MENINGITIS IN CHILDREN

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MENINGITIS AND ENCEPHALITIS

Case

CASE

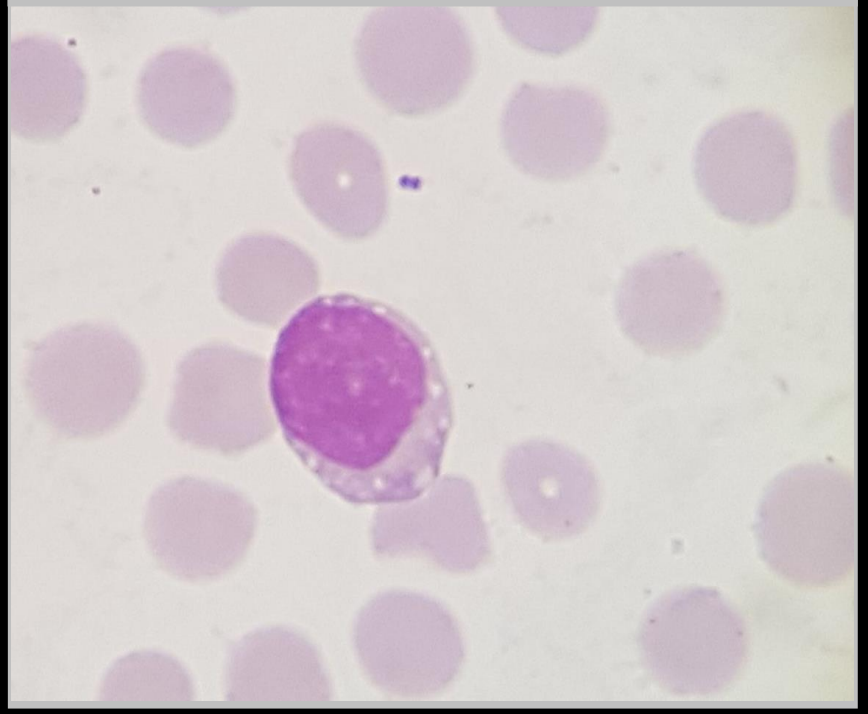
Özdemir H, Kendirli T, Çiftçi E, İnce E. Purpura fulminans in a child due to Neisseria meningitidis. Infection, 40, 717-718 (2012).

CASE

MENINGITIS AND ENCEPHALITIS

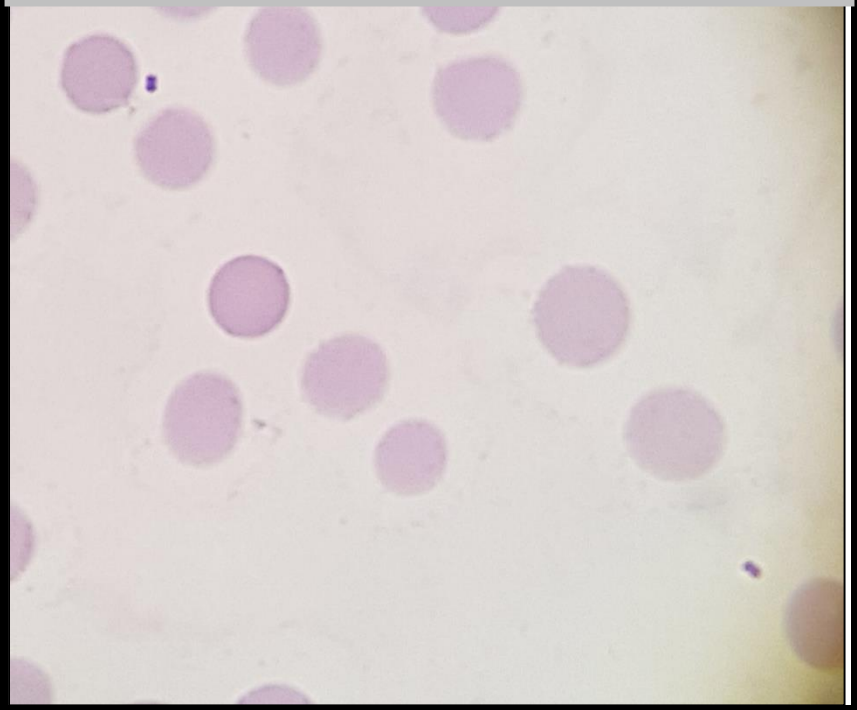
Case

CASE



Peripheral Blood Smear

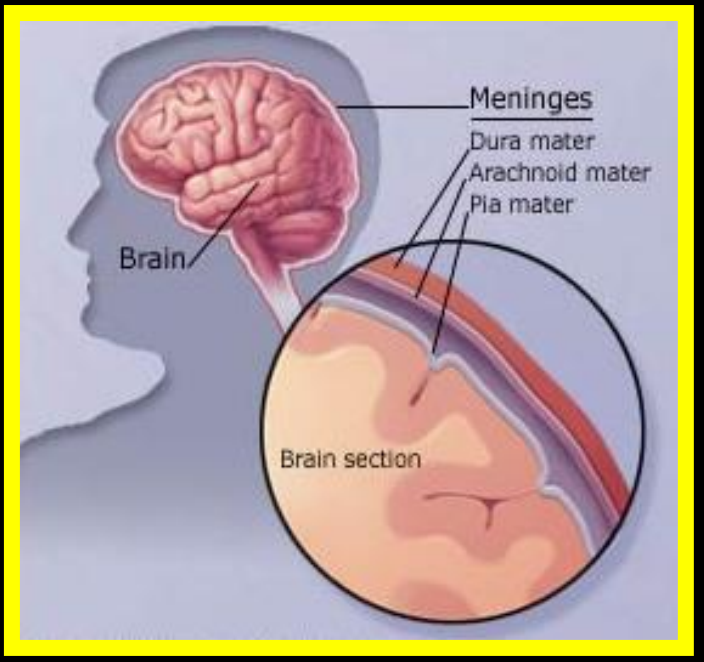
CASE



MENINGITIS

Definition

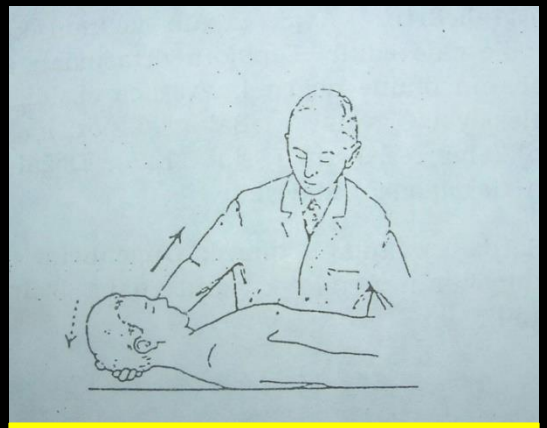
- Meningitis is inflammation of the meninges covering the brain and spinal cord.
- Most often, bacteria or viruses are the causative agent, but fungi or parasites can also cause meningitis.
- Viral meningitis is more common and generally has a milder course.
- Bacterial meningitis is often more severe and can cause long-term complications or death.



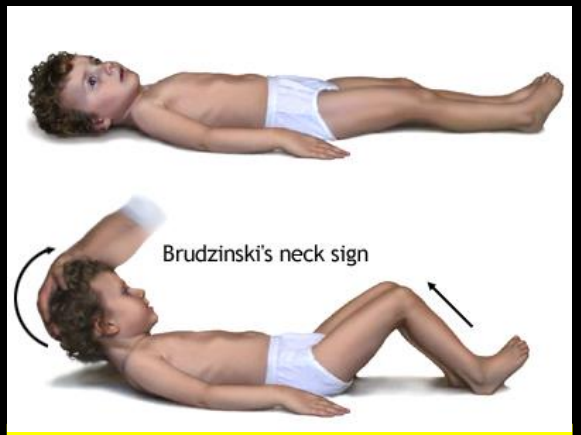
MENINGITIS AND ENCEPHALITIS

Symptoms and Signs

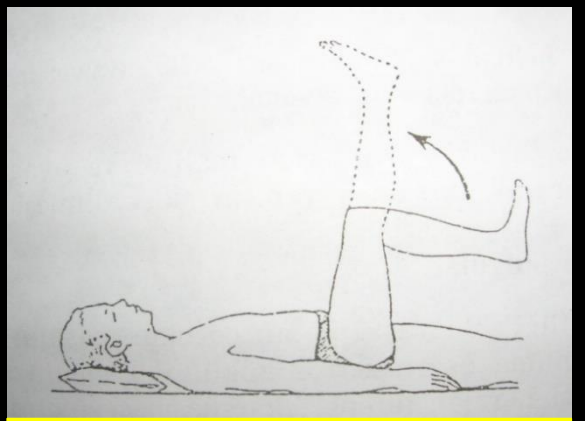
- Stiff neck
- Kernig's sign positivity
- Brudzinski's sign positivity
- Bulging fontanelle
- Decreased level of consciousness
- Convulsive status epilepticus



Stiff neck



Brudzinski's sign



Kernig's sign

MENINGITIS AND ENCEPHALITIS

Symptoms and Signs

- Consider meningococcal disease in any child with fever and a non-blanching rash, particularly if any of the following features are present:
  - An ill-looking child
  - Lesions larger than 2 mm in diameter (purpura)
  - A capillary refill time of 3 seconds or longer

Meningococcal rash

MENINGITIS AND ENCEPHALITIS

Diagnosis

- **The diagnosis of meningitis is made by CSF examination obtained by lumbar puncture (spinal tap).**

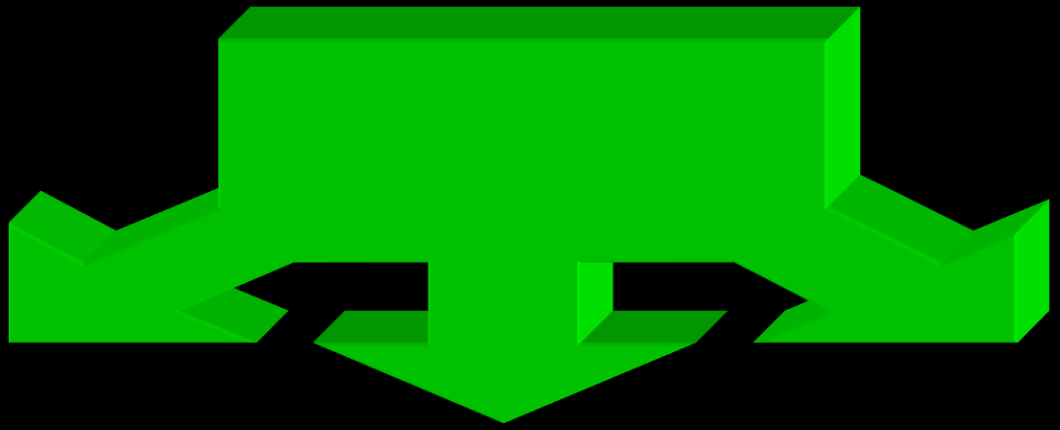
MENINGITIS AND ENCEPHALITIS

CSF Findings

	Opening Pressure (mm Hg)	Cell Count (WBC Cells/microL)	Protein (mg/dL)	Glucose (mg/dL)
Normal	**8 - 15** (100 - 180 mm of H_2O) *with patient lying on their side*	**0 - 5**	**< 40**	**40 - 70**
Bacterial	↑	↑ **PMNs**	↑	↓
Viral	↑ or **normal**	↑ **Lymphocytes**	↑ or **normal**	**normal**
Fungal/TB	↑	↑ **Lymphocytes**	↑	↓

BACTERIAL MENINGITIS

Treatment



Antibiotic Treatment

Dexamethasone

General Management

BACTERIAL MENINGITIS
Antibiotic Treatment

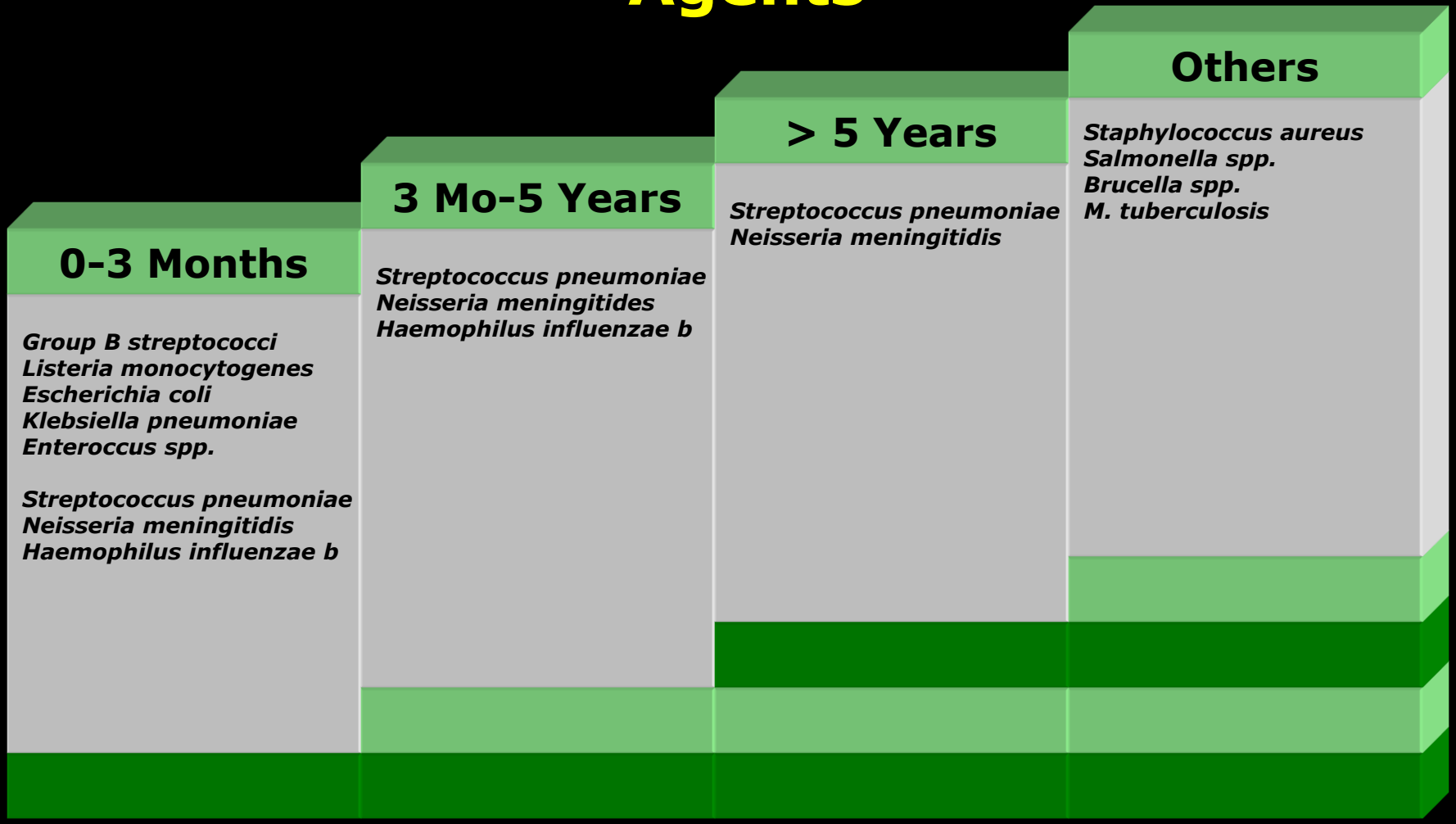
1. **Empirical (initial) antibiotic treatment**
2. **Agent-specific treatment**

BACTERIAL MENINGITIS
General Principles in Empirical Treatment

1. **Considering etiologic agents by age group**
2. **Considering the regional antibiotic resistance of the predicted agent**

BACTERIAL MENINGITIS

Agents



BACTERIAL MENINGITIS

Agents

Multicenter Hospital-Based Prospective Surveillance Study of Bacterial Agents Causing Meningitis and Seroprevalence of Different Serogroups of *Neisseria meningitidis*, *Haemophilus influenzae* Type b, and *Streptococcus pneumoniae* during 2015 to 2018 in Turkey

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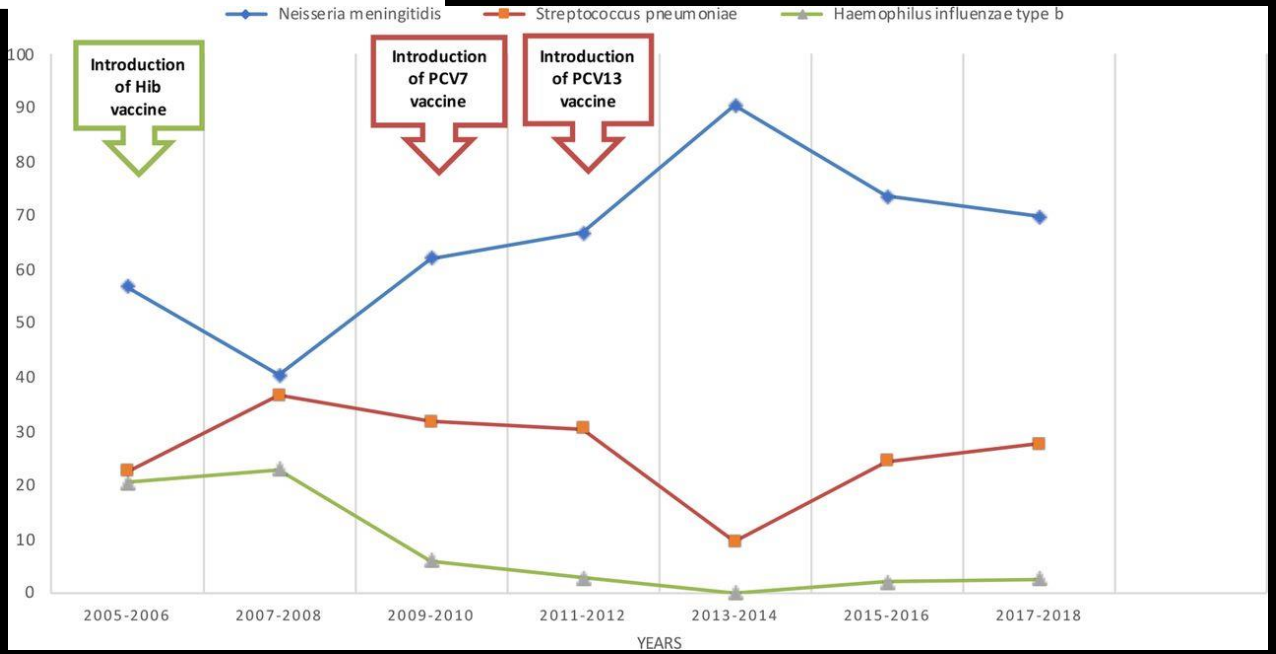


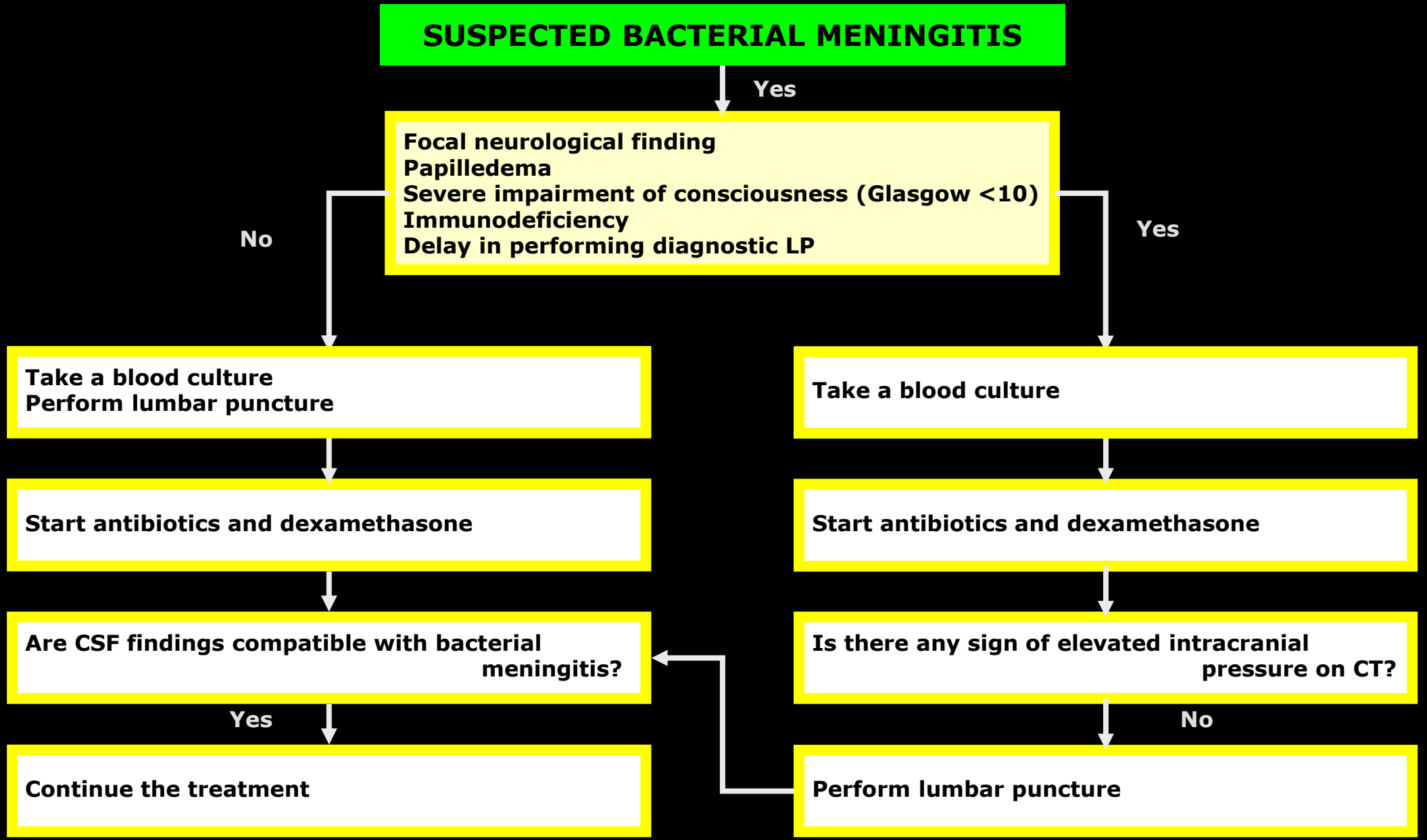
BACTERIAL MENINGITIS

The Importance of Early Diagnosis and Treatment

Long duration of symptoms negatively affects disease prognosis.

Delay in CSF sterilization negatively affects disease prognosis.

Antibiotic treatment should be started as soon as possible!



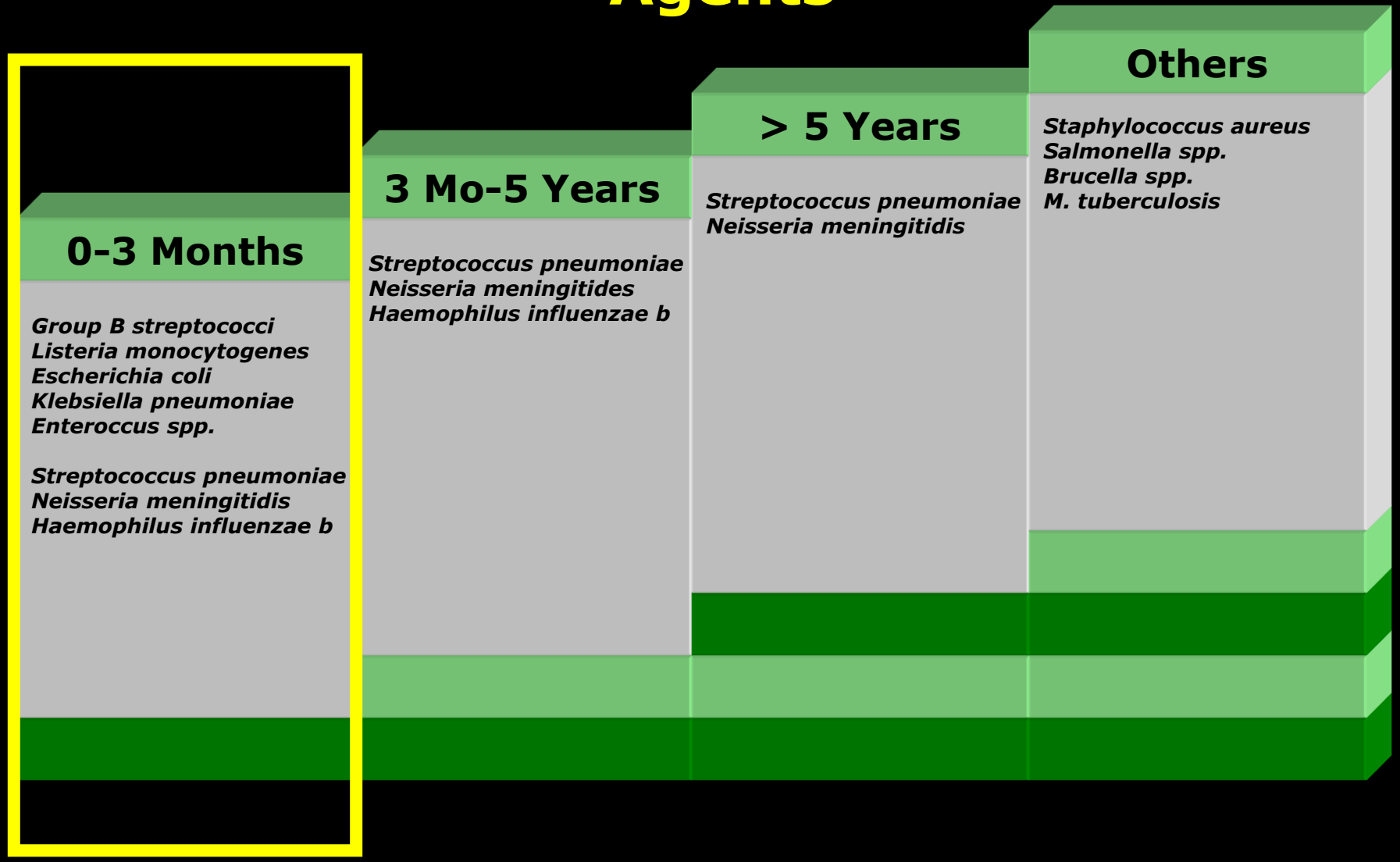
BACTERIAL MENINGITIS

Antibiotic Dosage

ANTIBIOTIC	TOTAL DAILY DOSE mg/kg (number of doses)		
	0-7 DAYS	8-28 DAYS	> 28 DAYS
Ampicillin	150 (3)	200 (3-4)	300 (4)
Cefotaxime	100-150 (2-3)	150-200 (3-4)	225-300 (3-4)
Ceftriaxone	-	-	100 (1-2)
Chloramphenicol	25 (1)	25-50 (1-2)	75-100 (4)
Vancomycin	20-30 (2-3)	30-45 (3-4)	60 (4)
Rifampin	-	10-20 (2)	10-20 (1-2)
Penicillin G	150 000 U (2-3)	200 000 U (3-4)	300 000 U (4-6)
Meropenem	-	-	120 (3)
Cefepime	-	-	150 (3)
Amikacin	15-20 (2)	30 (3)	20-30 (3)

BACTERIAL MENINGITIS

Agents



BACTERIAL MENINGITIS
Antibiotic Treatment at 0-3 Months

1 **Ampicillin + Aminoglycoside**

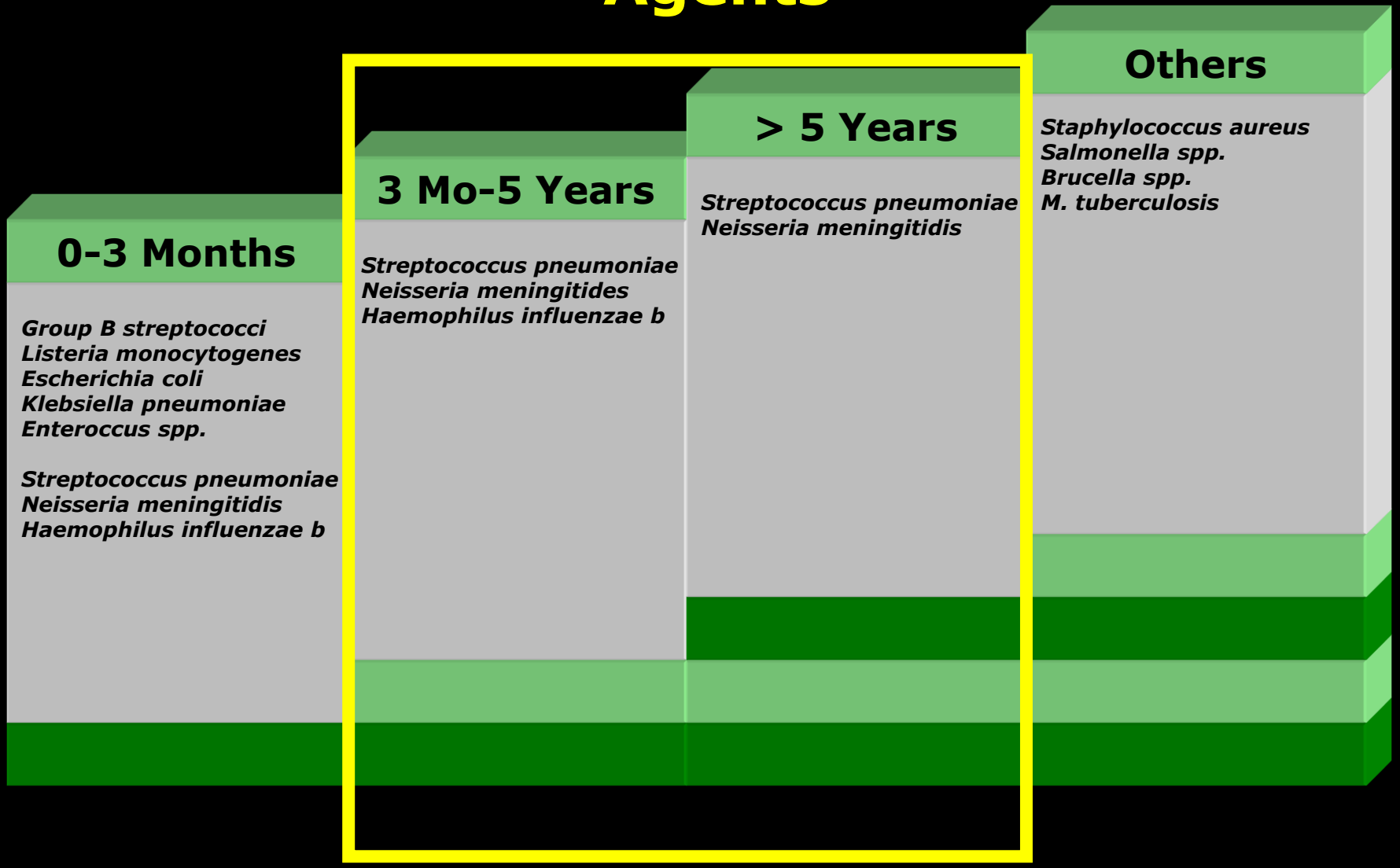
2 **Ampicillin + Cefotaxime/Ceftriaxone**

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment: Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Standard treatment: *S. pneumoniae* susceptible to penicillin	Intravenous dose[a]
Neonates <1 month old	Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside		Age <1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h)

BACTERIAL MENINGITIS

Agents



BACTERIAL MENINGITIS

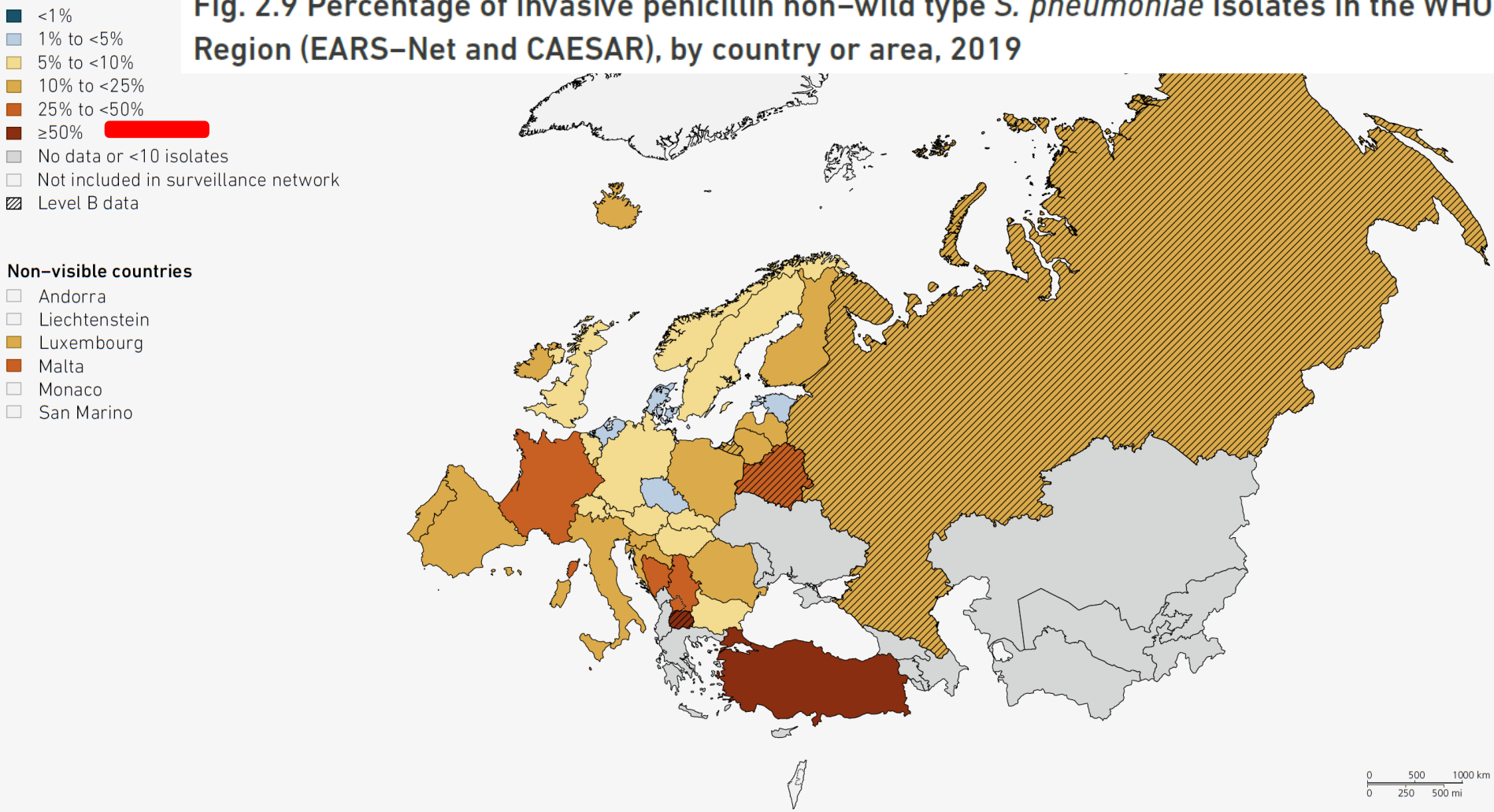
Antibiotic Susceptibility: *S. pneumoniae*

Penicillin and cephalosporin resistance is a concern.

Resistance Breakpoints According to MIC

	SUSCEPTIBLE	RESISTANT
Penicillin	≤0.06 μg/mL	≥0.12 μg/mL
Cephalosporin	≤0.5 μg/mL	≥2.0 μg/mL

Fig. 2.9 Percentage of invasive penicillin non–wild type *S. pneumoniae* isolates in the WHO European Region (EARS–Net and CAESAR), by country or area, 2019



Level B data: the data provide an indication of the resistance patterns present in clinical settings in the country or area, but the proportion of resistance should be interpreted with care. Improvements are needed to attain a more valid assessment of the magnitude and trends of AMR in the country or area. See section 5.2 for more information about levels of evidence, which are only provided for CAESAR countries and areas.

EARS–Net countries: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.
CAESAR countries and areas: Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Switzerland, Tajikistan, Turkey, Turkmenistan, Ukraine, Uzbekistan and Kosovo[1]. Data for Serbia and Kosovo[1] were combined for this map.
[1] All references to Kosovo in this document should be understood to be in the context of the United Nations Security Council resolution 1244 (1999).

Data sources: 2019 data from the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR, ©WHO 2020) and 2019 data from the European Antimicrobial Resistance Surveillance Network (EARS–Net, ©ECDC 2020). Data for Slovenia were obtained from the Slovenian National Institute of Public Health.
Map production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

BACTERIAL MENINGITIS
Vancomycin or Rifampicin Treatment

There is uncertainty regarding the benefit of adding vancomycin or rifampicin to a third-generation cephalosporin in pneumococcal meningitis patients in the setting of decreased susceptibility rates of pneumococci. We systematically evaluated the literature for studies of the efficacy of vancomycin and rifampicin in infections caused by pneumococci resistant to third-generation cephalosporins, but only animal studies were identified [86–88]. These showed that ceftriaxone combined with either vancomycin or rifampicin resulted in a higher rate of CSF sterilization after 24 hours compared to monotherapy with ceftriaxone. Another animal study showed the superiority of ceftriaxone combined with either rifampicin or rifampicin and vancomycin compared to ceftriaxone combined with vancomycin. Although there is no clinical evidence for adding vancomycin or rifampicin in the setting of lower pneumococcal susceptibility rates, the committee advises addition of vancomycin or rifampicin to third-generation cephalosporins based on *in vitro* susceptibility patterns [89]. The advised duration of treatment is 10–14 days [3,40,90].

BACTERIAL MENINGITIS
Vancomycin or Rifampisin Treatment

Vancomycin increases treatment effectiveness in cephalosporin-resistant pneumococcal meningitis.

Hearing loss is more common in those given early vancomycin!

Vancomycin should be given at least 2 hours after cephalosporin.

Buckingham SC, et al.
Early vancomycin therapy and adverse outcome in children with pneumococcal meningitis
Pediatrics 2006; 117: 1688-1694

BACTERIAL MENINGITIS
Antibiotic Treatment

Microorganism	Standard treatment	Alternatives	Duration
Streptococcus pneumoniae			
Penicillin susceptible (MIC <0.1 µg/mL)	Penicillin or amoxicillin/ampicillin	ment should include vancomycin or rifampicin. However, some	
Penicillin resistant (MIC >0.1 µg/mL), third-generation cephalosporin susceptible (MIC <2 µg/mL)	Ceftriaxone or cefotaxime	experts advise the use of ceftriaxone or cefotaxime as empiric	
Cephalosporin resistant (MIC ≥2 µg/mL)	Vancomycin *plus* rifampicin, or vancomycin *plus* ceftriaxone or cefotaxime, or rifampicin *plus* ceftriaxone or cefotaxime[c]	treatment instead of vancomycin or rifampicin when true resistance to third-generation cephalosporin (minimum inhibitory concentration (MIC) >2 mg/L) is not to be expected. When risk	
Neisseria meningitidis			
Penicillin susceptible (MIC <0.1 µg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	7 days
Penicillin resistant (MIC ≥0.1 µg/mL)	Ceftriaxone or cefotaxime	Cefipime, meropenem, ciprofloxacin or chloramphenicol	7 days
Listeria monocytogenes	Amoxicillin or ampicillin, penicillin G[d]	trimethoprim-sulfamethoxazole, moxifloxacin,[b] meropenem, linezolid	At least 21 days
Haemophilus influenzae			
β-Lactamase negative	Amoxicillin or ampicillin	Ceftriaxone, cefotaxime or chloramphenicol	7–10 days
β-Lactamase positive	Ceftriaxone or cefotaxim	Cefepime, ciprofloxacin, chloramphenicol	7–10 days
β-Lactamase negative ampicillin resistant	Ceftriaxone or cefotaxime *plus* meropenem	Ciprofloxacin	7–10 days
Staphylococcus aureus			
Methicillin sensitive	Flucloxacillin, nafcillin, oxacillin	Vancomycin, linezolid, rifampicin,[e] fosfomycin,[e] daptomycin[b]	At least 14 days
Methicillin resistant	Vancomycin[f]	Trimethoprim/sulfamethoxazole, linezolid, rifampicin,[e] fosfomycin,[e] daptomycin	At least 14 days
Vancomycin resistant (MIC >2.0 µg/mL)	Linezolid[f]	Rifampicin,[e] fosfomycin,[e] daptomycin[b]	At least 14 days

BACTERIAL MENINGITIS

Treatment in Children ≥ 3 Months of Age

Suspected Bacterial Meningitis

↓

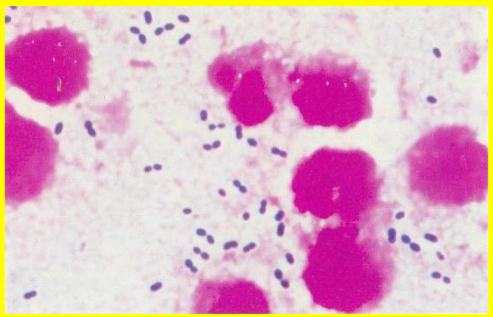
Lumbar Puncture

↓

Ceftriaxone/Cefotaxime + Dexamethasone

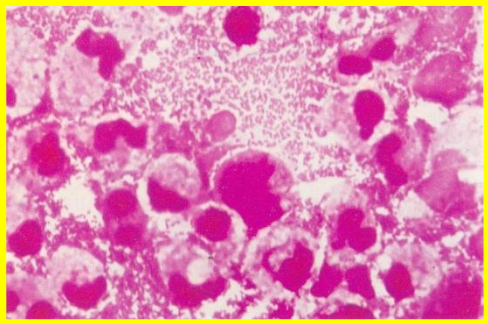
↓

GRAM STAINING

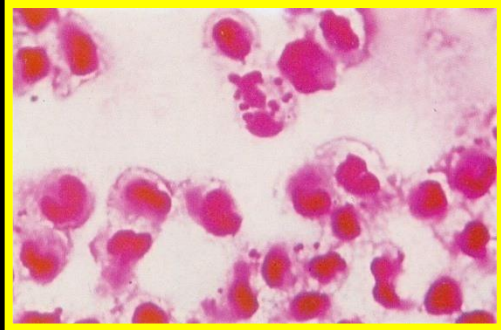


Gram (+) diplococci
Cephalosporin + Vancomycin
Dexamethasone

Undetected
Cephalosporin + Vancomycin
Dexamethasone



Gram (-) cocobacilli
Cephalosporin
Dexamethasone



Gram (-) diplococci
Cephalosporin
Dexamethasone STOP

BACTERIAL MENINGITIS
Treatment in Children ≥ 3 Months of Age

Suspected Bacterial Meningitis

↓

Lumbar Puncture

↓

Ceftriaxone/Cefotaxime + Dexamethasone

↓

GRAM STAINING

↓

CSF CULTURE/PCR

S. pneumoniae
Penicillin susceptible
Penicillin/Cephalosporin
Vancomycin STOP
Penicillin resistant
CS S: Cephalosporin
CS I/R: CS +Vancomycin
Rifampin in special cases
Dexamethasone

Undetected
Cephalosporin + Vancomycin

Dexamethasone

H. influenzae
Cephalosporin
Vancomycin STOP

Dexamethasone

N. meningitidis
Penicillin
Ampicillin
Cephalosporin

Vancomycin STOP

Dexamethasone STOP

BACTERIAL MENINGITIS
Treatment in Children ≥ 3 Months of Age

Suspected Bacterial Meningitis

↓

Lumbar Puncture

↓

Ceftriaxone/Cefotaxime + Dexamethasone

↓

GRAM STAINING

↓

CSF CULTURE/PCR

S. pneumoniae
Penicillin susceptible MIC ≤0.06 µg/mL
Penicillin/Cephalosporin
Vancomycin STOP

Dexamethasone

S. pneumoniae
Penicillin resistant MIC >0.06 µg/mL
Cephalosporin S MIC ≤0.5 µg/mL: Cephalosporin Vancomycin STOP
Cephalosporin I [MIC = 1 µg/mL] or R [MIC ≥2 µg/mL]: Cephalosporin + Vancomycin
Rifampin in special cases

Dexamethasone

BACTERIAL MENINGITIS

Agent-Specific Treatment: *S. pneumoniae*

Rifampin may be added to the regimen (if the isolate is susceptible) in the following settings:

- ❑ **If the isolate has a high MIC for cephalosporins (≥4 µg/mL)**
- ❑ **If the patient appears to be failing vancomycin**
- ❑ **If repeat cerebrospinal fluid culture is not sterile**
- ❑ **If the patient was treated with dexamethasone**

Ceftriaxone/Cefotaxime + Vancomycin + Rifampin

Vancomycin	**Should not be used as monotherapy!**
Rifampin	**Should not be used as monotherapy!**

BACTERIAL MENINGITIS
Monitoring the Effectiveness of Treatment

REPEAT LUMBAR PUNCTURE

- Patients who have a poor clinical response despite 24 to 36 hours of appropriate antibiotic
- Patients with cephalosporin-resistant *S. pneumoniae* meningitis
- Patients with high bacterial burden in CSF
- Patients with *S. pneumoniae* meningitis who were treated with dexamethasone
- Penicillin/cephalosporin resistant *S. pneumoniae* meningitis
- Gram-negative bacillary meningitis
- Persistent or recurrent fever

LP should be considered to check whether the pathogen has been eradicated

BACTERIAL MENINGITIS
Monitoring the Effectiveness of Treatment

REPEAT LUMBAR PUNCTURE

- CSF cultures from the repeat LP grow a pathogenic organism
- CSF examination shows >30% neutrophils
- CSF examination shows CSF glucose of <20 mg/dL (or <20% of the blood glucose level)

Reexamination of the CSF in these settings informs decisions about extending duration of therapy and/or changing the antibiotic regimen

BACTERIAL MENINGITIS
Duration of Antibiotic Treatment

N. meningitidis	: **7 days**
H. influenzae **type b**	: **7-10 days**
S. pneumoniae	: **10-14 days**
S. agalactiae **(GBS)**	: **14-21 days**
S. aureus ***(including MRSA)***	: **At least 14 days**
L. monocytogenes	: **At least 21 days**
Gram-negative bacillary	: **At least 21 days** **or 2 weeks after first negative culture** **(whichever is longer)**

BACTERIAL MENINGITIS
Discontinuation of Antibiotic Treatment

It is not necessary to perform a lumbar puncture check at the end of treatment in uncomplicated *S. pneumoniae, H. influenzae* type b, and *N. meningitidis* meningitis.

Lumbar puncture should be repeated at the end of treatment:

- **Newborns**
- **Gram-negative bacillary meningitis**
- **Patients who did not respond to the treatment after 48-72 hours**

Criteria for discontinuation of treatment:

- **CSF glucose returns to normal**
- **Absence of polymorphonuclear leukocytes in CSF**
- **No growth in CSF culture**

BACTERIAL MENINGITIS
Alternative Therapies

Microorganism	Standard treatment	Alternatives	Duration
Streptococcus pneumoniae			
Penicillin susceptible (MIC <0.1 μg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	10–14 days
Penicillin resistant (MIC >0.1 μg/mL), third-generation cephalosporin susceptible (MIC <2 μg/mL)	Ceftriaxone or cefotaxime	Cefepime, meropenem, moxifloxacin[b]	10–14 days
Cephalosporin resistant (MIC ≥2 μg/mL)	Vancomycin *plus* rifampicin, or vancomycin *plus* ceftriaxone or cefotaxime, or rifampicin *plus* ceftriaxone or cefotaxime[c]	Vancomycin *plus* moxifloxacin,[b] linezolid	10–14 days
Neisseria meningitidis			
Penicillin susceptible (MIC <0.1 μg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	7 days
Penicillin resistant (MIC ≥0.1 μg/mL)	Ceftriaxone or cefotaxime	Cefipime, meropenem, ciprofloxacin or chloramphenicol	7 days
Listeria monocytogenes	Amoxicillin or ampicillin, penicillin G[d]	trimethoprim-sulfamethoxazole, moxifloxacin,[b] meropenem, linezolid	At least 21 days
Haemophilus influenzae			
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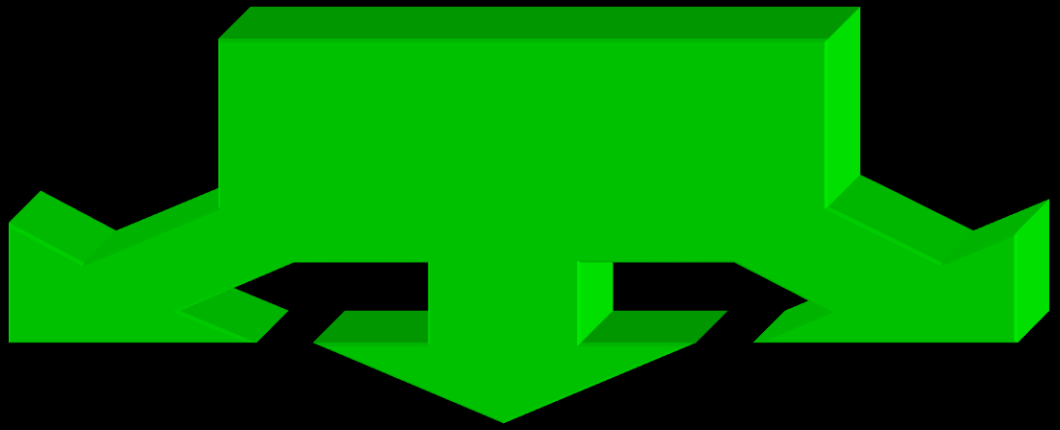
Vancomycin resistant (MIC >2.0 μg/mL)	Linezolid[f]	Rifampicin,[e] fosfomycin,[e] daptomycin[b]	At least 14 days

BACTERIAL MENINGITIS

Treatment



Antibiotic Treatment

Dexamethasone

General Management

BACTERIAL MENINGITIS

Dexamethasone

Benefits

a. Reduce hearing loss
b. Reduce other neurological sequelae
c. Reduce mortality

Harms

a. May reduce antibiotic penetration into CSF
b. It can create a false sense of well-being and make clinical evaluation difficult.

Given before or simultaneously with antibiotics

It can be started within the first 4 hours after antibiotic treatment

DOSAGE

0.15 mg/kg/dose, 4 times a days, 2 or 4 days

Table 7 Empirical treatment recommendations for suspected bacterial meningitis

Initial treatment recommendations*					
CMG	3rd-generation cephalosporin (ceftriaxone^ or cefotaxime)	3rd generation-cephalosporin (ceftriaxone^ or cefotaxime) plus a penicillin (amoxicillin, ampicillin or penicillin)	Aminoglycoside (gentamicin) plus a penicillin (amoxicillin or ampicillin)	Add: glycopeptide (vancomycin)	Add: corticosteroids (before or with first dose of antibiotics)
EFNS Europe	P, A	E		Older children and adults**	Yes
ESCMID Europe	P, A	N, A > 50 years, or if risk factor for *L. monocytogenes*	N	**,^	Yes^ up to 4 h post-antibiotics
DSI Denmark	A	A if risk of *L. monocytogenes*			Yes
SPILF France	P, A	P, A if suspected L. monocytogenes°		If S. pneumoniae	Yes"
DGN: BM Germany	A	A		A**	Yes
HPSC Ireland	P > 2 m, A	N, P < 2 months	N, P < 2 months	**,^	Yes up to 24 h post-antibiotics
NVN Netherlands	P, A	N, A			Yes
MHSSE# Spain	P				Yes
NICE UK	P > 3 m	N, P < 3 months		If travel outside of the UK	Yes^^ up to 12 h post-antibiotics
UKJSS UK	A	A > 60 years		Pending travel history	Yes up to 12 h post-antibiotics
SIGN# Scotland	P > 3 m	N, P ≤ 3 months			Yes up to 24 h post-antibiotics
IDSA USA/ Global	P, A	N, A > 50 years	N	P, A	P^, infants if Hib, A
AEPED Spain	P	N, P ≤ 3 months		**,^	Yes
MSF Global	P > 3 m, A	N, P ≤ 3 months	N, P ≤ 3 months		Yes^
NNF Norway	NS	NS			Yes

BACTERIAL MENINGITIS
Treatment in Children ≥ 3 Months of Age

Suspected Bacterial Meningitis

↓

Lumbar Puncture

↓

Ceftriaxone/Cefotaxime + Dexamethasone

↓

GRAM STAINING

↓

CSF CULTURE/PCR

S. pneumoniae
Penicillin susceptible
Penicillin/Cephalosporin
Vancomycin STOP
Penicillin resistant
CS S: Cephalosporin
CS I/R: CS +Vancomycin
Rifampin in special cases
Dexamethasone

Undetected
Cephalosporin + Vancomycin

Dexamethasone

H. influenzae
Cephalosporin
Vancomycin STOP

Dexamethasone

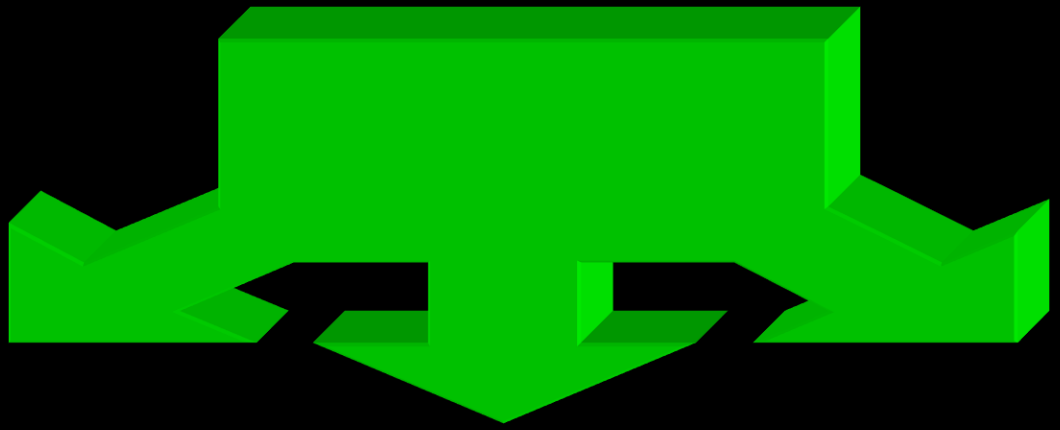
N. meningitidis
Penicillin
Ampicillin
Cephalosporin

Vancomycin STOP

Dexamethasone STOP

BACTERIAL MENINGITIS

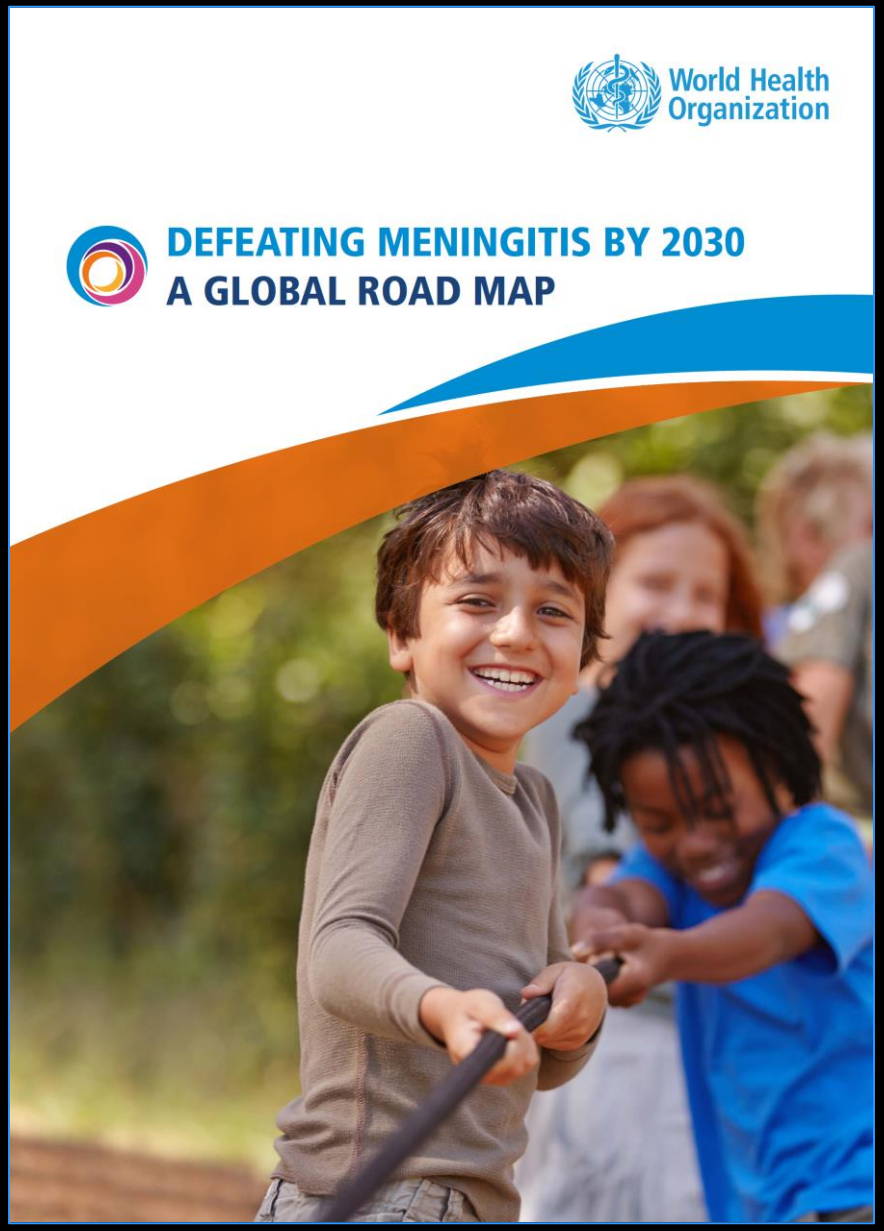
Treatment



Antibiotic Treatment

General Management

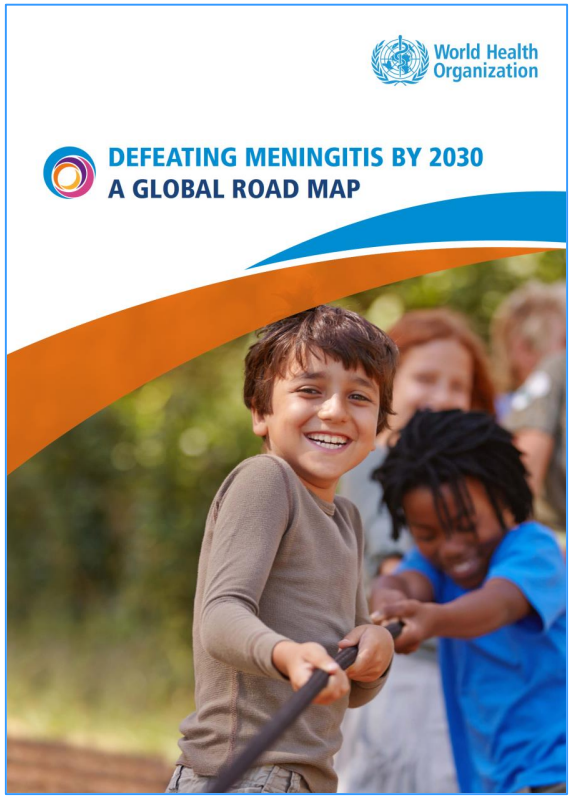
Dexamethasone



Defeating meningitis by 2030: a global road map

ISBN 978-92-4-002640-7 (electronic version)
ISBN 978-92-4-002641-4 (print version)

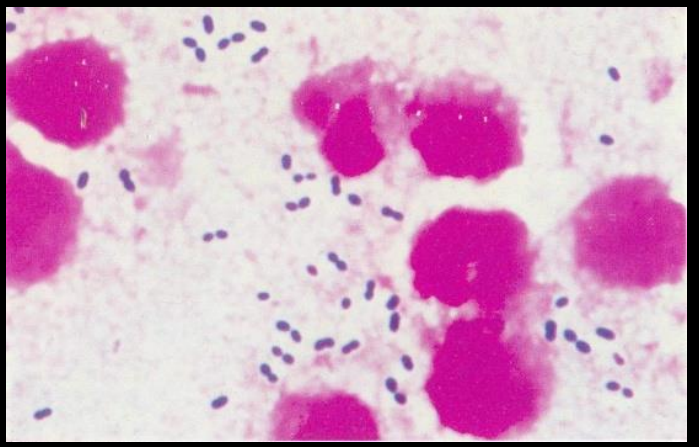
- By 2030, countries have committed to:
  - eliminating bacterial meningitis epidemics;
  - reducing cases of vaccine-preventable bacterial meningitis by 50% and deaths by 70%;
  - reducing disability and improving the quality of life for meningitis survivors.



QUESTION: WHAT HAVE WE LEARNT?

You see the CSF gram stain of a 5-month-old child diagnosed with meningitis.

Which one is suitable for empirical treatment?



A. Ceftriaxone
B. Ceftriaxone+Vancomycin
C. Ceftriaxone+Vancomycin+Rifampin
D. Ceftriaxone+Dexamethasone
E. Ceftriaxone+Vancomycin+Dexamethasone
F. Ceftriaxone+Vancomycin+Rifampin+Dexamethasone

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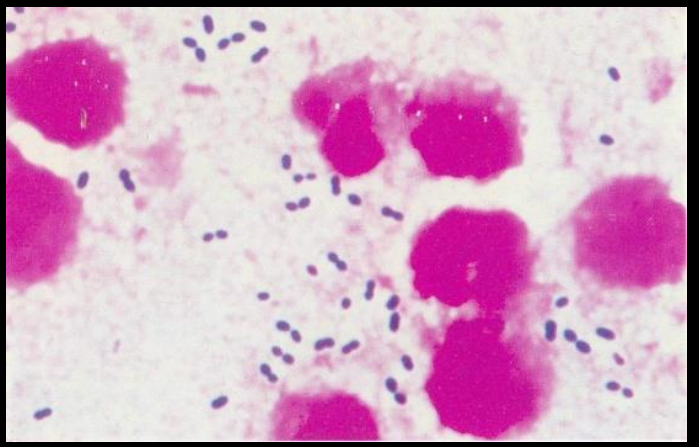

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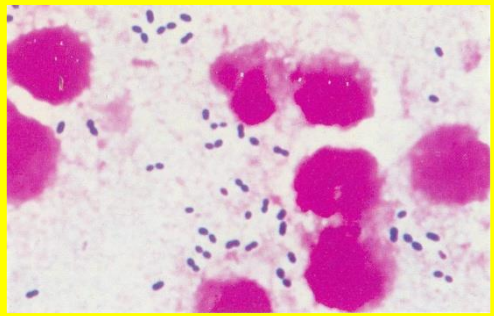
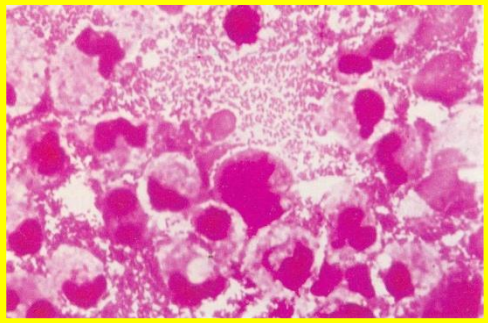
GRAM STAINING

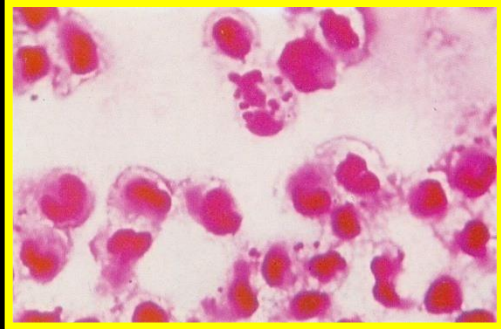


Gram (+) diplococci
Cephalosporin + Vancomycin
Dexamethasone

Undetected
Cephalosporin + Vancomycin
Dexamethasone



Gram (-) cocobacilli
Sefalosporin
Dexamethasone



Gram (-) diplococci
Cephalosporin