TABLE OF EVIDENCE

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Schmutzhard 1995 2 prospective, randomized, controlled, multicenter Hungary, Czech Republic, Portugal, Spain, Austria (15 centers) April 92 - June 93. N=56 randomized N=29 evaluable	adults	clinical sign BM CSF abnormalities	- Blactam allergy - prior history meningitis cl creat ≤ 50 ml/min - hepatic insufficency - immunodeficiency - CNS abscess - congenital abnormalities of the spine - penetrating wounds - fracture or foreign bodies in CNS	- meropenem 40mg/kg/8h (max 6g/24h) (n=28) - ceftriaxone (100 mg following by 80 mg/kg (max 4g/d) (n=11) or cefotaxime (75 to 100 mg/kg/8h max 12g/d) (n=17) dexa admitted (0.15mg/kg/6h 4d) equally distributed Duration: 7 d *N. mening*, 10 d *H. infl* and 10 d *S. pneum.*, 14d others Meropenem / Cephalo *N. menin* 5 / 3 *S. pneumo* 6 / 8 *H. infl* 0 / 1 Others 4 / 3	Clinical evaluation neurological status fever Bacteriological evaluation CSF day 0,18-36h Blood day 0,18-36h Auditory function assessed at the end of treatment and at 6 weeks Six Week posttreatment Clinical evaluation Neurological evaluation Audiological evaluation Some patients: evaluation at 6 months Safety evaluation	11 patients not evaluable, 45 evaluable 29 bacteriologically evaluable imbalance of sex (M=17, Ceph=11) median age M=46, ceph=31 dexa idem Clinically cure: 100% M, 77% Ceph Bacterial clearance: 100% M vs 95% Ceph same rate of death unrelated to R/same rate of neuro/audio sequelae same rate of drug related adverse events No statistical results given	Not given	- Meropenem is as effective as cephalosporins - Meropenem is active against pathogen resistant to cephalosporins - Good tolerance at meropenem 6 g
Marhoum 1993 March 89 to Dec 90 Marocco 1 center N=36 randomised 26 bacterio positive	> 16 years	clinical sign BM with: *N. mening* on CSF (culture or Ag) or clinical signs BM plus purulent CSF + plus epidemic situation (more bacterio + in peni group than ceftriax group)	penicillin allergy	- ceftriax 2g/d for 2d (n=16) vs - penicillin 300.000UI/kg/d in 6 doses for 6 days (n=20) confirmed meningococcal meningitis: 26 (9 ceftriax vs 17 peni) (22 serotypes A, 3B and 1 Y)	Clinical assessment fever 0 neurological evaluation Biological CSF day 0,1,5 blood day 0,5 Cure/failure follow up at 2 months	Similar response to therapy (clinical and CSF) all CSF culture neg at 24h Cure: 13/16 cef (81%) vs 19/20 peni (95%) 2 failures in ceft. because > 2d therapy 1 death in each group At 2 months: no neurologic sequelae	Not given	CFX 2g 2d is as effective than pen 6d in selected cases (severe meningitis not eligible for 2d therapy-persistent signs of BM) Imbalance of sex (> male in peni)
NI Girgis 1988 Egypt Study period? single or multicenter? N=100	children and adults 70C/30A 5m-28y Median 9 y	clinical sign of BM and pos CSF culture	Not given	- ceftriax 100 mg/kg/d im/iv (n=50) vs - ampi 160mg/kg/d + Chlor 100mg/kg/d divided/6h im/iv (n=50) Duration of treatment not given CFX / AMCHL *N. menin* 26 / 22 *S. pneumo* 17 / 18 *H. infl* 7 / 10	Clinical assessment fever neurological status Bacteriological assessment CSF day 0,18-36h, day6 Mortality	No difference in clinical evolution for meningeal signs and defervescence No difference in biological evolution (CSF and blood). All cultures negative at 18h No difference in mortality: CFX: 7, AMCHL: 10 Timing of assessment not done! No assessment of clinical adverse events	Not given	CFX =AMCHL No data about duration of treatment

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Zavala 1988 Mexico 1 center N=26	> 14 years	- clinical signs of BM(+ CSF suggestive for BM) and pos CSF culture (! CSF shunt, CNS diseases, skull # not exluded)	- Penicillin allergy - Bacterio negative - Concomitant AB - Renal or hepatic diseases - Pregnancy	- Ceftriax (CFX) iv 4g/d (2g when sterile CSF) (n=13) - Ampi cillin (200-400 mg/kg/d) or ampi + chloram (2-3g/d in 4 divided doses) (n=12) Criteria to stop the R/: biological normalisation of CSF (CSF leuco < 150 and PMN<20%) CFX / AMCHL *H. infl* 2 / 0 *N. mening* 0 / 0 *Staph.epi.* 3 / 0 *S. pneumo* 5 / 8 *E. coli* 2 / 4 *Salmonella* 1 / 0	Clinical assessment fever CSF assessment CSF at 24h, day 5, 10 if CSF pos at 24h, repeated at 48h, if still positive, withdrawn of the study Adverse events	Cure rate 100% CFX vs 92% AM/AMCHL In both group fever persisted > 48h, no difference in defervescence Difference in decreasing PMN in CSF (p<0.0005) in favour of CFX CFX all cultures neg at 24h AM / AMCHL: 3/13 pos at 24h, 1/3 pos at 48h (withdrawn, resistant to ampi) Difference in duration of therapy: CFX 9.9 ± 1.8d vs AMCHL 12,3+/-1.45d. (p<0.0005) No adverse reaction in CFX vs 3 rash and 3 diarrhea in AM/AMCHL (no statistical analysis) No data about sequelae	Not given	CFX at least = AM/AMCHL More rapidly normalisation of CSF and shorter duration of treatment with CFX. Diversity of pathogens! Few patients!
Girgis 1987 (data extracted from the study of 1988) Egypt, N=30 Period of study? single or multicenter?	> 16 years Median 21,8	clinical signs BM + pos CSF culture	Not given	- ceftriax (CFX)100mg/kg/1xd (max4g) iv (n=15) - ampi 160mg/kg/d + chlor100mg/kg/d divided /6h iv (n=15) Duration? CFX / AMCHL *N. menin.* 11 / 10 *S. pneumo.* 4 / 5	Clinical assessment fever neurological status Bacteriological assessment CSF day0,18-36h, day6 Mortality	No difference in clinical assessement 1 death in each group at 24 h defervescence 3,4 vs 3,5 days Full consciousness 3,9 vs 3,5 days	Not given	CFX = AMCHL CFX more convenient, saving nursing time and expenses
Bryan 1985 Brazil 1 center 52 enrolled/36 analysed	children and adults	Phase B: - >6h survival after hospitalization - pos CSF culture or > 10. 000 leukocytes /mm3, protein >250mg/dl, glucose <20mg/dl	Phase B: prior use of AB and neg culture	- Phase A: PK en CSF concentration (ceftriax (CFX) 80mg/kg/d + ampicillin) - Phase B: CFX 80mg/kg/d (initial dose 100mg/kg/d) iv vs conventional dose of AMCHL iv (18 patients in each group) Duration: 10 days (*N. meningitidis:* 7 d.) No data about pathogen distribution	Clinical assessment Fever Meningeal signs Sequelae Laboratory assessment CSf d0, 24-48h,d10-12 Safety	groups comparable regarding to case-fatality ratio, cure rate, resolution with sequelae, type and severity of sequelae, time to sterilize the CSF (83%-85%/24h), drug related Adverse events (diarrhea) CSF bactericidal titers 16-24h after R/: 1/64 to>1/2048 vs 1/8 to 1/32 3 deaths in AMCHL vs 4 deaths in CFX group	Number tabel	CFX= AMCHL With higher bactericidal CSF titers in CFX High mortality rate: poor general condition of the patients on admission

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Johansson 1982 Randomised multicenter(n:7) open controlled study 67 enrolled, 50 included, 40 evaluated Mar 1980 - Apr 1981	Children and adults (> 3 months)	Clinical symptoms BM+ purulent CSF(n=50) or Pos CSF (skull # and osteitis included)	- Allergy to penicillins/cephalosporins, - Infants < 3 m, - immunosuppression, - intraventricular shunts, - CNS malformation - Pregnant women - Suspected resistance to cefuroxime or ampi/chloram	- AMCHL (n= 19) Ampi 50-70mg/kg/6h (adults: 3g/6h) + Chloram 22-25mg/kg/6h (adults: 1/4 of ampi dosis/6h) Minimal treatment 5 days of bitherapy (5 patients continued with chloram alone for 5 days, 12 continued with ampicillin for 3.3 days) - Cefuroxime 60-75mg/kg/8h (adults 3g/8h) (n= 21) Treatment for 7-14 days (minimum 5d.) *H. infl* 20, *N. menin* 11, *S. pneumo* 5, others 4.	Clinical assessment: at the end of treatment (cure/improvement/complications) Hearing evaluation after 6 weeks (subjectively or audiometry) Bacteriological assessment Blood and CSF day 0 CSF after 48/h (AB concentrations in serum and CSF)	Complete clinical cure: AMCHL 14/19 vs Cefurox 18/21 Two deaths in each group CSF after 48/h sterile: 100% (n:33) One patient with hearing defect in cefurox group No serious adverse effects 2 *S. pneumo* Chloram R, 2 *H. infl* Blactamases + (*S. pneumo* more common in cefurox vs *N. menin.* in AMCHL)	Not clear Physician blinded until allocation	Cefurox =AMCHL Few patients
Overturf GD 1977 California 1 center Mar 1975 - Mar 1976 N=86 randomized	>2m-60 y (54<10y)	Signs and symptoms BM and bacterio + (blood or CSF culture) (10 pat with neg culture, but purulent CSF)	- other than *S. pneumoniae, N. meningitidis, H infl* - clinical indication for the use of a second antimicrobial agent - penicillin allergy	Ampicillin or Carbenicillin - 200mg/kg/day 6 x divided iv (20 first patients) - 400mg/kg/day 6 x divided iv (all others) (loading dose: 65mg/kg) Duration: Therapy stopped when CSF glucose>50, CSF protein<75mg/100ml, CSF leukoc <30/mm and afebrile for 5 d Pathogens: *H influenzae:* 41, *S pneumoniae:* 22, *N meningitidis:* 13Unknown: 10	Bacteriological evaluation CSF at day 1,3,7,10,14,21 Clinical evaluation: daily Safety	No differences Carbenicillin vs Ampi in days of hospitalisation, days of fever, days to meet the predefined CSF criteria Same rate of sequelae at discharge Median treatment: 13,5d CSF culture *(H influenzae)* at day 1: CB 38% pos vs Amp 5.8% pos (without correlation with outcomes) Adverse effects: CB: 27% vs Amp: 17.5% (eosinophilia, fever, rash) 3 deaths in AMP group	randomized by hospital number	Ampicillin= Carbenicillin (all organisms susceptible)

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
PEDIATRIC								
I Roine 2000 Chili 1 center Mar 88 - Sept 93 Aug 96 - Dec 96 102 enrolled 100 analysed	>3 months	Signs, symptoms + CSF suggestive for BM: Pos culture or Clinical signs of BM + 2/3 criteria: CSF WBC >1000 CSF glucose < 40 CSF protein > 40	- previous developmental abnormalities - fatal outcome<d4 - unknowm etiology of BM - not fullfilling the criteria for rapid initial recovery during the first 4d of R/ (n=77)	Ceftriax (CFX) 100 mg/kg once a day during the first five days (dexamethasone permitted, equally distributed 33 vs 24%). If rapid initial recovery, assigned to one of two R/ groups before the fifth dose of CFX: Children born on an even date: 4d Children born on a odd date: 7 d of therapy with ceftriax (n=53 vs n=47) All children hospitalized at least 7d CFX reinstated if any criteria suggesting relapse CFX 4d / CFX 7d *H. infl.*: 14 / 12 *S. pneumo*: 5 / 8 *N. menin*: 21 / 13 Unknowm: 13 / 12 Other: 0 / 2	Clinical assessment d5 to d7 level of consciousness, neck stiffness bulging fontanel, reaction to surroundings, convulsions, fever Bacteriological assessment: CSF at 24-36h Biological assessment: CRP day5 to day7 Long term outcomes: convulsions or readmissions neuro and audio sequelae within 1 to 3 months of discharge	Similar short term recovery Long term recovery mean followup time: 6.3 ± 5months mean number visits: 2.8 ± 1.3 no difference in sequelae 1 recurrence at 46d discharged (4d) with *H. infl* meningitis (no prophylaxis of the family) No difference with or without dexa	Assigned on date of birth (even date/odd date) No ITT?	Rapid initial recovery defined as: daily clinical improvement absence of an other infection absence of convulsion >3d R/ absence of focal convulsions absence of focal neuro signs negative CSF at 24 to 36h of R/ Abbreviated course of AB is safe for patient who shows rapid initial recovery for *N. menin* and *H. infl.* Caution with *S. pneumo* regarding to the emergence of resistance (7d)
CM Odio 1999 blinded, multicenter (Costa rica, USA, Dominican republic) Dec.92 - Dec.96 N randomised: 258 N evaluable: 154	2m to 12 y	signs and symptoms BM (IDSA criteria) + pos CNS culture (AB within the 24 h OK if diagnosis of BM) evaluable if at least 48h R/. (culture neg or at least 1 dose R/: only in the safety analysis)	Previous BM Polymicrobial BM Cefotax resistant bacteria Significant underlying conditions (HIV,…) History of seizure behavioral, motor or developmental abnormality Known hearing deficit Cystic fibrosis Active viral hepatitis CNS abnormality Laboratory evidence of organ dysfunction Blactam allergy Trial drug <30d Any rapidly progressive or underlying disease that interfere with evaluation	meropenem 40 mg/kg/8h (n=129) vs cefotaxime 45 mg/kg/6h (n=129) + dexa 0.15mg/kg/6h 4d (all patients) Duration: 7d *N. menin*, 7-10d *H. infl.*, 10-14 d *S. pneumo*. No data about pathogen distribution.	Clinical assessment IDSA: Cure, survival with mild neuro sequelae, survival with severe neuro sequelae, death. at entry, 24-48h, end of R/, 5-7w after R/ and 5-7months: clinical, neuro, audio, comportemental evaluation Microbio efficacy IDSA: CSF at 24-36h eradication, eradication with relapse, delayed sterilization, persistence. (not fully evaluable if no control CSF) Adverse events	Similar efficacy no difference: cure, survival, death or neurological sequelae no difference in audiologic sequelae no difference in microbiologic efficacy safety analysis: no clinical or biological difference, seizure idem, no drug related reaction	1:1 no ITT	Meropenem = Cefotaxime Patients from Dominican Republic: more severe, higher duration of symptoms before admission, more neuro and audio sequelae.

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Scholz 1998 multicenter (7) Germany n=99 enrolled n= 82 evaluable Dates?	6w-16y	Signs and symptoms BM and pos CSF culture (gram or culture)		ceftriax (CFX) 100 mg/kg/d (1dose) d1 then 75 mg/kg/d vs cefotax 200mg/kg/d (div 4)^(n=51 vs n=48) 4 d for *N. meningitidis*, 7d others (dexa admitted, equally distributed 73 vs 60%) ceftriax / cefotax *N. mening* 22 / 19 *S. pneum* 8 / 8 *H. infl* 8 / 7 *S. agalactiae* 0 / 1 Unidentified 6 / 3	Clinical assessment clinical signs fever, neuro and audio sequelae microbiol assessment CSF evolution d1,d2 and end of R/ Adverse events 90 d follow up	Similar efficacy: sequelae: 13,7 vs 23,6 (NS) All CSF culture neg at 24h in ceftriax vs all but one in cefotax (- at 48h) Same rate of failure: (prolonged R/ 10 pts: fever or CSF abnormalities) Same rate of Adverse events (diarrhea) !12/44 patients with biliary pseudolithiasis in ceftriax group (asymptomatic, without clinical consequence)	Not given	Ceftriaxone = Cefotaxime Pseudolithiasis in Ceftriaxone
Klugman KP 1995 multicenter France, Israel South Africa, Argentina Apr.92 - Jul.93 n=190 enrolled n= 139 evaluable	3m - 14y (1y median)	signs and symptoms BM and pos CSF culture. (all in safety analysis, efficacy analysis n=139)	Blactams allergy Previous history of BM Survival beyond 48h unlikely Renal or hepatic impairment Immunodeficiency Congenital abnormalities of CNS Penetrating wound Skull fracture Foreign body in CNS	mero 40 mg/kg/8h vs cefotax 75 to 100 mg/kg/8h (n=75 vs 64 efficacy) Duration: 7d *N. meningitidis,* 10 d *S. pneumoniae, H. influenzae*, 14d other BGN +/- dexa 0.15 mg/kg/6h 4d (n=185) equally distributed No data about pathogen distribution	Clinical and neuro assessment 24h, 6w cure, sequelae, death auditory function assessment Bacteriological assessment CSF culture d1,18-36h	No difference in outcome Eradication at 18-36h: 97% vs 98% Seizure during therapy: idem Other adverse events: idem all isolates sensitive to AB	Computer-generated sealed envelopes in blocks. The centers were not aware of the block size, and each center had a unique randomization scheme.	Meropenem = Cefotaxime
Saez-Llorens 1995 Panama, Texas n=103 enrolled n=90 evaluable	2m-15y	signs and symptoms BM + abnormal CSF and/or pos culture.	Blactams allergy Resistant strain Renal or hepatic disease Previous CNS abnormalities	cefepime 50 mg/kg/8h vs cefotaxime 50 mg/kg/6h for 7 to 10 d. (n=43 vs n=47) + dexa (all patients) cefepime / cefotaxime *H. infl* 18 / 28 *S. pneumo* 7 / 3 *N. menin* 9 / 5 other BGN or G+ 1 / 5	Bacteriological assessment blood and CSF day 0, 24h if pos at 24h, repeated Clinical assessment cure and sequelae days with fever and signs Audiometry safety during hospitalisation and at discharge if abnormal, at 2-6m	84 % CSF +, 54% Hémocultures + All culture neg at 24-30h Same rate of deaths 7% Same rate of clinical cure Same rate of sequelae 24% (persistent 16%) Same safety	A list of randomisation	Cefepime = Cefotaxime

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Martin E, 1990 multicenter (14) Switzerland N=119 enrolled N=92 evaluable Nov 1983 - Apr 1985	3 w-16 y	Signs and symptoms BM and culture + (efficacy analysis) Only pts with repeated spinal tap (-) within 15h after first dose of CFX	Structural abnormalities of the brain or spinal cord Recent neurosurgical procedure Blactam allergy Secondary exclusion group: - no repeated spinal tap at 24h - culture-negative CSF - CSF pathogens too infrequent to randomize (5 out of the 27 first patients had culture + at 15h and were shifted to the exclusion group. This restriction was abandoned after the 27th patient.)	ceftriax (CFX) iv 100mg/kg/d (max 4g/d) 2 days, single daily, followed by CFX iv/im 60mg/kg/d (max 3g/d) single daily dose. Duration of therapy: Gr 1: 4d *N Menin*, 6d H Infl, 7d *S pneumo* (n=47) Gr 2: 8d, 12d and 14d (n=45) Gr 3: secondary exclusion group: minimum 10d (n=27) No adjunctive steroids *H. infl*: 67, *N.Menin:* 32, *S. pneumo:* 9, *E. Coli:* 3, *S. Agalactiae:* 1.	Bacteriological assessment: CSF at admission and at 24h Clinical assessment Neurological: daily Audiometry, impedance Measurements, brainstem auditory (rarely) before discharge If Sequelae: evaluation within 3-6m after discharge	55 moderately ill, 40 severe, 24 critical No treatment failure (addition AB or change) 90% recovered completely: children critically ill on admission had lowest clinical cure rate (67%-70%) and the incidence of sequelae was much higher (38% vs 6%). Critically ill + *H. infl*: complete cure 92%, *N. menin* 43%, *S. pneumo* 25%. Good tolerance Fever normalisation within 4 d in 78%. Lower rate of recurrent/prolonged fever in short course vs full course (p=0.06 NS)	Each center was provided with serially numbered protocols in blocks of five.	Short course CFX is as efficient as full course therapy. Predictive of sequelae: pathogen and critical status on admission
Schaad U.B. 1990 multicenter(3) Switzerland N=106 Randomized N=106 Evaluable Mar 1986 - Jan 1989	>6w-16 y	Signs and symptoms BM and bacterio pos	- Newborn infants - allergy to betalactam antibiotics - renal, hepatic or central nervous system abnormalities - fulminant meningitis that led to death within 48 hours (n=8) - meningitis due to gram negative enteric organisms, enterococci, staphylococci and listeria.	- Ceftriaxone (CFX) 100mg/kg/d iv once daily (n=53) - Cefuroxime 240mg/kg/day Iv in four divided doses (n=53) Duration of treatment: *H infl*: 7 days, *N menin*: 7 days, *S pneumo*: 9 days Steroids were not used. *H infl* CFX 27 Cefurox 35 *N menin* 18 12 *S pneumo* 7 6 *Strepto. B* 1 0	Bacteriological assessment: Blood and CSF at admission CSF at 24 hours, if remained positive, lumbar punctures were done every 24 hours until sterile. Clinical assessment: daily and 8-10 weeks after discharge if abnormal 4-6 months later (neuro/audio). Safety: daily Abdominal ultrasonography in CFX group (since April 1987) at the start and at the end of treatment.	MICs: all strains were highly susceptible to ceftriax, 1 strain decreased sensitivity to cefur CSF culture positive after 24h ceftriaxone 1/52 vs cefurox 6/52 (NS) All cultures neg at 48h. Biliary pseudolithiasis: ceftriax 16/35 (46%) vs cefurox 0/35 (S). These 16 pat were significantly older and many were female. 19% symptomatic, spontaneous resolution. Same rate of neuro sequelae. Hearing impairment at 8-10 weeks: ceftriax 2/53 (4%) vs cefurox 9/53 (17%) (p=0.052)	Randomization with computer-generated lists prepared separately for each center	Trend to delayed sterilization in cefur (p=0.11NS) and to more sensorineural hearing loss (p=0.052) More pseudolithiasis in CFX (p=0.001)

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Kavaliotis J 1989 Greece 1center July 1985 - Dec 1987 n=52 included n=46 evaluable	3m-12y (M: 29m)	Signs and symptoms BM and pos CSF or blood culture	- Allergy to cephalosporins - Renal or hepatobiliary diseases - Other antibiotics prior to admission	Short treatment (n=26): 4d *N menin* (11), 6d *H infl* (12), 7d *S pneumo* (3) Standard duration of treatment (n=26): 8d *N menin* (16), 12d *H infl* (9), 14d *S pneumo*(4) Ceftriaxone iv (CFX) 100mg/kg/d (max 4g) initial dose then continued with 60mg/kg/d. (If the infection persisted after short course, continue to full course n=0)	Bacteriological assessment: CSF on admission and prior to the second dose Clinical evaluation: daily At discharge physical and neurological examination, evaluation of hearing.	All strains sensitive to CFX, all cultures neg at 24h Clinical cure rate: 98% Same rate of complete cure, neuro and audio sequelae. Same safety	Computer-generated randomisation list	Short course = full course (Excepted in population excluded: CSF + at 24h, continued meningeal inflammation or superinfection)
1989 Multicenter (12 sites) Finland 1984 - 1986 n=220 randomised n=197 evaluable	3m-15y	CSF culture pos or signs and symptoms of BM + suggestive CSF: leucocyte > 10^3/l + 1 out of the criteria: blood culture + or CSF gram stain + or CSF Antigen +.	Not given	- Chloramphenicol 100mg/kg 4/d iv (n:53)vs - Ampicillin 250mg/kg /d iv and chloramphenicol initial (n:46) - Cefotaxime 150mg/kg /d iv (n:51) - Ceftriaxone 100mg/kg /d IV (n:50) (first dose of each drug increased by 50%) Complete treatment: n=150, change of R/ n=13 No steroids Duration: 7 d. (17 longer) Pathogens: *H infl* 146 , *N menin* 32, *S pneumo* 13, unknown 9	Bacteriological assessment Several bacteriological and biochemical ones performed in CSF, blood and urine. CSF on admission, at 12-24h, at d4 and d7. Clinical assessment Daily, follow up at discharge, 2weeks, 2-3-6 months after. Audiometry and evoked potentials for hearing deficits.	- CSF + after 12h: 38%, after 24h 17%. - Earlier sterilization of CSF at 24h with cephalo vs AMCHL ($p<0.05$) - Earlier sterilization in *N menin.* ($p<0.01$) and in *H. infl* if ceftriax used ($p<0.05$) - if failures = recurrence, bacteremia, prolongation or modification R/: 10 failures/chloram, 2 failures/cefotax, 1 failure/ceftriax, 0 failure/ampi (NS) - if failure = death Chloram is less effective than ceftriax and ampi ($p<0.01$) and cefotax ($p<0.05$) - Same rate of sequelae - Adverse events: more diarrhea in ceftriax vs cefotax ($p<0.01$). Pseudodlithiasis in ceftriaxone group.	Randomisation by means of a list at the ward. The name of the next antimicrobial on the list was obtainable by phone 24 h a day.	Chloramphenicol less effective (failure = deaths) Same rate of sequelae Same safety except for diarrhoea/ pseudolithiasis in ceftriax
Haffejee 1988 South Africa, 1 center Single-blind trial Mar 1983 - July 1987 n=33 enrolled n=31 evaluable	1m-9 year	Signs and symptoms BM and CSF pos (culture or antigen)	- neonates - antibiotics within 3 days prior to diagnosis	- Standard therapy (n=15): penicillin 5.10^5-10^6 U/6h + chloramphenicol 80-100 mg/kg/day in 3-4 divided doses. Once sensitivity results obtained only one drug was used. (8 first patients also received sulphadiazine 100mg/kg/day) - Cefotaxime 100-200mg/kg/day in 2-3 divided doses (n=16) IV therapy for 3-5 days, thereafter penicillin and cefotax was given IM, chloramphenicol and sulphadiazine orally. Duration: 10-14 days *H infl* 10 / 11 *N menin* 2 / 2 *S pneumo* 3 / 1 *Strepto B* 0 / 1 GNB 0 / 1 (Peni+chlor / Cefotax)	Bacteriological assessment: CSF (and blood) on admission,d2,d5 and d14 Clinical evaluation Fever Neuro sequelae (few data) (no hearing loss assessment)	Deaths: 3/ 15 in standard group, 2/16 in CTX (NS) Clinical cure rate: Standard R/: 80% vs cefotax 87.5% (NS) CSF culture neg (NS): Standard: 77% d2, 15%d5, 8%d14 Cefotax: 81%d2, 19%d5 1 child in each group developed sequelae No difference in adverse effects	Not given	Peni+chloram = cefotax Delay to sterilization in Pen/CL (NS)

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Marks 1986 USA Multicenter (n=5) April 1984 - Aug 1985 N=126 randomised N=107 evaluable	3m-16y	Signs and symptoms BM and bacterio + (blood and/or CSF culture or antigen)	- Parenteral antibiotics (previous 48h) - Shunt infections - Hepatic or renal dysfunction - Allergy to penicillins or cephalosporins - uncommon pathogen	- Cefuroxime 225mg/kg/d in 3 divided doses (n=57) - AMCHL: Ampicillin 300-400mg/kg/d in 4 divided doses plus chloramphenicol 75-100mg/kg/d in 4 divided doses. (Ampi was continued as single agent if CSF was ampi susceptible, chloram was given when *H infl* beta-lactamase positive (n=14)) Duration: alternated patient in each group received 7 or 10 d of treatment (n=30 vs n=64) No steroids Rifampin prophylaxis: Cefurox 52% vs AMCHL 55% Pathogens: *H infl* 83%, *S pneumo* 11%, *N menin* 6%.	Bacteriological assessment: CSF day0, at 24-48 h (at the end: at the discretion of clinician) Blood culture on admission and at 24h Clinical evaluation Daily examination and 1 to 2 w after discharge Audiologic evaluation at or within the month post discharge Follow up after 2-14m: 83%	All strains sensitive to cefurox or chloram, 3 strains *H. infl* resistant to ampi. Clinical cure: cefurox 94% vs AMCHL 93% All CSF (-) at 24-48h for *S pneumo* and *N menin*, 4/39 *H. infl* B + at 24-48h in cefur vs 0 AMCHL (p=0.11) No difference in neuro and audio sequelae: 13% neurodevelopmental sequelae (hearing loss 4AMCHL vs 5 cefurox), 3 deaths. Side effects: uncommon and minor (diarrhea, rash) ! Prodromal period longer (p=0,045) and more oral AB before admission (p=0,034) in cefurox group.	Computer-generated lists prepared separately for each center	Cefurox = AMCHL in clinical efficacy) 7days vs 10 days of treatment: no difference in outcome, complications and relapse
Rodriguez 1986 Dominican Republic Aug 1983 - ? 1 center N=100 N=75 evaluable	1m-15y	Clinical signs BM and bacterio + for efficacy analysis (Blood and/or CSF)	- Allergy to study drug - Resistant organisms - CSF culture negative for bacteriologic efficacy - Effective therapy within 48 h before admission - Renal or hepatobiliary disease - Neutropenia (<1500) - Deaths within 48 h	- Ceftazidime 150mg/kg/d IV (max 6g) div 3 doses (n=61) vs - AMCHL: Ampicillin 400mg/kg/d div 6 doses and chloramphenicol 75-100mg/kg/d div 4 doses (n=39) (therapy was narrowed once pathogen was identified) Duration: 10-14 days, *N. menin* 8 d No steroids Pathogens: *H infl* 51%, *S pneumo* 21%, *N Menin* 18%, *Salmonella* 4%, *Pseudomonas* 2%, *Strepto B* 2%.	Bacteriological assessment: CSF day0, after 24-48h All positive CSF and blood cultures were repeated. Laboratory measurements every 3-5 days during therapy Clinical evaluation Fever Neurologic (gross sequelae) Follow up 2–6 months after discharge	All strains *H. infl* sensitive to ampicillin Ceftazidim: 88% cured, 2% clinicallly improved,10% died. Follow up: 2 neurological sequelae. AMCHL: 81% cured, 1% clinically improved, 15% died. Follow up: 1 neurological sequelae: no difference No difference in adverse events	A computer-generated list	Ceftazidim = AMCHL No difference in death, cure and sequelae No difference in safety

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Odio 1986 Costa Rica 1 center Mar 1983 - Nov 1984 N=85 children enrolled and evaluable	2m-10y	Signs and symptoms BM and bacterio pos (CSF culture or Gram stain)	- Neural tube defects - Renal or hepatic disease - Recurrent invasive bacterial infections	- AMCHL: Ampi 50mg/kg/dose and chloramphenicol 25mg/kg/dose IV every 6h. (n=43)(chloramphenicol was given alone orally after the 5th day) vs - Cefotaxime 50mg/kg/dose IV every 6h (n=42) Duration: min 10 days. (Prolongation if CSF >150WBC/mm3 with >60%PN or CSF glucose <40mg/dl on day10 with/without BM signs) Steroids used for septic shock: cefotax 14% vs AMCHL 16% Pathogens: AMCHL Cefotax *H infl* 79 91 (NS) *S pneumo* 21 9 *N menin* 0 0	Bacteriological assessment: Blood and CSF culture on admission and daily until negative Clinical evaluation Mortality, days of fever, days of hospitalisation, BM signs and symptoms Neuro evaluation: at the end of R/, 4-6w, 3-6m. Auditory evaluation	No *H infl* Blactamases +. 7% death in each group Sterile CSF culture after 24h: cefotax100% vs AMCHL 84 % (S?) More days with fever in AMCHL (NS) Same rate of sensory deficits and developmental delay. Significant difference in motor sequelae at discharge: AMCHL 41% vs cefotax23% (p=0,043), but no longer significant after 4 months: 17% vs 8%. Same rate of adverse events	A list of randomized therapy assignments.	Cefotaxime = AMCHL at least Longer delay to sterilization in AMCHL (S?)
Jacobs 1985 Arkansas May 1983 - Aug 1984 N=50 children	1w -16y (mean: 20m)	Signs and symptoms BM and CSF culture pos	Sterile CSF	- Cefotaxime IV 50/mg/kg/dose/6h (n=23) vs - AMCHL: Ampicillin IV 50-100mg/kg/6h and chloramphenicol IV 25mg/kg/dose/6h (n=27) (After culture, the therapy was modified, gentamicin (2.5mg/kg/8h) substituted to chloram if <1month) Pathogens: *H Infl* 29, *S Pneumo* 8, *N Menin* 8, *Strepto B* 3, *Salmonella enteritidis*: 2	Bacteriological assessment CSF, blood, urine d0 CSF at 48h (all pts in cefotax, in case of no clinical improvement in AMCHL) Biological evaluation at admission, day 4-5, at the end of therapy Clinical evaluation: auditory deficits at discharge and 2 m after Neurological examination at discharge, after 2 weeks, after 2 months.	All CSF cultures sterile at 48h Clinical cure: cefotax100% vs AMCHL96% (NS)1 death (AMCHL) Survival without sequelae: cefotax78% vs AMCHL77% Complications/sequelae similar in both groups Duration of therapy (median 11,5d) similar Duration of fever similar No adverse drug reactions	Not given	Cefotaxime = AMCHL Mean concentration of cefotaxime in CSF higher (better penetration or accumulation)
Barson 1985 Ohio Apr 1982 - Dec 1983 Enrolled: n=54 Evaluated: n=50	1m -15y mean 14m	Signs and symptoms BM and CSF suggestive (50 bacterio +)	- Severe renal or hepatobiliary disease - Allergy to beta-lactam antibiotics	- AMCHL: ampicillin (200mg/kg/day) and chloramphenicol (100mg/kg/day) IV div 6/h (n=23) (After the isolate was identified, monotherapy) vs - Ceftriaxone (CFX) loading dose 75/mg/kg, followed by 50mg/kg every 12 h IV (n=27) Duration: minimum10 d (*S pneumo* 14d) Pathogens: *H. infl* 42, *S. pneumo* 4, *N. menin* 3, *Strepto B* 1	Bacteriological assessment CSF day0,at 12h and repeated daily until sterilization Biological evaluation Clinical evaluation: daily Fever Neurological complications Audiometry at discharge (follow up) Safety	Sterile CSF at 12h: AMCHL 60% vs CFX 67% *H. infl*: 19% blactamase + No death More neurological complications and hearing loss in AMCHL (33%vs 14%) but not significant Side effects: more mild diarrheae in CFX (59%vs 22%, p<0,01)	A computer-generated randomization list.	CFX = AMCHL in children older than 2 months of age. Ampicillin should be added in the regimen in infants 1 to 2m *(listeria monocytogenes)*

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Lin 1985 Dallas 1 center Feb 1983 - Dec 1983 N=115 enrolled N=79 analyzed	>1m (children, median age 10 yrs)	Signs and symptoms BM and bacterio pos: 80 (1 early death) 78 positive CSF culture, 1 positive *H. influenzae* antigen test in urine.	Beta-lactam allergy	- Ceftriaxone IV, initial dose of 75mg/kg, followed by 50mg/kg every 12h: *N meningitidis:* 7d treatment, *S. pneumoniae*, *H influenzae*, *S agalactiae:* randomized to 7d (n=35) or 10 d (n=35) treatment Pathogens: *H. infl* 57, *N menin* 9, *S pneumo* 8, *S agalactiae* 5	Bacteriological assessment Blood and CSF culture on-admission. CSF culture after 18-24h.CSF after 48h (repeated CSF if still positive). CSF at completion of therapy Clinical evaluation: Daily during hospitalization Fever evolution Neurological complications 6 w after discharge: hearing evaluation, physical and neurological examination Adverse events	CSF at 24h: 91% sterile in the 2 groups (100% sterile if *N menin*). After 48 h: all sterile. Neurological complications: 11% in the 2 groups, 0% if *N menin* Same rate of prolonged fever (>5d) (0 pts in *N. menin*) Days of hospitalisation: 7d: median 8d vs 10d: median 10d (*N. menin*: median 8 d) No difference in hearing loss (30% vs 32%) Well tolerated	A computer-generated randomized number list	7 days = 10 days for *S.pneu*, *H. infl.* Prolongation beyond 7 days recommended for: - group B streptococcal or coliform meningitis - continued signs of meningeal inflammation - extreme abnormalities of the CSF at day seven.
Shann 1985 New Guinea Multicenter (3) N=367 Bacterio pos: 181 May 1979 - June 1983	Children (79% <24m)	Signs and symptoms BM and CSF pos or CSF polymorph count >100cells/ml or CSF polymorph count>20cells/ml with CSF protein>1.0g/l or CSF glucose<2.2mmol/l		- Chloramphenicol 25mg/kg IM 6/h, once clinical improvement, 25mg/kg orally 6/h (n=183) - Chloramph. iv 25mg/kg/6h + Peni IV: 500 000 U to 2MiU /3h.according to the body weight. Once improvement: chloram 25mg/kg /6h orally + peni: IM /6h Duration: 14 days Pathogens: *H. infl* 90, *S. pneumo* 72, *N. menin* 15, others 4	Treatment failed if the child died Death and gross brain damage	Same rate of mortality and poor outcome: 26% vs 27% and 38 vs 40% Imbalance between the 2 groups: Chloram.group: more children ill since more than 5daysChloram+peni: more children with convulsions. Discharged well: 49% CL vs 47% CL+PEN	A table of random numbers was used to prepare sealed, numbered envelopes.	Chloram = Chloram+peni Not directly useful in Europe Follow up not possible (rural villages, poor communication)
Congeni 1984 USA Jan 1982 - Dec 1982 Enrolled n=56 Randomized n=45	1day-15y	Signs and symptoms BM and bacterio pos (n=45)	- Allergy to penicillin or cephalosporins - Sterile CSF culture	- Ceftriaxone 50mg/kg/12h(n=22) vs - AMCHL (n=23): ampicillin 200-400mg/kg/d and chloramphenicol 75/mg/kg/d in 4 doses.(Neonati< 1 month: genta 2.5mg/kg/8h instead of chloram). After culture and susceptibility only ampi was continued or penicillin (Spneumo, *N menin*) or chloramphenicol. Duration: minimum 10d Pathogens: *H infl* 30, *S pneumo* 6, *N menin*, *Strepto B* 3, *S epidermidis* 1, *E coli* 1	Bacteriological assessment: CSF admission and at 24h (1h after administration of the drug) CSF bactericidal activity Blood analysis Clinical evaluation: daily Duration of fever Audiometry at discharge	Trend toward fewer days of fever in CFX (NS) Trend to a more rapid sterilization in CSF: Sterile at 24h (13/18 vs 19/20 CFX) (NS) 1 death in each group Complications and sequelae: AMCHL10/18 vs CFX 6/20 (NS) Same rate of adverse events (diarrheae)	Computer-generated randomization	CFX = AMCHL at least Ceftriaxone group: in vitro superior to AMCHL

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Wells 1984 Arkansas May 1983 - Feb 1984 Enrolled: 37 Randomized: 30	1w-16y 2pat<1m	Signs and symptoms BM and CSF culture pos	- Encephalopaty - Prior CNS infection - Hepatic or renal insufficiency	- AMCHL: ampi 50-100mg/kg/6h IV and chloram 25mg/kg/dose/6h IV (2 children <1m: gentamicin 2.5mg/kg/dose/8-12h) After culture results switch to penicillin (*S pneumo*, *N menin*). (Chloramphenicol was discontinued in case of *H infl* sensitive to ampi) (n=18) - Cefotaxime: 50mg/kg/6h IV (n=12) Duration: 10-14 d Pathogens: AMCHL cefotax *H infl* 12 8 *S pneumo* 2 2 *N menin* 2 1 *Strepto B* 2 0 *Salmonella* 0 1	Bacteriological assessment Blood, urine, CSF analysis on admission, CSF one hour after dose and on day 2 (cefotaxime group) Bactericidal activity concentration of cefotaxime in blood, urine and CSF Clinical evaluation Auditory evaluation at the end of R./ EEG in case of seizures CT in case of intracranial pathology Safety	All CSF cultures sterile at 24h (n=21) 5 *H. infl* resistant to ampi One death in the standard group Clinical cure: (NS) AMCHL 94% vs cefotax 100% Sequelae: (NS) AMCHL30% (5/18) vs cefotax17% (2/12) No adverse drug reactions	Not given	Cefotaxime = AMCHL Few patients
Aronoff 1984 Ohio 1 center Enrolled: n=19 + 3 pat with CSF shunt infection	2m-18y	Signs and symptoms and CSF suggestive for BM Bacterio pos: CSF or blood culture (n=17) (3 pts with shunt infection)	- allergy to betalactam agents - infections caused by organisms not susceptible to ceftriaxone/ ampicillin/ chloramphenicol	- Ceftriaxone (CFX) 50mg/kg/12h IV (n=11) - Ampicillin 200-300mg/kg/ d and chloram 100mg/kg/d IV divided in 4 doses. Ampi continued alone when the organism was susceptible to both agents. - Shunt infection: n=3: CFX without randomisation Duration: 10-14 days Pathogens: 14 *H infl*, *N menin* 2, *S pneumo* 1	Bacteriological assessment CSF at 24-48h Blood analysis prior to therapy, every 4 days and 24 h after completion of therapy Clinical evaluation: daily Safety	7 *H infl* in each group! Same neurological abnormalities, no death CFX: shorter duration of fever (NS). CSF cultures at 24/48h were sterile in all children. Well tolerated	Not given	CFX = AMCHL Few patients
Steele 1983 Arkansas, 1 center Enrolled: n=30 Pos CSF culture: 30	14d- 14 y	Signs and symptoms BM and CSF culture pos	- Early-onset neonatal meningitis - culture-negative CSF - meningitis with ventriculoperitoneal shunts	- AMCHL: Ampicillin 200-400mg/kg/d IV div 4 doses and Chloram 100mg/kg/d IV div 4 doses (n=15) vs - Ceftriaxone 100mg/kg/d in two divided doses (n=15) Duration: At least 5 days AB IV. *N menin* 7d, *H infl* 10 d, *S pneumo* 14 d, others 21 d. (In some pat chloramorally and ceftriaxIM the last day or two of treatment) Pathogens AMCHL CFX *H infl* 9 6 *S pneumo* 3 5 *Strepto B* 2 1 *N menin* 1 1 *E coli* 0 2	Bacteriological assessment CSF day 0, at 24-48h, 24 h after end of therapy CFX-group: drug concentration measurements in CSF and serum at 24-48h Biological measurements prior to therapy and every 4 days until discharge Clinical evaluation: daily	All CSF sterile after 24-48h No death Shorter fever in CFX ($p<0.05$) Neurologic sequelae 3 m after treatment: 3/15 AMCHL vs 2/15 ceftriax (NS) Same adverse events	Not given	CFX = AMCHL

References	Type of population	Inclusion and exclusion Criteria		Intervention	Outcomes	Results	Randomisation	Conclusions
Del Rio 1983 Dallas, 2 centers Enrolled: n=92 Evaluated: n=78 Nov 1981 - Sept 1982	>6 weeks 51<12m	Signs, symptoms and CSF bacterio pos: 72 (6 bacterio neg, but CSF abnormalities suggestive)	- infants less than 6 week old - allergy to beta-lactam antibiotics	- AMCHL: Ampi 200mg/kg/day in 4 doses and chloram 100mg/kg/day in 4 doses IV (n=39). When the susceptibility was known, therapy continued with ampi or chloram vs - Ceftriaxone (CFX): Loading dose: 75/mg/kg, followed by 50mg/kg every 12h Duration: 10 days (*N menin* 7 d) Pathogen: *H infl* 54, *S pneumo* 6, *N menin* 9, *Strepto B* 2, *Strepto A* 1, No isolate: 6	Bacteriological assessment On admission: blood and CSF Repeated CSF after 4-12h (n=40) remaining patients repeated CSF after 13-70h. If repeated CSF culture positive, another lumbar punction 24h later. In the ceftriaxone group: hepatic, renal and haematological function control at the beginning and end of R/. Clinical assessment daily Auditory testing 1-5 m after completion of therapy	28% *H. infl* Blactamase + Ceftriax: greater bactericidal activity ($p<0.0001$) No deaths and no significant differences in sequelae, prolonged fever. (Hearing evaluation: ceftriax 63% vs AMCHL 47%) More diarrhea in ceftriaxone group ($p<0.05$)	Not given	CFX = AMCHL CFX advantage of greater bactericidal activity and a twice-daily dosage schedule saves time and expense.