ESCMID Postgraduate Education Course

Meningitis Update 2013

Treatment of community-acquired meningitis including difficult to treat organisms like penicillin-resistant pneumococci and guidelines (ID perspective)

Stefan Zimmerli, MD

Institute for Infectious Diseases

University of Bern

institute for infectious diseases
University of Bern

Outline

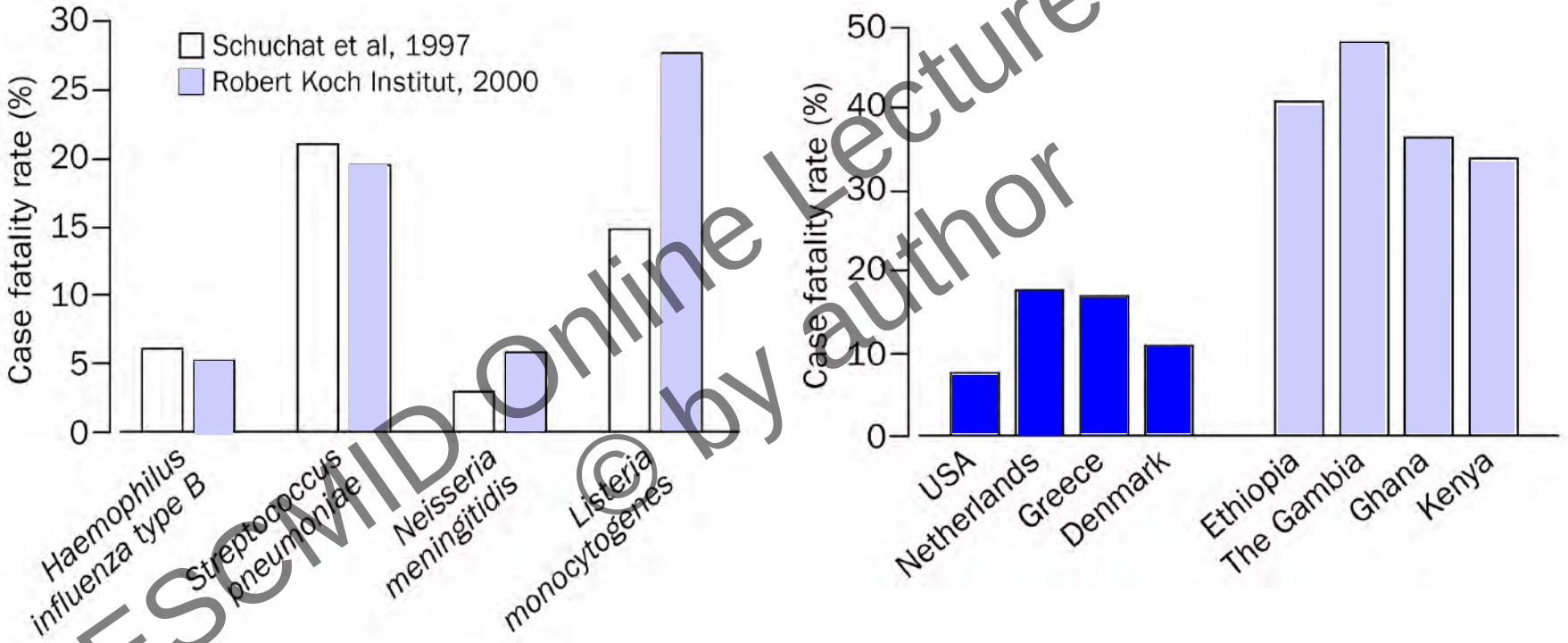
Focus on adult community-acquired meningitis

Recommended treatment for

- *S. pneumoniae*
- *N. meningitidis*
- *H. influenzae*
- *L. monocytogenes*

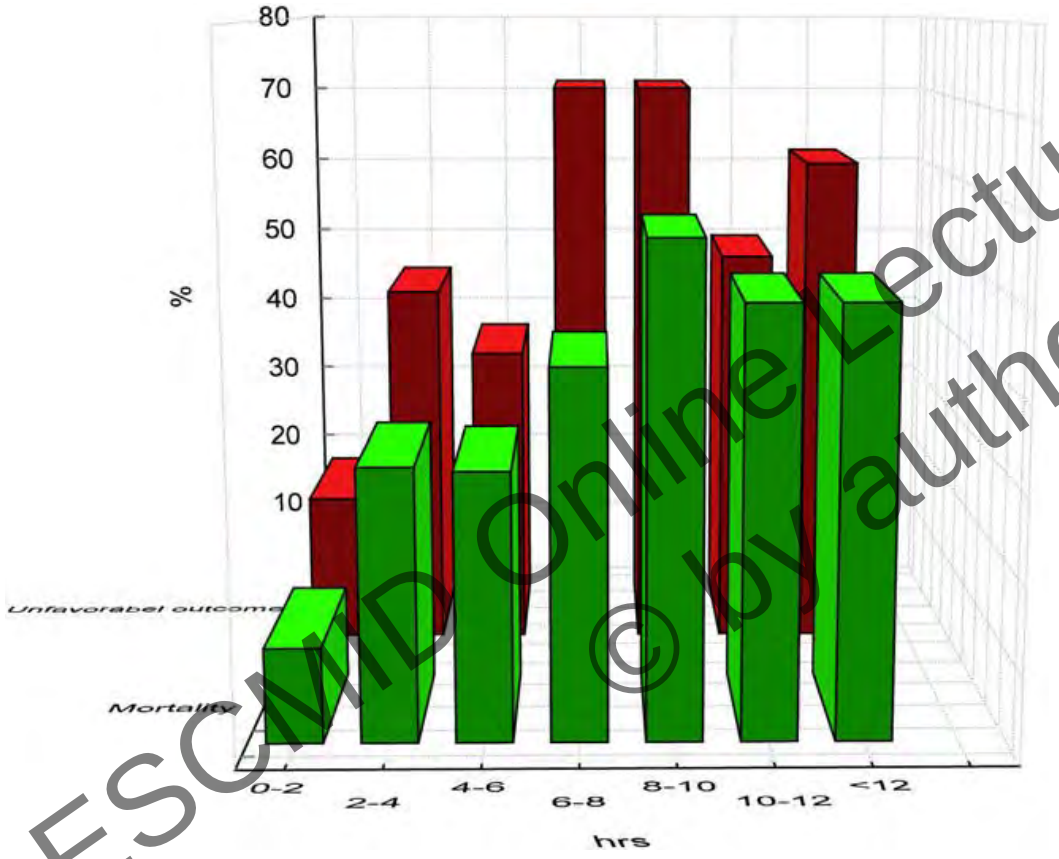
Recommended empirical treatment of meningitis

BACTERIAL MENINGITIS: *Mortality, Pathogen & Region*



Koedel et al. Lancet Infect Dis. 2002 Dec;2(12):721-36.

Shorten the time to the first dose of adequate antibiotics!



Mortality and unfavorable outcome as a function of time to the first dose of adequate antibiotics.

„ The delay in antibiotic therapy correlated independently to unfavourable outcome. The odds for unfavourable outcome may increase by up to 30% per hour of treatment delay..“

Køster-Rasmussen et al., Antibiotic treatment delay and outcome in acute bacterial meningitis, J Infect (2008)

Treatment recommendations for *S. pneumoniae*

Microorganism, susceptibility	Standard therapy	Alternative therapies
Streptococcus pneumoniae		
Penicillin MIC		
<0.1 μg/mL	Penicillin G or ampicillin	Third-generation cephalosporin,[a] chloramphenicol
0.1–1.0 μg/mL[b]	Third-generation cephalosporin[a]	Cefepime (B-II), meropenem (B-II)
≥2.0 μg/mL	Vancomycin plus a third-generation cephalosporin[a,c]	Fluoroquinolone[d] (B-II)
Cefotaxime or ceftriaxone MIC ≥1.0 μg/mL	Vancomycin plus a third-generation cephalosporin[a,c]	Fluoroquinolone[d] (B-II)

Tunkel AR. CID 2004;39:1267

Treatment of drug-resistant pneumococcal meningitis.

Add rifampicin to third generation cephalosporin plus vancomycin if:

isolate is susceptible to rifampicin,

clinical or bacteriological response is delayed

cefotaxime or ceftriaxone MIC >4 µg/mL.

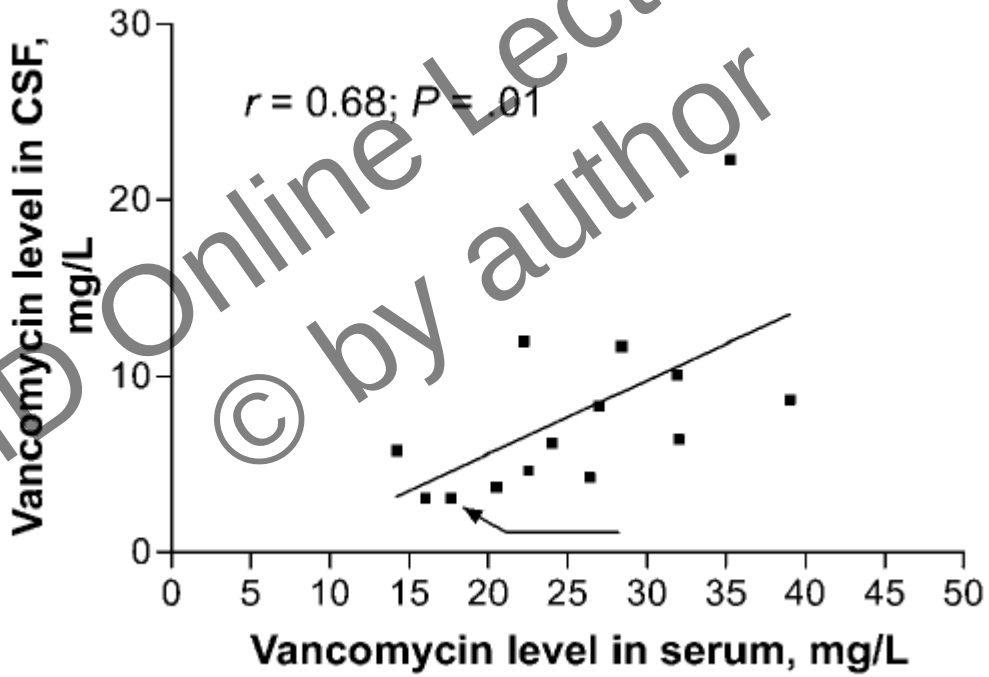
Hameed and Tunkel Curr Infect Dis Rep 2010;12:274

Dexamethasone use and vancomycin penetration into the CSF in bacterial meningitis

Patient	Vancomycin concentration		Vancomycin MIC, mg/L	Outcome
	Serum, mg/L	CSF, mg/L		
1	35.30	22.30	0.75	Died, irreversible coma
2	24.0	6.20	0.75	Survived
3	39.0	8.70	0.75	Survived
4	22.50	4.70	1.00	Survived
5	31.90	10.10	0.38	Survived with neurological sequelae
6	22.20	12.00	0.5	Survived
7	28.40	11.70	≤1	Died, septic shock
8	20.50	3.70	≤1	Survived
9	17.62	3.11	NP[a]	Survived
10	27.0	8.30	0.38	Survived
11	26.4	4.30	NP[b]	Survived, with neurological sequelae
12	16.0	3.10	0.38	Survived
13	32.0	6.40	0.25	Died, irreversible coma
14	14.2	5.80	0.25	Survived
All, mean value ± SD	25.5 ± 7.3	7.9 ± 5.1	0.62 ± 0.29	

Richard JD CID 2007; 44:250

Correlation between seum and CSF levels of vancomycin in bacterial meningitis treated with dexamethasone



Richard JD CID 2007; 44:250

Efficacy of moxifloxacin against *S. pneumoniae*

Species	*n*	Minimal inhibitory concentration (mg/l)		
		MIC_{50}	MIC_{90}	MIC range
S. pneumoniae	1609	0.12	0.12	0.007–0.5
Penicillin-susceptible	1253	0.06	0.12	0.03–0.25
Penicillin-intermediate	315	0.06	<0.12	0.008–0.5
Penicillin-resistant	135	<0.12	0.12	<0.12–2.0
Macrolide-intermediate + -resistant	35	0.12	0.12	0.06–0.12

Pharmacokinetics of moxifloxacin

CSF penetration 50 – 85%

High CSF penetration even in non-inflamed meninges

C_{max} reached within 1–4 h

Plasma half-life 11.6–15.6 h

Pharmacodynamics

Table 2. Pharmacodynamic parameters predictive of the outcome associated with various classes of antimicrobials.

Parameter, class of antimicrobial
T >MIC
Penicillins
Cephalosporins
Carbapenems
Macrolides
C_{max}:MIC
Aminoglycosides
Fluoroquinolones
AUC_{24}:MIC
Fluoroquinolones
Azalides
Ketolides

NOTE. AUC_{24}, 24-h area under plasma concentration curve; C_{max}, peak serum concentration; T >MIC, time above the MIC.

Wispelwey CID 2005;40:S440

Pharmacodynamics of moxifloxacin

Table 3. Comparison of pharmacodynamic parameters for quinolones used to treat *Streptococcus pneumoniae* infection.

Agent (dose)	MIC_{90}, mg/L	AUC_{24}, mg/h/L	Free drug, %	Free AUC, mg/h/L	Free AUC:MIC
Ciprofloxacin (750 b.i.d.)	1.0	40	70	28	28
Levofloxacin (500 q.d.)	1.0	48	70	34	34
Levofloxacin (750 q.d.)	1.0	101	70	70	70
Gatifloxacin (400 q.d.)	0.25	33	80	26	106
Moxifloxacin (400 q.d.)	0.12	48	50	24	200

Wispelwey CID 2005;40:S440

Moxifloxacin pharmacokinetics in CSF

Table 1. Pharmacokinetic Parameters of Moxifloxacin Based on Total (bound plus unbound) Concentrations for 4 Patients

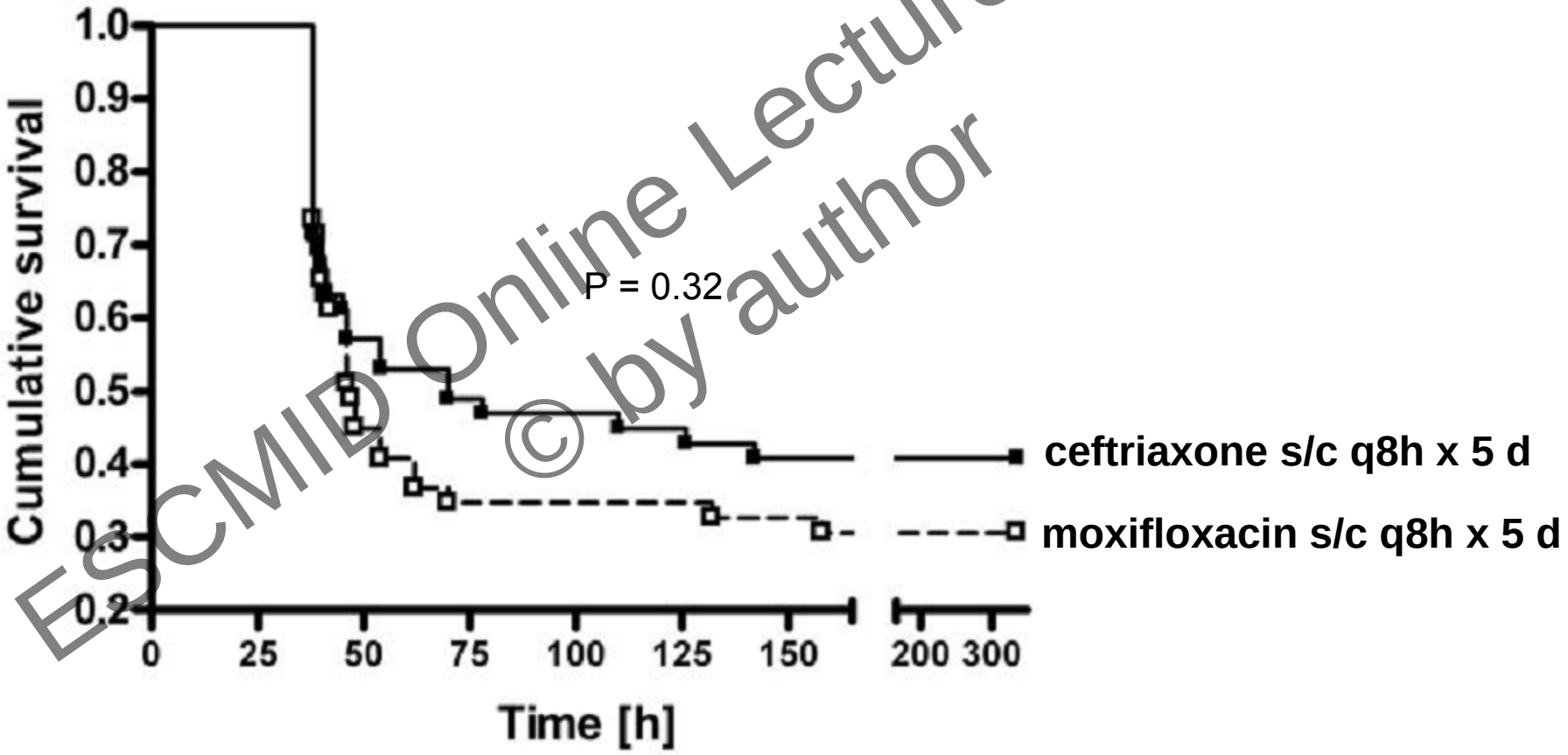
Parameter	Plasma sample, moxifloxacin daily dose		CSF sample, moxifloxacin daily dose	
	400 mg	800 mg	400 mg	800 mg
AUC_{0-24h}, mg× h/L	24.4 (20.5–24.5)	38.3 (32.2–42.4)	18.1 (14.8–19.8)	28.4 (24.9–28.9)
C_{max}, mg/L	2.57 (1.79–3.47)	3.65 (3.31–4.09)	1.29 (1.04–1.50)	2.22 (1.72–2.63)
T_{max}, h	1.0 (1.0–1.3)	2.0 (2.0–2.5)	4.0 (3.8–5.5)	4.0 (3.8–5.5)
C_{min}, mg/L	0.21 (0.17–0.26)	0.37 (0.24–0.48)	0.19 (0.14–0.24)	0.33 (0.25–0.38)
$T_{1/2}$, h	6.7 (6.0–7.5)	5.8 (5.0–10.0)	6.0 (5.7–7.3)	7.0 (6.4–7.4)
Cl/F, L/h	14.9 (12.6–30.6)	19.2 (15.3–24.62)	18.8 (17.5–34.6)	25.7 (24.2–31.2)
V_d, L	159 (143 161)	140 (139–142)	NA	NA
Geometric mean AUC/MIC ratio (range)	103 (60–196)	186 (132–322)	84 (56–154)	132 (95–226)

For 400 mg p.o. qd AUC ratio CSF/Plasma = 0.82

Alffenaar JWC et al CID 2009;49:1080

Moxifloxacin for pneumococcal meningitis in mice

Start treatment 30 h post intracerebral infection



Djukic M. et al. Neurocrit care 2005;2:325

Meropenem vs. cefotaxime for bacterial meningitis

Prospective multicenter study on 258 children and infants with suspected or documented bacterial meningitis randomly assigned to receive meropenem or cefotaxime

Clinical Response	Meropenem		Cefotaxime	
	End of treatment (n = 79)	5- to 7-wk follow-up (n = 76)*	End of treatment (n = 75)	5- to 7-wk follow-up (n = 72)
Cure with no sequelae	36 (46)†	41 (54)	42 (56)	42 (58)
Survival with sequelae	41 (52)	34 (45)	30 (40)	29 (40)
Mild sequelae	21	11	20	17
Severe sequelae‡	20	23	10	12
Death	2 (3)	1 (1)	3 (4)	1 (1)
Microbiologic response				
Eradication	75 (95)		72 (96)	
Delayed sterilization§	2 (3)		1 (1)	
Relapse		1¶		0
Persistence	0		0	
Died before follow-up assessment‖	2		2	

Odio CM Pediatr Infect Dis J 1999;18:581

Treatment recommendations for *N. menigitidis*

Microorganism, susceptibility	Standard therapy	Alternative therapies
Neisseria meningitidis		
Penicillin MIC		
<0.1 μg/mL	Penicillin G or ampicillin	Third-generation cephalosporin,[a] chloramphenicol
0.1–1.0 μg/mL	Third-generation cephalosporin[a]	Chloramphenicol, fluoroquinolone, meropenem

Chloramphenicol preferred choice in β-lactam allergic

Tunkel AR. CID 2004;39:1267

Treatment recommendations for specific pathogens

Listeria monocytogenes	Ampicillin or penicillin G[e]	Trimethoprim-sulfamethoxazole, meropenem (B-III)
Streptococcus agalactiae	Ampicillin or penicillin G[e]	Third-generation cephalosporin[a] (B-III)
Escherichia coli and other Enterobacteriaceae[g]	Third-generation cephalosporin (A-II)	Aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole, ampicillin
Pseudomonas aeruginosa[g]	Cefepime[e] or ceftazidime[e] (A-II)	Aztreonam,[e] ciprofloxacin,[e] meropenem[e]
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Third-generation cephalosporin,[a] cefepime, chloramphenicol, fluoroquinolone
β-Lactamase positive	Third-generation cephalosporin (A-I)	Cefepime (A-I), chloramphenicol, fluoroquinolone

Tunkel AR. CID 2004;39:1267

Treatment recommendations for *Listeria monocytogenes*

Ampicillin 6x/d 2 g IV ± gentamycin 5mg/kg/d in 3 daily doses

Meropenem 3x/d 2 g IV

TMP/SMX at 20 mg TMP/kg/day in 2-4 doses

Inadequate initial treatment had no effect on outcome in 9/30 patients in Dutch Meningitis Cohort Study

Brouwer MC. CID 2006;43:1233

Listeria monocytogenes meningitis: complications and outcome

Variable	Proportion of patients (%)
Complication	
Seizures	6/30 (20)
Cardiorespiratory failure	10/30 (33)
Receipt of mechanical ventilation	7/30 (23)
Sepsis	5/30 (17)
Hyponatremia	25/30 (83)
Recurrent fever	11/28 (39)
Persisting fever	11/30 (37)
Impaired consciousness	12/30 (40)
Other complications[a]	7/30 (23)
Outcome	
Score on the Glasgow outcome scale	
1 (death)	5/30 (17)
2 (vegetative state)	0/30 (0)
3 (severe disability)	1/30 (3)
4 (moderate disability)	2/30 (7)
5 (mild or no disability)	22/30 (73)
Sequelae at discharge	
Hemiparesis	2/25 (8)
Cranial nerve palsy[b]	2/25 (8)

Brouwer MC. CID 2006;43:1233

IDSA treatment recommendations

Table 3. Recommendations for antimicrobial therapy in adult patients with presumptive pathogen identification by positive Gram stain.

Microorganism	Recommended therapy	Alternative therapies
Streptococcus pneumoniae	Vancomycin plus a third-generation cephalosporin[a,b]	Meropenem (C-III), fluoroquinolone[c] (B-II)
Neisseria meningitidis	Third-generation cephalosporin[a]	Penicillin G, ampicillin, chloramphenicol, fluoroquinolone, aztreonam
Listeria monocytogenes	Ampicillin[d] or penicillin G[d]	Trimethoprim-sulfamethoxazole, meropenem (B-III)
Streptococcus agalactiae	Ampicillin[d] or penicillin G[d]	Third-generation cephalosporin[a] (B-III)
Haemophilus influenzae	Third-generation cephalosporin[a] (A-I)	Chloramphenicol, cefepime (A-I), meropenem (A-I), fluoroquinolone
Escherichia coli	Third-generation cephalosporin[a] (A-II)	Cefepime, meropenem, aztreonam, fluoroquinolone, trimethoprim-sulfamethoxazole

NOTE. All recommendations are A-III, unless otherwise indicated. In children, ampicillin is added to the standard therapeutic regimen of cefotaxime or ceftriaxone plus vancomycin when *L. monocytogenes* is considered and to an aminoglycoside if a gram-negative enteric pathogen is of concern.

[a] Ceftriaxone or cefotaxime.
[b] Some experts would add rifampin if dexamethasone is also given (B-III).
[c] Gatifloxaxin or moxifloxacin.
[d] Addition of an aminoglycoside should be considered.

Tunkel AR. CID 2004;39:1267

Treatment recommendations based on age and predisposing condition

Predisposing factor	Common bacterial pathogens	Antimicrobial therapy
Age		
2–50 years	*N . meningitidis, S. pneumoniae*	Vancomycin plus a third-generation cephalosporin[a,b]
>50 years	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin[a,b]

Tunkel AR. CID 2004;39:1267

Recommended daily dose (dosing interval in hours)

Ampicillin	12-15 g (4)
Aztreonam	6–8 g (6–8)
Cefepime	6 g (8)
Cefotaxime	8–12 g (4–6)
Ceftazidime	6 g (8)
Ceftriaxone	4 g (12–24)
Chloramphenicol	4–6 g (6)
Ciprofloxacin	1200 mg (8–12)
Gentamicin	3 - 5 mg/kg (8)
Meropenem	6 g (8)
Moxifloxacin	400 mg (24)
Penicillin G	24-30 Mio IU (4)
Rifampin	600 mg (24)
Trimethoprim-sulfamethoxazole	10–20 mg/kg (6–12)
Vancomycin	30–60 mg/kg (8–12)

Infect Dis Clin N Am 23 (2009) 925–943 ; Expert Opin. Pharmacother. (2009) 10(16)

Duration of therapy

Microorganism	Duration of therapy, days
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumoniae	10–14
Streptococcus agalactiae	14–21
Aerobic gram-negative bacilli[a]	21
Listeria monocytogenes	⩾21

Tunkel AR. CID 2004;39:1267

Summary

No treatment-relevant changes in epidemiology or resistance development in the past 10 years for community-acquired meningitis

Empirical treatment for <50 y - cefotaxime or ceftriaxone + vancomycin

Empirical treatment for >50 y – add amoxicillin

Use vancomycin at high dose: 3 x/d 15 mg/kg; trough-level 15-20 mg/L

Concomitant dexamethasone does not interfere with vancomycin CSF penetration

For *S. pneumoniae* addition of vancomycin ± rifampicin to ceftriaxone or cefotaxime will treat highly resistant isolates