



**Coördinatiecommissie Antibioticabeleid / Commission  
de coordination de la politique antibiotique**

# **Evidence-Based Guidelines for the Hospital Use of Antibiotics**

## **BACTERIAL MENINGITIS Adults & Children**

**First draft**

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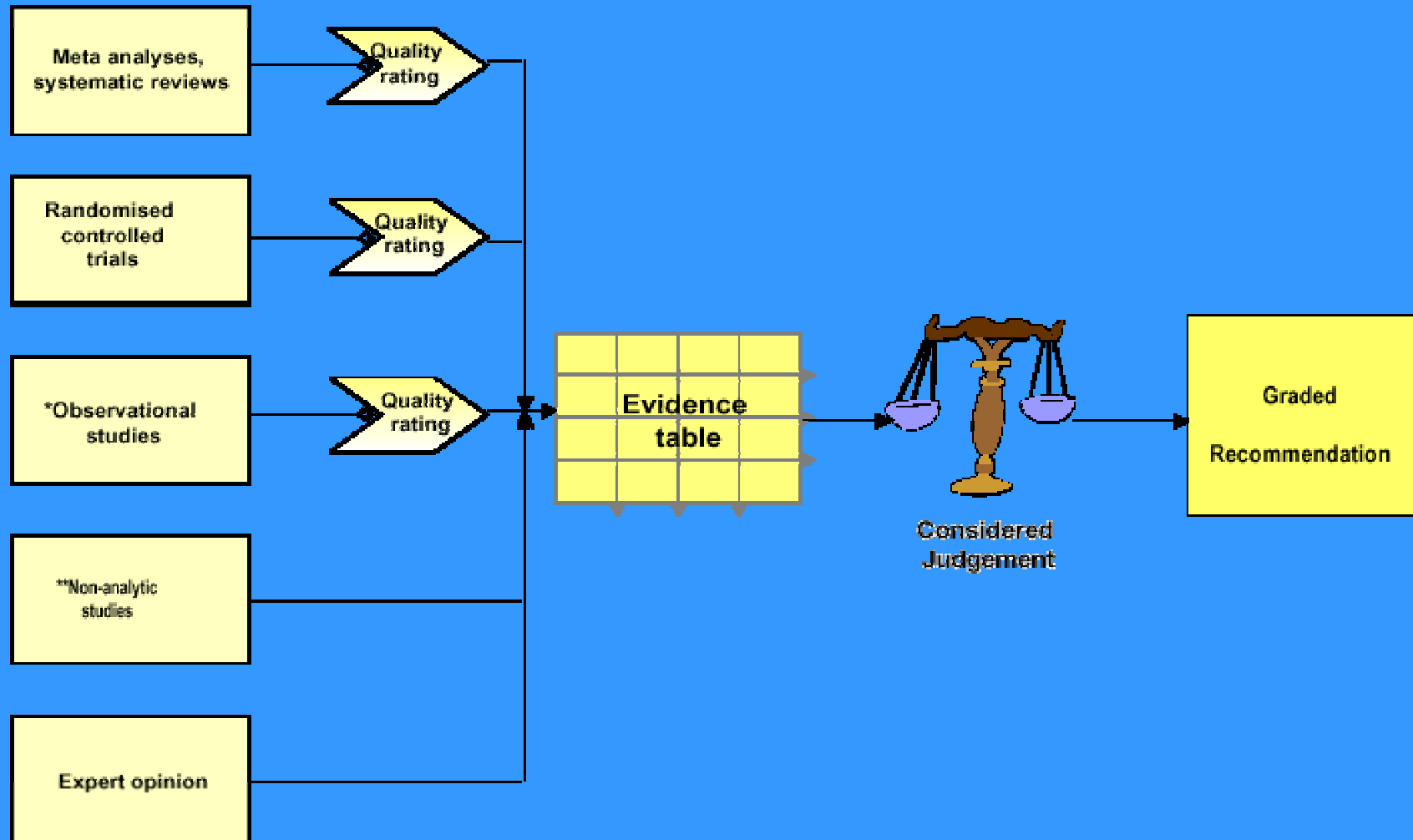
# Introduction

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**The views in this draft are not intended to be implemented in clinical practice at this stage !**

# Evaluation of the literature



# Criteria for considering studies



- \* **Inclusion criteria:** clinical signs suggestive of BM on admission and bacteriological documentation (Gram-stain, antigen, culture)
- \* **Exclusion criteria:** no description of the population and of the end-points.  
( mortality, sequelae, safety).  
History of neurological abnormalities.  
Studies with less than 20 patients.

# AB treatment in childhood BM



- \* **20 RCTs** evaluated, 2 excluded (1960-2000)
  - Few children under 1 month of age
  - 10/20 with acceptable methodology
- \* **3 major pathogens** evaluated:
  - H. influenzae b* > *N. meningitidis* > *S. pneumoniae*
- \* **Type 2 error**: sub-analysis by pathogen
  - Most studies < 100 evaluable patients
- \* **No study with resistant strains of *S. pneumoniae* or with *L. monocytogenes***

# AB treatment in children BM



- \* **3<sup>rd</sup> G cephalos'** vs pen or ampi + **CHL** (9). Same efficacy: trend towards earlier sterilization, fewer neurological sequelae. **CHL alone**: less effective.
- \* **Cefurox vs ampi + CHL or ceftriax** (2): same efficacy, trend towards a delay of sterilization / ↗ hearing loss.
- \* No difference between **3<sup>rd</sup> G cephalos'** agents (1) nor between **3<sup>rd</sup> G-4<sup>rd</sup> G cephalos'** (1), excepted for biliary pseudo-lithiasis (ceftriaxone)
- \* No difference between **3<sup>rd</sup> G cephalos'** and **meropenem** (2)
- \* **Ceftazidime vs ampi + CHL**: same efficacy  
(19 *S. pneumoniae* / 90)

# AB treatment in children BM



## \* **Duration of treatment** (*case-series*)

<b>Standard (16):</b>	<i>N. meningitidis</i>	7 d
	<i>H. influenzae</i>	7-10 d
	<i>S. pneumoniae</i>	10-14 d

**Short course (2)** : 4d, 6d, 7d vs 8d,12d,14d

*As effective (rapid recovery) but few patients by pathogen*

\* **Dosage:** *no dose-ranging studies comparing different dosage of the same AB (case--series)*

# Steroid therapy in children BM



## \* 5 meta-analysis, 1 more thorough (1997)

11 RCTs, 848 patients: 522 Hib, 122 *S. pneu*, 125 *N. men*  
Dexamethasone 4d 0,6 mg/kd/d, only 4 RCTs with  
the same timing of administration.

- Decrease of hearing loss in Hib BM.
- Trend towards decrease of severe hearing loss in *S. pneu* (*Significant if early administration but vulnerable to exclusion of 1 study...*)
- No efficacy on other neurological disorders.

## \* 2 RCTs >1996: trend towards higher mortality (1), 2d vs 4d similar (n=113, only 11 *S. pneumo*)



# AB treatment in adult BM



- ✧ **7 RCTs** included, 1 excluded
- ✧ **No studies with acceptable methodology**
  - Meropenem vs 3<sup>rd</sup> G cephalos' (1)
  - Ceftriaxone vs ampi + CHL (4)
  - Cefuroxime vs ampi + CHL (1)
  - Ceftriaxone vs penicillin (*N. meningitidis*, 1)
- ✧ **No comparison of duration of treatment and of dosages**
- ✧ **Case reports on *L. monocytogenes* BM**

# Steroid therapy in adult BM



- \* No meta-analysis available
  - \* 2 RCTs with unacceptable methodology
- ↳ Lack of evidence of any advantage

# Global microbiological data



## \* Pathogen distribution:

< 3 months: *Group B strepto, L. monocytogenes, E. coli and S. pneumoniae.*

Children: *S. pneumoniae, N. meningitidis and H. influenzae*

Adults: *S. pneumoniae, N. meningitidis and H. influenzae + L. monocytogenes (> 50y)*

# Global microbiological data



## \* **Dramatic decrease of Hib BM** since vaccination

↳ *S. pneumoniae* & *N. meningitidis*

↳ ▲ age distribution (mean 20 years)

## \* **Emergence of *S. pneumoniae* resistant to penicillin**

↳ variability according to:

- countries / geographic areas
- primary infection sites

# Belgian microbiological data (2000)



- \* ***N. meningitidis*** > ***S. pneumoniae*** >> Hib
- \* ***N. meningitidis***: incidence 2,6/10<sup>5</sup>, ↑ type C  
94.4% MIC penicillin < 0,064 µg/ml  
No resistance to 3<sup>rd</sup> G cephalos'
- \* ***S. pneumoniae***: 51 strains (CSF) (45% < 5 y, 33% > 50y)  
Serotypes 6,14,9,19  
21,5% resistant to penicillin (HLR: 0)  
7,8% resistant to 3<sup>rd</sup> G cephalos' (HLR:1)
- \* In 1999, 4 reported cases of **Hib** BM

# Treatment of resistant *S. pneumo*



- \* Case-reports, case-series, animal studies
- \* **Vancomycin + 3<sup>rd</sup> G Cephalos'**! Steroids (adults)  
+ rifampin ?
- \* **Meropenem**: in vitro efficacy, case-reports of  
treatment failure
- \* **3<sup>rd</sup> G Cephalos' HD** (intermediate strains  $0,5 \mu\text{g/ml} < \text{MIC} < 1$ )  
300 mg/kg/ d max. 24g/d but reports on failure
- \* **Routine control spinal tap after 48h of AB** (particularly  
if poor evolution)

# Evidence: Antibiotic therapy



Management	Antibiotic therapy	Level of evidence
Empiric therapy	cefotax or ceftriax (> 1 month)	1b
	Children < 3 months and adults > 50y (or suggestive presentation) : + ampi	3

# Evidence: Antibiotic therapy



	Antibiotic therapy	Level of evidence
Documented therapy	<b><i>N. meningitidis</i></b> : peni or ampi or 3 <sup>rd</sup> GC. Duration: 7d (or 5d if rapid recovery and 3 <sup>rd</sup> GC).	1b 3
	<b><i>S. pneumoniae</i></b> : wait the MIC peni and 3 <sup>rd</sup> GC:	4
	Peni S: Peni or ampi	1b
	Peni R-3 <sup>rd</sup> GC S: 3 <sup>rd</sup> GC	3
	Peni R-3 <sup>rd</sup> GC I-R: vanco + 3 <sup>rd</sup> GC (or meropenem ?)	3
	(3 <sup>rd</sup> GC I: high dose cefotax ?)	
Duration: 10-14d (7d if rapid recovery and 3 <sup>rd</sup> GC)	3	



# Evidence: Antibiotic therapy



	Antibiotic therapy	Level of evidence
Documented therapy	<b><i>H. influenzae</i></b> : 3 <sup>rd</sup> GC or ampi (if S). Duration: 7-10 d	1b 3
	<b><i>S. agalactiae</i></b> : peni (15-21d) + genta (3d)	3
	<b><i>E. coli</i></b> : 3 <sup>rd</sup> GC, 21d	3
	<b><i>L. monoc</i></b> : ampi 15-21d + genta	3

# Evidence: Antibiotic therapy



## Dosage (Level 3)

### Children

Peni 250.000 UI/kg/d (div 6)

Ampi 200 mg/kg/d (div 4)

Cefotax 200-300 mg/kg/d (div 4)

Ceftriax 80-100 mg/kg/d (div 1-2)

Genta 7,5 mg/kg/d (div 3)

### Adults

24 MIU/d (div 6)

12g/d (div 6)

12 (18-24)g/d (div 6)

4g/d (div 2)

5 mg/kg/d (div 3)

# Evidence: Steroid therapy



\* **Adults:** no evidence of benefit

\* **Children:**

- Not vaccinated Hib or unknown: dexamethasone 0,6 mg/kg/d (div 4) for 2 d.
- If dexamethasone is administered in a other situation (no HL evidence of benefit): before or concomitant to AB and for 4d.

# Ongoing



- ✦ **Antibiotic prophylaxis** (secondary case)
- ✦ **Clinical management**
  - Timing of the AB and LP
  - Timing and indication of cerebral CT
  - Viral meningitis

# GDG Bacterial Meningitis



- \* **Neurology:** **M. Van Zandijcke**, Sint Jan Brugge  
**C. Sindic**, Saint-Luc Bruxelles
- \* **Pediatrics:** **S. Van Lierde**, Tienen  
**J. Levy**, Saint-Pierre, Bruxelles  
**L. Maieux**, Antwerp
- \* **Intensive care:** **T. Dujernier**, Saint-Pierre Ottignies
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**JP. Thys**, Erasme Bruxelles
- \* **Microbiology:** **J. Verhaegen**, Gasthuisberg Leuven  
**P. Demol**, CHU Liège

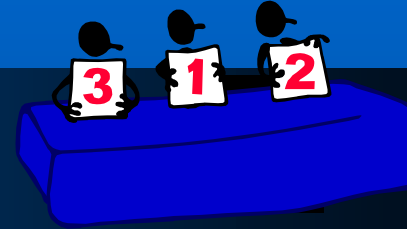
# BACTERIAL MENINGITIS Adults & Children



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[www.health.fgov.be/antibiotics](http://www.health.fgov.be/antibiotics)





# Interactive discussion

In meningitis due to *N. meningitidis*, a third generation cephalosporin may be administered during the all course of treatment.

1

strongly disagree

2

disagree

3

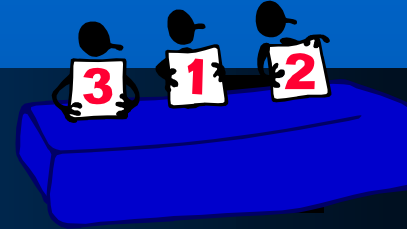
I don't know

4

agree

5

strongly agree



# Interactive discussion

**A short course of AB therapy (cephalos) is appropriate in case of rapid recovery**

1

strongly disagree

2

disagree

3

I don't know

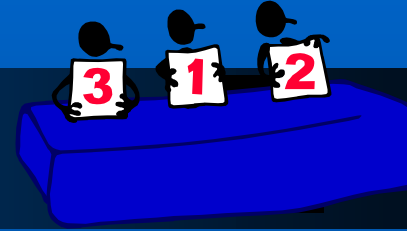
4

agree

5

strongly agree





# Interactive discussion

High dose of cefotaxime is appropriate in the treatment of intermediate strains of *S. pneumoniae*  
(Peni R, cephalo I)

1

strongly disagree

2

disagree

3

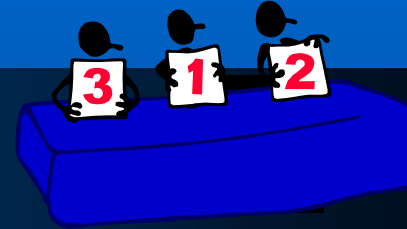
I don't know

4

agree

5

strongly agree



# Interactive discussion

**Ampicillin has to be added to a third generation cephalosporin in adult older than 50 years old.**

1

strongly disagree

2

disagree

3

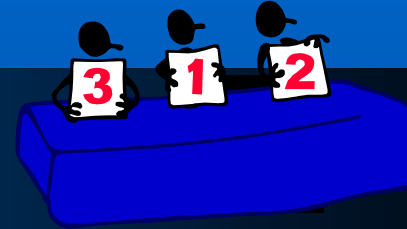
I don't know

4

agree

5

strongly agree



# Interactive discussion

**Dexamethasone has to be administered even  
if children are vaccinated against  
type b *H. influenzae***

1

2

3

4

5

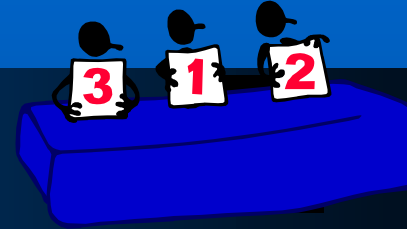
strongly  
disagree

disagree

I don't  
know

agree

strongly  
agree



# Interactive discussion

**Dexamethasone should be included in the treatment of adult BM**

1

2

3

4

5

strongly disagree

disagree

I don't know

agree

strongly agree