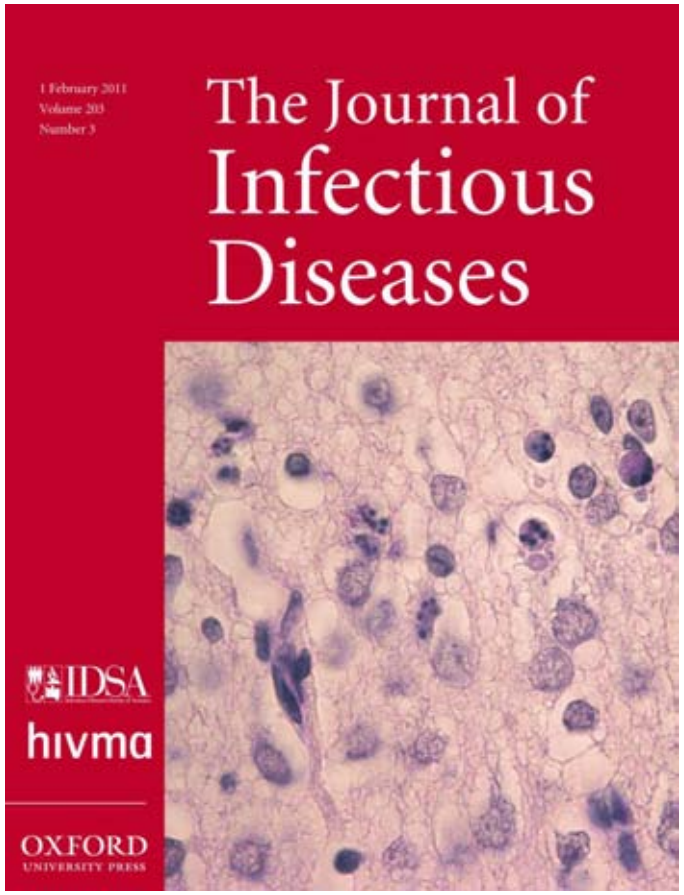


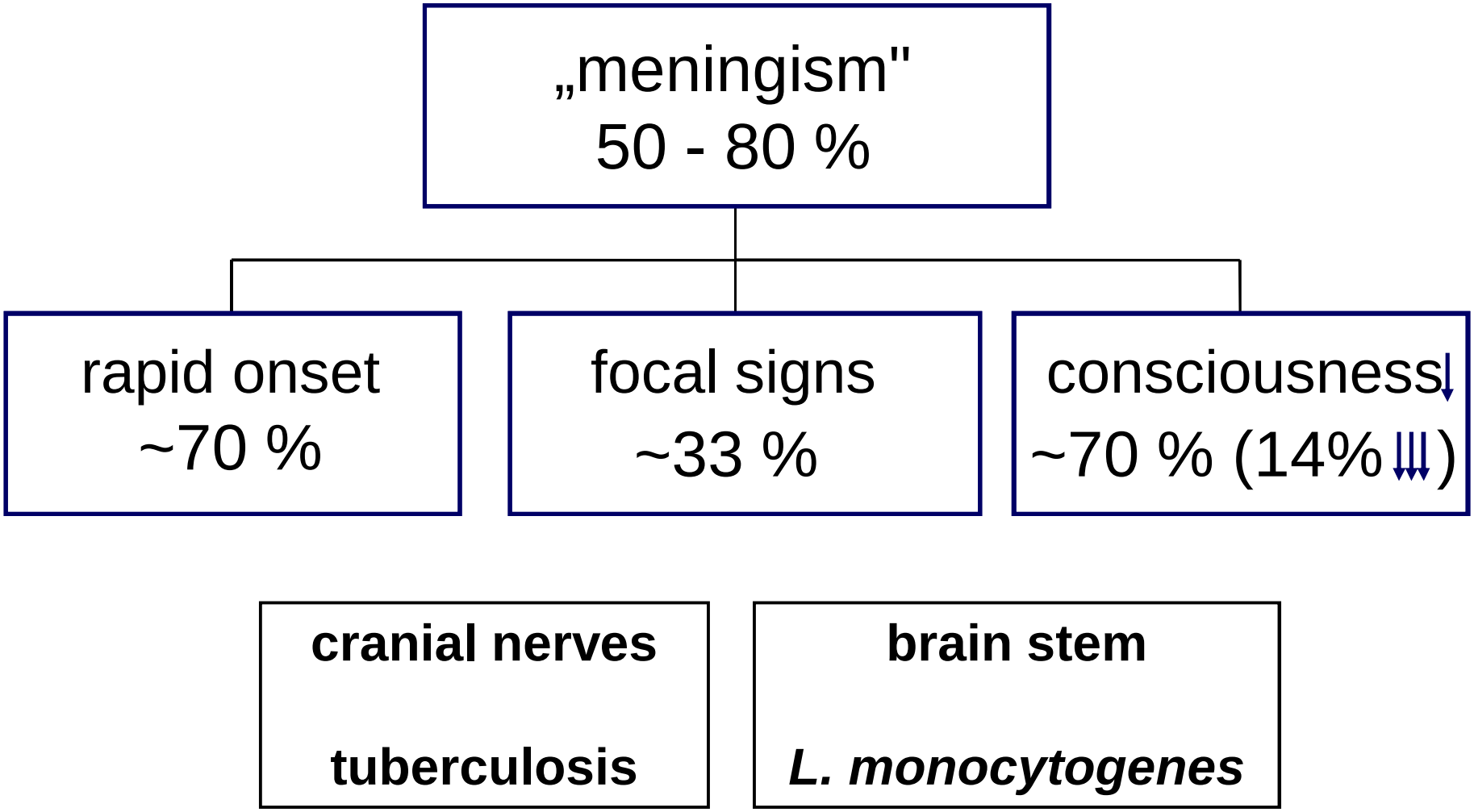
Emergency Management of CNS Infections

WCN Vienna, TC 36, Emergency Neurology

Joerg R. Weber

Klinikum Klagenfurt, Austria

Clinical presentation of Bacterial Meningitis



	Non-cirrhotic (n = 573)		Cirrhotic (n = 29)		
	n/total	%	n/total	%	p
Length of disease >4 days	92/566	16	9/28	32	0.029
Mean age (years)	49.6 ± 19		55.8 ± 12		NS
Gender (male)	255/573	44	13/29	44.8	NS
Fever	509/544	93.6	24/26	92	NS
Headache	455/528	86	17/23	73.9	NS
Nuchal rigidity	514/559	91.9	21/28	75	0.008
Vomiting	394/522	75.5	16/27	59	NS
Obtunded-comatose[b]	427/568	75	25/28	89	NS
Hemiparesis	58/567	10	3/28	10.7	NS
Seizures	95/569	16.7	4/26	15	NS
Shock	43/573	7.5	4/29	13.8	NS
Escherichia coli aetiology	7/573	1	5/29	17	0.000
Listeria monocytogenes aetiology	28/573	4.9	5/29	17	0.017
Neisseria meningitidis aetiology	223/573	38.9	6/29	20.6	0.049
Streptococcus pneumoniae aetiology	178/573	31	8/29	27.5	NS
Unknown aetiology	72/573	12.5	1/29	3	NS

Cabellos 2008 *Clin Microbiol Infect* 14:35-40

Bacteria

- ***Streptococcus pneumoniae* 40%**
- ***Neisseria meningitidis* 40%**

Listeria monocytogenes 7%

(Haemophilus Influenza)

E. coli, staphylococci, pseudomonas

2-8/100000/year

De Gans 2002 *NEJM* 347:1549-56

Isolated Bacteria (Spain, n = 278)

Organism	n(%)
Streptococcus pneumoniae	135 (48.5)
Neisseria meningitidis	63 (22.6)
Listeria monocytogenes	46 (16.5)
Haemophilus influenzae	9 (3.2)
Escherichia coli	4 (1.4)
Streptococcus agalactiae	4 (1.4)
Others	17 (6.1)

Amaya –Villar 2010 *BMJ Inf Dis* 10:324


A
Scarborough M and Thwaites GE,
Lancet Neurol 2008
B
C
D
E
F

	Non-cirrhotic (n = 573)		Cirrhotic (n = 29)		
	n/total	%	n/total	%	p
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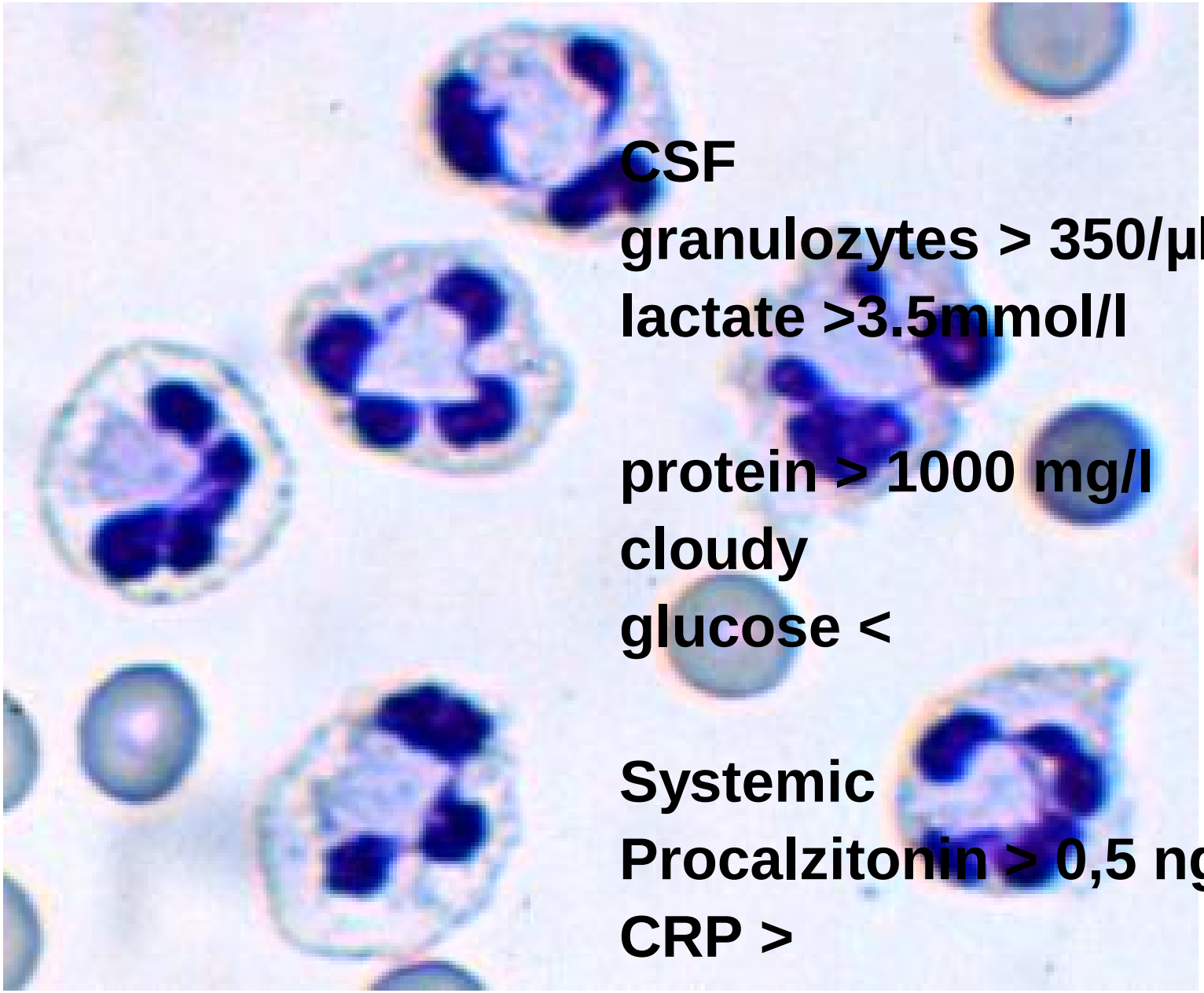
Cabellos 2008 *Clin Microbiol Infect* 14:35-40



CSF

granulozytes > 350/µl, > 95%

lactate >3.5mmol/l

protein > 1000 mg/l

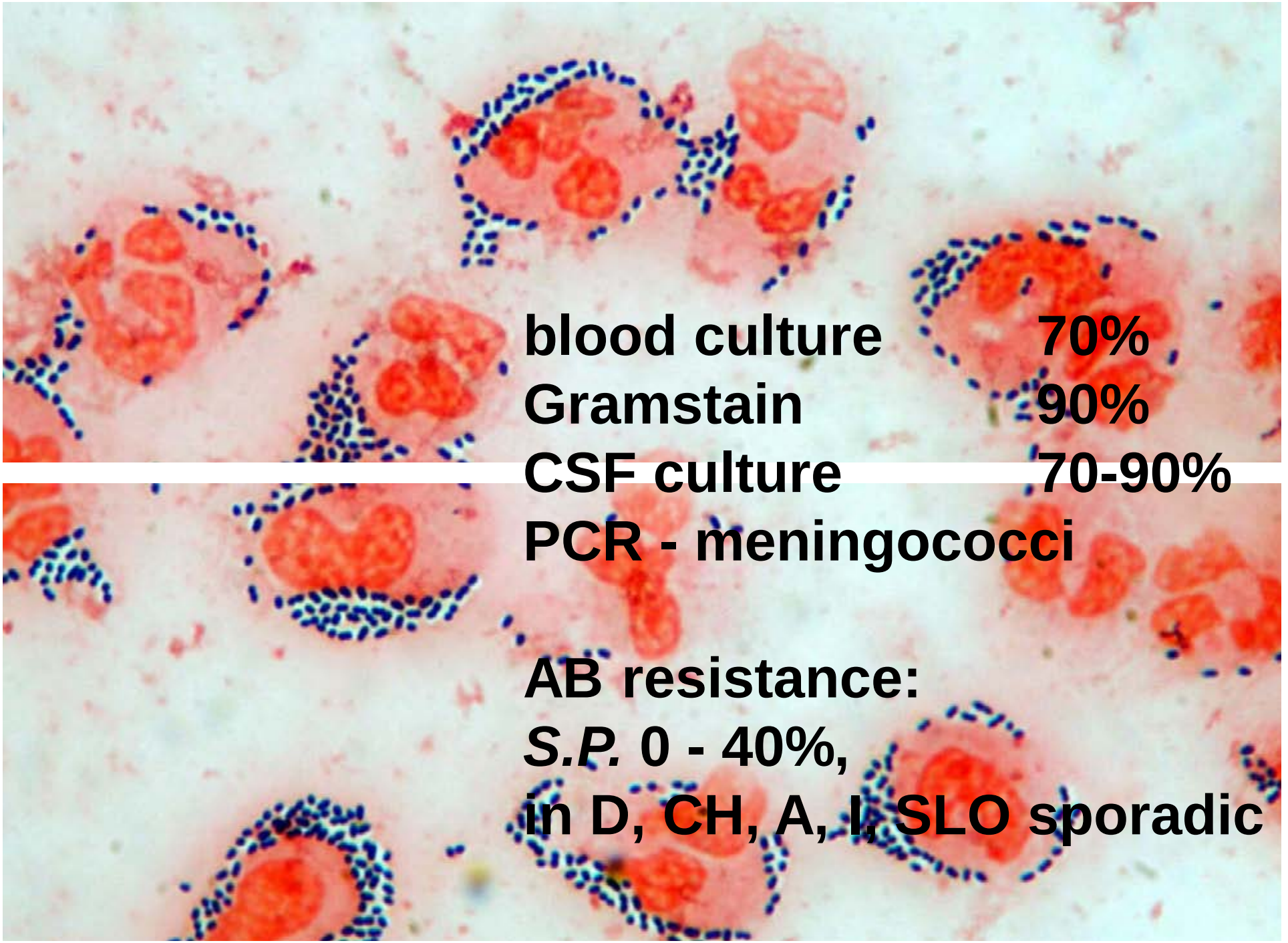
cloudy

glucose <

Systemic

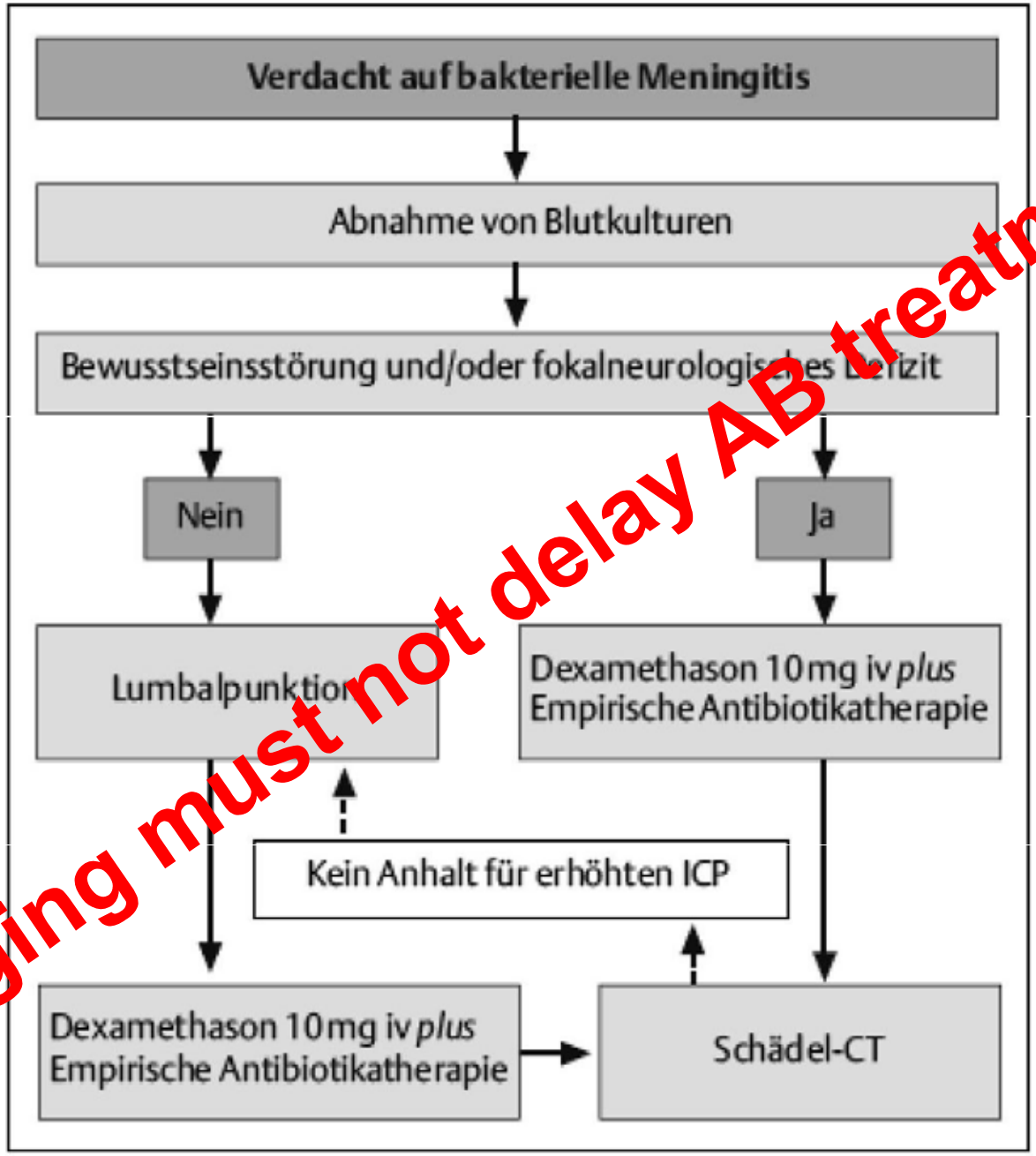
Procalzitonin > 0,5 ng/ml

CRP >



blood culture 70%
Gramstain 90%
CSF culture 70-90%
PCR - meningococci

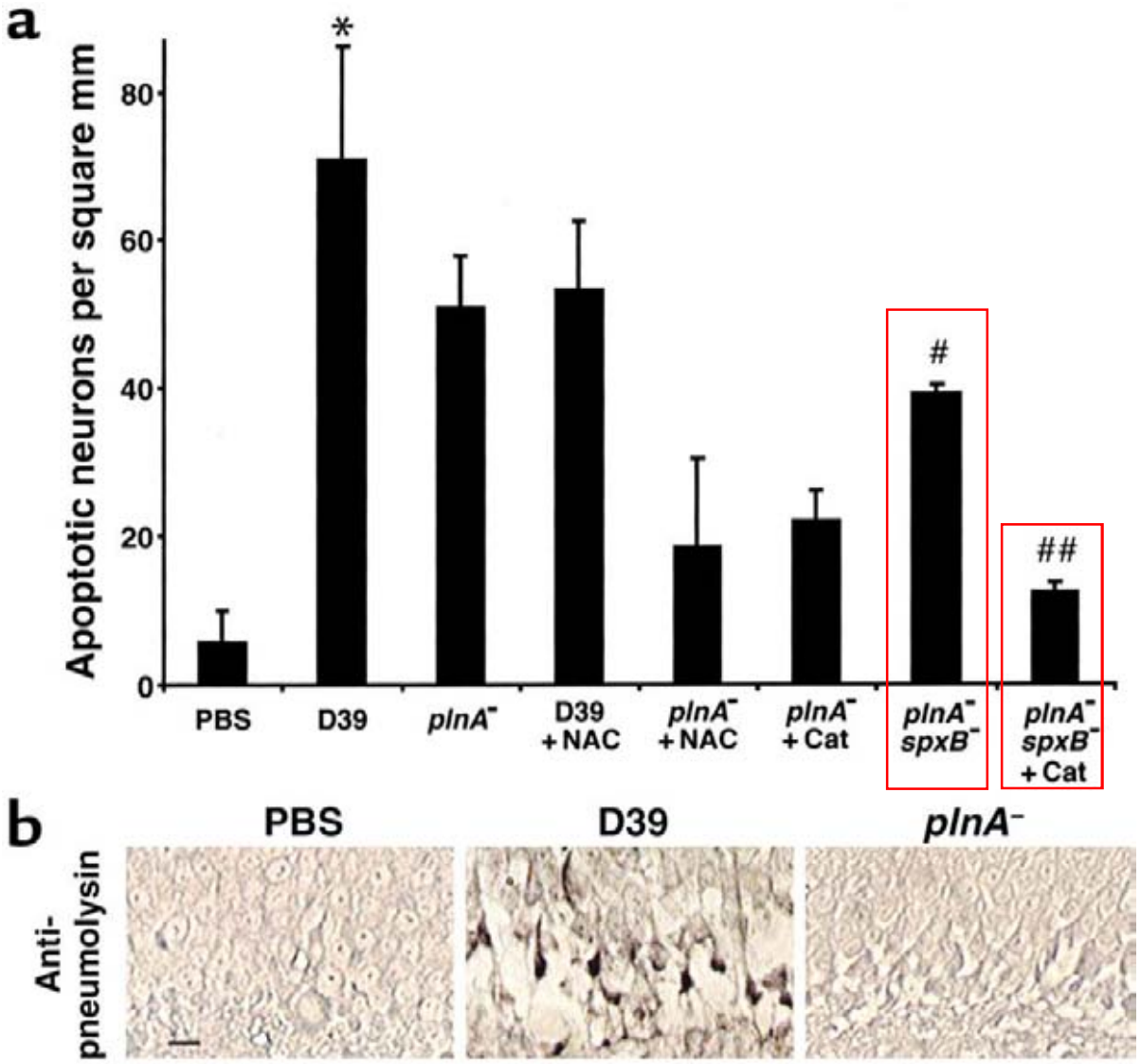
AB resistance:
S.P. 0 - 40%,
in D, CH, A, I, SLO sporadic



Imaging must not delay AB treatment

H. C. Diener u. a., Leitlinien für Diagnostik und Therapie in der Neurologie

Bacteria destroy neurons



Braun 2002 *J Clin Invest* 109:19, Zweigner 2004 *J Exp Med* 200:99
Bermpohl, Halle et al. 2005 *J Clin Invest* 115:1607

Early antibiotic administration prevents cognitive impairment induced by meningitis in rats

Tatiana Barichello[a,*], Geruza Z. Silva[a], Ana L. Batista[a], Geovana D. Savi[a], Gustavo Feier[b], Clarissa M. Comim[b], João Quevedo[b], Felipe Dal-Pizzol[a]

[a] *Laboratório de Fisiopatologia Experimental and Instituto Nacional de Ciência e Tecnologia Translacional em Medicina, Programa de Pós-Graduação em Ciências da Saú Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense, 88806-000 Criciúma, SC, Brazil*

[b] *Laboratório de Neurociências and Instituto Nacional de Ciência e Tecnologia Translacional em Medicina, Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense, 88806-000 Criciúma, SC, Brazil*

Empiric ABs - de Gans 2002

Amoxicillin or Penicillin	77 %
3a Cephalosporin	8 %
Amoxicillin or Penicillin + 3 Gen. Cephalosporin	8 %

AB resistance

pneumococci		0 (78)
meningococci	intermediär	1 (80)

De Gans 2002 *NEJM* 347:1549-56

Empiric AB treatment

"community aquired"

1. Ceftriaxon 1 x 2 g + Ampicillin 4 x 3 g)

www.dgn.org LL2012

2. Penicillin 4 x 5 x 10^6 U/d (+ Ampicillin)

3. Amoxicillin (6 x 2 g)

"in hospital, after neurosurgery"

1. Vancomycin 2 x 1g + Ceftazidim 3 x 2 g iv

2. Vancomycin 2 x 1g + Meropenem 3 x 2g

***Understand your AB resistance geographically and in hospital*!!!**

Preclinical ABs?

PLAIN LANGUAGE SUMMARY

Pre-admission antibiotics for suspected cases of meningococcal disease

Meningococcal disease is a contagious, bacterial disease caused by Neisseria meningitidis (*N. meningitidis*) that often leads rapidly to death. Administering antibiotics as soon as the condition is suspected, and while waiting for the diagnosis to be confirmed, has been advocated as a method of preventing death and the disabling consequences of this disease.

We found no randomised controlled trials that compared pre-admission antibiotics with placebo or no intervention. In the one randomised controlled trial we identified, a single injection of either ceftriaxone (a relatively expensive, newer antibiotic) or a long-acting form of chloramphenicol (an inexpensive antibiotic) were found to be equally effective in preventing death and the disabling consequences in suspected, non-severe cases of meningococcal disease. Due to the serious complications of meningococcal disease, it would be diffic s soon as the diagnosis is suspec ococcal cases will provide insigh

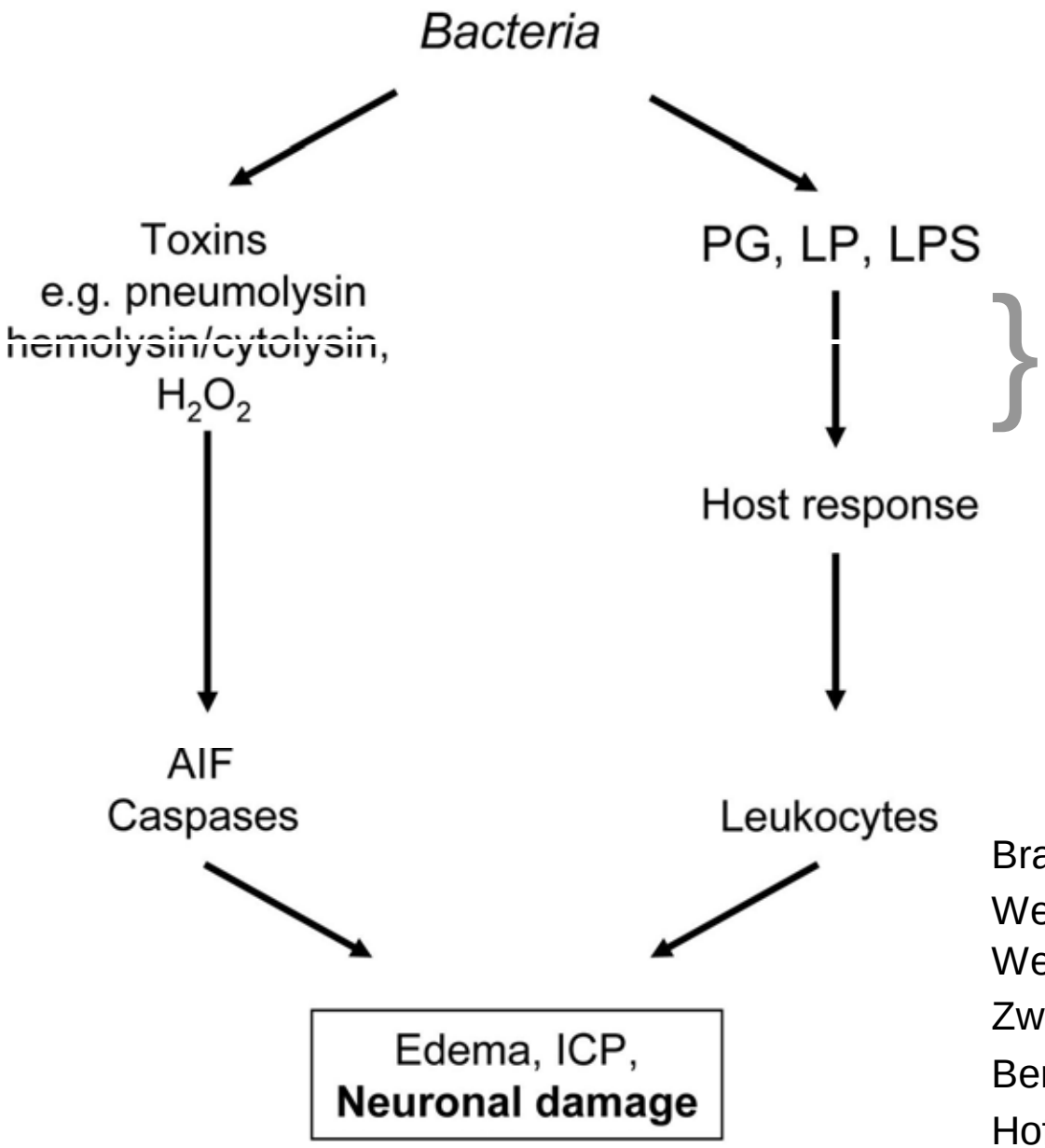
It would be difficult for ethical reasons … comparing the use of antibiotics, as soon as the diagnosis is suspected, versus no antibiotics.

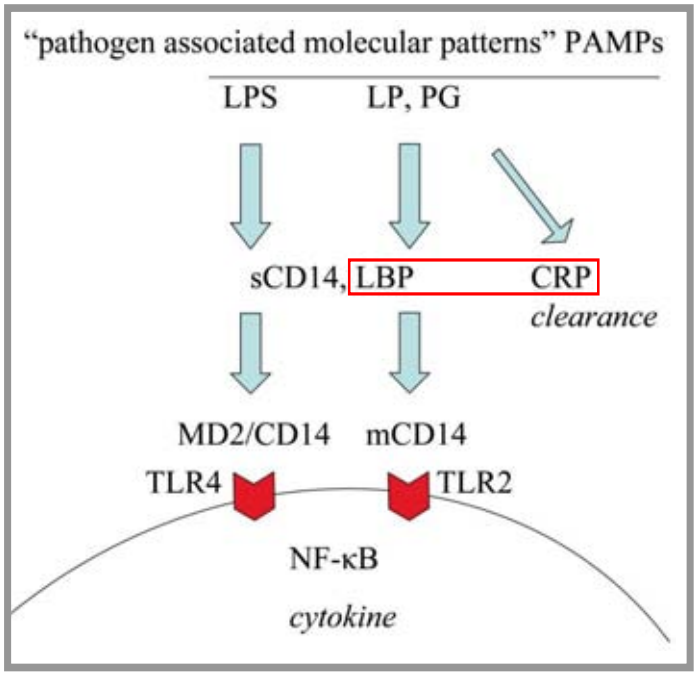
Cochran Lib 2008

TABLE 4. GUIDELINES FOR THE DURATION OF ANTIBIOTIC THERAPY.

PATHOGEN	SUGGESTED DURATION OF THERAPY (DAYS)
H. influenzae	7
N. meningitidis	7
S. pneumoniae	10–14
L. monocytogenes	14–21
Group B streptococci	14–21
Gram-negative bacilli (other than *H. influenzae*)	21

Quagliarello et al, 1997 NEJM





Braun et al. 2002 *J Clin Invest*
Weber et al. 2003 *Immunity*
Weber et al. 2003 *Curr Opin Immunol*
Zweigner et al. 2004 *J Exp Med*
Bermpohl, Halle et al. 2005 *J Clin Invest*
Hoffmann et al. 2007 *J Clin Invest*
Weber et al. 2007 *J Neuroimmunol*
Reiss et al. 2007 *J Infect Dis*

The New England
Journal of Medicine

VOLUME 347 NOVEMBER 14, 2002 NUMBER 20

DEXAMETHASONE IN ADULTS WITH BACTERIAL MENINGITIS

JAN DE GANS, PH.D., AND DIEDERIK VAN DE BEEK, M.D., FOR THE EUROPEAN DEXAMETHASONE IN ADULTHOOD BACTERIAL MENINGITIS STUDY INVESTIGATORS*

Dexamethasone in BM

Death				
All patients	11/157 (7)	21/144 (15)	0.48 (0.24–0.96)	0.04
S. pneumoniae	8/58 (14)	17/50 (34)	0.41 (0.19–0.86)	0.02
N. meningitidis	2/50 (4)	1/47 (2)	1.88 (0.76–20.1)	1.00
Other bacteria	1/12 (8)	1/17 (6)	1.42 (0.10–20.5)	1.00
Negative bacterial culture	0/37	2/30 (7)	—	0.20

4 x 10 mg/d
for 4 days
first dose before/with AB!

De Gans 2002 *NEJM* 347:1549-56

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De Gans 2002 *NEJM* 347:1549-56

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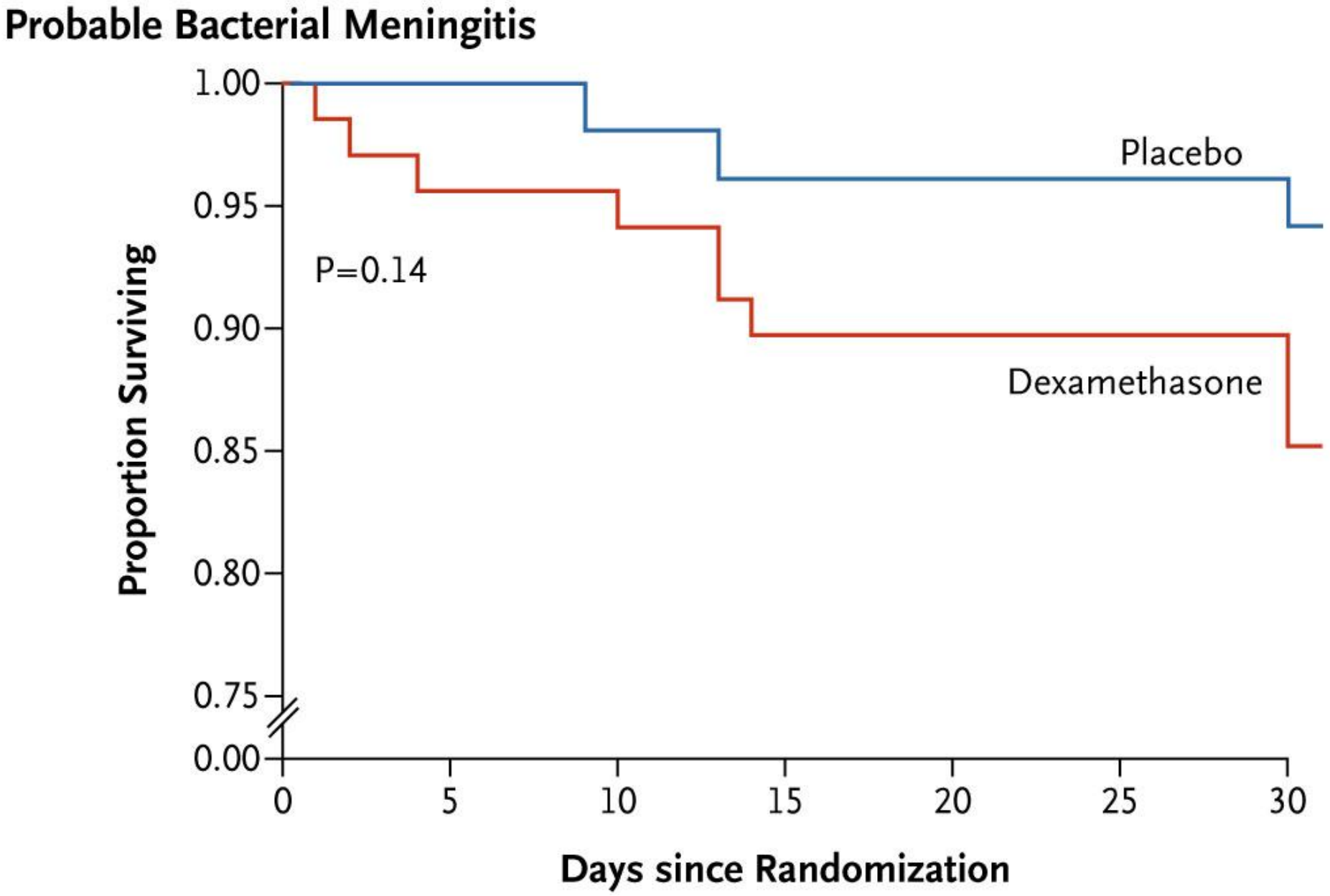
De Gans 2002 *NEJM* 347:1549-56

Dexamethasone in BM

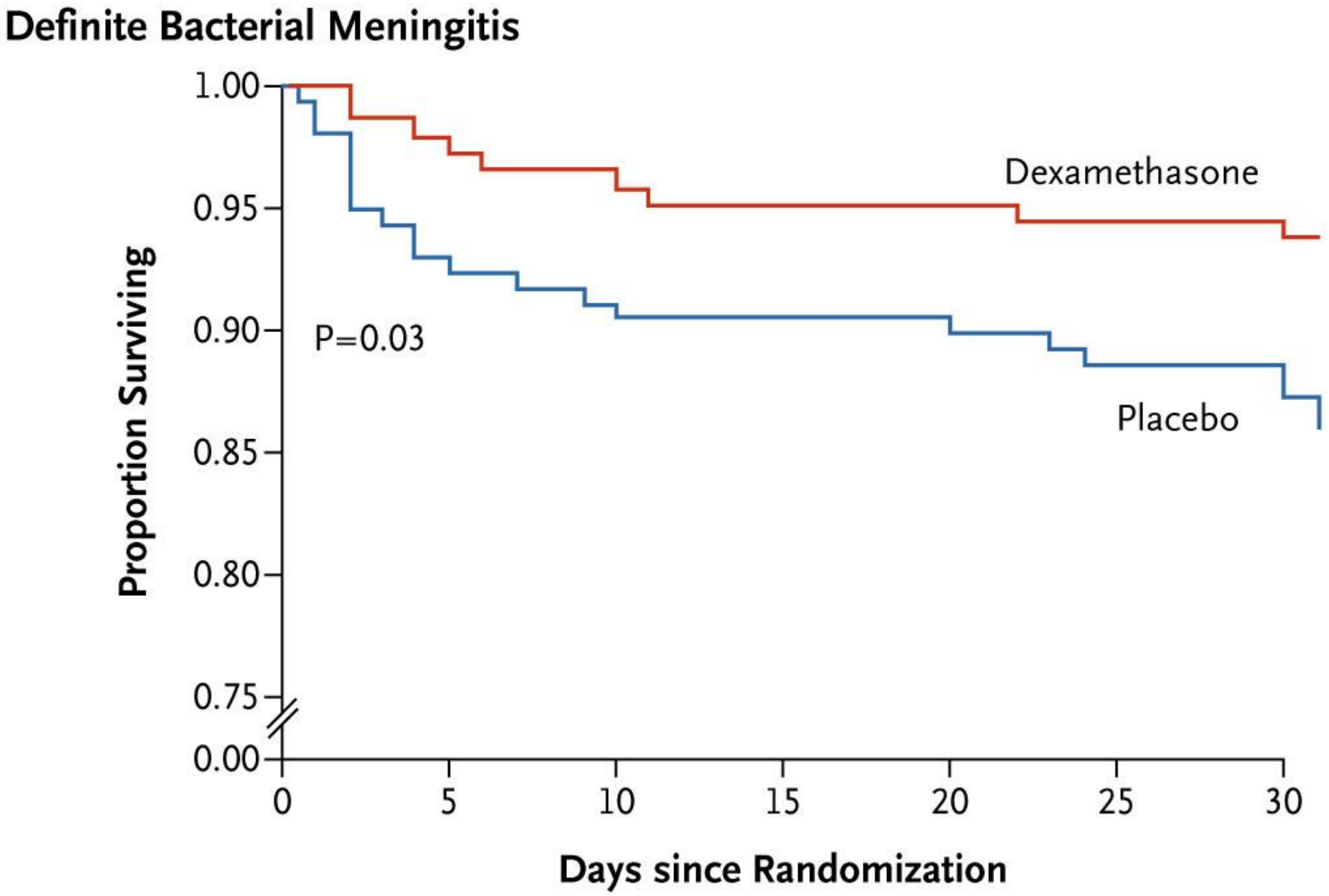
Outcome and Culture Results	Dexamethasone Group	Placebo Group
	no./total no. (%)	
Unfavorable outcome		
All patients	23/157 (15)	36/144 (25)
Streptococcus pneumoniae	15/58 (26)	26/50 (52)
Neisseria meningitidis	4/50 (8)	5/47 (11)
Other bacteria	2/12 (17)	1/17 (6)
Negative bacterial culture‡	2/37 (5)	4/30 (13)
Death		
All patients	11/157 (7)	21/144 (15)
S. pneumoniae	8/58 (14)	17/50 (34)
N. meningitidis	2/50 (4)	1/47 (2)
Other bacteria	1/12 (8)	1/17 (6)
Negative bacterial culture	0/37	2/30 (7)

GOS after 8 weeks
„Unfavourable“ 2-4

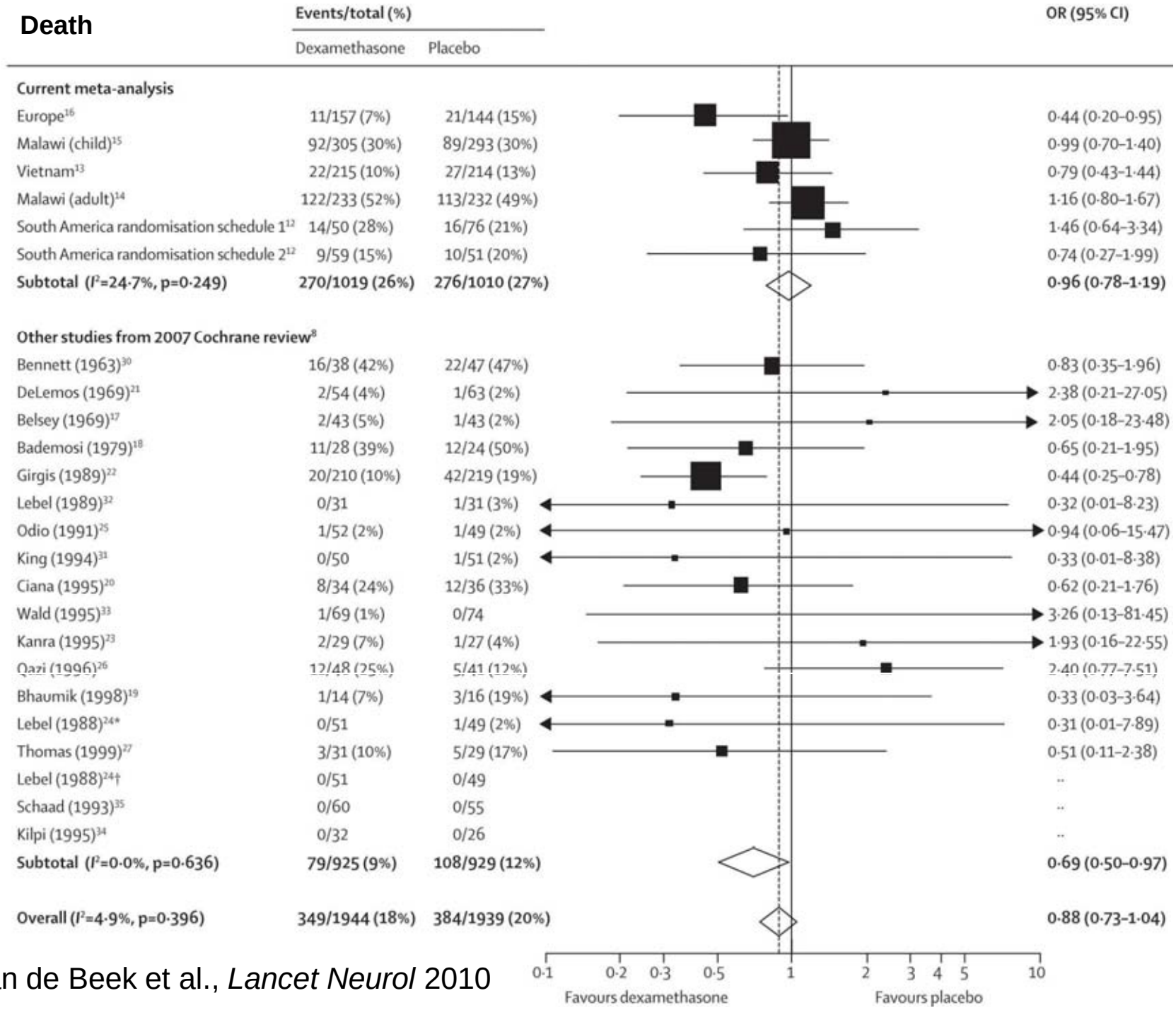
De Gans 2002 *NEJM* 347:1549-56



Nguyen et al., *NEJM* 2007



Nguyen et al., *NEJM* 2007



Van de Beek et al., *Lancet Neurol* 2010

Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis

Characteristics	2006-2009	1998-2002	Difference (%)	*p* Value
No. of episodes	357	352		
Clinical course, n (%)				
Neurologic complications[b]	239 (60)	263 (75)	−15	<0.001
Seizures	60/344 (17)	85/349 (24)	−7	0.025
Cardiorespiratory failure	133 (37)	134 (38)	−1	0.823
Score on Glasgow Outcome Scale, n (%)				
1 (death)	71 (20)	107 (30)	−10	0.001
2 (vegetative state)	0	3 (1)	−1	
3 (severe disability)	18 (5)	17 (5)	0	
4 (moderate disability)	50 (14)	50 (14)	0	
5 (no or minor disability)	218 (61)	175 (50)	+11	0.002

Brouwer 2010 *Neurology* 75:1533

MANAGEMENT of BACTERIAL MENINGITIS

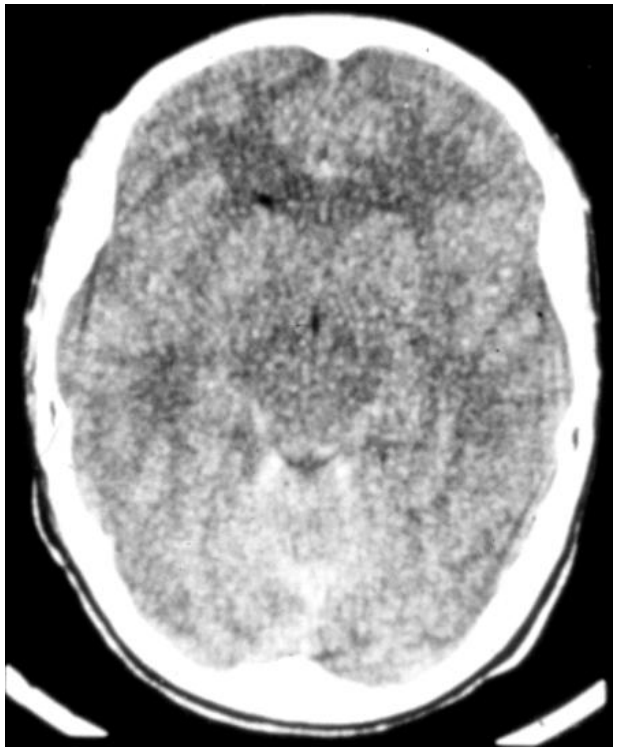
no diagnostic delay!

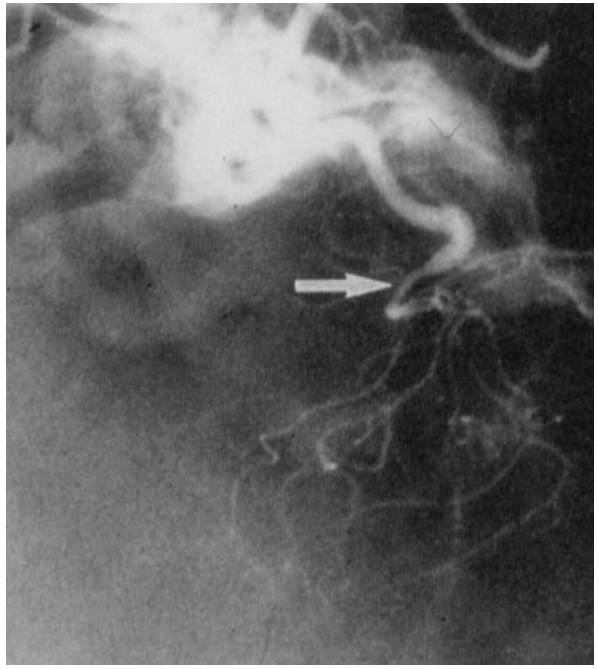
dexamethasone
+
AB

LP	**resistance, other causes**
CCT/MRT	**hydrocephalus, edema, hypodense areas**
MR- Angio	**SVT, Vasculitis**
EEG	**nonconvulsive SE**
TCD	**stenosis**

24 h **48 h**

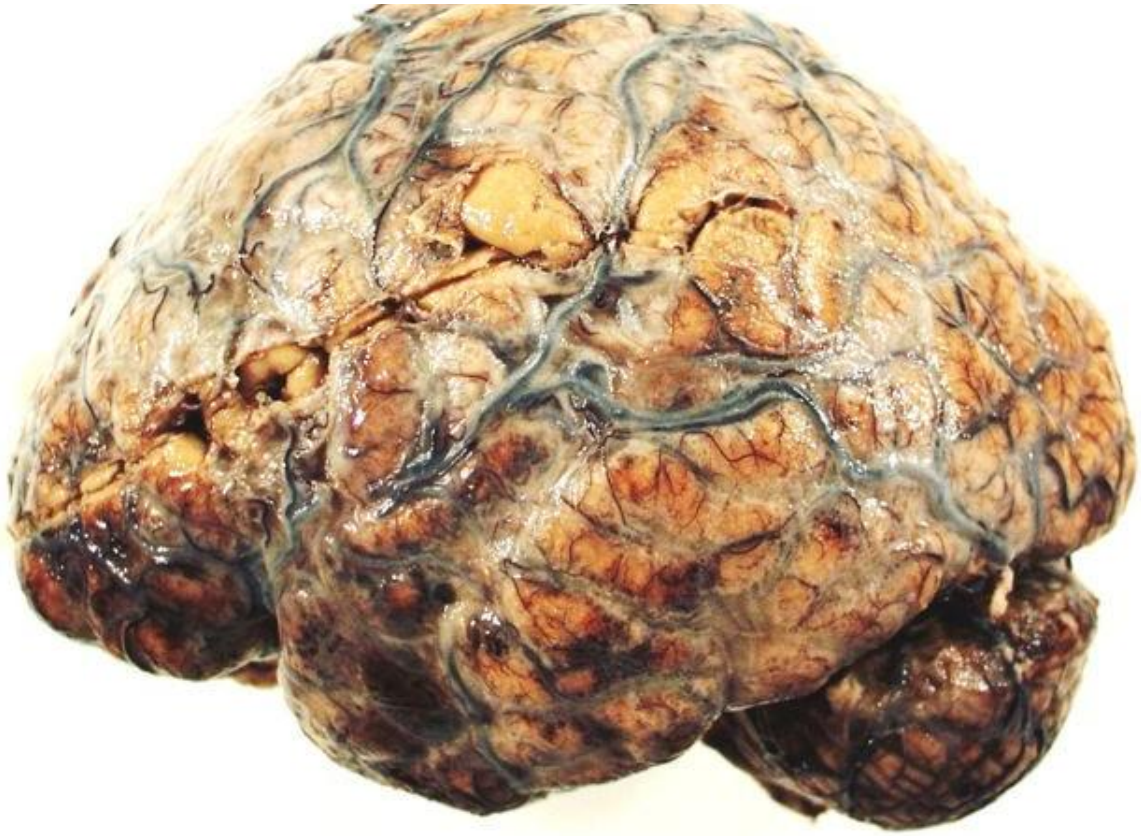
decrease consciousness, new focal signs

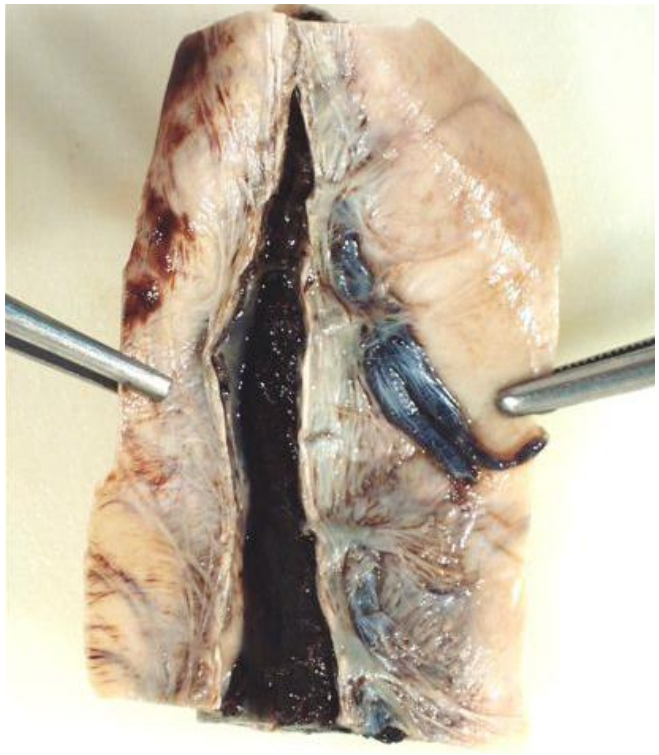




pneumonia

arthritis





Stroke bei BM

	Bacterial meningitis with cerebral ischaemia ($n = 6$)	Bacterial meningitis without cerebral ischaemia ($n = 62$)	p value
Female sex, n (%)	4 (67)	27 (43)	0.278
Age, years, median (range)	52 (30–78)	49 (16–81)	0.576
Leucocytes in CSF, cells/µl, median (range)	960 (133.3–2,218.7)	3,330 (136.3–165,376.7)	**0.012**
CSF lactate, mg/dl median (range)	80.5 (60–154)	100 (19–251)	0.513
Reduced level of consciousness on admission, n (%)	6 (100)	28 (45.2)	**0.01**
Treatment with dexamethasone, n (%)	3 (50)	31 (50)	1.0

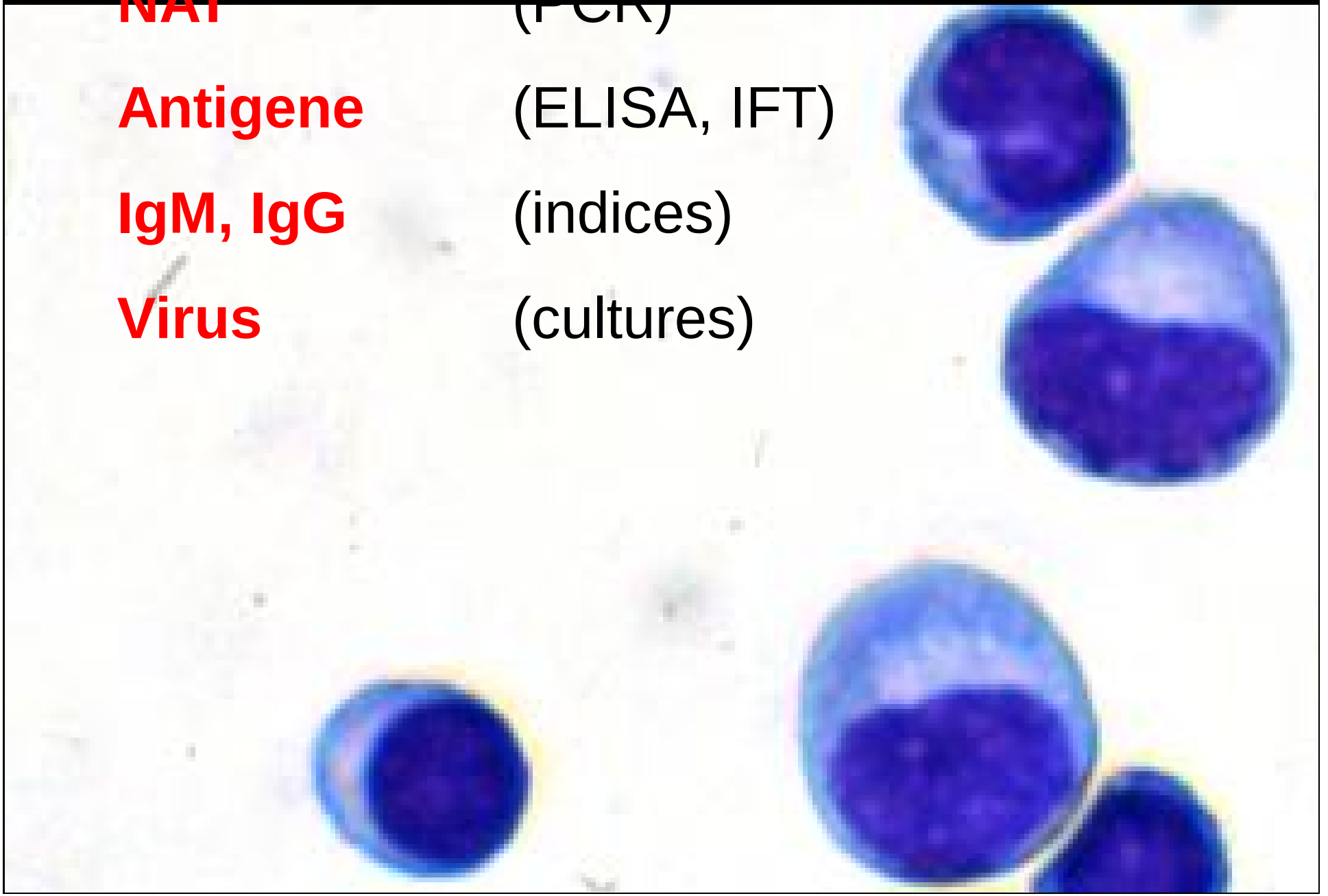
Katschhanov et al., JN 2009

NAT (PCR)

Antigene (ELISA, IFT)

IgM, IgG (indices)

Virus (cultures)

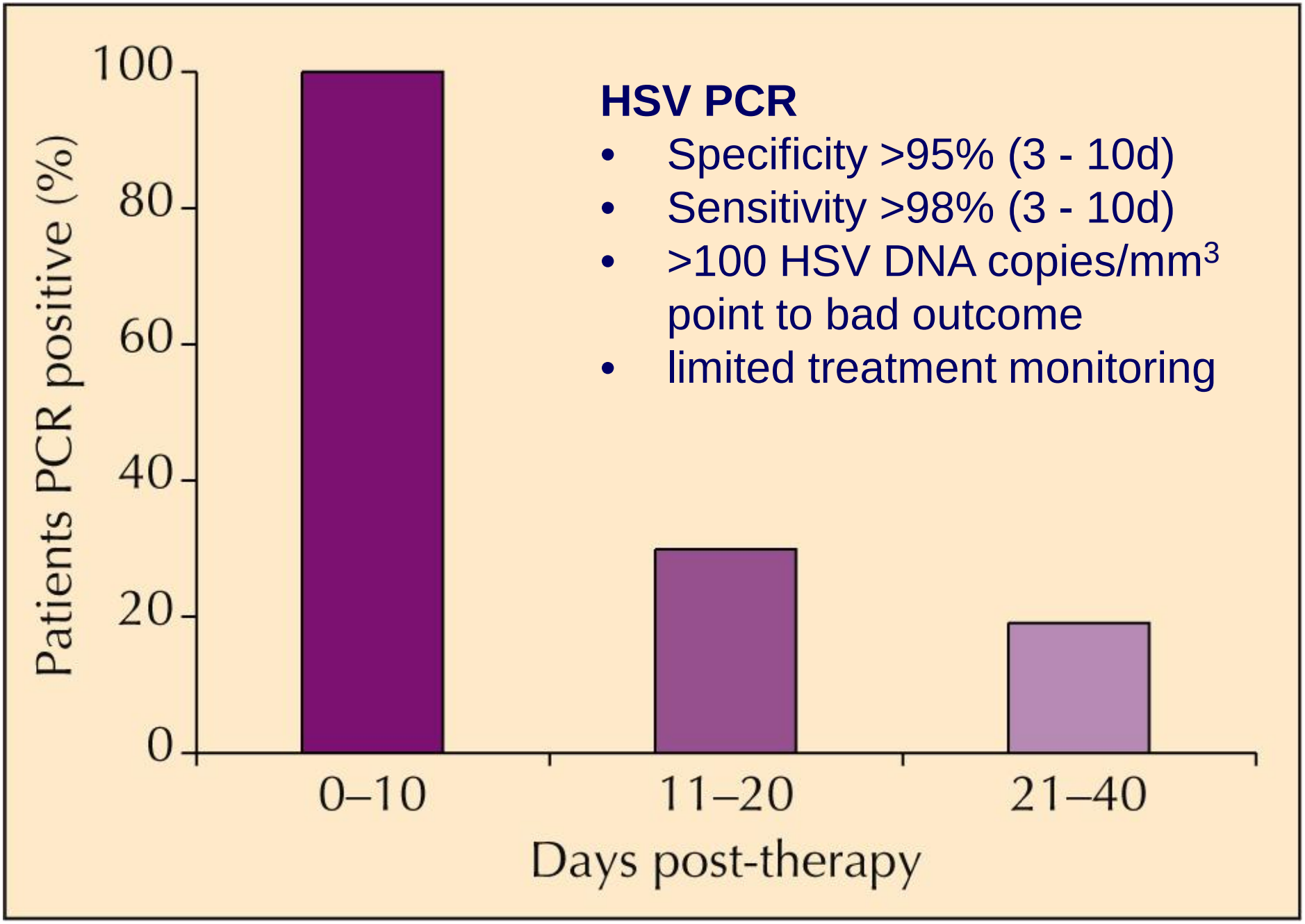


Clinical Presentation
HSV Encephalitis

Unspecific „flu like“ symtoms at the beginning

	Whitley 1982	*Sköldenberg 1984*
Fever	**92 %**	**100 %**
Focal neurology	**97 %**	**90 %**
CSF pleocytosis	**95 %**	**90 %**

MRI and EEG pattern



Lakeman et al. 1995 *J Infect Dis* 171:857–863

Dose adaptation Acyclovir

Creatininclearance	
> 50 ml/min	**3 x 10mg/kg/d**
25 - 50	**2 x 10mg/kg/d**
10 - 25	**1 x 10mg/kg/d**

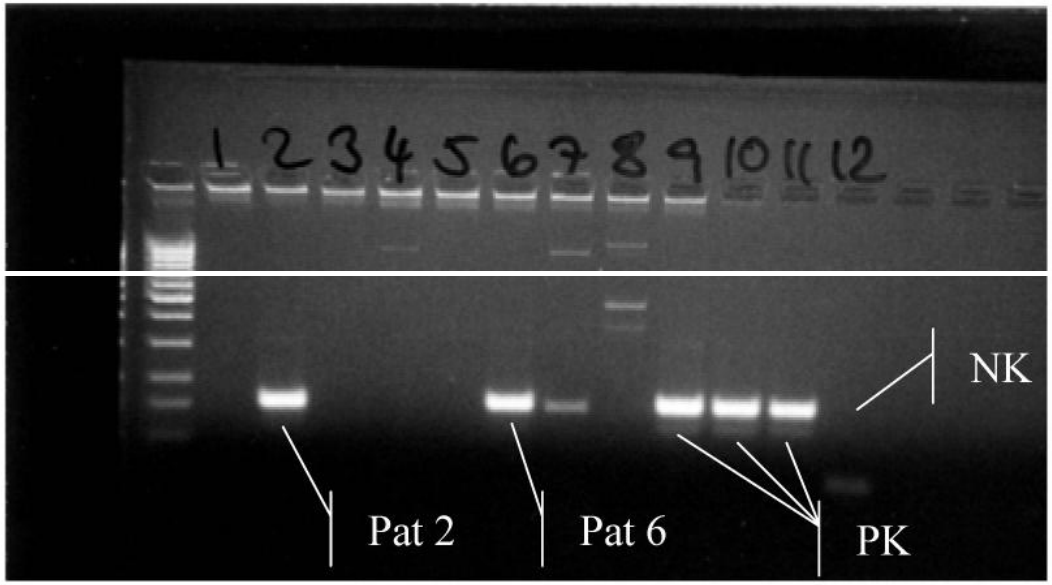
(150- age) x KG x k / creatinin
=
creatininclearance (approximate)

k = 0,9 female
k = 1,1 male

Enteroviruses

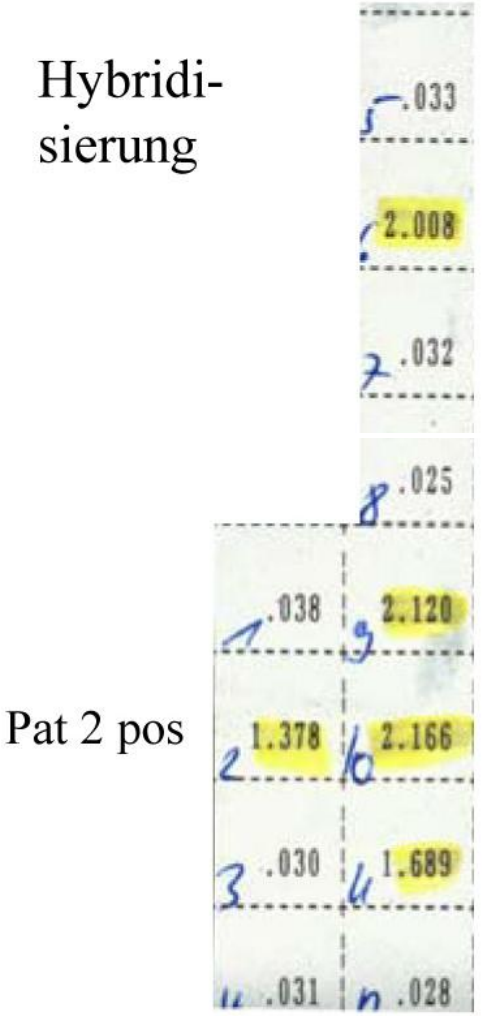
Patientin 31 Jahre mit aseptischer Meningitis, 10 Tage stationär
Ehemann ebenfalls mit Meningitis

Gelelektrophorese der Amplifikate

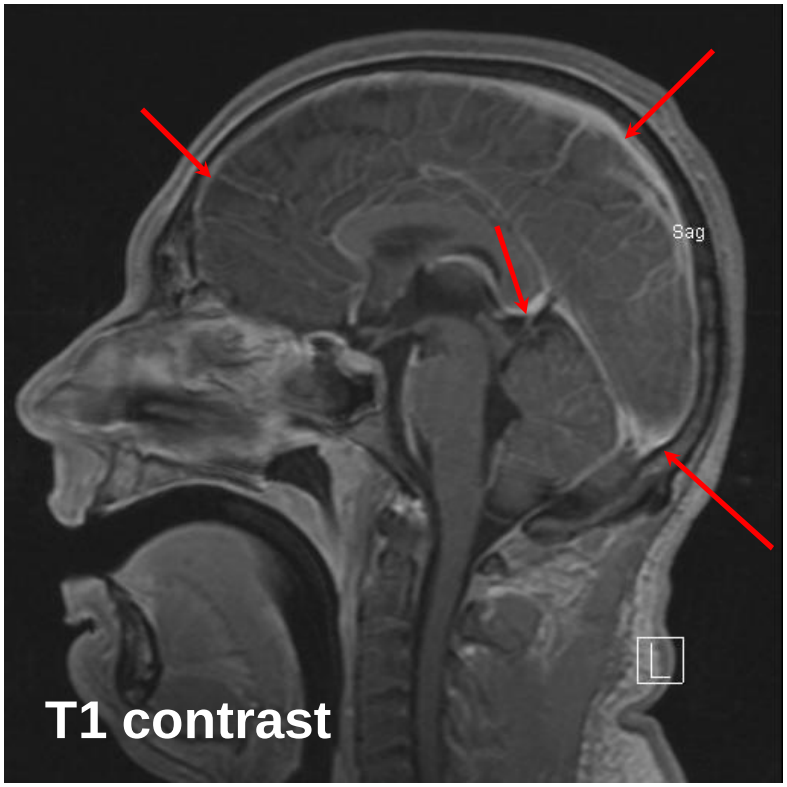


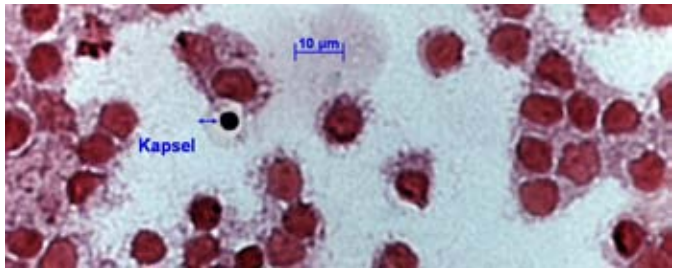
1-8	Patientenproben
9-11	Positivkontrollen 10^{-4}-10^{-6}
12	Negativkontrolle

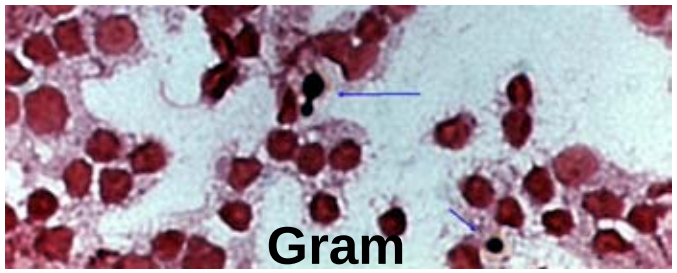
Hybridi-
sierung

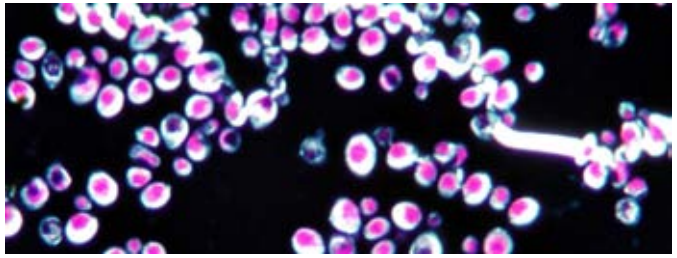


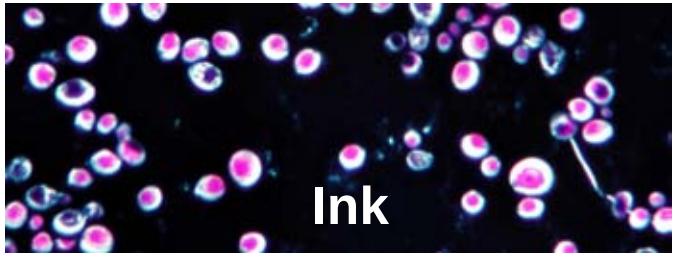
Cryptococcus neoformans



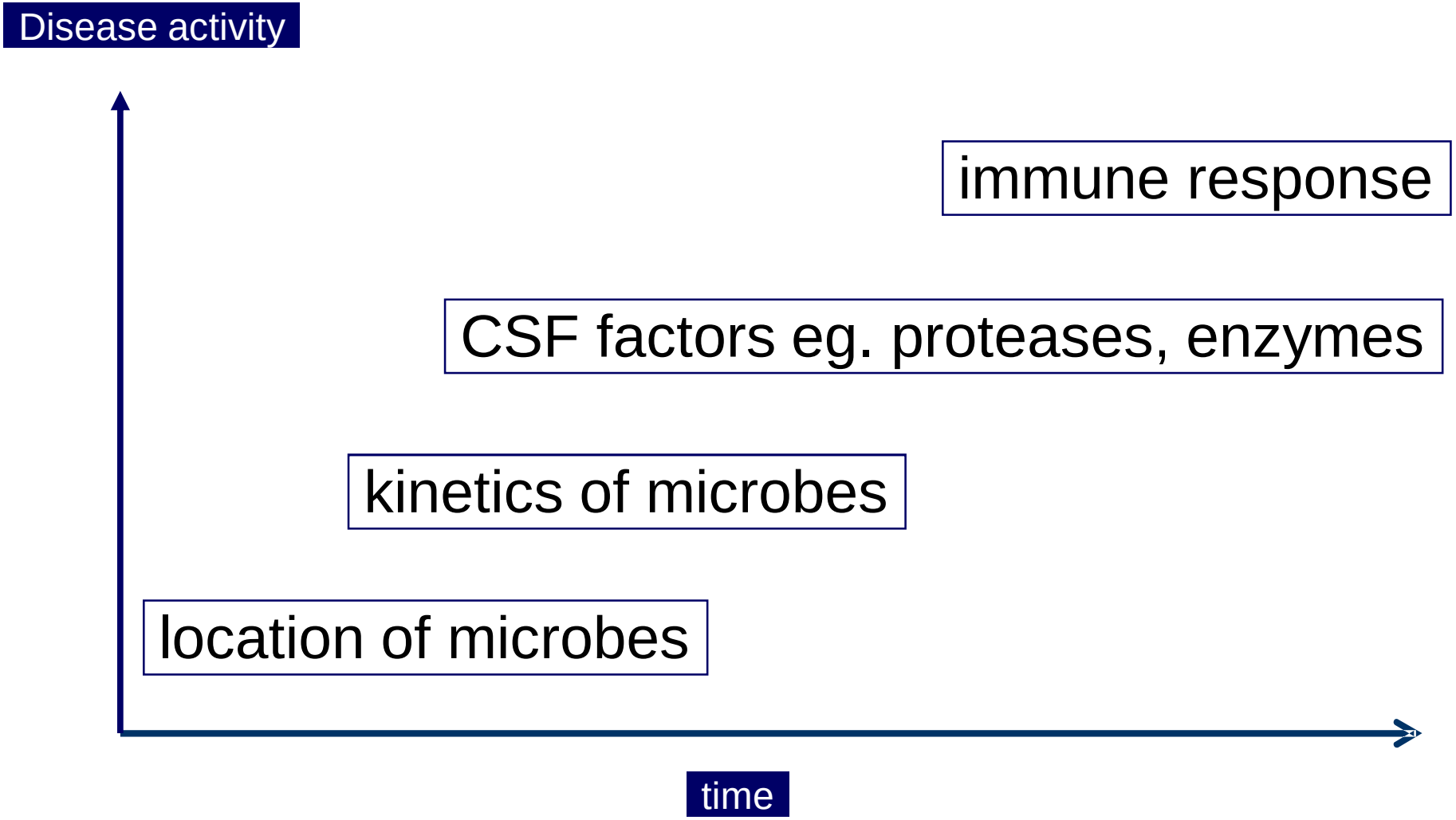








Influences on NATs



In Search of Encephalitis Etiologies: Diagnostic Challenges in the California Encephalitis Project, 1998–2000

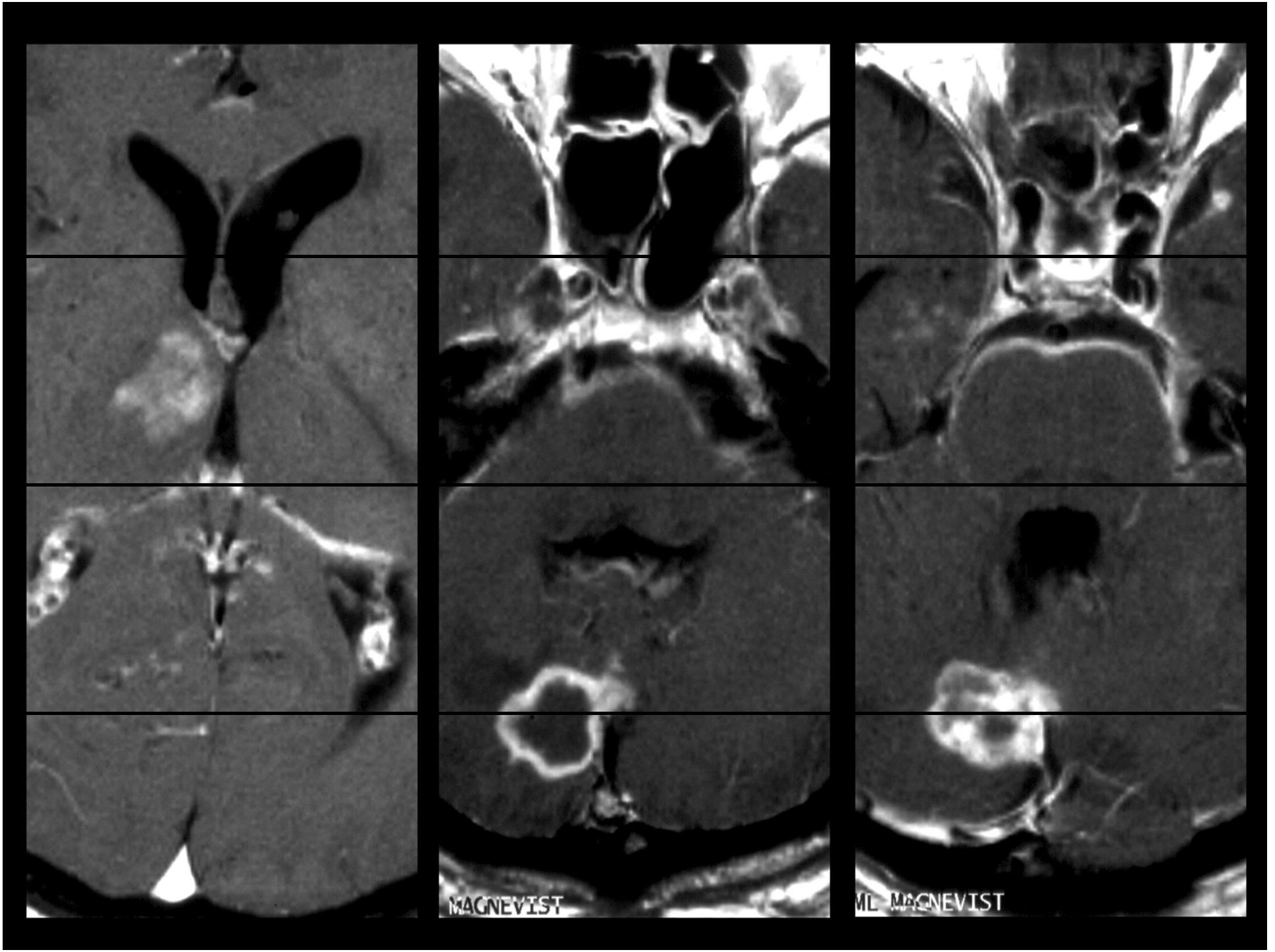
Carol A. Glaser,[1] Sabrina Gilliam,[1] David Schnurr,[1] Bagher Forghani,[1] Somayeh Honarmand,[1] Nino Khetsuriani,[2] Marc Fischer,[3] Cynthia K. Cossen,[1] and Larry J. Anderson[2]

[1]Viral and Rickettsial Disease Laboratory, California Department of Health Services, Richmond, California; and [2]Respiratory and Enteric Viruses Branch and [3]Meningitis and Special Pathogens Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

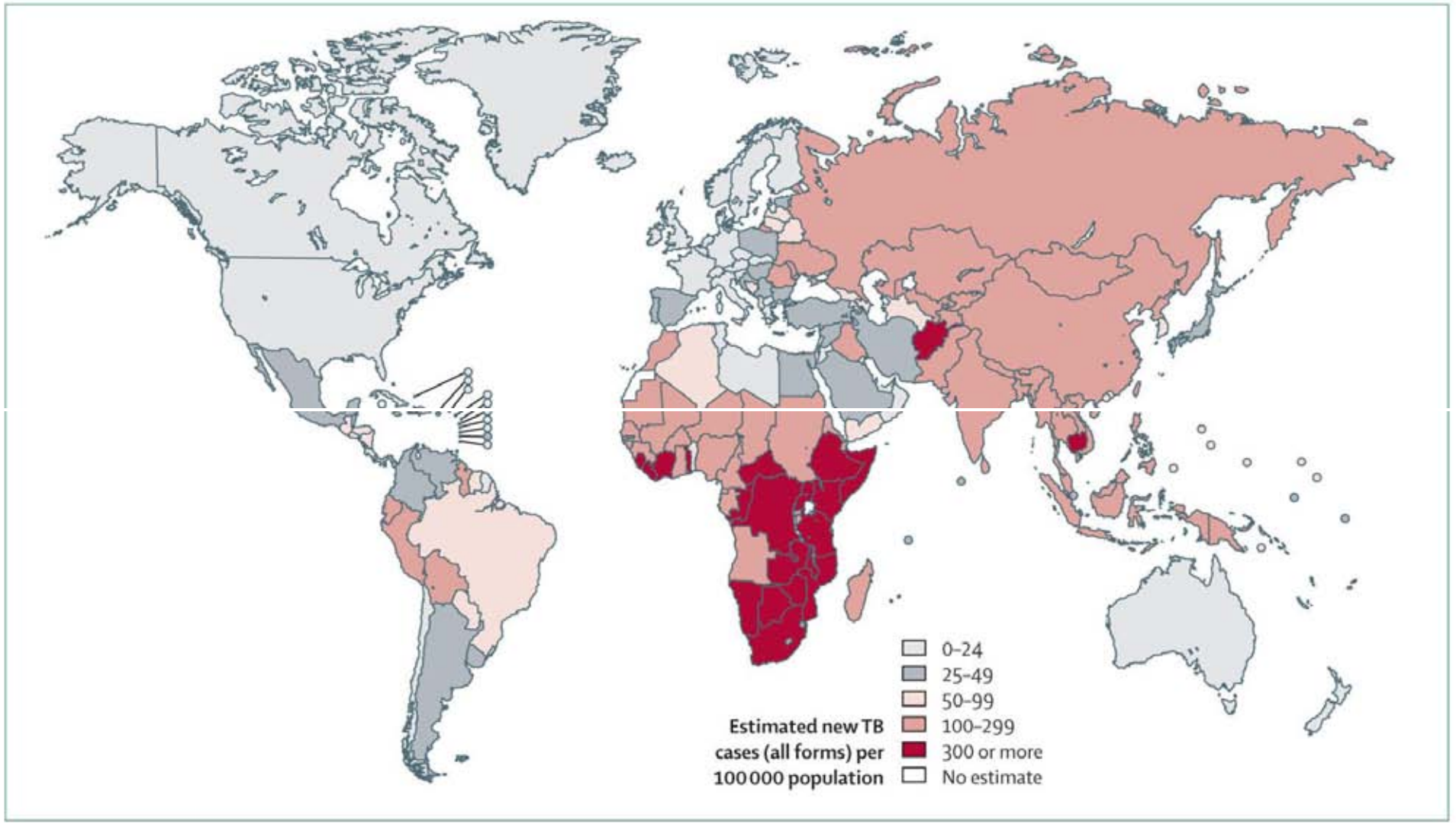
62 % no proven cause!!!

25 % with proven microbiology

The Cal … ize the clinical a … viruses, enterovi … formed at the Vi … mation collected … ho met our case … itis was found ir … nd in 2 cases (1… d in 32 cases (10 … luation, the etiology of 208 cases (62%) remained unexplained.


MAGNEVIST
ML MAGNEVIST

TBC worldwide



Diagnostic steps

1. Tuberculintest (Mendel-Mantoux-Methode, QuantiFERON®-TB Gold test)
2. Radiology
3. Bacteriology
    1. Microscopy >10^4 TB/ml
    2. Culture
        1. liquid (10 TB/ml 1-2 weeks)
        2. Non liquid (100 TB/ml 3-4 weeks)
    3. PCR/NAT Sensitivity 80-90%
    4. Species
    5. Molecular typing
    6. Sensitivity tests

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Accuracy of real-time PCR, Gram stain and culture for *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae* meningitis diagnosis

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Abstract

Background: Although cerebrospinal fluid (CSF) culture is the diagnostic reference standard for bacterial meningitis, its sensitivity is limited, particularly when antibiotics were previously administered. CSF Gram staining and real-time PCR are theoretically less affected by antibiotics; however, it is difficult to evaluate these tests with an imperfect reference standard.

Methods and findings: CSF from patients with suspected meningitis from Salvador, Brazil were tested with culture, Gram stain, and real-time PCR using *S. pneumoniae, N. meningitidis,* and *H. influenzae* specific primers and probes. An antibiotic detection disk bioassay was used to test for the presence of antibiotic activity in CSF. The diagnostic accuracy of tests were evaluated using multiple methods, including direct evaluation of Gram stain and real-time PCR against CSF culture, evaluation of real-time PCR against a composite reference standard, and latent class analysis modeling to evaluate all three tests simultaneously.

Results: Among 451 CSF specimens, 80 (17.7%) had culture isolation of one of the three pathogens (40 *S. pneumoniae,* 36 *N. meningitidis,* and 4 *H. influenzae*), and 113 (25.1%) were real-time PCR positive (51 *S. pneumoniae,* 57 *N. meningitidis,* and 5 *H. influenzae*). Compared to culture, real-time PCR sensitivity and specificity were 95.0% and 90.0%, respectively. In a latent class analysis model, the sensitivity and specificity estimates were: culture, 81.3% and 99.7%; Gram stain, 98.2% and 98.7%; and real-time PCR, 95.7% and 94.3%, respectively. Gram stain and real-time PCR sensitivity did not change significantly when there was antibiotic activity in the CSF.

Conclusion: Real-time PCR and Gram stain were highly accurate in diagnosing meningitis caused by *S. pneumoniae, N. meningitidis,* and *H. influenzae,* though there were few cases of *H. influenzae.* Furthermore, real-time PCR and Gram staining were less affected by antibiotic presence and might be useful when antibiotics were previously administered. Gram staining, which is inexpensive and commonly available, should be encouraged in all clinical settings.

Summary

- **Acute „community aquired“**
  CNS infections are emergencies!

- **Rapid diagnosis of bacterial, HSV and fungal Meningoencephalitis is essential!**
- **Immediate antimicrobial treatment reduces mortality and morbidity!**
- **Treatment recommendations in BM are different in Europe, the US and countries with limited resources!**

- **Create local treatment guidelines!**
- **Neuro Critical Care is important!**
- **Time is Brain not just in Stroke!**