Bacterial Meningitis: Issues in Management

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India


India
60° E
70° E
80° E
90° E
AFGHANISTAN
IRAN
PAKISTAN
CHINA
TIBET
Srinagar
Boundaries in dispute
Indus
Amritsar
Ludhiana
Chandigarh
Delhi
New Delhi
Moradabad
Himalaya
Brahmaputra
Mt. Everest
29,029 ft. (8,848 m)
NEPAL
BHUTAN
Darjeeling
Shillong
Imphal
BANG
Persian Gulf
Tropic of Cancer
U.A.E.
Gulf of Oman
SAUDI ARABIA
20° N
OMAN
Jaipur
Agra
Lucknow
Ganges
Jodhpur
Thar Desert
Kanpur
Allahabad
Varanasi
Ahmadabad
Bhopal
Jabalpur
Jamshedpur
Vadodara
Indore
Bhavnagar
Nagpur
Raipur
Calcutta
Surat
Cuttack
Nashik
Godavari
Bay of Bengal
MYANMAR (BURMA)
Mumbai (Bombay)
Ahmadnagar
Pune
Solapur
Arabian Sea
Krishna
Hyderabad
Visakhapatnam
Kakinada
Vijayawada
0 300 Miles
0 300 Kilometers
Hubli
Kurnool
Nellore
Andaman Islands (INDIA)
Mangalore
Chennai (Madras)
10° N
Laccadive Islands (INDIA)
Mysore
Bangalore
Port Blair
Kozhikode
Coimbatore
INDIAN OCEAN
Kochi
Madurai
Alappuzha
Thiruvananthapuram
Nicobar Islands (INDIA)
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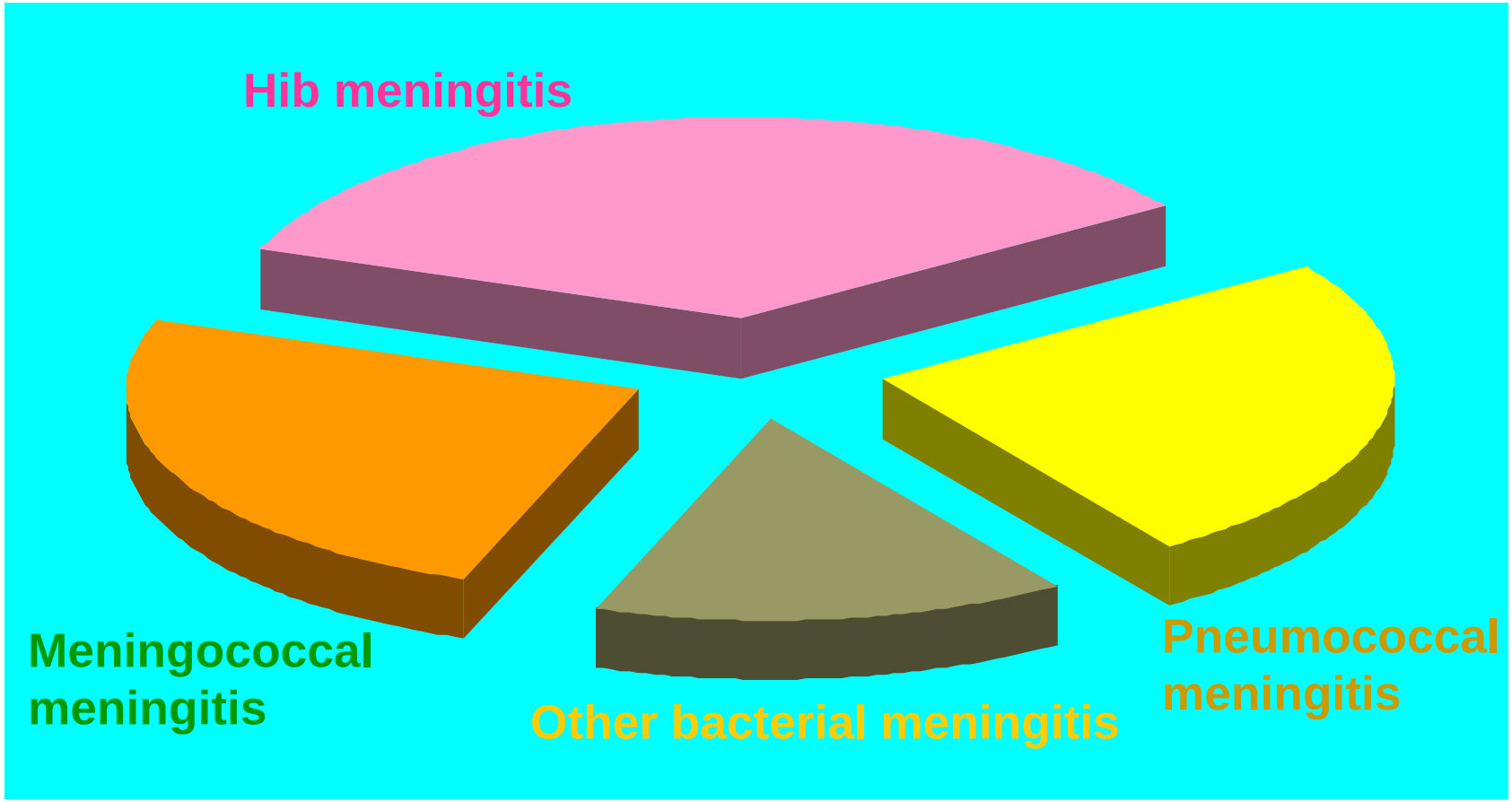
Acute Bacterial Meningitis

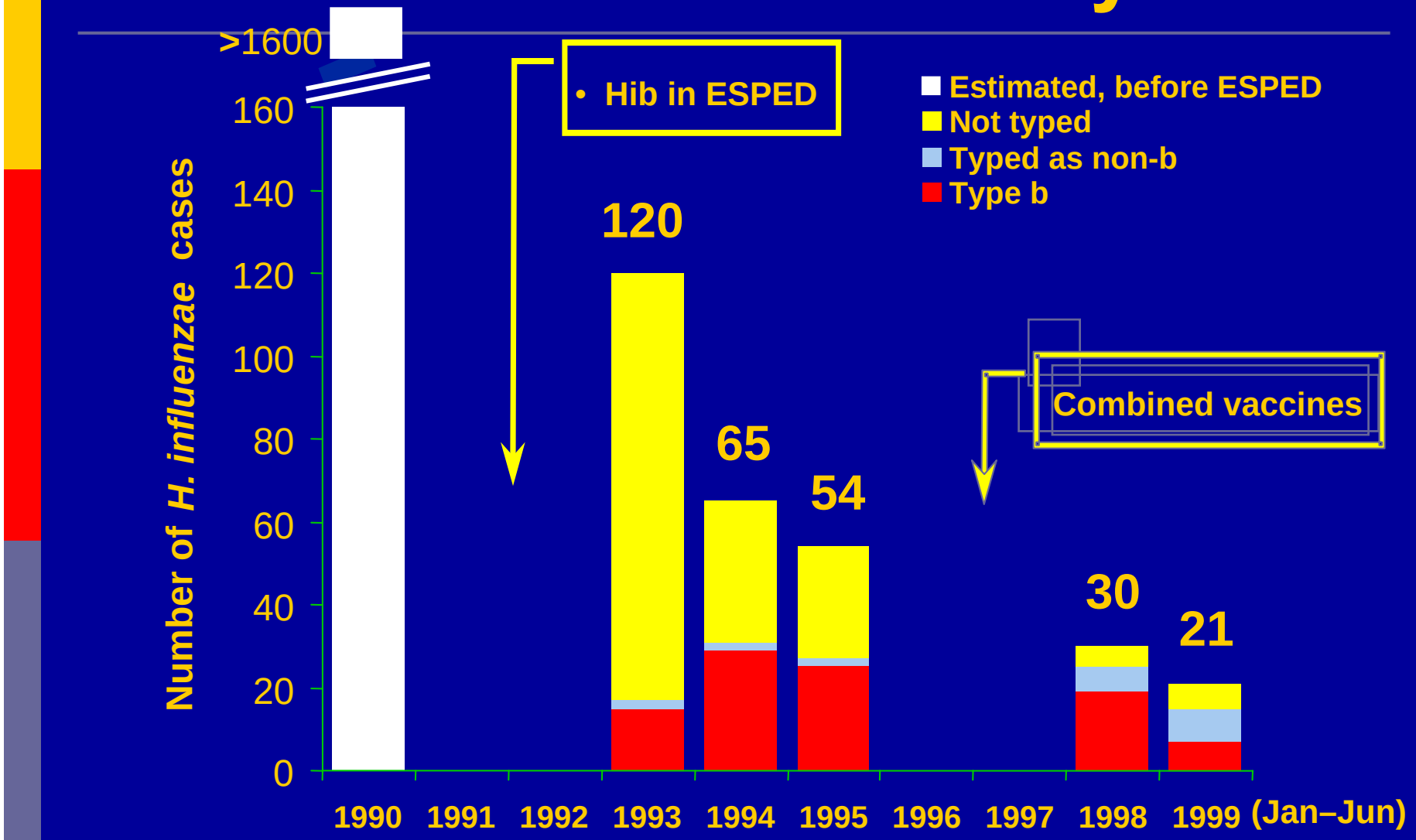
- United States Estimates
- Brazil, the attack rate might be as high as 45 cases per 100,000 population per year.
- Meningitis belt of Africa– Mortality varies, but has been estimated between 25% and 35%.
- Major epidemiological changes – 1. A dramatic decrease in meningitis. 2. Penicillin resistance may be very high (Landerdale TL et al 2005).
- Fatality rate for meningitis caused by Enterobacteriaceae is much higher, about 85%.

Bacterial meningitis with emphasis on disease in children/adolescents

Pre-immunisation era



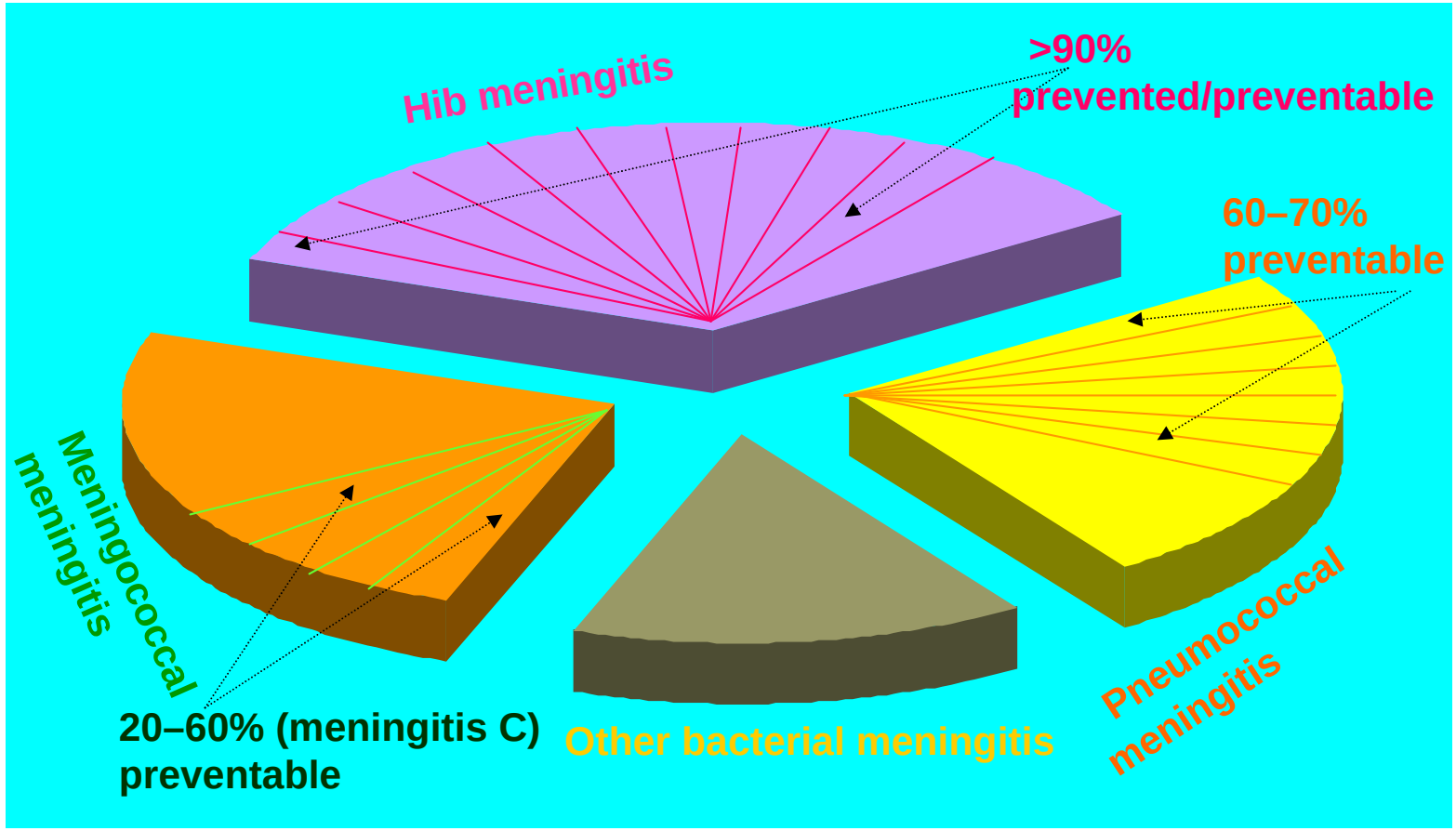
Invasive *Haemophilus influenzae* disease in Germany



Adapted from: von Kries R. Monatsschr Kinderheilkd, 1997;145:136–43.

Bacterial meningitis with emphasis on disease in children/adolescents

Immunisation era



Bacteriologic Trends of Bacterial Meningitis

- 94% reduction of *H. influenzae*
- Global increase of cases due to multiple-drug resistant *S. pneumoniae*

Cochlear implants and meningitis

- A new risk group for meningitis: as of 2002, nearly 60,000 people worldwide received cochlear implants
- 30 times higher risk, highest in the perioperative period
- Perioperative period: Streptococcus pneumoniae (M.C), Acinetobacter baumanii, Enterococcus and E.coli , Later - Haemophilus influenzae (type b and nontypable)

Reefhuis J, et al. N Engl J Med. 2003

- High risk group – Models with a positioner,

Reefhuis J, et al. N Engl J Med. 2003

inner ear malformation in combination with a CSF leak.

Phelps PD, et al. Am J Otol. 1994

ISSUES IN MANAGEMENT

- Clinical Diagnosis
- Who needs intensive Care? & How?
- Antimicrobial Therapy- which agent(s), & how long?
- Role of Dexamethasone!
- Raised ICP- How to treat?
- Should fluids be restricted?

PEDIATRIC EMERGENCY CARE

Printed in U.S.A.

Signs of meningeal irritation at the emergency department: How often bacterial meningitis?

RIANNE OOSTENBRINK, MD, KAREL G.M. MOONS, PhD, CHANTAL C.W. THEUNISSEN, MSc, GERARDA DERKSEN-LUBSEN, MD, PhD, DIEDERICK E. GROBBEE, MD, PhD, HENRIËTTE A. MOLL, MD, PhD

Frequency of bacterial meningitis related to specific signs of meningeal irritation among children with meningeal irritation assessed by the pediatrician

Positive sign	Children ≤1 year (n = 88)	Children >1 year (n = 168)	All children (n = 256)
Neck stiffness	18/56 (32%)		
Kerning's sign	0/5 (0%)		
Brudzinski's sign I or II	1/8 (13%)		
Tripod phenomenon	Not applicable		
Irritability	37 (32%)		–50%)
Bulging fontanel	11/34 (32%)		(32%; 17–51%)
At least one sign of meningeal irritation	23/88 (26%)	76/168 (45%)	99/256 (39%; 33–45%)

Irritability and bulging fontanel were more predictive in infants

Meningitis was present in only 42%with those presenting with neck rigidity to pediatric emergency

Combination of signs did not improve the predictability

Bacterial Vs Viral

Table 2 Sensitivities and specificities for the five clinical decision rules applied to our population of 166 children

Rules	No.	Meningitis: Bacterial n	Bacterial (%)	Viral n	Viral (%)	Sensitivity %	Sensitivity (95% CI	Specificity %	Specificity (95% CI
Jaeger *et al*[5]	113*								
Treatment		16	(94)	8	(8)	94	(73–99)		
No treatment		1	(6)	88	(92)				
Bonsu and Harper[15]	161								
Treatment		20	(100)	61	(43)	100	(84–100)		
No treatment		0	(0)	80	(57)				
Freedman *et al*[3]	160								
Treatment		20	(100)	122	(87)	100	(84–100)	13	(8–19)
No treatment		0	(0)	18	(13)				
Nigrovic *et al*[1]	151								
Treatment		20	(100)	45	(34)	100	(84–100)	66	(57–73)
No treatment		0	(0)	86	(66)				
Oostenbrink *et al*[14]	119*								
Treatment		10	(83)	30	(28)	83	(55–95)	72	(63–80)
No treatment		2	(17)	77	(72)				

*The high number of missing data is explained by the items required for the application of these rules that are not systematically collected in our paediatric emergency room.

Study concluded that Nigrovic et al offered maximum sensitivity and specificity & has better clinical applicability

Dubos F etal, Arch Dis Child 2006

Conditions Requiring Admission to PICU at PGIMER

Clinical states	Total (n=88) 1994-96	Total (n-147) 1997-2000	Within 48 hours
Clinical raised ICP	39(44%)	68	36/39,93%
Coma (Low GCS<8)	52(59%)	76	All at presen'tion
Shock	21(24%)	33	12/21,57%
Respiratory distress/ failure	18(20%)	43	
Status epilepticus	34(39%)	47	31/34(91%)

Singhi s et al, *Annals of Tropical Paediatrics* (2004) 24, 133–14

INTUBATION

Needed in 29 of 88 (33%), 60 of 147 our ABM patients -

- Coma, Poor or irregular respiratory effort
- Raised ICP (8,28%)
- Airway instability (3,10%)
- A combination (3,10%)
- Shock

45% short -term intubation (≤2 days)

Singhi s et al, *Annals of Tropical Paediatrics* (2004) 24, 133–140

ABM:WHICH ANTIBIOTIC ?

- Covers all common pathogens
- Sterilize CSF at earliest – delayed sterilization of csf > 24 hours (***Lebel and Mccraken 1989, Schaad 1990)***
- Deteterminants of poor outcome:
  - Higher organism load – ***(Feldmen 1977).***
  - Poor choice,
  - Indicate inadequate dose of antibiotics

Objetives of AntibioticTherapy During Bacterial Meningitis

- Rapid sterilization of CSF.
- T > MIC - MBC in CSF for 90% of the dose interval.

CSF Penetration of Antibiotics During BM

$C_{CSF} / C_{SERUM} = \%$

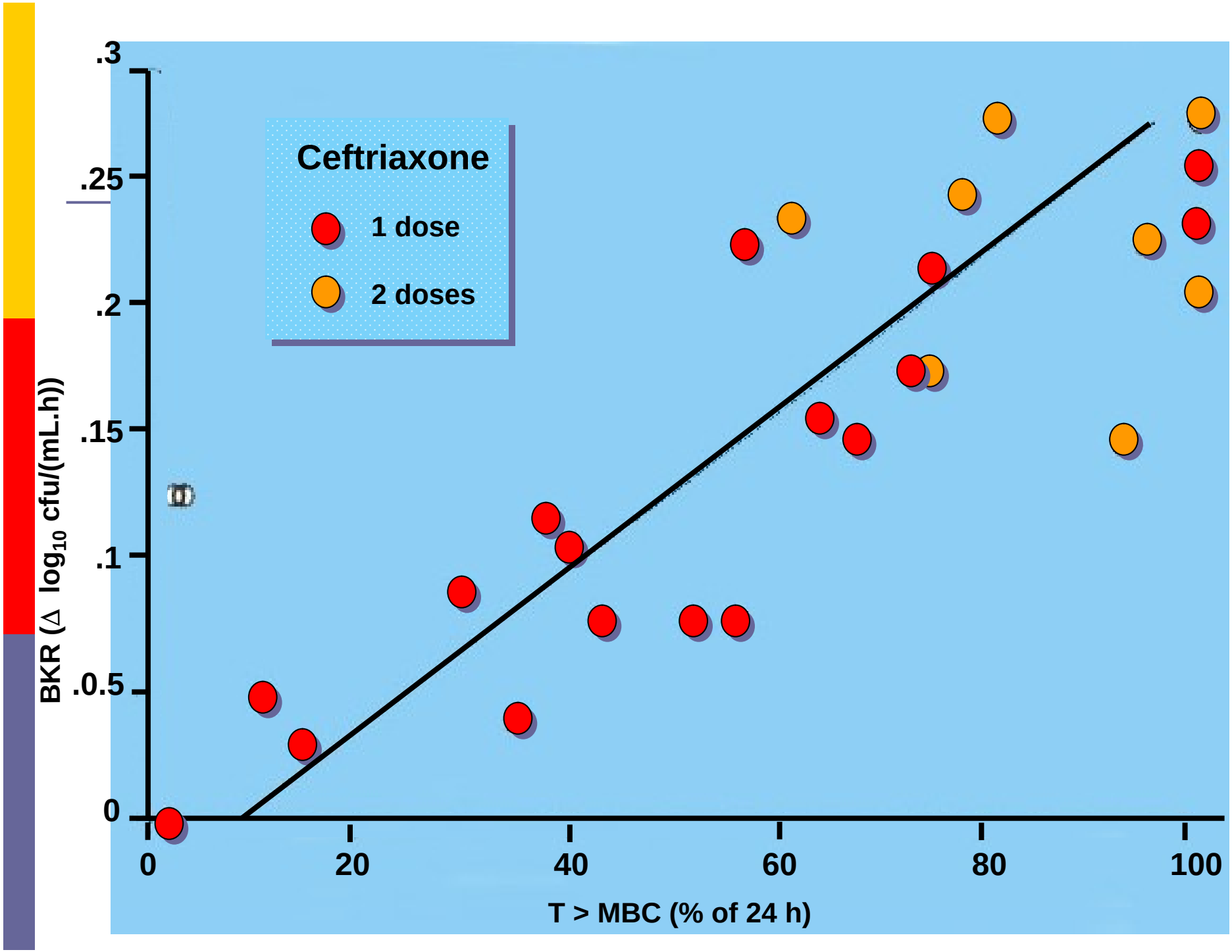
	Humans	Animals
Cefotaxime	10.1	3. 9
Ceftriaxone	1.5 - 9	6 - 12
Cefepime	10	16 - 22
Meropenem	21	6. 4
Ofloxacin	42 -72	40 - 60
Gatifloxacin	50	30 - 50
Trovafloxacin	23	19 - 27
Vancomycin	7 - 14	5 - 13
Rifampin	7 - 56	18 - 22

Lutsar I. Clin Infect Dis 1998;27:1117-29

CSF Half Life (in hours) of Antibiotics During BM

	Humans	Rabbits
Ampicillin	2.1 - 3.6	0.8
Cefotaxime	9.3	1.0
Ceftriaxone	16.8	7 - 8
Trovafloxacin	10.7	2.4 - 3.8
Gatifloxacin	ND	3.8
Meropenem	ND	ND
Gentamicin	ND	2.3
Vancomycin	ND	7 - 8

Lutsar I. Clin Infect Dis 1998;27:1117-29


Ceftriaxone
1 dose
2 doses
BKR (Δ log10 cfu/(mL.h))
.3
.25
.2
.15
.1
.05
0
0
20
40
60
80
100
T > MBC (% of 24 h)

Effect of Corticosteroids on Antibiotic and Bacterial Clearance in CSF

Organism	Agent	↓ Concent.	↓ Clearance
E. Coli	Gentamicin	Yes	No
h PRSP	Vancomycin 20 mg	Yes	Yes
h PRSP	Vancomycin 40 mg	Yes	No
PSSP	Ampicillin	Yes	No
PSSP	Ceftriaxone	Yes	No
ICRSP	Ceftriaxone	No	Yes
h PRSP	Trovafloxacin	No	No
h PRSP	Rifampin	No	No

PRSP= Pen R *S. penumoniae*

CRSP= Cephalosp R *S. pneumoniae*

h= highly

i= intermediate

Leitson I et al CID 1998;27:1117-29

Clinical Experience with other Antibiotics

Drug	Control Drug	Efficacy	Safety
Meropenem[1,2]	Cefotaxime	Comparable	Comparable
Cefepime[3]	Cefotaxime	Comparable	Comparable
Cefepime[4]	Ceftriaxone	Comparable	Comparable
Trovafloxacin[5]	Ceftriaxone +/- Vancomycin	Comparable	Comparable

1: AACh, 1995; 39:1140-46
2: PIDJ, 1999; 18:587-90
3: AACh, 1996; 39:937-40
4: AACh 1997
5: PIDJ. 2002; 21:14-22

Therapy of Bacterial Meningitis

Age group	Standart	Alternative
≤ 12 weks*	Cefotaxime + Ampicillin	Ampicillin + Gentamicin
> 12 weeks to 50 yrs.	Cefotaxime Ceftriaxone Penicillin **	Ampicillin + Cloramphenicol
≥ 50 years*	Cefotaxime + Ampicillin	Ampicillin

** Concern of L. monocytones and GBS*

*** For susceptible S. penumoniae and N meningitides*

Therapy of Bacterial Meningitis
Special Conditions

Condition	Likely Pathogens	Choice of Antibiotics
With impaired cellular immunity	*L. monocytogenes* Gram-negative bacilli	Ampicillin plus Ceftazidime
With head trauma, neurosurgery or CSF-Shunt	Staphylococci Gram-negative bacilli or *S. pneumoniae*	Vancomycin plus ceftazidime

Physiochemical properties influencing antimicrobial penetration into CNS

Physiochemical Property	Effect on central nervous system penetration
Lipophilicity	Highly lipophilic drugs more readily penetrate the CNS
Protein binding	Highly protein-bound drugs have reduced CNS penetration
Molecular weight	Substances >500-800 d have reduced ability to penetrate the BBB
Ionization	Polar, ionized compounds are less likely to cross the BBB. Polarity can vary for many drugs with changes in physiologic pH
Active transport	Specialized active transport cells in the choroid plexus may excrete drugs across the vessel wall

Ziai WC & Lewin III, JJ, Crit Care Clinics, 2007.

THERAPY OF *S. pneumoniae* Meningitis

		Precaution
PSSP	Penicillin	
PRSP	Cefotaxime Ceftriaxone	LP at 24-36 hrs
CRSP	↑ Cefotaxime or Ceftriaxone + Vancomycin / Rifampin	LP at 24-36 hrs

Empiric Antibacterial Therapy

	Suspected pathogens	Antibiotic	Dose
Neonates and infants	Group B streptococcus	Cefotaxmine	150 mg/kg
< 3 months	Listeria monocytogenes	Ampicillin /	50 mg/ kg, q 6h
		Gentamicin	7.5 mg/kg
Children and infants	Neisseria meningitidis	Cefotaxime	200 mg/kg/day
>1 months	Strept. pneumoniae	or Ceftriaxone	100 mg/kg/day
	H. influenzae b	± Vancomycin	60 mg/kg/day

IDSA guideline, Clin Infect Dis 2004

Duration Of Therapy

IDSA guidelines, Clin infect Dis 2004

- H. influe- 7 days
- Meningococcus- 7 days
- Pneumococcus- 10-14 days
- Other Streptococcus – 2-3 weeks
- Gram Negatives- 3 weeks

Resistant Pneumococcus– Consider Rifampicin

Shorter Courses- 7 days vs 10 days

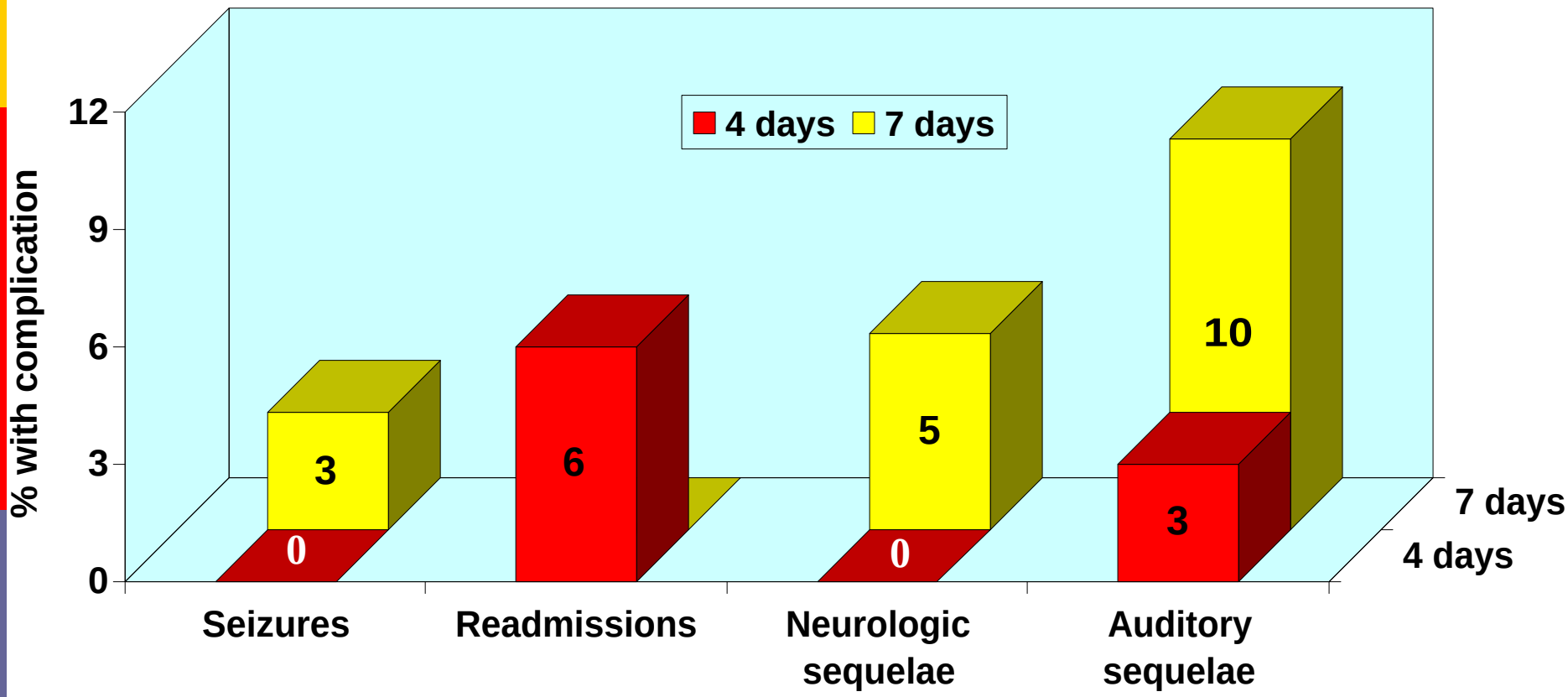
(KaushalM, Singhi et al J Trop Pediatr, 2002)

Time to Sterilize CSF After Parenteral Antibiotics

Meningococcus:	**2 hrs (15´ to 2 hrs)**
Pneumococcus:	**4 hrs (4 to 10 hrs)**
GBS:	**8 hours**

Kanegaye JT et al. Pediatrics 2001;108:1169-74

Therapy of Bacterial Meningitis: 4 vs 7 days



Roine et al. Pediatr Infect Dis J. 2000; 19:219-22

ABM : DEXAMETHASONE.

- Reduces brain water, CSF pressure, pleocytosis, lactate and TNF -a activity in experimental meningitis
- Lepper and Spies, 1957-58, Hydrocort of no Value
- Lebel et al 1988, Dexamethasone reduced hearing deficit
- Evidence to support routine use- Insufficient in devloping countries

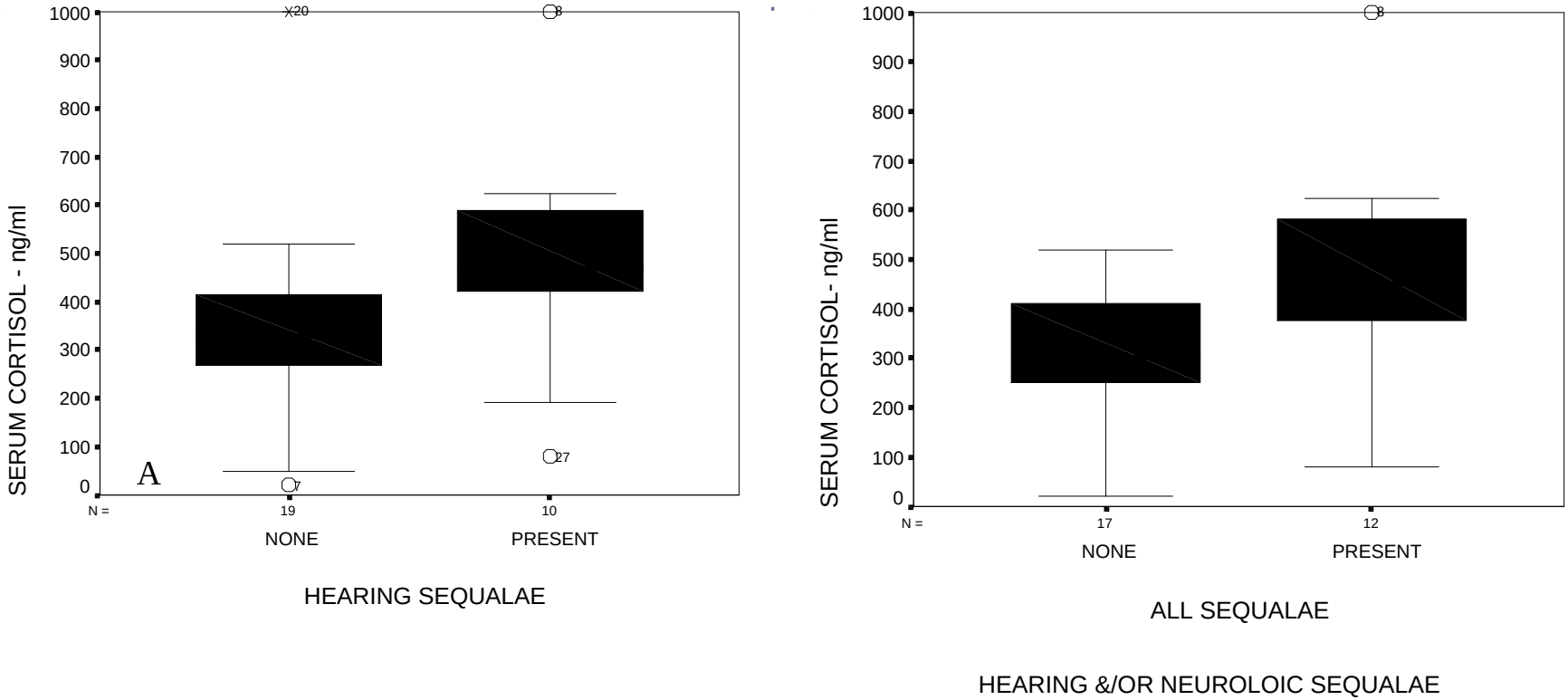
  (*Malawi study, Molyneux et al , Lancet 2002*)
- Some evidence- may be helpful in *H.influenzae* type b meningitis

ABM : DEXAMETHASONE.

- *American Academy of Pediatrics, Sub-committee on Infectious Diseases, 2003*
- *H.influenzae* type b, and pneumococcal meningitis
- Must be given 0.15 mg/kg/dose 6 hourly,before the antibiotics.
- Two -day regimen or four-day regimen (Feigin RD et al 2004)

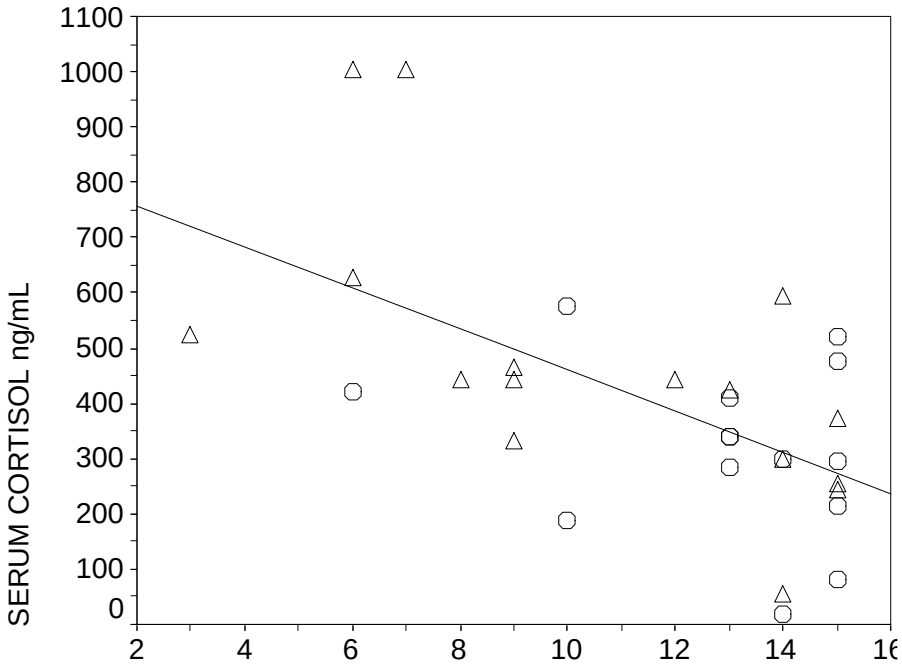
Serum Cortisol in meningitis

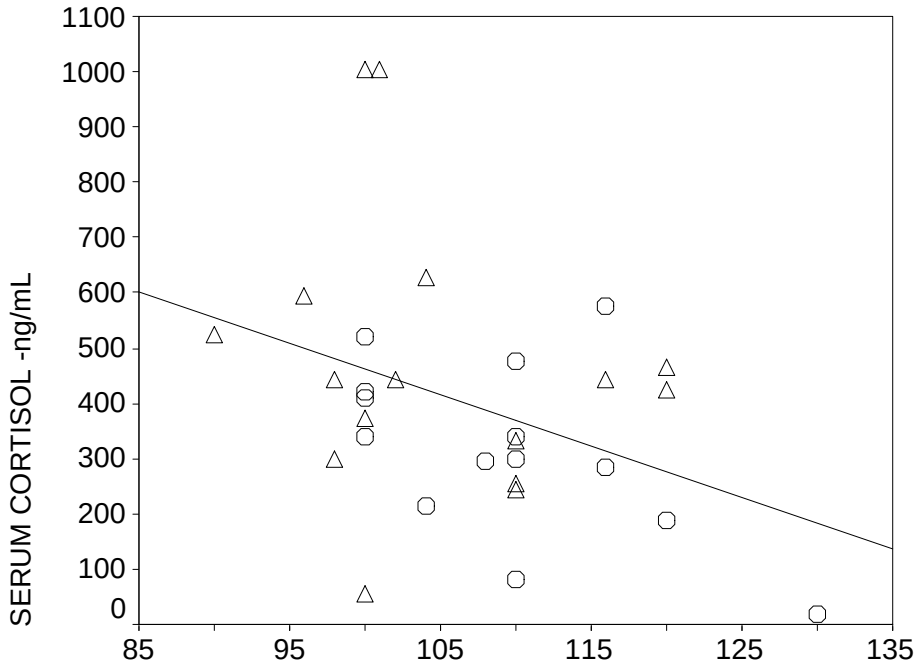
Singhi S and Bansal A, Pediatr Crit Care Med 2006; 7:74 –78



Box-plot comparing serum cortisol level of patients with hearing sequelae (median, 469; 10th to 90th centile, 91–962.5 ng/mL) or without hearing sequelae (*A*) (median, 330; 50–520 ng/mL) and patients with neurologic and/or hearing sequelae (median, 450;113–887.5 ng/mL) and patients without any sequelae (*B*) (median, 300; 44–616 ng/mL).

Serum Cortisol in meningitis



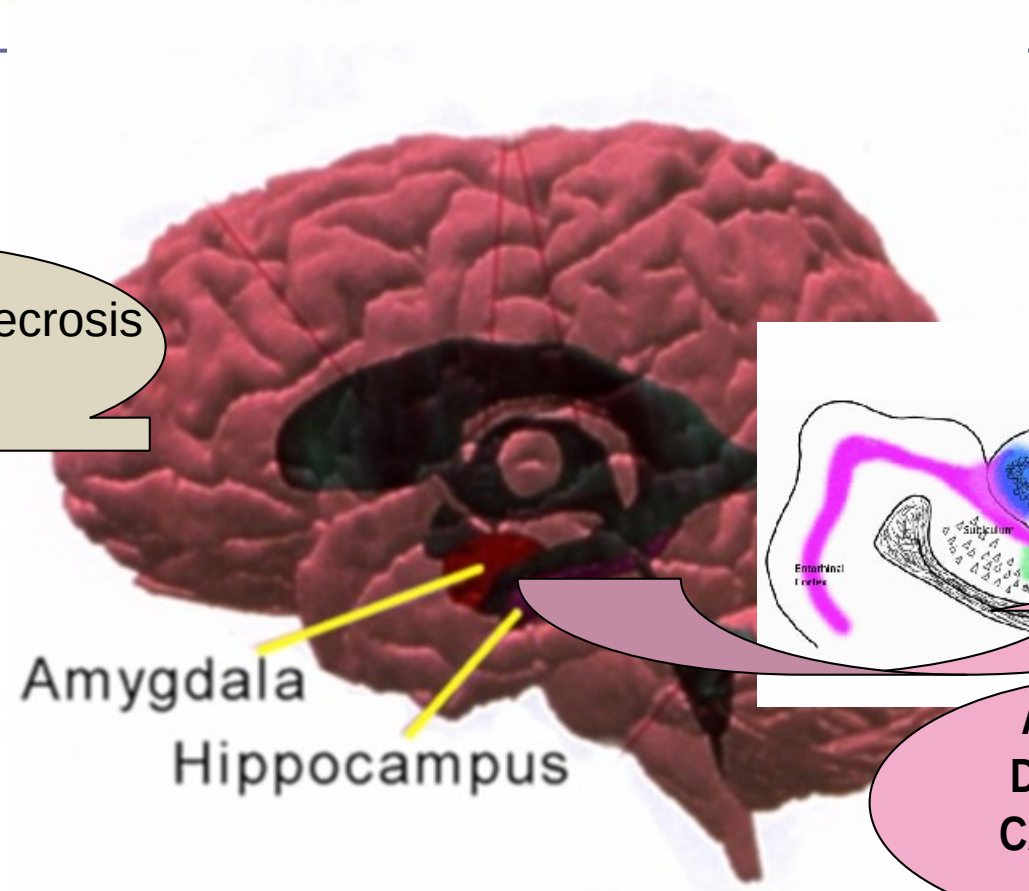


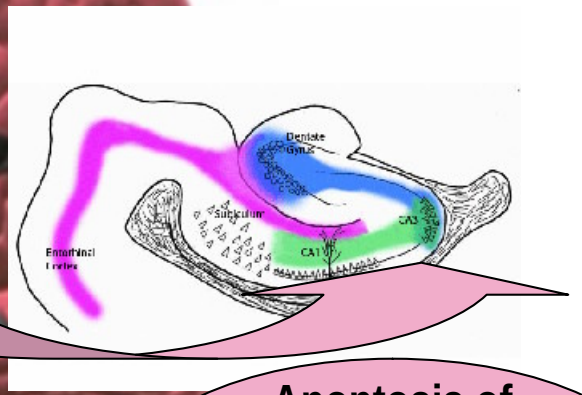
Correlation of serum cortisol with Glasgow Coma Scale score (*left*) (for all patients, Pearson's *r* .59, *p* .001; bacterial group, *r* .63;aseptic group, *r*.27) and with systolic blood pressure (*right*) (for all patients, Pearson's *r*.38; bacterial group, *r*.23; aseptic group, *r*.52). The *open circle* - aseptic meningitis, and the *open triangle* - bacterial meningitis.

Newer anti-inflammatory therapies in meningitis

Pathophysiology

Acute neuronal necrosis
Of cortex

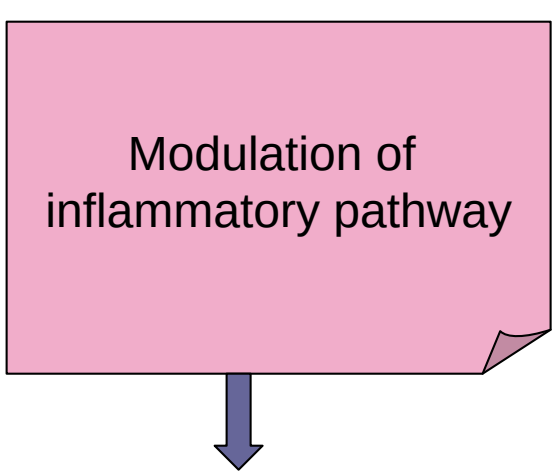




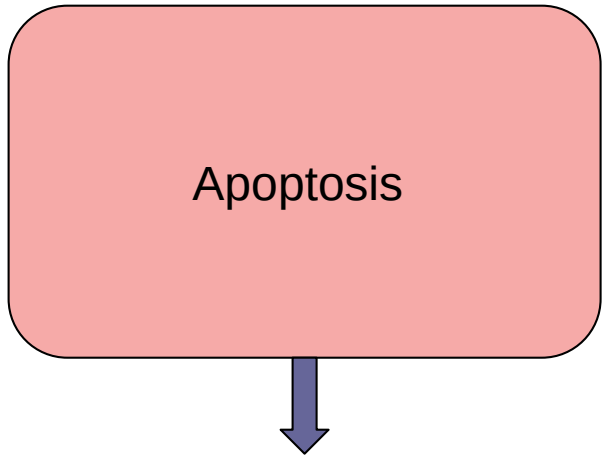
Apoptosis of Dentate gyrus CA1-CA4 areas

Learning and memory deficits

Potential treatment options



- Bacterial killing and release of bacterial components
- Recognition of bacterial components and initiation of inflammatory reaction
- Modulation of inflammatory reaction
- Inhibition of inflammatory mediators



- Modulation of apoptotic pathway

Summary of novel therapies

			Neuronal injury		
Intervention	Compound	Pathogen	Cortex	Hippocampus	Mortality
iNOS inhibition	Aminoguanidine	GBS	increase	ND	ND
Endothelin agonist	Bosentan	SP	decrease	no change	no change
Antioxidants	PBN	SP	decrease	increase	no change
		GBS	decrease	decrease[a]	ND
	NAC	SP	decrease	no change	no change
	DFO	SP	decrease	no change	no change
	TLM	SP	decrease	no change	decrease
MMP inhibition	GM-6001	SP	decrease	ND	ND
MMP + TACE inhibition	BB-1101	SP	decrease	decrease	decrease
	TNF484	SP	decrease	non change	no change [
TNF-α neutralization	Neutralizing Ab	GBS	no change	decrease[a]	decrease[b]
Attenuation of inflammation	Dexamethasone	SP	ND	increase	no change
		GBS	decrease	ND	no change
Caspase inhibition	Ac-DEVD-CHO	SP	ND	decrease	ND
Neurotrophin	BDNF	SP	ND	decrease	no change
		GBS	decrease	decrease[a]	no change
Glutamate antagonist	Kynurenic acid	GBS	decrease	decrease[a]	ND

Denis Grandgirard and Stephen L. Leib, Curr Opin Pediatr, 2006

RAISED INTRACRANIAL PRESSURE

- Early increase inflammatory vasogenic edema(increased permeability).
- Next cytotoxic edema, and increased volume - CSF, BLOOD
- Later interstitial edema due to ⇑ permeability and hydrocephalus.
- Raised ICP may further compromise CBF and ischemic injury to various cells - worsening of cytotoxic edema.
- Vicious cycle of edema and compromise CBF - progressive brain amage.

ABM:RAISED INTRACRANIAL PRESSURE

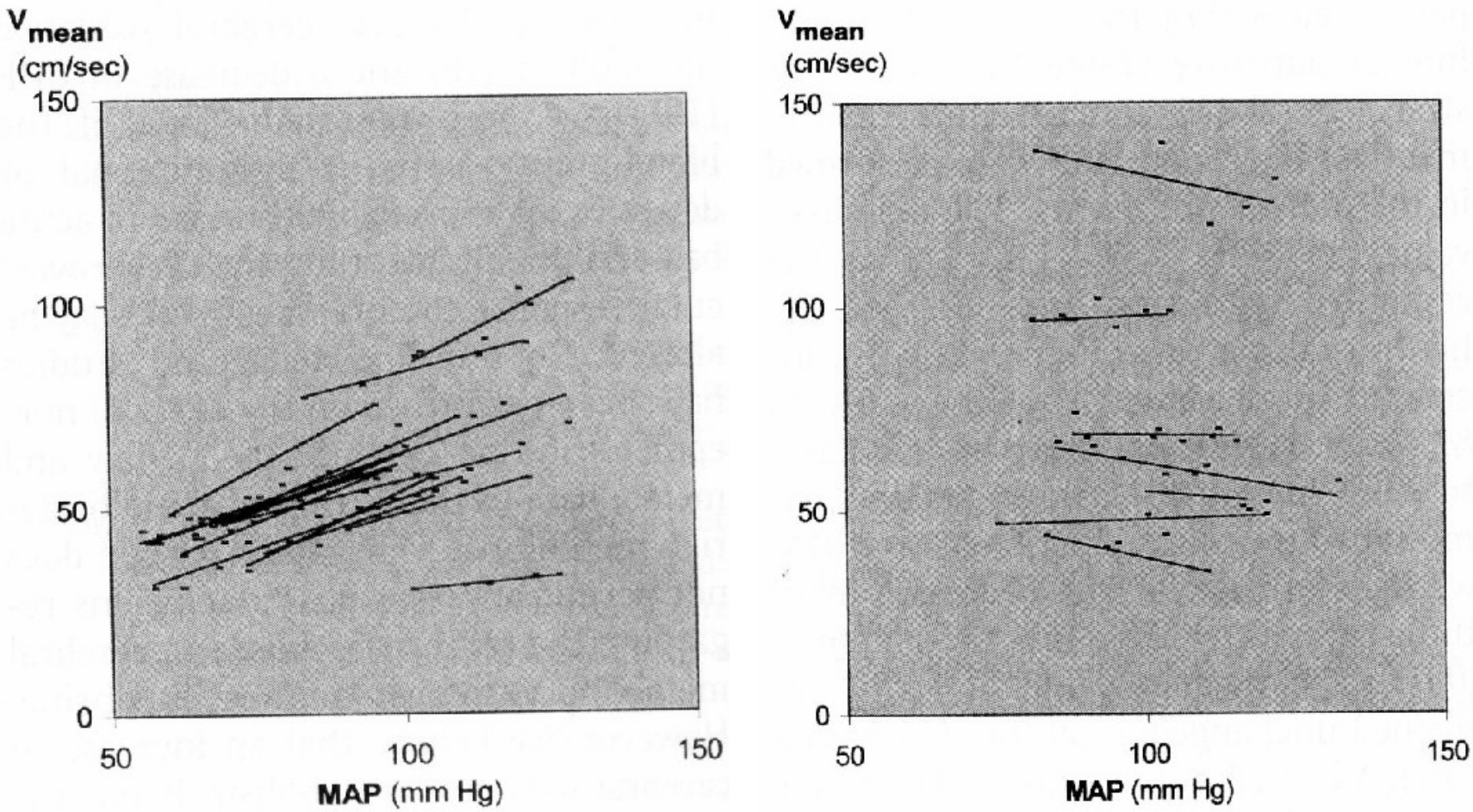
- Maximum Increase <24 -48 hours

  (Minns 1989)
- Cerebral Herniation <8 hours

  (Horwitz et al 1980)
- Cerebral herniation was seen in 30% of children dying
- In our PICU, clinical features of raised ICP 44% (39/88, 68/147) of children. Anterior fontanel was bulging

Cerebral autoregulation

(Moller et al, Crit Care Med 2000)



ABM : RAISED INTRACRANCIAL PRSSURES

- DEREASED CBF in 80%,by 30-70% in one-third poor outcome
- CBF decreases especially in the subcortical white matter.
- DECREASED CPP : <30-50 mmHg poor outcome.

RAISED INTRACRANIAL PRESSURE

Goals of management

- Reduction in ICP - to prevent herniation.
- Maintenance of optimal CBF- to prevent further hypoxic ischemic injury.
- Reduction in cerebral metabolic rate - to prevent demand supply mismatch.

TREATMENT RAISED ICP

CT/ MRI Scan - Cerebral edema

- **Normal CBF unlikely**
- **Mannitol (4-6 h) preserve circulation**
- **Hyperventilation - Harmful !**
- **Reduce CBF < ischemic threshold. Role needs further study (Body and Kroll 1994)**

TREATMENT RAISED ICP

CT/ MRI Scan –edema/infarct

- Improve CPP,
- maintain BP,
- dexamethasone for vasculitis

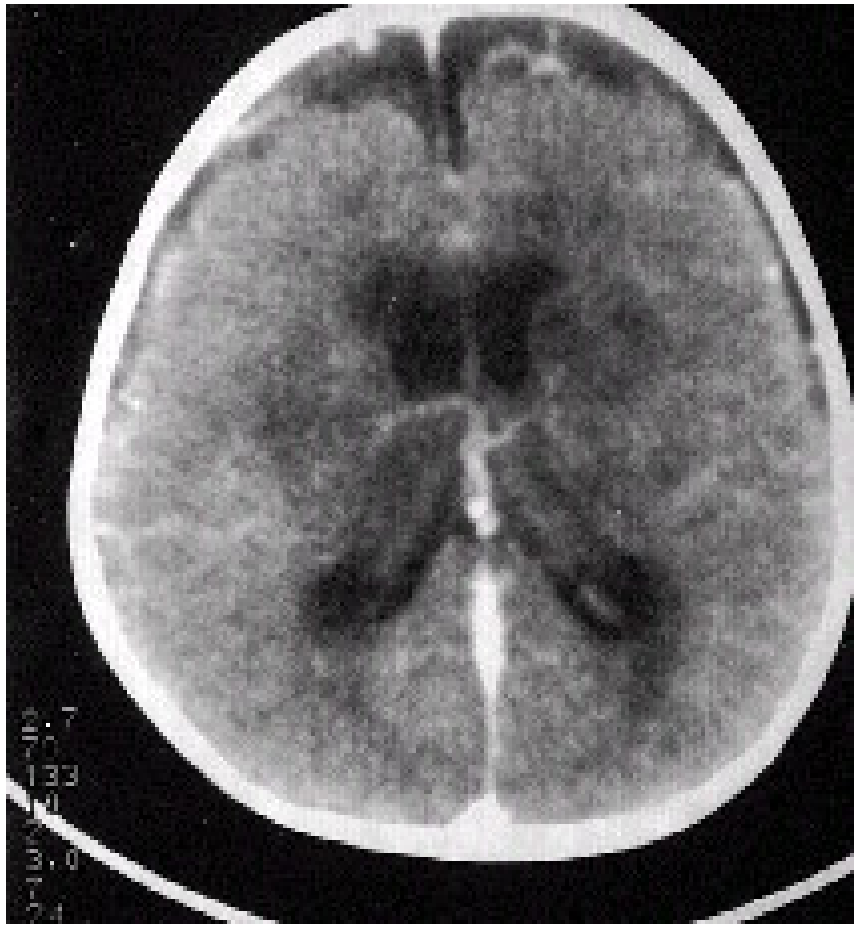
ABM: RAISED ICP

SD Effusion

- drain (only if ⇑ ICP)

ABM: RAISED ICP

CT/MRI Scan - Vent Dilatation



- CSF removal
- decreased production - Diamox,
- increased reabsorption - dexamethasone.

OSMOTIC DIURETICS

- Mannitol most effective osmotic agent, 0.25-0.5 gm/kg/dose, q 4-6 hourly
- may also reduce CBF, by vasoconstriction
- Avoid dehydration and hypovolemia.

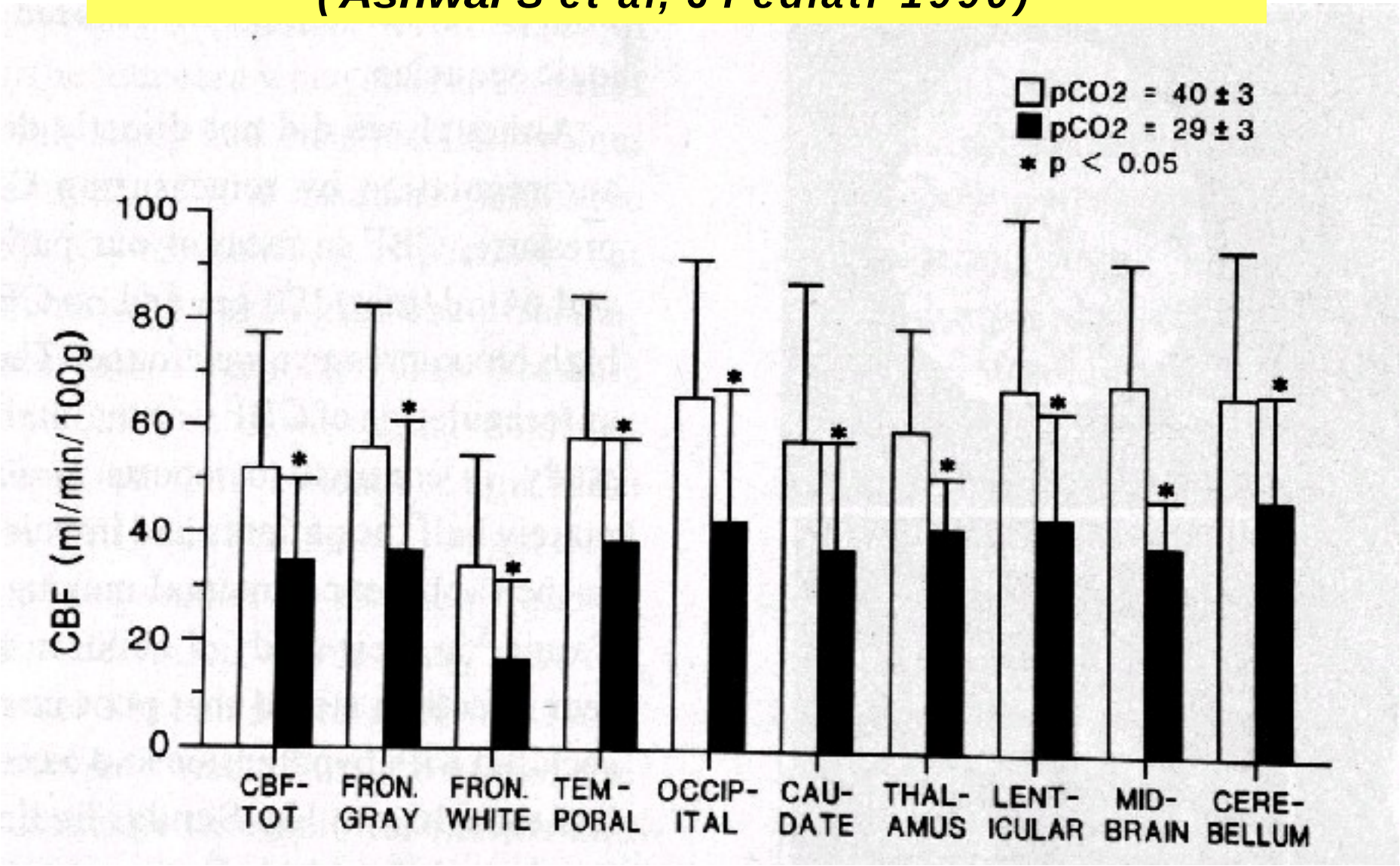
ABM:MANITOL & OUTCOME

Mannitol	Nos.	Died
Yes	32	10 (31%)
No	112	10 (8.9%)
		P=0.001

Mannitol-Polyuria		Died
Yes	16	7 (44%)
No	16	3 (19%)
		P= 0.1

ABM:CBF & Hyperventilation

(Ashwal S et al, J Pediatr 1990)



Raised ICP-Hyperventilation

- Prolonged Hyperventilation reduces global CBF ***(Moller et al, J Physiol 2000)*** and brain tissue oxygen pressure ***(Carmano Suazo JA et al, Crit Care Med 2000)***
- Manual hyperventilation in acute setting
- Short term hyperventilation 25% to our patients
- Prolonged hyperventilation (>1 hour causing PaCO2 <28 torr is not recommended.

Seizure & Status Epilepticus

Singhi S et al , Annals Trop Pediatrics,2004

- In 30%-40%, 90% within 48 h
- Prompt Control - Diazepam I.V., Set Infusion 0.005-.06 mg/kg/min (m-0.03), 1-8 days (mean 3.4)
- Thiopental, Paralysis and Ventilation

ABM:SHOCK

- 10-15% of hospitalised children
- Septic, Neurogenic
- VOLUME EXPANSON –Crystalloids-initial,Colloids- Plasma
- INOTROPES- dopa/dobutamine
- Elective ventilation
- Monitoring- CVP, arterial B.P.
- In our patients < 48 h - 57%
- Inotropes : 57%, 4.2 (upto 10) days

ABM : VENTILATION

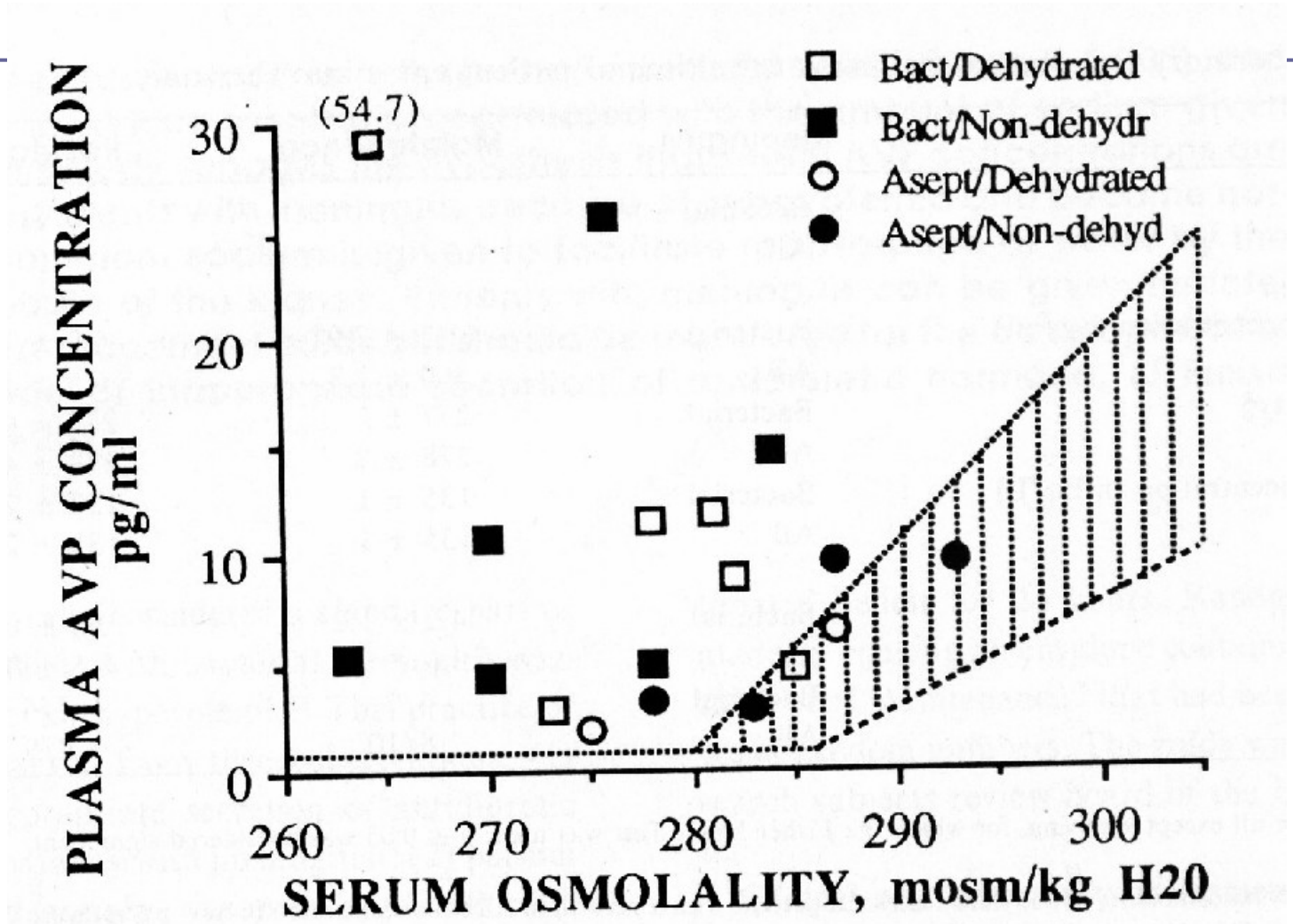
- Indications: in 19/88, & 23/147
  - Airway instability, control, ICP, Coma, Resp.depression, Shock GCS < 8 in 50%
- Within 48 h in 60%, upto 2 days - 46%, 7 days - 86%.
- Death - 10/32, 31% (***Madagame et al 1995, Singhi et al)***
- Stability among two - third of survivors
- Poor predictors:
  - hypotension, PRISM Score < 20

ACUTE BACTERIAL MENINGITIS
Should fluids be restricted ?

- Is there an excess body water?
- If so, where is the excess, and does it contribute to of cerebral edema or severity of illness?
- Is it possible to modulate changes in Body water by fluid therapy?

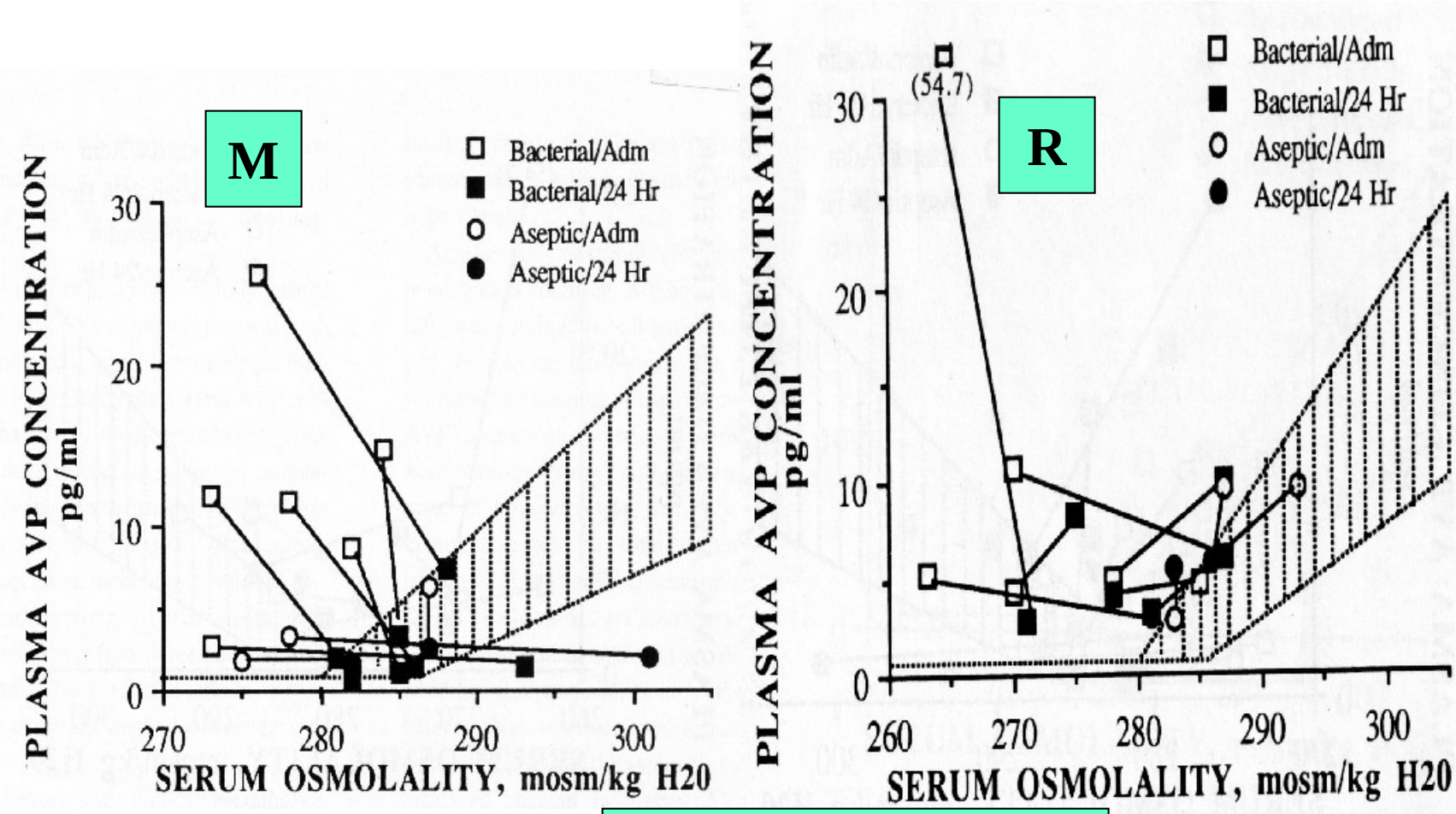
  Does fluid restriction reduce cerebral edema and improves cerebral blood flow and perfusion?
- Does fluid restriction improve the outcome - morbidity and mortality ?

ABM: AVP & Posm relationship



Powell et al, J Pediatr 1990

Effect of Fluid regimen on AVP & Posm relationship



Powell et al, J Pediatr 1990

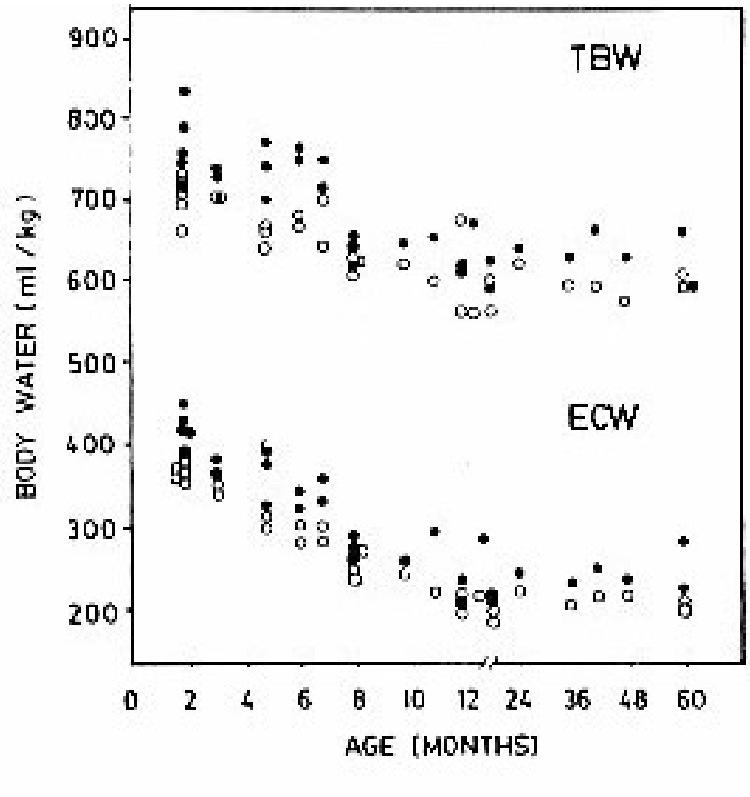
Studies on fluid/electrolyte balance in meningitis

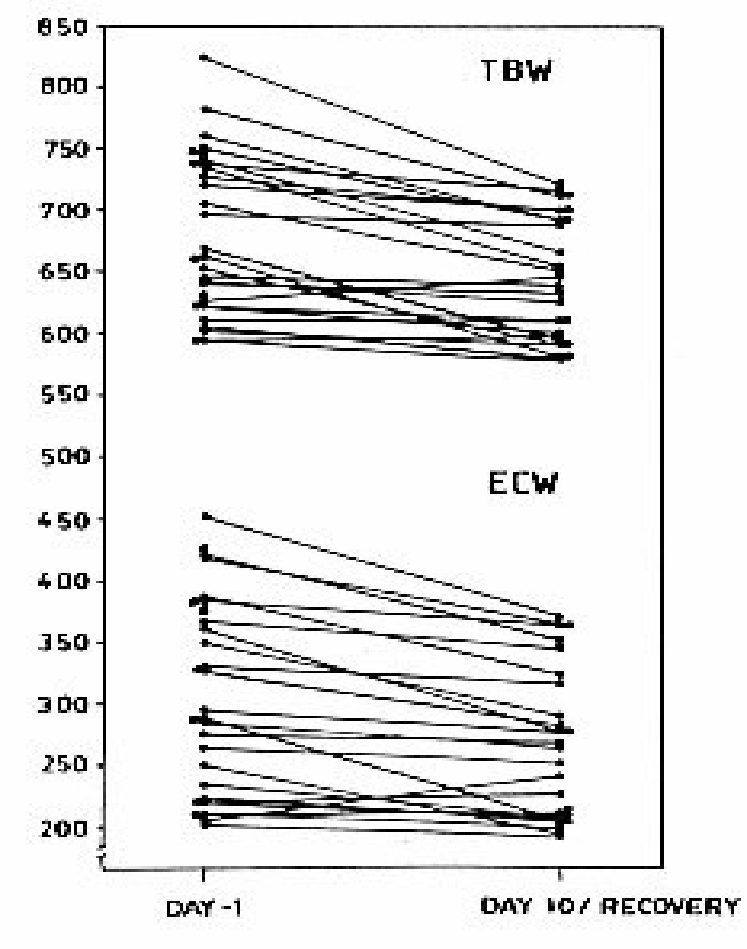
Study	Finding	Number studied	Interpretation
Reynolds 1972	Low serum, high urine Na	1	SIADH
Feigin 1977	hyponatraemic 58%, ADH Increased-86%	124	SIADH
		17	SIADH
Kaplan & Feigin,1978	ADH higher than controls	14	Contributes to brain oedema
Garcia 1981	CSF- ADH increased	20	SIADH
Shann 1985	HypoNa- 50%		

Studies on fluid/electrolyte balance

Study	Finding	Number studied	Interpretation
Kanakriyeh 1987	HypoNa-32%, but only 7% SIADH	85	Fluid restriction not recommended
Powell 1990	ADH lower after fluid load	13 (7 more fluid)	Hypovolaemia leads to ADH secretion
Padilla 1991	Urine ADH high in BM	? < 18	Clinically none with SAIDH
Taeuber 1993	No effect of fluid regime on oedema	rabbits	High fluid does not contribute to oedema
Singhi 1995	Increased, bad outcome with fluid restriction	50 children	Fluid restriction not indicated

ABM:Body Water Changes





Singhi et al, PIDJ 1995

ABM: FLUID THERAPY : HYPOTHESIS

- ECW Excess, elevated plasma ADH concentration, and mild systemic hypertension are compensatory mechanisms to overcome raised ICP and maintain cerebral perfusion (Singhi et al 1995)

HYDRATION STATUS & CBF

Studies in Rabbits, Tureen et al, 1992

16 h after infection

Group	MABP	CBF	CSF lactate	Arterial lactate
	mmHg	ml/min per 100g	mmol/ltr.	mmol/ltr.
Low Fluid	69.3 ± 9.3	54.7 ± 14.3	6.9 ± 2.8	1.6 ± 1.1
High Fluid	84.3 ± 9.4	64.3 ± 3.3	5.3 ± 2.7	1.1 ± 0.5

2.2 Kg , *Strep. Pneumonae*, 50ml v/s 150 ml/kg

HYDRATION STATUS & CBF

Studies in Rabbits, Tureen et al, 1992

4-6 h after antibiotics

Group	MABP	CBF	CSF lactate	Arterial lactate
	mmHg	ml/min per 100g	mmol/ltr.	mmol/ltr.
Low Fluid				
Treated	55.5 ±12.5	36.5 ± 25.1	12.6 ± 4.4	2.9 ± 1.6
Control	65.2 ± 3.6	54.0 ± 12.5	10.9 ± 3.6	2.0 ± 1.2
High Fluid				
Treated	77.9 ± 11.0	63.6 ± 10.3	9.6 ± 2.5	1.5 ± 0.7
Control	77.6 ± 7.1	62.4 ± 24.3	9.8 ± 4.5	1.8 ± 0.6

FLUID THERAPY- Restriction

- Fluid restriction may decrease mean arterial blood pressure, cerebral blood flow and perfusion **(Tureen et al 1992,1993)** and probably worsen the outcome

E.Coli MENINGITIS IN RABBITS

(Tauber et al 1993, J. Inf Dis)

- Fluid restriction (↓ in body weight by 5%) versus high fluid regime (↑ in BWT by 5%) had no measurable effect on degree of brain edema.
- Fluid restricted animals had significantly higher CSF lactate and lower CSF glucose.
- High amount of fluid did not aggravate brain edema.

Outcome of Acute Meningitis with Respect to Fluid Therapy & Serum Na

Outcome	Group A (No Hyponatremia)		Group B (Hyponatremia)	
	R	M	R	M
Intact survival	6 (46%)	7 (64%)	5 (33%)	7 (64%)
Survival with sequelae	4(31)	2 (18)	6 (40)	4 (36)
Died	3 (23)	2 (18)	4 (27)	0
Total	13	11	15	11

Chi square = 5.5, df = 6, P = 0.48

Outcome of Acute Meningitis with Respect to Fluid Therapy & Serum Na

Outcome	Group A+B (irrespective of Hyponatremia)	
	R	M
Intact survival	11	14
Survival with sequelae	10	6
Died	7	2
Total	28	22

Chi square = 5.5, df = 6, P = 0.48

ABM: FLUID THERAPY : HYPOTHESIS

- ECW Excess, elevated plasma ADH concentration, and mild systemic hypertension are compensatory mechanisms to overcome raised ICP and maintain cerebral perfusion ***(Singhi et al 1995)***
- Fluid restriction ma y decrease mean arterial blood pressure, cerebral blood flow and perfusion ***(Tureen et al 1992,1993)*** and worsen the outcome.

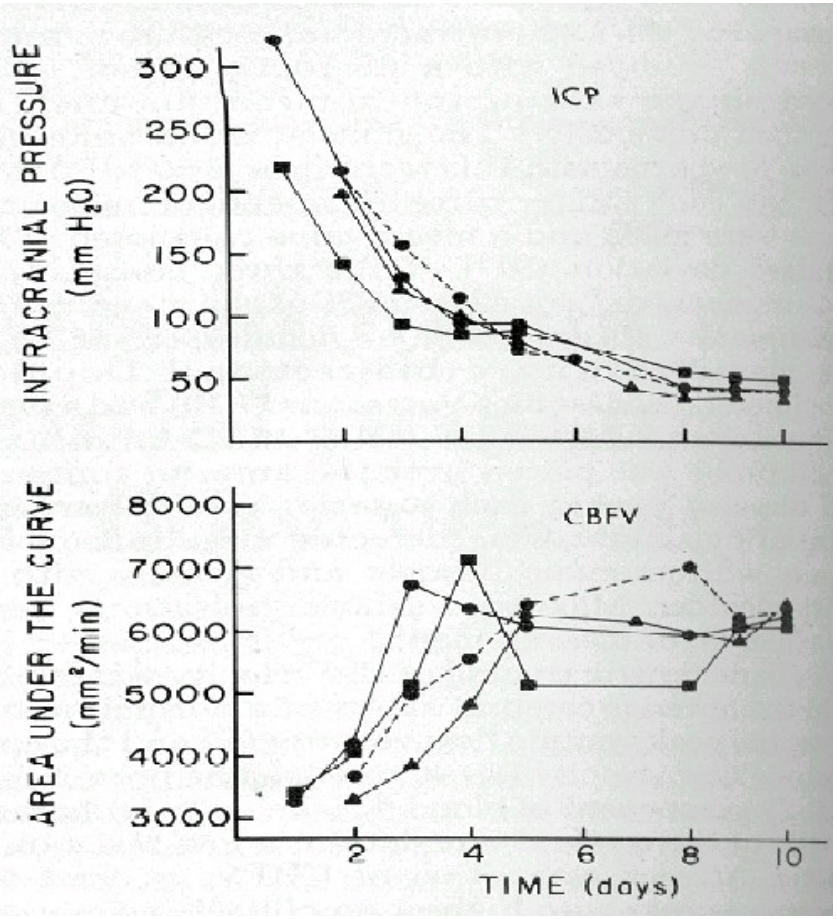
Outcome Acute Meningitis According to Reduction in ECW after 48 hours of Fluid Therapy

Outcome	Group I (≥10 ml/kg Reduction)	Group II (No or ≤ 10 ml/kg Reduction)
Intact survival	10 (36)	15 (68)
Survival with sequelae	11 (39)	5 (23)
Died	7 (25)	2 (9)

More mortality and sequalae in reduced ECW Group, (**RR 2.2, P =0.046 Death vs. survival (1 + 2)**

Singhi et al, Pediatr Inf Dis J 1996)

ICP & Cerebral Blood Flow
(McMenamin & Volpe 1984)

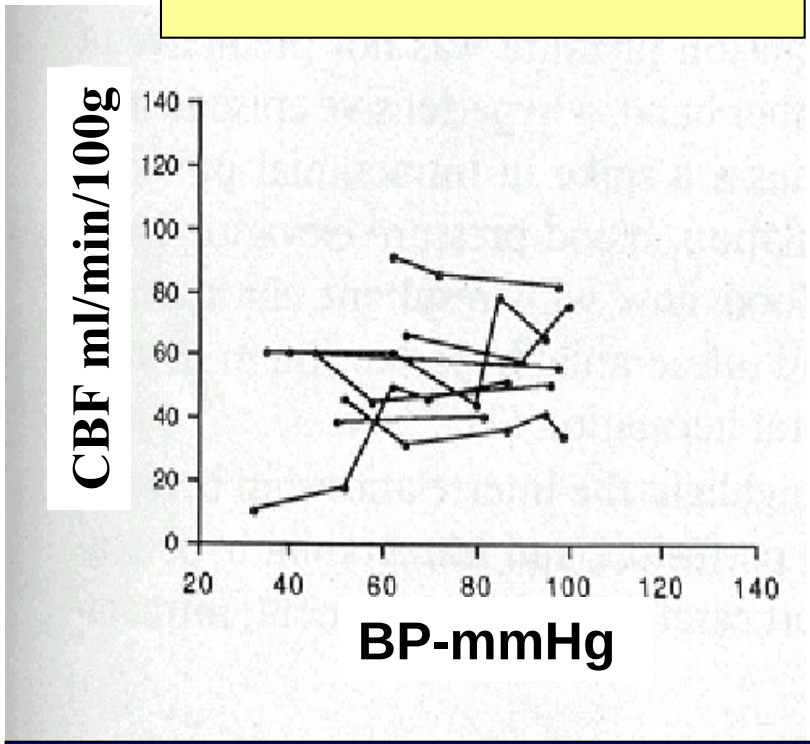


- ICP was markedly elevated in the first three days of illness. With resolution of intracranial hypertension in the next few days, CBFV ↑ by 80%.

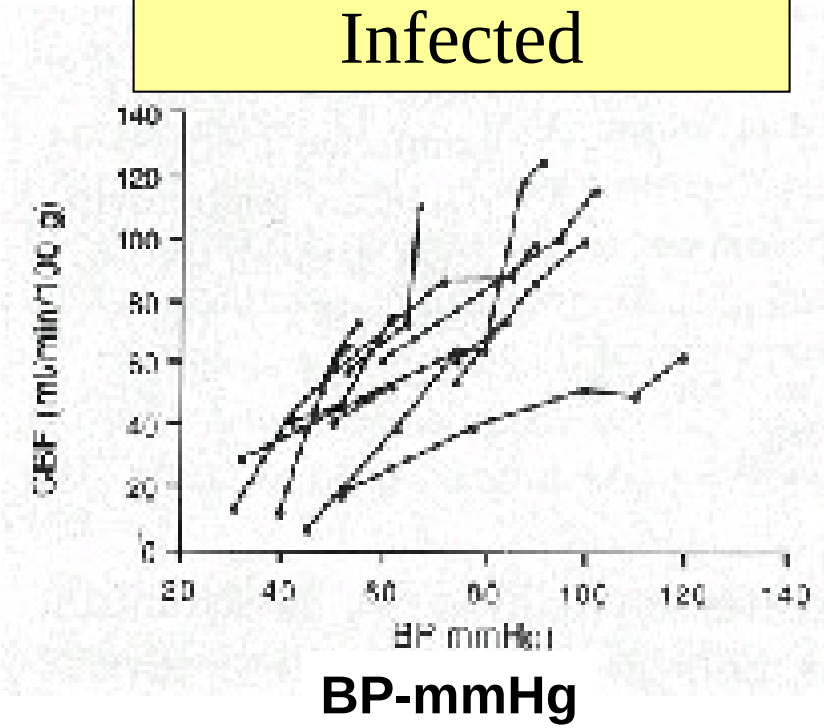
Cerebral Blood Flow & BP

Experimental Meningitis –Rabbits, Tureen et al 1990

Uninfected



Infected

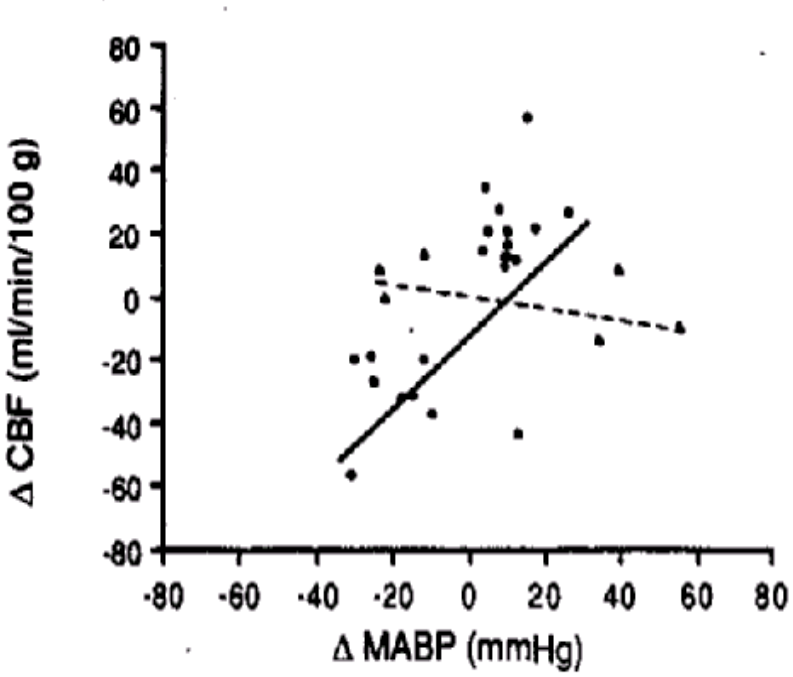


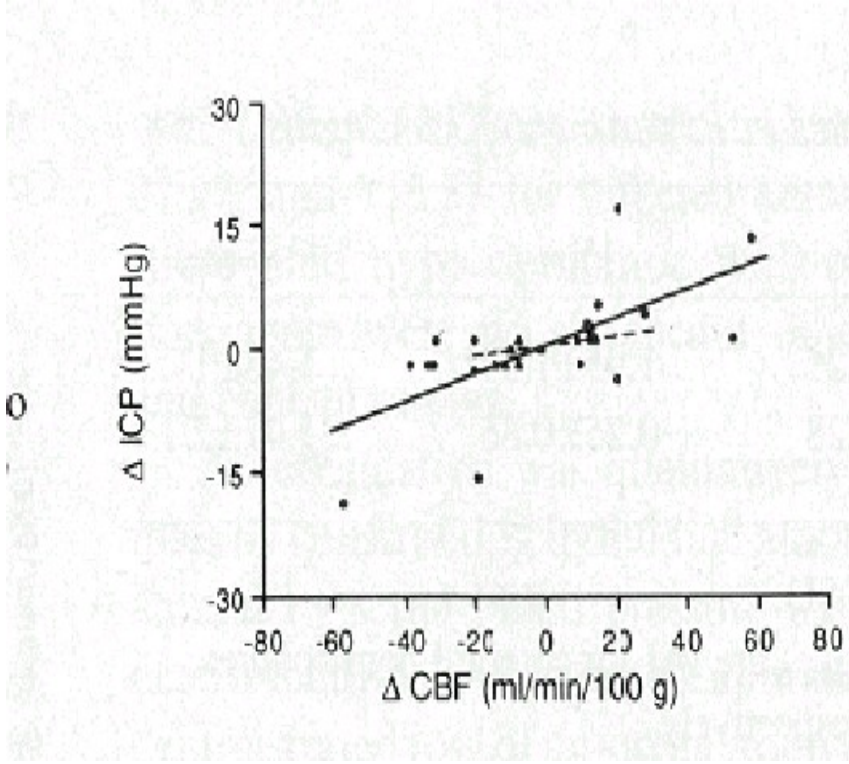
CBF was pressure passive with MABP through a range of 30-120 tor

Cerebral autoregulation

Experimental Meningitis - Rabbits

Tureen et al, 1990

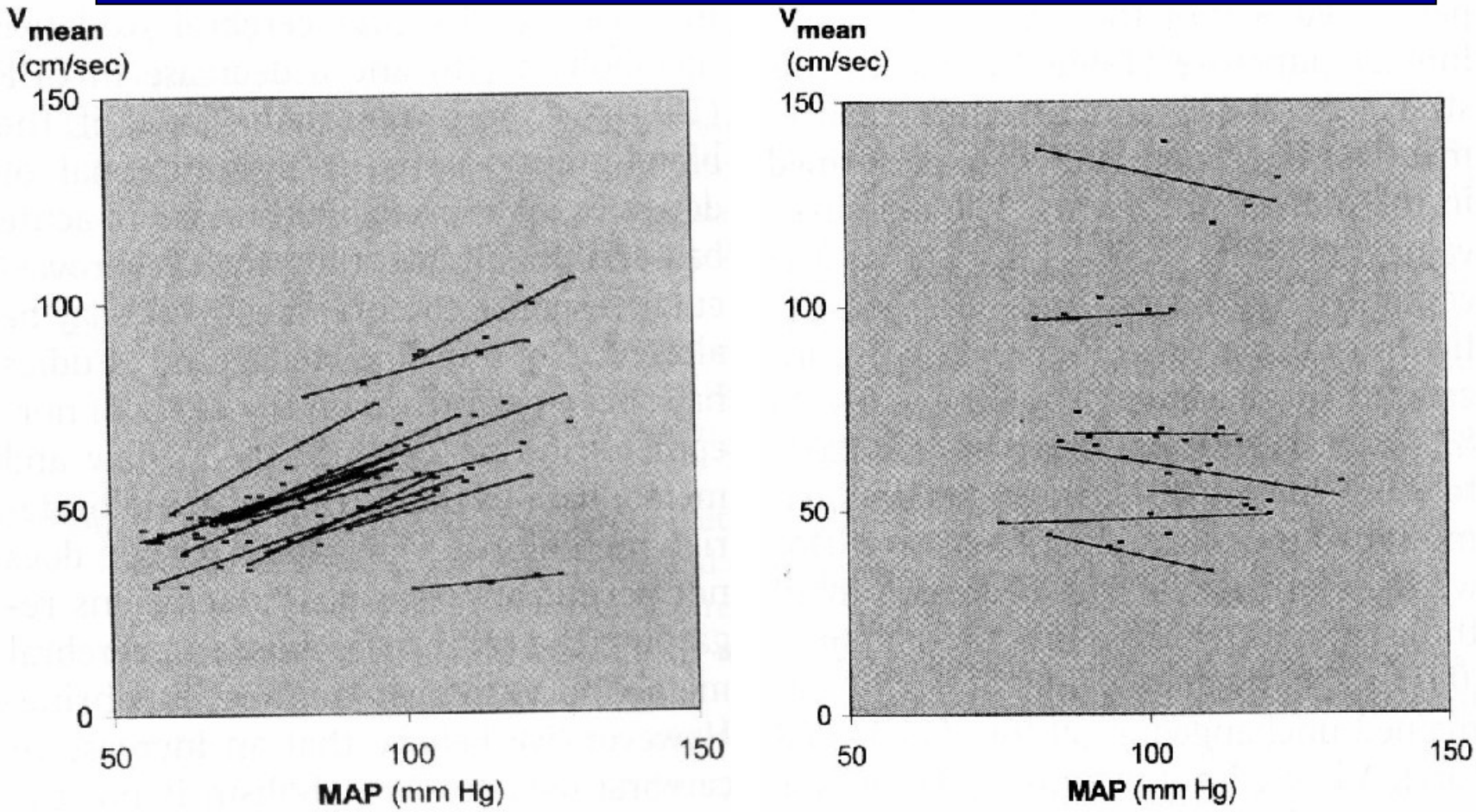




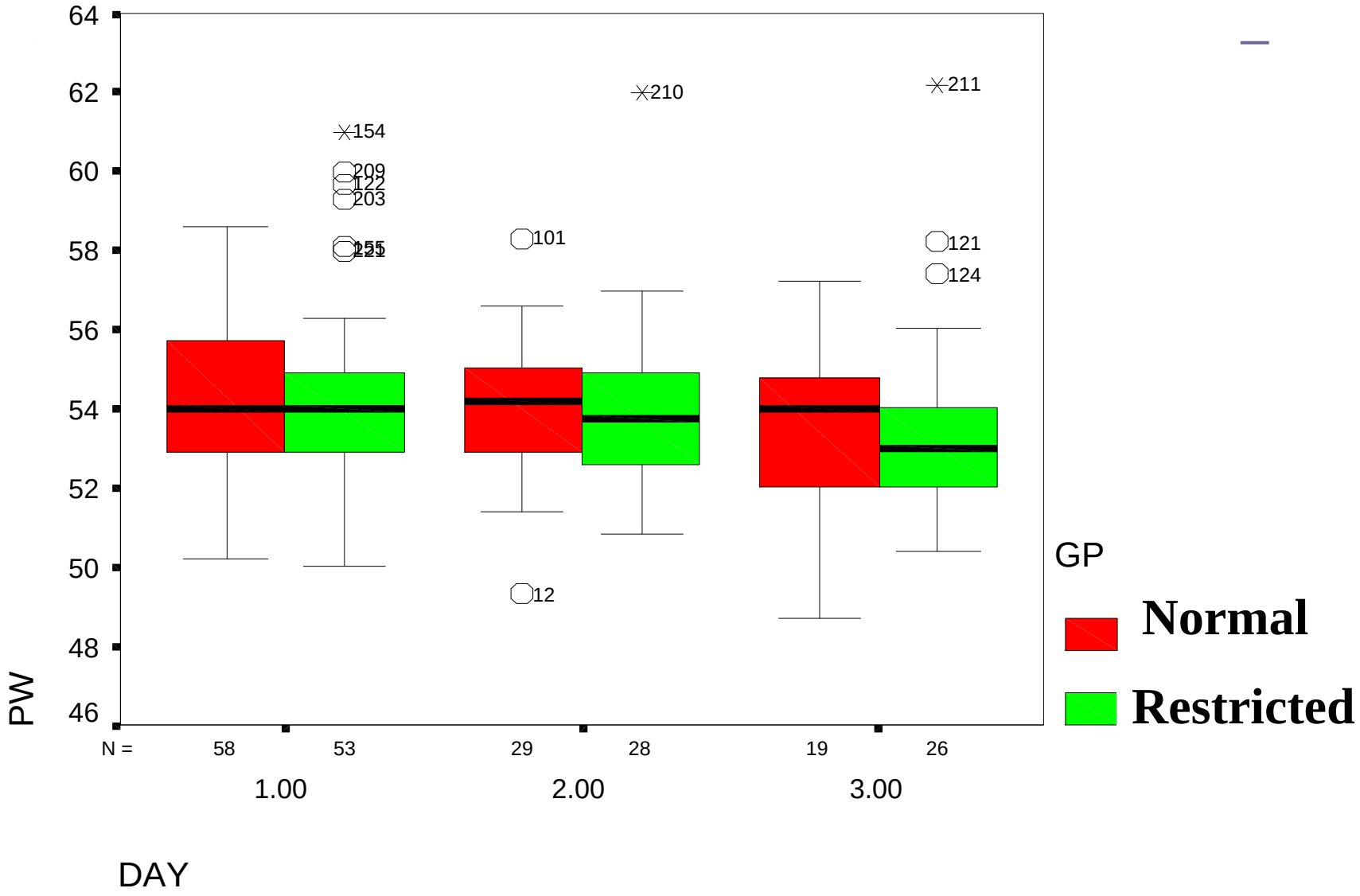
Critical dependency of C.Perfusion on systemic BP

Cerebral autoregulation

(Moller et al, Crit Care Med 2000)



Fluid Restriction Causes Hypovolemia



Fluid Therapy

(Duke T et al, Annals of Tropical Pediatrics 2002; 22: 145-157)

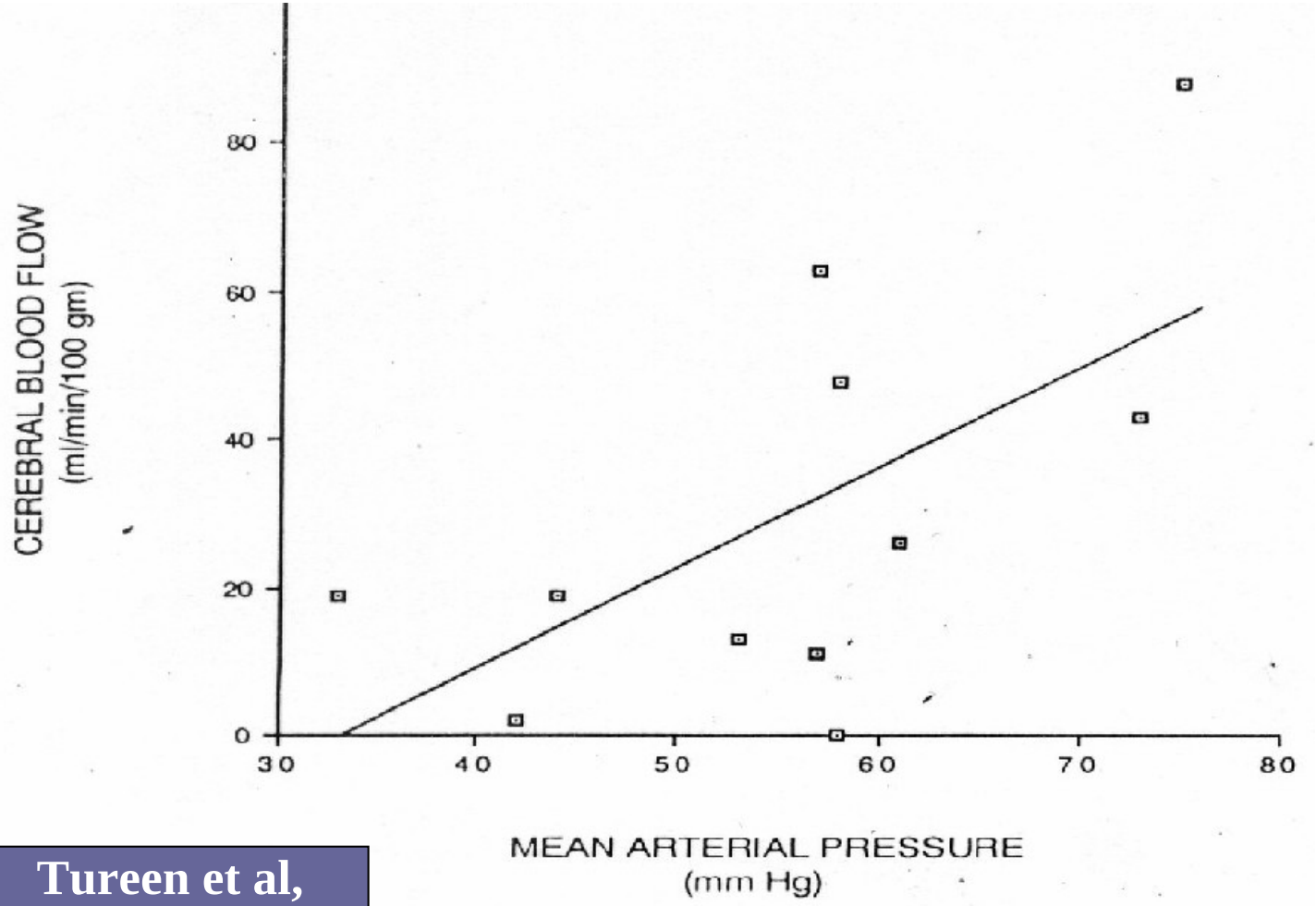
- Probability of an adverse outcome was 24.7% in the intravenous group and 33.1% in the oral-restricted group (RR 0.75, 0.53-1.04, p=0.08).
- Sunken eyes or reduced skin turgor at presentation were risk factors for an adverse outcome (OR 5.70, 95% CI 2.87-11.29) and were most strongly associated with outcome in the fluid-restricted group.

Outcome of patients with respect to plasma volume (PW) decrease on day 3 as compared to day 1

Fluid Group	n	Outcome	
		Survived	Died
Normal fluids			
❑PW-decreased	15	11 (73.3%)	**4 (26.7%)**
❑PW- Increased/same	56	48 (85.7%)	8 (14.3%)
Restricted fluids			
❑PW-decreased	24	14 (58.3%)	**10 (41.7%)***
❑PW- Increased/same	38	35 (92.1%)	3 (7.9%)

*P<0.05, Chi-square test

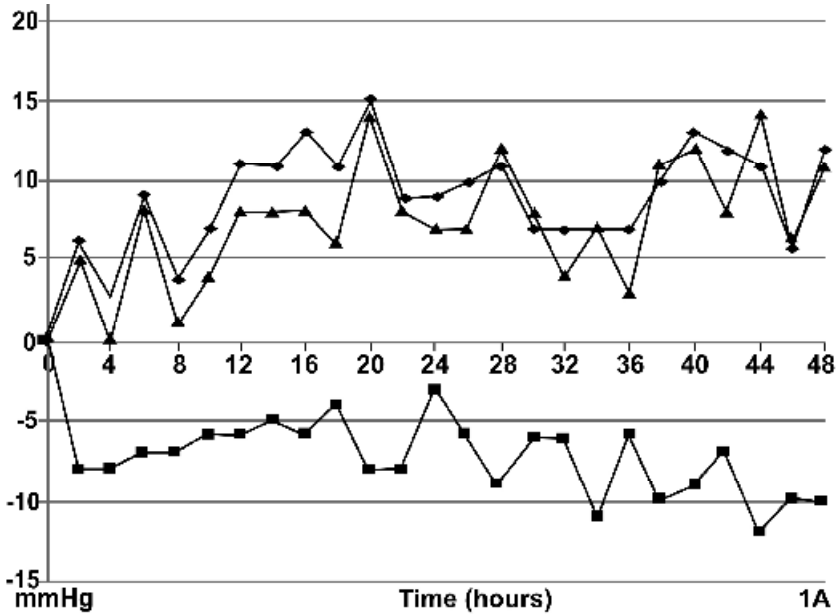
BP & CBF in Meningitis

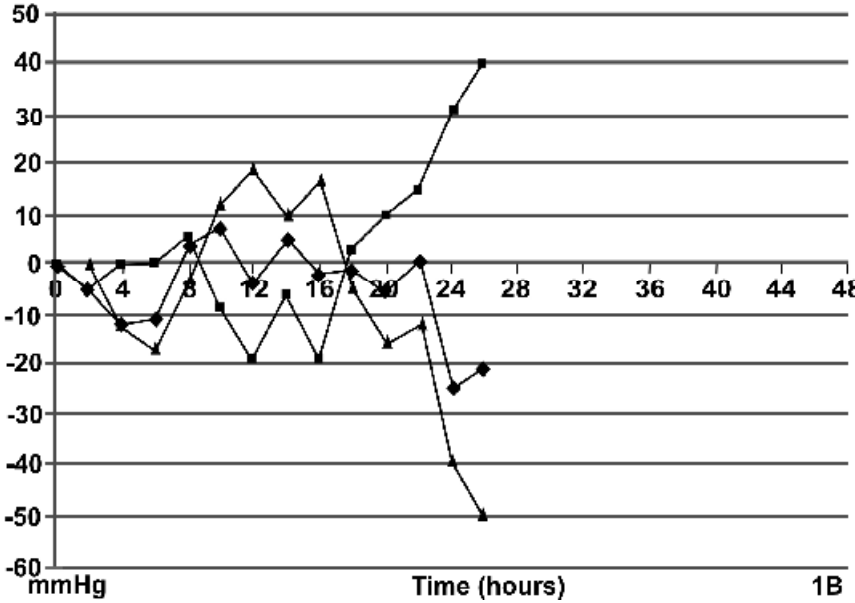


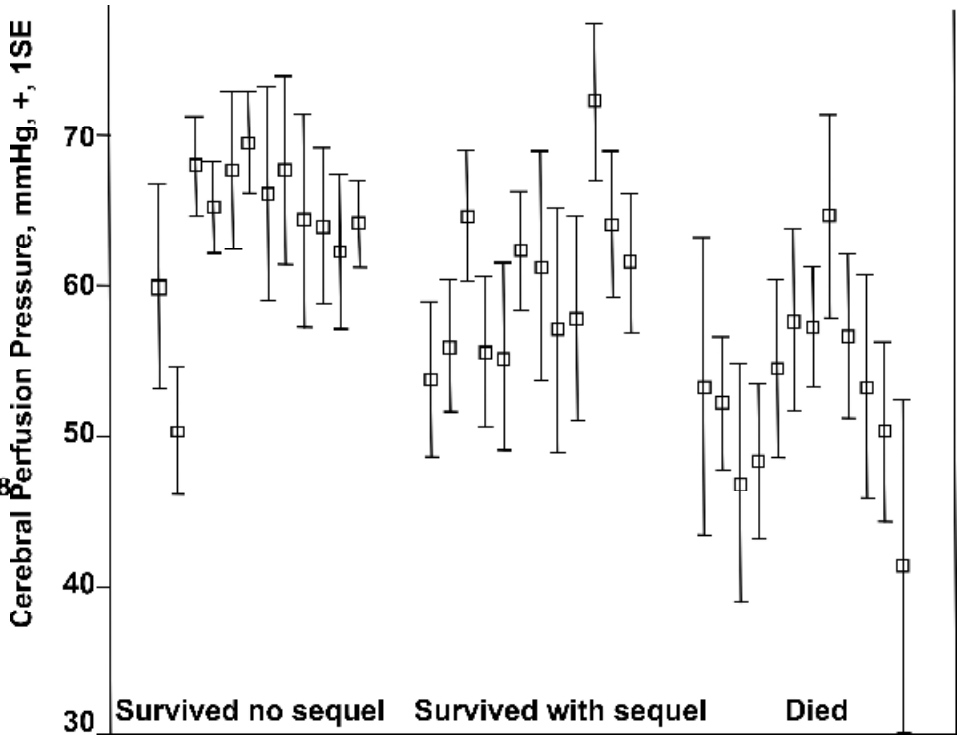
**Tureen et al,
J Clin Inv 1992**

CPP targeted therapy

J Child Neurol 2007, in press







Thankyou