



17th CONSENSUS CONFERENCE ON ANTI-INFECTIVE CHEMOTHERAPY

Practice guidelines for acute bacterial meningitis (except newborn and nosocomial meningitis)

Short version

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INTRODUCTION

Community-acquired bacterial meningitis is characterized by the association of an infectious syndrome and, at CSF examination, the presence of bacteria and/or other highly significant abnormalities. In proven case of meningitis and in suspected cases as well, the pathway of clinical management is similar and urgent treatment is definitely needed.

The goal of the present consensus conference is to adapt the 1996 recommendations to the present situation. The following situations have been excluded from the field of this conference: meningitis in the newborn child (less than 1 month), tuberculous meningitis, *purpura fulminans*, and prevention as a whole (immunisation and/or chemoprophylaxis of contact cases).

Concerning the particular case of *purpura fulminans*, the Jury recalls the recommendations related to the immediate management, established by the French High Council for Public Hygiene (www.sante.gouv.fr/htm/dossiers/cshpf/cs231.htm), dated September 22, 2006, and confirmed by the document N°DGS/5C/2006/458 dated October 23, 2006

(www.infectiologie.com/site/medias/documents/officielsmeningo_circ_2006.pdf):

“Outside the hospital, all patients showing signs of infection together with (at physical examination of a patient totally undressed) presence of purpura lesions unresponsive to pressure, one or more of those being necrotic or ecchymotic and 3mm or more in diameter, must immediately receive a first dose of anti-meningococcal antibiotic, preferably by the IV route, otherwise intramuscular, regardless of the circulatory condition of the patient. The patient must be urgently transferred to the hospital, preferably to one providing intensive care to patients that age. The intervention of an intensive care mobile unit is justified, assuming it is available within 20 minutes. If not, the transportation will be by the most rapidly available vehicle. In all cases, the physician must inform the emergency room of the hospital that a suspected case of *purpura fulminans* is about to arrive and that they should be ready to start its management”.

According to the French National Institute for Health Surveillance (www.invs.sante.fr/), the incidence of acute community-acquired bacterial meningitis in 2006 was 2.23/100 000, all age brackets and bacterial species together. In 2002, the incidence was much higher in the child as compared to the adult patient: 44/100 000 in children less than 1 year, 6.9/100 000 in those 1 to 4 years. Bacterial epidemiology is age-related. In the 1 to 3 months age bracket, 4 species are responsible: group B streptococcus, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and, uncommonly, *Escherichia coli*. In the child 3 to 12 months, the pneumococcus accounts for half of the cases, closely followed by the meningococcus. After 1 year and up to 24, the pneumococcus and the meningococcus account for approximately 95% of the cases, the importance of the latter increasing along with the age. In the adult over 24, the species encountered are (in a decreasing order) *S.pneumoniae* (50% of cases in the young adult, 70% after the age of 40), *N.meningitidis* and uncommonly *Listeria monocytogenes*, *Haemophilus influenzae* and the group B streptococcus (5-10% each).

In France, mortality at the acute phase (globally 20% in the adult and 10% in the child) and sequelae (approx. 30%) of acute community-acquired bacterial meningitis remain

high, particularly for pneumococcal meningitis and blood culture-positive meningococcal disease.

The Jury considers that a better outcome for acute community-acquired bacterial meningitis requires early recognition and perfect management of the degree of emergency, including initiation as soon as possible of the appropriate antimicrobial chemotherapy, preceded when indicated by steroid therapy. This requires, even before admission, the earlier detection of suspected cases, the immediate transfer of the patients to the emergency room where lumbar puncture and antibiotic therapy will be considered, together with other interventions depending on the clinical condition. As soon as meningitis is identified or reasonably suspected, administration of antimicrobials is the most urgent decision regardless of poor circulatory parameters or risk factors for the lumbar puncture.

Recent scientific data have led to a better knowledge of the role and indications of steroid therapy which should be initiated before, or at the latest together with the first dose of antibiotics.

New diagnostic tests are useful in certain situations when the contribution of conventional microbiologic tests is insufficient.

Several decision-making algorithms based on biological or on mixed biological and clinical parameters, have been published. Their goal is to distinguish bacterial meningitis from other acute meningitis in order to minimize the number of unjustified admissions and antibiotic administrations.

Cefotaxime and ceftriaxone are the cornerstones of antimicrobial chemotherapy in patients with acute community-acquired bacterial meningitis, except in those uncommon cases of *Listeria* meningo-encephalitis (almost exclusively observed in patients over 50 years). Administration of the most appropriate dosage is absolutely necessary to bacterial eradication. Today there are no data to support a different selection of molecules.

In patients with meningitis of proven or suspected pneumococcal aetiology, whether a combination of antimicrobials may be beneficial remains controversial.

After discharge, the follow-up should be better organized and applied to all patients, adults and children as well. The data collected should allow identification of sequellae in the middle and in the long term.

Since the previous consensus conference in 1996 the epidemiological situation has changed. First a National Plan for the Preservation of Antibiotics Efficacy was implemented in 2001. Second the heptavalent conjugated antipneumococcal vaccine became available for use in children in 2002. The most recent data available from the National Reference Centre for Pneumococcus Surveillance confirm a reduction in the number of meningitis strains with reduced penicillin susceptibility and a rise in the proportion of serotypes that are not included in the vaccine. These observations raise questions about further evolution of the spectrum of strains involved in invasive pneumococcal disease such as meningitis, and about their resistance to antimicrobials, particularly to third generation cephalosporins.

This situation requires specific public health surveillance procedures, involving those structures participating in the surveillance of adult and paediatric bacterial meningitis such as the National Reference Centre for Pneumococcus Surveillance

(www.onerba.org/rubrique.php3?id_rubrique=12), the Pneumococcus Regional Observatories, the EPIBAC network (www.invs.sante.fr/surveillance/epibac/donnees.htm), the GPIP/ACTIV (www.sfpediatric.com/fr/groupe-de-specialites/gpip.html) and www.activ-info.net/journee/jpipa2006/grimpreldelarocque.pdf), and the medical personnel in general.

It appears equally necessary to start a prospective survey of pneumococcal meningitis cases, recording predisposing factors, therapy, and clinical and bacteriological evolution. Any significant modification in epidemiology or clinical presentation as observed by any of the participating surveillance authorities would induce the appropriate modification of today's recommendations.

QUESTION 1

In case of suspicion of bacterial meningitis, what is the most appropriate initial management?

1.1 In which situations should bacterial meningitis be considered?

Early recognition of situations that suggest a case of bacterial meningitis is crucial to reduce the time between onset of first symptoms and treatment, a key factor to a better prognosis. Before admission the diagnostic procedures must give a particular importance to the most sensitive signs and symptoms, while specificity is of greater importance after admission.

In febrile children, and whatever the age, the early manifestations of meningococcal disease require that a particular attention should be paid by the parents and by the physician: change in complexion, cold hands and feet, pain in the legs, non specific skin rash, are enough to urgently seek extended medical evaluation in the hospital. The Jury recommends that families and general practitioners should be widely informed of the early signs of paediatrics sepsis.

In the infant, and regardless of body temperature, physical examination must look for signs of serious bacterial infection such as modification in presentation or behaviour (changes in complexion, altered general condition, impaired reactions and relations with other persons, absence of smiles). A fever of more than 39.5 °C is by itself evidence for severity.

In infants less than 3 months anyone of the following signs requires admission in the hospital for medical management and lumbar puncture, according to the Jury:

- Unusual behaviour (high pitched cry, fussy behaviour, irritability, somnolence and lethargy);
- tachycardia with normal blood pressure, skin coloration time >3 seconds, cyanosis;
- neurological abnormalities (full or bulging fontanel, nuchal hypotonia, global hypotonia); meningism is absent in most cases.;
- convulsion;
- purpura.

In infants 3 months to 2 years the usual clinical symptoms are more commonly – although not constantly – observed. The combination of seizures and fever in a child

less than 9 months requires a lumbar puncture. In children 9 to 12 months lumbar puncture should be considered. The older the child, the greater the similarity with the clinical presentation of adult meningitis. In brief, lumbar puncture is rather widely indicated in children 3 months to 2 years.

In the adult, the sensitivity of the trilogy fever + meningism + consciousness impairment, for the diagnostic of community-acquired bacterial meningitis is 45%. Two or more of the following signs or symptoms are present in 95% of adult patients with bacterial meningitis : headache, fever, meningism, consciousness impairment. The classical trilogy is more common in pneumococcal than in meningococcal meningitis. Skin signs, particularly purpura lesions, are suggestive of meningococcal infection. The sensitivities of the Kernig sign, the Brudzinski sign, and that of meningism, are poor.

In the adult and the child over 2 years:

- there is a very high probability of meningitis in a patient with fever, meningism, and either headache or an impaired consciousness;
- there is also a high probability of meningitis in patient with fever and purpura, particularly if headache is also present;
- meningitis must be considered in a patient with fever and either convulsions or neurological focal signs;
- the physician must keep in mind the possibility of meningitis in a patient with fever and headache even in absence of impaired consciousness, neurological focal signs or meningism. In the absence of alternatives, lumbar puncture must be considered, particularly in the presence of biological inflammatory changes consistent with bacterial infection (elevated CRP and/or procalcitonin).

1.2 Which are the biological tests necessary to determine the bacterial aetiology of meningitis?

The following tests are recommended in all cases:

1. Biochemistry, cytology and microbiology on a CSF sample. Consequently, the sample must be collected in 3 test tubes (total volume: 40 to 100 drops *i.e.* 2 to 5 mL in adult patients, 40 drops *i.e.* 2 mL in children). The microbiologist must be properly informed and receive all clinically relevant information. Results of cytology, chemistry and Gram stain must be made available to the medical personnel in charge of the patient within one hour after lumbar puncture. In case the Gram stain is positive, the antimicrobial susceptibility testing should be made directly on the specimen. If the Gram stain indicates a high probability of *S.pneumoniae*, E-tests are recommended, at least for cefotaxime and ceftriaxone. CSF culture remains the test of reference. It confirms the diagnostic, identifies the causative organism, and determines its susceptibility to antibiotics. In case of positive CSF culture, antimicrobial susceptibility testing must follow the recommendations of the Antimicrobial Testing Committee of the French Society for Microbiology (<http://www.sfm.asso.fr/nouv/general.php?pa=2>). In case of pneumococcal meningitis, the Jury recommends MIC determination for amoxicillin, cefotaxime and ceftriaxone.
2. One or more blood cultures.

The following tests are optional:

1. CSF immunochromatography (Binax NOW *Streptococcus pneumoniae*® test) if the clinical context strongly suggests bacterial meningitis, particularly in case of negative CSF stain. In contrast, latex haemagglutination tests are not recommended.
2. PCR on the CSF sample. In case of negative Gram stain despite a strong suspicion of meningitis the Jury recommends PCR for meningococcus, PCR for pneumococcus (assuming immunochromatography is not done yet), or universal PCR. In case the probability of bacterial meningitis seems low, it is recommended to perform *Enterovirus* PCR. If positive, bacterial PCRs can be avoided and antibacterial chemotherapy discontinued.
3. Blood PCR for meningococcus, in case meningococemia is strongly suspected.
4. Biopsy of purpura skin lesions, tested with meningococcus PCR, Gram stain and culture, particularly if antimicrobial chemotherapy was initiated before lumbar puncture, or if the CSF Gram stain was negative or not done for any reason.
5. CSF lactate assay: a concentration < 3.2 mmol/L is quite rarely associated with bacterial meningitis.
6. Serum procalcitonin assay: a concentration < 0.5 ng/mL is quite rarely associated with bacterial meningitis.

The Jury encourages the use of the three algorithms that are available to help differentiate between bacterial and viral meningitis: the Hoen's software for children and adult patients, the Bacterial Meningitis Score and the Meningitest (children only).

1.3 Who are those patients in whom CT-scan should be done before lumbar puncture?

It is exaggeratedly common in France to realise cerebral imaging (usually a CT-scan) before lumbar puncture in patients with suspected meningitis.

The problems raised by this strategy can be summarized as follows:

1. Lumbar puncture is necessary for the diagnostic of meningitis.
2. In bacterial meningitis, the earlier the antibiotic treatment, the higher the probability of recovery.
3. CSF cultures turn negative quite rapidly after antimicrobials are administered. A strategy such as: antibiotics administration followed by CT-scan and followed by lumbar puncture, may well lead to negative CSF cultures, because of a significant additional delay.
4. The theoretical risk of lumbar puncture is brain herniation.
5. The mechanisms able to cause brain herniation are pressure imbalance due to some obstacle to CSF circulation, and cerebral lesions causing mass effect. Intracranial hypertension is common in severe cases of meningitis but is not by itself a contra-indication to lumbar puncture.

In a patient with suspected bacterial meningitis, cerebral imaging is indicated only in case of (Level C):

- neurological focal signs;
- consciousness impairment with a Glasgow score ≤ 11 ;

- recent or ongoing seizures, partial or generalized in patients older than 5, only if hemi-corporeal in younger children.

Brain herniation actually occurs most of the time in patients with a normal CT-scan. Lumbar puncture is contra-indicated in patients with or without CT-scan, as long as they show ongoing signs of herniation (unilateral mydriasis, respiratory or cardiac irregularities, hiccup, rigidity and pronation involuntary arms movements). In patients with a CT-scan showing mass effect or signs of herniation, lumbar puncture is also contra-indicated.

Ophthalmoscopic examination may be difficult to perform in the context of emergency and papillary oedema may be absent in case of brain oedema is recent. Consequently it is not required before lumbar puncture.

QUESTION 2

What is the most appropriate antimicrobial therapy in a patient with meningitis presumably of bacterial origin?

2.1a How urgent is antimicrobial therapy in a patient with meningitis presumably of bacterial origin?

In case of bacterial meningitis, initiation of antimicrobial chemotherapy is remarkably urgent since early treatment is correlated with survival and outcome in the middle term. Data obtained on animal models show that one more hour of evolution without antibiotics is associated with the generation of hundreds of thousands more bacteria at the site of infection.

In patients, a correlation between time to initiation of antibiotic therapy and outcome is demonstrated. Several studies show that a poor prognosis is associated with a delay of more than 3 hours between arrival in the emergency room and antibiotics administration.

Recommendation.

Antimicrobial therapy must be administered not later than 3 hours, and as far as possible within one hour upon arrival at the hospital, regardless of the time onset since meningitis has presumably started (Level B).

2.1b Who are those patients for whom it is necessary to administer antimicrobials even before lumbar puncture?

The lumbar puncture is the cornerstone of diagnostic. Any circumstance causing the lumbar puncture to be delayed, necessitates the initiation of a first line antibiotic regimen of antibiotics since early treatment and favourable outcome are narrowly correlated.

In three situations should antibiotic therapy be initiated before lumbar puncture:

- *purpura fulminans*;
- hospital management is unavailable within 90 minutes;
- lumbar puncture is contra-indicated for one of the following reasons:

- pre-existing blood coagulation abnormality, effective anticoagulant therapy, clinical suspicion of serious haemostasis trouble (active bleeding);
- risk of cerebral herniation;
- unstable circulatory condition.

In such a situation, a blood culture before administration of antibiotics and during the initial management of the patient is recommended. Lumbar puncture will be done as soon as possible once the relevant abnormalities are corrected.

2.2 Which antibiotics should be used in a patient with meningitis presumably of bacterial origin (in case of positive CSF Gram stain and in case of negative CSF Gram stain)?

Considering the data available today, particularly in terms of epidemiology, most Jury members consider that if the appropriate third generation cephalosporin compound is administered at its optimal dosage, adjunction of vancomycin (as mentioned in the 1996 recommendations) is not any more justified for the treatment of pneumococcal meningitis.

Nevertheless data from the literature show that in paediatric cases of presumably pneumococcal meningitis, a combination of vancomycin with the appropriate third generation cephalosporin is not contra-indicated.

Table 1. First line antibiotic therapy of acute bacterial meningitis in relation with CSF Gram stain.

Positive Gram stain	Antibiotic	Dosage*
Gram+ cocci (pneumococcus is suspected)	Cefotaxime or ceftriaxone	300 mg.kg ⁻¹ .d ⁻¹ either divided in 4 infusions or by 24h constant infusion, after an initial loading dose of 50 mg.kg ⁻¹ over 1 h**. 100 mg.kg ⁻¹ .d ⁻¹ in 1 or 2 infusions.
Gram- cocci (meningococcus is suspected)	Cefotaxime or ceftriaxone	200 mg.kg ⁻¹ .d ⁻¹ either divided in 4 infusions or by 24h constant infusion, after an initial loading dose of 50 mg.kg ⁻¹ over 1 h. 75 mg.kg ⁻¹ .d ⁻¹ in 1 or 2 infusions.
Gram+ rods (<i>Listeria</i> is suspected)	Amoxicillin + gentamicin	200 mg.kg ⁻¹ .d ⁻¹ either divided in 4 infusions or by 24h constant infusion. 3 to 5 mg.kg ⁻¹ .d ⁻¹ in one single daily infusion.
Gram- rods (<i>E.coli</i> is suspected) <i>In children less than 3 months</i>	Cefotaxime or ceftriaxone + <i>gentamicin</i>	200 mg.kg ⁻¹ .d ⁻¹ either divided in 4 infusions or by 24h constant infusion, after an initial loading dose of 50 mg.kg ⁻¹ over 1 h. 75 mg.kg ⁻¹ .d ⁻¹ in 1 or 2 infusions . <i>3 to 5 mg.kg⁻¹.d⁻¹ in one single daily infusion.</i>
Negative Gram stain		
Listeria is not suspected <i>In children less than 3 months</i>	Cefotaxime or ceftriaxone + <i>gentamicin</i>	300 mg.kg ⁻¹ .d ⁻¹ either divided in 4 infusions or by 24h constant infusion, after an initial loading dose of 50 mg.kg ⁻¹ over 1 h***. 100 mg.kg ⁻¹ .d ⁻¹ in 1 or 2 infusions <i>3 to 5 mg.kg⁻¹.d⁻¹ in one single daily infusion.</i>
Listeria is suspected***	Cefotaxime or ceftriaxone + amoxicillin + gentamicin	300 mg.kg ⁻¹ .d ⁻¹ either divided in 4 infusions or by 24h constant infusion, after an initial loading dose of 50 mg.kg ⁻¹ over 1 h***. 100 mg.kg ⁻¹ .d ⁻¹ in 1 or 2 infusions. 200 mg.kg ⁻¹ .d ⁻¹ either divided in 4 infusions or by 24h constant infusion. 3 to 5 mg.kg ⁻¹ .d ⁻¹ in one single daily infusion.

* In the child maximum daily doses are 12g and 4g for cefotaxime and ceftriaxone, respectively.

** The loading dose administration and the 24h infusion should be initiated concomitantly.

*** Context (age, immunodepression...), progressive onset of symptoms, rhombencephalus involvement (cranial nerve palsy and/or cerebellous syndrome).

QUESTION 3

Besides antimicrobials, what is the initial therapeutic management of patient with meningitis presumably of bacterial origin?

3.1 What are the indications and the mode of administration of steroids?

Dexamethasone is the only adjunctive therapy of bacterial meningitis evaluated in convincing clinical trial. Its anti-inflammatory effect requires administration before initiation of antimicrobial therapy.

One meta-analysis of randomised studies raised the conclusion that dexamethasone was useful in children for the prevention of profound deafness, assuming the aetiologic agents were *H.influenzae* or *S.pneumoniae* and that the first administration of dexamethasone was given prior to – or at the time of – the first dose of antibiotics.

One European double blind randomised study versus placebo, including 301 adults with bacterial meningitis, demonstrated that early treatment with dexamethasone given prior to – or at the time of – the first dose of antibiotics, significantly reduced the probability of death or neurological sequelae after 8 weeks of evolution. The benefit of dexamethasone was greater in patients with pneumococcal meningitis and was not negatively counterbalanced by any increased incidence of neurological sequelae or steroid-related deleterious side effects.

Utility of steroids remains non demonstrated in immunocompromised patients and in those in whom bacterial meningitis has not been microbiologically confirmed.

Recommendations:

Dexamethasone injection is recommended immediately before – or concomitantly with – the first dose of antibiotics in the following cases

- microbiologically documented pneumococcal (level A) or meningococcal (level B) meningitis in adult patients, and pneumococcal or *H.influenzae* meningitis in paediatric patients (level A).
- suspected bacterial meningitis without bacteriological confirmation, in adults and infants 3 to 12 months of age, in whom administration of first line antibiotic therapy has been nevertheless decided, for the following reasons
 - o lumbar puncture is delayed by cerebral imaging;
 - o CSF is macroscopically trouble, if not grossly purulent;
 - o CSF Gram stain is negative but other CSF and blood tests indicate bacterial meningitis.

The initial dose is 10 mg in adults and 0.15mg.kg^{-1} in children, to be repeated q. 6h during 4 days.

This treatment is not recommended in immunocompromised patients and in those already treated with parenteral antibiotics. Dexamethasone therapy must be discontinued if bacterial meningitis is ruled out and in children when meningococcal meningitis is authenticated.

3.2 Are other treatments urgently needed and in which setting should they be administered?

Setting for management: after diagnostic and treatment in the emergency room, it is crucially important to select adequately the most appropriate orientation for the patient. Criteria for admission in ICU are as follows:

- extensive purpura;
- Glasgow score ≤ 8 ;
- neurological focal signs;
- *status epilepticus*;
- unstable circulatory condition.

Even in the absence of such criteria, the Jury recommends meeting with the ICU medical personnel to discuss, for each patient, the best orientation. If the decision is taken not to admit the patient in ICU, it must be however in a setting providing close (*i.e.* hourly) medical supervision of consciousness and haemodynamics over the first 24h for the least.

Treatment of convulsions

Treatment of convulsions and prevention of such recurrences is justified and relies upon usual antiepileptic agents. The benefit of primary prevention with such drugs is not demonstrated.

Treatment of intracranial hypertension

Symptomatic intracranial hypertension is common and is associated with a high risk of poor outcome. The management includes correction of low arterial pressure (IV fluids, inotropic drugs) and control of intracranial pressure. Those methods commonly recommended are a 20-30° elevated position of the head, sedation, and mechanical ventilation. Mannitol, administered as a single bolus, may be considered in emergency in cases with life-threatening intracranial hypertension.

Control of electrolyte imbalance, fever, and hyperglycemia.

Recommendations are:

- conventional fluid and electrolyte administration with daily monitoring of blood sodium and diuresis, in order to identify and treat inappropriate antidiuresis;
- reduction of body temperature in cases of meningitis with severe intracranial hypertension and in patients in whom fever is not well tolerated, without aggressively seeking a return to normal of the temperature;
- reduction of glycemia to <1.5 g/L (8.3 mmol/L) with intravenous insulin, in patients with severe sepsis, and after stabilisation of haemodynamics.

QUESTION 4

What are the modalities of further management?

4.1 What are the mode of administration and the duration of antimicrobial therapy after the initial phase?

In case of favourable evolution, the antibiotic therapy should be adapted to the microbiological results, according to the Jury of the conference (Table 2). In contrast, the initial antibiotic regimen should remain unchanged for a total duration of 14 days if no bacteriological documentation is available, although the diagnostic of bacterial meningitis remains considered (no serious alternative to bacterial meningitis; clinical presentation is suggestive). If bacteriological documentation lacks, the reality of bacterial meningitis is questionable and other diagnostics must be considered.

Table 2. Antibiotic treatment of community-acquired bacterial meningitis after bacteriological documentation.

Species, susceptibility	Antibiotic treatment*	Total duration
<i>Streptococcus pneumoniae</i>		
Amoxicillin MIC <0.1mg/L	Amoxicillin is preferred : 200 mg.kg ⁻¹ .d ⁻¹ either divided in 4 to 6 infusions or by 24h constant infusion. Continuation of third generation cephalosporin therapy is an alternative. If MICs of cefotaxime or ceftriaxone are <0.5 mg/L, dosage should be reduced to 200 and 75 mg.kg ⁻¹ .d ⁻¹ , respectively.	10-14 days**
Amoxicillin MIC ≥0.1mg/L	Cefotaxime, 300 mg.kg ⁻¹ .d ⁻¹ (200 if MIC <0.5 mg/L), either in 4 to 6 infusions or by 24h constant infusion, or ceftriaxone 100 mg.kg ⁻¹ .d ⁻¹ (75 if MIC <0.5 mg/L), in 1 or 2 infusions.	10-14 days**
<i>Neisseria meningitidis</i>		
Amoxicillin MIC <0.1mg/L	Amoxicillin or continuation of the third generation cephalosporin.	
Amoxicillin MIC ≥0.1mg/L	Cefotaxime 200 mg.kg ⁻¹ .d ⁻¹ either divided in 4 to 6 infusions or by 24h constant infusion, or ceftriaxone 75 mg.kg ⁻¹ .d ⁻¹ in 1 or 2 infusions.	4-7 days***
<i>Listeria monocytogenes</i>	Amoxicillin plus gentamicin, 3 to 5 mg.kg ⁻¹ .d ⁻¹ in one single daily infusion over 30 min., during the first 7 days.	21 days
<i>Streptococcus agalactiae</i>	Amoxicillin	14-21 days
<i>Escherichia coli</i>	Cefotaxime or ceftriaxone, plus gentamicin during the first 2 days in infants <3 months.	21 days
<i>Haemophilus influenzae</i>	Cefotaxime or ceftriaxone.	7 days

*If dosage is not indicated, please see table 1. In children maximum doses are 12g/d and 4g/d for cefotaxime and ceftriaxone, respectively.

**Prefer 10 days in case of rapid improvement over 48h with a strain susceptible (MIC ≤0.5 mg/L) to the third generation cephalosporin administered (Level C).

*** Prefer 4 days in case of rapid improvement over 48h (Level C).

If after 48-72 hours the clinical evolution is not fully appropriate, a control lumbar puncture is recommended in patients with normal brain imaging. The clinical and the microbiology staffs should discuss strengthening the antimicrobial therapy. The third generation cephalosporin will be maintained at its maximum dosage, possibly associated to rifampicin (10 mg.kg⁻¹ q.12h in adults, 20 mg.kg⁻¹ q.12h in children) or vancomycin (15 mg.kg⁻¹ by intravenous infusion over 1h as a loading dose, followed by a 60 mg.kg⁻¹.d⁻¹ constant infusion). Fosfomycin is an alternative. Second line therapy depends upon the strain identified.

Treatment failures confirmed by a positive CSF culture after more than 48h of therapy, require detailed investigations, according to the Jury:

- search for an abscess requiring drainage;
- verification that management is in agreement with guidelines, in terms of time to initiation of therapy, dosage, modes of administration;
- determination of the CSF concentration of the third generation cephalosporin, and comparison with the MIC for the responsible organism.

4.2 Is it useful and indicated to take later CSF specimens?

The main objective of controlling CSF is to verify that it rapidly turns sterile.

The Jury recommendations are that

- patients with favourable evolution do not routinely necessitate a control lumbar puncture ;
- a control lumbar puncture is necessary in patients with meningitis due to a strain of pneumococcus with a MIC > 0.5 mg/L for the third generation cephalosporin administered;
- it is also necessary, whichever the aetiologic agent, when, after 48-72h of therapy, the evolution of meningitis is not clearly favourable : non improvement consciousness and/or persistence of septic signs. Cerebral imaging must be made prior to lumbar puncture to identify empyema or other intracerebral complications that may require a neurosurgical intervention. One extra CSF specimen will be used for measurement of the CSF concentration of the third generation cephalosporin.

Lumbar puncture may also be performed after 48-72h of therapy of meningitis due to uncommon bacteria (i.e. others than *S.pneumoniae*, *N.meningitidis*, *Haemophilus* and *Listeria*).

4.3 What are the indications of brain imaging?

Imaging is not necessary in every patient with pneumococcal or meningococcal meningitis and is generally not urgent. However it may significantly influence a number of therapeutic decisions.

The main clinical signs that indicate that imaging is necessary are :

- onset of new neurological signs: convulsions, palsies (hemiparesis, tetraparesis, cranial nerve palsies others than VI), intensification of cephalalgias, vision modification;
- unexplained persistence, later than 72h after treatment was started, of fever of more than 38.5°, impaired consciousness, or intense cephalalgias;

- rapid augmentation of the cranial perimeter in a child of less than 2 years.

Brain imaging is absolutely necessary in case of

- meningitis due to bacteria others than *S.pneumoniae* or *N.meningitidis*,
- paediatric pneumococcal meningitis, particularly in children younger than 2 years, in the absence of any focal ENT bacterial infection, or in immunized children when meningitis is due to a serotype included in the vaccine.

Brain or spinal RMI is also indicated to investigate for dermal sinus in children with meningitis due to *Staphylococcus* or *Enterobacteriaceae*, and in case of polymicrobial meningitis.

Brain MRI with contrast, and, whenever necessary, MR angiography, are more efficient than CT-scan. However, if RMI is not available, a CT-scan with contrast allows identification of most of the complications.

All adult and paediatric patients with pneumococcal or *Haemophilus* meningitis must be clinically investigated for osteomeningeal breaches (past head trauma?). RMI is necessary in case of multiple episodes of meningitis, and in patients with a history of serious head trauma (particularly in the previous months), neurosurgery, hypophyseal surgery, certain ENT surgical procedures, and also in case of CSF leakage by the nose or the ear.

4.4 Is there a specific mode of intervention regarding the primary focus of infection?

At admission the patient must be clinically investigated for hypoacusia, otalgia, otorrhea. Otoscopy must be performed. Nasal cavities must be examined for rhinosinusual exudation.

Management of ENT portals of entry require the expertise of the ENT specialist:

- in case of otitis media, tympanocentesis is recommended;
- in acute mastoiditis, today's therapeutic management includes antibiotics and middle ear drainage by tympanocentesis; surgery may be required in case the evolution is not favourable after 48 h of antibiotic administration;
- in case of persisting sinus abscess or prolonged sepsis, drainage is indicated;
- CSF otorrhea or rhinorrhea may heal spontaneously. In case of persistence, the breach must be identified using endoscopy, CT-scan or MRI, and treated surgically.

In case of breach, antipneumococcal immunization is recommended. In the child younger than 5 years, the conjugate vaccine is recommended. There are no scientific reasons to administer prophylactic antimicrobial therapy, or to maintain a patient on antibiotics during the interval before the breach is treated. It should however be done as soon as possible, according to the Jury. There is no agreement upon the best agenda for surgery after meningitis.

4.5 Who are the patients requiring medical attention in the long term? What kind of follow-up is appropriate?

The Jury recommends a follow-up for all patients after bacterial meningitis.

At the time of discharge and not later than 2 weeks after completion of therapy, adults and children must be clinically evaluated for neurological signs and tested for

hypoacusia using age-adapted tests. In case of deafness, the patient must be referred to the ENT specialist to be investigated for a possible cochlear ossification process.

The Jury recommends questioning the immunologist about investigations that may be of interest in young adult and children in case of

- prior serious infections in this child, his brothers or sisters;
- recurrent meningitis;
- meningitis due to a vaccine serotype in a child adequately immunized; (pneumococcal conjugated vaccine, *Haemophilus* vaccine or meningococcal vaccine);
- infections due to uncommon pathogens, including unusual serotypes of *N.meningitidis* (Y, W135, X and Z).

The Jury recommends that adult patients should be investigated for predisposing factors such as diabetes, chronic alcoholism, cancer, cirrhosis, hemopathy, and HIV infection (if a risk factor is present). In case of pneumococcal meningitis, plasma protein electrophoresis is recommended.

It is recommended that one month after discharge from the hospital, the patient should be evaluated for neurological signs and hypoacusia. In case anti-epileptics were administered during the acute phase, they may be discontinued in the absence of further convulsion, after electroencephalography and confirmation by a neurologist or a neuro-paediatrician. In the very young child, cranial perimeter must be monitored.

After meningitis, children must be clinically monitored each quarter during one year with a particular attention paid to audition and behaviour at school. In the adult a particular attention will be paid to audition, cognitive sequellae, and depression. The Jury recommends to improve identification and management of long-term sequellae, particularly audition impairment.