PIDSP 19th Annual Convention

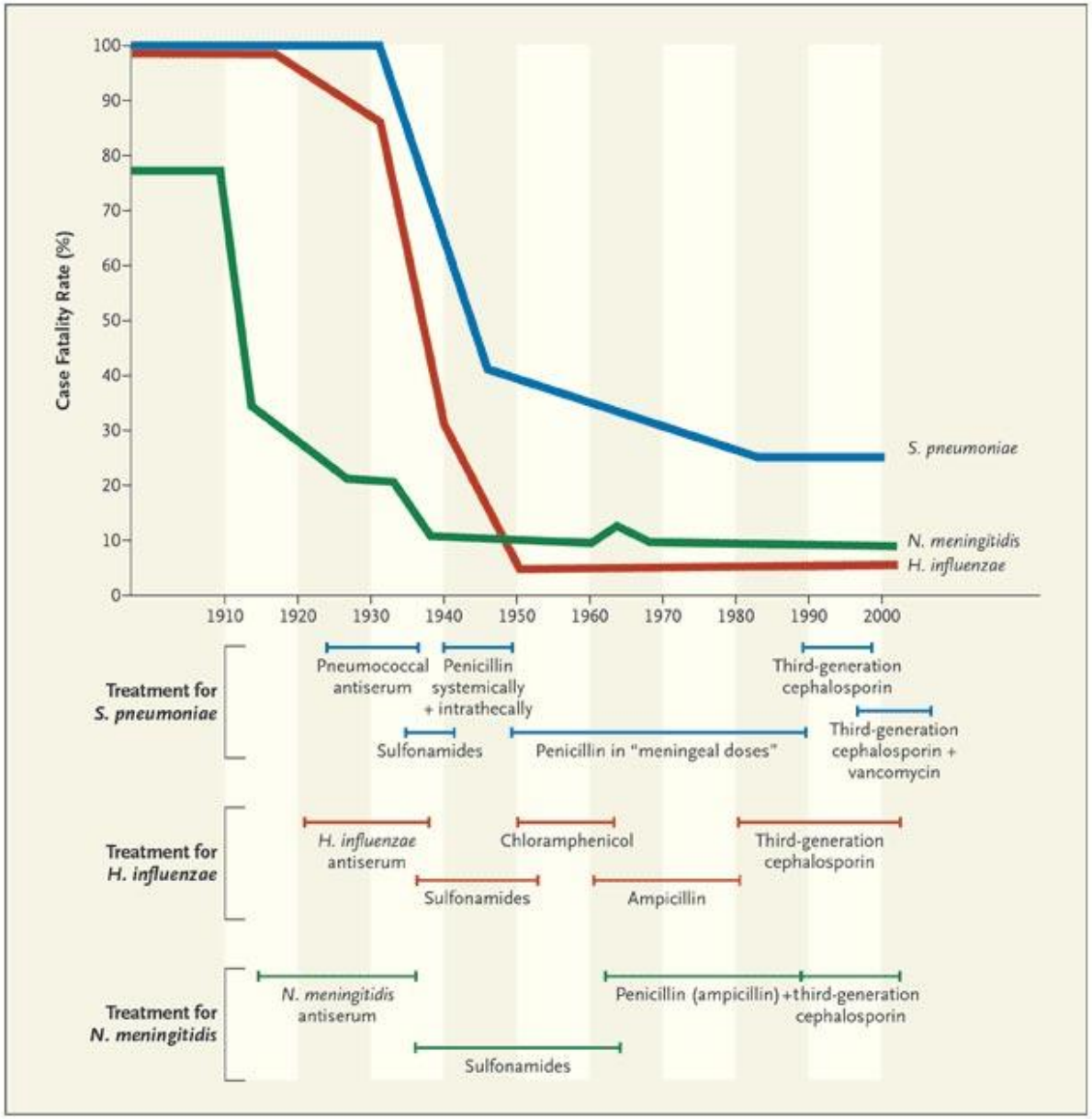
February 16, 2012

CNS INFECTIONS : Spotlight on Bacterial Meningitis

MARISSA B. LUKBAN, MD, FPPS, FPNA, FCNSP
University of the Philippines - College of Medicine
Department of Pediatrics and Neurosciences

Objectives:

- To present the epidemiological picture of bacterial meningitis worldwide and locally (Philippine General Hospital)
- To review the clinical practice guideline on the performance of lumbar puncture in children with a first febrile seizures
- To highlight the various ancillary tests available in the diagnosis of bacterial meningitis
- To discuss the current recommendations on antibiotic management of bacterial meningitis



Case Fatality Rates

Bacterial Meningitis – A View of the Past 90 years (1910-2000)

Swartz, NEJM 2004

Active Bacterial Core Surveillance

Whitney
NEJM 2003

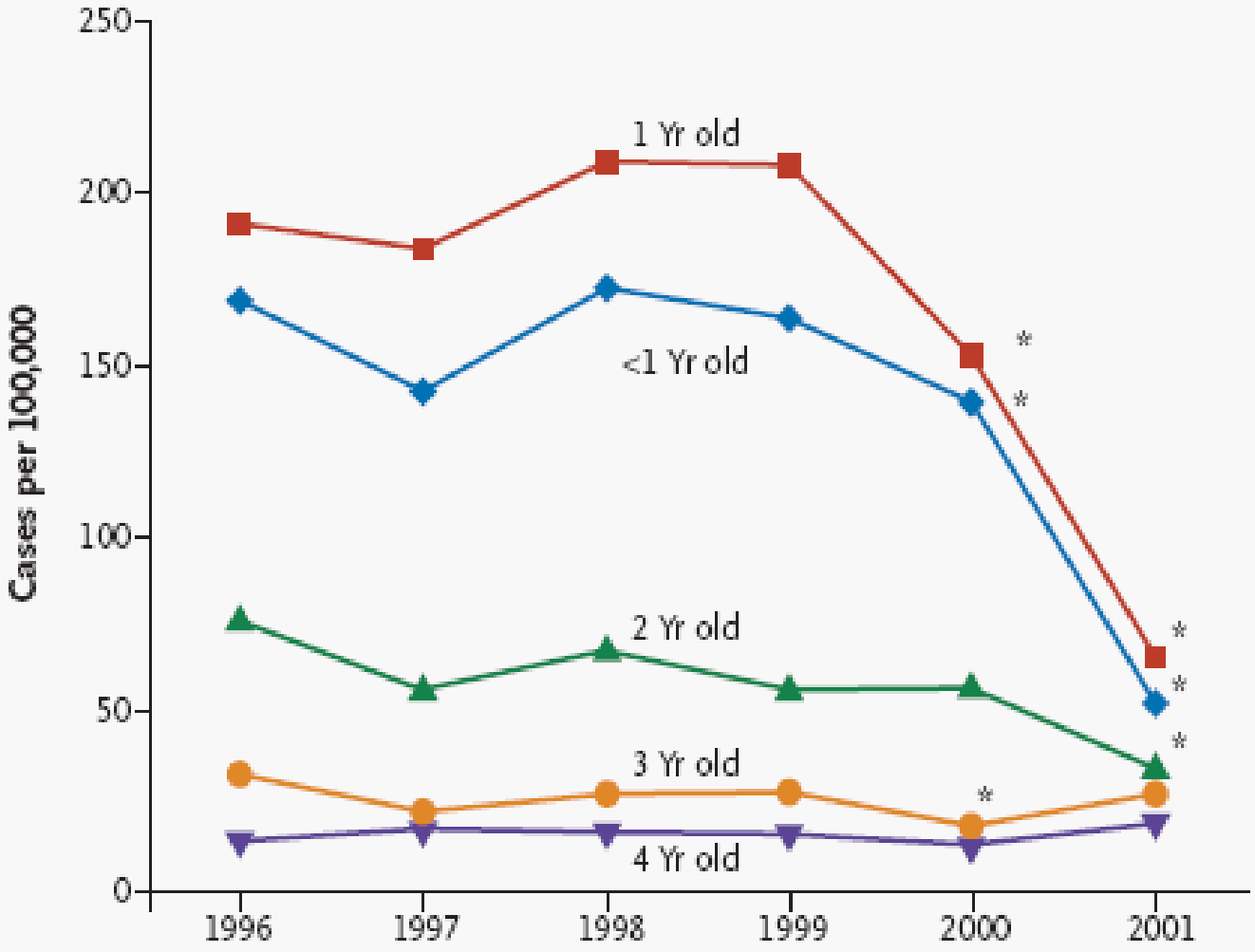


Figure 1. Rates of Invasive Pneumococcal Disease among Children under Five Years Old, According to Age and Year.

TABLE 1. Incidence of meningitis caused by *Haemophilus influenzae* type b in children aged 0 to 5 years in selected areas of the world before and after introduction of conjugate vaccines[a]

Geographic area (yr of comparison)	No. of cases/100,000 population	
	Prevaccination	Postvaccination
United States (1987 vs 1995)	54	<1
Canada (1985 vs 1994)	~44	<1
Brazil (1988–1996 vs 1997)	22	10
Chile (1995 vs 1998)	40	<2
Uruguay (1992-1993 vs 1995)	17–22	1
Scandinavia (1970s vs 1995)	31	<1
Austria (1991 vs 1993–1996)	11	<1
Netherlands (1970s vs 1993-1994)	22–40	0.3
Spain (1993–1995 vs 1997)	14	~0
Switzerland (1976–1990 vs 1991–1993)	25	8
United Kingdom (1991-1992 vs 1993-1994)	15	0.6
Israel (1989–1992 vs 1995)	18	<1
Australia (1991-1992 vs 1993-1994)	21	6
The Gambia (1990–1993 vs 2002)	60	0
Kenya (2000-2001 vs 2004-2005)	66	7.6
Malawi (1997–2002 vs 2005)	20–40	0
Uganda (2001 vs 2003–2006)	42	<3

Brouwer 2010

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

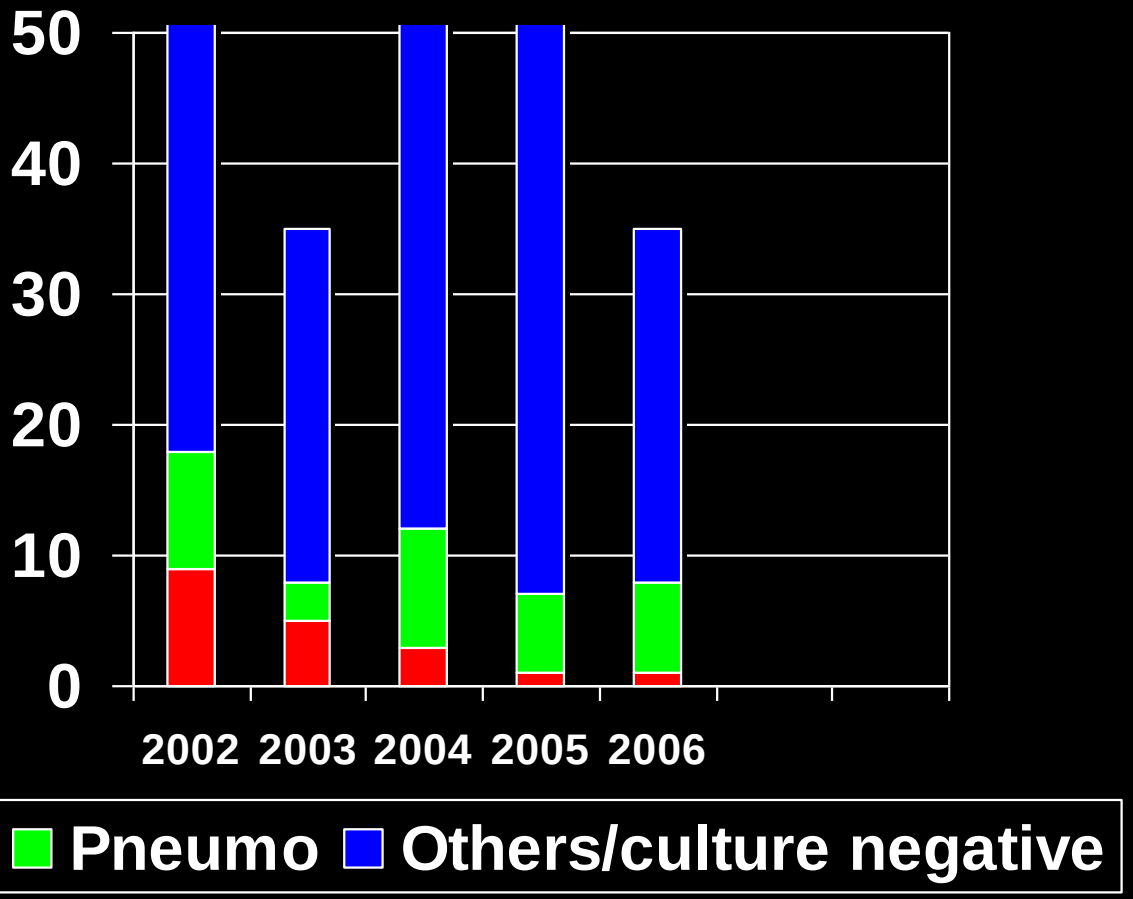
Bacterial Meningitis in the United States, 1998–2007

Michael C. Thigpen, M.D., Cynthia G. Whitney, M.D., M.P.H., Nancy E. Messonnier, M.D., Elizabeth R. Zell, M.Stat., Ruth Lynfield, M.D., James L. Hadler, M.D., M.P.H., Lee H. Harrison, M.D., Monica M. Farley, M.D., Arthur Reingold, M.D., Nancy M. Bennett, M.D., Allen S. Craig, M.D., William Schaffner, M.D., Ann Thomas, M.D., Melissa M. Lewis, M.P.H., Elaine Scallan, Ph.D., and Anne Schuchat, M.D., for the Emerging Infections Programs Network

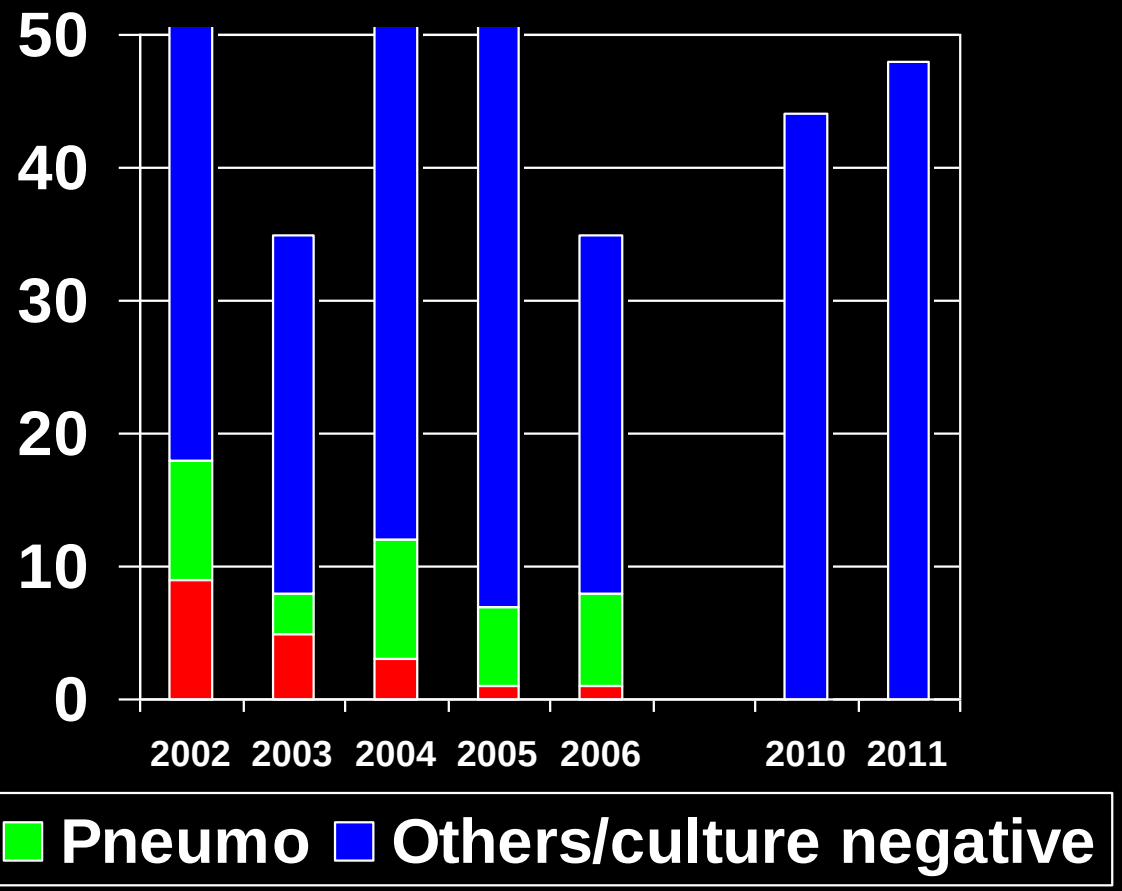
- **3188 pts with Bacterial Meningitis;466/3155 (14.8%) died**
- **31% DECREASE in incidence comparing 1998-99 vs 2006-07**
- **Median age: INCREASE from 30.3 yrs vs 41.9 yrs**
- **Most common organism: Strep Pneumoniae, Group B Strep, Neisseria, Hemophiluns influenze, Listeria**

Thigpen NEJM 2011

Frequency Distribution of Bacterial Meningitis in Philippine General Hospital 2002-2006 (5 year survey)



Philippne General Hospital
Department of Pediatrics
Inpatient Census (2010-2011)

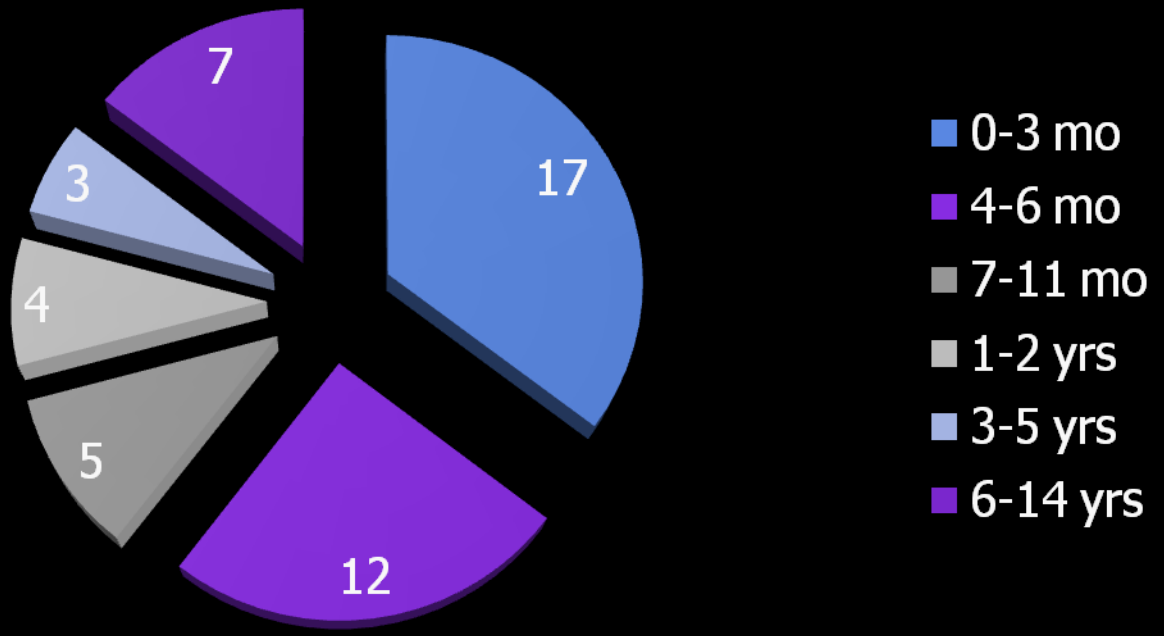


Philippine General Hospital Department of Pediatrics Inpatient Census (2011)

- 116 in patient admissions with meningitis
  - 63 (54%) pts with tuberculous meningitis
  - 46 (39%) pts with bacterial meningitis
  - 7 (6%) pts with viral/aseptic meningitis

Philippine General Hospital Department of Pediatrics Inpatient Census (2011)

60% are 6 months and below
70.8% are less than age 1 year



Diagnostic Examinations

To diagnose bacterial meningitis CSF examination is mandatory. CSF culture is the "gold standard" for diagnosis and it is obligatory to obtain the in vitro susceptibility of the causative organism to rationalize treatment

Van de Beek, NEJM, 2006

PPS/PNA/CNSP 2004 Clinical Practice Guideline on the first Febrile Seizure

Clinical Question: Among children with a first febrile seizure, is lumbar puncture recommended to rule out meningitis

- **CSF analysis is not the test that confirms the diagnosis of febrile seizure per se**
- **CSF analysis is the gold standard for the alternative diagnosis of meningitis**
- **AGE plays a crucial role in decision to do lumbar puncture**

Local Studies on the prevalence of bacterial meningitis in children presenting with a first febrile seizure

- **Mangubat & Robles (East Avenue Medical Center)**
  - **Retrospective study of 198 children aged 3 months to 6 years – 1% prevalence**
- **Dilangalen & Perez (Cotabato Regional and Medical Center)**
  - **Retrospective study of 339 children – 7% prevalence**

Local Studies on the prevalence of bacterial meningitis in children presenting with a first febrile seizure

- **San Nicolas & Lukban (Philippine General Hospital)**
  - **Prospective study on validity indices of clinical parameters in predicting lumbar puncture yield of children with febrile seizures -11/50 (22%) abnormal CSF suggestive of meningitis**
  - **Discrimate factors in the clinical signs and symptoms that differentiate children with meningitis (70% identified)**
    - **Complex febrile seizure**
    - **Fever of more than 3 days**
    - **Vomiting or drowsiness at home**
    - **Physician visit in past 48 hours**

Significant Clinical Parameters associated with Bacterial Meningitis

- duration of fever of more than 3 days
- the presence of anorexia, vomiting and sleep disturbances
- a physician consult within 48 hours prior to seizures
- the presence of ear discharge
- abnormal neurologic findings like nuchal rigidity and focal signs
- depressed level of consciousness and
- occurrence of seizures at the Emergency Room.

Philippine Clinical Practice Guideline on the first Febrile Seizure
RECOMMENDATION STATEMENT

Lumbar puncture is strongly recommended for children below 18 months for a first simple febrile seizure.

For those children >/= 18 months of age, lumbar puncture should be performed in the presence of clinical signs of meningitis (meningeal signs, sensorial changes)

Diagnostic Examinations: The CSF

Relationship between serum and CSF glucose is highly linear For every increase of 1 mg/dl of serum glucose, CSF glucose levels increase by 0.56 mg/dl (95% CI 0.56-0.57 R2 0.94)

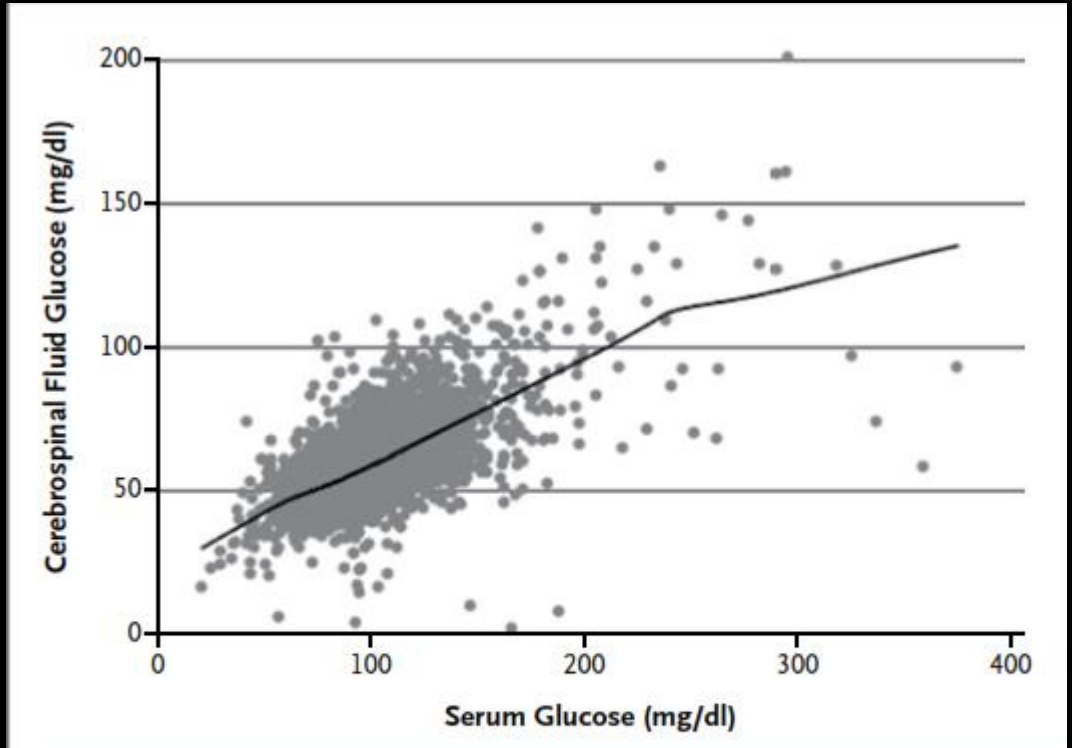
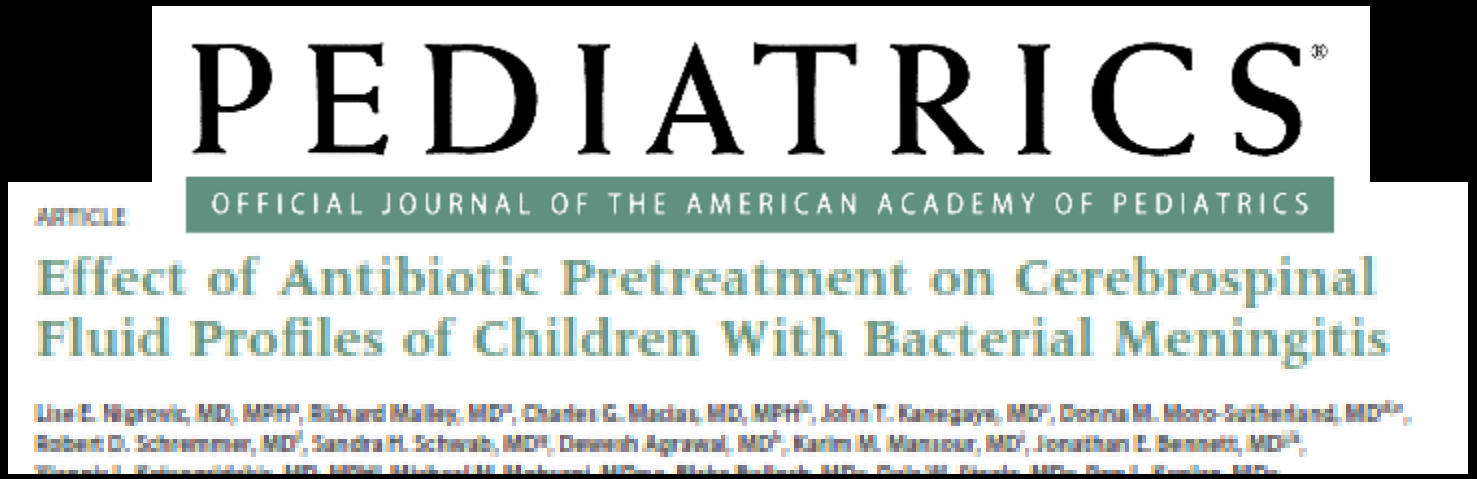


Figure 1. The Relationship between Levels of Glucose in Serum and Cerebrospinal Fluid in Children 18 Years of Age or Younger.

Ratios were calculated with the use of locally weighted scatterplot smoothing (bandwidth, 0.8) for children with serum glucose levels of 400 mg per deciliter or less.

Nigrovic, NEJM, 2012

The Cerebrospinal Fluid Exam



PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

ARTICLE

Effect of Antibiotic Pretreatment on Cerebrospinal Fluid Profiles of Children With Bacterial Meningitis

Lisa E. Nigrovic, MD, MPH[a], Richard Malley, MD[a], Charles G. Macias, MD, MPH[b], John T. Kanegaye, MD[a], Donna M. Moro-Sutherland, MD[a,c], Robert D. Schremmer, MD[d], Sandra H. Schwab, MD[a], Deepak Agrawal, MD[b], Karim M. Mansour, MD[e], Jonathan E. Bennett, MD[a,b],

20 USA ER Departments 2001-2004

Antibiotic pretreatment = received within 72 hrs from LP

- Rates of positive gram stain did not differ
- Rates of positive CSF and blood cultures less
- Not associated with total WBC and neutrophil count
- Increased glucose and decreased protein content

Nigrovic 2008

Ancillary Diagnostic Examinations

- Gram staining
- Blood Culture
- Latex Agglutination – antisera directed against capsular polysaccharide of meningeal pathogen
- PCR – presence of bacterial DNA in CSF
- Skin biopsy
- Serum inflammatory markers
  - Increased serum procalcitonin
  - Increased C reactive protein

Pathogen	Sensitivity (%)[a]			
	Blood culture	CSF Gram stain	Latex agglutination test[b]	PCR
Haemophilus influenzae	25–90	25–65	78–100	72–92
Streptococcus pneumoniae	60–90	69–93	59–100	61–100
Neisseria meningitidis	40–60	30–89	22–93	88–94
Listeria monocytogenes	10–75	10–35	NA	NA
Streptococcus agalactiae	80–85	80–90	NA	NA
Streptococcus pyogenes	60–65	66–73	NA	NA
Streptococcus suis	50	50	NA	99
Staphylococcus aureus	75–100	20–44	NA	NA

Sensitivities of various diagnostic tests to determine microbial etiologies of patients with community acquired bacterial meningitis

Brouwer 2010

Prognostic Factors related to Sequelae and Poor Outcome

- Presence of seizures
- Low CSF glucose
- High CSF protein
- Absence of rash
- Positive blood culture
- Etiology – Pneumococcal and Meningocoocal

Vasilopoulou, Greek Meningitis Registry
BMC Infectious Disease 2011

RECOMMENDATIONS ON TREATMENT

- Based on subgroups according to age and common organisms
- Guided by prevailing antibiotic susceptibility and resistance in the region
- Generics Law
- Clinical setting
  - Malnutrition
  - Finances
  - Access to vaccination

CLINICAL SUBGROUP	EMPIRIC THERAPY	PREDOMINANT ORGANISMS
NEONATE, EARLY ONSET	Ampicillin 150 mkday [q8h] plus Gentamicin 5mkday [q12h] or Cefotaxime 100-150mkday [q8-12] or Ceftriaxone 80-100mkday [q12-24h]	S. Agalactiae, E. Coli, Listeria Monocytogenes
NEONATE, LATE ONSET	Ampicilllin 200mkday [q6-8h] plus Gentamycin 7.5 mkday [q 8h] or Cefotaxime 150-200 mkday [q6-8h]	S. Agalactiae, L. monocytogenes , Gram negative bacilli
INFANTS AND CHILDREN	Cefotaxime 225-300 mkday [q6-8h] or Ceftriaxone 80-100 mkday [q12-24h] plus vancomycin 60mkday [q6h]* (if with high cephalosporin resistance)	S. Pneumoniae, N. meningitidis

CLINICAL SUBGROUP	EMPIRIC THERAPY	PREDOMINANT ORGANISMS
ADULTS	Expanded spectrum cephalosporin plus Vancomycin 30–60 mkday [q8-12h] *	Strep Pneumoniae, Neisseria Meningitidis
ELDERLY AND IMMUNO-COMROMISED	Expanded spectrum cephalosporin plus ampicillin 12g/day [q4h] plus Vancomycin 30 60mkday [q 8-12h]*	S. Pneumoniae, N. Meningitidis L. Monocytogenes
COMMUNITY ACQUIRED RECURRENT	Expanded spectrum cephalosporin plus Vancomycin 30–60 mkday [q 8-12h]*	S. Pneumoniae, N. Meningitidis, H. Influenzae
NOSOCOMIAL	Vancomycin 30-45 mkday [q 8-2] plus Ceftazidime 6g/day [q 8h] or Meropenem 6g/day [q 8h]	S. Aurerus, S Epidermidis, aerobic gram negative bacilli

MICROORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPY
HEMOPHILUS INFLUENZAE		
B LACTAMASE (-)	Ampicillin	Ceftriaxone/Cefotaxime; Cefipime; Chloramphenicol; Aztreonam; Fluroquinolone
B LACTAMASE (+)	Ceftriaxone/ Cefotaxime	Cefipime; Chloramphenicol; Aztreonam; Fluroquinolone
BLNAR	Ceftriaxone/ Cefotaxime plus Meropenem	Ceftriaxone/Cefotaxime plus Fluroquinolone
		Brouwer 2010

MICROORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPY
STREPTOCOCCUS PNEUMONIAE		
PENICILLIN MIC <0.1 UG/ML	Penicillin G or Ampicilllin	Ceftriaxone/ Cefotaxime; Chloramphenicol
PENICILLIN MIC 0.1-1.0 UG/ML	Ceftriaxone/ Cefotaxime	Meropenem; Cefipime
PENICILLIN MIC >2.0UG/ML	Vancomycin plus third gen cephalosporin	Ceftiaxone/ Cefotaxime plus moxilocaxin
STREPTOCOCCUS PYOGENES	Penicillin	Ceftriaxone/ Cefotaxime
STREPTOCOCCUS AGALACTIAE	Ampicillin or Penicillin G (may need to add aminoglycoside)	Ceftriaxone/ Cefotaxime

Brouwer 2010

MICROORGANSIM	STANDARD THERAPY	ALTERNATIVE THERAPY
NEISSERIA MENINGITIDIS		
PENICILLIN MIC < 0.1 UG/ML	Penicillin G or Ampicillin	Ceftriaxone/ Cefotaxime; Chloramphenicol
PENCILLINE MIC 0.1-1 UG/ML	Ceftriaxone/ Cefotaxime	Chloraphenicol; Fluroquinolone; Meropenem

Brouwer 2010

MICROORGANISM	STANDARD THERAPY	ALTERNATIVE THERAPY
STAPHYLOCOCCUS AUREUS		
METHICILLIN SENSITIVE	Oxacillin or nafcillin	Vancomycin, Meropenem, Linezolid, Daptomycin
METHICILLIN RESISTANT	Vancomycin	Trimethoprim-Sulfa; Linezolid; Daptomycin
STAPHYLOCOCCUS EPIDERMIDIS	Vancomycin	Linezolid

Brouwer 2010

Vital Role of Pediatricians

- There remains a lot to be done to replicate the success of high-income countries in decreasing the incidence of bacterial meningitis thru wide spread vaccination in resource-poor countries like the Philippines.

- There is a need for local government initiatives to make vaccinations more accessible to all beyond the EPI program.

Vital Role of Pediatricians

- **The pediatrician is strategically situated as he/she can act as an advocate for the prevention of meningitis and is the key to averting the disastrous complications of this disease thru early recognition and appropriate management.**

Thank you