

Management of neonatal meningitis

Dr Paul T Heath

Paediatric Infectious Diseases Unit /

Vaccine Institute

St. George's, University of London.

Incidence of neonatal bacterial meningitis

| Location | Period | Incidence /1000 live births | < 2500g |
|---------------|---------|--------------------------------|---------|
| Leeds | 1947-60 | 0.5 | |
| USA (NIH) | 1959-66 | 0.46 | 1.36 |
| California | 1962-87 | 0.3 | 2.8 |
| E+W | 1985-7 | 0.2 | 2.5 |
| Oxford Region | 1984-91 | 0.25 | |
| E+W | 1996-7 | 0.2 | 1.7 |

~ 250 cases / year in the UK

| | | | |
|----|---------|---|--|
| UK | 2010-11 | ? | |
|----|---------|---|--|

Etiology of neonatal bacterial meningitis (% of cases)

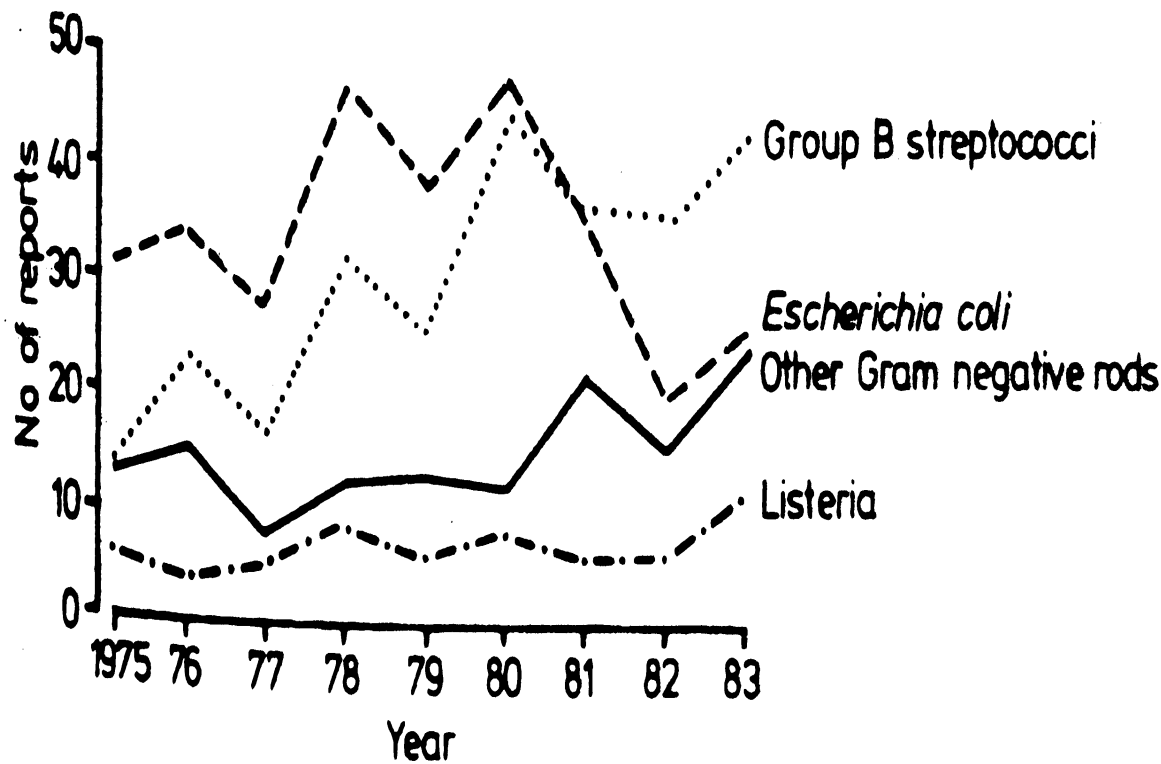


FIG 3—Organisms implicated in cases of neonatal meningitis.

| | E+W 1985-7 | E+W 1996-7 | UK 2010-11 |
|--------------------------|---------------|---------------|---------------|
| Group B streptococci | 39 | 48 | |
| Escherichia coli | 26 | 18 | ? |
| Other Gram negative rods | 12 | 8 | |
| Listeria | 6 | 6 | |
| | 7 | 5 | |

Etiology of neonatal bacterial meningitis

12 neonIN units 2006-8 (neonin@sgul.ac.uk)

| | |
|---------------|---|
| GBS | 7 |
| E coli | 7 |
| CoNS | 3 |
| Enterobacter | 2 |
| S aureus | 1 |
| Pseudomonas | 1 |
| Enterococcus | 1 |
| Citrobacter | 1 |
| Acinetobacter | 1 |
| Diphtheroids | 1 |
| S. viridans | 1 |

- 26 infants
 - 5 < 48h; 21 > 48h
 - median GA 29 wk;
 - median Bwt 1320g
- 0.19/1000 live births
 - 1.7/1000 neonatal admissions

Neonatal meningitis: mortality

- E+W 1985-7:

- GBS 27/112 = 22% overall 25%

- E coli 18/72 = 25%

(Arch Dis Child 1991;66:603-7)



- E+W 1996-7:

- GBS 8/69 = 12%

overall 10%

- E coli 4/26 = 15%

(Arch Dis Child Fetal Neonatal Ed 2001;84:F85-9)

- UK 2000-1:

- GBS 16/109 = 12%

(Lancet 2004;363:292-4)

Neonatal meningitis: disability at 5 years of age

| | 1985-7 n = 274 | 1996-7 n = 166 |
|----------|-------------------|-------------------|
| severe | 7% | 5% |
| moderate | 18% | 18% |
| mild | 24% | 26% |
| none | 50% | 51% |

Long term consequences of infection in premature babies

Table 3. Neurodevelopmental Outcomes From Univariate Analyses by Infection Group vs Uninfected Infants

| Outcomes | No./Total (%) With Outcome by Infection Group* | | | | |
|--------------------|--|--------------------|----------------|-----------------|-----------------------------------|
| | Uninfected | Clinical Infection | Sepsis Alone | Sepsis Plus NEC | Meningitis With or Without Sepsis |
| MDI <70 | 439/2003 (22) | 478/1428 (33)‡ | 661/1791 (37)‡ | 109/262 (42)‡ | 70/183 (38)‡ |
| PDI <70 | 250/1983 (13) | 345/1407 (25)‡ | 472/1762 (27)‡ | 87/258 (34)‡ | 49/183 (27)‡ |
| CP | 181/2144 (8) | 216/1520 (14)‡ | 328/1906 (17)‡ | 59/277 (21)‡ | 37/193 (19)‡ |
| Vision impairment | 115/2137 (5) | 165/1520 (11)‡ | 275/1893 (15)‡ | 45/275 (16)‡ | 31/193 (16)‡ |
| Hearing impairment | 21/2110 (1) | 29/1513 (2)† | 58/1882 (3)‡ | 13/271 (5)‡ | 3/191 (2) |
| NDI | 576/1976 (29) | 614/1419 (43)‡ | 861/1778 (48)‡ | 142/267 (53)‡ | 89/184 (48)‡ |

Abbreviations: CP, cerebral palsy; MDI, mental development index; NEC, necrotizing enterocolitis; NDI, neurodevelopmental impairment; PDI, psychomotor development index.

*Results were similar when infants whose birth weights were 401 to 750 g vs 751 to 1000 g were analyzed as separate groups. Information was missing on MDI for 426 children, PDI for 500, CP for 53, vision impairment for 75, hearing impairment for 126, and NDI for 469.

† $P \leq .05$ vs uninfected, by χ^2 test.

‡ $P \leq .001$ vs uninfected, by χ^2 test.

Neonatal meningitis: early recognition

- Non-specific and
- signs \equiv sepsis
- fever / hypothermia
distress (all > 50%)
bulging / full fontanel
- no data on timing
features often appear
a worse outcome

TABLE 2
Clinical features of septic babies without (n=30) and with (n=8) meningitis

| Features | Septic babies No. (%) | Meningitis cases No. (%) |
|----------------------|--------------------------|-----------------------------|
| Fever | 6 (20.0) | 3 (37.5) |
| Lethargy | 17 (56.7) | 5 (62.5) |
| Poor feeding | 20 (66.7) | 6 (75.0) |
| Convulsion | 18 (60.0) | 6 (75.0) |
| Respiratory distress | 12 (40.0) | 4 (50.0) |
| Apneic attack | 10 (33.3) | 4 (50.0) |
| Cyanosis | 5 (16.7) | 2 (25.0) |
| Jaundice | 15 (50.0) | 5 (62.5) |
| Bulged fontanel | 0 | 0 |
| High pitched cry | 0 | 0 |

- low level of consciousness at hospital admission is a predictor of poor outcome

Neonatal meningitis: diagnosis

- Non-specific clinical signs
 - L.P. needs to be a part of a routine screen -
.....but how often are LPs performed?
 - ASGNI: 1992-02: 3966 infants with sepsis; LP in 51%; meningitis in 8%.
(Arch Dis Child Fetal Neonatal Ed 2005;90:F324–F327)
 - Oxford: 1988-91, 42% admitted NNU had LP; 0.9% had meningitis
(Arch Dis Child 1993;69:514-7)

Neonatal meningitis: diagnosis

- LP only when blood culture +ve?
 - **BUT +ve CSF with -ve BC**
 - 6/39 (Visser et al)
 - 12/43 (Wiswell et al)
 - 35/92 (Garges et al)
 - 9/27 (Vergnano et al)

Neonatal meningitis: diagnosis

- normal CSF white cell count, glucose and protein levels does NOT preclude meningitis:
 - 9111 neonates had LP, 95 meningitis - 13% had normal CSF
(Pediatrics 2006;117;1094-1100)
- defer LP if shock / respiratory distress / signs ↑ICP
- pretreatment with antibiotics does not prevent diagnosis
 - those who received antibiotics 12 -72 h pre LP had significantly ↑ glucose and ↓ protein vs. those who did not receive them or received them < 4h **but no influence on CSF WBC**
(Pediatrics 2008;122:726–730)
- important role for non-culture methods of detection (PCR)
 - 62 cases with preRx: +ve culture 29%, +ve PCR 58%
(J infect Chemother 2009; 15:92-8)

Neonatal meningitis: Empiric antibiotic therapy

Requirements:

- Cover the most likely pathogens
- Excellent CSF penetration

| Organism | % |
|-------------------------------|--|
| Group B <i>Streptococcus</i> | 48 |
| <i>Escherichia coli</i> | 18 |
| <i>S. pneumoniae</i> | 6 |
| <i>Listeria monocytogenes</i> | 5 |
| <i>Neisseria meningitidis</i> | 4 |
| <i>H. influenzae</i> | <1 |
| Other Gram +ve | 12 (1 <i>S aureus</i> , 2 <i>S epi</i>) |
| Other Gram -ve | 8 (6 on NNU) |

Holt et al (2001)

Empiric antibiotic therapy

Community (NICE)* (50% of cases < 3 months of age admitted from home)

- amoxicillin + cefotaxime

Neonatal Unit*

- cefotaxime + amoxicillin + aminoglycoside;
consider vancomycin

- *ampicillin, cefotaxime and gentamicin resistance among *E. coli* isolates are increasing (61%, 12%, 8.5%) in 2007*
- earlier discharge policies from neonatal units
- Ex NNU neonates may have persistent colonisation with resistant bacteria after discharge

[J Clin Microbiol. 2008 Feb;46(2):560-7]

*Health Protection Agency. Antimicrobial Resistance and Prescribing in England, Wales and Northern Ireland, 2008. London: Health Protection Agency, July 2008.

Neonatal infections in Asia

Table 3 Sensitivities of Gram-negative organisms causing late-onset sepsis

| Organism | C ^S G ^S | C ^S G ^R | C ^R G ^S | C ^R G ^R (%) | Total |
|------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------------------------|-------|
| <i>Acinetobacter</i> species | 6 | 4 | 7 | 3 (15) | 20 |
| <i>Escherichia coli</i> | 14 | 1 | 5 | 5 (20) | 25 |
| <i>Enterobacter</i> species | 11 | 2 | 12 | 3 (11) | 28 |
| <i>Klebsiella</i> species | 35 | 2 | 2 | 31 (44) | 70 |
| <i>Proteus</i> species | 0 | 0 | 2 | 1 (33) | 3 |
| <i>Pseudomonas</i> species | 3 | 1 | 6 | 6 (37) | 16 |
| <i>Serratia</i> species | 9 | 0 | 1 | 3 (23) | 13 |
| Other Gram-negative bacilli | 1 | 0 | 2 | 2 (40) | 5 |
| Total | 79 (44%) | 10 (6%) | 37 (21%) | 54 (30) | 180 |

C, third-generation cephalosporin (cefotaxime or ceftazidime for *Pseudomonas*); G, gentamicin; S, sensitive; R, resistant.

Neonatal meningitis: Empiric antibiotic therapy

- Infection with *L. monocytogenes* is rare; ~ 5% of cases
- Most cases are <7 days of age, in premature infants and are related to maternal infection.
- Traditionally, pregnancy-associated *L. monocytogenes* has been considered up to 3 months of age.
- Current epidemiological data indicate nearly all pregnancy-associated cases present clinically in the first month of life.
 - of 72 cases of listeria meningitis diagnosed between 1990 and 2007, only 1 occurred at > 4 weeks of age*
- Optimal therapy for this pathogen requires a penicillin.

Neonatal meningitis:

Empiric antibiotic therapy: current UK practice

- 45% include a cephalosporin
 - In 12%, cephalosporin as monotherapy
- 19% do not include any penicillin
- 5% (11) used a triple combination
(cephalosporin + a penicillin + aminoglycoside)

Neonatal meningitis: antibiotic therapy (NICE evaluation)

- No RCTs were found comparing antibiotics currently used to treat meningitis in infants younger than 3 months.
- No RCTs were found that evaluated the optimal duration of antibiotic treatment for bacterial meningitis in infants younger than 3 months.

Neonatal meningitis: role for new antibiotics?

European multicenter network of Meropenem in neonatal sepsis and meningitis (NeoMero)

- evaluate the PK, safety and efficacy of meropenem in comparison to standard care in neonates and infants aged <3 months with late-onset sepsis
- evaluate its PK and safety in bacterial meningitis

Adjunctive therapy (sepsis)

Immunoglobulin

- Systematic review

(Ohlsson, Lacy. Cochrane Database Syst Rev. 2004(1):CD001239.)

- 7 RCT`s = 262 neonates with proven infection
- mortality
 - RR 0.55 (0.31-0.98); NNT 11 (5.6-100)
- “insufficient evidence to support routine IVIG for treatment: further research needed”
 - INIS study (<http://www.npeu.ox.ac.uk/inis>)

Adjunctive therapy (sepsis)

G- or GM - CSF

- RPCT: VLBW, clinical sepsis + neutropenia = safe; mortality 1/13 vs 7/15 at 12 mo

(Arch Dis Child Fetal Neonatal Ed 2001;84:F172-176)

- prophylaxis for reduction of sepsis in <32 week, small for gestational age neonates (PROGRAMS trial): no benefit.

(Lancet. 2009;373(9659):226-233)

Neutrophil infusions?

Combinations: neutrophils + IVIG?, G-CSF + IVIG?

Adjunctive therapy (meningitis)

- Corticosteroids?
 - Review of 47 cases, chloro / sulpha / strep, 1953-61, Sydney: 64% enteric GNB (no GBS)
 - Mortality 41% CS vs 75% no CS (p=0.05)

(Arch Dis Child 1963; 38:391:6)

Adjunctive therapy (meningitis)

- Corticosteroids?
 - Study of 52 cases: dex vs no dex
 - (1st dose pre ab), cefotaxime + ampicillin; 1993-5, Jordan: 79% enteric GNB (3 cases GBS).
 - Mortality 22 % CS vs 28% no CS; CNS deficit 30% vs 39% (NS) (Eur J Ped 1999;158:230-3).
- Oral glycerol?
 - Recent paediatric study indicates better outcome than dexamethasone (Clin Infect Dis 2007;45:1277-86).

Neonatal meningitis: risk factors for poor outcome

.....pathogen, prematurity

| E.Coli (85/14) | OR (death) |
|--------------------------|------------|
| Hypotension on admission | 8.4 |
| Hypotension @ 12h | 36 |
| Seizures @ 12 h | 11 |

Clin Microbiol Infect 2008; 14: 685–690

| All (256/18) | OR (death) |
|-------------------|------------|
| Coma on admission | 11 |

Arch. Dis. Child. Fetal Neonatal Ed. 2001;84;85-89

| GBS (237/39) | OR (death) |
|--------------|------------|
| shock | 23 |
| coma | 16 |
| Seizures | 6 |

Archives de Pédiatrie 2008 ;15:S126-S132

| GBS (76/5) | OR (death) |
|----------------------|------------|
| Shock @ presentation | 24 |
| ↓ platelets | 42 |

J Maternal-Fetal and Neonatal Medicine 2008; 21(1): 53–57

| All (76/25) | p (adverse outcome) |
|-------------|---------------------|
| hypotension | <0.001 |
| coma | <0.001 |
| inotropes | <0.001 |
| seizures | <0.001 |

Pediatrics 2000;106:477– 482

Improving the outcome from neonatal infection

- The goal of circulatory support in shock is the maintenance of oxygenation and adequate tissue perfusion; the priority in achieving this is fluid resuscitation to restore intravascular volume.
 - strict and early goal-directed fluid resuscitation, vasopressor therapy and transfusion of adults with severe sepsis
(N Engl J Med 2001;345:1368-77)
 - early aggressive fluid resuscitation in children
(JAMA 1991;266:1242-5)
 - delayed reversal of shock associated with worse outcome; every hour of failure to reverse shock results in doubling of risk of death
(Pediatrics 2003;112:793-9)
- No high-quality studies were found assessing initial fluid therapy in neonates with suspected or confirmed bacterial meningitis (NICE).

Improving the outcome from neonatal infection

- Better management
 - Earlier recognition
 - Appropriate empiric antibiotics
 - Newer antibiotics?
 - Better supportive care?
 - Adjunctive therapy?
- Prevention
 - Chemoprophylaxis (IAP): GBS
 - GBS vaccines? (SPn vaccines) (Ecoli vaccines)
 - Infection control

Bacterial meningitis in babies <90 days of age:
defining the current burden of disease and
identifying opportunities for improving the outcome.
(NEOMEN)

Objectives:

To define

- the minimum incidence of meningitis in the UK and Ireland;
 - the bacterial pathogens (and the antibiotic resistance profiles);
 - the clinical presentation;
 - the mortality and short-term complication rates of meningitis;
 - the current management.
-
- To identify opportunities for improving the outcome through detailed analysis of early case management relative to an evidence based optimal standard.

