

Therapy of bacterial meningitis

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Changing epidemiology of bacterial meningitis, US, 1986-2003

	1986	1995	1998-2003*
<i>H. influenzae</i>	45%	7%	7%
<i>S. pneumoniae</i>	18%	47%	61%
<i>N. meningitidis</i>	14%	25%	16%
<i>S. agalactiae</i>	5.7%	12%	14%
<i>L. monocytogenes</i>	3.2%	8%	2%
Median age	15m	25y	39y
≈ no. cases/year	12,920	5755	4450

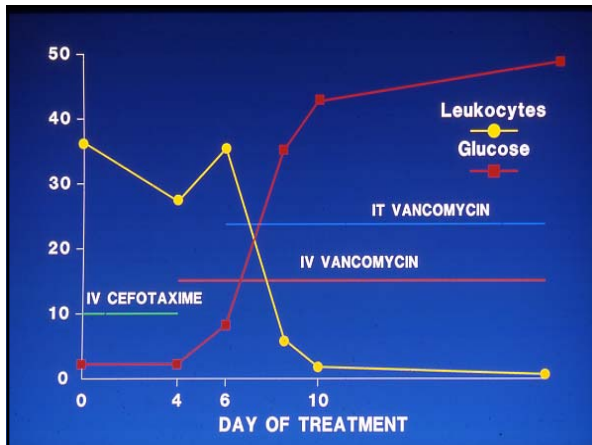
*43rd IDSA meeting, 2005, abstract 65

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S. pneumoniae resistance in the USA (2002-3)

penicillin	34.2 %
ceftriaxone	6.9
erythromycin	29.5
clindamycin	9.4
tetracycline	16.2
TMP-SMX	31.9
<QRDRs>	21.9

Doern GV, et al. Clin Infect Dis 2005; 41: 139-48.



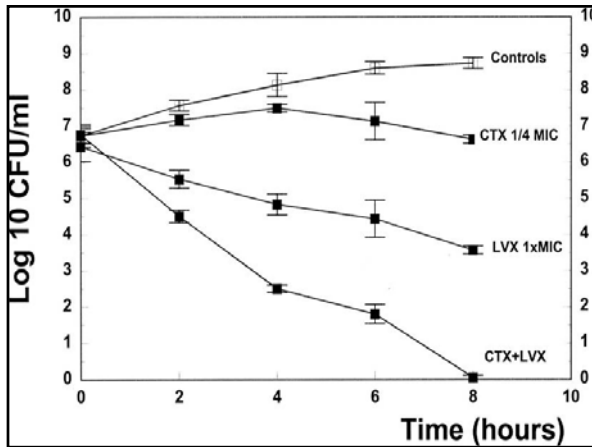
Potential Regimens for Treatment of Presumed Penicillin-resistant Pneumococcal Meningitis

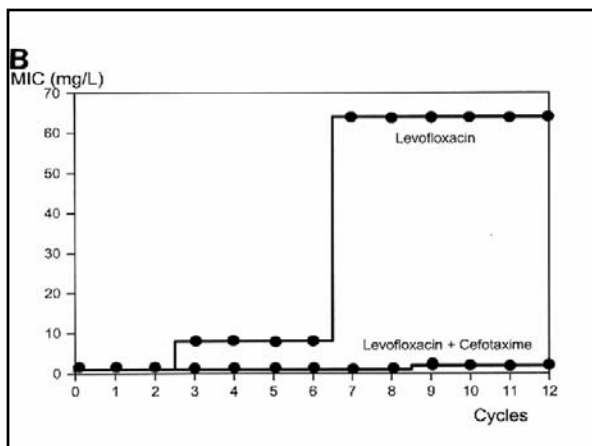
- Ceftriaxone or cefotaxime (TGC)
- Vancomycin
- Chloramphenicol
- Vancomycin plus rifampin
- Ampicillin plus TGC
- Synercid®
- Meropenem
- Quinolones
- TGC plus vancomycin
- TGC plus quinolone
- Linezolid
- Daptomycin

Cefotaxime – levofloxacin synergy in experimental pneumococcal meningitis

	$\Delta \log_{10}$ cfu/ml csf/h
controls	-0.09
cefotaxime	-0.49
levofloxacin	-0.47
c+l	-1.04

Kuhn F, et. al. Antimicrob Agents Chemother 2003; 47:2487-91.





Pneumococcal meningitis in the ICU

n=156; prospective, observational (33% death)
38% nonsusceptible to penicillin OR for death

nonsusceptible strain	6.83
≥ 3 hours to first dose	14.12
CSF wbc > 1000	0.30

Auburtin M, et al. Crit Care Med 2006; 34: 2758-65.

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Meningitis in the ICU; GCS and mortality

GCS	Mortality (%)
3-8	33
9-12	10
13-15	0

Intensive Care Med 2003; 29: 1967-73.

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Drotrecogin alfa for meningitis and sepsis? (median Apache II=22)

	ICH (%)
bacterial meningitis	5.7
all others	1.0

Crit Care 2005; 9: R331-43.

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CSF vancomycin levels in adults with pneumococcal meningitis receiving corticosteroids (n=13)

suspected pneumococcal meningitis; ICU
ceftotaxime, vancomycin (60 mg/kg/d
i.v. infusion after 15 mg/kg,
dexamethasone
mean vancomycin levels serum 25.2, CSF
7.2
↑ CSF/serum with ↑ CSF protein

Richard J-D, et al. Clin Infect Dis 2007;
44:250-5.

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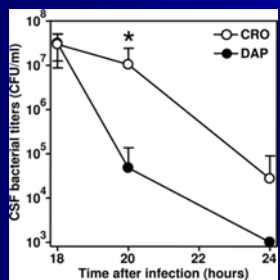
Daptomycin vs. ceftriaxone for experimental pneumococcal meningitis in rats

faster bacterial clearance
reduced inflammation (e.g. ↓ MMP 9)
reduced cortical damage (0/30 vs. 7/28)

Grandgirard D, et al. Antimicrob Agents Chemother
2007; 51: 2173-8.

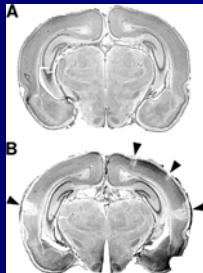
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FIG. 1. Bacterial titers in CSF of daptomycin (DAP)- and ceftriaxone (CRO)-treated animals. Titers were determined before initiation of the therapy (18 h after infection; n = 18 for each group), 2 h later (20 h after infection; n = 9 per group), and 6 h later (24 h after infection; n = 9). The origin of the y axis was set to the bacterial titer detection limit of 10³ CFU/ml. *, titers were significantly different at 20 h after infection (P < 0.015). At 24 h after infection, the titers for the daptomycin-treated animals were under the detection limit.



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FIG. 3. Representative histological sections of daptomycin-treated (A) or ceftriaxone-treated (B) animals stained with cresyl violet 40 h after infection. Regions of decreased neuronal density (arrowheads) were found only in the cortices of the ceftriaxone-treated animals.



"Short" course therapy of meningococcal disease (≤ 5 days)*

Studies = 9
Years 1974 – 1995
No. patients = 278
Deaths = 6.8%; treatment prolonged = 2.2%;
relapses = 0%
Rx: penicillin, chloramphenicol, ceftriaxone
Deaths ≤ 36 h: $\geq 67\%$
Sterile CSF: 31/32 ≤ 24 h; 83/83 @ 1-3 days

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Community-acquired *L. monocytogenes* meningitis in adults (1998-2002)

696 episodes Dutch meningitis cohort
30 (4%) Listeria; mean 65 years, all 10 immunocompetent > 50 years
27% > 4 days until presentation
GS(-) in 60%; 46% (+) BC
17% mortality (30% inadequate Abx)

Brouwer MC, et al. Clin Infect Dis 2006; 43:1233-8.
Lorber B. Clin Infect Dis 2007; Mar 1.

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**Human *S. suis* outbreak,
Sichuan, China 2005**

n=215, all slaughtered pigs
STSS (28%), 62% died
Sepsis (24%), meningitis (48%)
Clonal strain

**Yu H, et al. Emerg Infect Dis 2006;
12:914-20.**

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**Community-acquired bacterial
meningitis in the “elderly”
(≥ 60 years)**

**37% in elderly (classic symptoms the
same)**
***S. p.* elderly 68%; *N. m* < 59 years 50%**
complications 72% vs. 57%
mortality 34% vs. 13%
died CR failure 25% vs. 13%
died brain herniation 2% vs. 23%

**Weisfelt M, et al. J Am Geriatric Soc 2006;
54:1500-7.**

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**Complications during the clinical
course in adults with meningitis**

	%
cardiorespiratory failure	29
hyponatremia	26
DIC	8
seizures	15-23
brain edema	6-10
vascular	15-20
hearing loss	14-20

e.g. van de Beek D, et al. N Engl J Med 2004; 351: 1849-59.

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ICP monitoring in children with meningitis in the USA

1997 and 2000; age <17 on MV
ICP monitors used in 7%; associated with age (5-17 vs. < 1 year), patient volume, hospitals in the West; mortality 19.6%; no change with ICP monitor (↑ LOS, charges).

Odetola FO, et al. Pediatrics 2006; 117:2279-80.

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Corticosteroids and adult meningitis

301 patients, 5 countries, 9 years
Dexamethasone 10 mg i.v. q6h x 4d
~2/3 *S. pneumoniae*, *N. meningitidis*
77/108 *S. pneumoniae* isolates tested,
all MIC <0.1 µg/ml

*de Gans J, et al. N Engl J Med 2002; 347:1549-56.

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Corticosteroids and adult meningitis

Overall:

Unfavorable outcome; RR 0.59; p=0.03

Mortality; RR 0.48; p=0.04

Pneumococcal:

Unfavorable outcome; 26% vs 52%; RR 0.50; p=0.006

Mortality; 14% vs 34%

*de Gans J, et al. N Engl J Med 2002; 347: 1549-56.

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Long term outcome after dexamethasone in adults with meningitis

87 patients, median time to F/U 99 months
 No difference dex vs. placebo in neuropsychological evaluation, sequelae hearing loss, cognitive dysfunction (latter 21% vs. 6% S. p vs. N. m.)

Weisfeldt M, et al. Ann Neurol 2006; 60:456-68.

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Dexamethasone in meningitis, Vietnam

1996-2005; n=435, age ≥ 14 years
 61% prior Abx; ≈ 27% *S. suis* (vs 12-13% *S. pneumoniae*)
 definite 69.0%, probable 18.3%
 other 2.8% (HIV < 0.9%)

NEJM 2007; 357:2431-40

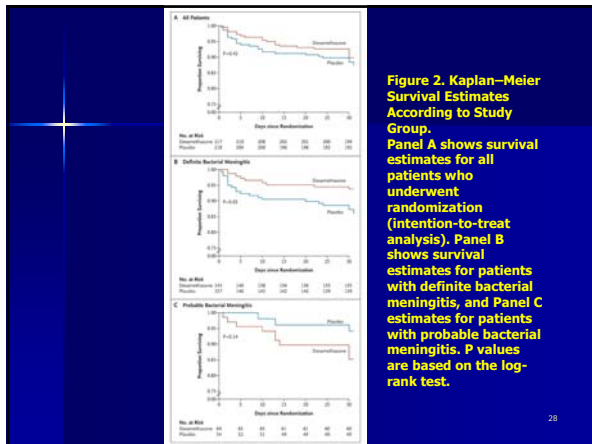
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Relative risk of death (RRD) dexamethasone in meningitis, Vietnam

	RRD (95% CI)	p value
definite meningitis	0.43 (0.20-0.94)	0.03
probable meningitis	2.65 (0.73-9.63)	0.14
gram-positive	0.06 (0.01-0.45)	0.006
gram-negative	1.65 (0.52-5.21)	0.39

NEJM 2007; 357:2431-40

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Deafness following meningitis, Vietnam

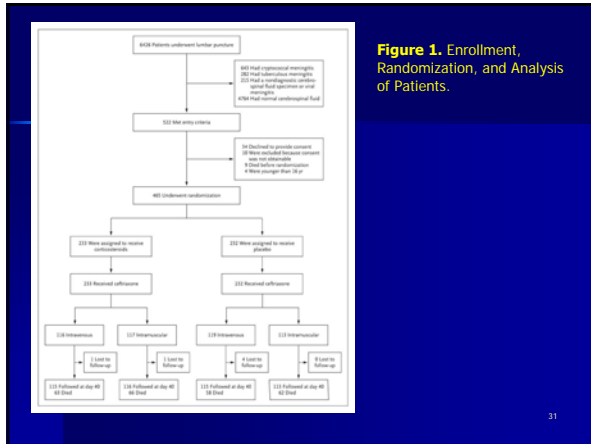
	deaf at least one ear (%)		
	dexa	placebo	p value
definite	9.6	21.8	0.008
definite + probable	11.7	21.3	0.02
<i>S. suis</i>	12.3	37.7	0.003

NEJM 2007; 357:2431-40

Dexamethasone in meningitis, Malawi

2002-2005; n=465, age ≥ 16 years
 36-38% prior Abx; 59% *S. pneumoniae*
 Definite 70%, probable 22%, other 8% (90% HIV)

NEJM 2007; 357:2441-50

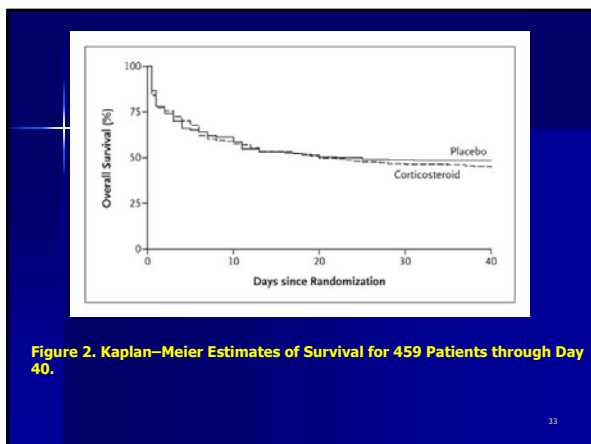


**Unadjusted odds ratio,
dexamethasone vs placebo for
meningitis, Malawi**

odds ratio (day 40)

ITT	1.14
proven or probable	1.13
proven	1.16
pneumococcal	1.10

NEJM 2007; 357:2441-50



Meningitis and mortality at 40 days; multivariate analysis

	odds ratio
age \geq 32 years	1.96
GCS < 12	4.10
Hb < 10	2.19
<i>S. pneumoniae</i>	0.56
HIV positive	1.35 (p=0.4)

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Mortality at 40 days, meningitis, Malawi, iv vs im ceftriaxone

	odds ratio
ITT	0.88
proven + probable	0.85
proven	1.13
pneumococcal	1.06

NEJM 2007; 357:2441-50

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Glycerol and/or dexamethasone, Latin America

1996-2003; 6 countries; n=654; ages 2 mos-16 years (median 10-13 mos)
37% prior Abx; Hib > Spn > Nm (26% unknown) 13% died

Clin Infect Dis 2007; 45: 1277-86

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Primary outcomes, bacterial meningitis, Latin America

	odds ratio		
	dxm + placebo	dxm + glycerol	glycerol + placebo
death	0.82	0.69	0.58
severe sequelae	0.48	<u>0.39</u>	<u>0.31</u>
combined	0.65	<u>0.55</u>	<u>0.44</u>
hearing loss	0.79	0.73	0.96

Clin Infect Dis 2007; 45: 1277-86.

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References

van de Beek D, de Gans J, Tunkel AR et al. Community-acquired bacterial meningitis in adults. N Engl J Med 2006; 354: 44-53.

Fitch MT, van de Beek D. Emergency diagnosis and treatment of adult meningitis. Lancet Infect Dis 2007; 7: 191-200.

Mai MTH, Chau TTH, Thwaites G, et al. Dexamethasone in vietnamese adolescents and adults with bacterial meningitis. N Engl J Med 2007; 357: 2431-40.

Scarborough LM, Gordon SB, Whitty CJM, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med 2007; 357: 2441-50.

Peltola H, Roine I, Fernandez J, et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: A prospective, randomized double-blind, placebo-controlled trial. Clin Infect Dis 2007; 45: 1277-86.

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Thank You
and
The End!

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