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Preface

The Belgian Antibiotic Policy Coordination Committee (BAPCOC) has the honour to present the clinical guideline 'Antibiotic treatment, steroid therapy and prophylaxis for community-acquired bacterial meningitis in immunocompetent adults and children admitted to the hospital'. The guideline is presented to you as a brochure with a description of the development process, the relevant scientific literature and the recommendations, and as two leaflets with a summary of the recommendations for adults and for children. The guideline will also be published on the BAPCOC website (www.health.fgov.be/antibiotics) where you will be able to consult the evidence table and a critical appraisal of the RCTs (for brevity these are not included in this brochure).

The development of clinical guidelines is one of the primary tasks of BAPCOC in an effort to promote the correct use of antimicrobials to combat the problem of microbial resistance. As such the working group 'Hospital Care' set out to develop national guidelines on several topics, including acute pyelonephritis and bacterial meningitis.

A multidisciplinary development group of experts was set up and two development group managers, with experience in guideline development, were appointed. The SIGN-methodology was used and the report is based on the principles of the AGREE-instrument. Finally, the guideline was also validated by the Belgian Center of Evidence Based Medicine (CEBAM).

We wish to thank the development group managers and all members of the multidisciplinary development group for their essential contribution to this guideline.

We hope this guideline can promote good medical practice and will prove to be a valuable tool for your clinical practice.

With kind regards,

C. DECOSTER
President of BAPCOC

Prof. Dr. W. PEETERMANS
President of the working group 'Hospital Care'

1. Introduction

This report is not intended to be construed or to serve as a standard of medical care for an individual patient. Standards of medical care are determined on the basis of all clinical data available and are subject to change as scientific knowledge and technology advance. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome in every patient, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor in light of the clinical data presented by the patient and the diagnostic and treatment options available.

It is expected that this guideline will be adopted after local discussion involving clinical staff. Significant departures from the national guideline as expressed in a local guideline should be documented and the reasons for the differences explained. It is highly recommended that departures from the (local) guideline be documented in the patient's case notes at the time that the relevant decision is taken. Copying of this guideline for the purpose of producing local guidelines will be consented upon simple request.

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2. Description of development process

This clinical guideline development project is intended to assist clinicians in making decisions about appropriate and effective care for their patients. To avoid that this guideline would be liable to bias and not reflect current medical knowledge, the guidelines are based on a systematic review of the literature and not just on a consensus of expert opinion. For this specific subject, Belgian microbiological data on the relevant pathogens, including their resistance profiles, were taken into account.
In principal, the methodology of Scottish Intercollegiate Guidelines Network (SIGN) was used (see http://www.sign.ac.uk). This report is structured around the accepted criteria for validity of guidelines and based on the principles of the *Appraisal of Guidelines for Research and Evaluation in Europe (AGREE) instrument.*

This guideline was reviewed by independent clinical and methodological experts (via the Belgian Center of Evidence Based Medicine, for a detailed description of the methodology, see www.cebam.be).

This guideline should be re-evaluated in a period of 2 to 4 years if new evidence becomes available. In the meanwhile, all correspondence is welcome on BAPCOC@health.fgov.be

3. Background

Community-acquired bacterial meningitis (BM) is one of the most severe infections carrying high morbidity and mortality rates. In the nineties, the annual incidence of BM ranged from approximately 2-3 per 100,000 inhabitants in US or France, to 100-500 per 100,000 in Africa. Clinical outcome is dramatically influenced by the quality and the early initiation of treatment. Antibiotic therapy should be started as early as possible, before the results of cerebro-spinal fluid (CSF) culture and sensitivity testing are available. So appropriate management requires the selection of an empiric antibiotic regimen that is active against the most common pathogens. In adults and children > 3 months, the latter include *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* type b *(Hib). Listeria monocytogenes* should also be considered in neonates, aged patients or in some clinical presentations such as meningo-encephalitis, subacute BM or focal neurological signs. In the neonatal period, group B *S. agalactiae, Listeria monocytogenes* and *E. coli* are predominant.
The most substantial change in the epidemiology was characterized by the dramatic decrease of *H. influenzae* type b BM in those countries that implemented a program of vaccination with conjugate *Hib* vaccine. This has modified the age distribution of BM. Before vaccination, 2/3 of the cases (after the neonatal period) occurred in children less than 5 years-old with a median age around 24 months while nowadays the median age has increased to around 20 years. So, the peak incidence is now observed among children < 5 years-old, adolescents and in the elderly. Another worldwide epidemiologic trend is the increasing rate of penicillin-resistant *S. pneumoniae.*

Analysis of medical practice (see separate report) demonstrates a variable duration of antibiotic treatment for both bacterial and viral meningitis. The choice of antibiotics seems as a whole more adequate. Evidence-based literature provides information on empiric therapy according to patient's age and on the type and duration of antibiotic therapy according to the pathogen.

Regarding the role of anti-inflammatory therapy, papers reported on the efficacy of dexamethasone for the prevention of hearing loss following *H. influenzae* type b meningitis in children. Thus, routine use has been recommended since 1994. However, with vaccination, *Hib* meningitis has almost disappeared in developed countries, so that BM is predominantly caused by *N. meningitidis* and *S. pneumoniae* and the benefit of dexamethasone seems more debatable in these indications. Recommendations can be formulated on the current role of adjunctive corticosteroid therapy in bacterial meningitis as well as for the prevention of secondary cases.

4. Objectives

The main objective of this project is the development of evidence-based guidelines for antibiotic therapy of community-acquired BM in the hospital, for immunocompetent adults and children. The implementation of these guidelines should first optimize treatment and prophylaxis and then reduce the overuse, the inappropriate use and the use of newer antibiotics when preexisting ones show at least a comparable efficacy.

These particular guidelines cover the following clinical questions: What is the most appropriate treatment for patients with BM? Is the routine use of dexamethasone recommended? What is the most appropriate antibiotic regimen for the prophylaxis of secondary cases?
Recommendations will be formulated for both adults and children.

The target users of these guidelines are all doctors involved in the treatment of patients hospitalized with community-acquired BM.

The multidisciplinary guideline development group consisted of specialists in neurology, pediatrics, infectiology, intensive care, emergency care and microbiology (list of members included under the heading conflict of interests).

These guidelines are applicable to patients with BM acquired in Belgium, since the results of the microbiological survey of Belgian resistance patterns were taken into consideration in the development process.

5. Text of review

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

The evaluation of antibacterial treatment, steroid therapies and prophylaxis for BM is based on existing evidence-based guidelines, the results of meta-analysis and systematic review or randomized-controlled comparative studies with adequate statistical power. For some pathogens, no randomized trials are available and so other types of studies were taken into consideration. They will be taxed as such with a lower level of evidence and a lower grade of recommendation in this review.

Antibiotic and corticosteroid therapy
Criteria for inclusion: clinical signs and symptoms of bacterial meningitis on hospital admission, with a proportion of bacteriologically documented BM. Ideally, pathogen distribution has to be available.
Criteria for exclusion: Studies were excluded if there was no detailed description of the population, no detailed description of the evaluated end-points or less than 20 patients included in total.
Time period: For adults and children: 1960-2001

Antibiotic prophylaxis
Criteria for inclusion: Evaluation of the eradication of carriage in household and/or close contacts with an index case with *N. meningitidis* or Hib meningitis. Some studies on eradication of carriage without any contact with an index case have been included.
Criteria for exclusion: Studies were excluded if there was no detailed description of the population, no detailed description of the evaluated end-points or less than 20 patients included in total.
Time period: For adults and children: 1960-2001

Types of participants

Patients (adults and children) with "community-acquired acute meningitis":

1. Clinical symptoms of meningitis: various combinations of clinical features including headache, fever, neck stiffness, altered mental status, focal neurological findings, rash, Kernig sign, Brudzinski sign,…
2. Cerebrospinal fluid (CSF) compatible with bacterial infection: diminished CSF glucose, polymorphonuclear pleocytosis, increased CSF proteinorachy, subsequently classified according to the identified pathogen (gram stain, culture and/or specific antigen).
   {Typical CSF results in BM: opening pressure > 30 cm (normal<17), WBC > 500/mm^3 (normal<5) with > 80% neutrophils (normal:0%), glucose < 40 mg/dl (normal: > 40 or 2/3 normal plasma value) and protein > 200 mg/dl (normal:<50)}
3. Ideally, studies including patients with a history of neurologic abnormalities (central nervous system (CNS) abscess, CNS shunt, congenital abnormalities of the spine, penetrating wounds, neurosurgery, fracture or foreign bodies in the CNS) should be excluded, but these data are often lacking.

Regarding antibiotic prophylaxis, the population evaluated was household and/or close contacts of the index case. In some studies, only carriers that were selected in a definite population without contact with an index case were evaluated.

Types of interventions

Antibiotic treatment, adjunctive steroid therapy and antibiotic prophylaxis. Data included type of drug, dose and duration of treatment. The route of administration of antibiotic treatment should be intravenous. However, trials with mixed routes can also be considered for inclusion.

Types of outcome measures

Antibiotic treatment:
Primary end-points: death and disabling sequelae such as neurologic impairment and hearing loss.
Secondary: safety, rapidity of CSF sterilization, length of hospital stay, costs.
Steroid therapy:
Primary: death, short and long-term neurologic sequelae and hearing loss.
Secondary: safety.
Secondary prophylaxis:
Primary: eradication of the naso-pharyngeal carriage rate of secondary cases.
Secondary: safety, compliance and drug resistance.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

1. Existing guidelines:

Searching Internet guideline clearinghouses and Medline, the following were retrieved:
- IDSA (http://www.idsociety.org/pg/toc.htm under practice guidelines)
- John Hopkins University (http://www.hopkins-id.edu/)
- SIGN (http://www.sign.ac.uk)

2. PubMed search (Medline)/Grateful Med (Medline, Healthstar):

Both the primary terms and the related MeSHs (medical subject headings) were searched for separately. The following limits were used to restrict the search:
For adults

Meningitis /therapy (MESH); 1960 to 2000
For children:
Meningitis / therapy; 1960 to 2000
For antibiotic prophylaxis, the search also included the terms "meningitis and prophylaxis" and "nasopharyngeal carriage and eradication".
For corticosteroid therapy, the search also included the terms 'meningitis and dexamethasone' and 'meningitis and corticosteroids'
For all these subjects, a separate search was performed for the different types of publication: *meta-analysis, randomized controlled trial, clinical trial, review, practice guideline.*

3. Cochrane library / Database of abstracts of review of effectiveness (DARE) / controlled Clinical Trials (CCT) registry

All these databases were searched with the primary term: *meningitis*

METHODS OF THE REVIEW

Using PubMed (Grateful Med as control), the Cochrane Library, DARE and CCT, studies were retrieved using the above mentioned search strategy. In a first step the abstracts of all articles were scanned to extract the relevant articles. Studies already present in a 'higher' category (e.g. a randomised controlled trial (RCT), which is already presented in a selected meta-analysis, or a study identified as clinical trial, which is also an RCT), were omitted at the lowest level.

The searches were performed independently by the two guideline development group (GDG) managers and could be reviewed by the members of the development group. The publications that were selected as potential source of evidence, were critically appraised guided by a checklist. Evidence tables were then compiled to summarise all the validated studies. These instruments were prepared by the GDG managers and subsequently reviewed and adapted by the GDG members in consecutive rounds.

DESCRIPTION OF STUDIES

I. ANTIBIOTIC TREATMENT

A. Meta-analysis, Randomised Controlled trials (RCTs)

ADULTS

No meta-analysis is available. Seven randomized controlled studies are available in adult patients, none with a low risk of bias, however (see critical appraisal table). Three of these included children. The number of patients with a bacteriologically documented BM was less than 40. *H. influenzae, S. pneumoniae* and *N. meningitidis* were the commonest pathogens in all studies but one (in the study by Marhoum only patients with *N. meningitidis* BM were included). These studies were performed before the emergence of penicillin resistant *S. pneumoniae.*

In Johanssen's study, cefuroxime (high dosage) was found as efficient as ampicillin plus chloramphenicol (AMCHL) with CSF sterilization obtained at 48h in all cultured patients. Bryan, Zavala and Girgis found equivalence between ceftriaxone and AMCHL in terms of mortality, sequelae and safety. However, Zavala reported that ceftriaxone decreased more rapidly the amount of polymorphonuclear cells (PMN) in the CSF, with a trend to an earlier sterilization. Bryan showed a higher CSF bactericidal titer with ceftriaxone than AMCHL. Johansson and Zavala reported chloramphenicol resistant strains of *S. pneumoniae.* In Schmutzhard's study, meropenem was as efficient as third generation ceph-

alosporins. Marhoum only evaluated *N. meningitidis* BM and concluded that 2 days of ceftriaxone was equally effective as a 6 day-penicillin course, except for severe BM with persistent neurological signs (exclusion criteria in this study).

No evaluation of different dosages of the same antibiotic was available. The most common dosages were:
ceftriaxone 100 mg/kg/d first day then 80 mg/kg once daily (with a maximum of 4g/d)
cefuroxime 3g/8h (1 study)
cefotaxime 75-100 mg/kg/8h (max 12 g/d, 1 study)
variable doses of ampicillin and chloramphenicol (4 studies) (ampicillin 160- 280 mg/kg/d div 4 doses + chloramphenicol 50-100 mg/kg/d div 4 doses or 2-3g/d).

No studies that evaluated different duration of treatment with the same drug were retrieved and those described above in general did not use the same duration of antibiotic therapy.

No randomized trials are available on *L. monocytogenes* BM.

CHILDREN

Studies of better quality are available in children. The studies of Overtuff, Shann and Aronoff, however, were not taken into account: they were flawed by major sources of bias, included very few evaluable patients (Aronoff) or evaluated ABs that are not available in Belgium (Overtuff, Shann)(see critical appraisal table).

In the studies in which epidemiologic data were available, all but two (Roine, Scholz) found *H. influenzae* as the main pathogen. Other common pathogens were *S. pneumoniae* and *N. meningitidis*. Group B *Streptococcus, E. coli* and *Salmonella* spp. were rare. In some studies, the exclusion criteria were unclear especially regarding history of previous neurological diseases. Among the 20 evaluable studies, only 5 included a minority of children less than 1 month of age (Martin, Jacobs, Congeni, Wells, Steele).

In 9 studies comparing third generation cephalosporins (ceftriaxone or cefotaxime) versus ampicillin or penicillin plus chloramphenicol, cephalosporin therapy was at least as efficient as AMCHL. Some studies (Haffejee, Odio 2, Congeni, del Rio) showed a trend to an earlier CSF sterilization with cephalosporins but significance was reached only in the study of Peltola. Only one study (Barson) showed a trend towards less neurological sequelae and one study showed a significantly shorter duration of fever (Steele). In 3 out of the 9 studies, diarrhea was more frequent in the cephalosporin group. In one study (Peltola) in which chloramphenicol was used as a single agent, this therapy was significantly less effective in terms of mortality, recurrence, and rapidity of CSF sterilization.

The efficacy of cefuroxime and AMCHL were similar (Marks) (rate of cure and sequelae) but with a trend towards a later sterilization in *H. influenzae* BM treated with cefuroxime. Schaad compared cefuroxime versus ceftriaxone and showed a trend to a delay of CSF sterilization and to increased hearing loss (p=0,059) in the cefuroxime group.

Comparing third and so-called 'fourth' generation cephalosporins (Scholz, Saez-Lorens), no difference in efficacy was found between ceftriaxone and cefotaxime or between cefotaxime and cefepime. In some studies with ceftriaxone, more cases of biliary pseudolithiasis were reported but without clinical implications and therapeutical modifications (Scholz, Schaad, Peltola). Similarly, no difference was

found between meropenem and cefotaxime (Odio 1, Klugman). Rodriguez analysed ceftazidime versus AMCHL with no difference (19/90 *S. pneumoniae*). However, the use of ceftazidime is questionable due to its low in vitro activity against gram-positive bacteria (*S. pneumoniae*, Group B *Streptococcus*).

Standard duration of antibiotic therapy was: 7 days for *N. meningitidis*, 7-10 days for *H. influenzae* and 7-14 days (or more) for *S. pneumoniae* in 16 studies (Odio1, Klugman, Saez-Lorens, Schaad, Peltola, Haffejee, Rodriguez, Barson, Marks, Odio2, Lin, Barson, Congeni, Wells, del Rio, Steele). A shorter course of therapy was evaluated in 3 reports: in Roine's report evaluating ceftriaxone, patients with *S. pneumoniae*, *N. meningitidis* and *H. influenzae* BM that showed a rapid initial recovery (within 4 days) had the same rate of cure/sequelae after a total of 5 days versus 7 days of treatment. Martin and Kavaliotis analysed 4,6,7 days versus 8,12 and 14 days of therapy for *N. meningitidis*, *H. influenzae* and *S. pneumoniae*, respectively. In these two studies, the short course was as effective as the full one. These studies, however, included a limited number of cases, particularly with *S. pneumoniae*. So their conclusion that short course of antibiotic is as effective as the full one has to be taken with caution. Sholz (ceftriaxone vs cefotaxime) treated BM caused by *N. meningitidis* for 4d and those caused by the 2 other pathogens for 7 days. Peltola (cephalosporins versus AMCHL) treated BM due to these 3 pathogens for 7 days. No comparison of two different durations of therapy was done in these last 2 studies, but the reported rate of mortality/sequelae was similar to the other ones.
BM due to *S. pneumoniae* was by far the least evaluated one. No study was available for *L. monocytogenes* BM.

No evaluations of different dosages of the same AB are available. The most common dosages were:
ceftriaxone 100 mg/kg/d first dose then 60-100 mg/kg once a day
cefotaxime 150-300 mg/kg/d div 3-4 doses
cefepime 150 mg/kg/d div 3 doses
cefuroxime 240 mg/kg/d div 4 doses
meropenem 120 mg/kg/d div 3 doses
ampicillin 200-400 mg/kg/d div 4 doses + chloramphenicol 75-100 mg/kg/d div 4 doses.

B. Other types of publications

Scottish consensus on acute BM in immunocompetent adults (Beggs): Few data are available on the methodology used to develop these consensus guidelines. Concerning the antibiotic therapy, no recommendation reached a grade superior to III and some of them are questionable in the light of the results of available randomized studies.

	Recommendations	Grade
MANAGEMENT	- Pre-hospital AB: benzylpenicillin 2 MiU iv/im	WP
	- No delay in AB administration (after blood culture)	III
	- LP in all adults with suspected BM except if signs of intracranial hypertension, coagulation disorder or severe sepsis or confidence in the clinical diagnosis of meningococcal infection	III
	- CT or NMR if papilloedema or focal neurological signs	III

EMPIRIC ANTIMICROBIAL THERAPY	- Typical meningococcal rash: benzylpenicillin 4 MiU iv/4h or ampicillin iv 2g/4h.	III
	- Without typical rash, age<50y: ceftriaxone 2g/12h or cefotaxime 2g/6h.	IV
	- If LP delayed without typical rash or patient coming from an area with penicillin resistant *S. pneumoniae*, add vancomycin 500 mg/6h or 1g/12h (or rifampin 600 mg/12h iv).	IV
	- For adults > 50y, without typical rash: consider addition of ampicillin 2g/4h to cephalosporins	IV
	If ß-lactam anaphylaxis: chloramphenicol iv 25 mg/kg/6h plus vancomycin. Add co-trimoxazole if > 50y.	IV
DOCUMENTED THERAPY	- If Gram (-) diplococci: benzylpenicillin 4 MiU iv/4h or ampicillin iv 2g/4h.	IV
Gram stain	- If Gram (+) diplococci: cephalosporins. Consider adding vancomycin (or rifampin) if patient deteriorates or comes from *S. pneumoniae* resistant area.	IV
	- If Gram (+) cocco-bacilli suggestive of *L. monocytogenes*: ampicillin 2g/4h + gentamicin 5 mg/kg/24h	IV
Culture	- *N. meningitidis*: benzylpenicillin 4 MiU iv/4h or ampicillin iv 2g/4h. (if anaphylaxis: chloramphenicol, WP). Duration: at least 5 days (III)	IV
	- *S. pneumoniae*: Peni S: benzylpenicillin 4 MiU iv/4h or ampi 2g/4h. Peni R but cephalosporin S: ceftriaxone 2g/12h or cefotaxime 2g/6h. Peni and cephalosporins R: cephalosporins + vancomycin + rifampin or cefotaxime 300 mg/kg/d (max.24g) with LP at 24-36h. Duration: 10-14 d.	IV WP+IV
	- *H. influenzae*: third generation cephalosporin, at least 10 days.	WP
	- *L. monocytogenes*: ampicillin 2g/4h + gentamicin 5 mg/kg/24h. Duration: 10-14d.	IV

(**Ia**: evidence from meta-analysis, **Ib**: evidence from at least 1 RCT, **IIa**: evidence from at least 1 well-designed controlled trial without randomisation, **IIb**: evidence from at least 1 other type of well-designed quasi-experimental study, **III**: evidence from well-designed non-experimental descriptive studies, **IV**: from expert committee reports or opinion/clinical experience of respected authorities, **WP**: opinion of this working party)

Conférence de consensus française (SPILF1) This consensus focused on BM in children and adults. They advocate an LP before the administration of AB if possible, but recommend blood culture and antibiotherapy before CT-scanning if the latter is required. Recommendations are based on Gram stain and culture. Recommendations are similar to the Scottish consensus except for the use of amoxicillin instead of ampicillin.

***S. pneumoniae* resistant to penicillin**: only case reports as well as in vitro and animal studies are available about the treatment of meningitis due to resistant *S. pneumoniae*. If the isolates are fully sensitive to third generation cephalosporins (MIC ≤ 0.5µg/ml), the latter are recommended. If no longer fully sensitive, the association of vancomycin + third generation cephalosporin (standard dosage) is advocated.
Some papers reported on a decreased penetration of vancomycin and ß-lactams in the CSF if dexamethasone is administered concomitantly in adult BM (human and animal models, Viladrich, Paris, Cabellos) but this was not reported in children. For this reason, the association with rifampin has been proposed if corticosteroids are prescribed with vancomycin + cephalosporins (Nau).
Meropenem has been proposed in case of intermediate or resistant strains to third generation cephalosporins, owing to the high bactericidal activity reported in vitro, but some authors reported failure of therapy in humans and animal models (Friedland, Fitoussi, Vandecasteele).
Another alternative is proposed in case of intermediate sensitivity of *S. pneumoniae* to third generation cephalosporins (0.5µg/ml < MIC < 2 µg/ml): a higher dosage of cefotaxime, 300 mg/kg/d div 6 doses (max.24g) (Viladrich), but some treatment failures are reported.
Some authors propose to control the spinal tap 48h after the start of antibiotics either systematically or in case of poor clinical evolution, particularly if dexamethasone was given.

C. Microbiological data

LITERATURE DATA

Epidemiology in USA (1995) (Schuchat)
Data collected from active, population-based surveillance for culture-confirmed meningitis and other invasive bacterial disease during 1995 in laboratories serving all the acute care hospitals in 22 counties of four States (total population: more than 10 million). The rates were compared with those of 1986 that were obtained by a similar surveillance.

Organisms	N° cases 1995	% of total 1995	Case fatality rate (%) 1995	Incidence (N/100,000) 1995	Incidence (N/100,000) 1986	% change
H. influenzae	18	7	6	0.2	2.9	- 94%
S. pneumoniae	117	47	21	1.1	1.1	+ 4%
N. meningitidis	62	25	3	0.6	0.9	- 33%
S. agalactiae	31	12	7	0.3	-	-
L. monocytogenes	20	8	15	0.2	-	-

Age specific incidence, 1995 (cases/100,000 population)

Age	*H. infl*	*S. pneumo.*	*N. mening.*	*S. agalactiae*	*L. monocyt.*
< 1 month	0	15.7	0	125	39.2
1-23 months	0.7	6.6	4.5	2.8	0
2-29 years	0.1	0.5	1.1	0.1	0.04
30-59 y	0.2	1	0.3	0.05	0.1
≥ 60 y	0.07	1.9	1.1	0.1	0.6

Age distribution of BM, 1986 versus 1995 (Number (%) of cases)

The number of cases of BM has decreased by 55% in 1995 versus 1986, except for adult patients: < 1 month -28%, 1-23 m. -87%, 2-18y. -41% versus > 18y. +10%.

Epidemiology in pediatrics, Seattle (Dawson)
806 cases (1 center) of BM in children, from 1981 to 1995. *S. agalactiae, E. coli and L. monocytogenes* were the most common in 87 neonatal cases. In childhood meningitis: *H. influenzae* type b, *S. pneumoniae* and *N. meningitidis* were the most common. *H. influenzae* was the most common until 1991 (73% from 1981 to 1985, 69% from 1986 to 1990, but 16% thereafter).

Epidemiology France (SPILF2)
Relative frequency of pathogen according to age (%). France, EPIBAC, 1996.

Pathogen	<1y (%)	1-2y	3-4y	5-14y	15-39y	40-64y	>64y	Incidence (N/100,000)
H. influenzae	6	8	25	12	4	12	1	0.14
N. meningitidis	25	49	34	62	41	6	5	0.5
L. monocytogenes	2	6	0	2	3	12	19	0.12
S. pneumoniae	28	37	41	24	51	70	72	0.88
S. agalactiae	39	0	0	0	2	1	3	0.22

Listeria monocytogenes
Schuchat, (1995) reported meningitis in 36% of all cases of invasive listeriosis (45% of cases of invasive listeriosis occurred in patients ≥ 60 y). Mylonakis concluded in a review of the literature that, outside pregnancy and the neonatal period, 36% of CNS listeriosis occurred in patients without underlying diseases and with a higher incidence before the age of 3 years and after the age of 45-50. In 42% there were no meningeal signs on admission. Gram stain of the CSF was negative in 2/3 of cases. One third of the patients had focal neurological signs. Overall mortality was 26% (higher if seizures or in those older than 65 y). He recommended ampicillin for a minimum of 15-21days (in association with an aminoglycoside for at least the first 7-10 d). Lorber reported that CNS infection with *L. monocytogenes* was often a meningo-encephalitis with altered consciousness and sometimes a parenchymal brain infection such as cerebritis or abscess. A CSF Gram stain was positive in about 40% and 2/3 of patients had bacteremia. No controlled trials have ever been carried out to determine the best choice of antibi-

otics or the optimal duration of therapy for listeria infection. Recommendations are based on data obtained from in vitro studies, animal models and clinical experience from a limited number of cases: in the absence of positive CSF Gram stain, it is recommended that the initial therapy for BM in all adults older than 50 should include either ampicillin or trimethoprim-sulfamethoxazole. On the basis of the synergy observed in vitro and in animal models, most authorities suggest the addition of gentamicin for the treatment of culture-proven *Listeria* meningitis (Gellin, Nieman, Cherubin, Winslow, Meyer). In case of intolerance to penicillin, trimethoprim-sulfamethoxazole is thought to be the best alternative single agent. Patients with *Listeria* meningitis should be treated for at least 3 weeks (rhombencephalitis or brain abscess: at least 6 weeks). Steroid therapy should probably be avoided since impairment of cellular immunity due to corticosteroid is a major risk factor for listeriosis.

BELGIAN MICROBIOLOGICAL DATA

Data From "Institut Scientifique de Santé Publique/Wetenschappelijk Instituut Volksgezondheid" based on microbiological analysis from reference laboratories.
These data indicate that BM in Belgium is more frequently caused by *N. meningitidis.*

N. meningitidis (2000) (IPH/EPI reports Nr. 2000)
During the seventies, there was an outbreak with an incidence of infection of 5/100,000 inhabitants per year, mainly due to serotype B. Thereafter, the situation became endemic with an incidence of 1 case per 100,000 inhabitants and per year.

In 2000, 267 strains were isolated from cases of meningitis or bacteremia, with an annual incidence of 2.6 cases/100,000. The serogroup B was predominant (64% of the strains versus 33% for the serogroup C). Among the 13 deaths (mortality 4.9%), 6 were ascribed to serogroup B and 7 to serogroup C.

In 2001, 380 strains were isolated from cases of meningitis or bacteremia (119 meningitis, 134 meningitis + bacteremia, 104 bacteremia and 23 unknown). The annual incidence (3.7/100,000) increased by 42% as compared with 2000. The incidence peaked in January and May 2001. The sex ratio (male/female) was 1.24. Children younger than 5 years and those between 15-18 years represented 40% and 18% of the affected population, respectively.
Serogroups were determined in 362 cases, and the serogroup C is now predominant (49% of the strains versus 47.5% for the serogroup B). The serogroup C is more often incriminated in adolescents and adults as 51% of the serogroup C cases and 34 % of the serogroup B cases were aged more than 15 years. Among the 27 reported deaths (mortality 7.1%), 3 were due to serogroup B, 22 to serogroup C and 2 to serogroup W135. The mortality rate is the highest in the group affected by the serogroup C (12,5%). Regarding the sensitivity to antibiotics: all strains remain sensitive to cefotaxime, ciprofloxacin and rifampin. Eight percent (30) of the strains showed a MIC to penicillin > 0.06 mg/ml (and <2 mg/ml) as compared to 2% in 1997 and 1998. This pattern of resistance seems to increase in parallel with the incidence of the serogroup C.

AGE	**0-11m**	**1-4y**	**5-9y**	**10-14y**	**15-19y**	**20-24y**	**25-44y**	**45-64y**	**≥ 65y**
N	(45)	(106)	(44)	(23)	(68)	(21)	(34)	(20)	(18)
(%)	11,9%	28%	11,6%	6,1%	17,9%	5,5%	9%	5,3%	4,7%

S. pneumoniae (2000-2001) (reference laboratory data, KUL, Leuven)

• During 2000, 102 laboratories sent 1220 *S. pneumoniae* strains: 77,8 % came from blood cultures and pleural sites. 54 strains (4,4%) were isolated from cerebrospinal fluid (main serotypes were: 6, 14, 9 and 19). During 2001, 99 laboratories sent 1434 strains and 80,6% of the pneumococci were isolated from blood and pleural sites. 46 strains came from cerebrospinal fluid (main serotypes -over 10% each - were 14,9,6,19 then 18,7,8,3).

Age distribution in *S. pneumoniae* BM:
2000: < 1 y: 15 cases, 1-4 y: 9, 5-9y: 2, 10-19y: 0, 20-50y: 9, > 50y: 18 (1 unknown). The age distribution was similar in 2001.

• Resistance to antibiotics:

Sites	**year**	**Resistance to Penicillin (%)**	**Resistance to Third generation cephalosporins (%)**
Blood + pleura	1998	9.9	
	1999	14.7	
	2000	15.2	4.8
	2001	12.9	0.3
Meningitis (n=54)	1998	12.5	
	1999	7.6	3.1
	2000	22.2	7.4
	2001	6.5	0
Otitis	1998	28.2	
	1999	29.3	
	2000	28.6	9.9
	2001	27.4	1.8

In 2000, no highly resistant strains to penicillin were found. Among the 7.4% cephalosporin resistant strains of *S. pneumoniae* that were isolated from CSF, only one had a MIC of 1.5 mg/l (fully resistant ≥ 2 mg/l). Regarding the MIC of meropenem, these strains were one or two dilutions more susceptible. In 2001, all strains isolated from the CSF had a 3G cephalosporin MIC < 0.5 mg/l and only 0.3% of the strains isolated from blood culture had a decreased susceptibility to 3G cephalosporins (0,5 < MIC ≤ 1,5 mg/l).

• For all 237 CSF isolates collected in Belgian hospitals between 1997 and 2000 (ICAAC abstract 01-A-36814-ASM): the 10 most common serogroups, representing 76% of the isolates, were 14,6,9,19,23,18,4,10, 8, and 12 in decreasing order of frequency. Thirty six percent of these strains were isolated in children < 5 years old. In this age group, the number of serogroups was more limited and 81.4% are included in the 7-valent conjugate vaccine. Reduced susceptibility to penicillin was observed in 12.6% with only 2.1% fully resistant ones (> 1 µg/ml). They belonged to the serogroups 14,23 and 21.

H. influenzae (1999)
There is a decrease in the incidence of severe, invasive (blood and/or CSF) infections since the beginning of the nineties: 133 cases in 1992 as compared to 72 in 1998 and 48 in 1999.

Site distribution (%) in 1999

Sites	Blood	CSF	Blood+CSF	Otitis	Others
< 5y (n=159)	2	0.6	-	96.6	0.8
> 5y (n=115)	30.4	2.6	-	60.9	6.1

Resistance to antibiotics: No specific data about meningitis, but for all sites together (1999, P. Demol, University Hospital of Liège, unpublished data) 16% of *H. influenzae* were ß-lactamase producers.

L. monocytogenes (2001) (ISP/WIV)
Fourty nine invasive infections were reported to the reference laboratory in 2001: 6 perinatal cases (mother or child), 7 meningo-encephalitis and 36 bacteremia. The highest incidence was reported in adults aged more than 60 years (33 cases) but 12 cases were reported in adults between 21 and 60 years. All strains were fully susceptible to ampicilline, gentamicine and trimethoprim-sulfamethoxazole.

II. STEROID THERAPY

A. Meta-analysis and RCTs

Five meta-analyses are available, with varying inclusion criteria and conclusions (Havens 1989, Geiman 1992, Yurkowski 1993, Prasad 1995, Mc Intyre1997):
-The meta-analysis of Havens did not show any benefit for the administration of steroid therapy, but the author included only 4 RCTs with 4 different types and dosages of steroids (children).
- The meta-analysis reported by Geiman and by Yurkowski (analysing administration of dexamethasone 0,6mg/kg/d div 4 doses for 4d) included the same studies except for one published in 1969. The evaluated RCTs used different antibiotic regimens but included only BM in children. The authors insisted on the variability of the definition of neurological sequelae and evaluation of hearing loss. Yurkowski showed a benefit from dexamethasone administration regarding all types of hearing loss mixed together. Geiman did not find any benefit regarding mortality and non-auditory sequelae but bilateral hearing loss was significantly reduced. In this population (n=463) 73% of BM-cases were due to *H. influenzae*.
- The meta-analysis of Prasad included 7 RCTs (n=1113) but evaluated meningitis in both children and adults without evidence of any benefit from steroids.
- The most thorough meta-analysis is Mc Intyre's report. He included 11 RCTs (n=848) from 1986 to 1996, that evaluated BM in children with the same regimen of dexamethasone (but only 4 studies with the same timing of administration). In 9 trials, the distribution of causative organisms was available: the proportion of *Hib* BM decreased from 80% in early studies to 50-58% in the later ones (522 Hib, 122 *S. pneumoniae*, 125 *N. meningitidis*). Effects on hearing loss: a significant difference in the incidence of severe hearing loss was found between organisms in the placebo population: 11.6% of 233 *Hib* and 19.6% of 56 *S. pneumoniae* versus 0% of 50 *N. meningitidis*. In *H. influenzae* BM: dexamethasone decreased significantly any hearing loss (regardless of the timing of administration before, with or after AB). In *S. pneumoniae* BM, the combined odds ratio for all available studies favored treatment,

but not significantly regarding severe hearing loss and with a considerable heterogeneity among studies. In studies in which dexamethasone was administered early, a significant protective effect was seen, but this result is affected by the exclusion of one study. No effect was found when any hearing loss was evaluated. Effects on other neurological sequelae: pooled results of all studies suggested protection but were not statistically significant (if one study with very late administration of dexamethasone is excluded, protection became significant, suggesting the importance of the timing of administration of dexamethasone). Data on specific organisms (6 studies): no significant results when *Hib* and *S. pneumoniae* were considered separately.
The data on age distribution were often unavailable, so the influence of age could not be assessed. Complications: a trend to a higher rate of GI bleeding was found for those treated with 2 to 4 days of dexamethasone (0.8% vs 2.3%), but this was significant only if 4 days of dexamethasone was compared to the placebo group (0.4%).

Since the meta-analysis of McIntyre, 4 RCTs have been published (after 1996):
- In the study of Qazi (n=89 children, Pakistan): a trend towards a higher mortality rate was found in the dexamethasone group but the population was characterized by a high rate of culture negative CSF (55%), a high rate of AB treatment before admission (48%) and a delayed presentation (42% more than 4d after the onset of symptoms).
- Thomas published an RCT including adult patients (n=60) that demonstrated no advantage for dexamethasone (within 3 h after AB), but the two groups were not comparable (patients sicker and older in the placebo group).
- Gupta also included only adult patients to evaluate dexamethasone 8mg/6h for 7 days in BM without significant difference between the two groups.
- Finally, Syrogiannopoulos reported an RCT comparing a 2d versus a 4d regimen of dexamethasone (before AB) in childhood BM (n=113, Greece). BM was due to *N. meningitidis* in 50% and *H. influenzae* in 40% of cases. No difference was found between the two groups. The author concluded that a 2 day-regimen was as effective as a 4 day-one. This has to be taken with caution considering the low rate of sequelae in *N. meningitidis* BM and the decreasing incidence of *H. influenzae*, most sequelae being reported in *S. pneumoniae* which is the least evaluated in this report. The rate of complications, including GI bleeding, was similar.

A protocol is ongoing in the Cochrane library (issue 4, 2000 Beek, van de Gans, Mc Intyre, Prasad) to determine whether adjuvant corticosteroid therapy in BM reduces the proportion of patients with hearing loss or neurological deficits, decreases mortality and has significant adverse events.

B. Other types of publications

Conférence de consensus française (SPILF1) This consensus recommended that steroids be given before antibiotics in purulent BM in children: dexamethasone 0,6 mg/kg/d divided in 2 or 4 doses during 2 (or 4 d).
Scottish consensus on acute BM in immunocompetent adults (Beggs) Dexamethasone 4-6 mg 6-hourly (no duration proposed) shortly before or simultaneously with AB in case of impaired level of consciousness, focal neurological signs, markedly raised opening pressure or cerebral oedema (CT).
The single report on the use of dexamethasone (before AB) in neonatal BM is the Daoud prospective non randomized trial. No difference was found. GNB were the main pathogens (no *H. influenzae*).
In vitro studies: There is a possibility of a diminished efficacy of antibiotic therapy in adult patients (vancomycin, third generation cephalosporins) with concomittant administration of dexamethasone in case of penicillin-resistant *S. pneumoniae*. (Cabellos)

III. ANTIBIOTIC PROPHYLAXIS

Temporary nasopharyngeal carriage is a characteristic of meningococci, pneumococci and *Hib*. Chemoprophylaxis is used to eradicate nasopharyngeal (NP) carriage of bacteria in close contacts of the index patient and thus to prevent the development of disease. Pneumococci also have the potential to spread through close contact but there are no data to recommend a chemoprophylaxis for close contacts of the index case with *S. pneumoniae* meningitis. Only 3 studies have been carried out in an epidemic context of *N. meningitidis* BM.

A. Meta-analysis and RCTs

No meta-analysis is available. Twelve RCTs were published and half of them suffered from significant flaws in their methodology. Only one showed the prevention of secondary cases of *Hib* severe disease in children younger than 4 years of age with rifampin compared to placebo (Band). For the other studies, the number of secondary cases was low (or nul) and thus prevention of secondary cases cannot be used as a criteria for efficacy. Eradication of naso-pharyngeal carriage was the primary end-point in all these studies. The population that was analyzed in these studies included most often children and adults.

Eradication of carriage of *N. meningitidis*

Two studies analyzed the effect of different regimens on meningococci nasopharyngeal carriage out of context of contact with an index case (Girgis, Dowd). The first showed a similar eradication rate (93%/95%) between azithromycin 500 mg 1 dose and rifampin 600 mg bid for 2 days in female students (> 18-years old). The other one reported a poor efficiency in eradication of meningococci with penicillin and ampicillin, although ampicillin was better than penicillin.
The 3 other studies evaluated chemoprophylaxis of household contacts of an index case with BM. Cuevas compared ciprofloxacin 15 mg/kg 1 single dose (>18y: 750 mg) versus rifampin 10 mg/kg bid for 2 days in children older than 2 years and in adults: the rate of eradication was similar at day 7 and 14 (91%/ 97%) and tolerance was comparable. Schwartz compared rifampin 10 mg/kg bid for 2 days versus ceftriaxone IM (125mg < 15y, 250 mg > 15y): the rate of eradication was higher in the ceftriaxone group at day 6 (97%/75%) and at day 14 (97%/81%). In this study, compliance with rifampin was not assessed and too few contacts were enrolled in the rifampin group (41 versus 71). Munford compared 4 groups: sulfadiazine versus rifampin versus minocycline versus rifampin+ minocycline, demonstrating that rifampin alone and rifampin+minocycline were better than sulfadiazine, but with a poor tolerance to the antibiotic association. This study reported the emergence of resistant *N. meningitidis* strains after rifampin exposure.

Eradication of carriage of *Hib*

All studies were done in context of contact with an index case with invasive *Hib* disease. The study of Cox was excluded since only a low number of carriers were evaluated. Compared with placebo, rifampin was clearly shown more efficient in the eradication of carriage, in the studies of Glode, Band, Murphy and Daum. Glode compared rifampin 20 mg/kg od versus 10 mg/kg bid for 4 days versus placebo. Both rifampin groups were better than placebo, but fewer patients were included in the 10 mg/kg bid group to be compared with the 20 mg/kg od group (one rifampin resistant strain post-exposure). Band reported the protection of secondary cases with rifampin 20 mg/kg od for 4 days in the group of children younger than 4 years and a higher eradication rate (97% vs 28%) compared with placebo. No post-treatment resistant strain was found. Murphy reported a higher rate of eradication with rifampin 20 mg/kg od for 4 days (max. 600 mg daily, children) versus placebo, but with a higher efficacy in children older than 5 years. Emergence of one resistant strain was reported. Daum reported a significantly

higher eradication rate with rifampin 10 mg/kg bid for 2 days versus placebo, but when stratified by age, this was no longer significant in the group of children younger than 5 years, without report of post-exposure resistant strains.
Daum2 compared rifampin 10mg/kg bid with rifampin plus trimethoprim 2.67mg/kg bid for 2 days, without difference, without emergence of resistant strains but with a higher eradication rate in children older than 5 years. Green compared rifampin 20 mg/kg once a day (maximum 600 mg/day) for 2 days versus 4 days without difference, but the number of carriers wasn't sufficient to reach significance. Siblings <12years showed a higher rate of carriage and one case of Hib persistance with a rifampin resistant strain was reported.

B. Other types of publications

Scottish consensus on acute BM in immunocompetent adults (Beggs)

Patients prophylaxis: all patients with meningococcal infection, not treated by third generation cephalosporin: rifampin 600 mg/12h po 4 doses or ciprofloxacin po 500 mg 1 dose (IIb).
Contacts prophylaxis: *N. meningitidis*: Contacts of cases caused by a vaccine preventable serogroup (A,C) should be offered vaccination (WP). Adults and children, close contacts: rifampin 600 mg/12h (Children: 10 mg/kg/12h < 12y, 5mg/kg/12h < 11 months) 4 doses (IV) or ciprofloxacin 500 mg 1 dose (adults and children > 12y) (IV) or ceftriaxone 250 mg IM 1 dose (125 mg iv 1 dose if < 12y) (IV).
H. influenzae: if children below 48 months among household contacts who are not or incompletely vaccinated, then all home contacts should receive rifampin 20 mg/kg/24h for 4 d and any unvaccinated child should be vaccinated (WP).

Gaunt, Halstensen: 2 non-randomized, controlled studies have been reported, analyzing the rate of eradication of *N. meningitidis* with fluoroquinolones in adult carriers. Gaunt used 500 mg of ciprofloxacin 1 single dose and Halstensen 400 mg of ofloxacin, showing a high rate (> 90%) of eradication at d30 without emergence of resistance.

Judson: reported the eradication of all *N. meningitidis* carriers with 125 mg of ceftriaxone IM in a controlled study.

Reports from Eskola, Munford, Ward and Zangwill showed that up to 33% of secondary cases of meningococcal disease develop within 2-5 d after the presentation of the index case. Spread within a week is described in *Hib* and pneumococcal disease. Thus, chemoprophylaxis has to be prescribed rapidly after the diagnosis of the index case and vaccination is not a substitute to chemoprophylaxis.

Allen reported that the secondary attack rate of meningococcal disease is around 2-4/1000 without chemoprophylaxis (rates of secondary attack during epidemics have been reported as high as 59/1000). This rate is a thousand-fold higher than the overall rate of meningococcal disease in the general population. Regarding invasive Hib disease, Cochi and Ward showed that there is a 1% risk of secondary disease during two months for the day care contacts - 25 times higher than the expected rate of primary Hib disease in the same age group- and the risk for young siblings (< 5 y.) may be increased as high as 500-fold.

CDC meningococcal group, De Wals, Sivonen demonstrated that close household contacts (or in day care centers or in closed populations such as military recruits) of the index case are at much higher risk. This is a major reason for attempting chemoprophylaxis in these contacts.

Different definitions of close contacts have been published, including criteria used in randomized studies. A simple one has been outlined by Kaiser: "close contacts are individuals who frequently sleep and eat in the same dwelling with the index case". A schoolmate is not a close contact, not even if the students share the same classroom, unless they sat close to each other (Jacobson, Feigin). A boy or girlfriend should receive prophylaxis.

Hospital personnel are not at special risk unless they participated in a mouth to mouth resuscitation or were otherwise exposed to the patients secretions. (Salmi)

Naso-pharyngeal swabs are not indicated to identify patients at special risk: a positive culture gives no information as to when the agent was contracted since colonization with meningococci and *Hib* may persist for months. (Greenfield, Turk)

No data support chemoprophylaxis in case of pneumococcal meningitis.

Whatever the drug chosen, chemoprophylaxis will probably not prevent incubating disease and is never a substitute for close surveillance.

6. Recommendations

ANTIBIOTIC TREATMENT

ADULTS (RCTs in adults + extrapolated data from RCTs in children)

1. Empiric antibiotic therapy: Third generation cephalosporins (cefotaxime or ceftriaxone) are now the drugs of choice for BM considering the resistance of *S. pneumoniae* to penicillins and the side effects of chloramphenicol (B: extrapolated from 1+/++ children RCTs). Ampicillin should be added in patients > 45-50 yrs (higher risk of *L. monocytogenes* BM) (3, D), particularly in the absence of a characteristic rash and in the presence of a subacute evolution, signs of meningo-encephalitis, focal neurological findings or some other risk factors (3, D).
Recommended doses: cefotaxime 200 mg/kg/d div 4-6 doses (max 12g) or ceftriaxone 80-100mg/kg/d div 2 doses (max. 4g/d). Ampicillin 200-300 mg/kg/d div 6 doses (max. 12g) (3, D). If the patient comes from an area with a high incidence of penicillin resistant *S. pneumoniae*, vancomycin should be added to the 3G cephalosporin (3,D) (cfr. below) or meropenem should be considered (6g/d div 3doses) (3, D). In case of life-threatening IgE-mediated penicillin allergy, vancomycin plus aztreonam may be proposed (4,D), associated with trimethoprim-sulfamethoxazole -10mg/kg/d of the trimethoprim component div 2-3 doses- if the coverage of *L. monocytogenes* is indicated (3,D).

2. Pathogen specific antibiotic therapy:
N. meningitidis: Penicillin 24 MiU/d div 6 doses or ampicillin 200-300 mg/kg/d div 6 doses (max. 12g) (or third generation cephalosporin cefotaxime 200 mg/kg/d div 4-6 doses (max 12g) or ceftriaxone 80-100mg/kg/d div 2 doses (max. 4g/d) (extrapolated data from children RCTs 1+/++, B)).
Duration of therapy: standard duration of treatment is 7 days for penicillin, ampicillin and 3G cephalosporins (3, D). With 3G cephalosporins, 4-5 days have been reported equally effective in children with rapid clinical improvement (extrapolated data from children RCTs 3, D).

S. pneumoniae: wait for the determination of the MIC to penicillin and third generation cephalosporins before adjustment of treatment (3,D).
- **MIC penicillin <0.1µg/ml**: penicillin 24MiU/d (0,25 MiU/kg/d) div 6 doses (extrapolated from children RCTs 1+/++, B).
- **MIC penicillin ≥ 0.1µg/ml**: adjust the treatment according to the cephalosporin MIC:
MIC cephalo < 0.5µg/ml: cefotaxime 200 mg/kg/d div 4-6 doses (max 12g) or ceftriaxone 80-100 mg/kg/d div 2 doses (max. 4g/d)(extrapolated from children RCTs 1+/++, B).
MIC cephalo ≥ 0.5µg/ml: meropenem 6g/d div 3 doses or vancomycin 2g/d div 2-4 doses + cefotaxime or ceftriaxone standard dosage (3,D). Some experts propose as possible alternative for MIC **cephalosporin ≥ 0.5µg/ml but <2µg/ml**: cefotaxime 18-24g/d (300mg/kg) div 6 doses (3, D). In cephalosporin resistant strains, some experts suggest adding rifampin 1200 mg/d div 2 doses to the association vancomycin+cephalosporin, because of the low rate of penetration of vancomycin in the CSF, especially if corticosteroids are administered (4,D). A control of the spinal tab has to be done within 24-48 hours in case of poor clinical evolution and/or a resistant strain of *S. pneumoniae* (4.D).

Duration of treatment: in sensitive strains: 10-14 d is the standard duration of treatment for penicillin, ampicillin and 3G cephalosporins (3,D). With 3G cephalosporins, 7 days has been reported as effective as 14 d in children without persistent signs of infection and fully sensitive strains (extrapolated from children RCTs 3, D). No data are available for infection with resistant strains: a standard duration (10-14 days) should be recommended in these cases.

H. influenzae:
ß-lactamase (-): ampicillin 12g/d div 6 doses or cefotaxime 200mg/kg/d div 4-6 doses (max.12g/d) or ceftriaxone 80-100 mg/kg/d div 2 doses (max. 4g/d) (extrapolated from children RCTs 1+/++, B) (Studies in children showed a trend to a more rapid sterilization with cephalosporins but without clinical correlation with death or sequelae).
ß-lactamase (+): third generation cephalosporins (extrapolated from children RCTs 1+/++, B).
Duration: 7-10d is the standard for ampicillin or third generation cephalosporins (3, D). With 3G cephalosporins, 6 days have been reported as effective as 12d in children with rapid improvement (extrapolated from children RCTs 3, D).

L. monocytogenes: No RCT available. Ampicillin 12g/d div 6 doses (or penicillin 18-24Miu/d div 6 doses) ± gentamicin 5mg/kg/d div 3 doses (treatment with both drugs at least initially until improvement 4,D) or trimethoprim-sulfamethoxazole 10mg/kg/d (of the trimethoprim component) div 2-3 doses (3,D). Duration of therapy: 21d if meningitis or longer if rhombencephalitis/brain abscess (6 weeks) (3,D).

CHILDREN

Due to reported cases of bacterial resistance (no data available in Belgium) and the side effects of chloramphenicol, this drug is no longer recommended in Belgium as alternatives are available.

Children < 3 months: Thirteen studies included only a minority of children of less than 3 months. Only one study included neonates < 1 week. In this age group, main pathogens are: *group B streptococci, E. coli, L. monocytogenes*, *S. pneumoniae* and *N. meningitidis*. (de Louvois, Bell, SPILF1).
Empiric therapy: third generation cephalosporin + ampicillin (3,D). During the first month of life, ceftriaxone is not recommended due to the risk of hyperbilirubinemia and biliary sludge. Nosocomial organisms have to be considered in infants that spent a few days in the ICU, but this is not regarded as a community-acquired bacterial meningitis.
Documented therapy:
E. coli: third generation cephalosporin. Duration: 21d. (3,D)
S. agalactiae: penicillin + gentamicin for the first 72h. Duration: 15-21d. (3,D)
L. monocytogenes: ampicillin + gentamicin. Duration: 21d. (3,D)
S. pneumoniae: cfr.below. Duration: 10-14days (3,D).

Antibiotic	Posology: 1 week > children < 1 month (weight>2kg)	Posology: children> 1 month
Ampicillin	200mg/kg/d div 4 doses	200mg/kg/d div 4 doses (max. 8g)
Cefotaxime	200mg/kg/d div 4 doses	200mg/kg/d div 4 doses (max. 10g)
Ceftriaxone	Not indicated before one month	100 mg/kg/d div 1-2 doses (max. 4g)
Meropenem	120 mg/kg/d div 3 doses but very few data available. The manufacturer recommends the use of meropenem after 3 months of age.	120 mg/kg/d div 3 doses (max. 6g)
Penicillin G	200.000 U/kg/d div 6 doses	400.000 U/kg/d div 6 doses (max. 20 MiU)
Vancomycin	45 mg/kg/d div 3 doses	60 mg/kg/d div 4 doses (max. 2g)
Gentamicin	7,5 mg/kg/d div 3 doses	7,5 mg/kg/d div 1 or 3 doses
Amikacin	30mg/kg/d div 3 doses	20mg/kg/d div 1-2 doses

Children 3 months to 18 years

Empiric therapy: third generation cephalosporins: cefotaxime 200 mg/kg/d div 4-6 doses (max 12g) or ceftriaxone 80-100 mg/kg/d in 1 or 2 doses (max. 4g/d). (1++, A).

Documented therapy:
N. meningitidis: penicillin 0,25 MiU/kg/d div 6 doses or ampicillin 200 mg/kg/d div 4 doses (or third generation cephalosporin)(1++, A). Duration of therapy: standard treatment is 7d for penicillin, ampicillin and third generation cephalosporins (3, D). With third generation cephalosporins 4-5 days have been reported equally effective in children with rapid clinical improvement (3, D).

S. pneumoniae: wait for the determination of the MIC to penicillin and third generation cephalosporins before adjustment of treatment (3,D).
- **MIC penicillin < 0.1µg/ml**: penicillin 0,25 MiU/kg/d div 6 doses (1+/++, A).
- **MIC penicillin ≥ 0.1µg/ml**: adjust the treatment according to the cephalosporin MIC:
MIC cephalo < 0.5µg/ml: cefotaxime 200 mg/kg/d div 4 doses (max 12g) or ceftriaxone 80-100 mg/kg/d in one or 2 doses (max. 4g/d)(1+/++, A).
MIC cephalo ≥ 0.5µg/ml: vancomycin 60mg/kg/d div 4 doses + cefotaxime or ceftriaxone standard dosage (3,D) or meropenem 120mg/kg/d div 3 doses (max. 6g/d). Some experts propose as possible alternative for MIC **cephalosporin ≥ 0.5µg/ml but <2µg/ml**: cefotaxime 300mg/kg/d (max. 24 g/d) div 6 doses (3, D). In cephalosporin resistant strains, some experts suggest adding rifampin 10-20 mg/kg/d (max. 1200 mg) div 2-4 doses to the association vancomycin+cephalosporin, because of the low rate of penetration of vancomycin in the CSF, especially if corticosteroids are administered (4,D). A control of the spinal tab has to be done within the first days in case of poor clinical evolution and/or a resistant strain of *S. pneumoniae* (4,D).
Duration of treatment: in sensitive strains, 10-14 d is the standard treatment for penicillin, ampicillin and 3G-cephalosporins (3,D) With third generation cephalosporins, 7 days has been reported as effective as 14 d in children without persistent signs of infection and fully sensitive strains (3,D). No data are available for infection with resistant strains: standard duration 10-14d in these cases.

H. influenzae:
ß-lactamase (-): ampicillin or 3G cephalosporins (trend to a more rapid sterilization with cephalosporins but without clinical correlation with death or sequelae) (1+, A).
ß-lactamase (+): third generation cephalosporins (1+, A).
Duration: 7-10d is the standard for ampicillin or third generation cephalosporins (3, D). 6d of 3G cephalosporins has been reported as efficient as 12d in children with rapid improvement (3, D).

STEROID THERAPY

ADULTS: No conclusive data are available on the benefits of dexamethasone in adult BM.
A study published very recently had as main conclusion that early dexamethasone treatment improves outcome in adults with acute bacterial meningitis. Since the year of publication was 2002, it was not included in the present review. {Early dexamethasone treatment in adults with acute bacterial meningitis (cloudy CSF, positive Gram staining or CSF leucocyte count more than 1000 per cubic millimeter) was evaluated in a randomized, double-blind, placebo-controlled, multicenter trial: 10 mg of dexamethasone was administered before or with the first dose of antibiotic and was given every 6 hours for 4 days. A total of 301 patients were evaluated. Treatment with dexamethasone was associated with a reduction of unfavorable outcome (risk ratio 0,59, p=0,03), especially in the subgroup of *S. pneumoniae* meningitis (risk ratio 0,50, p=0,006) and without an increased risk of gastro-intestinal bleeding (de Gans).}

CHILDREN: No conclusive data are available on the benefits of dexamethasone therapy in the neonatal period. In older children, the benefit of dexamethasone was established only in case of *Hib* meningitis.
For those children who are not vaccinated against *Hib*, dexamethasone 0,6 mg/kg/d div 4 doses for 2 days (2+, B) (before the first dose of AB) is recommended (2+, B).
In other cases, no clear data are available on the benefit of dexamethasone and its use has to be balanced with the possible risk of GI bleeding. Nevertheless, if dexamethasone is considered it has to be given before administration of the antibiotics and for 4 days (4,D). (Not sufficient data to support 2 days of therapy in BM other than those due to *H. influenzae*).

Remarks: A recent systematic review of adjuvant corticosteroid therapy (18 studies, 1853 patients) was performed and the authors concluded that adjuvant corticosteroids were beneficial in the treatment of children, reducing severe hearing loss in bacterial meningitis caused by *Haemophilus influenzae* as well as meningitis with other species. In adults, there was a reduction in case-fatality, however data were scarse. Adverse events were not significantly increased (van de Beeck). Since it was only an abstract presented at the 42nd ICAAC 2002, it was not included in the present review.

ANTIBIOTIC PROPHYLAXIS

Recommendations on antibiotic prophylaxis are mainly based on the higher rate of secondary cases in close contacts of an index case and on the efficacy of prophylaxis on eradication of the naso-pharyngeal carriage (*N. meningitidis* and *H. influenzae*). Only one RCT showed a benefit for prevention of secondary disease with rifampin in case of *Hib* invasive disease. Thus, except in case of prophylaxis of *Hib* meningitis with rifampin, the grade of recommendation has to be considered D.
Eradication of index case: Considering the low rate of NP eradication with the penicillins, the index patient treated with penicillin or ampicillin, without any 3G cephalosporins, should receive prophylaxis before discharge (4,D).

N. meningitidis

- Prophylaxis has to be given within 24-48h after the diagnosis of the index case (3,D).
- Which contacts: for all close and prolonged contacts
  1. Household contacts.
  2. Contacts outside the home: higher risk may be defined as frequently sleeping and eating in the same dwelling/room as the index case, or in schools, students who sat near the index. Another definition frequently used: contact spending 4 hours or more per day with the index during 5 of the 7 days before the hospitalization of the index case (3,D).
     Practically:
     - girl- or boyfriends,
     - close contacts in a child care home, educational stays and any type of dormitories.
     - distinction is made between children before primary school and children in primary schools and older (regarding the risk of transmission) (3,D):
     - prophylaxis is recommended for all children of the same section in a day nursery (crèche) and all children of the same class in a nursery school or special teaching school.
     - from primary school onwards, only children with close contacts or who sat near the index are concerned by this prophylaxis. If a second case of *N. meningitidis* meningitis is documented in the class within the month, prophylaxis will be given to all children of the class.

3. Health care workers: no indication unless direct exposition to respiratory droplets: Persons who, during the first 48hours of the acute phase have had unprotected airway exposure to respiratory droplets generated from coughing or during airway management, mouth to mouth resuscitation, tracheal intubation or suctioning.

- Recommended antibiotic:

Adults: - Ciprofloxacin 500 mg or ofloxacin 400 mg one single dose (3,D) or
- Rifampin 600 mg bid for 2 days (3,D)! drug interactions (notably, with oral contraceptives)
[Considering the very few data available on azithromycin, it has to be reserved in case of intolerance/contraindication to the above mentioned antibiotics: azithromycin 500 mg one single dose (4,D)].

Pregnant or lactating women: Ceftriaxone IM 250 mg one single dose (3,D) or
Azithromycin 500 mg one single dose (4,D)

Children: - Rifampin 10 mg/kg bid (5mg/kg < 1 month) for 2 days (3,D) or
- Ciprofloxacin 15 mg/kg one single dose (children > 5 years) (3,D). (Ciprofloxacin has been administered to children > 2 years in the study of Cuevas, but in Belgium, the scientific insert limits the prescription to children above 5 years of age)
[Considering the very few data available on azithromycin, it has to be reserved in case of intolerance/contraindication to the above mentioned antibiotics: azithromycin 10 mg/kg one single dose (4,D). (to prescribe a syrup: Rifampin 2gm + agar-agar 5gm + raspberry syrup ad 100 ml for a final concentration of 100 mg rifampin/5 ml of syrup)].

H. influenzae type b

- Prophylaxis has to be given within the week after the diagnosis of the index case (3,D).
- Which contacts:

1. Household contacts: Considering the fact that invasive infection threatens non vaccinated-infants, mainly younger than 4-5 years, and that carriage is mainly demonstrated in young siblings, prophylaxis has to be given if at least one child less than 4 years old, non vaccinated or incompletely vaccinated, is included in the household (extrapolated 1+, B).
2. Child care facilities: In the presence of a single case of meningitis and if facility attended by unvaccinated or incompletely vaccinated children below 2 years, consider prophylaxis of all the children and personnel. (4,D). If all contacts > 2 years: no prophylaxis, regardless of the vaccination status. With ≥ 2 cases of meningitis within 2 months: and if facility attended by unvaccinated or incompletely vaccinated children: prophylaxis recommended for all children and personnel. (4,D)

- Recommended antibiotics:

Adults: Rifampin 600 mg od for 4 days (extrapolated1+, B)

Children: Rifampin 20 mg/kg once a day for 4 days (maximum 600 mg/day) (extrapolated 1+, B)
(Ceftriaxone IM 250 mg one single dose should be used alternatively, in case of rifampin contraindication (4,D))

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8. Table of evidence and critical appraisal of RCTs

The table of evidence and critical appraisal of the randomized controlled studies included for analysis are available on the BAPCOC website ***(www.health.fgov.be/antibiotics)***.

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10. Levels of evidence and grades of recommendations according to the revised SIGN grading system

LEVELS OF EVIDENCE

1++	High quality meta analysis, sytematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta analysis, systematic reviews, or RCTs with a low risk of bias
1-	Meta analysis, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATIONS

A

A least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B

A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 1++ or 1+

C

A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; *or*

Extrapolated evidence from studies rated as 2++

D

Evidence level 3 or 4; *or*

Extrapolated evidence from studies rated as 2+

11. Guidelines

ADULTS

Grade of recommendation is given according to the type of molecule. Regarding the dosage of antibiotics, no comparison available thus level of evidence 3, grade D

EMPIRIC THERAPY	Cefotaxime 12g/d div 4-6 doses or ceftriaxone 4g/d div 2 doses	B
	Add ampicillin 12g/d div 6 doses in patients > 50y or if subacute evolution, meningo-encephalitis, focal neurological signs (without characteristic rash) or some risk factors.	D
	In patients coming from an area with resistant *S. pneumoniae,* consider the addition of vancomycin to third generation cephalosporins or treatment with meropenem 6g/d div 3 doses.	D
DOCUMENTED THERAPY	***N. meningitidis:*** Penicillin 24MiU/d div 6 doses or ampicillin 12g/d div 6 doses or cefotaxime 12g/d div 4-6 doses or ceftriaxone 4g/d div 2 doses.	B
	Duration: standard duration for ampicillin or penicillin or 3G cephalosporins is 7 days. If cephalosporins and rapid improvement 4-5d could be proposed.	D
	S. pneumoniae:	
	Penicillin S (MIC<0.1µg/ml): penicillin 24 MiU/d div 6 doses.	B
	Penicillin I or R (MIC ≥ 0.1µg/ml: adjust the treatment according to the MIC of the third generation **cephalosporins.**	D
	MIC < 0.5µg/ml: cefotaxime 12g/d div 4-6 doses or ceftriaxone 4g/d div 2 doses.	
	MIC ≥ 0.5µg/ml: vancomycin 2g/d div 4 doses + cefotaxime or	D
	ceftriaxone (standard dosage) or meropenem 6g/d div 3 doses.	D
	Consider the addition of rifampin with this last association, particularly if steroids are administered.	D
	Control the spinal tab within 2 days of therapy in case of poor clinical evolution and/or resistant strain.	D
	Duration: standard therapy of penicillin, ampicillin or cephalosporins 10-14d. If rapid improvement, sensitive strains and cephalosporins 7d could be proposed.	D
	H. influenzae: third generation cephalosporins or ampicillin (only in sensitive strains).	B
	Duration: standard duration of ampicillin or cephalosporins: 7-10d. If rapid improvement and cephalosporin therapy, 6 d could be proposed.	D D
	L. monocytogenes: ampicillin 12g/d div 6 doses ± gentamicin	D

	5 mg/kg/d div 1-3 dose(s) or trimethoprim-sulfamethoxazole 10mg/kg/d (trimethoprim dose) div 2-3 doses. Duration: at least 3 weeks in case of meningitis, 6 weeks in case of rhombencephalitis or brain abscess.	D
CORTICO-STEROIDS	No conclusive data from systematic review. (A recent study shows beneficial effect in cases with signs of bacterial meningitis such as cloudy CSF, positive Gram's staining or CSF leucocyte count more than 1000 per cubic millimeter, mainly due to *S. pneumoniae*) If administered in case of suspected bacterial meningitis, it has to be done before or with the first dose of antibiotic and at 10 mg (dexamethasone) every 6 hours for 4 days	C
ANTIBIOTIC PROPHYLAXIS	***N. meningitidis***: prophylaxis has to be given within 24-48h of diagnosis of the index case, to the household or close contacts (contact spending 4 hours or more per day with the index during 5 of the 7 days before the hospitalization of the index case).	D
	- Health care-workers: Persons who, during the first 48hours of the acute phase have had unprotected airway exposure to respiratory droplets of the index case during airway management, mouth to mouth resuscitation, tracheal intubation or suctioning	D
	- Adult antibiotic prophylaxis: ciprofloxacin 500 mg 1 single dose or ofloxacine 400 mg 1 single dose or rifampin 600 mg bid for 2 days.	D
	- Pregnant/lactating woman: ceftriaxone 250 mg IM 1 single dose.	D
	- Considering the very few data available on azithromycin, it should be reserved in case of intolerance/contraindication to the other drugs: azithromycin 500 mg 1 single dose	D
	H. influenzae: prophylaxis has to be given within one week after diagnosis of the index case.	D
	- to the household contacts if there is at least one child less than 4 years, not or incompletely vaccinated, among the household members.	B
	- In a child care facility: * single case of BM: if attended by non-vaccinated or incompletely vaccinated children < 2 years, consider prophylaxis of all the children and staff. If all contacts > 2 years: no prophylaxis. * ≥ 2 cases of BM within 2 months: and if facility attended by non-vaccinated or incompletely vaccinated children, prophylaxis recommended to all children and staff.	D
	- Antibiotic prophylaxis: rifampin 600 mg od for 4 days (ceftriaxone 250 mg IM one single dose if rifampin contraindication)	B

CHILDREN

Grade of recommendation is given according to the type of molecule. Regarding the dosage of antibiotics, no comparison available thus level of evidence 3, grade D

EMPIRIC THERAPY	Cefotaxime 200mg/kg/d (max. 12g/d) div 4 doses or ceftriaxone 80-100mg/kg/d (max. 4g/d) div 2 doses	A
	Children < 3 months: add ampicillin 200 mg/kg/d div 4 doses.	D
DOCUMENTED THERAPY	***N. meningitidis:*** penicillin 0,25MiU/kg/d div 6 doses or ampicillin 200 mg/kg/d div 4 doses (or third generation cephalosporin). Duration: standard duration for ampicillin or penicillin or third generation cephalosporins: 7 days. If cephalosporins and rapid improvement 4-5d could be proposed.	A D D
	S. pneumoniae: **Penicillin S (MIC<0.1µg/ml)**: Penicillin 0,25 MiU/kg/d div 6 doses. **Penicillin I or R (MIC ≥ 0.1µg/ml)**: adjust the treatment according to the third generation cephalosporins MIC. **MIC < 0.5µg/ml**: third generation cephalosporins. **MIC ≥ 0.5µg/ml**: vancomycin 60mg/kg/d div 4 doses + third generation cephalosporins (standard dosage) or meropenem 120mg/kg/d div 3 doses (max.6g/d). Control the spinal tab within the first days of therapy in case of poor clinical evolution and resistant strain. Duration: standard therapy of penicillin, ampicillin or cephalosporins 10-14d. If rapid improvement, sensitive strains and third generation cephalosporins 7d could be proposed.	A D A D D D D D
	Type b *H. influenzae (Hib)*: third generation cephalosporins or ampicillin (only in susceptible strains). Duration: standard duration of ampicillin or cephalosporins: 7-10d. If rapid improvement and cephalosporin therapy, 6 d could be proposed.	A D
	L. monocytogenes: ampicillin 200mg/kg/d div 4 doses + gentamicin 3-5 mg/kg/d div 1-3 dose(s) or trimethoprim-sulfamethoxazole 10mg/kg/d (trimethoprim dose, max. 600 mg, not indicated in children < 6 weeks) div 2-3 doses. Duration: at least 3 weeks in case of meningitis, 6 weeks in case of rhombencephalitis or brain abscess	D D
	E.coli: third generation cephalosporins for 3 weeks.	D
	S. agalactiae: penicillin for 15-21d + gentamicin for the first 72h.	D

CORTICO-STEROIDS	No benefit demonstrated in the neonatal period. Outside the neonatal period: - Dexamethasone 0,6 mg/kg/d in 4 doses has to be administered in case of acute bacterial meningitis in non or incompletely vaccinated children for *Hib*. If Hib meningitis is established, 2 days of dexamethasone is enough. - *Hib* vaccinated children: No conclusive data are available in case of acute bacterial meningitis due to other pathogens. Considering the possible efficacy in case of *S. pneumoniae* BM, dexamethasone could nevertheless be administered at 0,6mg/kg/d in 4 doses. If *S. pneumoniae* BM is established, 4 days is the standard duration of treatment as there are no data on a 2 day course of dexamethasone in BM due to this pathogen.	D D B D D
ANTIBIOTIC PROPHYLAXIS	***N. meningitidis**:* prophylaxis has to be given within 24-48h of diagnosis of the index case. - Who: • household contacts • index case in a day nursery or nursery school: all children in the same section. • index case in primary school or older: only close contacts, children who sat near the index, close friends. • close contacts spending 4 hours or more per day with the index during 5 of the 7 days before the hospitalization of the index case (cfr.text) - Antibiotic prophylaxis: Rifampin 10 mg/kg (5 mg/kg < 1 month)(max. 600mg/dose) bid for 2 days or ciprofloxacin 15 mg/kg (max. 500 mg) 1 single dose for children > 5 years. (Azithromycin should be reserved in case of intolerance/contra-indication to the other drugs, 10 mg/kg (max. 500mg) 1 single dose) ***H. influenzae**:* prophylaxis has to be given within the week after diagnosis of the index case. - to household contacts if there is at least one child less than 4 years, not or incompletely vaccinated, among the household members. - In a child care facility: single <u>case of BM</u>: if attended by nonvaccinated or incompletely vaccinated children < 2 years, consider prophylaxis for all the children and staff. If all contacts > 2 years: no prophylaxis. ≥ <u>2 cases of BM within 2 months</u>: and if facility attended by non-vaccinated or incompletely vaccinated children, prophylaxis recommended for all children and staff; - Antibiotic prophylaxis: rifampin 20 mg/kg (max. 600 mg) od for 4 days.	D D D D B D B