

ANTIBIOTIK BLOOD BRAIN BARRIER

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The “blood-brain barrier (BBB)”

- Kapiler pembuluh darah di SSP mempunyai **tight junctions** yang menyusun BBB.
- Kapiler pembuluh darah di SSP terbungkus **sel glia pericapillar** yang menyusun BBB.
- Sel endotel kapiler pembuluh darah di SSP mempunyai **P-glycoprotein** yang memompa obat keluar endotel

The “blood-brain barrier (BBB)”

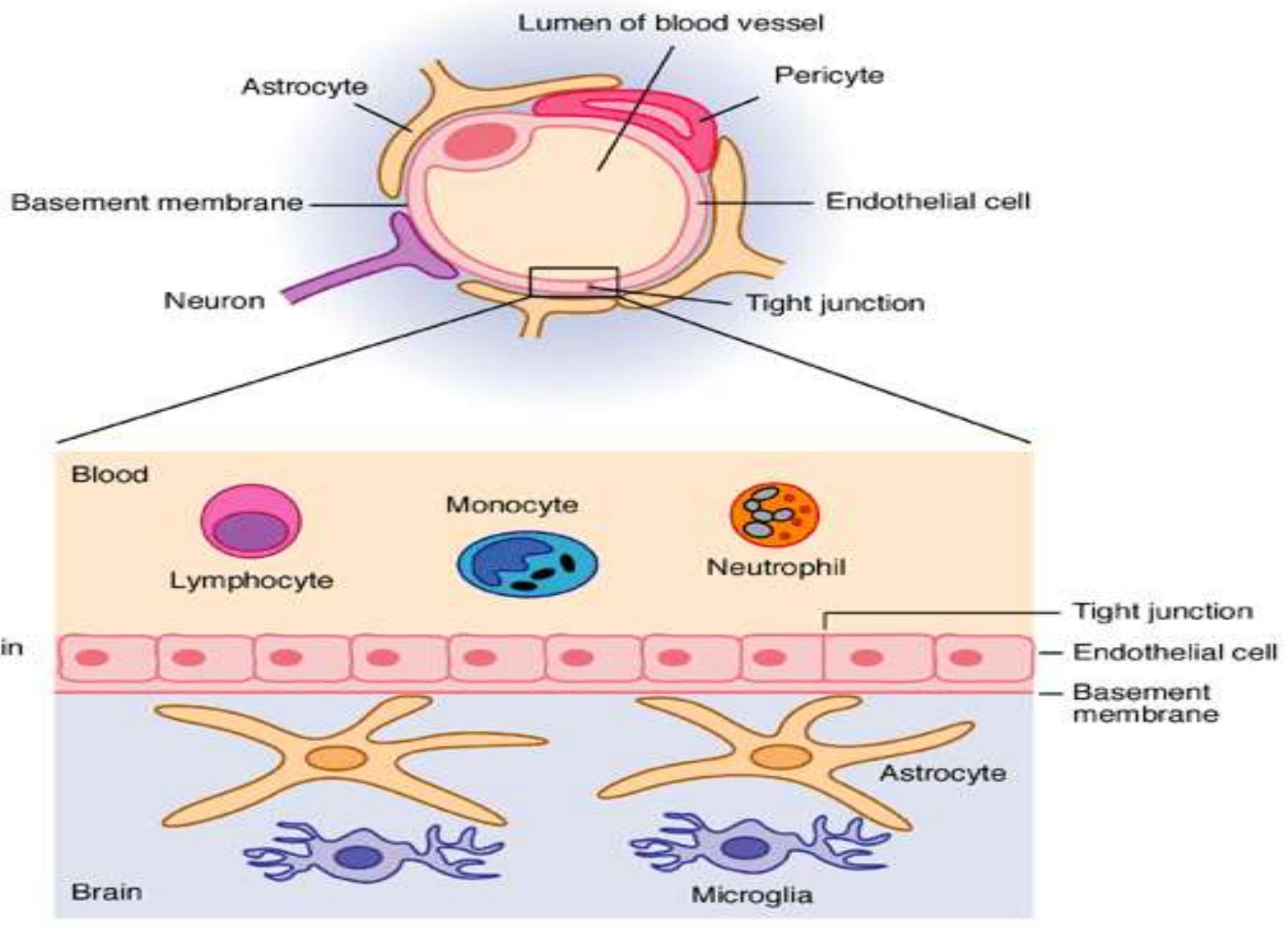
- BBB hambat masuknya obat yang hidrofilik (larut air) ke dalam SSP
- BBB tidak berfungsi pada ischemia dan inflamasi.
- BBB menyebabkan berkurangnya efek obat ke SSP

Blood-Brain Barrier

1. Lipofilik (larut lemak) lebih mudah menembus BBB
2. Bermuatan negatif lebih mudah menembus BBB daripada bermuatan positif
3. Kadar CO₂ tinggi / O₂ rendah sebabkan vasodilatasi → menurunkan BBB
4. Trauma & inflamasi menurunkan BBB

Blood-Brain Barrier

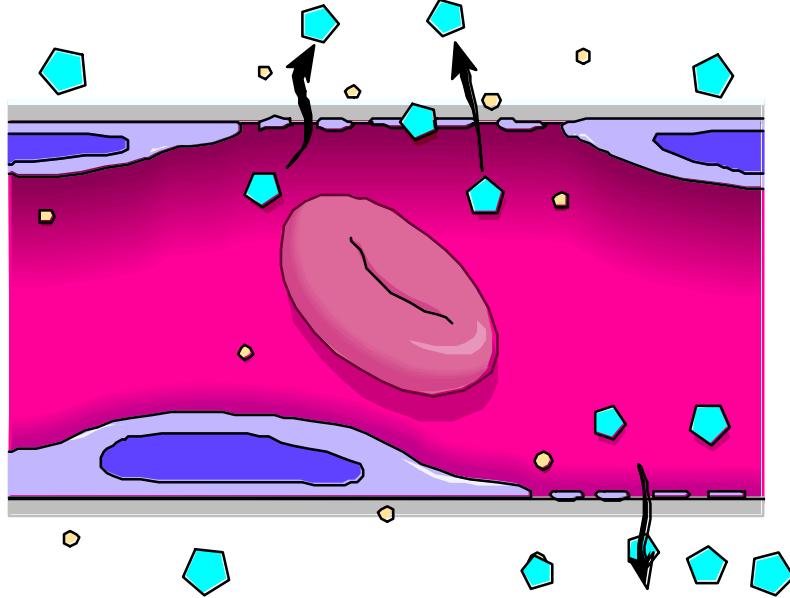
5. Beberapa area SSP **tidak terlindungi BBB** – the circumventricular organs (CVO) sekitar ventrikel 3 dan 4:
 - parts of the hypothalamus - median eminence
 - Neurohypophysis
 - pineal gland
 - area postrema
 - subfornical organ
 - subcommissural organ



The blood-brain barrier (BBB)

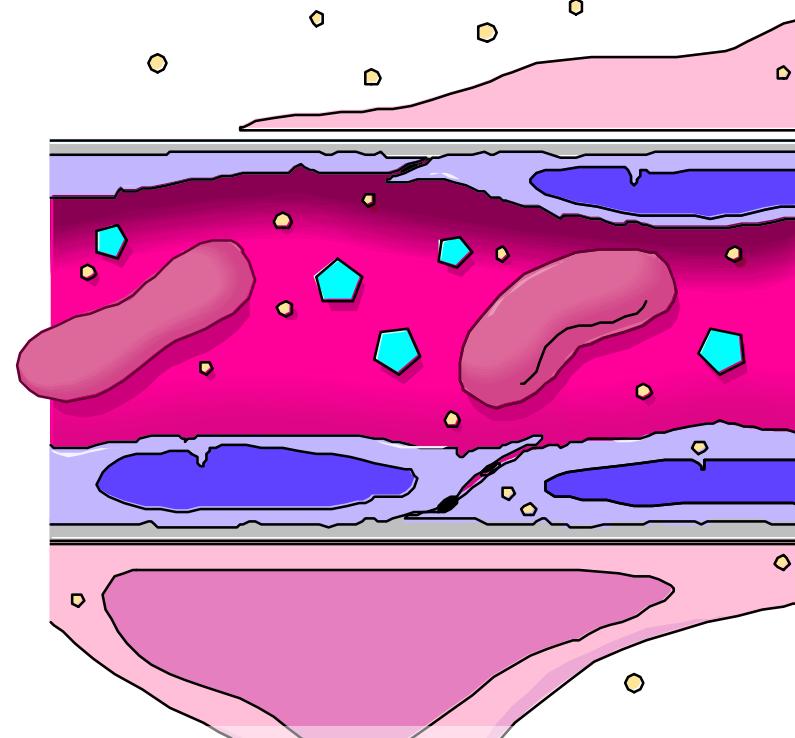
Selectivity of the Blood Brain Barrier

Peripheral Capillary



◆ - Protein
○ - Glucose

Brain Capillary



permeability restricted to:

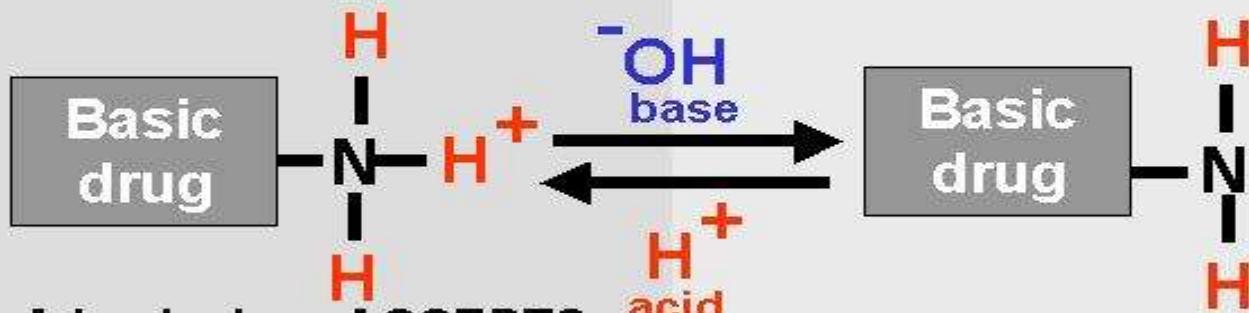
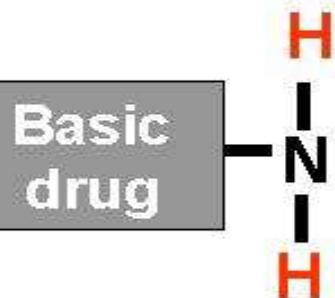
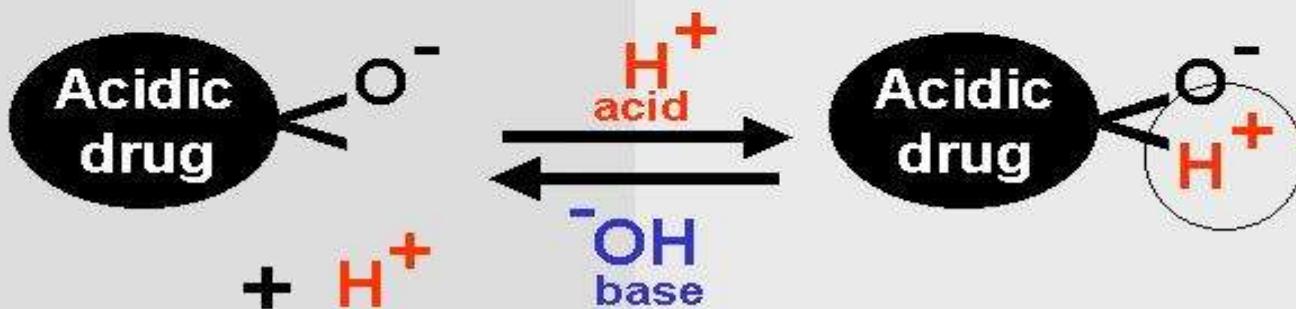
- small molecules (<600D)
- lipophilic substances

Uncharged drug

WATER SOLUBLE
drug must be charged
to be excreted in urine

LIPID SOLUBLE
drug must be uncharged
to cross a membrane

(water = $\text{H}^+ + \text{-OH}$)



Fungsi BBB menurun pada:

- 1. Hipertensi**
- 2. Bayi → belum terbentuk sempurna**
- 3. Hiper Osmolalitas**
- 4. Paparan mikrowave**
- 5. Paparan radiasi**
- 6. Infeksi → inflamasi**
- 7. Trauma, iskemia, inflamasi, tekanan tinggi**

**ANTIBIOTIK
KUMAN GRAM (+)**

Penisilin

- **Narrow-spectrum**
 - Penicillin G (IV)
 - Penicillin VK (PO)
- **Penicillinase-resistant → Antistaphylococcal**
 - Cloxacillin, dicloxacillin (PO)
 - Nafcillin (IV)
 - Oxacillin (IV)
- **Extended-spectrum**
 - Ampicillin/.Amoxicillin (PO)
 - Amoxicillin + clavulanate (PO)
 - Piperacillin (IV)
 - Ticarcillin (IV)

Cephalosporins

1st → Gram (+)

2nd → spektrum lebih luas → Gr (-) Gr (+) ↓

3rd → spektrum Gr (-) ↑ Gr (+) ↓

→ Serious Gram negative infections

– CeftriAXone and cefotAXime → menembus BBB

– Ceftazidime → anti-Pseudomonal

4th cefepime → Anti-Pseudomonal coverage

Spektrum Gr (-)/Gr (+) baik

5th Ceftaroline

→ MRSA

	Pola 1	Pola 2	Pola 3
Karakter P-Dinamik	<ul style="list-style-type: none"> - concentration dependent - PAE sedang sampai lama 	<ul style="list-style-type: none"> - time dependent - PAE minimal sampai sedang 	<ul style="list-style-type: none"> - time dependent - PAE lama
Jenis Antibiotik	Aminoglikosida Fluorokuinolon Metronidasol Amfoterisin B Ketolid Daptomisin	Beta laktam Makrolid Klindamisin Oksazolidin Flusitosin	Tetrasilkin Azitromisin Glikopeptid Kuinopristin Flukonasol
Dosing Regimen	Maksimumkan dosis / konsentrasi obat	Maksimumkan duration of exposure	Optimalkan jumlah obat keseluruhan
Parameter P-Kinetik	Peak Level dan AUC	Time above MIC	AUC

DAYA PENETRASI ANTIBIOTIK

BBB

Compound (reference[s] for CSF penetration)	AUC_{CSF}/AUC_S^b	
	Uninflamed or mildly inflamed meninges	Strong meningeal inflammation
Penicillins	0.02	0.2
Penicillin (46, 107, 108, 194, 246)		
Nafcillin (164)		
Cloxacillin (46, 217)	0.0087	
Amoxicillin (18, 35)		0.058
Ampicillin (35, 46, 72)		
Mezlocillin (94)		
Piperacillin (51, 168)	0.034	0.32
β -Lactamase inhibitors	0.07	0.1
Clavulanate (18)	0.037	0.084
Sulbactam (72)		
Tazobactam (168)	0.106	

Compound (reference[s] for CSF penetration)	AUC_{CSF}/AUC_S^b	
	Uninflamed or mildly inflamed meninges	Strong meningeal inflammation
Cephalosporins	0.007-0.1	0.15
Cefazolin (111)		
Cephalexin (46)		
Cefuroxime (112, 229)		
Cefotaxime (96, 175, 194, 195, 230)	0.12	0.04, 0.17
Ceftriaxone (47, 118, 141, 162, 175, 195, 236)	0.007	
Ceftazidime (24, 70, 83, 156, 160, 172, 265)	0.057	
Cefixime (165)		
Cefepime (213)		0.103
Cefpirome (73, 181, 262)		0.145, 0.31

Compound (reference[s] for CSF penetration)		AUC _{CSF} /AUC _S ^b
	Uninflamed or mildly inflamed meninges	Strong meningeal inflammation
Carbapenems	0.2	0.3
Imipenem (15, 155, 263)		0.14
Meropenem (34, 41, 142, 170)	0.047, 0.21, 0.25	0.39
Aminoglycosides	0.2	Not available
Gentamicin (28, 46)		
Netilmicin (29, 55, 177)	0.24	
Amikacin (26, 76)		
Fluoroquinolones	0.3–0.7	0.7–0.9
Ciprofloxacin (173, 261)	0.24, 0.43	0.92
Ofloxacin (169)	0.62	
Levofloxacin (189, 223)	0.71	
Moxifloxacin (4, 5, 105)	0.46	0.79 (0.71–0.94)
Chloramphenicol (46, 74, 270)	0.6–0.7	0.6–0.7
Macrolides (98)		
Clarithromycin (137)	Not available	0.18

Compound (reference[s] for CSF penetration)	AUC_{CSF}/AUC_S^b
	Uninflamed or mildly inflamed meninges
Tetracyclines Doxycycline (56, 107, 108, 269)	Ratios of individual CSF and serum samples suggest AUC ratio ~0.2
Fosfomycin (75, 115, 193)	Ratios of individual CSF and serum samples suggest AUC ratio ~0.2
Linezolid (20, 252)	0.18 (0.09–0.27)
Metronidazole (93, 101, 258)	Not available
	Not available
	0.87

Compound (reference[s] for CSF penetration)		AUC_{CSF}/AUC_S^b
	Uninflamed or mildly inflamed meninges	Strong meningeal inflammation
Rifamycins		
Rifampin (52, 62, 89, 106, 150, 163, 174)	0.22	Not available
Trimethoprim and sulfamethoxazole (57, 125, 257)		
Trimethoprim	0.18	0.42–0.51
Sulfamethoxazole	0.12	0.24–0.30
Glycopeptides		
Vancomycin (2, 31, 65, 192, 205)	0.18, 0.14	0.30 (0.29–0.48)

Compound (reference[s] for CSF penetration)	AUC_{CSF}/AUC_S^b	
	Uninflamed or mildly inflamed meninges	Strong meningeal inflammation
Antituberculosis drugs	Not available	
Isoniazid (53, 54, 62, 106, 228)		0.86 (0.78–1.17)
Pyrazinamide (54, 106)		
Ethambutol (25, 85)		
Streptomycin (62, 106)		
Ethionamide (62)		

Empirical antimicrobial therapy for community-acquired bacterial meningitis,

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	

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 ^a
<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

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.

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

Antibiotic	Total daily dose	Dose interval (hour)
Amikacin ^b	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

Antibiotic	Total daily dose	Dose interval (hour)
Gentamicin ^b	5 mg/kg	24
Meropenem	6 gr	8
Metronidazol	1500 mg	8
Penicillin	12x10 ⁶ units	4 (or continuous)
Rifampicin	600	24
Tobramycin ^b	5 mg/kg	24
Trimethoprim-sulfamethoxazole (TMP/SMX)	10-20 mg/kg iv (based on TMP component), max. 960/4800 mg TMP/SMX iv	8
Vancomycin ^b	30-45 mg/kg, max. 2000 mg	12