbar puncture is essential to establish the diagnosis. An empirical antibiotic therapy should be initiated in all situations requiring lumbar puncture delay because of the close association between prognosis and rapid time to treatment initiation. Additional investigations should not delay the antibiotic therapy initiation [30,70]. Antibiotic administration before lumbar puncture is associated with a risk of negative CSF culture and should therefore only be considered when the minimum reasonable delay cannot be respected or in case of lumbar puncture contraindications. The need for blood cultures before hospital administration of antibiotics should be emphasized.

Recommendations: The antibiotic therapy should be initiated before lumbar puncture (but after blood culture) in the three following situations:

- purpura fulminans;
- patients who cannot be admitted to hospital within 90 minutes [54];
- contraindication to the immediate lumbar puncture (Question 1).

The lumbar puncture should be performed as soon as possible following correction of abnormalities — whenever possible. Several experts do not recommend performing the lumbar puncture in patients presenting with purpura fulminans, even when abnormalities have been corrected.

12.3. Which antibiotic therapy should be prescribed to patients presenting with a suspicion of bacterial meningitis?

Community-acquired bacterial meningitis is associated with a high morbidity and case fatality [3,71–73]. Bacterial meningitis case fatality is highly reduced if the antibiotic therapy is initially adapted to the causative agent in terms of *in vitro* susceptibility [74–84], and sequelae are less common when CSF sterilization is rapidly obtained [85,86]. The first-line antibiotic therapy choice depends on epidemiological data (prevalence of bacterial species and susceptibility profiles) and on the pharmacokinetic and pharmacodynamic parameters of antibiotics. The following rationale aims to:

- update the recommendations adopted in 2008 [87] on antibiotic therapy during the first hours of meningitis management;
- and to suggest "alternatives" for patients presenting with a history of severe allergy to antibiotics and/or rare or very rare bacterial resistance.

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12.3.1. Epidemiological data

The epidemiological changes described here are based on the Epibac network data [88], the mandatory report of meningococcal or *Listeria monocytogenes* meningitis, the national reference centers (pneumococci, *Haemophilus influenzae*, meningococci, *Listeria*, streptococci), and for children on data from the Observatory for Pediatric Bacterial Meningitis (French acronym GPIP/ACTIV) [89]. Epibac is a network of voluntary microbiological hospital laboratories coordinated by the French public health agency (Santé publique France) since 1997, which aims to collect data of bacterial meningitis caused by the six most common causative agents of severe community-acquired bacterial infections: *H. influenzae*, *N. meningitidis*, *S. pneumoniae*, group A and B streptococci, and *L. monocytogenes*. The incidence of bacterial meningitis in metropolitan France is measured taking into account the Epibac network coverage and 78% exhaustiveness for data collection by participating hospitals — for the most recent available data. Meningitis cases only diagnosed by PCR are excluded from the analysis; they account for more than 30% of reported meningococcal meningitis cases but for less than 5% of meningitis cases caused by other microorganisms [88].

The epidemiological changes should be compared with the update of vaccination recommendations implemented in 2008 [90,91].

- Group C meningococcal vaccination has been recommended since 2010 in France in all newborns aged 12 to 24 months, with a catch-up vaccination for children and young adults aged below 25 years [90]. The most recent vaccination coverage data (source: sample of individuals benefitting from social security in the general population — French acronym EGB) highlights the failure of this strategy [92]. The vaccination coverage among newborns aged 12 to 24 months slowly increased between 2011 and 2015 (from 48% to 70%), but it did not really increase among older age groups (targeted by the vaccination strategy) and is still insufficient. The vaccination coverage for the age group 10–14 years was just slightly above 30% in 2015 and lower rates were reported for the 15–19-year (23%) and 20–25-year (7%) age groups. However, this temporary extension of vaccination (catch-up vaccine) to other age groups (2 to 24 years) is essential to reach herd immunity. Considering the insufficient vaccination coverage among adolescents and young adults, one cannot rely on herd immunity to indirectly protect infants aged below one year who are not included in the 2010 vaccination strategy [93]. Primary vaccination with NEISVAC is therefore recommended since 2016 in France at 5 months, with a booster at 12 months [94]. The serogroup B meningococcal recombinant vaccine (European marketing authorization in 2013), currently used in the United Kingdom, is not recommended in France yet except in some hyperendemic areas when cluster of cases are observed and for some at risk patients [95].
- In June 2010 the 7-valent pneumococcal conjugate vaccine (PCV7, serotypes 4, 6B, 9 V, 14, 18 C, 19F, and 23F) has been replaced by the 13-valent pneumococcal conjugate vaccine (PCV13, PCV7 serotypes + serotypes 1, 3, 5, 6A, 7F, and 19A) for children aged below 2 years [90]. Since April 2013 vaccination with PCV13 followed by the 23-valent polysaccharid pneumococcal vaccine is recommended in older children and adults at higher risk of pneumococcal invasive infection [91]. High vaccination coverage with PCV13 is currently observed among children aged below 2 years (> 90% since 2010).

Although vaccination coverage for group C meningococcal infections is still too low to induce the required herd immunity, these new recommendations — especially those relating to pneumococcal vaccination — led to substantial changes in the epidemiology of bacterial meningitis [93].

12.3.2. Pediatric meningitis (excluding neonatal meningitis)

Since the last 2008 consensus conference, the introduction of new vaccination recommendations against the causative agents of meningitis has led to a substantial change in their epidemiology [90,96]. The latest data published by GPIP/ACTIV indicates that group B *Streptococcus* is the leading cause of meningitis (57.2%) in infants aged below 2 months, while the leading cause is *S. pneumoniae* in infants aged between 2 and 12 months (44%). *N. meningitidis* and *S. pneumoniae* respectively account for half and a third of meningitis cases in infants aged above 1 year. The case fatality of pediatric bacterial meningitis remains stable at approximately 7% with variations depending on the pathogen and age, with a higher case fatality in infants aged below 2 months (11%) (Table 2).

12.3.2.1. S. pneumoniae. A reduced incidence of pneumococcal meningitis and of all pneumococcal invasive infections is being observed in France and abroad [97–100]. The incidence of pneumococcal meningitis has indeed significantly decreased in France between 2009 and 2014 in all age groups (Table 3) and especially among children aged < 2 years (66% decrease) [88].

12.3.2.2. N. meningitidis. The 2015 incidence of meningococcal invasive infections was 8.5/100,000 (64 cases) among newborns aged < 1 year. It ranged from 3 to 1/100,000 among children aged between 1 and 4 years (64 cases) and was approximately 0.9/100,000 among children aged between 5 and 14 years (50 cases). Serogroup B is predominant in all age groups and accounts for more than 60% of pediatric cases. The proportion of serogroup C ranges from 22% among newborns aged < 1 year to 36% among children between 5 and 14 years of age. Serogroup Y accounts for < 10% of cases among children and serogroup W remains rare (< 5%) [88,101]. The report rate of meningococcal invasive infections continued to decrease between 2005 and 2015 among newborns aged < 1 year. The increased report rates of meningococcal invasive infections observed between 2010 and 2014 among newborns aged < 1 year and among children aged 1–4 years were no longer observed in 2015. The incidence of serogroups Y and W meningococcal invasive infections increased in all age groups, except among the 5–14-year age group (Fig. 2).

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Table 2
Distribution of meningitis cases by age group and bacterial etiology, data collected by the GPIP/ACTIV Observatory from 2010 to 2014.
Répartition des méningites par groupe d'âge et par étiologie bactérienne, données cumulées de l'Observatoire GPIP/ACTIV, de 2010 à 2014.

Bacterial species	< 2 months n = 173 (12.8%)	2–11 months n = 498 (36.7%)	12–23 months n = 147 (10.8%)	24–59 months n = 201 (14.8%)	5–17 years n = 337 (24.9%)	Total n = 1356	Case fatality
N. meningitidis	14 (8.1)	158 (31.7)	77 (52.4)	100 (49.8)	163 (48.4)	512 (37.8)	2.7
Group B	12 (6.9)	120 (24.1)	57 (38.8)	77 (38.3)	110 (32.6)	376 (27.7)	2.4
Group C	2 (1.2)	22 (4.4)	12 (9.2)	9 (4.5)	33 (9.8)	78 (5.8)	1.3
Group Y	0	6 (1.2)	1 (0.7)	3 (1.5)	6 (1.8)	16 (1.2)	6.3
S. pneumoniae	16 (9.3)	219 (44.0)	48 (32.7)	74 (36.8)	126 (37.4)	483 (35.6)	9.3
Streptococcus agalactiae	99 (57.2)	55 (11)	1 (0.7)	0	2 (0.6)	157 (11.6)	9.6
H. influenzae type b	0	19 (3.8)	14 (9.5)	8 (4)	9 (2.7)	50 (3.7)	4
E. coli	29 (16.8)	28 (5.6)	0	0	1 (0.3)	58 (4.3)	8.9
Streptococcus pyogenes	1 (0.6)	1 (0.2)	2 (1.4)	3 (1.5)	9 (2.7)	16 (1.2)	12.5
L. monocytogenes	0	2 (0.4)	0	2 (1)	1 (0.3)	5 (0.4)	0
Mycobacterium tuberculosis	0	1 (0.2)	1 (0.7)	5 (2.5)	5 (1.5)	12 (0.9)	16.7
Other	14 (8.1)	15 (3)	4 (2.7)	9 (4.5)	21 (6.2)	63 (4.6)	6.3
Case fatality	11.6	7.2	7.5	3	4.8	6.6	

Table 3
Incidence and number of pneumococcal meningitis cases reported between 2009 and 2014 by age group [88].
Incidence et nombre de cas de méningites à pneumocoque entre 2009 et 2014 par tranche d'âge [88].

Age groups	Years		Decrease (%)
	2009	2014	
< 23 months			
Incidence/100,000	6.3	2.2	−66
Number of cases	96	33	
2–4 years			
Incidence/100,000	0.9	0.5	−40
Number of cases	20	12	
5–14 years			
Incidence/100,000	0.6	0.4	−31
Number of cases	42	29	

12.3.2.3. Other bacteria currently responsible for pediatric meningitis. The end of the mandatory BCG vaccination did not lead to an increase in tuberculous meningitis cases, which account for 0.9% of pediatric meningitis cases (Table 2) [102,103]. Group B streptococcus is responsible for slightly more than 10% of pediatric meningitis cases (excluding newborns) and the EPIBAC data reported 16 patients aged between 2 and 11 months in 2014 [88]. *H. influenzae* meningitis accounts for 3.7% of pediatric meningitis cases and the EPIBAC network reported 20 cases in 2014 [88]. *Escherichia coli* is observed in 4.3% of cases and *Listeria* meningitis (nine cases reported by EPIBAC in 2014) and group A streptococcal meningitis remain rare in children (Table 2). According to GPIP/ACTIV, 16 pediatric cases of *Listeria* meningitis were reported among 4066 children aged > 1 month between 2001 and 2012 (i.e., 0.39% of meningitis cases in infants aged > 1 month). Only two patients were aged below 3 months. *L. monocytogenes* is now very rarely responsible for bacterial meningitis in children (including infants). The systematic addition of amoxicillin in children aged below 3 months is not justified in the absence of listerioris evidence (rhombencephalitis).

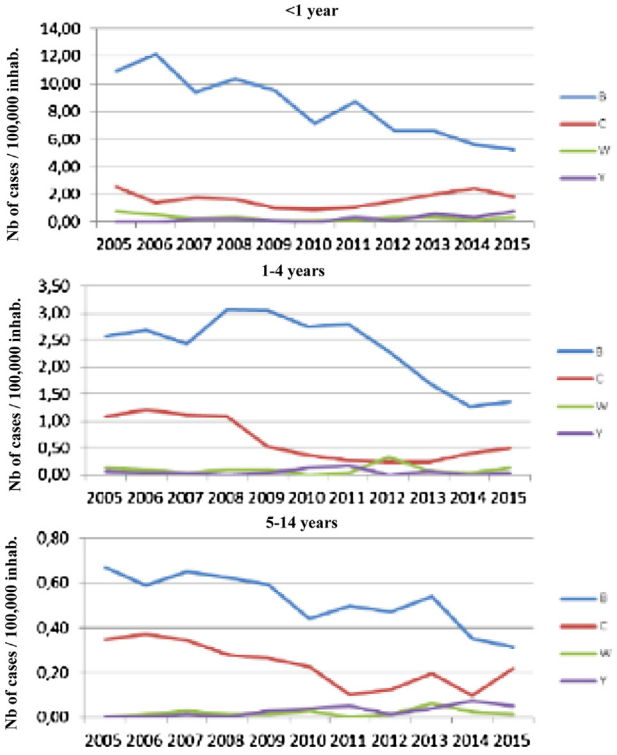

Fig. 2. Reporting rates of meningococcal invasive infections for the main serogroups by age group, between 2005 and 2015 [101].
Évolution des taux de notification des IIM pour les principaux sérogroupes par âge, entre 2005 et 2015 [101].

To sump up, since 2009 the epidemiology of pediatric meningitis is dominated by a decreased incidence of pneumococcal meningitis, especially among children aged below 2 years who are targeted by the PCV13 vaccine.

12.3.3. Adult meningitis

Irrespective of the etiology, the incidence of bacterial meningitis in adults was 1.74 cases per 100,000 inhabitants aged 15 years or above in 2013–2014; thus accounting for slightly

Table 4
Incidence rate[a] of bacterial meningitis per 100,000 inhabitants aged ≥ 15 years by age and microorganism, EPIBAC, Santé publique France, metropolitan France, 2013–2014.
Taux d'incidence[a] des méningites bactériennes pour 100 000 habitants ≥ 15 ans selon l'âge et le micro-organisme, EPIBAC, Santé publique France, France métropolitaine, 2013–2014.

Age groups	15–24 years		25–39 years		40–64 years		≥ 65 years		All aged > 15 years	
	IR/10^5	%	IR/10^5	%	IR/10^5	%	IR/10^5	%	IR/10^5	%
S. pneumoniae	0.22	14	0.47	43	1.18	69	1.52	59	0.96	55
N. meningitidis	1.23	79	0.40	36	0.26	15	0.22	9	0.42	24
L. monocytogenes	0.03	2	0.06	5	0.12	7	0.41	16	0.16	9
H. influenzae	0.03	2	0.08	7	0.06	3	0.22	9	0.10	6
S. agalactiae	0.02	1	0.06	5	0.05	3	0.07	3	0.05	3
S. pyogenes	0.01	1	0.03	3	0.04	2	0.11	4	0.05	3
Total	1.55	100	1.09	100	1.71	100	2.55	100	1.74	100

IR: incidence rate.
[a] Corrected incidence for comprehensiveness purposes.

more than 900 cases per year. A decreased incidence (−19%, $P < 10^{-4}$) has therefore been observed compared with that of 2008–2009 (1.93 cases per 100,000 inhabitants aged 15 years or above). This is due to the decreased incidence of pneumococcal and meningococcal meningitis as well as to a stable incidence of other types of bacterial meningitis [88].

- The introduction of the PCV7 vaccine was associated with a paradoxical increase in adult pneumococcal meningitis between 2001–2002 and 2008–2009 [10], but the incidence of pneumococcal meningitis decreased following the introduction of the PCV13: by 23% ($P < 10^{-4}$) among individuals aged above 15 years [88]. This decreased incidence was observed in all age groups, except in the 15–24-year age group. The high vaccination coverage, the efficacy of the PCV13 vaccine against the strains of the six additional serotypes (including serotypes 19A and 7F), and the stable number of meningitis cases caused by non-vaccine serotypes seem to explain these positive changes (EPIBAC – unpublished data) [104].
- The incidence of meningococcal meningitis decreased by 24% ($P = 0.007$) among adults between 2008–2009 and 2013–2014 [88]. This decreased incidence was mainly observed among young adults aged 15–24 years, and was mainly due to the decreased incidence of group B meningococcal infections [101]. No decrease in the incidence of group C meningococcal invasive infections in adults was observed because of the insufficient vaccination coverage for group C meningococcal infections [93].
- The incidence of other types of bacterial meningitis did not change substantially among adults over the same period.

These changes did not substantially change the epidemiology of adult bacterial meningitis. *S. pneumoniae* and *N. meningitidis* are still mostly responsible for adult bacterial meningitis. They respectively account for 55% and 24% of cases, i.e. 500 and 220 cases per year in 2013–2014. *L. monocytogenes* is the third cause of bacterial meningitis. The respective proportion of microorganisms vary by age (Table 4). *N. meningitidis* is most common in adolescents and young adults, accounting for 79% of cases among the 15–24-year age group and for 60% of cases among the 25–29-year age group. *S. pneumoniae* is responsible for 64% of meningitis cases in adults aged above 30 years. Etiologies are slightly more diverse among elderly patients: *S. pneumoniae* accounts for 59% of adult bacterial meningitis cases, *L. monocytogenes* for 16% of cases, *N. meningitidis* for 9% of cases, *H. influenzae* for 9% of cases, and group A and B streptococci for less than 5% of cases. The relative importance of *L. monocytogenes* meningitis among elderly adults should be highlighted. Age and the increase in chronic diseases and in associated immunodeficiency causes seem to contribute to this relative importance [56,105].

To sum up, despite a decreased incidence of pneumococcal meningitis due to the indirect effect of infant vaccination with PCV13, *S. pneumoniae* remains the leading cause of bacterial meningitis in adults. *N. meningitidis* is the leading cause of meningitis in adults aged below 30 years. *L. monocytogenes* is the second cause of bacterial meningitis in elderly individuals.

12.3.4. Antibiotic susceptibility

12.3.4.1. S. pneumoniae. The national reference center for pneumococci has been evaluating the susceptibility of 3073 pneumococcal strains responsible for meningitis since 2006 [103]. The incidence of pneumococci with reduced susceptibility to beta-lactams responsible for meningitis has significantly decreased. From 2006 to 2014, their prevalence decreased from 34 to 21% for penicillin, 17 to 5% for amoxicillin, and 4 to 1% for cefotaxime (Fig. 3). The most recent 2016 data reports the following rates of pneumococci responsible for meningitis with reduced susceptibility to beta-lactams: 26% for penicillin, 6.2% for amoxicillin, and 2% for cefotaxime.

In 2014 ($n = 271$), although 21% of strains responsible for meningitis showed reduced susceptibility to penicillin (MIC > 0.064 g/ml), the proportion of strains with reduced susceptibility to the recommended first-line molecules for the treatment of meningitis was substantially lower. Irrespective of age, 1.5% of strains had reduced susceptibility to cefotaxime (MIC > 0.5 mg/l) but no strain was resistant to the molecule (all have MICs < 2 mg/l). The highest cefotaxime MIC measured in 2014 was 1 mg/l. This MIC was observed in four strains, including three isolated from adult patients (serotype 19A, 19F, and 35B) and one isolated from a 34-month-old child (serotype

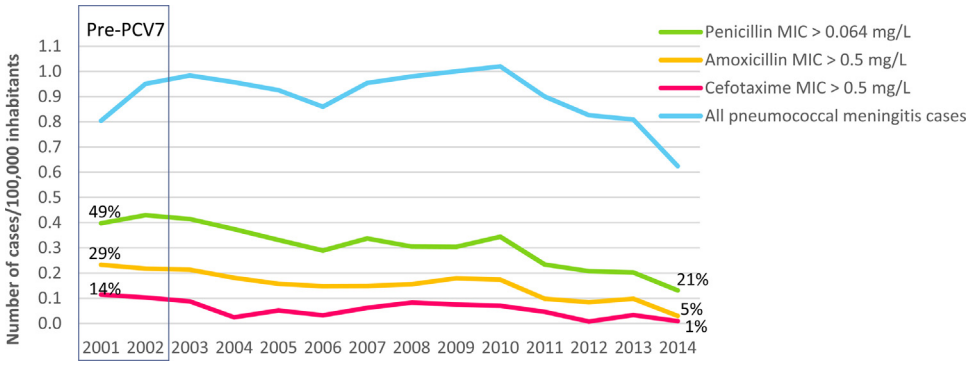

Fig. 3. Incidence rate of pneumococcal meningitis with reduced susceptibility to beta-lactams (penicillin, amoxicillin, cefotaxime), France 2001–2014. The blue curve refers to the incidence rate of all pneumococcal meningitis cases [104]. Pre-PCV7, period before the introduction of the 7-valent conjugate vaccine.
Évolution du taux d'incidence des méningites à pneumocoque de sensibilité diminuée aux bêtalactamines (pénicilline, amoxicilline, céfotaxime), France 2001–2014. La courbe bleue indique le taux d'incidence de tous les cas de méningites à pneumocoque [104]. Pre-PCV7, période précédant l'introduction du vaccin conjugué 7-valent.

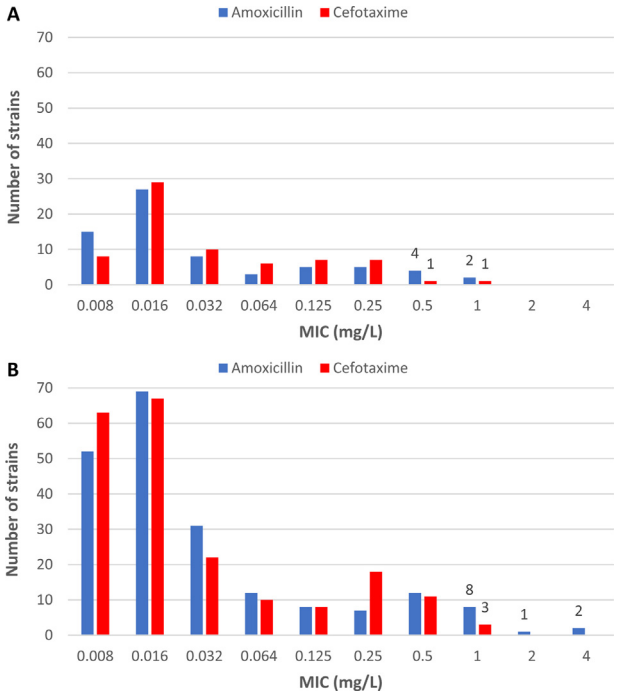

Fig. 4. Distribution of pneumococcal strains isolated from meningitis in France in 2014 depending on their amoxicillin and cefotaxime MICs: children (0–15 years, $n = 69$) (A); adults (> 15 years, $n = 202$) (B) [104].
Répartition des souches de pneumocoque isolées de méningites en France en 2014 en fonction de leur CMI d'amoxicilline et de céfotaxime : enfants (0–15 ans, n = 69) (A) ; adultes (> 15 ans, n = 202) (B) [104].

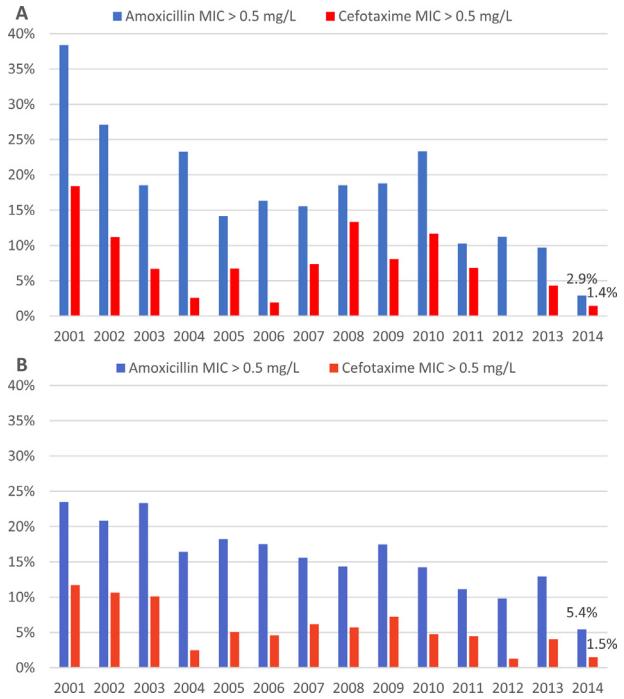

Fig. 5. Pneumococcal strains with reduced susceptibility to amoxicillin or cefotaxime (%) isolated from meningitis in France, 2001–2014: children (0–15 years) (A); adults (> 15 years) (B) [104].
Pneumocoques de sensibilité diminuée à l'amoxicilline ou au céfotaxime (%) isolés de méningites en France, 2001–2014 : enfants (0–15 ans) (A) ; adultes (> 15 ans) (B) [104].

19A). Amoxicillin MIC was > 0.5 mg/l for less than 5% of strains and > 2 mg/l for 0.7% of strains. The highest amoxicillin MIC measured in 2014 was 4 mg/l. This was observed in two strains isolated from adults (Fig. 4).

The proportion of pneumococci with reduced susceptibility to amoxicillin or cefotaxime has therefore not really been different between children and adults since 2012 (Fig. 5). Antibiotic susceptibility of *S. pneumoniae* strains isolated from patients presenting with meningitis in 2016 is displayed in Table 5.

This trend is concomitant with the significant decrease in the incidence of pneumococcal meningitis due to the direct and indirect effects of the vaccination of children aged below 2 years with PCV7 vaccine and then with the PCV13 vaccine. Most strains with reduced susceptibility to beta-lactams were represented by vaccine serotypes (6B, 9V, 14, 19F, 23F, 19A, and 6A) no longer observed in pediatric meningitis (< 2 years) and which incidence has significantly decreased in the rest of the population (Fig. 6) [104,106].

These significant epidemiological changes led the Pediatric Infectious Diseases Group of the French Pediatrics Society to update its initial recommendations for the treatment of pneumococcal meningitis [107]. In 2008 the GPIP was still

Table 5
Antibiotic susceptibility of *S. pneumoniae* strains isolated from patients presenting with meningitis in 2016.
Sensibilité aux antibiotiques des souches de S. pneumoniae *isolées de méningites en 2016.*

Antibiotics	Thresholds (mg/l)[a]		Strains (*n*)	%S	%I	%R	MIC_{50}	MIC_{90}
	S	R						
Penicillin G(excluding meningitis)	≤ 0.06	> 2	402	73.9	26.1	0.0	0.016	0.5
Penicillin G (meningitis)	≤ 0.06	> 0.06	402	73.9	–	26.1		
Amoxicillin(excluding meningitis)	≤ 0.5	> 2	402	93.8	5.7	0.5	0.016	0.5
Amoxicillin (meningitis)	≤ 0.5	> 0.5	402	93.8	–	6.2		
Cefotaxime	≤ 0.5	> 2	402	98.0	2.0	0.0	0.016	0.25
Vancomycin	≤ 2	> 2	402	100	0.0	0.0	0.25	0.5
Rifampicin	≤ 0.06	> 0.5	402	100	0.0	0.0	–	–

S: susceptible; R: resistant: I: intermediate resistance; MIC: minimum inhibitory concentration.
[a] As per the 2016 CASFM-EUCAST guidelines.

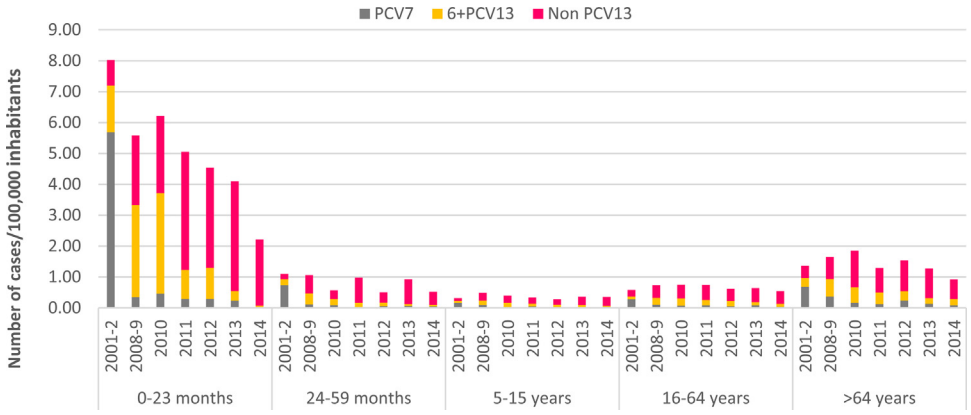

Fig. 6. Incidence of meningitis by serotype group and age, France, 2001–2014 (Sources: data from EPIBAC and the national reference center for pneumococci, [104]) (PCV7, serotypes of the 7-valent conjugate vaccine; 6 + PCV13, serotypes of the 13-valent conjugate vaccine not included in the PCV7; non-PCV13, serotypes not included in the PCV13).
Évolution de l'incidence des méningites par groupe de sérotypes selon l'âge, France, 2001–2014 (Sources : données EPIBAC et CNR des Pneumocoques, [104]) (PCV7, sérotypes du vaccin conjugué 7-valent; 6 + PCV13, sérotypes du vaccin conjugué 13-valent non contenus dans le PCV7 ; non PCV13, sérotypes non contenus dans le PCV13).

recommending the addition of vancomycin to high doses of 3GC (because of the emergence of serotype 19A clones with reduced susceptibility to beta-lactams), but this recommendation is no longer included in the 2014 updates: only high doses of 3GCs are recommended [107].

The incidence of pneumococcal meningitis with reduced susceptibility to beta-lactams has now bottomed out since the start of the surveillance in 2001 — in all age groups (Figs. 7 and 8).

12.3.4.2. N. meningitidis. Susceptibility profiles of *N. meningitidis* strains isolated from patients presenting with invasive meningococcal infections were defined by the national reference center for meningococci for the antibiotics of therapeutic or prophylactic interest (penicillin G, amoxicillin, injectable 3GCs, rifampicin, and ciprofloxacin) [108]. In 2015 all strains assessed at the national reference center ($n = 322$) were susceptible to 3GCs, rifampicin, and ciprofloxacin. However, just like in 2006, 30% of these strains showed reduced susceptibility to penicillin G and amoxicillin.

The empirical treatment with a 3GC is therefore highly likely to be effective when administered at the high dosage usually recommended in this indication. However, the use of amoxicillin at high dosage is probably ineffective against strains with reduced susceptibility to penicillin G and amoxicillin (Table 6).

12.3.4.3. H. influenzae. The susceptibility profiles of *H. influenzae* strains have not substantially changed since 2005. Eighteen per cent (84/470) of all strains assessed at the *Haemophilus* national reference center in 2013 (*vs* 19% in 2005) were resistant to amoxicillin (MICs > 2 mg/l) through penicillinase secretion, and 18% (85/470) (*vs* 19% in 2005) had a modified PLP3 with amoxicillin MICs between 2 and 16 mg/l and cefotaxime MICs between 0.064 and 1 mg/l. These percentages vary according to the type of sample and serotype. PLP3 modification (preferred target of cephalosporins) is associated with reduced cross susceptibility to all beta-lactams, although at variable rates depending on the position and number of mutations, and type of beta-lactam. Resistance to amoxicillin is often moderate, with MICs ranging from 1 to 16 mg/l (modal MIC at 2 mg/l). Clavulanic acid does not restore susceptibility to amoxicillin. The activity of first-generation and second-generation cephalosporins is reduced, just like that of carbapenems. 3GCs remain the most active cephalosporins, with MICs rarely exceeding 0.125 mg/l.

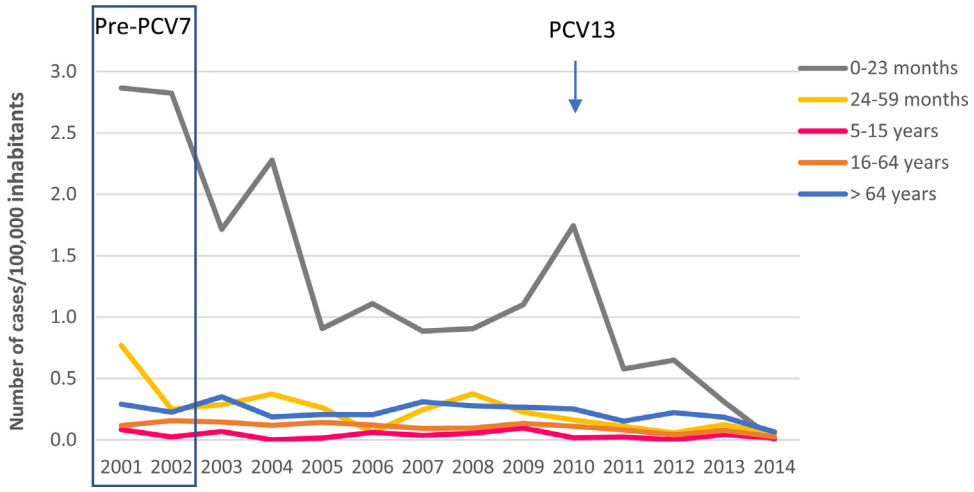

Fig. 7. Incidence of pneumococcal strains with reduced susceptibility to amoxicillin (MIC > 0.5 mg/l) isolated from meningitis, by age group (Sources: data from EPIBAC and the national reference center for pneumococci, unpublished data). Pre-PCV7, period before the introduction of the 7-valent conjugate vaccine; PCV13, introduction of the 13-valent conjugate vaccine.
Incidence des pneumocoques de sensibilité diminuée à l'amoxicilline (CMI > 0,5 mg/L) isolés de méningites, selon le groupe d'âge, France, 2001–2014 (Sources : données EPIBAC et CNR des Pneumocoques, non publiées). Pre-PCV7, période précédant l'introduction du vaccin conjugué 7-valent ; PCV13, introduction du vaccin conjugué 13-valent.

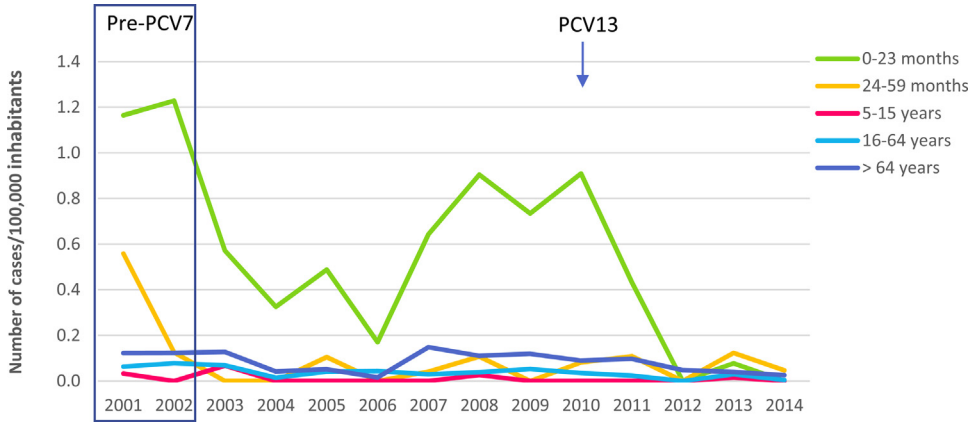

Fig. 8. Incidence of pneumococcal strains with reduced susceptibility to cefotaxime (MIC > 0.5 mg/l) isolated from meningitis, by age group, France, 2001–2014 (Sources: data from EPIBAC and the national reference center for pneumococci [104]). Pre-PCV7, period before the introduction of the 7-valent conjugate vaccine; PCV13, introduction of the 13-valent conjugate vaccine.
Incidence des pneumocoques de sensibilité diminuée au céfotaxime (CMI > 0,5 mg/L) isolés de méningites, selon le groupe d'âge, France, 2001–2014 (Sources : données EPIBAC et CNR des Pneumocoques [104]). Pre-PCV7, période précédant l'introduction du vaccin conjugué 7-valent ; PCV13, introduction du vaccin conjugué 13-valent.

Table 6
Antibiotic susceptibility of *N. meningitidis* strains isolated from patients presenting with meningitis.
Sensibilité aux antibiotiques des souches de N. meningitidis *isolées de méningites.*

Antibiotics	Thresholds[a]		Strains (*n*)	MIC_{50}	MIC_{90}	Range	Percentage of strains with reduced susceptibility
	S (mg/l)	R (mg/l)					I and R (%)
Penicillin G	≤ 0.06	> 0.25	322	0.064	0.250	0.012-0.5	30
Amoxicillin	≤ 0.125	> 1	322	0.125	0.380	0.012-1	30
3GC	≤ 0.125	> 0.125	322	0.004	0.008	0.002-0.094	0
Ciprofloxacin	≤ 0.03	0.06	322	0.004	0.006	0.002-0.047	0
Rifampicin	≤ 0.25	> 0.25	322	0.023	0.094	0.002-0.5	0

3GC: third-generation cephalosporins; S: susceptible; R: resistant; I: intermediate resistance; MIC: minimum inhibitory concentration.
[a] As per the 2013 CASFM guidelines.

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Table 7
Thresholds for the four main bacteria responsible for community-acquired meningitis.
Concentrations critiques pour les quatre principales bactéries responsables de méningites communautaires.

Antibiotics	*Streptococcus pneumoniae*		*Neisseria meningitidis*		*Haemophilus influenzae*		*Listeria monocytogenes*	
	Thresholds (mg/l)							
	S if ≤	R if >	S if ≤	R if >	S if ≤	R if >	S if ≤	R if >
Penicillin G	0.064	0.064[a]	0.064	0.25	–	–	1	1
Amoxicillin	0.5	0.5[a]	0.125	1	2	2	1	1
Cefotaxime	0.5	2	0.125	0.125	0.125	0.125	–	–
Vancomycin	2	2	–	–	–	–	–	–
Rifampicin	0.064	0.5	0.25	0.25	1	1	–	–
Meropenem	0.25	1[a]	0.25	0.25	0.25	1[a]	0.25	0.25
Ciprofloxacin	–	–	0.032	0.032	0.064	0.064	–	–
Co-trimoxazole	–	–	–	–	–	–	0.064	0.064

S: susceptible; R: resistant.
[a] As per the 2013 CASFM guidelines.

Nineteen per cent (29/156) of invasive strains assessed at the *Haemophilus* national reference center in 2013 were resistant to amoxicillin (MIC > 2 mg/l), including only two strains with a modified PLP3. No strain was resistant to injectable 3GCs (MIC ≤ 0.125 mg/l) [109]. Only one strain (0.6%) was resistant to fluoroquinolones, and all were susceptible to rifampicin. However, *H. influenzae* strains with higher resistance level have been isolated in France since 2013 from patients presenting with pulmonary tract infections, and in 2016 from a patient presenting with meningitis. These strains are resistant to oral cephalosporins (cefpodoxime and cefixime) but also to cefotaxime (MICs ranging from 0.25 to 1 mg/l). They show intermediate susceptibility to meropenem (MIC ≥ 0.5 mg/l), and most of them remain susceptible to ceftriaxone (O. Gaillot, national reference center for *Haemophilus* infections, private data).

12.3.5. Other bacteria

As for the susceptibility of other bacteria to antibiotics, it should be reminded that *L. monocytogenes* is naturally resistant to cephalosporins. No change in *L. monocytogenes* susceptibility to antibiotics has been reported over the past years. Regarding aminoglycosides, the prognostic analysis of patients enrolled in the MONALISA cohort and presenting with *Listeria* bacteremia and/or neurolisteriosis highlights the association between a better prognosis in terms of case fatality at 3 months and aminoglycoside prescription [110]. Adding aminoglycosides to amoxicillin in case of *Listeria* meningitis suspicion is always recommended, even more so when microbiological documentation is available.

Susceptibility of *E. coli* strains isolated from meningitis patients is not specific. Resistance to aminopenicillins is high (48% to 60% of strains), but resistance to 3GCs and to gentamicin reported for all invasive strains reached almost 10% in 2013 [111].

Breakpoints suggested in 2017 by the CA-SFM and EUCAST are presented in Table 7 for the four bacteria most commonly responsible for community-acquired meningitis.

12.3.6. Conclusion

Since the last consensus conference on meningitis (2008), the most important changes focused on the epidemiology of pneumococcal meningitis with a significant decrease in the incidence of vaccine serotype pneumococcal meningitis, especially in children aged below 2 years who are the main target of the PCV13 vaccine. The resulting decreased number of pneumococci with reduced susceptibility to beta-lactams may lead to considering an update of treatment guidelines. As for *N. meningitidis*, it is necessary to increase vaccination coverage with the meningococcal C polysaccharide conjugate vaccine. English results to come on the use of a protein meningococcal vaccine (active against a large proportion of group B *N. meningitidis* strains but also potentially active against other serogroups) may influence future therapeutic recommendations.

12.4. Objectives of the antibiotic therapy in bacterial meningitis

12.4.1. Case fatality

The case fatality significantly decreases when the antibiotic therapy is adapted to the *in vitro* susceptibility [75,81,112–114]. This has been observed for almost all types of bacterial meningitis, irrespective of the causative agent. The first-line antibiotic therapy should therefore be carefully chosen.

12.4.2. Morbidity

The second objective of bacterial meningitis treatment is to avoid sequelae. Sequelae are less common if CSF sterilization is rapidly obtained [85,86]. The proportion of sterilized CSF 12 or 24 hours after treatment initiation depends on the bacterium [115]: pneumococcal meningitis is associated with longer time to CSF sterilization [116]. “Early” sterilization takes approximately the same time for all administered antibiotics, provided the bacterium is susceptible to the antibiotic [115].

12.4.3. Objectives

We can now clarify the “anti-bacterial” objectives of treatments thanks to the above-mentioned observations. Considering the bacterial concentrations initially observed after the first

lumbar puncture (approximately 5 log/ml for *S. pneumoniae* and *Haemophilus*, and 4 log/ml for meningococci) [117] and the need for early CSF sterilization, the operational treatment objective is to reach an *in vivo* bactericidal level of 0.5 log CFU/ml/h. This data can only be assessed with an analysis of experimental model results.

12.4.4. Pharmacokinetics and pharmacodynamic parameters

Several reviews focused on the analysis of these parameters [118–121].

Pharmacodynamic parameters more often focus on the minimum bactericidal concentration (MBC) than on the MIC, while efficacy parameters depend on the antibiotic class. A strong correlation is observed between the three main parameters: concentration ratio in CSF/MBC (CCSF/MBC), area under the curve of CSF concentration (AUCCSF) and MBC ratio, and concentration time fraction in CSF/MBC (TCSF/MBC). On the basis of experimental works, CCSF/MBC ratio ≥ 5 is associated with early sterilization [119,122,123].

Antibiotic administration modalities may also be suggested based on the analysis of experimental results. For the use of 3GCs in the treatment of experimental pneumococcal meningitis "resistant" to 3GCs, it has been demonstrated that the TCSF/MBC ratio had to be at least equal to 95% of time to obtain sterilization [123]; this may also be expressed by the need for a minimum concentration (in CSF) always higher than the MBC. Beta-lactam prescription therefore requires immediately efficient CSF concentrations.

12.5. Administration modalities

Antibiotic penetration into the subarachnoid space is the first requirement needed to eradicate bacteria from the CSF. It depends on the physicochemical properties of antibiotics [119,124,125] or on their susceptibility to cellular efflux [126]. Lipophilic antibiotics (quinolones, rifampicin, and to a lesser extent linezolide), antibiotics with low molecular weight (quinolone, rifampicin, fosfomycin), and those with low protein binding are associated with a more rapid and more important diffusion. Other factors play a role in antibiotic penetration such as inflammation of the meninges, which facilitates the diffusion of beta-lactams in the meninges [119].

Some antibiotic molecules may also be administered via continuous infusion following a loading dose to obtain optimal and rapid diffusion [125]. Continuous infusion helps optimize the probability of antibiotic therapy success in case of systemic infections [127] and increases the meningeal and cerebromeningeal penetration of antibiotics. Continuous infusion is particularly useful with beta-lactams with a relatively short half-life and with glycopeptides such as vancomycin. However, the benefit of the continuous infusion in case of bacterial meningitis has not been clinically proven.

12.6. Most frequently used molecules

Guidelines resulting from the analysis of epidemiological, bacteriological, and PK/PD data address the role of injectable 3GCs and vancomycin.

12.6.1. Cephalosporins

Cefotaxime and ceftriaxone are most frequently used because of their bactericidal properties and their good diffusion in CFS [128]. Ceftriaxone has a slightly better *in vitro* activity profile against *S. pneumoniae* than cefotaxime [129]. However, cefotaxime may be administered at very high doses without inducing adverse events. Ceftriaxone has high protein binding rate, which may theoretically limit its diffusion in CSF [130].

12.6.2. Vancomycin

Vancomycin is only used in combination, either via continuous infusion following a loading dose or through clustered injections to optimize CSF concentrations. A proportional relation may be observed between serum and meningeal concentrations [131,132]. Using continuous infusion and even with corticosteroid addition, sufficient CSF levels of vancomycin are obtained when vancomycin blood levels are at least 25–30 mg/l [132].

Tolerability of *S. pneumoniae* to vancomycin seems rare although more frequent in case of resistance to beta-lactams. It is also associated with poorer treatment response and relapses [133–138]. These findings are also observed in experimental models [135]. No pneumococcal strain tolerant to vancomycin has been observed in France so far.

12.6.3. Treatment foresight

Many clinical and experimental studies demonstrated the limitations of vancomycin in the management of community-acquired pneumococcal meningitis:

- ineffectiveness of vancomycin alone in obtaining a cure following pneumococcal meningitis, leading to the contraindication of vancomycin alone [139];
- no potentialization of 3GC bactericidia in experimental models of pneumococcal meningitis [140,141];
- benefits of vancomycin in experimental models, when adding a 3GC, only if the pneumococcus is resistant to the 3GC (MIC > 2 mg/l); very rare in France (no strain reported in 2014);
- reduced penetration of vancomycin in the CSF in case of co-administration of dexamethasone [122] (currently highly recommended). Reduced penetration has been associated with delayed sterilization in experimental meningitis with resistant strain to 3GCs and concomitant administration of corticosteroids [142];
- the risk of nephrotoxicity of vancomycin is higher in adults when administered at high doses [143]. Adding vancomycin should therefore not be suggested in the absence of benefits and in case of toxic risks. This data is not available in children.

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Good results in experimental meningitis evaluating rifampicin were reported: the 3GC + rifampicin combination was superior to the 3GC + vancomycin combination. The authors of a mouse study reported that rifampicin reduced lipoteichoic and teichoic acid concentrations as well as early mortality [144]. Another study conducted in rabbits assessed the administration of rifampicin prior to ceftriaxone versus ceftriaxone alone. The authors reported that rifampicin administration prior to ceftriaxone reduced CSF concentrations of lipoteichoic acids as well as the incidence of neurological lesions [145]. Clinical prospective studies are required. However, the authors of a clinical retrospective study reported that adding rifampicin to a 3GC was not associated with better prognosis in the multivariate analysis [6].

12.7. Arguments for a monotherapy with high doses of 3GC (cefotaxime or ceftriaxone) for pneumococcal meningitis

12.7.1. Epidemiology

In 2014 no pneumococcal strain resistant to cefotaxime or ceftriaxone was isolated from adults and children presenting with meningitis. One strain with intermediate resistance (MIC > 0.5 mg/l; ≤ 2 mg/l) to cefotaxime was isolated from children (MIC = 1 mg/l) (out of 69 pneumococcal strains) and three were isolated from adults (MIC = 1 mg/l) (out of 202 pneumococcal strains).

12.7.2. Clinical studies and analysis of treatment failures

The authors of an observational, multicentric, and prospective study of 156 adult patients hospitalized in the ICU for pneumococcal meningitis reported that the addition of vancomycin was not associated with reduced mortality in patients presenting with an infection caused by pneumococci with reduced susceptibility to penicillins [65]. Adequate antibiotic therapy for patients presenting with pneumococcal infection with MIC ≥ 0.5 mg/l was defined as one dose of cefotaxime ≥ 200 mg/kg/day or ceftriaxone ≥ 100 mg/kg/day associated with vancomycin 40–60 mg/kg/day after a loading dose. The authors reported that case fatality was associated with the infection severity at admission, with the reduced susceptibility to penicillin of the pneumococcus, and with time to antibiotic therapy administration > 3 hours following admission. The co-administration of vancomycin in case of pneumococci with reduced susceptibility to penicillins did not improve the immediate or late prognosis. A literature analysis published in 1998 [139] assessed pneumococcal meningitis cases associated with clinical and/or microbiological failure of cephalosporins. Of 16 reported cases (13 children, including 10 aged between 4 and 19 months and three adults), 13 strains had cefotaxime and ceftriaxone MICs ≥ 2 mg/l (range: 2–16), and three strains had MICs ranging between 0.5 and 1 mg/l. The ceftriaxone dose administered for the first of these three cases was apparently too low (4 g/day for a 33-year-old adult with unknown weight). The cefotaxime MIC of the second case was 0.5 mg/l while that of ceftriaxone was 0.05 mg/l; this is indicative of a technical problem. The third case was associated with clinical failure despite cefotaxime MIC at 1 mg/day and a cefotaxime dose of 240 mg/kg/day. Except for the last case patient reported, cephalosporin failure observed in this study was either due to very high MICs (> 2 mg/l) — no longer observed nowadays — or to an insufficient dose. Viladrich et al. [146] assessed 10 adult cases of pneumococcal meningitis with reduced susceptibility to cephalosporins treated with high doses of cefotaxime (300 mg/kg/day, maximum 24 g/day). MICs were respectively 0.5 mg/l ($n = 3$), 1 mg/l ($n = 5$), and 2 mg/l ($n = 2$) and minimum bactericidal concentrations ranged between 1 and 4 mg/l. The authors concluded to an adequate treatment tolerability and to good effectiveness with cure without relapse observed in 9/10 patients. One death was reported, but it occurred eight days after treatment completion when meningitis was cured.

12.7.3. Pharmacokinetic/pharmacodynamic parameters

Considering the above-mentioned PK/PD parameters, most clinical failures of 3GC treatments for pediatric pneumococcal meningitis were observed with cefotaxime doses ≤ 200 mg/kg/day and with strains with elevated MICs (≥ 0.5 mg/l) [79,147,148]. Increasing the beta-lactam dose was recommended to increase antibiotic concentrations in the CSF and consequently increase the inhibitory quotient numerator [139].

As early as 1997 Friedland considered the use of a monotherapy with high doses of cephalosporins for pediatric pneumococcal meningitis [149]. Cefotaxime concentrations were measured in 20 children treated with cefotaxime 300 mg/kg/day and dexamethasone. The median CSF concentration was 4.7 μg/ml. CSF bactericidal activity was observed in 94% of susceptible strains, but in only 72% of strains with intermediate resistance and 44% of resistant strains. Other studies reported highly diverse rates of 3GCs in CSF. Goldwater [150] (2005) thus assessed the rate of 3GCs in the CSF of 14 children treated with ceftriaxone 100 mg/kg/day or with cefotaxime 200 mg/kg/day who had undergone a second lumbar puncture. The lowest rate was 0.58 mg/l and the highest rate was 35 mg/l, with a median rate of approximately 3 mg/l. No failure was observed as strains had low MICs of approximately 0.01 mg/l. The same diversity of rates was observed in a study of 19 patients who received 300 mg/kg/day of cefotaxime associated with vancomycin, without dexamethasone injection. The median CSF rate of cefotaxime was 4.4 mg/l (1.9–10.7 mg/l).

Compared with studies assessing lower doses of cefotaxime (200 mg/kg/day), increasing the dose of cefotaxime to 300 mg/kg/day in children does not seem to be associated with a significant increase in CSF concentrations [151]. The CSF levels observed in this study were not high enough to reach the optimal inhibitory quotient for strains with cefotaxime MICs ≥ 0.5 mg/l. Required values for the inhibitory quotient are also not reached for strains with MICs of 1 mg/l. No clinical study is available to assess the potential impact of insufficient concentrations on clinical outcome.

12.7.4. Evolution

It is currently not possible to assess the evolution of pneumococcal resistance in the short term and medium term. The current situation is probably due to the impact of vaccination

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policies and of strategies aiming to reduce antibiotic consumption. The emergence of new strains is in any case foreseeable and should trigger close monitoring of resistance, through active surveillance based on existing networks such as the pediatric observatory and the COMBAT cohort of adult meningitis.

The definition of failure should therefore be clarified. All failures should be bacteriologically documented. Antibiotic concentrations in CSF should be measured whenever possible to collect data on treatment effectiveness.

12.7.5. Pediatric specifics

In 2008 the French Infectious Diseases Group (GPIP) of the French Pediatrics Society suggested maintaining the systematic prescription of vancomycin at the initial phase of the pneumococcal meningitis treatment because of the frequency of strains with reduced susceptibility to beta-lactams (serotype 19A mainly) in infants and children [107]. Epidemiological and microbiological changes have recently been observed in France for bacteria responsible for meningitis following the use of the 13-valent pneumococcal conjugate vaccine. Therefore, the systematic addition of vancomycin is no longer required. It should be restricted to cases where injectable 3GC MICs are > 0.5 mg/l. Obtaining 3GC CSF concentrations five times higher than the MIC is in that case not guaranteed. An early switch with IV amoxicillin (200 mg/kg/day, four times a day) is recommended if the strain is susceptible to the molecule (amoxicillin MIC ≤ 0.5 mg/l).

GPIP also suggested favoring cefotaxime (instead of ceftriaxone) at the initial dosing of 300 mg/kg/day divided into four intravenous infusions because of the very long half-life of ceftriaxone and of its high digestive concentrations. These properties may favor the emergence of Enterobacteriaceae strains resistant to 3GCs through ESBL production [152]. However, the theoretical risk in terms of ecological impact should be assessed and compared with the benefit/risk ratio of such choice.

On the basis of currently available data and especially epidemiological data, when the optimal dose of 3GC is administered for the treatment of pneumococcal meningitis, the systematic addition of vancomycin is not justified in adults and children.

12.8. First-line antibiotic therapy for acute community-acquired meningitis, except in newborns

Guidelines for the first-line antibiotic therapy depend on the positivity of the direct examination or PCR tests (Table 8). Corticosteroids may be administered before antibiotics. Patients presenting with meningitis and turbid CSF should be prescribed an empirical antibiotic therapy as soon as the physician performing the lumbar puncture notices the turbid CSF. Physicians should NOT wait for the results of the direct examination and the CSF biochemical analysis to initiate antibiotics; while waiting for Gram staining results, the choice of empirical antibiotic therapy should comply with treatment guidelines for meningitis with a negative direct examination. Later on, the choice of antibiotics should take into consideration the results of the direct examination, as soon as they are available.

12.8.1. Positive direct examination or positive PCR tests

12.8.1.1. S. pneumoniae suspicion. A monotherapy with cefotaxime 300 mg/kg/day is recommended. The administration is performed intravenously either with a continuous infusion or a discontinuous infusion with a minimum of four infusions (75 mg/kg/6 h). The daily dose for the continuous infusion is initiated immediately after the administration of a loading dose of 50 mg/kg over one hour. Ceftriaxone may be administered at a dosage of 100 mg/kg/day as one or two intravenous infusions. A pharmacokinetic modeling study reported the benefit of ceftriaxone administration as two infusions daily in patients with normal renal function (glomerular filtration rate > 30 ml/min) [153]. Although cefotaxime has better parmacokinetic parameters (higher protein binding for ceftriaxone) and ceftriaxone shows better microbiological data (MIC usually one dilution lower than cefotaxime), there is no clinical study available to recommend one molecule over the other. However, considering the very long half-life of ceftriaxone and its high digestive concentrations, this molecule could be more likely to favor the emergence of Enterobacteriaceae strains resistant to 3GCs through the production of extended-spectrum beta-lactamases [152].

There is no consensus on the maximum dose in adults: some studies report doses of 24 g/day of cefotaxime [146]. Children (< 15 years of age) may receive cefotaxime at the maximum daily dose of 12 g (4 g maximum for ceftriaxone). Doses should be adjusted to the renal function. Measuring residual plasma concentrations after 48 hours of treatment may be indicated when administering a daily dose > 10 g/day, or in patients aged > 70 years or with a creatinine clearance < 30 ml/min.

12.8.1.2. N. meningitidis suspicion. A monotherapy with cefotaxime 200 mg/kg/day is recommended. The administration is performed intravenously either with a continuous infusion or a discontinuous infusion with a minimum of four infusions (50 mg/kg/6 h). The daily dose for the continuous infusion is administered concomitantly with the loading dose of 50 mg/kg over one hour. Ceftriaxone may be administered at a dose of 75 mg/kg/day as one or two intravenous infusions.

12.8.1.3. Listeriosis suspicion. A two-drug combination therapy is recommended with intravenous amoxicillin 200 mg/kg/day divided into 4 to 6 infusions and intravenous gentamicin 5–6 mg/kg/day as a single daily dose over 30 minutes.

12.8.1.4. H. influenzae suspicion. A monotherapy with cefotaxime 200 mg/kg/day is recommended. The administration is performed intravenously either with a continuous infusion or a discontinuous infusion with a minimum of four infusions (50 mg/kg/6 h). The daily dose for the continuous infusion is administered concomitantly with the loading dose of 50 mg/kg

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Table 8
First-line treatment of acute bacterial meningitis by CSF direct examination (in case of turbid CSF, the antibiotic therapy should be immediately initiated before receiving the direct examination results).
Traitement de 1re intention des méningites bactériennes aiguës en fonction de l'examen direct du LCS (en cas de LCS trouble ; initier l'antibiothérapie sans attendre les résultats de l'examen direct).

	Antibiotics	Dosage[a]
Positive direct examination/PCR		
Pneumococcal suspicion (Gram+ cocci)	Cefotaxime or ceftriaxone	Cefotaxime: 300 mg/kg/day IV, either as 4 infusions or as a continuous administration with a loading dose of 50 mg/kg over 1 hour[b] Ceftriaxone: 100 mg/kg/day IV, as 1 or 2 infusions
Meningococcal suspicion (Gram− cocci)	Cefotaxime or ceftriaxone	Cefotaxime: 200 mg/kg/day IV, either as 4 infusions or as a continuous administration with a loading dose of 50 mg/kg over 1 hour[b] Ceftriaxone: 75 mg/kg/day IV, as 1 or 2 infusions[c]
Listeriosis suspicion (Gram+ bacillus)	Amoxicillin + gentamicin	Amoxicillin: 200 mg/kg/day IV, either as 4 infusions or as a continuous administration Gentamicin: 5 mg/kg/day IV in adults, as a single daily infusion 5–8 mg/kg in children
H. influenzae suspicion (Gram− bacillus)	Cefotaxime or ceftriaxone	Cefotaxime: 200 mg/kg/day IV, either as 4 infusions or as a continuous administration with a loading dose of 50 mg/kg over 1 hour[b] Ceftriaxone: 75 mg/kg/day IV, as 1 or 2 infusions[c]
E. coli suspicion[d] (Gram− bacillus)	Cefotaxime or ceftriaxone	Cefotaxime: 200 mg/kg/day IV, either as 4 infusions or as a continuous administration with a loading dose of 50 mg/kg over 1 hour[b] Ceftriaxone: 75 mg/kg/day IV, as 1 or 2 infusions[c]
Negative direct examination/PCR		
With no evidence for listeriosis	Cefotaxime or ceftriaxone	Cefotaxime: 300 mg/kg/day IV, either as 4 infusions or as a continuous administration with a loading dose of 50 mg/kg over 1 hour[b] Ceftriaxone: 100 mg/kg/day IV, as 1 or 2 infusions[c]
With evidence for listeriosis[e]	Cefotaxime or ceftriaxone + amoxicillin + gentamicin	Cefotaxime: 300 mg/kg/day IV, either as 4 infusions or as a continuous administration with a loading dose of 50 mg/kg over 1 hour[b] Ceftriaxone: 100 mg/kg/day IV, as 1 or 2 infusions[c] Amoxicillin: 200 mg/kg/day IV, either as 4 infusions or as a continuous administration Gentamicin: 5 mg/kg/day IV in adults, as a single daily infusion 5–8 mg/kg in children

Renal failure: cefotaxime: same dose during the first 24 hours; after 24 hours, 25% reduction for GFR of 30–60 ml/min, 50% reduction for GFR of 15–30 ml/min, 75% reduction for GFR lower than 15 ml/min. High antibiotic doses should not be adjusted in patients receiving continuous hemofiltration. For ceftriaxone, if the creatinine clearance is < 30 ml/min: same dose during the first 24 hours (as 2 injections/24 hrs); after 24 hours, 50% reduction of the dose which is administered once; no dosing adjustment if creatinine clearance ≥ 30 ml/min.

[a] Maximum daily dose, in children: cefotaxime = 12 g/day, ceftriaxone = 4 g/day.
[b] The continuous daily infusion and the loading dose should be concomitantly administered.
[c] Two daily infusions should be favored in case of a glomerular filtration rate of 30 ml/min and one daily infusion if < 30 ml/min.
[d] In case of ESBL-producing *E. coli* suspicion, meropenem 40 mg/kg three times daily as a slow IV infusion and expert advice.
[e] Predisposing factors, progressive onset of symptoms, rhombencephalitis, cranial nerve impairment, and/or cerebellar syndrome.

over one hour. Ceftriaxone may be administered at a dose of 75 mg/kg/day as one or two intravenous infusions.

12.8.1.5. E. coli suspicion. A monotherapy with cefotaxime 200 mg/kg/day is recommended. The administration is performed intravenously either with a continuous infusion or a discontinuous infusion with a minimum of four infusions (50 mg/kg/6 h). The daily dose for the continuous infusion is administered concomitantly with the loading dose of 50 mg/kg over one hour. Ceftriaxone may be administered at a dose of 75 mg/kg/day as one or two intravenous infusions.

When ESBL-producing *E. coli* meningitis is highly suspected (ESBL colonization or positive specimen from another site), cefotaxime or ceftriaxone should be replaced by meropenem 40 mg/kg three times daily as a slow IV infusion (expert advice required).

12.8.2. Negative direct examination and negative PCR tests

The distribution of microorganisms is in that case different, as detailed in Table 9 using the results of the COMBAT cohort of adult patients presenting with bacterial meningitis. As the sensitivity of the direct examination is lower in case of *Listeria* meningitis, the respective proportion of this microorganism is more important in patients presenting with meningitis with a negative direct examination (Table 9).

Evidence for listeriosis: age > 70 years, comorbidities, immunodeficiency, progressive onset of symptoms, rhombencephalitis (cranial nerve involvement and/or cerebellar syndrome).

Two scenarios are possible.

12.8.2.1. No evidence for listeriosis. A monotherapy with cefotaxime 300 mg/kg/day is recommended. The administration is performed intravenously either with a continuous infusion or a discontinuous infusion with a minimum of four infusions

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Table 9
Distribution of microorganisms in the COMBAT cohort of adult patients presenting with meningitis, by CSF direct examination results.
Répartition des microorganismes dans la cohorte des méningites de l'adulte COMBAT, en fonction des résultats de l'examen direct du LCS.

Microorganisms identified at culture	Total ($n=403$) *n* (%)	Positive direct examination ($n=294$)				Negative direct examination ($n=109$)
		Gram-positive cocci ($n=204$) *n* (%)	Gram-negative cocci ($n=63$) *n* (%)	Gram-positive bacilli ($n=6$) *n* (%)	Gram-negative bacilli ($n=21$) *n* (%)	*n* (%)
Streptococcus pneumoniae	211 (52.4)	179 (87.7)	0	0	0	32 (29.4)
Streptococcus other than *S. pneumoniae*	23 (5.7)	13 (6.4)	0	0	0	10 (9.2)
Neisseria meningitidis	89 (22.1)	1 (0.5)	58 (92.1)	0	1 (4.8)	29 (26.6)
Haemophilus influenzae	18 (4.5)	0	0	0	8 (38.1)	10 (9.2)
Listeria monocytogenes	20 (5.0)	0	1 (1.6)	6 (100.0)	0	13 (11.9)
Escherichia coli	4 (1.0)	0	0	0	4 (19.0)	0
Staphylococcus aureus	8 (2.0)	3 (1.5)	0	0	0	5 (4.6)
Other microorganisms	20 (5.0)	6 (2.9)	0	0	8 (38.1)	6 (5.5)
Unidentified microorganisms	10 (2.5)	2 (1)	4 (6.3)	0	0	4 (3.6)

(75 mg/kg/6 h). The daily dose for the continuous infusion is initiated immediately after the administration of a loading dose of 50 mg/kg over one hour. Ceftriaxone may be administered at a dose of 100 mg/kg/day as one or two intravenous infusions.

12.8.2.2. Evidence for listeriosis. A triple therapy with cephalosporin, amoxicillin, and aminoglycoside is recommended.

Cefotaxime is administered at the dose of 300 mg/kg/day. The administration is performed intravenously either with a continuous infusion or a discontinuous infusion with a minimum of four infusions (75 mg/kg/6 h). The daily dose for the continuous infusion is initiated immediately after the administration of a loading dose of 50 mg/kg. Ceftriaxone may be administered at a dose of 100 mg/kg/day as one or two intravenous infusions.

Amoxicillin is administered at the dose of 200 mg/kg/day intravenously, divided into 4 to 6 infusions.

Gentamicin is administered at the dose of 5 mg/kg/day intravenously as a single daily dose over 30 minutes in adults and at the dose of 5–8 mg/kg in children.

12.8.2.3. Beta-lactam allergy. Severe allergy to beta-lactams is defined as a history of immediate anaphylactic hypersensitivity, including anaphylactic shock. Except for these extremely rare cases, the use of cefotaxime or ceftriaxone is recommended. One should bear in mind that the CSF diffusion of aztreonam is poor. Meropenem could be used because of the associated low risk of cross allergy [154]. However, no data is available to draft guidelines in this rare situation. The infectious disease specialist's advice should be sought, and the first 24 hours of treatment may be monitored in the continuous monitoring unit (even if the patient's state does not require it) (Table 10).

12.8.2.4. Renal function and antibiotic therapy for bacterial meningitis. Drafting guidelines for the treatment of bacterial meningitis is difficult as high doses of antibiotics should be administered but as they should also be adjusted to the renal function. In addition, little data is available in the literature. As cefotaxime is mainly renally excreted (including 60% as unchanged form and 20% as active metabolites), the dosing regimen should be adjusted to the renal function. As the susceptibility of the causative agent is initially unknown, we suggest using high antibiotic doses the first 24 hours and then reducing them by 25% to 75% according to the renal function impairment (25% reduction for a glomerular filtration rate [GFR] between 30 and 60 ml/min, 50% reduction for a GFR between 15 and 30 ml/min, 75% reduction for a GFR below 15 ml/min). High antibiotic doses should not be adjusted in patients receiving continuous hemofiltration. The ceftriaxone dose should also be adjusted as it is equally excreted from the hepato-biliary and renal routes. A full dose may also be administered the first 24 hours (2 injections/24 h). A 50% reduction of the dose may be suggested when the creatinine clearance is < 30 ml/min (single administration) [153]. Plasma (to avoid excessive dosing) and CSF concentrations should be measured in all these situations to check if CSF antibiotic concentrations are at least 10 times higher than the MIC.

13. Question 3 – What is the initial therapeutic management for patients presenting with a suspicion of bacterial meningitis (excluding the antibiotic therapy)?

13.1. When should corticosteroids be prescribed and what is the recommended regimen?

Dexamethasone is the only adjuvant to the bacterial meningitis treatment to have been extensively assessed in clinical studies. Dexamethasone reduces the inflammation of the subarachnoid spaces and the vasogenic edema induced by meningitis, which are associated with potentially deleterious effects. This anti-inflammatory activity was highest in animal models when dexamethasone was administered before or at the same time as the first dose of antibiotic.

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Table 10
First-line treatment of acute bacterial meningitis by CSF direct examination in patients with severe allergy to beta-lactams (in case of turbid CSF, the antibiotic therapy should be immediately initiated before receiving the direct examination results).
Traitement de 1re intention des méningites bactériennes aiguës en fonction de l'examen direct du LCS chez les patients présentant de graves allergies aux bêtalactamines (en cas de LCS trouble; initier l'antibiothérapie sans attendre les résultats de l'examen direct).

	Antibiotics	Dosage
Positive direct examination/PCR		
Pneumococcal suspicion (Gram+ cocci)	Vancomycin AND Rifampicin OR Meropenem	Vancomycin: loading dose of 30 mg/kg over one hour, and then daily dose of 40–60 mg/kg/day to be adjusted to obtain residual plasma concentrations between 15 and 20 mg/l Rifampicin: children: 10 mg/kg, twice daily up to 600 mg/day; adults: 300 mg, twice daily; adults: 2 g three times daily
Meningococcal suspicion (Gram− cocci)	Ciprofloxacin OR Rifampicin	Ciprofloxacin: 800–1200 mg Rifampicin: children: 10 mg/kg, twice daily up to 600 mg/day; adults: 300 mg, twice daily
Listeriosis suspicion (Gram+ bacillus)	Trimethoprim-sulfamethoxazole	Trimethoprim-sulfamethoxazole: 10–20 mg/kg (of the trimethoprim component) as 4 doses/day
H. influenzae suspicion (Gram− bacillus)	Ciprofloxacin	Ciprofloxacin: 800–1200 mg
Negative direct examination/PCR		
No evidence for listeriosis[a]	Vancomycin AND Rifampicin	Vancomycin: loading dose of 30 mg/kg over one hour, and then daily dose of 40–60 mg/kg/day to be adjusted to obtain residual plasma concentrations between 15 and 20 mg/l Rifampicin: children: 10 mg/kg, twice daily up to 600 mg/day; adults: 300 mg, twice daily
With evidence for listeriosis	Vancomycin AND Rifampicin AND Trimethoprim-sulfamethoxazole	Vancomycin: loading dose of 30 mg/kg over one hour, and then daily dose of 40–60 mg/kg/day to be adjusted to obtain residual plasma concentrations between 15 and 20 mg/l Rifampicin: children: 10 mg/kg, twice daily up to 600 mg/day; adults: 300 mg, twice daily Trimethoprim-sulfamethoxazole: 10–20 mg/kg (of the trimethoprim component) as 4 doses/day

[a] Pediatricians recommend the combination of ciprofloxacin and vancomycin in children (expert advice).

A meta-analysis of randomized studies concluded to the benefit of dexamethasone in children as it helped reduce the frequency of severe hearing loss when the causative agent was *H. influenzae* or *S. pneumoniae* and when the first injection was administered before or at the same time as the first dose of antibiotics [155].

The most recent Cochrane meta-analysis (2015) included 25 randomized trials (1517 adults and 2511 children) for a total of 4121 bacterial meningitis cases [155]. Irrespective of the microorganism, findings from this meta-analysis revealed that corticosteroids were not associated with reduced case fatality but with morbidity improvement in terms of neurological sequelae reduction and hearing loss reduction. Taking into consideration the type of microorganisms or the country's socio-economic status, the subgroup analyses revealed that corticosteroids were associated with reduced case fatality for microbiologically confirmed pneumococcal meningitis only and in industrialized countries only.

In the randomized, double-blind, and placebo-controlled European study of 301 adult patients presenting with bacterial meningitis included in this meta-analysis, patients were followed up for an average of 13 years. The impact of corticosteroids on the reduction of case fatality, observed during the initial follow-up, was sustained up to 20 years after the initial episode [156].

The analysis of the prospective and observational Dutch cohort of 1412 episodes of bacterial meningitis included over eight years revealed that, irrespective of the microorganism, dexamethasone was independently associated with better prognosis (in terms of death or survival with sequelae) in patients presenting with pneumococcal meningitis (OR: 0.55; 95% CI: 0.38–0.80) and in those infected with other microorganisms (OR: 0.44; 95% CI: 0.23–0.85) [71]. The analysis of a Danish cohort of 1746 adults also suggests the positive impact of corticosteroids (case fatality: 10% versus 21%) in patients presenting with pneumococcal meningitis without any prior administration of corticosteroids [157].

Conversely, the prospective French study MONALISA reported that dexamethasone prescription was an independent risk factor for increased mortality, thus contraindicating its use when listeriosis is confirmed [110].

Time to corticosteroid initiation was assessed in 22 trials included in the 2015 Cochrane meta-analysis [155]. Corticosteroids were administered before or at the same time as antibiotics in 13 trials (3143 patients) and after antibiotics in nine trials (797 patients). No significant difference was observed in terms of dexamethasone benefit between both administration modalities based on the analysis of the various endpoints.

As most trials administered corticosteroids before or at the same time as the antibiotic therapy, this administration modality

is currently recommended. However, corticosteroids should be administered as soon as possible after antibiotic therapy initiation when they cannot be administered before or at the same time as antibiotics. No study assessing the maximum time to corticosteroid administration following antibiotic therapy initiation is available. On the basis of experts' advice, the 2016 European guidelines recommend a maximum time to corticosteroid administration of 4 hours [56]. The 2016 British guidelines recommend a maximum time of 12 hours [55].

Updated pediatric results from the most recent meta-analysis [155] confirmed the positive impact of dexamethasone on the prevention of neurological complications of pneumococcal and *H. influenzae* meningitis, without any impact on case fatality. No major benefit was observed in case of meningococcal meningitis except for severe invasive infection due to a hypervirulent clonal strain belonging to the ST-11 group. Additional analyses are, however, required to demonstrate such impact on patients presenting with meningococcal meningitis (excluding purpura fulminans). This meta-analysis also confirmed that corticosteroids had no deleterious effect in treated patients, but few pediatric studies have been performed on that matter.

Data from the National Observatory for Pediatric Bacterial Meningitis reveals that the 2008 guidelines have not been adequately followed. Overall, the prescription rate of dexamethasone has increased since 2008, even though slightly: from 33.2 to 38.3% ($P = 0.001$), irrespective of age and bacteria. The limitation of this study (source: C Lévy, National Observatory for Pediatric Bacterial Meningitis, GPIP/ACTIV) aiming to evaluate the impact of prescription delay on outcome is the absence of reliable data on this delay (before or after bacterial identification).

As a consequence, data gathered since 2008 does not justify the update of guidelines for dexamethasone use in infants and children presenting with bacterial meningitis (excluding newborns).

13.2. Recommendations

13.2.1. Adults

Dexamethasone injection is recommended, just before or at the same time as the first injection of antibiotics in case of:

- a suspicion of bacterial meningitis without microbiological confirmation, but with an empirical antibiotic treatment decision taken. This scenario is observed when:
  - the indication for brain imaging delays the lumbar puncture (neurological contraindications to the lumbar puncture) (Question 1),
  - the lumbar puncture is contraindicated for non-neurological reasons (Question 1),
  - turbid or even purulent CSF is observed at lumbar puncture,
  - a negative direct examination of CSF is observed at lumbar puncture, but other CSF and blood biological findings confirm the bacterial meningitis diagnosis;
- initial microbiological diagnosis indicative of:
  - pneumococcal bacterial meningitis (Binax positive and/or Gram-positive cocci at CSF direct examination),
  - meningococcal bacterial meningitis (Gram-negative cocci at CSF direct examination). Several experts do not recommend dexamethasone in this scenario.

The initial dose of dexamethasone in adults is 10 mg every 6 hours, for 4 days.

This treatment is not recommended in immunocompromised patients and in patients presenting with neuroinvasive listeriosis [12].

When the corticosteroid therapy cannot be administered just before or at the same time as the first injection of antibiotics, it should be administered as soon as possible up to 12 hours following antibiotic initiation.

Following definitive identification of the microorganism, dexamethasone should be continued for a total duration of four days in case of documented pneumococcal and *Haemophilus* meningitis. Whether or not to continue dexamethasone for four days in case of meningococcal meningitis is left to the physician's choice. There is no indication for continuing dexamethasone in case of meningitis caused by other microorganisms.

Onset of thrombosis with cerebral ischemia several days or several weeks later, following an initially favorable outcome, is observed in 1% of patients [158]. Most of these patients present with pneumococcal meningitis and have received dexamethasone. Most experts believe that dexamethasone should therefore be reintroduced when this rebound effect occurs without failure of the antibiotic therapy.

13.2.2. Children or infants

Dexamethasone injection is recommended, just before or at the same time as the first injection of antibiotics in case of:

- a suspicion of bacterial meningitis without microbiological confirmation, but with an empirical antibiotic therapy decision taken in infants aged between 3 and 12 months. This scenario is observed when:
  - the indication for brain imaging delays the lumbar puncture (neurological contraindications to the lumbar puncture) (Question 1),
  - the lumbar puncture is contraindicated for non-neurological reasons (Question 1),
  - turbid or even purulent CSF is observed at lumbar puncture,
  - a negative direct examination of CSF is observed at lumbar puncture, but other CSF and blood biological findings confirm the bacterial meningitis diagnosis;
- an initial microbiological diagnosis indicative of:
  - pneumococcal bacterial meningitis (Binax positive and/or Gram-positive cocci at CSF direct examination),
  - *H. influenzae* bacterial meningitis (Gram-negative bacilli at CSF direct examination).

The initial dose of dexamethasone in children is 0.15 mg/kg every 6 hours, for 4 days.

The benefit of a corticosteroid therapy initiated after the antibiotic therapy is not confirmed in children.

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This treatment is not recommended in immunocompromised children and in those who previously received parenteral antibiotics. Dexamethasone should be discontinued when bacterial meningitis is ruled out or when meningococcal or *Listeria* meningitis is confirmed.

13.3. Should other urgent measures be introduced and where should patients be managed?

13.3.1. Hospitalization ward

Patients presenting with a suspicion of bacterial meningitis are usually admitted to the emergency department. Diagnosis and treatment should be established and initiated in that department. Patients are then admitted to health facilities with variable means. Yet, the short-term outcome cannot be entirely predicted even when the patient's initial status is reassuring. The subsequent health facility should therefore be carefully chosen.

No objective criteria have been established to define a minimum qualitative standard as no study has ever compared prognoses depending on the hospitalization ward. However, admission criteria to the ICU have been suggested for children [3,4] and adults [7,13,15]:

- extensive purpura;
- Glasgow score ≤ 8;
- focal neurological signs;
- signs of brainstem involvement, usually indicative of intracranial hypertension: bradycardia, tachycardia, respiratory rate abnormalities;
- status epilepticus;
- hemodynamic instability.

Consultation with the ICU team is recommended for all patients, even in the absence of such criteria and irrespective of the patient's initial clinical status. In case of non-admission to the ICU, patients should be admitted to a ward where close monitoring of consciousness and hemodynamic parameters (every hour) can be implemented the first 24 hours minimum.

13.3.2. Treatment of seizures

Seizures are observed in 6–13% of adults and 20–30% of children at the initial phase of bacterial meningitis, most often within a few hours of admission. Unlike seizures observed several days after treatment initiation, early seizures in children are not indicative of unfavorable outcome when short and generalized [159]. Prolonged seizures may cause ischemic necrosis lesions and destruction of cortical neurons especially in the temporal lobe.

Seizure treatment — and consequently the (secondary) prevention of recurrences — should rely on conventional antiepileptic drugs (diphenylhydantoin or phenobarbital). The benefit of antiepileptic drugs administered for primary prevention has never been proven and such treatment cannot be recommended considering available data.

13.3.3. Treatment of intracranial hypertension (ICH)

Symptomatic ICH is common in patients presenting with meningitis and is associated with a higher risk of unfavorable outcome and death [160,161].

Maintaining the cerebral perfusion pressure is crucial to the management of bacterial meningitis at the acute phase, especially in case of severe presentations. The cerebral perfusion pressure depends on the difference between mean blood pressure and mean intracranial pressure.

Correction of low blood pressure initially relies on fluid replacement. Antihypotensive or inotropic agents are recommended in case of fluid replacement failure.

ICH decrease may be obtained with osmotic agents such as mannitol, glycerol, or hypertonic saline solution. Only glycerol has been recently assessed [162,163]. Peltola et al. included 654 children and randomized them into four treatment groups: IV dexamethasone (0.15 mg/kg/6 h for 48 hours), oral glycerol or via a feeding tube (1.5 mg/kg/8 h), administration of both products, or administration of double dummy. Mean Glasgow score at admission was 12. The most frequently observed bacterium in this study performed in South America was *H. influenzae*. No significant difference was observed between groups in terms of case fatality or overall risk of deafness. However, a significant reduction in the risk of severe neurological sequelae was observed in the glycerol group vs placebo (OR = 0.31; 95% CI = 0.13–0.76; $P = 0.01$) and to a lesser extent in the glycerol + dexamethasone group (OR = 0.39; 95% CI = 0.17–0.95; $P = 0.033$). These results were not confirmed in an Indian study including 58 children. Other studies are required to conclude on the benefit of such treatment. The use of glycerol is not recommended.

No human clinical data is available on the benefit of mannitol in the management of bacterial meningitis. A single bolus could nevertheless be suggested in case of immediately life-threatening ICH. The benefit of hypertonic saline solution, suggested in some experimental studies, has never been assessed in a randomized study and therefore cannot be recommended.

Severe ICH may also be treated as follows: rising the patient's head at 20–30°, sedation, mechanical ventilation [164]. Monitoring intracranial pressure may be discussed for the most severe presentations. A prospective study including a historical control group performed in Scandinavia with 105 adults, most of whom had pneumococcal meningitis, highlights the benefit of an "aggressive" management based on intracranial pressure level. This study also demonstrated that intracranial pressure was > 20 mmHg in 35 of 52 patients [165]. However, considering the absence of controlled studies, systematic intracranial pressure measurement cannot be recommended.

13.3.4. Preventing fluid and electrolyte disturbances, fever, and hyperglycemia

Fluid restriction has long been suggested at the acute phase of meningitis because of hyponatremia attributed to inappropriate antidiuresis. A meta-analysis [166] including the three studies assessing fluid restriction versus normal hydration demonstrated

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that fluid restriction was not associated with any benefit but with a higher risk of neurological sequelae at three months (RR 0.42; 95% CI 0.20–0.89). Conventional sodium and water intake combined with daily monitoring of natremia and diuresis are recommended to detect and to treat truly inappropriate antidiuresis.

No study focused on assessing the impact of an antipyretic treatment. Fever should be monitored but it can be poorly tolerated and increase the risk of seizure in children. Temperature of patients presenting with meningitis and severe intracranial hypertension should be lowered as well as when fever is not well tolerated, but physicians should not necessarily try to bring it back to normal. Moderate hypothermia (34–36 °C) in adults presenting with meningitis and coma is not recommended because it may worsen the patient's prognosis, as demonstrated in a randomized study [167].

Elevated glycemia (> 1.5 g/l or 8.3 mmol/l) is observed in more than one in two adult patients presenting with bacterial meningitis [12]. Yet, hyperglycemia in patients presenting with sepsis has deleterious effects on immunity and increases the risk of thrombosis [168]. Several scientific societies recommend using intravenous insulin therapy to lower the glycemia below 1.8 g/l following hemodynamic stabilization in adult patients presenting with sepsis [169]. It seems reasonable to comply with this recommendation in case of bacterial meningitis and sepsis in adults.

14. Question 4 – What is the subsequent management?

14.1. What is the antibiotic therapy and its duration after the initial phase?

The initial treatment should be reevaluated daily based on clinical outcome and as soon as the causative agent has been identified; MICs for amoxicillin, ceftriaxone, and cefotaxime should be kept in mind. The microbiology laboratory should immediately inform the medical team of the CSF culture positivity and MICs as soon as they have been determined.

14.1.1. Documented pneumococcal meningitis

When the clinical outcome is favorable, the choice of the antibiotic therapy depends on the pneumococcal MICs for 3GCs and amoxicillin (Table 11):

- 3GC MICs ≤ 0.5 mg/l:
  - when the amoxicillin MICs are ≤ 0.5 mg/l, the 3GC should ideally be replaced by amoxicillin 200 mg/kg divided into 4 to 6 infusions/day or as a continuous administration. Otherwise, the 3GC may be continued but dosage should be adjusted to the 3GC MICs,
  - the 3GC should be continued if the amoxicillin MICs are > 0.5 mg/l. The 3GC dose may be reduced (cefotaxime to 200 mg/kg/day or ceftriaxone to 75 mg/kg/day);
- 3GC MICs > 0.5 mg/l (1.5% of pneumococcal strains isolated from invasive infections in France in 2014).

It is here recommended to:

- always perform a control lumbar puncture with CSF culture, antibiotic concentration measurement in CSF and blood, and dosing adjustment based on concentration results. Several experts recommend always adding vancomycin for children and infants while waiting for the CSF culture results following control lumbar puncture;
- ask for the advice of an infectious disease specialist and a microbiologist when the culture is positive.

When the clinical outcome is unfavorable after 48–72 hours of treatment (no improvement of consciousness disorders and/or signs of sepsis), systematic brain imaging is recommended (ideally an MRI) to detect an empyema or intracranial complications that could require surgery. Control lumbar puncture and CSF culture are recommended in the absence of imaging abnormalities explaining the unfavorable outcome. An additional CSF sample should be collected to measure the 3GC concentration. The antibiotic therapy should be optimized following advice from the multidisciplinary team (infectious disease specialist and microbiologist):

- checking whether the administered 3GC doses are optimal (recommended dose and administration modalities, concentration/MIC ratio);
- choosing the 3GC with the lowest MIC;
- discussing whether a second antibiotic should be added: rifampicin (10 mg/kg every 12 hours in adults, or 20 mg/kg every 12 hours in children) or vancomycin (loading dose of 30 mg/kg over one hour, and then daily dose of 40–60 mg/kg/day to be adjusted to obtain residual plasma concentrations between 15 and 20 mg/l) or combination of vancomycin and rifampicin (no resistance to rifampicin and vancomycin among pneumococcal strains isolated in France in 2014).

Analyzing the cause of microbiological failures documented with the non-sterilization of the CSF culture after 48 hours of treatment for pneumococcal meningitis is recommended. The analysis should for instance check the compliance with guidelines (time to treatment initiation, adequate doses and administration modalities for the prescribed 3GC), look for undrained infectious sites (empyema, ventriculitis, suppurative otitis media, sinusitis), and measure the 3GC concentration in CSF and put it into perspective with the isolated pneumococcal MIC.

Guidelines on antibiotic therapy duration for pneumococcal meningitis are mainly based on treatment habits and experts' advice because randomized studies are lacking. Treatment should be discontinued after 10 to 14 days: after 10 days in case of rapidly favorable outcome (within the first 48 hours) and in case of beta-lactam-susceptible pneumococcal meningitis (3GC MIC ≤ 0.5 mg/l); after 14 days when both of these criteria are missing.

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Table 11
Antibiotic therapy switch for community-acquired bacterial meningitis following microbiological documentation.
Traitement antibiotique des méningites bactériennes communautaires de relais après documentation microbiologique.

Bacteria, susceptibility	Antibiotic therapy[a]	Total duration	Alternatives
Streptococcus pneumoniae[b]			
Cephalosporin MIC (cefotaxime or ceftriaxone depending on the 3GC received) ≤ 0.5 mg/l			
If amoxicillin MIC ≤ 0.5 mg/l	Preferably, IV amoxicillin 200 mg/kg/day or continuation of 3GC, but reduction of the cefotaxime dosage to 200 mg/kg/day or of the ceftriaxone dosage to 75 mg/kg/day (because 3GC MIC ≤ 0.5 mg/l)	10–14 days[c]	Combination of vancomycin and rifampicin
If amoxicillin MIC > 0.5 mg/l	IV cefotaxime: 200 mg/kg/day (because 3GC MIC ≤ 0.5 mg/l) or IV ceftriaxone: 75 mg/kg/day (because 3GC MIC ≤ 0.5 mg/l)	10–14 days[c]	Combination of vancomycin and rifampicin
Cephalosporin MIC (cefotaxime or ceftriaxone depending on the 3GC received) > 0.5 mg/l	IV cefotaxime: 300 mg/kg/day or IV ceftriaxone: 100 mg/kg/day A new lumbar puncture is required when the MIC is > 0.5 mg/l with another CSF culture and antibiotic concentration measurement[d]		Combination of vancomycin and rifampicin
Neisseria meningitidis			
Amoxicillin MIC ≤ 0.125 mg/l	Amoxicillin or continuation of 3GC	5–7 days[e]	Ciprofloxacin
Amoxicillin MIC > 0.125 mg/l	IV cefotaxime 200 mg/kg/day or IV ceftriaxone 75 mg/kg/day		
Listeria monocytogenes	Amoxicillin combined with gentamicin, 5 mg/kg/day as one IV infusion over 30 minutes for the first five days	14–21 days	Trimethoprim-sulfamethoxazole
Streptococcus agalactiae	IV amoxicillin 200 mg/kg/day	14–21 days	Combination of vancomycin AND rifampicin
Escherichia coli	Cefotaxime or ceftriaxone Advice of the infectious disease specialist in case of ESBL suspicion[f]	21 days	Advice of the infectious disease specialist
Haemophilus influenzae	Cefotaxime or ceftriaxone	7 days	Ciprofloxacin

History of anaphylactic shock due to penicillin: the "introduction of a 3GC with ICU monitoring" or the "combination of vancomycin/rifampicin" should be discussed depending on the benefit-risk ratio (risk of cross allergy versus use of a probably less effective two-drug combination therapy). History of anaphylactic shock due to a 3GC: contraindications to 3GCs, unless expert advice. Antibiotic therapy duration: lower end of the range in case of favorable outcome. Administration modalities: amoxicillin: 4 to 6 infusions or continuous administration; cefotaxime: 4 to 6 infusions or continuous administration; maximum daily dose: cefotaxime = 12 g/day in children; ceftriaxone: 1 or 2 infusions; maximum daily dose: ceftriaxone = 4 g/day in children; meropenem: 40 mg/kg three times daily as infusions of 3–4 hours each; maximum daily dose: meropenem = 6 g/day in children. Renal failure: cefotaxime: same dose during the first 24 hours; after 24 hours, 25% reduction for GFR of 30–60 ml/min, 50% reduction for GFR of 15–30 ml/min, 75% reduction for GFR lower than 15 ml/min. High antibiotic doses should not be adjusted in patients receiving continuous hemofiltration. For ceftriaxone, if the creatinine clearance is < 30 ml/min: same dose during the first 24 hours (as 2 injections/24 h); after 24 hours, 50% reduction of the dose which is administered once; no dosing adjustment if creatinine clearance ≥ 30 ml/min.

[a] If the dose is not indicated, please refer to Table 1.

[b] Susceptibility to both 3GCs (cefotaxime and ceftriaxone) should be tested if one of them has MICs > 0.5 mg/l, as MICs may differ.

[c] Rather 10 days in case of rapidly favorable outcome (within the first 48 hours) and pneumococci susceptible to the 3GC used (MIC ≤ 0.5 mg/l); expert advice if MIC > 0.5 mg/l for both 3GCs.

[d] Some experts recommend the systematic addition of vancomycin in children until results of the CSF culture following control lumbar puncture at 48 hours are available; if the CSF culture is positive, the 3GC-vancomycin or 3GC-rifampicin or vancomycin-rifampicin combination — depending on MICs — should be continued or the 3GC should be replaced by meropenem 40 mg/kg three times daily — to be discussed with the infectious disease specialist and the microbiologist.

[e] Rather 5 days with a rapidly favorable outcome (within the first 48 hours).

[f] ESBL: meropenem 40 mg/kg three times daily as a slow IV infusion and expert advice.

14.1.2. Documented meningococcal meningitis

When the clinical outcome is favorable, 3GC doses should not exceed 200 mg/kg/day for cefotaxime and 75 mg/kg/day for ceftriaxone (Table 11). When the amoxicillin MIC is ≤ 0.125 mg/l, the 3GC may be replaced by amoxicillin 200 mg/kg divided into 4 to 6 infusions/day or as a continuous administration. However, the short treatment duration of meningococcal meningitis does not require antibiotic de-escalation in this specific case.

Treatment should be discontinued after 4 to 7 days (4 days in case of rapidly favorable outcome with apyrexia within 48 hours).

No additional treatment for pharyngeal decontamination is indicated when patients have received at least 24 hours of 3GC treatment (i.e., all patients if initial recommendations have been followed).

14.1.3. Documented L. monocytogenes meningitis

The antibiotic therapy relies on the combination of amoxicillin 200 mg/kg divided into 4 to 6 infusions/day or as a continuous administration for a total duration of 21 days (reduced to 14

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days in case of favorable outcome), and gentamicin 5 mg/kg/day as a single 30-minute infusion the first five days (Table 11).

14.1.4. Other bacteria

Antibiotic treatments for other bacteria are displayed in Table 11.

14.1.5. Management strategies in the absence of microbiological documentation (sterile CSF and blood cultures at 48–72 hours; negative direct examination)

Several scenarios may be considered.

In case of favorable clinical outcome within the first 48 hours of the antibiotic therapy and if the initial CSF has been collected while the patient had already received prior antibiotic therapy, the diagnosis may be a partially treated bacterial meningitis. When the bacterial meningitis diagnosis is still considered (absence of alternative diagnosis; suggestive initial symptoms), the initial antibiotic therapy is continued for 14 days.

In case of unfavorable clinical outcome after 48–72 hours of treatment (no improvement of consciousness disorders and/or signs of sepsis), brain imaging should always be performed. In the absence of contraindication, a control lumbar puncture is recommended. If the second CSF analysis is still indicative of bacterial meningitis, one should rule out listeriosis or tuberculosis as 3GCs are not active against these bacteria and as they are difficult to identify.

Considering the diagnostic progress made over the past years, the absence of microbiological documentation should lead physicians to reconsider bacterial meningitis and to consider the main differential diagnoses: viral meningitis (enterovirus, herpes virus, HIV), drug-induced meningitis (NSAIDs, antibiotics, IV immunoglobulins, etc.), inflammatory meningitis (lupus, sarcoidosis, Behçet's disease, Kawasaki disease), cerebral venous sinus thrombosis, infectious site next to the meninges (epiduritis, spondylodiscitis, brain abscesses, empyema). *Spirochaeta* meningitis (Lyme disease, syphilis, leptospirosis) should be looked for by serological tests (± PCR) in case of a suspected source of contamination. Advice from a specialist (infectious disease specialist, neurologist, internal medicine specialist) is always welcome.

14.2. What are the benefits of and indications for cerebrospinal fluid control?

The main objective of CSF control testing is to check whether it is sterile (Table 12).

Sterilization is rapidly obtained with *N. meningitidis*: less than two hours are required according to a study including patients treated with a 3GC [116]. As for other bacteria, CSF culture is usually sterile after 24 hours of an adequate antibiotic treatment [170]. A significant modification of CSF cytological and biochemical parameters is also observed after 48 hours of treatment [171], but no data is available to conclude on treatment modifications.

In case of favorable clinical outcome, routine CSF control should only be performed in patients presenting with pneumococcal meningitis with MICs for the prescribed cephalosporin > 0.5 mg/l. CSF control may be performed after 48–72 hours of treatment for meningitis caused by unusual bacteria (other than *S. pneumoniae*, *N. meningitidis*, *Haemophilus*, and *Listeria*).

In case of unfavorable clinical outcome after 48–72 hours of treatment (no improvement of consciousness disorders and/or signs of sepsis), systematic brain imaging is recommended to detect an empyema or intracranial complications. A control lumbar puncture is recommended in the absence of abnormalities explaining the unfavorable outcome at brain MRI. An additional CSF sample should be collected to measure the 3GC concentration.

Clinical worsening should lead physicians to perform a lumbar puncture after brain imaging and to discuss the potential need for additional CSF investigations, jointly with the microbiology laboratory.

14.3. When are imaging tests indicated?

Brain imaging during treatment helps diagnose peri- or intraparenchymatous complications and potential bone and dura mater abnormalities that may increase the risk of recurrence (Table 13). This imaging test may also lead to changing the initial diagnosis if doubts remain.

The main complications of bacterial meningitis observed at brain imaging are directly linked to the bacterial infection (intraparenchymal abscess, subdural empyema, bone or inner ear bacterial infection) or are a consequence of it (stroke associated with vasculitis, insudation/ischemia associated with vein thrombosis, ventricular dilatation and dilatation of subarachnoid spaces). Few articles systematically and prospectively assessed the incidence and time to onset of these complications, their clinical signs, and the outcome. A prospective study of 86 adults presenting with pneumococcal meningitis reported arterial involvement (assessed by CT scan) in 22% of cases and vein thrombosis in 10% of cases. Cerebral edema was observed in 29% of cases, hemorrhage in 9% of cases, and hydrocephalus in 16% of cases [172]. The authors of that study reported 80% of complications during the first seven days and half of them during the first three days [173]. Another observational study of 696 adult bacterial meningitis episodes reported empyema or cerebritis observed by CT scan in 3.5% of cases [12].

Brain imaging performed to look for complications should not be systematic in patients presenting with pneumococcal or meningococcal meningitis with favorable outcome. It is rarely urgent, but treatment decisions may be taken after brain imaging: very rare neurosurgical procedures (3% in the prospective study of 87 patients) or treatment changes (extended antibiotic treatment or even anticoagulant treatment administration).

The main clinical signs requiring brain imaging are:

- onset of new neurological signs: seizures, paralysis (hemiparesis, tetraparesis, paralysis of the cranial nerves except for isolated paralysis of the sixth cranial nerve), increased severity of cephalgia, change in vision;

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Table 12
Indications for the control lumbar puncture.
Indications à une ponction lombaire de contrôle.

Outcome	Microorganisms	Rationale	Time
Favorable	*Streptococcus pneumoniae*	Only if 3GC MIC > 0.5 mg/l	48–72 hours of treatment
	Bacteria other than *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus*, and *Listeria monocytogenes*	Systematic	48–72 hours of treatment
Unfavorable	Irrespective of the microorganism	Systematic	After brain imaging if contraindication to an immediate lumbar puncture

Systematic cytological and biochemical analyses and culture. Antibiotic concentration measurement in CSF and blood should be concomitantly performed.

Table 13
Indications for brain imaging in patients presenting with bacterial meningitis.
Indications à l'imagerie cérébrale au cours des méningites bactériennes.

	Situations	Notes
Before lumbar puncture		
In case of neurological contraindications to the lumbar puncture		One pair of blood culture, corticosteroids, and antibiotic therapy before brain imaging
After lumbar puncture		
Should be systematically performed during patient management	*Streptococcus pneumoniae* meningitis and otitis, sinusitis, or mastoiditis	
	Bacterial meningitis caused by a bacterium other than *Streptococcus pneumoniae* or *Neisseria meningitidis*	
Occasional indications	Unexplained persistence of fever > 38.5 °C, consciousness disorders, and severe cephalgia after 48–72 hours of treatment	
	Onset of localization signs or consciousness disorders or seizures or unexplained fever	
Portal of entry investigation	No portal of entry observed for pneumococcal meningitis	
	Brain or spinal imaging is required to look for dermal sinus in children presenting with bacterial meningitis caused by staphylococci, Enterobacteriaceae, or multiple bacteria	
Breach investigation	Bacterial meningitis in patients with a history of brain injury	

- unexplained persistence of fever > 38.5 °C, consciousness disorders, and severe cephalgia after 48–72 hours of treatment;
- rapid increase of head circumference in newborns.

The prospective Dutch study of 696 adults presenting with bacterial meningitis reported seizures in 15% of patients (24% in those presenting with a pneumococcal infection) and focal deficits in 50% of patients (65% in those presenting with a pneumococcal infection) [12].

Brain imaging should always be performed in the following cases:

- meningitis caused by a bacterium other than *S. pneumoniae* or *N. meningitidis*;
- pneumococcal meningitis in children, especially after 2 years of age, in the absence of ENT bacterial infection or if the causative serotype was included in the vaccine administered to the child. Brain imaging here aims to look for a breach in the meninges.

Brain MRI with injection of contrast media and, if required, magnetic resonance angiography is the best examination to look for abnormalities of the brain parenchyma and/or of its vascularization, although no recent prospective study has assessed its sensitivity and specificity in the diagnosis of each complication mentioned.

When the MRI cannot be easily performed or puts the patient at risk, a CT scan with injection of contrast media should be performed as it helps diagnose most complications, although its sensitivity and specificity have never been officially measured.

Brain imaging during the early follow-up of bacterial meningitis helps look for acquired or congenital bone and dura mater lesions or chronic infections of the inner ear and mastoiditis to prevent recurrences. These lesions and infections should be clinically looked for in children and adults presenting with pneumococcal meningitis and in adults presenting with *Haemophilus* meningitis.

Factors associated with a bone and dura mater breach requiring an imaging test are severe head injury, especially if sustained in the previous months, recurrence of bacterial meningitis, history of neurosurgical procedure, pituitary gland surgery or some ENT procedures, rhinorrhea, or CSF otorrhea. Breach investigation should always be performed during the recovery phase in those cases.

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Brain or spinal imaging is required to look for congenital dermal sinus in children presenting with bacterial meningitis caused by staphylococci, Enterobacteriaceae, or multiple bacteria.

The diagnostic strategy relies on the clinical evaluation (including ENT evaluation) and on the MRI or CT scan with bone window and axial and frontal millimetric views, especially of the cribriform plate and ethmoid roof depending on cases.

14.4. How is the infection portal of entry managed?

ENT portals of entry, reported in 25% of cases (adults and children) [30,31], should always be looked for in case of community-acquired bacterial meningitis [77,78]. A prospective study performed in the Netherlands between 2006 and 2014 in patients aged above 16 years reported an ENT portal of entry (otitis or sinusitis) in 34% of patients presenting with meningitis (386/1,125). ENT-related meningitis cases reported in this study were associated with better prognosis ($P = 0.041$) [71]. They include otological, nasal and sinus sites. Their treatment depends on the etiology and sometimes requires drainage of purulent fluid associated with closure of the breach, if required. All purulent fluids should be microbiologically analyzed.

The systematic clinical examination of bacterial meningitis should look for hearing loss, otalgia, and otorrhea and requires otoscopy to confirm the purulent fluid or the perforation. The nasal cavity should also be examined to look for nasal and sinus discharge. Otological causes should be distinguished from nasal and sinus causes.

Otological causes: potential sources of infection are acute otitis media, mastoiditis (although more rarely), otitis media with cholesteatoma, osteomyelitis of the base of the skull [174]. Post-traumatic or post-surgical CSF discharge may be observed in the middle or inner ear, with abscess behind the eardrum or discharge through the ear canal if perforated [175].

The management of otological causes requires the advice of an ENT specialist:

- in case of ENT infection site suspicion;
- for acute otitis media: paracentesis is recommended as soon as possible to drain purulent fluids and to perform the bacteriological analysis;
- for acute mastoiditis: the current treatment combines antibiotics and drainage of the middle ear with paracentesis; surgery (mastoidectomy) may be indicated in case of unfavorable outcome after 48 hours. In case of chronic otitis (cholesteatoma mainly), specialized assessment and surgery should be considered at the end of the meningitis treatment;
- CSF discharge may spontaneously stop. If not, the breach — diagnosed by endoscopy, CT scan, or MRI — should be closed.

Nasal and sinus causes: bacterial sinusitis is most common. Post-traumatic or post-surgical rhinorrhea is also observed, although more rarely.

Sinusitis associated with bacterial meningitis is often frontal or ethmoid. It may be previously known or diagnosed during the course of bacterial meningitis. The CT scan confirms the presence of fluids and involvement of bone structures, mainly with sphenoidal localizations.

The MRI may be useful when cavernous sinus thrombosis is suspected. Ethmoiditis mainly presents as ocular signs (oculomotor palsy, sometimes mydriasis) and the CT scan is very helpful [176].

CSF rhinorrhea, usually unilateral, may be spontaneous or triggered by head movements or abdominal compression. The CSF analysis confirms the presence of glucose. Nasal endoscopy helps identify and localize the site of discharge. A potential breach should be looked for at MRI and/or CT scan with bone window and axial and frontal millimetric views, especially of the cribriform plate and ethmoid roof depending on cases (neurological advice required).

Management of nasal and sinus causes:

- drainage of sinus sites should be performed in case of fluid persistence or when the patient's general status is worrying despite antibiotic therapy administration. Endonasal drainage should be preferred but the surgical procedure may be discussed depending on the sinus localization;
- when rhinorrhea does not spontaneously stop, the breach should be closed through the endonasal or external route depending on the localization or size of the breach [177,178].

When a breach is observed, antipneumococcal vaccination is recommended as suggested in the vaccination calendar for people at high risk of invasive pneumococcal infection (i.e., initial administration of the conjugate vaccine followed by the polysaccharide vaccine two months later) [179]. There is no indication for antibiotic prophylaxis or for continuing the curative antibiotic therapy before closing the breach. Breach closure should be performed as soon as possible. There is, however, no consensus on the optimal time to surgical procedure.

14.5. What is the follow-up for each type of patients?

Pediatric and adult meningitis are associated with high case fatality and a high rate of neurological sequelae, despite good quality of care at the acute phase. The case fatality of pneumococcal meningitis is 11–37% (higher among adults) and neurological sequelae are observed in 30–50% of surviving patients. The rate of sequelae is also higher in adults than in children.

Neurological, hearing, cognitive, and psychological sequelae are common: 29–70% depending on studies [180].

Van de Beek's study [12] of adult patients uses the Glasgow Outcome Scale (GOS) at the end of meningitis. Score 1: death, 2: vegetative state without interaction with close relatives, 3: inability to live independently but responds to instructions, 4: moderate disability, independent living without work resumption, 5: mild or absent disability. The authors reported 21% of deceased patients, 13% of patients presenting with severe or moderate sequelae with hearing loss in 22% of surviving patients (mild: 31%; moderate: 21%; severe: 17%; or very severe: 31%; and unilateral in a third of cases). Long-term cognitive sequelae may also be observed in adults. A subgroup of patients who

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presented with pneumococcal meningitis with a GOS score of 5 at discharge were reevaluated several months later [181]. Cognitive impairment was observed in 27% of them, with decreased quality of life.

A meta-analysis of 1109 pediatric patients reported an 82.5% survival rate among children and major sequelae in 15% of cases — hearing loss 10.5%, including 5% of severe hearing loss, learning disability (4.2%), motor impairment (3.5%), seizures (4.2%) [182]. Case fatality and sequelae rates are higher in patients presenting with pneumococcal meningitis [182].

Some complications only observed in young children may improve over time. The authors of another study reported that out of 37% of children presenting with abnormalities at the end of meningitis, improvement was observed in many of them with 10% of hearing losses and 4% of neurological disorders at one year [183].

Pediatric hearing loss is observed at the early stage of meningitis and may be temporary or definitive. Inner ear impairment with cochlear ossification may be observed in the weeks following meningitis. The rate of hearing loss ranges from 10% to 13% depending on studies — lower than in adults — and depends on the causative agent (*S. pneumoniae*: 33%, *N. meningitidis*: 5%) [184].

Several studies suggest that some factors observed at admission are associated with the onset of sequelae: patient's characteristics (elderly or children aged below one year), causative agent (*S. pneumoniae*, resistance to antibiotics), clinical signs of severity especially consciousness disorders, neurological complications (focal signs, cerebral edema, paralysis of the cranial nerves — except for paralysis of the eighth cranial nerve), hemodynamic signs (septic shock), biological signs such as low cellular reaction, high bacterial load in CSF, positive blood cultures [172,185].

Seizures at admission are not indicative of poor prognosis, unlike late onset of seizures, prolonged seizures, or focal seizures persisting after discharge.

Considering the lack of data, all patients should be followed up after hospital discharge.

A neurological clinical examination should be performed before hospital discharge in children and adults.

An age-specific hearing test is recommended at the latest 15 days after treatment completion for pneumococcal or *Haemophilus* meningitis. Patients presenting with severe hearing loss should be rapidly referred to an ENT specialist to look for early cochlear ossification at MRI. Depending on the evaluation findings, cochlear implants may be rapidly required in children [186]. When implants are required, antipneumococcal vaccination is recommended as soon as possible as per the suggested vaccination schedule in the vaccination calendar for people at high risk of pneumococcal invasive infections [179].

Diseases or abnormalities that may have contributed to bacterial meningitis should be looked for, such as splenectomy or asplenia, sickle cell anemia, beta-thalassemia [76,187]. Predisposing chronic or immune diseases are observed in 10–45% of adult or pediatric studies [188,189].

In adults, diseases such as diabetes, chronic alcoholism, cancer, cirrhosis, hemopathy, and HIV infection should be looked for. Electrophoresis of plasma protein should also be performed in case of pneumococcal meningitis.

Severe infections in children should lead physicians to look for an immunodeficiency. They may start with a complete blood count to look for Jolly bodies, serum IgG, IgA, and IgM measurement, and vaccinal serologies. Evaluation of the complement level is essential in case of meningococcal meningitis and should be performed when the first episode is observed. Specialist's advice is recommended in children and young adults to discuss immunological investigations in case of a history of severe bacterial infection in children or among brothers and sisters, recurrent meningitis, vaccinal serotype meningitis in vaccinated children (conjugate vaccine against *S. pneumoniae*, *Haemophilus*, or *N. meningitidis*), or unusual bacterial infections including rare serogroup meningococcal infections (Y, W135, X, and Z).

14.5.1. One month after hospital discharge

A neurological examination is recommended, and hearing loss should be looked for.

When an antiepileptic treatment has been initiated at the acute phase and if no other episode has been observed, an electroencephalography should be performed, and the antiepileptic treatment may be discontinued based on the advice of the neurologist or neuropediatrician. Head circumference should be monitored in infants.

14.5.2. Up to one year following meningitis onset

Hearing tests should be performed every three months in children. These tests may be performed by the child's family (whispering) and by the family physician or pediatrician. Parents should also inform the child's teacher about any hearing disorder.

Adaptive capacities of adults should be assessed, and quality of life and depression scales should be used to distinguish hearing loss, cognitive sequelae, and depression.

14.5.3. More than one year following meningitis onset (children)

Family physicians or pediatricians should also monitor the child's school adjustment.

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Disclosure of interest

The authors declare that they have no competing interest.

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