



**SWAB Guidelines on Antibacterial Therapy of Patients with Bacterial Central Nervous System Infections.**

**Part 1. Community-acquired bacterial meningitis**

**Part 2. Nosocomial bacterial meningitis**

**Part 3. Bacterial intracerebral abscess**

**Part 4. Tuberculous meningitis**

Dutch Working Party on Antibiotic Policy (SWAB), 2012

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*SWAB Guidelines Bacterial CNS Infections*

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## Chapter 1.

### Introduction

#### General introduction

The Dutch Working Party on Antibiotic Policy (SWAB; Stichting Werkgroep Antibiotica Beleid), established by the Dutch Society for Infectious Diseases (VIZ), the Dutch Society of Medical Microbiology (NVMM) and the Dutch Society for Hospital Pharmacists (NVZA), develops evidence-based guidelines for the use of antibiotics in hospitalized patients in order to optimize the quality of prescribing, thus, contributing to the containment of antimicrobial drug costs and resistance. By means of the development of national guidelines, SWAB offers local antibiotic and formulary committees a guideline for the development of their own, local antibiotic policy.

These are the first SWAB guidelines on bacterial central nervous system infections. It is developed according to the Evidence Based Guideline Development method (EBRO; [www.cbo.nl](http://www.cbo.nl)). The AGREE criteria ([www.agreecollaboration.org](http://www.agreecollaboration.org)) provided a structured framework both for the development and the assessment of the draft guideline.

Twelve key questions were formulated concerning the antibiotic treatment of bacterial central nervous system infections. Using several data sources (see data sources) conclusions were drawn, with their specific level of evidence, according to the CBO grading system adopted by SWAB (Table 1).<sup>1</sup>

Subsequently, specific recommendations were formulated. Each key question will be answered in a separate chapter.

**Table 1a**

Methodological quality of individual studies.<sup>1</sup>

	Intervention	Etiology, prognosis
A1	Systematic review of at least two independent	A2-level studies
A2	Randomised Controlled Trial (RCT) of sufficient methodological quality and power	Prospective cohort study with sufficient power and with adequate confounding corrections
B	Comparative Study lacking the same quality as mentioned at A2 (including patient-control and cohort studies)	Prospective cohort study lacking the same quality as mentioned at A2, retrospective cohort study or patient-control study
C	Non-comparative study	
D	Expert opinion	

**Table 1b**

Level of evidence of conclusions

	Conclusions based on
1	Study of level A1 or at least two independent studies of level A2
2	One study of level A2 or at least two independent studies of level B
3	One study of level B or C
4	Expert opinion

#### Relationship between the SWAB Guidelines and the 2012 Guidelines on Meningitis by the Dutch Society for Neurology (Nederlandse Vereniging voor Neurologie)

The SWAB guidelines cover the antimicrobial therapy in children and adults with bacterial meningitis, brain abscesses and tuberculous meningitis. They do not cover other treatment components of bacterial meningitis, such as corticosteroids, osmotic agents and anticoagulants.<sup>2</sup> This is discussed extensively in the 2012 guidelines by the

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Dutch Society for Neurology (Nederlandse Vereniging voor Neurologie).<sup>3</sup> The Nederlandse Vereniging voor Neurologie guidelines adopted the SWAB guidelines on meningitis to be the treatment part of their meningitis guidelines.

### **Scope of the SWAB guidelines**

Core issues on cryptococcal meningitis are extensively discussed in the 2008 SWAB guidelines on fungal infections. Diagnostics for bacterial meningitis are briefly discussed in the introduction, but not systematically reviewed in these guidelines. Encephalitis falls outside the scope of these guidelines.

For this guideline we made a distinction based on the setting in which bacterial meningitis was acquired: community-acquired versus nosocomial. Further, we provide recommendations for empirical antimicrobial therapy for clinical subgroups of bacterial meningitis patients. The choice of initial antimicrobial therapy for these subgroups is based on the bacteria most commonly causing the disease, taking into account the patient's age and clinical setting, and patterns of antimicrobial susceptibility. After the results of culture and susceptibility testing have become available, antimicrobial therapy can be modified for optimal treatment.

## Definitions

### **Bacterial meningitis**

Bacterial meningitis is defined as a bacterial infection of the meninges, proven by cerebrospinal fluid (CSF) culture, CSF polymerase chain reaction (PCR), CSF gram stain or antigen testing, or suspected by clinical characteristics and/or CSF markers of inflammation (CSF leukocyte count, CSF protein and/or CSF glucose level).<sup>4</sup>

### **Brain abscess**

Brain abscess is defined as focal intraparenchymal bacterial infection in the cerebrum, cerebellum or midbrain identified by cranial computed tomography, magnetic resonance imaging or during neurosurgery.

### **Tuberculous meningitis**

Tuberculous meningitis is defined as an infection of the meninges caused by *Mycobacterium tuberculosis*, proven by CSF culture or CSF PCR, or suspected by clinical characteristics and/or CSF markers of inflammation (CSF leukocyte count, CSF protein and/or CSF glucose level) combined with evidence or suspicion of other foci of tuberculosis (*e.g.* lungs).

## **Other relevant definitions**

*Community-acquired bacterial meningitis*: bacterial meningitis acquired in the community.

*Nosocomial bacterial meningitis*: bacterial meningitis resulting from invasive procedures (*e.g.*, craniotomy, placement of internal or external ventricular catheters, lumbar puncture, intrathecal infusions of medications, or spinal anesthesia), complicated head trauma, or in rare cases, metastatic infection in patients with hospital-acquired bacteremia.<sup>4</sup>

*Empirical antibiotic therapy*: therapy that is started before the pathogen and its susceptibility patterns are known. The choice of antibacterial therapy is largely based on expected etiology and antimicrobial resistance.

## **Diagnosis of bacterial meningitis**

To diagnose bacterial meningitis, CSF examination is mandatory. CSF culture remains the gold standard for the diagnosis of bacterial meningitis; aerobic culturing techniques are obligatory for community-acquired bacterial meningitis. Anaerobic culture may be important for post-neurosurgical meningitis or for the investigation of CSF shunt meningitis. In a retrospective series of 875 community-acquired bacterial meningitis patients for whom the diagnosis was defined by a CSF white blood cell count of over 1,000 cells per mm<sup>3</sup> and/or more than 80% polymorphonuclear cells, the CSF culture was positive for 85% of cases in the absence of prior antibiotic treatment.<sup>5</sup>

CSF culture is obligatory to obtain the in vitro susceptibility of the causative microorganism and to rationalize treatment. CSF Gram staining, latex agglutination testing and PCR are additional diagnostic tools that might aid in etiological diagnoses, especially for patients with negative CSF cultures (i.e., after antibiotic pretreatment).<sup>6</sup> Characteristic CSF findings for bacterial meningitis consist of polymorphonuclear pleocytosis, hypoglycorrhachia, and raised CSF protein levels. A prediction model based on 422 patients with bacterial or viral meningitis showed that individual predictors of community-acquired bacterial meningitis were a glucose concentration of less than 1.9 mmol per liter (0.34 g/liter), a ratio of CSF glucose to blood glucose of less than 0.23, a protein concentration of more than 2.2 g per liter, or a white cell count of more than 2,000 cells per mm<sup>3</sup>.<sup>7</sup>

### Diagnosis of brain abscess

The most important investigation to diagnose brain abscesses is cranial imaging, either cranial tomography (CT) or magnetic resonance imaging (MRI).<sup>8,9</sup> These will usually show round contrast-enhancing lesions similar to intracranial malignancies. Using diffusion weight MRI a distinction can be made between tumor and cerebral abscess: typical brain abscesses are hyperintense on T2 and FLAIR images, show a cavity with ring enhancement on T1 with gadolinium and limited diffusion in the cavity. The microbiological diagnosis in brain abscesses can be difficult. In only a minority of cases the causative pathogen(s) is identified in blood cultures or CSF culture. Therefore, if no primary focus of infection can be identified, a stereotactic aspiration of the abscess should be considered.<sup>8,9</sup> Both aerobic and anaerobic cultures of the aspirate should be performed.

### Diagnosis of tuberculous meningitis

Tuberculous (TB) meningitis is difficult to diagnose, as presenting clinical features are usually non-specific.<sup>11,12</sup> CSF usually shows a predominant lymphocytic pleiocytosis (>50%), with a low CSF to blood glucose ratio (<0.5) and a high protein concentration (>1.0 g/L).<sup>12</sup> Due to usually low numbers of mycobacteria in the CSF, the yield of Ziehl-Neelsen staining is only adequate (80%) if a large volume of CSF is examined (>5 ml), and in some cases repeated investigations need to be performed.<sup>11</sup> PCR for detection of *Mycobacterium tuberculosis* has a lower sensitivity than Ziehl-Neelsen staining, but is especially useful in patients who already started anti-tuberculosis medication.<sup>11</sup> CSF Ziehl-Neelsen staining, TB culture and PCR may all remain negative. In some cases repeated CSF investigations will aid in establishing the diagnosis. An important clue to the diagnosis can be pulmonary tuberculosis, which should always be looked for by chest X-ray in patients suspected of TB meningitis. A prediction model was devised in a Vietnamese population, which showed that age below 36, blood leukocyte count below 15,000/ml, duration of illness >6 days, CSF leukocyte count below 750/ml and CSF neutrophil percentage <90% were all indicators of TB meningitis in that setting.<sup>12</sup>

### Key questions

- 1a. What is the epidemiology and optimal empirical antibiotic therapy of community-acquired bacterial meningitis in the Netherlands in neonates (0-28 days)
- 1b. What is the epidemiology and optimal empirical antibiotic therapy of community-acquired bacterial meningitis in the Netherlands in children (29 days – 16 years)

- 1c. What is the epidemiology and optimal empirical antibiotic therapy of community-acquired bacterial meningitis in the Netherlands in adults (> 16 years)?
2. What is the optimal antibiotic therapy and treatment duration for community-acquired bacterial meningitis?
  - a. caused by *Streptococcus pneumoniae*.
  - b. caused by *Neisseria meningitidis*
  - c. caused by *Listeria monocytogenes*
  - d. caused by *Haemophilus influenzae*
  - e. caused by *Streptococcus agalactiae*
  - f. caused by *Escherichia coli*
  - g. with negative CSF and blood cultures
- 3a. What is the epidemiology and empirical treatment of bacterial meningitis related to external CSF drainage?
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4. When should antibiotic treatment in patients with suspected postoperative bacterial meningitis be withdrawn?
5. How long should infected CSF catheters be treated before removal/replacement?
6. What are the indications and regimens for intraventricular antimicrobial treatment?
7. What is the epidemiology of bacterial intracerebral abscesses in Europe/US?
8. What is the optimal empirical antibiotic therapy in intracerebral abscesses?
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12. What is the optimal duration of therapy for tuberculous meningitis (*in preparation*)?

**Data sources**

***Community-acquired bacterial meningitis***

*The Netherlands Reference Laboratory for Bacterial Meningitis*

The most important source of information for bacterial meningitis in the Netherlands is the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM; <http://www.amc.uva.nl/index.cfm?pid=5627>). The NRLBM started collecting isolates of *Neisseria meningitidis* in 1959 and of other bacteria causing meningitis in 1975. The Reference Laboratory isolates are available for studies on the epidemiology of bacterial meningitis and on the pathogenicity and antibiotic susceptibility of isolates.

The objectives of the Reference Laboratory are to perform surveillance of bacterial meningitis, to describe the epidemiology of bacterial meningitis in the Netherlands, to provide keys for the development of potential vaccine components and to provide data about antibiotic susceptibility of isolates. The NRLBM receives isolates from >85% of all patients with bacterial meningitis in the Netherlands. It is not possible to grade the data from the NRLBM with a specific level of evidence. However, the committee considers these surveillance data to be the most reliable, as the NRLBM covers >85% of the Dutch patients with bacterial meningitis and assigned it a level A2.

*Dutch cohorts of adults with community-acquired bacterial meningitis*

The Dutch Bacterial Meningitis Study (DBMS) and MeninGene Study are 2 prospective cohort studies including adult patients with community-acquired meningitis in the Netherlands, who had bacterial meningitis confirmed by cerebrospinal fluid culture.<sup>10,11</sup> In both studies patients were identified by the NRLBM, which provided the names of the hospitals where patients with bacterial meningitis had been admitted 2-6 days previously. The treating physician was contacted, and informed consent was obtained from all participating patients or their legally authorized representatives. The Dutch Bacterial Meningitis Study lasted from 1998 to 2002 and included 696 patients. MeninGene started in 2006 and continues until today, and has thus far included over 1200 patients. Detailed information on patients with bacterial meningitis is collected through Case-record forms (CRF). CRFs are used to collect data on patients' history, symptoms and signs on admission, laboratory findings at admission, clinical course, outcome and neurologic findings at discharge, and treatment. We used data from these studies for all adults with bacterial meningitis.



### *Literature*

The NRLBM data does not distinguish between community-acquired and nosocomial bacterial meningitis. Therefore, we substantiated the NRLBM data with literature studies where appropriate using the following search strategy:

```
(((((("Meningitis, Bacterial"[Mesh]) OR (bacterial meningitis*[TIAB]) OR (pneumococcal meningitis*[TIAB]) OR (meningococcal meningitis*[TIAB]) OR (staphylococcal meningitis*[TIAB]) OR (nosocomial meningitis*[TIAB]) OR (hospital acquired meningitis*[TIAB]) OR (e coli meningitis*[TIAB]) OR (escherichia coli meningitis*[TIAB]) OR (neonatal meningitis*[TIAB]))) AND (("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents "[Pharmacological Action]) OR (antibiotic*[TIAB]) OR (antimicrobial*[TIAB]))) AND ((Humans[Mesh]) AND (English[lang]))) NOT (tuberc*[TI] OR anthra*[TI])) NOT (case reports[PT] OR editorial[PT]))
```

### ***Nosocomial bacterial meningitis***

#### *Literature*

Pubmed was searched using search strategies

Search 1): Pubmed search: bacterial meningitis related to internal/external CSF drainage

```
((("Ventriculoperitoneal Shunt"[Mesh] OR ventriculoperitoneal shunt*[TIAB]) OR (ventricular drain*[TIAB]) OR (lumbar drain*[TIAB]) OR (ventricular atrial drain*) OR (ventriculoatrial drain*[TIAB]) OR (ventriculopleural drain*[TIAB])) AND (("cross infection"[MeSH Terms] OR cross infection*[TIAB]) OR ("infection"[MeSH Terms] OR "infection"[TIAB])))
```

Search 2): Nosocomial bacterial meningitis (Selected from meningitis search)

```
(((((("Meningitis, Bacterial"[Mesh]) OR (bacterial meningitis*[TIAB]) OR (pneumococcal meningitis*[TIAB]) OR (meningococcal meningitis*[TIAB]) OR (staphylococcal meningitis*[TIAB]) OR (nosocomial meningitis*[TIAB]) OR (hospital acquired meningitis*[TIAB]) OR (e coli meningitis*[TIAB]) OR (escherichia coli meningitis*[TIAB]) OR (neonatal meningitis*[TIAB]))) AND (("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents "[Pharmacological Action]) OR (antibiotic*[TIAB]) OR (antimicrobial*[TIAB]))) AND ((Humans[Mesh]) AND (English[lang]))) NOT (tuberc*[TI] OR anthra*[TI])) NOT (case reports[PT] OR editorial[PT]))
```

### ***Brain abscess***

#### *Literature*

Pubmed was searched using search strategie:

```
(((((("Brain Abscess"[Mesh:noexp]) OR (Brain Abscess*[TIAB]) OR (cerebral Abscess*[TIAB]) OR (cerebellar Abscess*[TIAB])) OR (brain[TIAB] AND abscess*[TIAB])) AND (("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents "[Pharmacological Action]) OR (antibiotic*[TIAB]) OR (antibacterial agent*[TIAB]) OR (antimicrobial agent*[TIAB])) AND ((Humans[Mesh]) AND (English[lang]))) AND ((Humans[Mesh]) AND (English[lang]))) NOT (((("Brain Abscess"[Mesh:noexp]) OR (Brain Abscess*[TIAB]) OR (cerebral
```

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Abscess\*[TIAB]) OR (cerebellar Abscess\*[TIAB])) OR (brain[TIAB] AND abscess\*[TIAB])) AND (("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents "[Pharmacological Action]) OR (antibiotic\*[TIAB]) OR (antibacterial agent\*[TIAB]) OR (antimicrobial agent\*[TIAB])) AND ((Humans[Mesh]) AND (English[lang]))) AND (Humans[Mesh] AND Case Reports[ptyp] AND English[lang]))

Limits used were: English, not case reports, humans. This resulted in 517 hits (March 8<sup>th</sup> 2010)

To avoid differences due to geographical location, patients in Europe/North America/Western Asia (*i.e.*, Israel and Turkey) were included. Case series of >10 patients were included. Microbiological data were extracted from each study according to a pre-specified protocol.

Parts of the recommendations in these guidelines have been published previously.<sup>4,6,12</sup>

### **Tuberculous meningitis** (*in preparation*)

#### *Literature*

## Chapter 2

### Epidemiology and empirical antibiotic treatment of community-acquired bacterial meningitis

In patients with bacterial meningitis, other treatment next to antibiotics may be indicated. Adjunctive dexamethasone therapy needs to be administered simultaneous with the antibiotics in most children and adults with bacterial meningitis, and consultation with an ENT specialist may be necessary to assess whether surgical treatment of otitis or sinusitis is indicated. Although the SWAB guidelines only cover antibiotic therapy and refers to the 2012 guidelines by the Dutch Society for Neurology (Nederlandse Vereniging voor Neurologie) for adjunctive treatments, the committee likes to stress the importance of these therapies.

#### ***Key question 1a. What is the epidemiology and optimal empirical antibiotic therapy of bacterial meningitis in the Netherlands in neonates (0-28 days)?***

Common causative microorganisms of neonatal meningitis during the first week of life are *Streptococcus agalactiae* (Group B streptococci), *Escherichia coli*, and *Listeria monocytogenes* (Supplementary table 1).<sup>6,13-15</sup> Late-onset neonatal meningitis is formally classified as meningitis after the first week until the 28<sup>th</sup> day of life.<sup>13,16,17</sup> Late-onset neonatal meningitis may be caused by a wide variety of species, including staphylococci, and Gram-negative bacilli.<sup>6</sup> Children born with a hydrocephalus or those that develop a hydrocephalus after an intraventricular bleeding (on the neonatal intensive care unit) are often treated with repetitive CSF drainage from an Ommaya reservoir, or a temporary or permanent CSF shunt and are at increased risk of nosocomial meningitis.<sup>4,18</sup> The causative microorganisms in these children are different from those in “spontaneous” meningitis and are similar to those seen in nosocomial meningitis (Chapter 4).

Empirical therapy for neonatal meningitis should consist of amoxicillin combined with cefotaxime (Table 2). The use of gentamicin to cover neonatal meningitis due to Gram-negative bacteria has been debated. The recommendation for the addition of gentamicin has been based on data from in vitro studies, which showed synergistic activity with amoxicillin in antimicrobial killing of *S. agalactiae*.<sup>6,19</sup> However, as CSF concentrations are usually only minimally above the MIC, third generation cephalosporins are considered superior to gentamicin.<sup>17</sup> In neonates with suspected sepsis gentamicin is combined with amoxicillin, but physicians should be aware this regimen is sub-optimal for meningitis treatment. In neonates with suspected sepsis or meningitis CSF examination to establish whether concurrent meningitis is present is vital to determine the optimal empirical treatment. We recommend amoxicillin and cefotaxime in children with a high suspicion of bacterial meningitis. The dose is depends on gestational age and birth weight, and is given in the online SWAB-ID ([www.swab.nl](http://www.swab.nl)). Ceftriaxone is contraindicated in children < 4 weeks because of a high risk of precipitation of calcium-ceftriaxone complexes in the gallbladder.

***Ib. What is the epidemiology and optimal empirical antibiotic therapy of bacterial meningitis in the Netherlands for children (29 days – 16 years)?***

The most common causative bacteria of community-acquired bacterial meningitis in children aged 1 month and older are *S. pneumoniae* and *N. meningitidis*, causing 80% of cases in the Netherlands (Supplementary table 2). The remainder of cases is caused by group B streptococci, *E. coli*, *H. influenzae*, other Gram-negative bacilli, *L. monocytogenes*, and group A streptococci. The epidemiology has shifted substantially in the past 10 years and is still changing due to the introduction of the meningococcus group C vaccine (2002), and the 7- (2006) and 10-valent (2011) pneumococcal conjugate vaccines.<sup>6</sup>

Empirical coverage with a third generation cephalosporin (cefotaxime or ceftriaxone) is recommended based on a broad spectrum of activity and excellent penetration into the CSF under inflammatory conditions. Third generation cephalosporins are preferred in this age group above amoxicillin as resistance of *H. influenzae* to amoxicillin due to beta-lactamase production occurs in 11% of meningitis cases.<sup>20</sup> A clinical trial comparing cefotaxime with meropenem showed similar efficacy; therefore meropenem may be considered as alternative empirical treatment in children >3 months of age in specific cases (*e.g.* cephalosporin allergy).<sup>21</sup> However, the committee recommends keeping the use of meropenem restricted to the use as last resort antibiotic in bacterial meningitis patients.

***Ic. What is the epidemiology and optimal empirical antibiotic therapy of bacterial meningitis in the Netherlands for adults (> 16 years)***

All causative organisms of bacterial meningitis in adults from two nation-wide prospective cohort studies in the Netherlands, including 1500 patients, are presented in Supplementary table 3. *S. pneumoniae* is the most common causative microorganism of adult bacterial meningitis, and was identified in 70% of culture positive cases included between 2006 and 2010.<sup>22</sup> *N. meningitidis* was the second most common causative microorganism and is predominantly found in young adults.<sup>23</sup> The proportion of meningococcal meningitis decreased from 37% of bacterial meningitis cases between 1998-2002 to 16% in 2006-2010, probably due to vaccination against serogroup C and to normal variation in meningococcal disease incidence. Patients over 50 years of age and those with an immunocompromised state are at increased risk for *Listeria monocytogenes*, which is found in 5% of cases.<sup>24</sup> However, *L. monocytogenes* meningitis also occurs in previously healthy adults without risk factors (Supplementary table 4). Therefore age and immunocompromised status cannot be used to rule out *L. monocytogenes* meningitis. Meningitis due to mostly unencapsulated *H. influenzae* and group A streptococci occurs in 3-4% of cases. Other causative organisms occur sporadically.

There have been no randomized controlled trials or comparative studies to evaluate the optimal empirical antibiotic treatment in adults with bacterial meningitis. Therefore all recommendations are based on epidemiological data (level 4 evidence – expert opinion).

The committee recommends empirical therapy for bacterial meningitis in adults to consist of amoxicillin and a third generation cephalosporin (ceftriaxone or cefotaxime). Use of these antibiotics will ensure coverage of the

four most common causative microorganisms (pneumococci, *N. meningitidis*, *L. monocytogenes* and *H. influenzae*) and most sporadic causes. This combination therapy is preferred over monotherapy with third generation cephalosporins, as this does not cover *L. monocytogenes*, while monotherapy with amoxicillin does not cover  $\beta$ -lactamase producing *H. influenzae* strains and *E.coli*.

In the majority of patients the CSF or blood cultures will show the causative microorganism within 48 hours, with the exception of *L. monocytogenes* which is a notably slow grower.<sup>6</sup> If a microorganism is cultured, therapy can be adjusted accordingly (see Ch 3). If cultures are negative after 48 hours, the third generation cephalosporins can be discontinued, and monotherapy with amoxicillin will suffice because infection with  $\beta$ -lactamase producing *H. influenzae* is virtually excluded.

### Conclusions

Level 1	Early neonatal meningitis is most commonly caused by <i>S. agalactiae</i> , <i>E. coli</i> , and <i>L. monocytogenes</i> . Late neonatal meningitis is most commonly caused by staphylococci, and Gram-negative bacilli A2 Garges (2006) <sup>13</sup> , Holt (2001) <sup>15</sup> , NRLBM (2011) <sup>20</sup> B Hristeva (1993) <sup>14</sup>
Level 2	Bacterial meningitis in children is caused by <i>S. pneumoniae</i> (44%), <i>N. meningitidis</i> (39%) and <i>H. influenzae</i> (11%) A2 NRLBM <sup>20</sup>
Level 2	Bacterial meningitis in adults is caused by <i>S. pneumoniae</i> (62%), <i>N. meningitidis</i> (23%) <i>L. monocytogenes</i> (5%) and <i>H. influenzae</i> (3%) A2 NRLBM <sup>20</sup>
Level 3	Cefotaxime and meropenem are equally effective as empirical therapy for bacterial meningitis in children. However, meropenem should only be given in specific cases and kept as last resort. B Odio (1999) <sup>21</sup>
*	No comparative studies have been performed to evaluate empirical antibiotic therapy regimens for community-acquired bacterial meningitis in neonates and adults.

### Recommendations

1. Empirical antibiotic therapy in neonates with bacterial meningitis should consist of amoxicillin and cefotaxime. If a microorganism is cultured, therapy can be adjusted accordingly (see Ch 3).
2. Empirical antibiotic therapy in children aged 1 month-16 years with bacterial meningitis should consist of a third generation cephalosporin (cefotaxime or ceftriaxone). Meropenem may be used as an alternative in specific cases ( <i>e.g.</i> known allergic reactions). If a microorganism is cultured, therapy can be adjusted accordingly (see Ch 3).

3. Empirical antibiotic therapy in adults with bacterial meningitis should consist of the combination of amoxicillin and a third generation cephalosporin (ceftriaxone or cefotaxime).
4. If a microorganism is cultured in adults with bacterial meningitis, therapy can be adjusted accordingly (see Ch 3). If cultures are negative after 48 hours, the third generation cephalosporin can be discontinued, and monotherapy amoxicillin will suffice.

**Table 2.** Empirical antimicrobial therapy for community-acquired bacterial meningitis, stratified for age.

Age / risk group	Treatment	Alternative
Neonates*	amoxicillin 100-200 mg/kg/day (6h) and cefotaxime 50-150 mg/kg/day (8h)	amoxicillin 100-200 mg/kg/day (6h) and gentamicin 4 mg/kg/day (24-48h)
Children	ceftriaxone 100 mg/kg/day (max 4g) (24h) or cefotaxime 150 mg/kg/day (max 12g) (6h)	meropenem 120 mg/kg/day (max 6 g) (8h)
Adults	amoxicillin 6x2 g/dag plus ceftriaxone 2x2 g/day or cefotaxime 6x2 g/day	

Dosages derived from: SWAB-ID: Nationale antibioticaboekje van de SWAB, <http://customid.duhs.duke.edu/NL/Main/Start.asp>. Between brackets interval between dosages.

\* Dose and dosage interval dependent on gestational age and weight, see SWAB-ID for exact recommendations.

## Chapter 3

### Specific antimicrobial treatment

A summary of specific antimicrobial treatment for bacterial meningitis when a causative organism is identified is presented in Table 3. No randomized controlled trials or comparative studies have been performed to compare the efficacy of different antibiotics in bacterial meningitis due to specific bacteria. Therefore, the choice of specific antimicrobial therapy is based on bacterial susceptibility testing.

Studies on optimal treatment duration are scarce. A 2010 meta-analysis on randomized trials comparing short (4-7 days) versus long duration (7-14 days) of antibiotic therapy for bacterial meningitis concluded that there was no difference in outcome between treatment durations.<sup>25</sup> However, there were several biases in the included studies and the results can not be extrapolated to the unselected population of community-acquired bacterial meningitis.<sup>26</sup> A recent study performed in Malawi compared the use of a 5 day regimen with a the standard 10 day regimen in children with uncomplicated bacterial meningitis due to *H. influenzae*, *N. meningitidis* or *S. pneumoniae*. The study showed equality of both regimens.<sup>27</sup> However, the subgroup of children with pneumococcal meningitis was too small to conclude that there was no harm of early discontinuation, especially since the mortality was 8% in the 5 day regimen group vs. 5% in the 10 day group.<sup>27</sup> Therefore, the results of this trial can not be extrapolated to the Netherlands.

Currently, the duration of antibiotic treatment is based on expert opinion. New studies on optimal treatment duration are needed. The level of evidence for treatment duration is therefore categorized as level 4.<sup>28</sup>

**Table 3.** Specific antimicrobial therapy for community-acquired bacterial meningitis based on causative microorganism

Micro-organism	Standard treatment	Alternative therapy	Duration
<i>S. pneumoniae</i>			
MIC ≤0.06 g/ml	penicillin G	ceftriaxone or cefotaxime	10-14 days
0.06<MIC≤2.0µg/ml	ceftriaxone or cefotaxime	meropenem	10-14 days
MIC >2.0µg/ml	vancomycin plus either ceftriaxone or cefotaxime	vancomycin plus meropenem	
<i>N. meningitidis</i>			
MIC ≤0.25µg/ml	penicillin G	ceftriaxone or cefotaxime	7 days
MIC >0.25µg/ml	ceftriaxone or cefotaxime	meropenem or chloramphenicol	7 days
<i>H. influenzae</i>	ceftriaxone or cefotaxime	meropenem or chloramphenicol	7/10 days <sup>a</sup>
<i>L. monocytogenes</i>	amoxicillin or penicillin G	trimethoprim-sulfamethoxazole	≥21 days
<i>S. agalactiae</i>	penicillin G or amoxicillin	ceftriaxone or cefotaxime	≥14 days

<sup>a</sup>Duration of treatment in children 10 days, adults 7 days.

**Key question 2a. What is the optimal antibiotic therapy and duration for community-acquired bacterial meningitis caused by *Streptococcus pneumoniae*?**

Resistance of *S. pneumoniae* to penicillin and third generation cephalosporins (cefotaxime or ceftriaxone) has been reported to cause treatment failure.<sup>6</sup> The rate of pneumococcal resistance rates in the Netherlands is still very low, with only 0.5-1% strains showing intermediate resistance to penicillin ( $0.06 < \text{MIC} \leq 2.0$ ).<sup>10,11</sup> So far, one strain resistant to third generation cephalosporins has been described ( $\text{MIC} > 2.0$ ).<sup>29</sup> Therefore, in the overwhelming majority of patients with pneumococcal meningitis monotherapy with amoxicillin or penicillin suffices. When susceptibility testing shows intermediate resistance to penicillin, a third generation cephalosporin should be used. Patients at risk for infection with a resistant strain, such as inhabitants of countries with high pneumococcal resistance rates (e.g. South-European countries, or the US) or recent travelers from these countries should be treated with combination therapy consisting of vancomycin and a third generation cephalosporin until susceptibility testing is performed.<sup>6</sup> When the isolate shows resistance to penicillin ( $\text{MIC} > 2.0$ ), combination therapy of vancomycin and a third generation cephalosporin should be used. The duration of therapy for *S. pneumoniae* meningitis is 10 days, unless persistent or recurrent fever or other complications occur that warrant prolonged treatment.<sup>28</sup>

**Key question 2b. What is the optimal antibiotic therapy and duration for community-acquired bacterial meningitis caused by *Neisseria meningitidis*?**

Currently (2012), there is no consensus in Europe about the penicillin breakpoints of *N. meningitidis*. According to EUCAST the meningococcus has intermediate resistance (reduced susceptibility) when the penicillin MIC is  $> 0.06$  en  $\leq 0.25$  mg/l. Meningococcal strains with reduced susceptibility to penicillin have been described, but the clinical significance remains unclear. In the Netherlands, 17 of 392 (4%) meningococcal strains isolated from CSF between 2005-2009 showed intermediate resistance to penicillin. In 2010 the number increased to 10 out of 54 (19%). Penicillin-resistant strains are very rare. The majority of patients with *N. meningitidis* strains with intermediate resistance to penicillin reported in the literature have responded well to penicillin treatment.<sup>6</sup> Treatment failures have been described in a few case reports, and none of these occurred in the Netherlands. Therefore, treatment with amoxicillin or penicillin for 7 days remains first choice.<sup>28</sup> Infection with a penicillin-resistant strain ( $\text{MIC} > 0.25$ ) should be treated with a third generation cephalosporin.<sup>6</sup>

All meningococcal meningitis cases have to be reported to the Public Health Service (GGD/GG&GD). Household contacts and others who have been in close contact with meningococcal meningitis patients in the week prior to disease onset should receive prophylaxis to minimize the risk of secondary cases. Health care workers are only at risk after intimate contact such as mouth-to mouth resuscitation or endotracheal intubation. Rifampicin and ciprofloxacin are both effective as prophylaxis for treating patient contacts.<sup>3</sup> More information on this subject can be found in the bacterial meningitis guidelines of the Dutch Neurological Society.<sup>3</sup>



**Key question 2c. What is the optimal antibiotic therapy and duration for community-acquired bacterial meningitis caused by *Listeria monocytogenes*?**

Amoxicillin and penicillin are highly effective against *L. monocytogenes*, and one of these should be used in patients with proven or suspected *L. monocytogenes* meningitis. Third generation cephalosporins are ineffective against this pathogen and therefore empirical monotherapy with these agents in patients at higher risk for *L. monocytogenes* meningitis, e.g. elderly (>50 years) and immunocompromised patients, should be avoided.<sup>24</sup> As it is difficult to define patients that have an increased risk of *L. monocytogenes*, the empirical treatment for all adults includes amoxicillin to cover *L. monocytogenes*. Patients allergic to penicillin can be treated with trimethoprim-sulfamethoxazole.<sup>6</sup>

The addition of aminoglycosides is debated. Synergistic activity of gentamicin with other antibiotics has been shown in *in vitro* experiments. However, a cohort of 118 Spanish adults with *L. monocytogenes* disease showed increased mortality and renal failure in the aminoglycoside-treated patients.<sup>30</sup> Therefore, aminoglycosides are not advised in adults with *L. monocytogenes* meningitis. Minimal duration of treatment of *L. monocytogenes* meningitis is 21 days for children and adults.<sup>28,31,32</sup>

**Key question 2d. What is the optimal antibiotic therapy and duration for community-acquired bacterial meningitis caused by *Haemophilus influenzae*?**

The rate of beta-lactamase producing *H. influenzae* strains in the Netherlands has fluctuated in the last 25 years from 0.9% to 12.5%, with an average around 5% (data NRLBM). Therefore, third generation cephalosporins have become standard for *H. influenzae* meningitis, until susceptibility testing is performed. If the strain is susceptible to amoxicillin, amoxicillin should be used. The standard duration of therapy for adults is 7 days and for children 10 days.<sup>28,32</sup>

**Key question 2e. What is the optimal antibiotic therapy and duration for community-acquired bacterial meningitis caused by *Streptococcus agalactiae*?**

*S. agalactiae* is invariably susceptible to penicillin, amoxicillin, and cephalosporins. Treatment of *S. agalactiae* meningitis consists of penicillin or amoxicillin, and alternatively third generation cephalosporins can be used. The minimal advised treatment duration is 14 days, but courses up to 21 days should be considered in patients with a complicated disease course. In neonates with *S. agalactiae* meningitis gentamicin is added for 3 days.

**Key question 2f. What is the optimal antibiotic therapy and duration for community-acquired bacterial meningitis caused by *Escherichia coli*?**

*E. coli* strains are mostly susceptible to third generation cephalosporins and 30-40% is susceptible to amoxicillin. Strains producing extended spectrum beta-lactamases (ESBL) are increasing in frequency but have not been described in meningitis patients in the Netherlands so far. Treatment of *E. coli* meningitis consists of third generation cephalosporins combined with gentamicin during the first three days of treatment in neonates. In

children beyond the neonatal age and adults third generation cephalosporins are advised, or amoxicillin if the strain is sensitive to amoxicillin. When ESBL producing *E. coli* are suspected or proven, meropenem is the treatment of choice. The minimal advised treatment duration is 21 days.

**Key question 2g. What is the optimal antibiotic therapy and duration for community-acquired bacterial meningitis caused by unidentified pathogens (culture-negative cases)?**

In 10 to 20% of bacterial meningitis cases, defined by elevated CSF markers of inflammation, CSF and blood cultures remain negative.<sup>6</sup> No studies have been performed to determine the treatment regimen for these patients and the optimal duration of therapy is therefore also unclear. The given recommendations are based on the duration of therapy advised for the most common causative microorganisms. For children empirical therapy with a third generation cephalosporin should be continued for 14 days in culture-negative cases. In adults the empirical therapy can be changed, from amoxicillin combined with a third generation cephalosporin to monotherapy with amoxicillin for 14 days if after 48 hours cultures remain negative. Monotherapy amoxicillin is the antimicrobial therapy of choice in adults because infection with  $\beta$ -lactamase producing *H. influenzae* is virtually excluded if cultures remain negative after 48 hours. *L. monocytogenes* should still be covered after 48 hours as it is a slow growing microorganism. As *L. monocytogenes* is extremely rare in children beyond the neonatal age, monotherapy with a third generation cephalosporin suffices for children.

**Conclusions**

Level 1	No randomized controlled trials or adequate comparative studies have been performed to determine the optimal antibiotic treatment duration of bacterial meningitis caused by specific pathogens or in culture negative cases.  A1 Karageorgeopoulous (2007) <sup>25</sup> , vd Beek (2010) <sup>26</sup>
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**Recommendations**

1. Bacterial meningitis caused by penicillin susceptible ( $MIC \leq 0.06$ ) *S. pneumoniae* should be treated with penicillin 200.000 IU/kg/day (4h – maximum 12 million units) in children and penicillin 12 million IU /day (4h or continuously) in adults, for a minimum of 10 days. Meningitis due to *S. pneumoniae* with intermediate resistance ( $0.06 < MIC \leq 2.0$ ) should be treated with ceftriaxone 100 mg/kg/day (24h – max 4g) in children and ceftriaxone 4 g/day (12h) or cefotaxime 8-12 g/day (4-6h) in adults, for a minimum of 10 days. Meningitis due to penicillin-resistant *S. pneumoniae* ( $MIC > 2.0$ ) should be treated with vancomycin 60 mg/kg/day (12h – max 2g) plus ceftriaxone 100 mg/kg/day (24h – max 4g) in children and vancomycin 2 g/day (12h) plus ceftriaxone 4 g/day (12h) or cefotaxime 8-12 g/day (4-6h) in adults.
2. Bacterial meningitis caused by penicillin susceptible *N. meningitidis* should be treated with penicillin 200.000 IU/kg/day (4h – maximum 12 million units) in children and penicillin 12 million IU /day (4h or continuously) in adults, for 7 days. Penicillin resistant strains ( $MIC > 0.25$ ) should be treated with ceftriaxone 100 mg/kg/day (24h – max 4g) in children and ceftriaxone 4 g/day (12h) or cefotaxime 8-12 g/day (4-6h) in adults, for 7 days.

3. Bacterial meningitis caused by *L. monocytogenes* should be treated with amoxicillin 200 mg/kg/day (6h – max 12g ) in children and amoxicillin 12 g/day (4h) in adults, for at least 21 days.
4. Bacterial meningitis caused by *H. influenzae*,  $\beta$ -lactamase positive or  $\beta$ -lactamase unknown, should be treated with ceftriaxone 100 mg/kg/day (24h – max 4 g) in children and ceftriaxone 4 gr/day (12h) or cefotaxime 8-12 gr/day (4-6h) in adults, for 7 days. If the strain is susceptible to amoxicillin, it should be treated with amoxicillin 200 mg/kg/day (6h – max 12g) in children and amoxicillin 12g/day (4h) in adults, for 7 days.
5. Bacterial meningitis caused by *Streptococcus agalactiae* should be treated with penicillin 200.00 IU/kg/day (4h – maximum 12 million units) and penicillin 12 million units/day (4h or continuously) in adults, for at least 14 days.
6. Bacterial meningitis caused by *Escherichia coli* should be treated with cefotaxime plus gentamicin for 3 days in neonates (dose depends on gestational age and birth weight – SWAB website), ceftriaxone 100 mg/kg/day (24h – max 4g) for children and ceftriaxone 4g (12h) or cefotaxime 8-12g/day (4-6h) in adults, for 21 days. ESBL positive strains should be treated with meropenem 120mg/kg/day (8h - maximum 6 g) in children and 6g (8h) for adults.
7. Bacterial meningitis with negative CSF and blood cultures after 48 hours should be treated with ceftriaxone 100 mg/kg/day (24h – max 4g) in children and amoxicillin 12g/day (4h) in adults, for 14 days.

## Part 2.

### Nosocomial and posttraumatic bacterial meningitis

#### Chapter 4

#### Epidemiology and empirical antibiotic treatment of nosocomial and posttraumatic bacterial meningitis

##### **Key question 3a. What is the epidemiology and empirical treatment of bacterial meningitis related to external CSF drainage?**

External ventricular and lumbar drains are used for monitoring intracranial pressure and temporary diversion of CSF, or as part of treatment of infected internal catheters.<sup>4</sup> The risk of infection of external ventricular catheters is reported to be approximately 8%, while infection of external lumbar catheters has been estimated to occur in 5%.<sup>34</sup> Most common pathogens in infections of external CSF catheters are staphylococci, which are cultured in approximately 60% of cases. Common staphylococcal species are coagulase-negative staphylococci, mostly *S. epidermidis*, and *S. aureus* (Supplementary table 5).<sup>35-44</sup> Other common pathogens are *Klebsiella pneumoniae*, *Enterobacter* species, *Enterococcus faecalis*, *Acinetobacter* species and *Pseudomonas aeruginosa*. Multiple uncommon pathogens can be found in external CSF catheter infection and therefore empirical antibiotic coverage should be broad. A combination of vancomycin plus either ceftazidime or meropenem should be used (Table 4).<sup>4</sup>

##### **Key question 3b. What is the epidemiology and empirical treatment of bacterial meningitis related to internal CSF drainage?**

The reported incidence of meningitis associated with internal ventricular or lumbar catheters ranges from 4 to 17%.<sup>4,45,46</sup> Approximately 60% of cases are caused by *Staphylococcus* species, and other frequent pathogens are *Escherichia coli*, *K. pneumoniae*, *E. faecalis* and *Acinetobacter* species (Supplementary table 6).<sup>45-50</sup> Mixed infections were described in 17% of cases in a recent Swiss study including 71 patients.<sup>46</sup> Because of the wide range of pathogens and the occurrence of mixed infections the antibiotic coverage should be broad and should consist of vancomycin plus either ceftazidime or meropenem (Table 4).<sup>4</sup>

##### **Key question 3c. What is the epidemiology and empirical treatment of bacterial meningitis related to postoperative bacterial meningitis?**

Bacterial meningitis is a serious complication of neurosurgical procedures and occurs in 0.8-1.5% of patients who undergo craniotomy.<sup>4,51,52</sup> Development of bacterial meningitis has been associated with concomitant infection of the site of incision and duration of operation > 4 hours.<sup>4</sup> One third of meningitis cases develop within the first week after the operation, one third in the second week and one third after the second week.<sup>51</sup> Most cases are caused by *Staphylococcus* species (coagulase negative staphylococci, mostly *S. epidermidis* and *S. aureus*; Supplementary table 7<sup>52-57</sup>). *E. coli*, *K. pneumoniae*, *Enterobacter* spp, *Serratia* spp, *Acinetobacter* spp, and *P. aeruginosa* were all found in approximately 5% of cases. Frequent causes of community-acquired bacterial meningitis such as *Streptococcus pneumoniae* and *Haemophilus influenzae* occur infrequently in postoperative bacterial meningitis. Because the significance of coagulase negative staphylococci is not evident in the patients without internal or external drains, and vancomycin is inferior to  $\beta$ -lactam antibiotics in *S.aureus* infections,

empirical therapy should consist of flucloxacillin combined with ceftazidime, or meropenem monotherapy (Table 4).

**Key question 3d. What is the epidemiology and empirical treatment of posttraumatic bacterial meningitis?**

The incidence of meningitis after moderate and severe head trauma is estimated at 1.4%.<sup>4,58</sup> In patients with open cranial fractures the rate of meningitis is higher at 2-11%. Data on causative microorganisms in posttraumatic bacterial meningitis are scarce (Supplementary table 8).<sup>58</sup> Posttraumatic meningitis following skull base fractures are caused by microorganisms that colonize the nasopharynx (*S. pneumoniae*, *H. influenzae* and Group A streptococci),<sup>4</sup> while bacterial meningitis following an impression fracture of the skull will be likely caused by skin flora (staphylococci). Also in these patients the significance of coagulase negative staphylococci is not evident in the absence of internal or external drains, and vancomycin is inferior to  $\beta$ -lactam antibiotics in *S.aureus* infections. Therefore, empirical therapy in patients with skull base fractures consists of a third generation cephalosporin, and patients with bacterial meningitis following open skull fractures should likewise be treated with a third generation cephalosporin (ceftriaxone or cefotaxime)(Table 4).

**Conclusions**

Level 2	Bacterial meningitis related to external and internal ventricular drains, and postoperative bacterial meningitis is caused by <i>Staphylococcus</i> spp. in 50-60% of cases  B Vinchon (2006) <sup>45</sup> , Conen (2008) <sup>46</sup> , Walters (1984) <sup>47</sup> , Filka (1999) <sup>48</sup> , Kestle (2006) <sup>49</sup> , Sacar (2006) <sup>50</sup> , McClelland (2007) <sup>52</sup> , Aucoin (1986) <sup>53</sup> , Kourbeti (2007) <sup>54</sup> , Federico (2001) <sup>55</sup> , Wang (2005) <sup>56</sup> , Zarrouk (2007) <sup>57</sup>
Level 4	Bacterial meningitis following severe head trauma due to skull base fractures is mostly caused by <i>S. pneumoniae</i> , <i>H. influenzae</i> and group A streptococci and bacterial meningitis due to open skull fractures is mostly caused by skin flora (staphylococci).
*	No studies have been performed on empirical antibiotic therapy for nosocomial bacterial meningitis

**Recommendations**

1. Nosocomial meningitis associated with external or internal ventricular drains should be empirically treated with vancomycin plus either ceftazidime or meropenem (Table 4).
2. Postoperative bacterial meningitis should be treated with flucloxacillin combined with ceftazidime, or with meropenem monotherapy.
3. Posttraumatic bacterial meningitis due to a skull base fracture should be treated with a third generation cephalosporin.

4. Posttraumatic bacterial meningitis due to open skull fractures should be empirically treated with a third generation cephalosporin (ceftriaxone or cefotaxime).

**Table 4.** Empirical treatment of nosocomial bacterial meningitis in different subgroups<sup>a</sup>

Pathogenesis	Common bacterial pathogens	Antimicrobial therapy <sup>a</sup>
Postneurosurgery	Aerobic gram-negative bacilli, <i>S. aureus</i> , CNS <sup>b</sup>	Flucloxacillin plus either ceftazidime, or meropenem monotherapy <sup>c,d</sup>
Ventricular or lumbar catheter	CNS <sup>b</sup> , <i>S. aureus</i> , aerobic gram-negative bacilli, <i>Propionibacterium acnes</i>	Vancomycin plus either ceftazidime or meropenem <sup>c,d</sup>
Penetrating trauma	<i>S. aureus</i> , CNS <sup>b</sup> , aerobic gram-negative bacilli	Third-generation cephalosporin <sup>d,e</sup>
Basilar skull fracture (early)	<i>S. pneumoniae</i> , <i>H. influenzae</i> , group A β-hemolytic streptococci	Third-generation cephalosporin <sup>d,e</sup>

<sup>a</sup>The preferred daily dosages of antimicrobial agents in adult patients with normal renal and hepatic function are as follows: vancomycin 1000 mg every 12 hours, to be adjusted to maintain a serum vancomycin trough concentration of 15-20 µg/ml, ceftazidime 2 grams every 8 hours, meropenem 2 grams every 8 hours; in patients with severe penicillin and/or cephalosporin allergy, ciprofloxacin 400 mg every 8 hours can be used for treatment of infection caused by gram-negative bacilli; ceftriaxone 2 grams every 12 hours, cefotaxime 2 grams every 4 hours;

<sup>b</sup>Coagulase-negative *Staphylococcus* (mostly *S. epidermidis*)

<sup>c</sup>Choice of specific agent should be based on local antimicrobial susceptibility of aerobic gram-negative bacilli;

<sup>d</sup>For patients with severe allergy to penicillin and/or cephalosporins, a fluoroquinolone with in vitro activity against *P. aeruginosa* should be utilized;

<sup>e</sup>Ceftriaxone or cefotaxime.

## Chapter 5

### Withdrawal of antibiotic therapy in suspected postoperative meningitis.

#### ***Key question 4. When should antibiotic treatment in patients with suspected postoperative bacterial meningitis be withdrawn?***

A clinical suspicion of nosocomial bacterial meningitis should prompt a diagnostic workup and initiation of empirical antimicrobial therapy.<sup>4</sup> The most consistent clinical features are fever and a decreased level of consciousness, although they are non-specific and difficult to recognize in patients who are sedated or have just undergone neurosurgical treatment.<sup>4</sup> The British Society for Antimicrobial Chemotherapy recommends empirical treatment for all patients with signs of postoperative meningitis and withdrawal of treatment after 72 hours if the results of CSF culture remain negative.<sup>59</sup> This regimen was evaluated in a prospective study and showed to be associated with few complications in patients with negative CSF Gram stain and culture.<sup>57</sup> However, the effect of preventive use of antibiotics in ICU patients on this regimen is unknown. If a high suspicion of nosocomial bacterial meningitis remains even though CSF cultures are negative, prolongation of antibiotic treatment is advised. When the causative microorganism is identified the antibiotic regimen can be adapted according to the results of CSF culture and susceptibility testing.

#### **Conclusions**

Level 3	Empirical antibiotic therapy can be safely withdrawn after 72 hours in patients with suspected postoperative meningitis if CSF cultures remain negative.  B Zarrouk <sup>57</sup>
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#### **Recommendations**

1. In patients with suspected postoperative bacterial meningitis, empirical antibiotic treatment may be stopped if cultures remain negative after three days.

## Chapter 6.

### Duration of treatment before CSF catheter replacement

#### **Key question 5. How long should infected CSF catheters be treated before removal/replacement?**

If patients with internal ventricular catheters develop bacterial meningitis, the catheter should be removed to increase the chances of resolving the infection.<sup>4</sup> Observational studies showed that removal of the catheter hardware, followed by immediate replacement and intravenous antimicrobial therapy, cures approximately 65% of patients with catheter-related infections.<sup>60</sup> The internal catheter should be replaced with an external ventricular catheter to divert CSF and monitor CSF infection parameters, and this is associated with more rapid resolution of ventriculitis.<sup>4</sup> Conservative management (i.e., leaving the internal catheter in place and administering intravenous or intraventricular antimicrobial therapy) has generally been associated with a low success rate (approximately 35%).<sup>60</sup> Timing of reimplantation of the internal ventricular catheter depends on the causative microorganism and results of repeated CSF cultures. As a general guideline shunt infections with coagulase-negative staphylococci or *Propionibacterium acnes* are treated for 7 days before a new catheter is placed. However, if CSF cultures remain positive the catheter should only be placed after cultures have been negative for at least 10 consecutive days. For shunt infections by *S. aureus* and Gram-negative bacilli, 10 days of antimicrobial therapy after repeated negative cultures are recommended before placement of a new internal catheter.<sup>4</sup> When cultures remain negative 10 days of empirical treatment are recommended before placement of a new internal catheter.

### Conclusions

Level 3	Removal of infected internal ventricular drains and replacement by external ventricular drains combined with intravenous antibiotic treatment is associated with more rapid resolution of ventriculitis.  B Schreffler (2002) <sup>60</sup>
*	No randomized controlled trials or comparative studies have been performed to determine the timing of reimplantation of internal CSF catheters in patients with infected ventricular drains.

### Recommendations

1.	Reimplantation of CSF catheters in shunt infections caused by coagulase-negative staphylococci or <i>Propionibacterium acnes</i> can be performed after 7 days of antimicrobial therapy. If CSF cultures remain positive the catheter should only be placed after cultures have been negative for 10 consecutive days.
2.	Reimplantation of CSF catheters in shunt infections caused by <i>Staphylococcus aureus</i> , Gram-negative bacilli or in patients with negative CSF cultures can be performed 10 days after CSF cultures are negative.



## Chapter 7.

### Intraventricular antibiotic treatment

#### **Key question 6. What are the indications and regimens for intraventricular antimicrobial treatment?**

Direct infusion of antimicrobial agents into the ventricles through external ventricular catheters is sometimes necessary to treat infections after neurosurgical procedures or infections associated with CSF catheters that are difficult to eradicate with parenteral antibiotics alone.<sup>4,28,61,62</sup> The indications for intraventricular antibiotics are however, not well defined. The antibiotic is administered through the catheter, which should subsequently be closed for one hour. Dosages have been determined empirically and are generally adjusted according to the measured CSF concentration of the antibiotic.<sup>4</sup> Determination of CSF antibiotic concentration is performed in a sample taken just before the next dose. The trough concentration should be at least 10-20 times the minimal inhibitory concentration to achieve a constant sterilization of CSF.<sup>4</sup> Antibiotics most used for intraventricular administration are vancomycin and gentamicin (Table 5, adapted from <sup>4</sup>).

**Table 5.** Recommended dosages of antimicrobial agents administered by the intraventricular route.<sup>a</sup>

Antimicrobial agent	Daily intraventricular dose (mg)
Vancomycin	5-20 <sup>b</sup>
Gentamicin	1-8 <sup>c</sup>
Tobramycin	5-20
Amikacin	5-50 <sup>d</sup>
Polymyxin B	5 <sup>e</sup>
Colistin	10-20 <sup>f</sup>
Quinupristin/dalfopristin	2-5

<sup>a</sup>There are no data that define the exact dose of an antimicrobial agent that may be administered by the intraventricular route, but guidance may be given by use of MIC (see text) for use of agents in which concentrations can be measured. Medications administered by the intraventricular route should be preservative-free; <sup>b</sup>Most studies have utilized a 10 mg or 20 mg dose; <sup>c</sup>Usual daily dose is 1-2 mg for infants and children, and 4-8 mg for adults; <sup>d</sup>The usual daily dose is 30 mg; <sup>e</sup>Dosage in children is 2 mg daily; <sup>f</sup>In one study, patients received 10 mg administered every 12 hours

### Conclusions

*	No randomized controlled trials or comparative studies have been performed to evaluate the indications and regimens of intraventricular antimicrobial treatment.
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### Recommendations

1.	Intraventricular antibiotic treatment can be used to treat infections that react poorly to parental antibiotics alone, but indications are not well defined.
2.	The dosage of intraventricular treatment needs to be adjusted to the CSF antibiotic concentration, and should be 10-20 times the minimal inhibitory concentration of the causative micro-organism.

## Chapter 8.

### The epidemiology of bacterial intracerebral abscess in Europe/US.

#### **Key question 7: What is the epidemiology of bacterial intracerebral abscess in Europe/US?**

We identified 51 studies reporting bacterial causes of brain abscesses that met the inclusion criteria.<sup>63-112,113</sup> In these studies 3,583 patients were included (Supplementary table 9). In 2536 patients (71%) data on bacterial cultures were provided, and in 435 patients no culture was performed (17%). Cultures were negative in 30% and in studies reporting the number of cultured bacteria, 26% of the cultures were polymicrobial. This may be an underestimation as local microbiology data suggest that the rate of polymicrobial intracranial abscesses may be as high as 50%.

Of the 2,653 bacteria cultured in the included studies, *Streptococcus* species were the most prevalent and were identified in 36% of the positive cultures (Supplementary table 10). Specification of streptococcal species was not available for the majority of strains. Streptococci from the *milleri* group were the most frequently identified species, occurring in 9% of all patients and 72% of specified streptococcal species. *S. pneumoniae*, the most frequent pathogen of bacterial meningitis, was identified in only 3% of all positive cultures in brain abscess patients.<sup>6</sup> The second most common microorganisms identified in brain abscesses were *Staphylococcus* species (frequency 17%). *Staphylococcus aureus* was identified in 11% of patients and *Staphylococcus epidermidis* in 2%. The species were not specified of the remaining strains. Gram negative enteric bacteria were found in 12% of cases and most of these were *Proteus spp.* (7%). Other relatively frequent pathogens were *Bacteroides spp.* (7%), *Haemophilus spp* (3%) and *Peptostreptococcus spp* (3%). In these included studies 17% of bacteria were classified as ‘other’ or were not specified.

Anaerobe bacteria are present in virtually all polymicrobial abscesses and are frequently found in cerebral abscesses with a dentogenic focus. The frequency of anaerobes given in Supplementary table 10 may be an underestimation due to suboptimal culture techniques and transportation.

16S ribosomal DNA sequencing has expanded the yield of microbiological investigation in patients with intracerebral abscesses.<sup>114</sup> The number of causative pathogens identified by sequencing of brain abscess aspirate was over threefold higher compared to standard culture techniques (22 strains identified by culture vs. 72 by sequencing).<sup>114</sup> This technique is currently not commonly used, but will probably become part of routine diagnostics in the coming years.

#### **Key question 8: What is the optimal (empirical) antibiotic therapy in intracerebral abscess?**

No clinical trials have been performed to determine the optimal regimen in bacterial intracerebral abscesses, therefore the recommendations are all based on expert opinion.<sup>8,9</sup> Empirical treatment consists of a third generation cephalosporin (ceftriaxone or cefotaxime) combined with metronidazole in appropriate doses to penetrate the blood brain barrier. Alternatively penicillin may be used instead of third generation cephalosporins. After identification of the causative microorganism the antimicrobial therapy can be adapted according to the antimicrobial resistance pattern. In culture-negative cases the empirical therapy should be continued until clinical resolution (see question 10).

The primary source of infection can give a clue to which bacteria cause the cerebral abscesses. For instance, *Enterobacteriaceae* are the most frequently found in cerebral abscesses due to otogenic infections. However, since virtually all common pathogens have been reported for the various sources of infection, the choice of empirical antimicrobial therapy cannot be guided by the source of infection (*e.g.* dental abscess, endocarditis).

**Key question 9. What is the optimal dose of antimicrobial therapy?**

Only a limited number of antimicrobials have been studied for their penetration into brain abscesses, mostly in small studies.<sup>53</sup> Antimicrobials have to be able to first penetrate the blood brain barrier and then to achieve sufficient levels inside the abscess to resolve the infection. Penicillin concentrations were only found consistently in brain abscess pus if administered in a high dose of 24 million units per day.<sup>115</sup> Commonly advised doses of penicillin are however 12 million units per day in adults.<sup>8,9</sup> Other antimicrobials that have shown adequate or good penetration into the abscess cavity are metronidazole, vancomycin and third generation cephalosporins.<sup>53</sup> The dosage and dose intervals of antimicrobials commonly used for brain abscesses are presented in table 6. For vancomycin and aminoglycosides, the dose needs to be adjusted according to the peak and trough serum concentrations.

**Table 6.** Dosages of antibiotics for use in adults with bacterial brain abscesses.<sup>a</sup>

Antibiotic	Total daily dose	Dose interval (hour)
Amikacin <sup>b</sup>	15 mg/kg	24
Amoxicillin	12 gr	4
Azitromycin	1200-1500 mg	24
Cefotaxime	8-12 gr	4-6
Ceftazidime	6 gr	8
Ceftriaxone	4 gr	12
Chloramphenicol	4-6 gr or 50 mg/kg/day	6
Ciprofloxacin	800-1200 mg	8-12
Clindamycin	2400-4800 mg	6
Gentamicin <sup>b</sup>	5 mg/kg	24
Meropenem	6 gr	8
Metronidazol	1500 mg	8
Penicillin	12x10 <sup>6</sup> units	4 (or continuous)
Rifampicin	600	24
Tobramycin <sup>b</sup>	5 mg/kg	24
Trimethoprim-sulfamethoxazole	10-20 mg/kg iv (based on TMP component),	8
(TMP/SMX)	max. 960/4800 mg TMP/SMX iv	8
Vancomycin <sup>b</sup>	30-45 mg/kg, max. 2000 mg	12

Adapted from<sup>8</sup>. <sup>a</sup>Patients with normal hepatic and renal function, intravenous administration. <sup>b</sup>Adjust dosage based on peak and trough serum concentrations.

**Key question 10. What is the optimal duration of therapy?**

No studies have been performed to evaluate the optimal duration of therapy in bacterial brain abscesses. The common strategy is to treat the abscess at least 6 weeks and to use clinical, laboratory and radiological follow-up data to decide on further treatment beyond this period.<sup>8,9</sup> Studies on antimicrobial treatment duration for cerebral abscesses are needed.

**Conclusions**

*	No clinical trials have been performed to determine the optimal antibiotic treatment in bacterial intracerebral abscesses,
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**Recommendations**

1. Empirical treatment for bacterial cerebral abscesses consists of a third generation cephalosporin (ceftriaxone or cefotaxime) combined with metronidazole in appropriate doses to penetrate the blood brain barrier (Table 6). Alternatively, penicillin may be used instead of a third generation cephalosporin.
2. If a microorganism is cultured, therapy can be adjusted accordingly. In culture-negative cases the empirical therapy should be continued until clinical resolution.
3. The common strategy for antibiotic treatment of cerebral abscesses is to treat the abscess at least 6 weeks and to use clinical, laboratory and radiological follow-up data to decide on further treatment beyond this period.

## **Chapter 9**

### **Epidemiology, empirical antibiotic treatment and treatment duration of bacterial tuberculous meningitis (in preparation)**

*Key question 11. What is the epidemiology and empirical treatment for tuberculous meningitis (in preparation)?*

*Key question 12. What is the optimal duration of therapy for tuberculous meningitis (in preparation)?*

**Supplementary table 1.** Causative organisms of bacterial meningitis in neonates

<b>Data source</b>	Garges (2006) <sup>13</sup>	Holt (2001) <sup>15</sup>	Hristeva (1993) <sup>14</sup>	NRLBM	Total
Country	US	UK	UK	NL	
Age	0-150 days (NICU)	2-28 days	0-28 days	0-28 days	
Study period	1997-2004	1996-1997	1984-1991	2005-2010	
<b>Gram-positive</b>					
<i>Streptococcus agalactiae</i>	37	69	7	71	178 (54%)
<i>Streptococcus mitis</i>	0	0	1	0	1 (0.3%)
<i>Listeria monocytogenes</i>	1	7	1	1	10 (3.0%)
<i>Streptococcus pneumoniae</i>	2	8	0	3	13 (3.9%)
<i>Gram-positive cocci (not specified)</i>	12	0	0	0	12 (3.6%)
<i>Enterococcus spp.</i>	6	0	0	0	6 (1.8%)
<i>Staphylococcus aureus</i>	4	0	0	1	5 (1.5%)
<i>Other Gram-positive bacteria (not specified)</i>	0	17	0	2	19 (5.7%)
<b>Gram-negative</b>					
<i>Haemophilus influenzae</i>	2	1	0	0	3 (0.9%)
<i>Escherichia coli</i>	12	26	0	25	57 (15.7%)
<i>Enterobacter spp.</i>	4	0	0	0	4 (1.2%)
<i>Serratia spp.</i>	2	0	1	0	3 (0.9%)
<i>Acinetobacter spp.</i>	3	0	0	0	3 (0.9%)
<i>Pseudomonas spp.</i>	3	0	1	0	4 (1.2%)
<i>Proteus spp.</i>	1	0	0	0	1 (0.3%)
<i>Citrobacter spp.</i>	1	0	0	0	1 (0.3%)
<i>Salmonella spp.</i>	1	0	0	1	2 (0.6%)

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<i>Neisseria spp.</i>	2	5	0	0	7 (2.1%)
<i>Klebsiella spp.</i>	0	0	2	0	2 (0.3%)
<i>Achromobacter xylosoxidans</i>	0	0	1	0	1 (0.3%)
<i>Other Gram-negative bacteria</i>	0	11	1	7	19 (5.7%)
<b>Total</b>	<b>93</b>	<b>144</b>	<b>15</b>	<b>111</b>	<b>363</b>

**Supplementary table 2.** Causative organisms of bacterial meningitis in children aged 29 days-16 years

<b>Data source</b>	<b>NRLBM</b>
Study period	2005-2010
<b>Gram-positive bacteria</b>	
<i>Streptococcus pneumoniae</i>	305 (43.6%)
<i>Streptococcus agalactiae</i>	9 (1.3%)
<i>Streptococcus pyogenes</i>	14 (2.0%)
<i>Streptococcus sanguinis</i>	1 (0.1%)
“ $\alpha$ -haemolytic” <i>streptococcus</i>	1 (0.1%)
<i>Staphylococcus aureus</i>	4 (0.6%)
<i>Staphylococcus lugdunensis</i>	1 (0.1%)
<i>Staphylococcus capitis</i>	1 (0.1%)
<i>Staphylococcus epidermidis</i>	2 (0.3%)
Coagulase-negative <i>staphylococcus</i>	1 (0.1%)
<i>Listeria monocytogenes</i>	3 (0.4%)
<b>Gram-negative bacteria</b>	
<i>Neisseria meningitidis</i>	271 (38.8%)
<i>Haemophilus influenzae</i>	76 (10.9%)
<i>Escherichia coli</i>	10 (1.4%)
<b>Total</b>	<b>699 (100.0%)</b>



**Supplementary table 3.** Causative organisms in 1500 episodes of culture-proven community-acquired bacterial meningitis in adults

<b>Data source</b>	DBMS <sup>10</sup>	MeninGene <sup>11</sup>	
Study period	1998-2002	2006-2010	Total (%)
<b>Gram-positive bacteria</b>			
<i>Streptococcus pneumoniae</i>	352	582	934 (62.3%)
<i>Streptococcus pyogenes</i>	6	11	17 (1.1%)
<i>Streptococcus agalactiae</i>	5	9	14 (0.9%)
<i>Streptococcus constellatus</i>	1	0	1 (0.1%)
<i>Streptococcus milleri</i>	0	1	1 (0.1%)
<i>Streptococcus parasanguinis</i>	0	1	1 (0.1%)
<i>Streptococcus oralis</i>	1	1	2 (0.1%)
<i>Streptococcus suis</i>	4	5	9 (0.6%)
<i>Streptococcus salivarius</i>	2	2	4 (0.3%)
<i>Streptococcus bovis</i>	1	2	3 (0.2%)
<i>Streptococcus equi</i>	1	3	4 (0.3%)
<i>Streptococcus mitis</i>	1	2	3 (0.2%)
Group G <i>Streptococcus</i>	1	1	2 (0.1%)
<i>Streptococcus</i> (not specified)	1	2	3 (0.2%)
<i>Enterococcus faecalis</i>	0	2	2 (0.1%)
<i>Staphylococcus aureus</i>	9	12	21 (1.4%)
<i>Staphylococcus epidermidis</i>	1	0	1 (0.1%)
<i>Listeria monocytogenes</i>	30	42	72 (4.8%)
<b>Gram-negative bacteria</b>			
<i>Neisseria meningitidis</i>	257	91	348 (23.2%)
<i>Haemophilus influenzae</i>	14	26	40 (2.7%)
<i>Haemophilus parainfluenzae</i>	1	1	2 (0.1%)
<i>Escherichia coli</i>	4	7	11 (0.7%)
<i>Klebsiella pneumoniae</i>	1	1	2 (0.1%)
<i>Salmonella enteritidis</i>	0	1	1 (0.1%)
<i>Capnocytophaga canimorsus</i>	0	1	1 (0.1%)
<i>Pseudomonas aeruginosa</i>	0	1	1 (0.1%)
<b>Total</b>	<b>693</b>	<b>807</b>	<b>1500 (100%)</b>

**Supplementary table 4.** Causative organisms in culture-proven community-acquired bacterial meningitis in adults aged 17-50 without risk factors.

<b>Data source</b>	MeninGene <sup>11</sup>
Study period	2005-2010
Study group	17-50 years old, no risk factors <sup>a</sup>
<b>Gram-positive bacteria</b>	
<i>Streptococcus pneumoniae</i>	96 (52.4%)
<i>Streptococcus pyogenes</i>	6 (3.3%)
<i>Streptococcus agalactiae</i>	3 (1.6%)
<i>Streptococcus suis</i>	3 (1.6%)
<i>Streptococcus equi</i>	2 (1.1%)
<i>Streptococcus mitis</i>	1 (0.5%)
<i>Staphylococcus aureus</i>	2 (1.1%)
<i>Listeria monocytogenes</i>	3 (1.6%)
<b>Gram-negative bacteria</b>	
<i>Neisseria meningitidis</i>	59 (32.2%)
<i>Haemophilus influenzae</i>	7 (3.8%)
Mixed <sup>b</sup>	2 (1.1%)
<b>Total</b>	183

<sup>a</sup>Risk factors: recent head injury, cerebrospinal fluid leak, diabetes mellitus, immunosuppressive therapy, splenectomy, infection with human immunodeficiency virus (HIV).

<sup>b</sup>*Streptococcus equi* + *Pseudomonas aeruginosa*, *Streptococcus milleri* + *Fusobacterium nucleatum*

**Supplementary table 5.** Bacterial meningitis in patients with external CSF drains

<b>Study</b>	Mayhall <sup>116</sup>	Stenager <sup>117</sup>	Ohrstrom <sup>118</sup>	Coplin <sup>119</sup>	Lyke <sup>120</sup>	Wong <sup>121</sup>	Pfisterer <sup>122</sup>	Park <sup>123</sup>	Arabi <sup>124</sup>	Leverstein <sup>125</sup>	Schade <sup>126</sup>	<b>Total (%)</b>
Study period	1979-1981	1984	1981-1986	1992-1995	1995-1998	1998-2000	1993-1995	1995-2003	1999-2002	2004-2006	1999-2003	
Country	US	Denmark	Denmark	US	US	China	Austria	US	Saudi-Arabia	NL	NL	
<b>Gram-positive bacteria</b>												
<i>Streptococcus pyogenes</i>	1			1								2 (0.7%)
<i>Streptococcus mitis</i>	1											1 (0.4%)
<i>Streptococcus morbillorum</i>							1					1 (0.4%)
<i>Streptococcus spp</i> <sup>a</sup>		1					1		1			3 (1.1%)
<i>Enterococcus faecalis</i>	1	1					2		2	5	2	13 (4.8%)
<i>Staphylococcus aureus</i>	1		9	2			5		1	10	6	34 (12.6%)
<i>Staphylococcus epidermidis</i>		12					16					28 (9.4%)
CNS <sup>b</sup>	6		15	6	2	2	1	31	3	20	9	95 (35.3%)
<i>Staphylococcus saprophyticus</i>							1					1 (0.4%)
<i>Corynebacterium spp.</i>				1			2	2				5 (1.9%)
<i>Bacillus spp.</i>								1		2	1	4 (1.5%)
<b>Gram-negative bacteria</b>												
<i>Escherichia coli</i>	1									3	1	5 (1.9%)
<i>Klebsiella pneumoniae</i>	1		2	1	4		2	1		2	1	14 (5.2%)
<i>Enterobacter spp.</i>	2			1	2		4	1	4	2		16 (5.9%)

<i>Serratia spp.</i>	1				1			1				3 (1.1%)
<i>Proteus spp.</i>					1			1			1	3 (1.1%)
<i>Acinetobacter spp.</i>	2	1	1	1		2	1	1	6		1	16 (5.9%)
<i>Pseudomonas aeruginosa</i>				1			2	2	2	1		8 (3.0%)
<i>Flavobacterium spp.</i>								1				1 (0.4%)
Mixed				1				4		1		6 (2.2%)
Other	1				1		6	2				10 (3.7%)
Total	19	16	27	13	11	6	44	51	19	46	22	269

<sup>a</sup>Not specified, <sup>b</sup>Coagulase-negative *Staphylococcus*

**Supplementary table 6.** Bacterial meningitis in patients with internal CSF drains

Study	Walters <sup>127</sup>	Filka <sup>128</sup>	Vinchon <sup>45</sup>	Kestle <sup>129</sup>	Sacar <sup>130</sup>	Conen <sup>46</sup>	
Study period	1960-1979	1990-1997	1985-2005	2001-2004	2000-2004	1996-2006	
Country	Canada	Slovakia	France	US	Turkey	Switzerland	
<b>Gram-positive bacteria</b>							
<i>Streptococcus pneumoniae</i>			2				2 (0.3%)
<i>Streptococcus agalactiae</i>		1					1 (0.2%)
<i>Streptococcus</i> <sup>a</sup>		1				3	4 (0.6%)
<i>Enterococcus faecalis</i>	24	4	11		1	1	41 (6.3%)
<i>Staphylococcus aureus</i>	77	7	23	9	6	14	136 (20.9%)
CNS <sup>b</sup>		28				29	57 (8.8%)
<i>Staphylococcus epidermidis</i>	128		36	34	3		201 (30.9%)
<i>Listeria monocytogenes</i>			1				1 (0.2%)
<b>Gram-negative bacteria</b>							
<i>Neisseria meningitidis</i>			1				1 (0.2%)
<i>Haemophilus influenzae</i>			7				7 (1.1%)
<i>Flavobacterium spp.</i>					1		1 (0.2%)
<i>Escherichia coli</i>	48				1		49 (7.5%)
<i>Klebsiella pneumoniae</i>	43				1		44 (6.8%)
<i>Enterobacter spp.</i>		1			1	3	5 (0.8%)
<i>Acinetobacter spp.</i>		6			4		10 (1.5%)
<i>Pseudomonas aeruginosa</i>	19	4			2		25 (3.8%)
Gram negative rods <sup>a</sup>			19				19 (2.9%)
<b>Mixed</b>						12	12 (1.8%)
<b>Other</b>	8			27			35 (5.4%)
Total number of episodes	222	33	102	70	20	71	518
Total cultured bacteria	347	53	102	70	20	83	651

<sup>a</sup>Not specified, <sup>b</sup>Coagulase-negative *Staphylococcus*

**Supplementary table 7.** Postoperative bacterial meningitis

Study	McLelland III <sup>52</sup>	Aucoin <sup>131</sup>	Kourbeti <sup>132</sup>	Federico <sup>133</sup>	Wang <sup>134</sup>	Zarrouk <sup>135</sup>	
Study period	1991-2005	1976-1981	1996-2000	1989-1997	1986-2001	1998-2005	
Country	USA	USA	USA	Italy	Taiwan	France	
<b>Gram-positive bacteria</b>							
<i>Streptococcus pneumoniae</i>					3	2	5 (3.0%)
<i>Streptococcus</i> spp. <sup>a</sup>					3	2	5 (3.0%)
<i>Enterococcus faecalis</i>			1		1		2 (1.2%)
<i>Staphylococcus aureus</i>	8	2	2	9	13	5	39 (23.2%)
CNS <sup>b</sup>		1	5		7	3	16 (9.5%)
<i>Staphylococcus epidermidis</i>				19			19 (11.3%)
<i>Corynebacterium</i>				2			2 (1.2%)
<i>Propionibacterium acnes</i>	4						4 (2.4%)
<i>Bacillus</i> spp.			1		1		2 (1.2%)
<b>Gram-negative bacteria</b>							
<i>Haemophilus influenzae</i>			1		1	2	4 (2.4%)
<i>Escherichia coli</i>		1			5	2	8 (4.8%)
<i>Klebsiella pneumoniae</i>		4			3	1	8 (4.8%)
<i>Klebsiella oxytoca</i>					1		1 (0.6%)
<i>Enterobacter</i> spp.		1		1	3	1	6 (3.6%)
<i>Serratia</i> spp.		1	2	3	1	1	8 (4.8%)
<i>Proteus</i> spp.					1		1 (0.6%)
<i>Morganella morganii</i>					1	1	2 (1.2%)
<i>Acinetobacter</i> spp.			1	4	4		9 (5.4%)
<i>Pseudomonas aeruginosa</i>	1		1	1	5		8 (4.8%)
Mixed	2	2	3	7	5		19 (11.3%)

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Total	14	12	12	52	62	20	168
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<sup>a</sup>Not specified, <sup>b</sup>Coagulase-negative *Staphylococcus*

**Supplementary table 8.** Posttraumatic bacterial meningitis

<b>Study</b>	Baltas <sup>58</sup>
Country	Greece
Study period	1987-1992
<b>Gram-positive</b>	
<i>Staphylococcus haemolyticus</i>	1
<i>Staphylococcus cohnii</i>	1
<i>Staphylococcus epidermidis</i>	1
<i>Streptococcus pneumoniae</i>	1
<b>Gram-negative</b>	
<i>Escherichia coli</i>	2
<i>Klebsiella pneumoniae</i>	2
<i>Acinetobacter anitratus</i>	2
<b>Total</b>	11



**Supplementary table 9.** Culture results presented in 51 studies on intracerebral abscesses including 3583 patients.

<b>Characteristics</b>	<b>n/N (%)</b>
Culture data specified	2536/3583 (71%)
Culture not performed	435/2536 (17%)
Positive culture	1478/2101 (70%)
Monomicrobial	1083/1457 (74%)
Polymicrobial	374/1457 (26%)
Negative culture	623/2101 (30%)

**Supplementary table 10.** Overview of 2653 causative bacteria cultured from patients with intracerebral abscesses from 51 studies including >10 patients.

<b>Bacteria</b>	<b>No (%)</b>
<i>Staphylococcus spp</i>	454 (17.1%)
<i>Staphylococcus aureus</i>	292 (11.0%)
<i>Staphylococcus epidermidis</i>	62 (2.3%)
Staphylococci other/not specified	100 (3.8%)
<i>Streptococcus spp</i>	953 (35.9%)
Aerobic streptococci	39 (1.5%)
Haemolytic streptococci	34 (1.3%)
Anhaemolytic streptococci	27 (1.0%)
<i>Streptococcus milleri/ viridans</i> streptococci	219 (8.3%)
Microaerophilic streptococci	55 (2.1%)
<i>Streptococcus pneumoniae</i>	72 (2.7%)
<i>Streptococcus</i> other/not specified	397 (15.0%)
Gram negative enteric rods	313 (11.8%)
<i>Escherichia coli</i>	42 (1.6%)
<i>Klebsiella spp</i>	30 (1.1%)
<i>Proteus spp</i>	183 (6.9%)
Other Gram-negative enteric rods	58 (2.2%)
<i>Pseudomonas spp</i>	47 (1.8%)
<i>Haemophilus spp</i>	85 (3.2%)
<i>Actinomycetales</i>	80 (3.0%)
<i>Nocardia</i>	14 (0.5%)
<i>Actinomyces</i>	25 (0.9%)
<i>Corynebacterium</i>	29 (1.1%)
Other <i>Actinomycetales</i>	20 (0.8%)
<i>Peptostreptococcus spp</i>	88 (3.3%)
Anaerobic streptococci	71 (2.7%)
<i>Bacteroides spp</i>	181 (6.8%)
Other	199 (7.5%)
Not specified	253 (9.5%)

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