

Corticosteroids in meningitis

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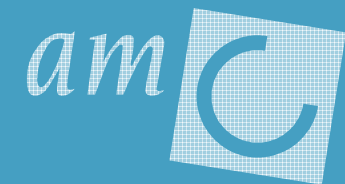
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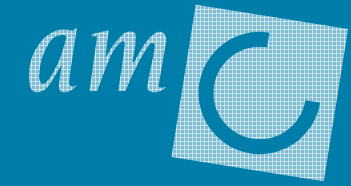
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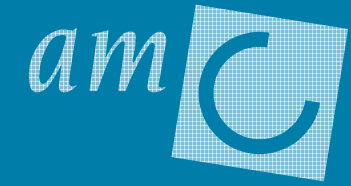


Conflicts of interest



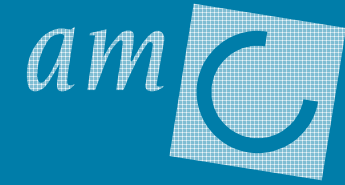
- No conflicts of interest
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 - European Society for Clinical Microbiology and Infectious Diseases
 - European Federation of Neurological Societies

Corticosteroids in meningitis

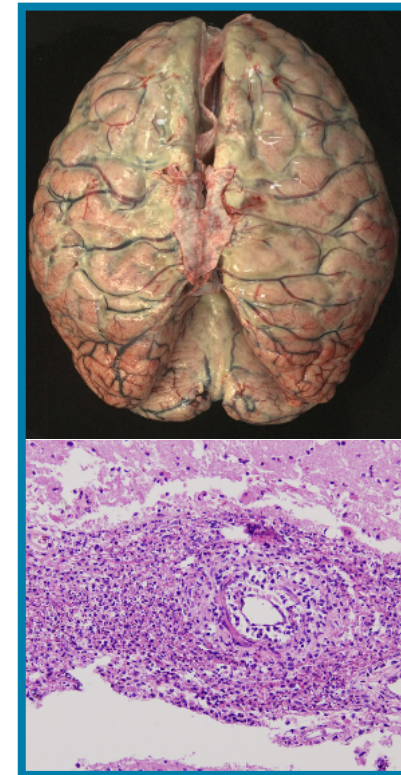


- Dexamethasone in bacterial meningitis
- Dexamethasone in tuberculous meningitis

Bacterial meningitis

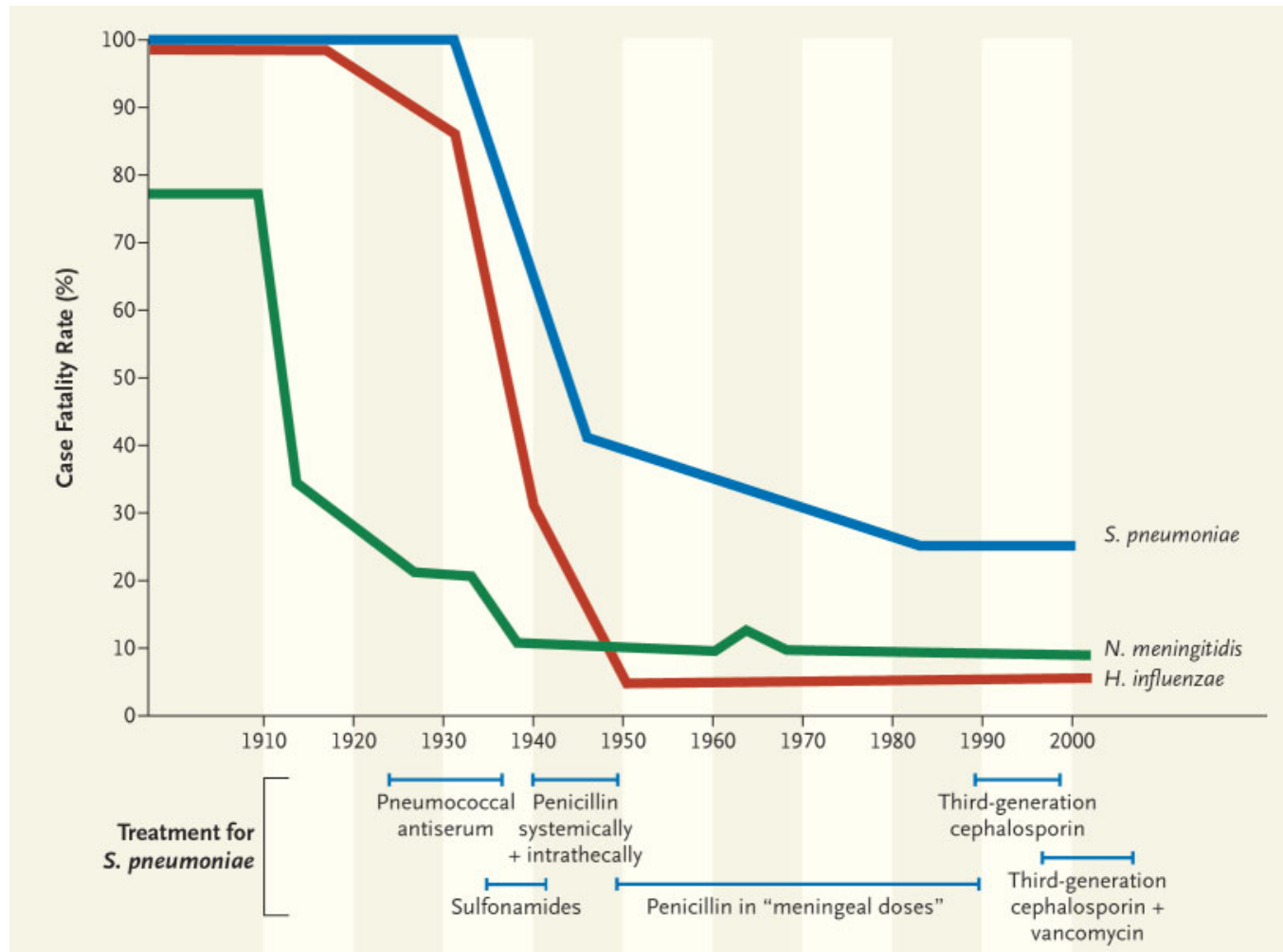
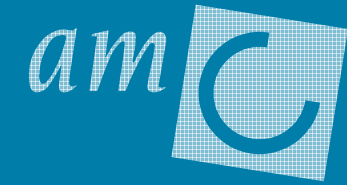


- 35,000 Europeans each year
- Most important causative microorganisms
 - *Streptococcus pneumoniae*
 - *Neisseria meningitidis*
- High mortality
- Frequently neurological sequelae



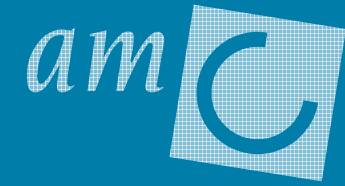
van de Beek *et al*, N Engl J Med, 2006
Brouwer *et al*, Clin Microbiol Rev, 2010

Meningitis mortality - history



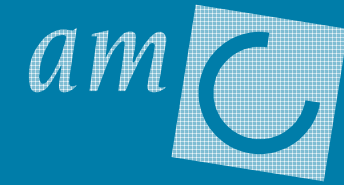
Schwartz, N Engl J Med, 2004

Bacterial meningitis treatment

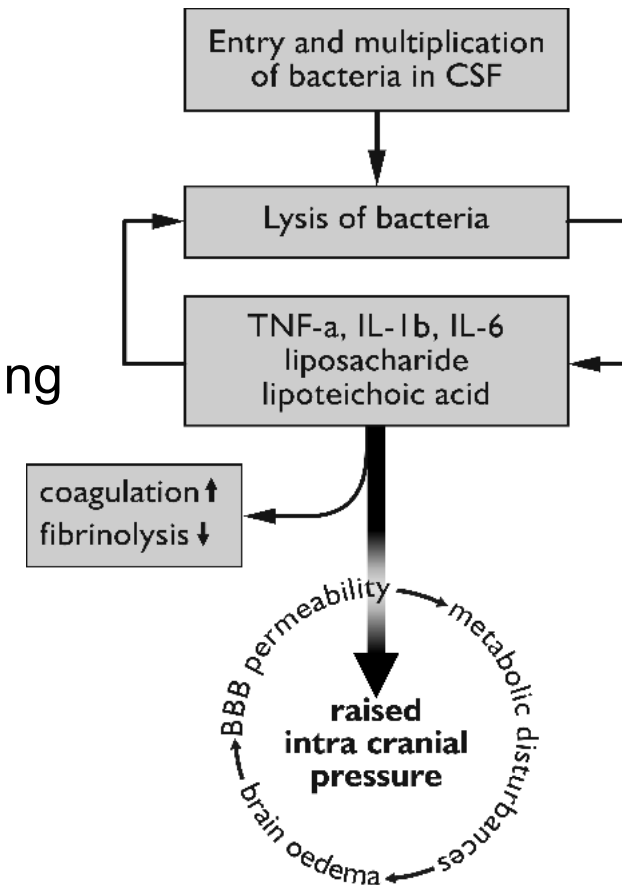


- Antibiotic treatment not enough to improve prognosis
- Long search for adjunctive treatment
 - Anti-inflammatory agents → corticosteroids, IgG, paracetamol
 - Neuroprotection → hypothermia
 - Osmotic agents → mannitol, glycerol
 - Anti-coagulants → heparin, activated protein C

Animal model and steroids

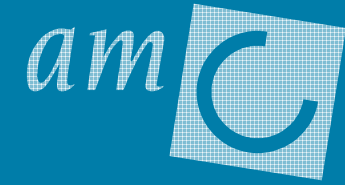


- Severity of disease
 - Bacterial load
 - Inflammatory response
- Inflammation continues after bacterial killing
- Severity inflammation ~ outcome
- Dexamethasone
 - Reduction inflammation
 - Reduction ICP



Scheld et al , J Clin Invest 1980
Giampolo et al, Ann Neurol 1981
Tauber et al, Am J Pathol 1992

Initial clinical studies

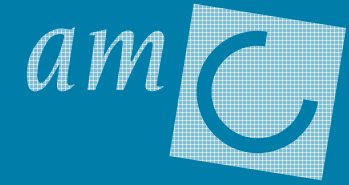


- First studies published 1963 / 1969 - no effect
- Animal experiments early '80s
- Several small trials in children '80-'90s
 - Reduction in severe hearing loss
 - *Haemophilus influenzae* meningitis
 - Conflicting results

Lebel et al, N Engl J Med 1988, 1989

Odio et al, N Engl J Med 1991

Meta-analysis 1997



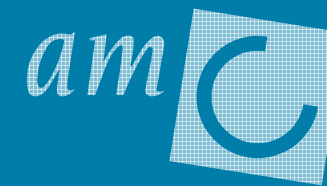
DXM reduces severe hearing loss

Only in *H. influenzae* meningitis

Vaccination *H. influenzae* type B 99% reduction cases

Trend towards lower mortality in pneumococcal meningitis

European dexamethasone trial 2002



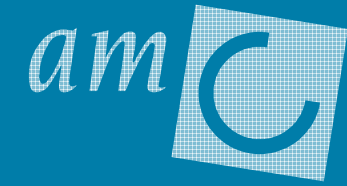
Randomized controlled trial 1993-2001

301 patients → 157 DXM, 144 placebo

DXM 10mg iv every 6 hours for 4 days, before or with antibiotics

	Death		Unfavorable outcome	
	DXM	Placebo	DXM	Placebo
All patients	11/157 (7%)	21/144 (15%)	23/157 (15%)	36/144 (25%)
<i>S. pneumoniae</i>	8/58 (14%)	17/50 (34%)	15/58 (26%)	26/50 (52%)

Following European DXM Trial



Treatment guidelines IDSA:

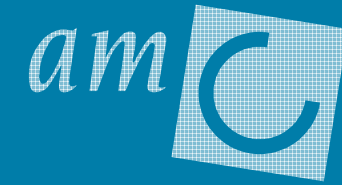


Standard treatment DXM in adults with bacterial meningitis

Proven effect only in pneumococcal meningitis

Stop DXM if meningococcus or other pathogen is identified

Negative trials 2002-2007



- Malawi, children, n=598, no effect
- Malawi, adults, n=465, no effect
- Vietnam, adults, n=217, no effect in suspected BM
 - However: reduced mortality confirmed BM
- South-America, children, n=654, reduction hearing loss *H. influenzae*
 - Methodological problems



Molyneux et al, Lancet 2002

Scarborough et al, N Engl J Med 2007

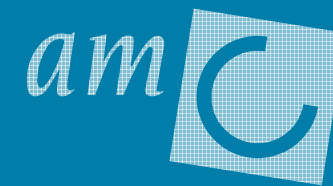
Nguyen et al, N Engl J Med 2007

Peltola et al, CID 2007

- False positive result European DXM trial?
- Differences in study population?
 - High rate of HIV positivity Malawi (90%)
 - Partially treated meningitis / tuberculous meningitis
 - Different genetic background?

- Data of individual patients included in meta-analysis
 - 5 Trials: Malawi (2), South-America, Europe, Vietnam
 - Search for subgroups that benefit from DXM
- No effect on mortality / hearing loss / neurological sequelae in prespecified subgroups
- Reduction hearing loss in survivors (post-hoc)
- Conclusion: effect DXM remains unproven

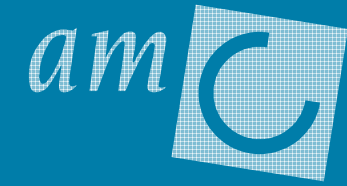
Cochrane meta-analysis 2010



- Inclusion of all RCTs on DXM in bacterial meningitis
- No effect on mortality overall
- Trend towards lower mortality in adults
- Lower rates of hearing loss and neurological sequelae
- Subgroups: lower mortality in pneumococcal meningitis
- Effect limited to high income countries



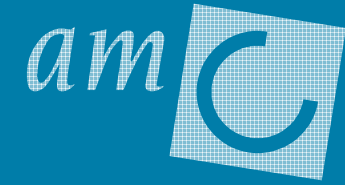
Value meta-analyses



- Individual patient data meta-analysis
 - Superior method
 - Ignores previous studies
- Cochrane meta-analysis
 - Includes trials of lower quality
 - More bias
- Back to own population
 - Fase IV (implementation) study in the Netherlands

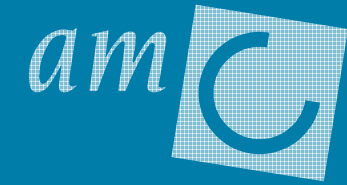


Implementation study Netherlands



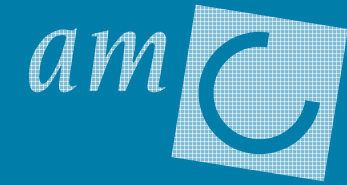
- Implementation of DXM in pneumococcal meningitis
- 2 nationwide prospective cohort studies in the Netherlands
 - 1998-2002, n=357, before DXM
 - 2006-2009, n=352, after DXM
- Inclusion criteria
 - Positive CSF culture, community acquired meningitis
- Multivariate analysis to correct for confounders

Baseline characteristics



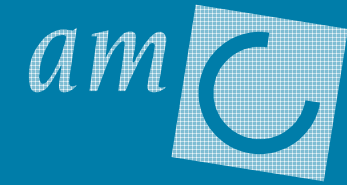
Characteristic	2006-2009 357 Episodes	1998-2002 352 Episodes	Absolute difference (%)
Age – year (means \pm SD)	59 \pm 15	58 \pm 17	
Male sex	167 (47%)	171 (49%)	-2%
Classic triad	206/352 (58%)	188/347 (54%)	-4%
Coma	65/257 (18%)	68/351 (19%)	-1%
Individual CSF predictors of bacterial meningitis	328/348 (94%)	301/320 (94%)	0%

Treatment characteristics



Characteristic	2006-2009 357 Episodes	1998-2002 352 Episodes	Absolute difference (%)
Delay in therapy due to imaging	155 (43%)	149 (42%)	+1%
Antibiotic treatment according to guidelines	118 (33%)	117 (33%)	0%
Strains in PCV7 vaccine	125/327 (38%)	149 (42%)	-4%
Antibiotic resistance rate	2/327 (0.6%)	2 (0.6%)	0%

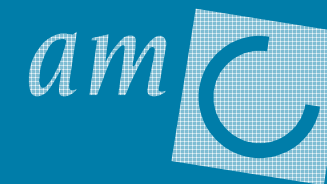
Dexamethasone treatment



Characteristic	2006-2009 357 Episodes	1998-2002 352 Episodes	Absolute difference
Dexamethasone received	329 (92%)	59 (17%)	75% ^{75%} *
Started before or with first dose of antibiotics	301 (84%)	11 (3%)	81%*
10mg QID for 4 days started before or with first dose of antibiotics	276 (77%)	11 (3%)	74%*

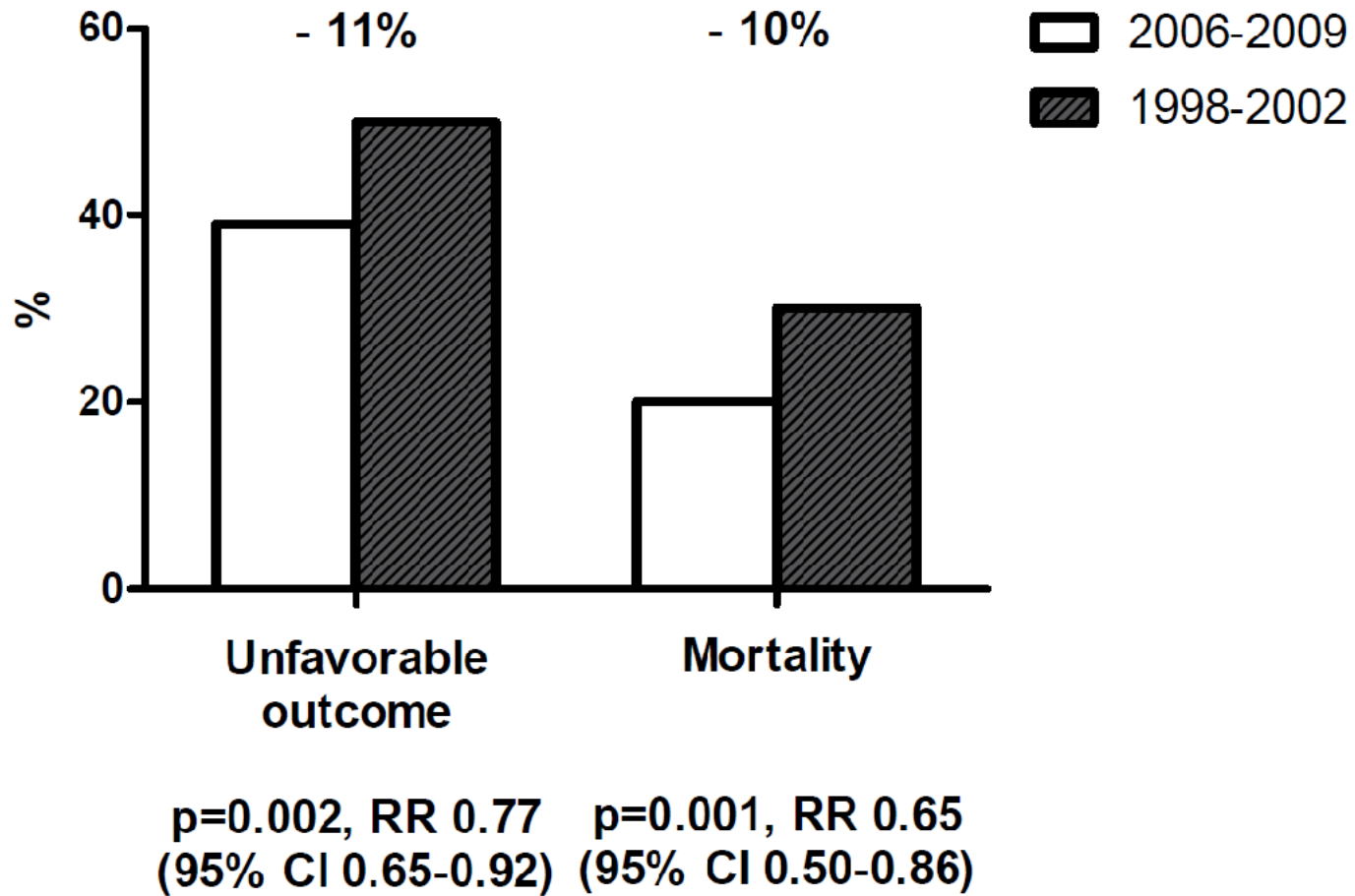
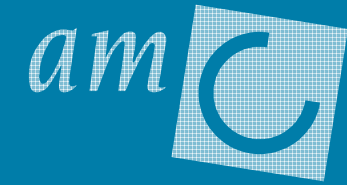
* p <0.001

Complications and outcome

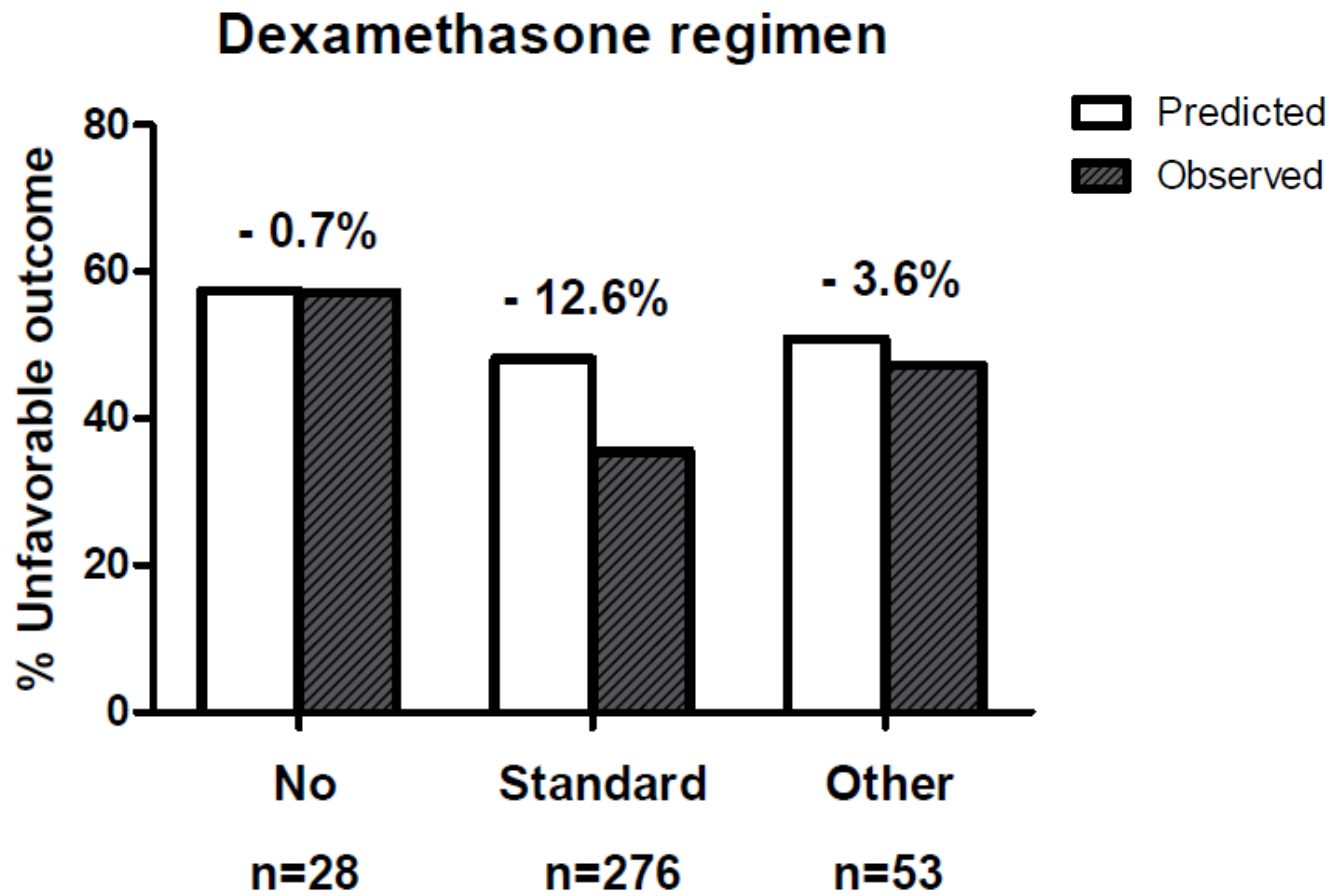
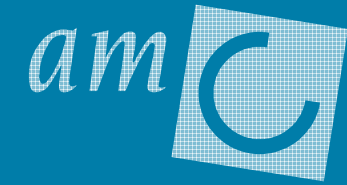


Characteristic	2006-2009 357 Episodes	1998-2002 352 Episodes	Absolute difference	P-value
Neurologic complications	239 (60%)	263 (75%)	-15%	0.001
Cardiorespiratory failure	133 (37%)	134 (38%)	-1%	0.82
Death	71 (20%)	107 (30%)	-10%	0.001
Complete recovery	218 (61%)	175 (50%)	+11%	0.002
Hearing impairment	33/280 (12%)	55/243 (22%)	-10%	0.001

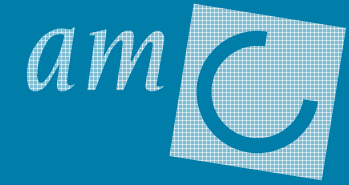
Outcome



Dexamethasone

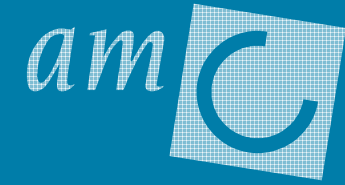


Conclusion implementation study



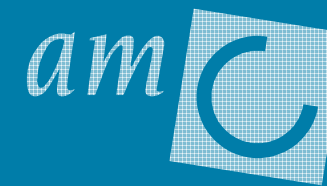
- After successful implementation DXM similar reduction in mortality and unfavourable outcome of pneumococcal meningitis as found in European trial
- No other explanation for improved prognosis but dexamethasone
- Supports further use of DXM

Implementation study 2 - meningococci



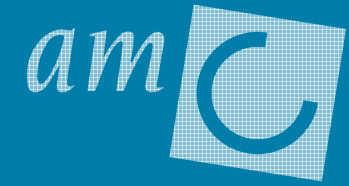
- Similar design
- 1998-2002, n=258 vs. 2006-2011, n=100
- Clinical presentation similar, less rash
- Strong reduction Serogroup C following vaccination
- DXM before or with antibiotics in 89% in 2006-2011 cohort
- Full 4 day course 81%

Implementation study 2 - meningococci



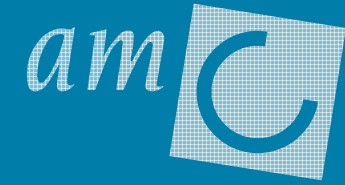
Characteristic	2006-2011 100 Episodes	1998-2002 258 Episodes	Difference
Arthritis	5/96 (5%)	32/258 (12%)	-7% (p=0.049)
Outcome			
Death	4 (4%)	19 (7%)	-3% (p=0.24)
Unfavorable outcome	12 (12%)	30 (12%)	0%
No or minor disability	88 (88%)	228 (88%)	0%
Neurologic findings at discharge			
Hearing impairment	3/96 (3%)	19/237 (8%)	-5% (p=0.10)

Implementation study 2 - conclusion



- DXM safe in meningococcal meningitis
- Reduces auto-immune arthritis
- Trend towards lower hearing loss

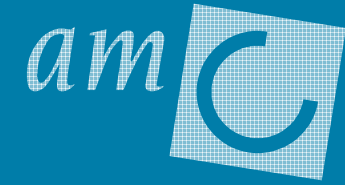
Implementation study 2 - conclusion



- DXM safe in meningococcal meningitis
- Reduces auto-immune arthritis
- Trend towards lower hearing loss

Why hesitate to give DXM?

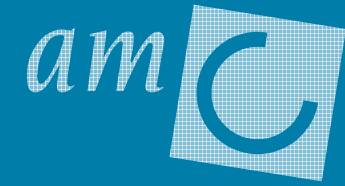
Is DXM harmful?



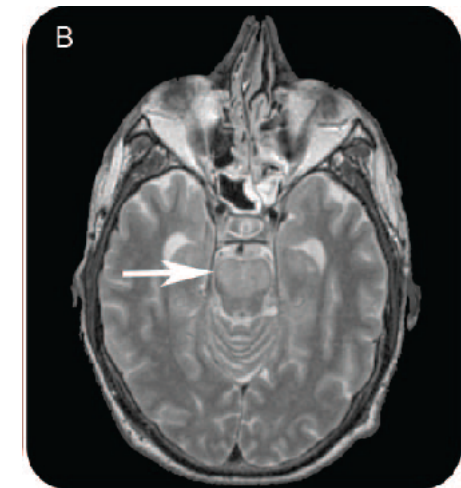
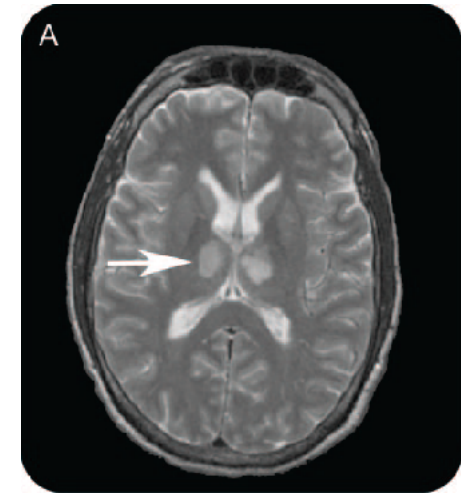
Are there complications of DXM therapy?

- Cohort studies / RCTs show no increase in
 - gastrointestinal bleedings
 - hyperglycemia requiring insulin
 - herpes zoster infections
- New complication?
 - Delayed intracerebral thrombosis

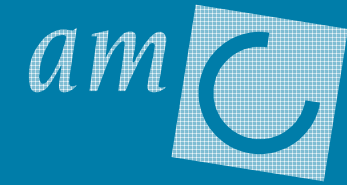
Delayed cerebral thrombosis



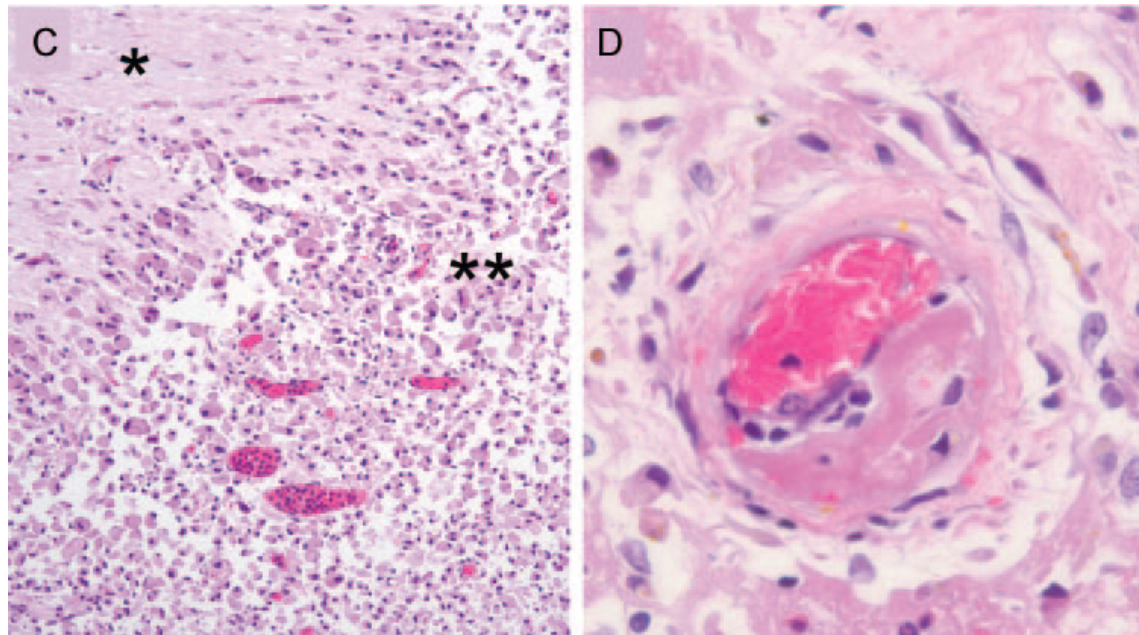
- 6 patients with pneumococcal meningitis
- DXM and antibiotics
- Excellent recovery
- Day 7-19 post admission fever, headache, coma
- Cerebral infarctions posterior circulation
- Inflammatory response CSF
- Negative CSF culture



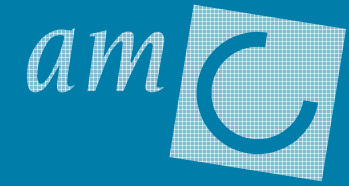
Delayed cerebral thrombosis



- 4 dead, 2 severely disabled
- Autopsy (n=2): diffuse intravascular thrombosis w/o vasculitis
- 2 surviving patients received high dose steroids



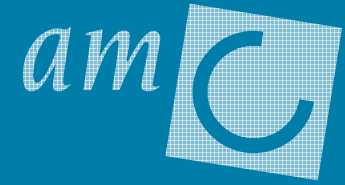
Delayed cerebral thrombosis



- Reactivation of inflammation after effect DXM wears off?
- Immunologic reaction targeting cerebral vessels
- Not described in pre-dexamethasone era
- Incidence 1-2%
- Treatment high dose steroids, followed by tapering

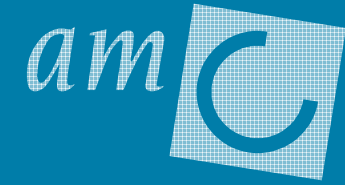
NB the patients were included in the implementation study

Conclusion DXM in bacterial meningitis



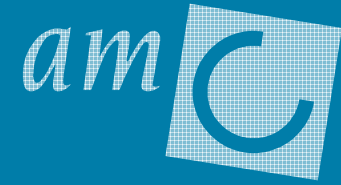
- DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries

Conclusion DXM in bacterial meningitis



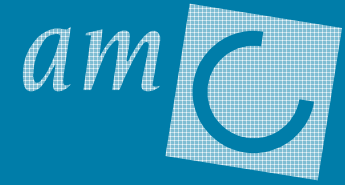
- DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries
- DXM is safe to give in adult meningococcal meningitis and reduces arthritis and probably hearing loss

Conclusion DXM in bacterial meningitis



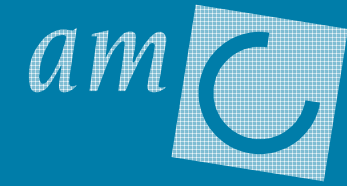
- DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries
- DXM is safe to give in adult meningococcal meningitis and reduces arthritis and probably hearing loss
- There is no effect of DXM in resource poor settings (Africa)

Conclusion DXM in bacterial meningitis

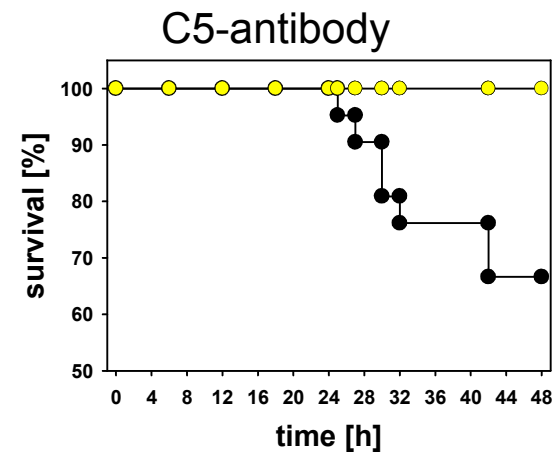
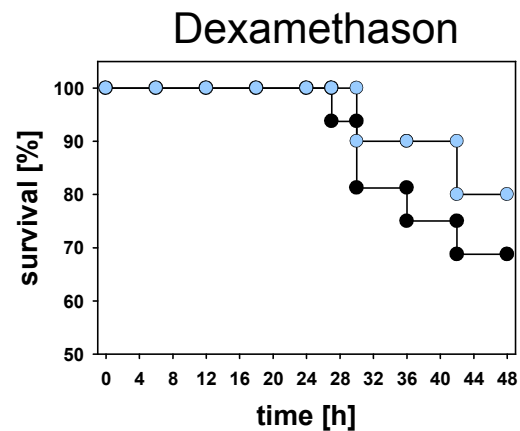


- DXM reduces mortality and sequelae in adult pneumococcal meningitis in high income countries
- DXM is safe to give in adult meningococcal meningitis and reduces arthritis and probably hearing loss
- There is no effect of DXM in resource poor settings (Africa)
- DXM reduces hearing loss in children
- DXM may be associated with delayed cerebral thrombosis

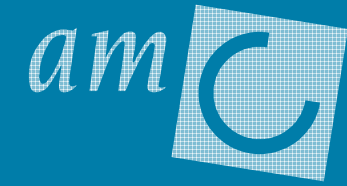
Future studies



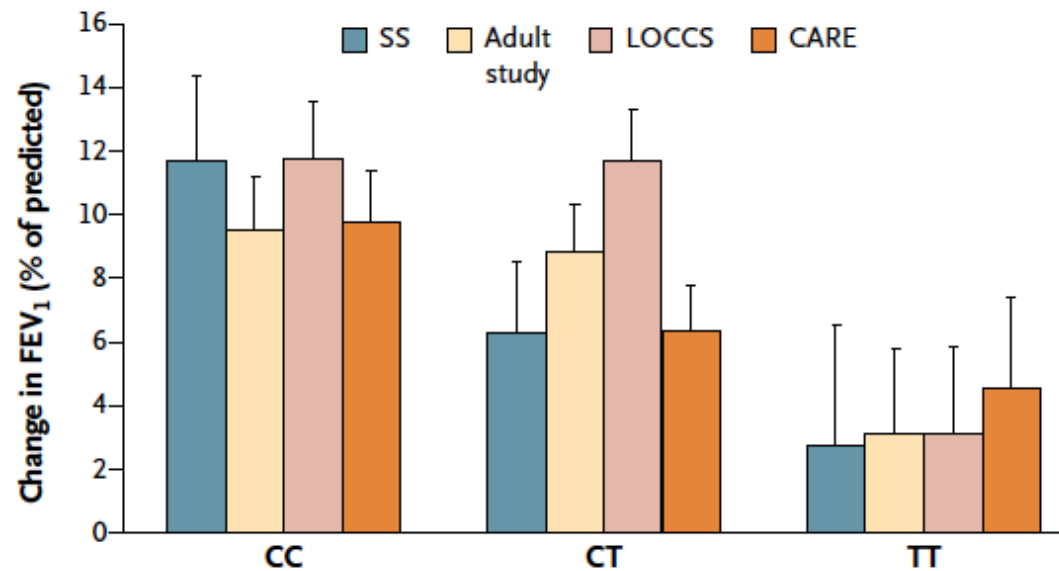
- No new DXM trials are currently performed
- New anti-inflammatory drugs may be superior
- Complement component 5 antibodies in mouse model superior to DXM.



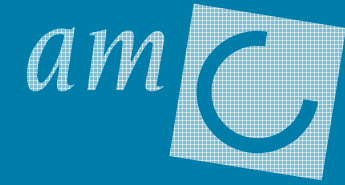
Future studies - genetics



- Study Tantisira *et al*, Oct 2011 N Engl J Med
- SNP glucocorticoid-induced transcript 1 gene
- SNP determines response to steroids in asthma



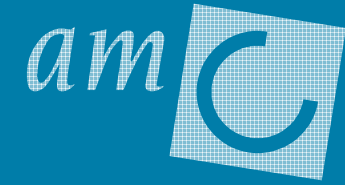
Genetic differences DXM treatment



- SNP *GLCC1* Rs37972
- Minor allele frequency
 - European ancestry 44%
 - Sub-saharan Africa 15%
- Potential cause of differences between populations in response to dexamethasone in bacterial meningitis
- Genetic association study in progress (NL)

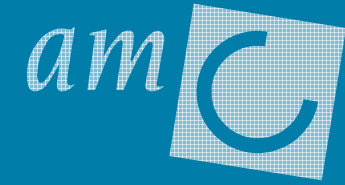
Dexamethasone in tuberculous meningitis

Tuberculous meningitis and DXM



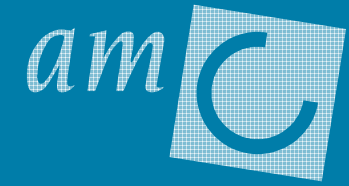
- Small studies since 1953 showed
 - Reduced CSF inflammation
 - Reduced incidence of neurological complications
 - Shorter time to recovery
 - No effect on mortality

Tuberculous meningitis and DXM



- Egypt, children, n=280, 1991
 - Reduced mortality
 - Only in severely affected patients
- South Africa, children, n=141, 1997
 - Reduced mortality
- Vietnam, adults, n=545, 2004
 - Reduced mortality

DXM in TBM for all?



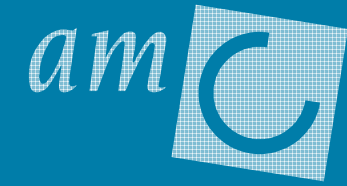
Untreated HIV

- No effect in HIV infected patients
- Vietnamese study showed no harm

Only severely affected patients?

- Vietnamese study showed effect in all categories of disease severity

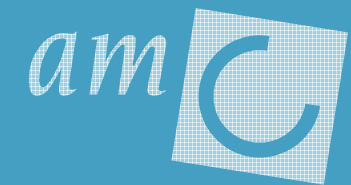
Conclusion DXM in TBM



- All patients with TBM should receive DXM
- Dose 0.3-0.4 mg/kg/day depending on grade
- Tapering over 6-10 weeks

Thank you for your attention

Questions?



Corticosteroids in meningitis

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