CNS Infection Cases
Part 1 : acute meningitides

Dr John Ferguson

jferguson@hnehealth.nsw.gov.au

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Infection types

- subarachnoid space (“meningitis”) ; confirmed by presence of WC in the CSF (adult > 5 cells /uL), neonate > 25 cells/uL
- generalized or focal involvement of brain tissue in the cerebral hemispheres, cerebellum, or brainstem.
  - when brain tissue is directly injured by a viral or other infection is referred to as “encephalitis,”
  - focal bacterial, fungal or parasitic infections involving brain tissue are classified as either “cerebritis” or “abscess,” depending on the presence or absence of a capsule.

Clinical syndromes

- Timing: Acute vs Subacute vs Chronic presentations
- Presentations
  - Headache with meningism (photophobia, neck stiffness)
  - Confusion / decreased level of consciousness / seizure
  - Febrile convulsion (infant)
- Differential diagnosis
  - Infective: primary CNS or secondary CNS involvement (e.g. embolus from endocarditis or bacteraemic metastatic abscess)
  - Non-infective

CSF Examination

- Appearance
- Biochemistry : glucose, protein
- Cell count
- Gram stain
- India ink
- [Rapid antigen detection (*S. pneumoniae*, *Cryptococcus*)
- Culture, identification, susceptibility tests
- PCR (if available)

Patterns of CSF findings

3: Typical profiles of cerebrospinal fluid in acute meningitis and encephalitis

Investigation	Reference range	Meningitis		Encephalitis
		Bacterial	Viral	
Opening pressure	< 30 mmH_2O	Raised	Normal	Increased
White cells				
Total count	< 5 x 10^6/L	Greatly increased	Moderately increased	Moderately increased
Differential	Lymphocytes (60%–70%), monocytes (30%–50%), no neutrophils or red blood cells	Neutrophils predominate	Lymphocytes predominate	Lymphocytes predominate
Glucose concentration	2.8–4.4 mmol/L	Decreased	Normal	Normal
CSF : serum glucose ratio	> 60%	Decreased	Normal	Normal
Protein concentration	< 0.45 g/L	Increased	Normal or slightly increased	Normal or slightly increased

CSF = cerebrospinal fluid.

A low glucose predicts bacterial meningitis

Glucose ratio CSF to blood works even better (<0.6)!

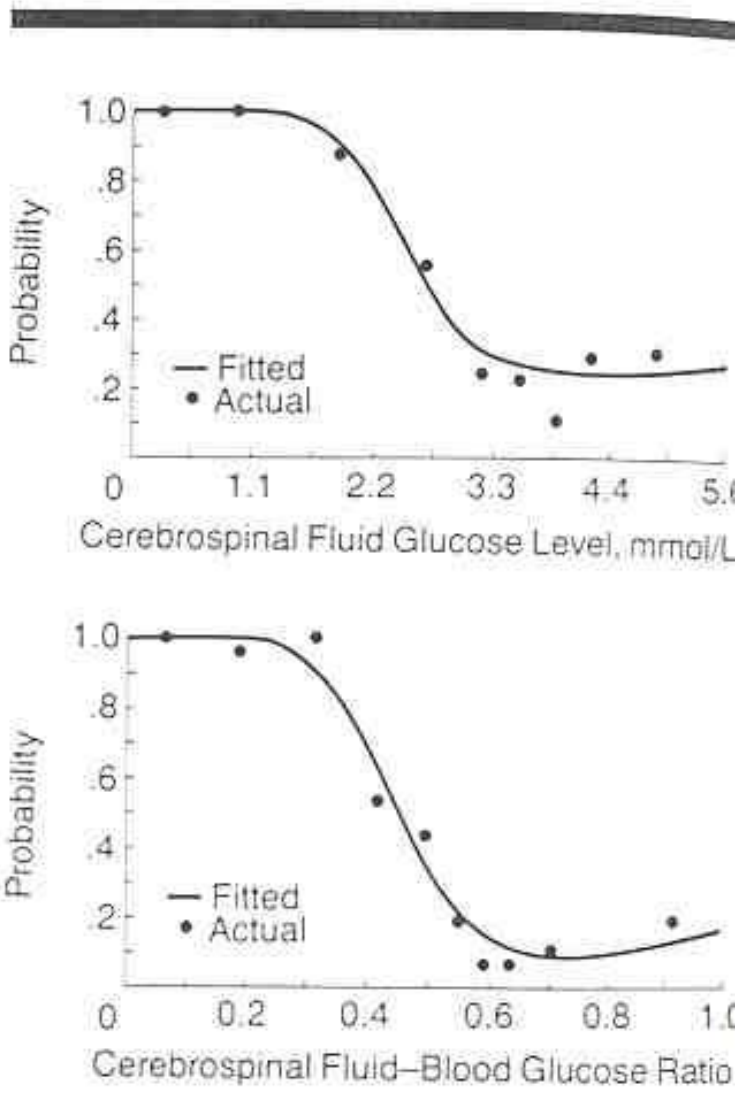


Fig 3.—Probability of bacterial vs viral meningitis as a function of cerebrospinal fluid glucose (top) and cerebrospinal fluid–blood glucose ratio (bottom).

Spanos et al 1989 JAMA n=422 cases

The higher the protein level , the more likely it is bacterial meningitis

However there are other potential causes for high CSF protein

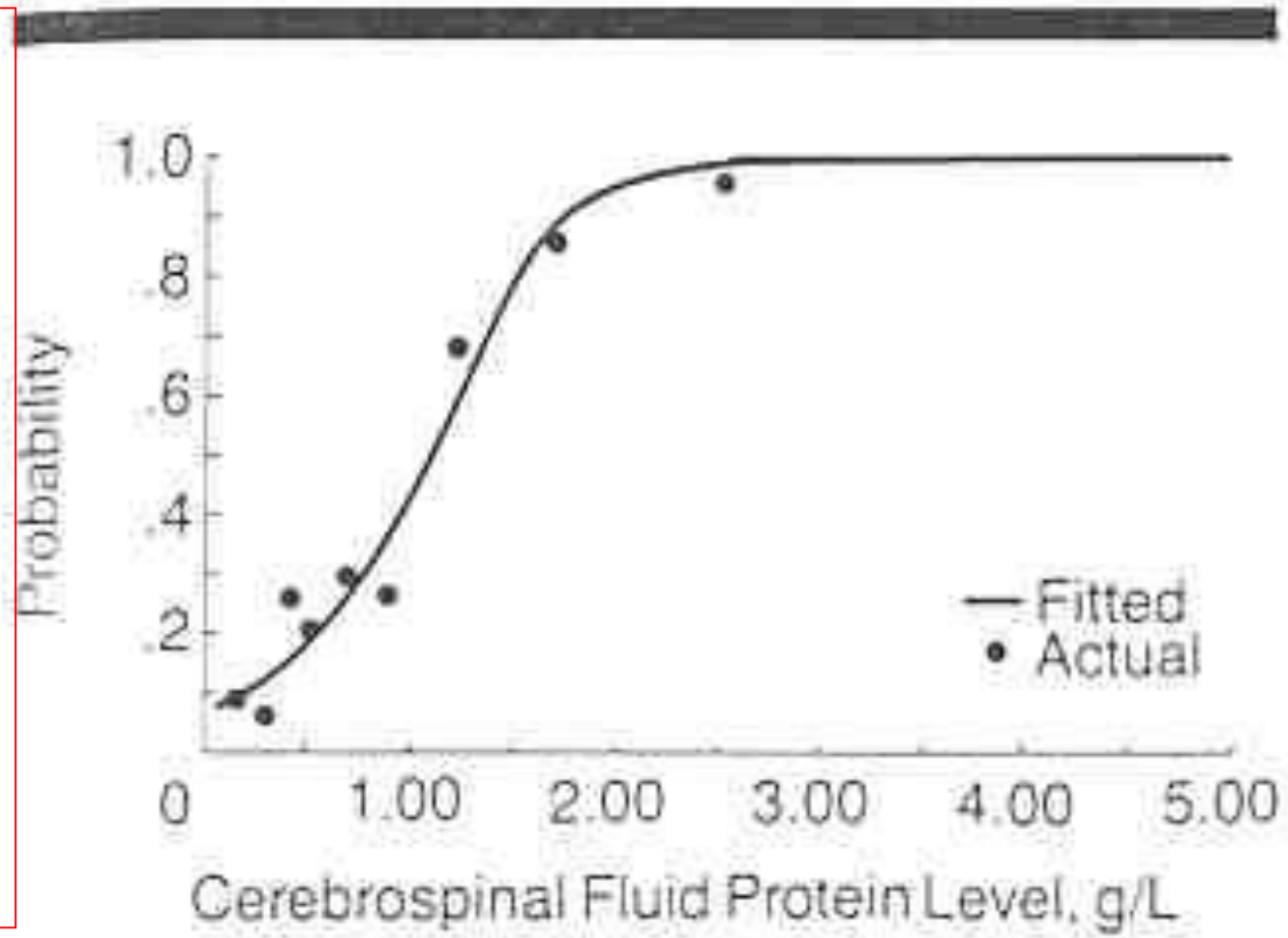


Fig 4.—Probability of bacterial vs viral meningitis as a function of cerebrospinal fluid protein.

ACUTE MENINGITIS

PNG considerations (non-viral) causes-

Streptococcus pneumoniae (‘pneumococcus’)

*Neisseria meningitidis (‘*meningococcus*’)*

Haemophilus influenzae type B (children < 5 yrs)

Syphilis

Cryptococcus neoformans (acute or chronic presentations)

Neonatal meningitis –Gram negative – *E. coli*, *Salmonella* or Gram positive- Streptococci, *Listeria*

Rarely:

[*Angiostrongylus cantonensis* – acute or chronic presentations (eosinophilic meningitis)

[*Naegleri fowleri* – amoebic meningitis – see Australian reference

CNS Case 1: 24yr old male with headache , photophobia, neck stiffness and pharyngitis; no antibiotics given. No rash.

FBC: WCC 16.2 x 10^9/L (14.4 neutrophils, 0.9 lymphocytes, 0.9 monocytes), platelet count normal

CSF : clear fluid

- white cells 13 x 10^6/L (12% polymorphs)
- red cells 15 x 10^6/L
- Gram stain: no organisms seen
- protein 0.92 g/L (normal <0.4)
- glucose 3.6mmol/L

Q1. *What do you think is going on? Interpret the CSF findings*

Q2. How can a microbiological diagnosis be confirmed?

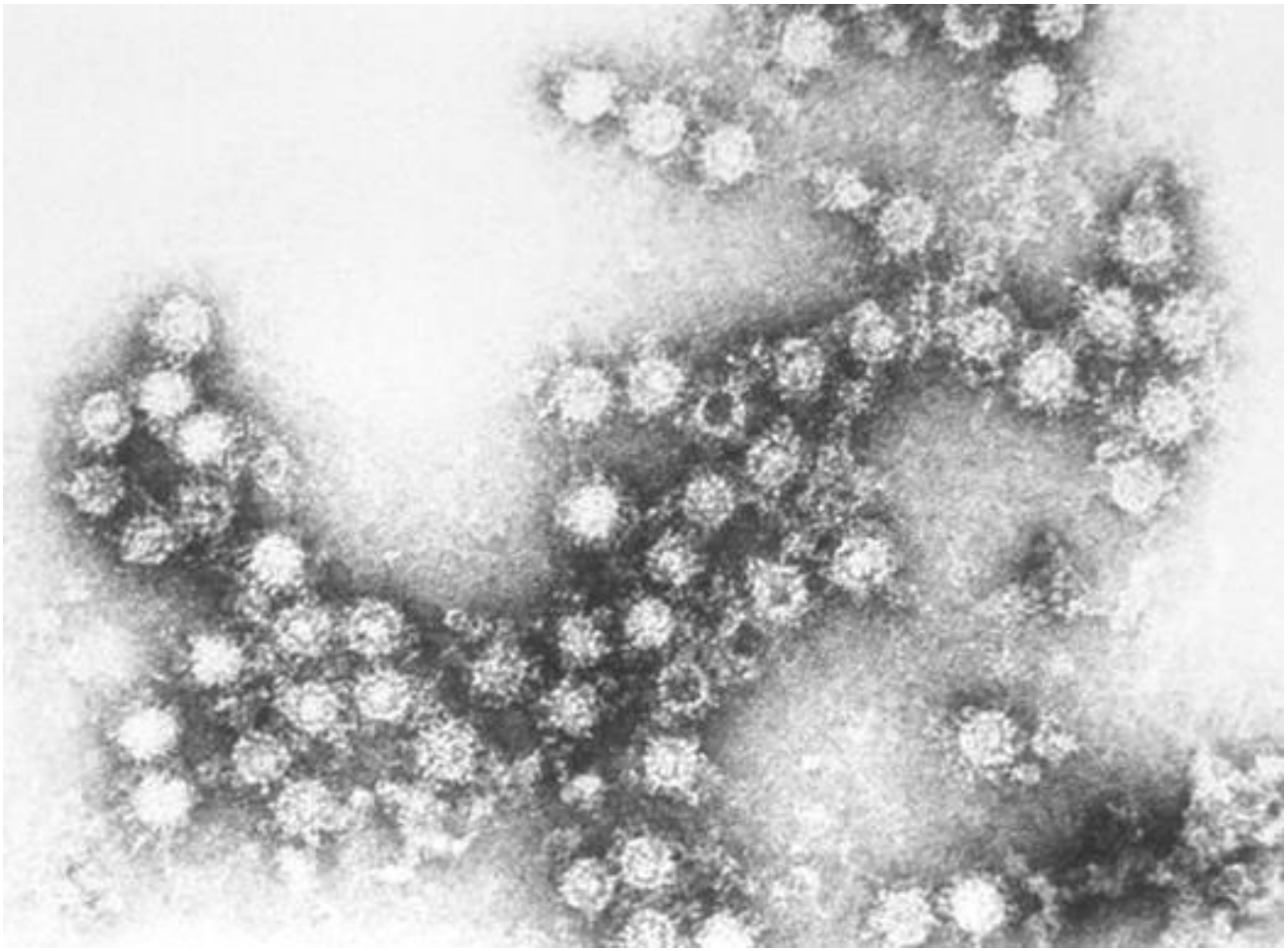
Q3. What management would you give?

CNS1: question answers

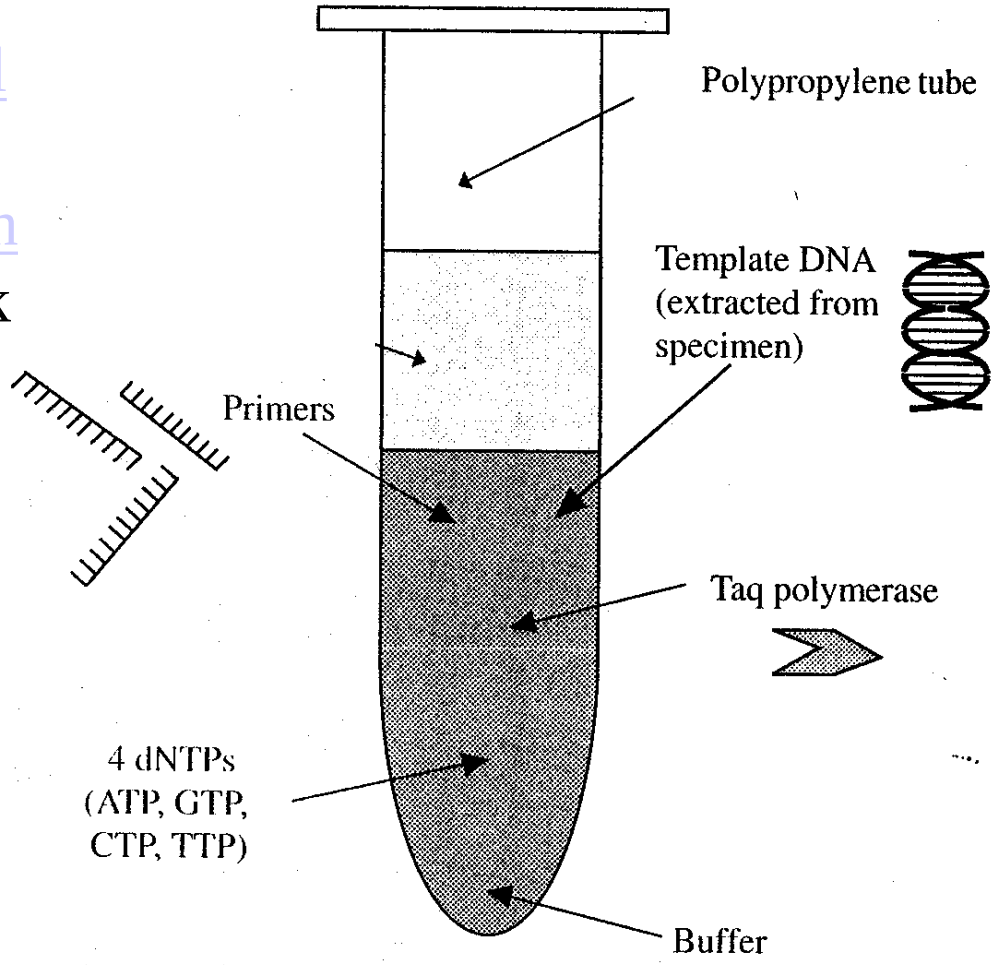
1. This is a typical picture for ‘aseptic’ meningitis. Always measure blood glucose at the same time as the CSF- the ratio of csf/blood is more discriminatory. See graph later on. Enteroviral infection tends to present in summer months in temperate countries; year round in PNG.
2. With findings such as these, one can be very confident that this is viral and further confirmation not really required. However direct antigen detection for enterovirus with PCR can be done. This test was positive.
3. It would be acceptable to treat this patient symptomatically and withhold antibiotics. Most patients get better over 1-2 weeks. No antiviral treatment available.

Another potential causes of this picture is HIV seroconversion.

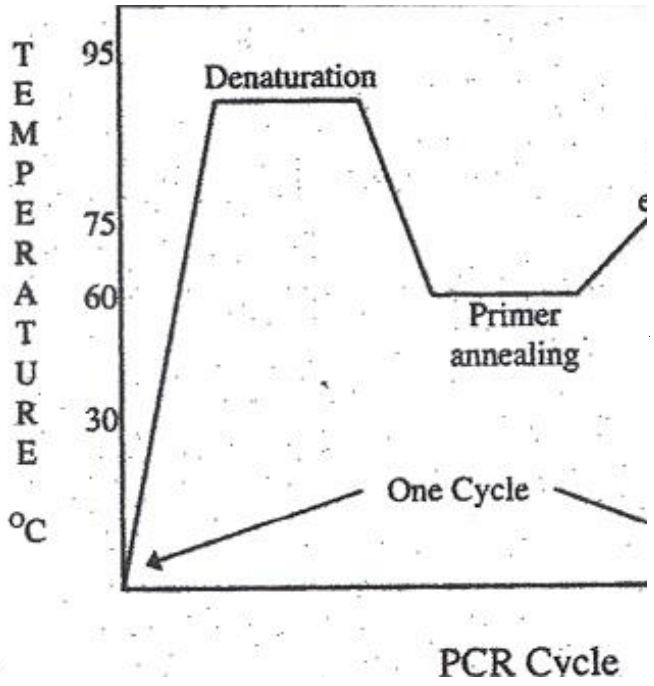
EM: enteroviruses- small RNA viruses, no envelope



http://www.dnalc.org/resources/animations/pcr.html See this link for an excellent animation of PCR

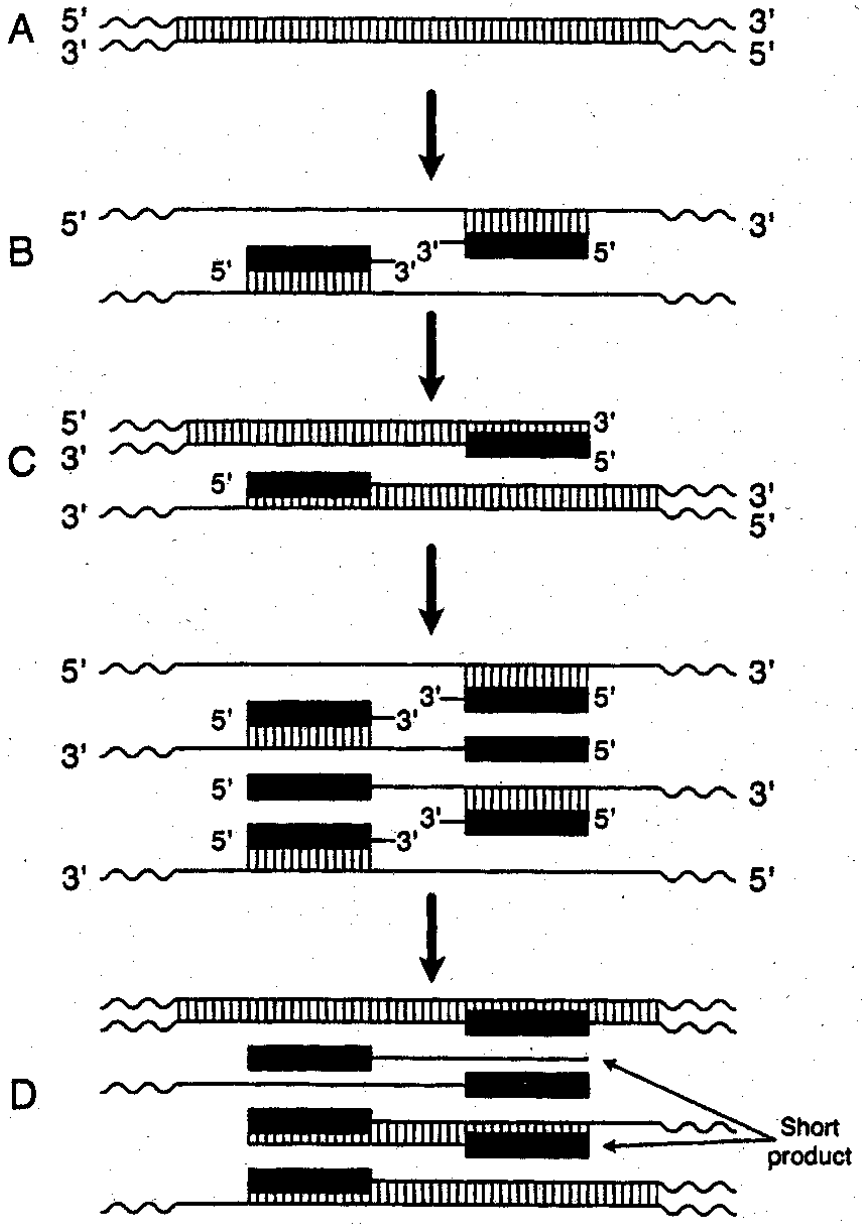


Constituents of PCR



Polymerase chain reaction

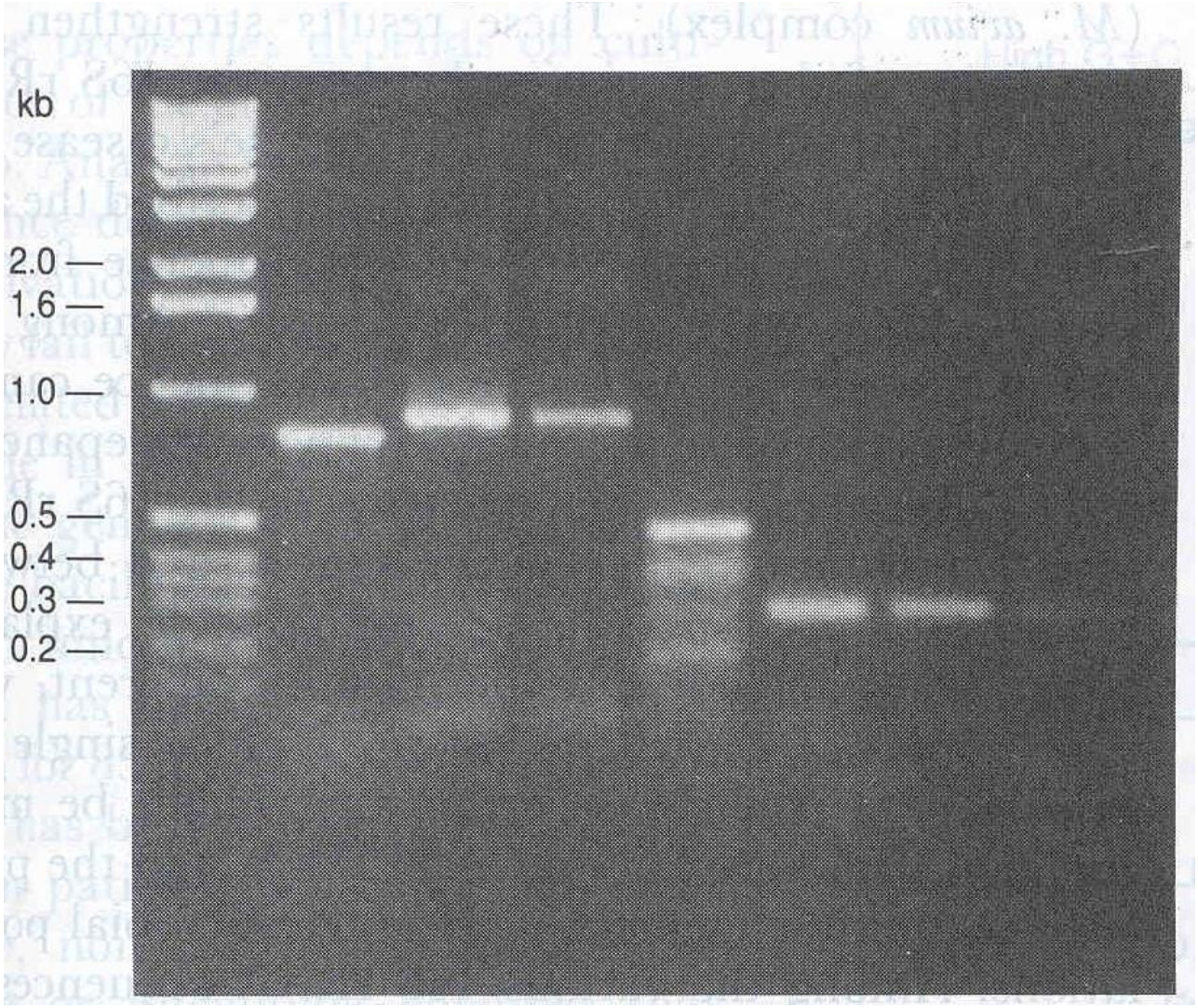
Mullis-K 1985

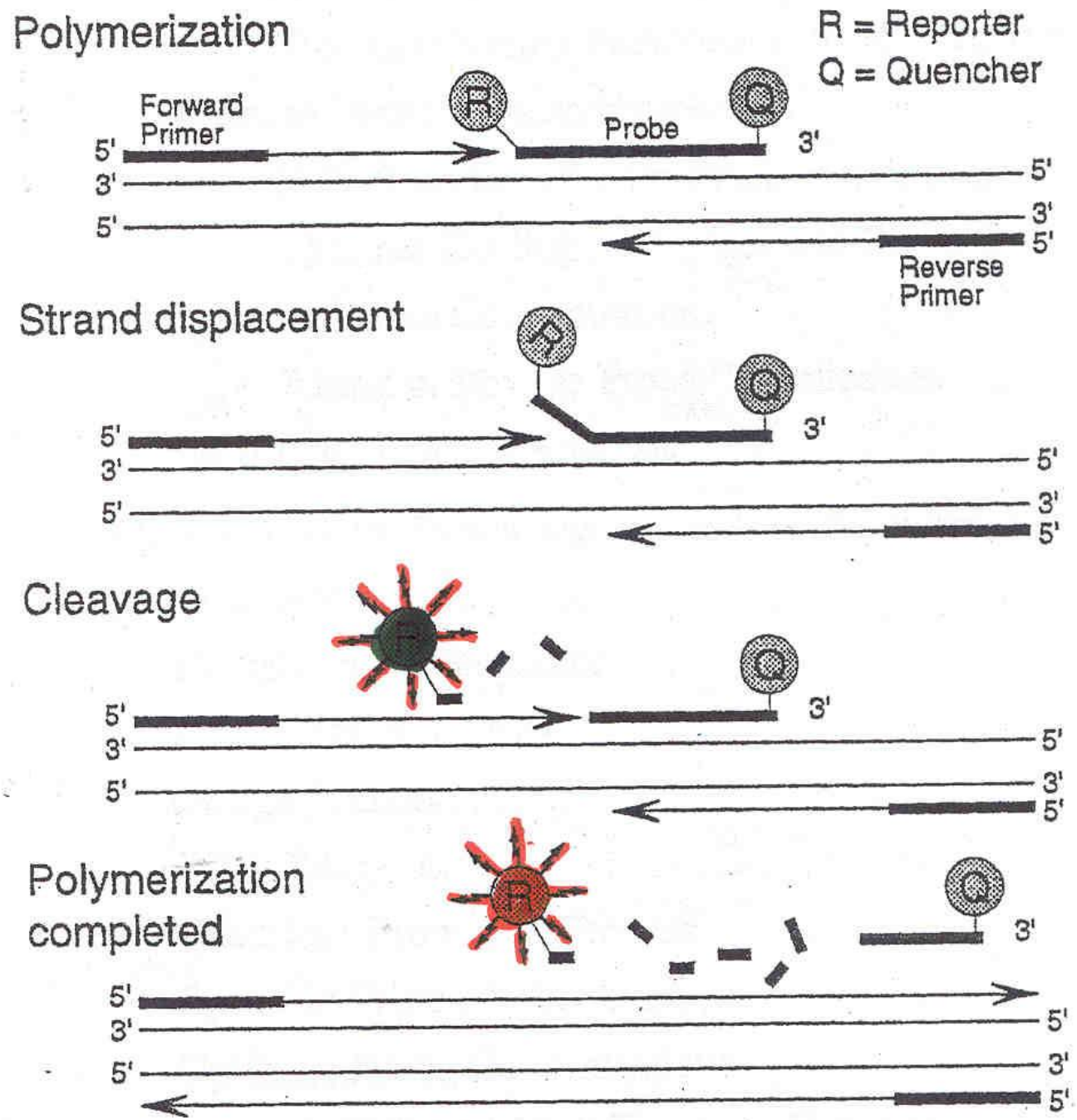


Cycle 1

Cycle 2

3. Detection of product





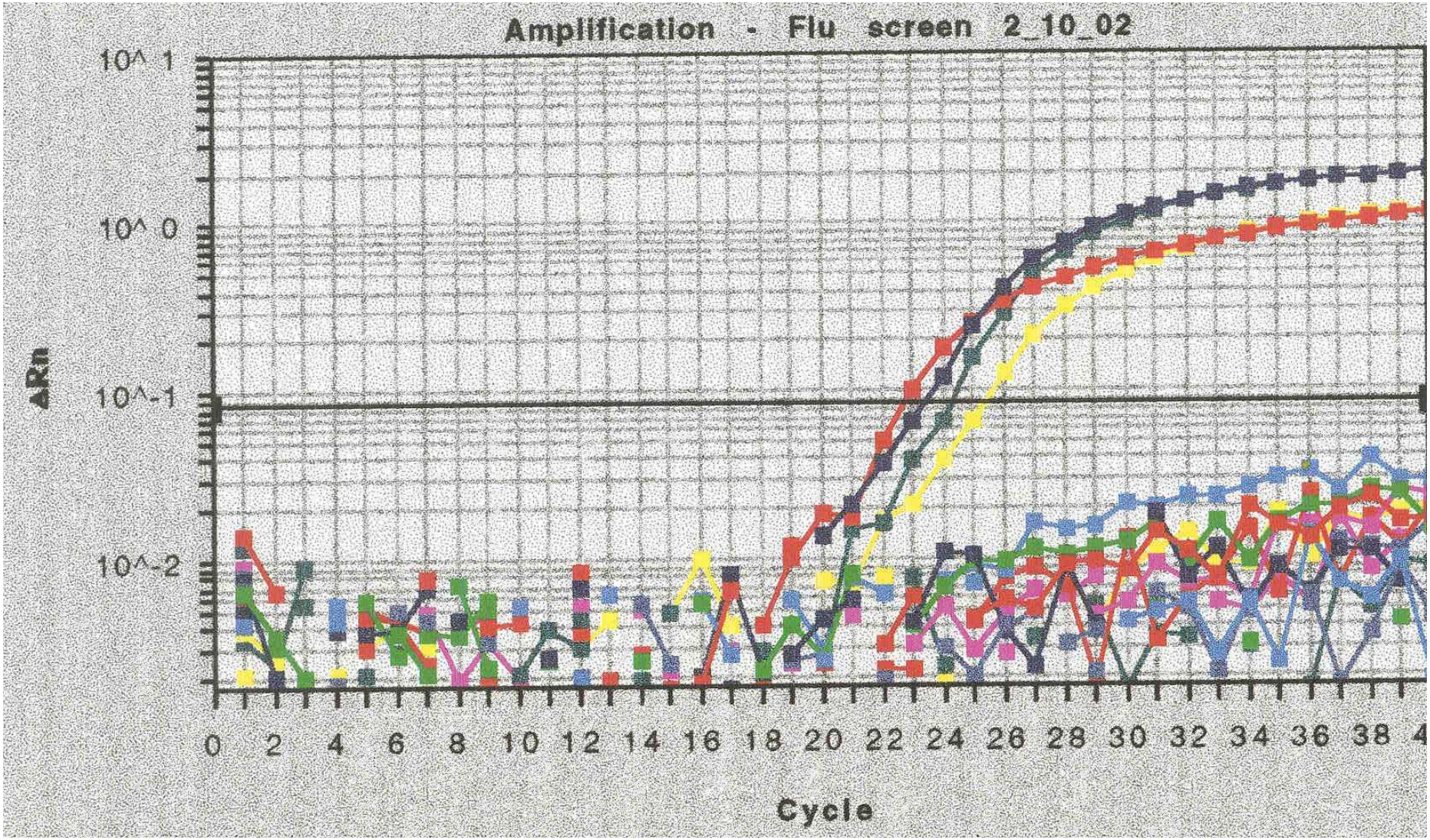
‘Real-time’ detection

‘Taqman’ probe

Binds to the PCR product by base pair matching;

Reporter molecule removed by DNA polymerase as it extends the strand

Reporter fluoresces


Amplification - Flu screen 2_10_02
10^ 1
10^ 0
10^-1
10^-2
ΔRn
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 4
Cycle

CNS Case 2: 21 year old male with a 4 day history. Initial sore throat, then myalgia and joint pain with swelling, then severe headache for 24 hrs. No rash.

On examination: No rash, febrile and tachycardic. Mild neck stiffness present.

FBC : WCC 22.2 x 10^9/L (15.2 neutrophils, 0.7 lymphocytes, 5.3 band forms (immature neutrophils), platelets normal

Blood culture taken

Questions:

1. What is your differential diagnosis?

2. Would you do a Lumbar puncture?

CNS2: question answers to 1, 2

1. Acute febrile illness with severe headache and some neck stiffness; bacterial meningitis must be suspected. Please think of some alternatives. The high band form and very high WCC are predictive of bacterial sepsis.

2. YES; only defer LP if there are contraindications such as shock, local sepsis in the lumbar region, focal neurological signs or significant decreased level of consciousness. Always be careful to check for neck stiffness and for Kernig's sign. If either are present then consider an LP.

CNS2: Progress: he was recalled the following morning because blood culture was growing Gram negative diplococci! CSF was taken:

CSF findings: turbid fluid

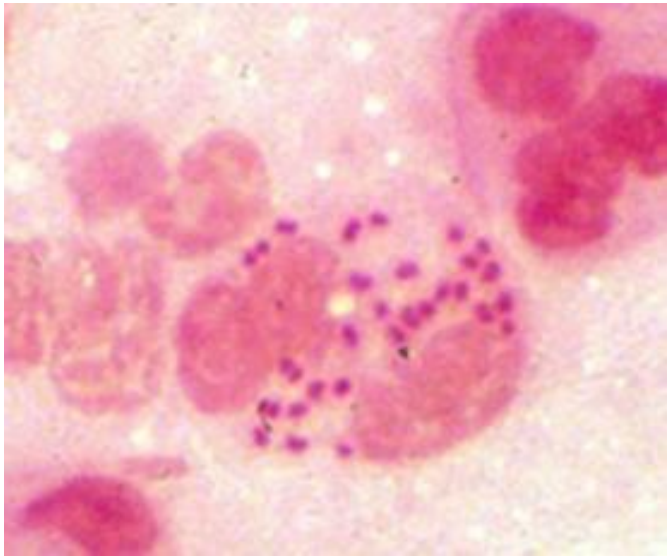
- white cells 8,320 x 10^6/L (94% PMN)
- red cells 400 x 10^6/L
- gram stain : gram negative diplococci (scanty)
- protein 2.81 g/L (normal <0.4)
- glucose 0.1mmol/L (very low)

Questions :

3. What is the microbiological diagnosis?

4. What treatment is indicated?

5. What public health action might be Indicated?

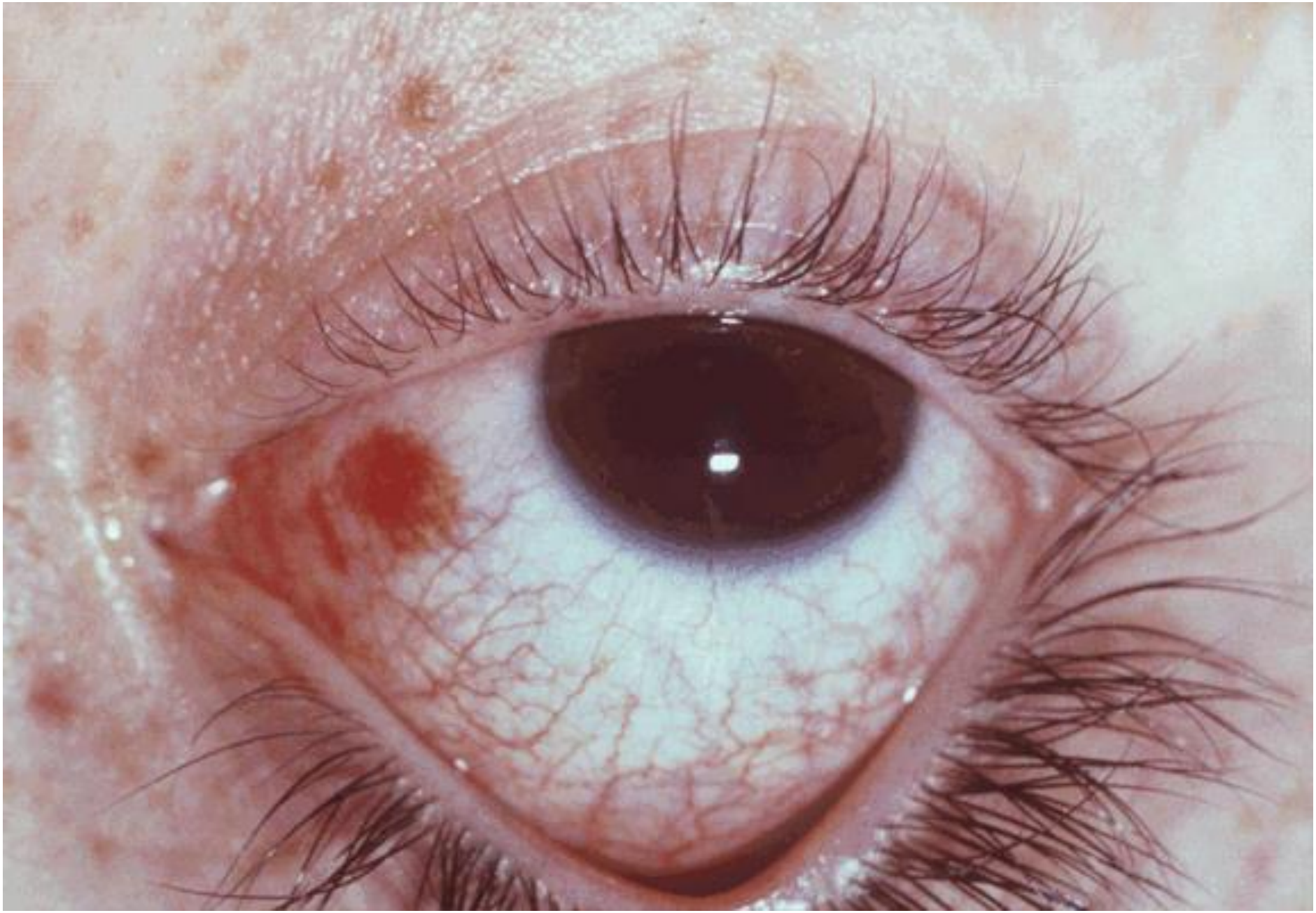


CNS2: question answers 3,4, 5

3. The diagnosis is meningococcal sepsis with meningitis. **A small conjunctival haemorrhage was found in one eye** and his knees, wrists and ankles were swollen due to a septic polyarthritis from meningococcus.
4. Treatment of meningococcal disease is with ceftriaxone (empirically) and later (if microbiologically confirmed) benzylpenicillin at high dose - 1.8g 4hrly intravenous. Steroids (IV dexamethasone for 4 days) not strictly necessary in meningococcal disease BUT recommended for meningitis due to *Strep. pneumoniae* or due to *Haemophilus influenzae* type B. Steroids must be given before or soon after the first antibiotic dose to work. They reduce long-term neurological sequelae (deafness etc)
5. Public health: antibiotic prophylaxis can be given to close contacts of the case to prevent them developing disease

Meningococcal rash is variable

- Not always present! Takes at least 12 hrs to appear
  - haemorrhagic = petechiae and/or purpura
  - Unusual maculopapular ‘ flea bitten’ which fades or becomes haemorrhagic
- May appear anywhere but:
  - esp. under areas of pressure from elastic, underwear



Clinical features- bacterial meningitis

- Headache
- Classical triad of fever, neck stiffness and altered state of consciousness is present in 2/3. Nearly all will have at least one of these as well
- Focal neurology- cranial nerve palsies 10-20%
- Seizures 5-10% generalised seizures
- Elderly or immune-compromised - may present with only confusion/obtundation

CNS Case 3: 14 yr old boy involved in a fight at the local pool. Fractured nose and sustained some grazes. Presented 3 days later to doctor with headache and backache. GP detected fever, a positive Kernig's sign with mild neck stiffness. Referred to Hospital where following investigations were performed:

FBC: WCC 12.6 x 10^9/L (Neutrophils 10.7)

Blood cultures

CSF: white cells 3,235 x 10^6/L (90% PMN)

- red cells 160 x 10^6/L
- gram stain : no organisms seen
- protein > 7.5g/L (normal <0.4)
- glucose 2.3 mmol/L

Questions:

1. What is your interpretation of the CSF findings?

2. What would you do now?

CNS3: question answer 1

1. High CSF PMN count and protein level suggest meningitis. However the CSF glucose level is relatively normal, given the enormous increase in protein and cells. Also odd is the absence of organisms on Gram stain. A Gram stain without visible organisms may occur in early meningococcal meningitis; however the CSF findings show a degree of inflammation that implies late meningitis. Pre-treatment with antibiotics might explain absence of organisms on Gram stain but not the other findings. The absence of neck stiffness is also inconsistent. **It all doesn't add up!**

CNS3: question answer 2

2. Treatment for bacterial meningitis was given. The following day the blood culture was positive with gram positive cocci resembling staph.

Question 3:

What do you think is going on now?

CNS3: question answer 3

- The CSF findings are suggestive of a **parameningeal site of infection** (ie an infective focus that is lying against the meninges somewhere- in bone or middle ear or nasal sinus). The back pain history was not recognised to be more prominent than headache in this boy's story but in retrospect, this was his biggest complaint. *Staph. aureus* grew in his blood, another important clue.
- The initial meningitis antibiotics were changed to dicloxacillin and his condition improved over 1 week. He went home after 10 days and then re-presented with more severe lumbar back pain. A lumbar epidural abscess with osteomyelitis of a vertebral body was diagnosed by CT scan. He recovered after prolonged high dose antibiotic treatment.
- The presumption is that he developed a blood stream infection with staph after the nose trauma (in staph carriers, the anterior nose is a site of a large quantity of staph colonisation) and that the bacteraemia then localised to a bruised area of lumbar spine and the epidural space

Purulent CSF

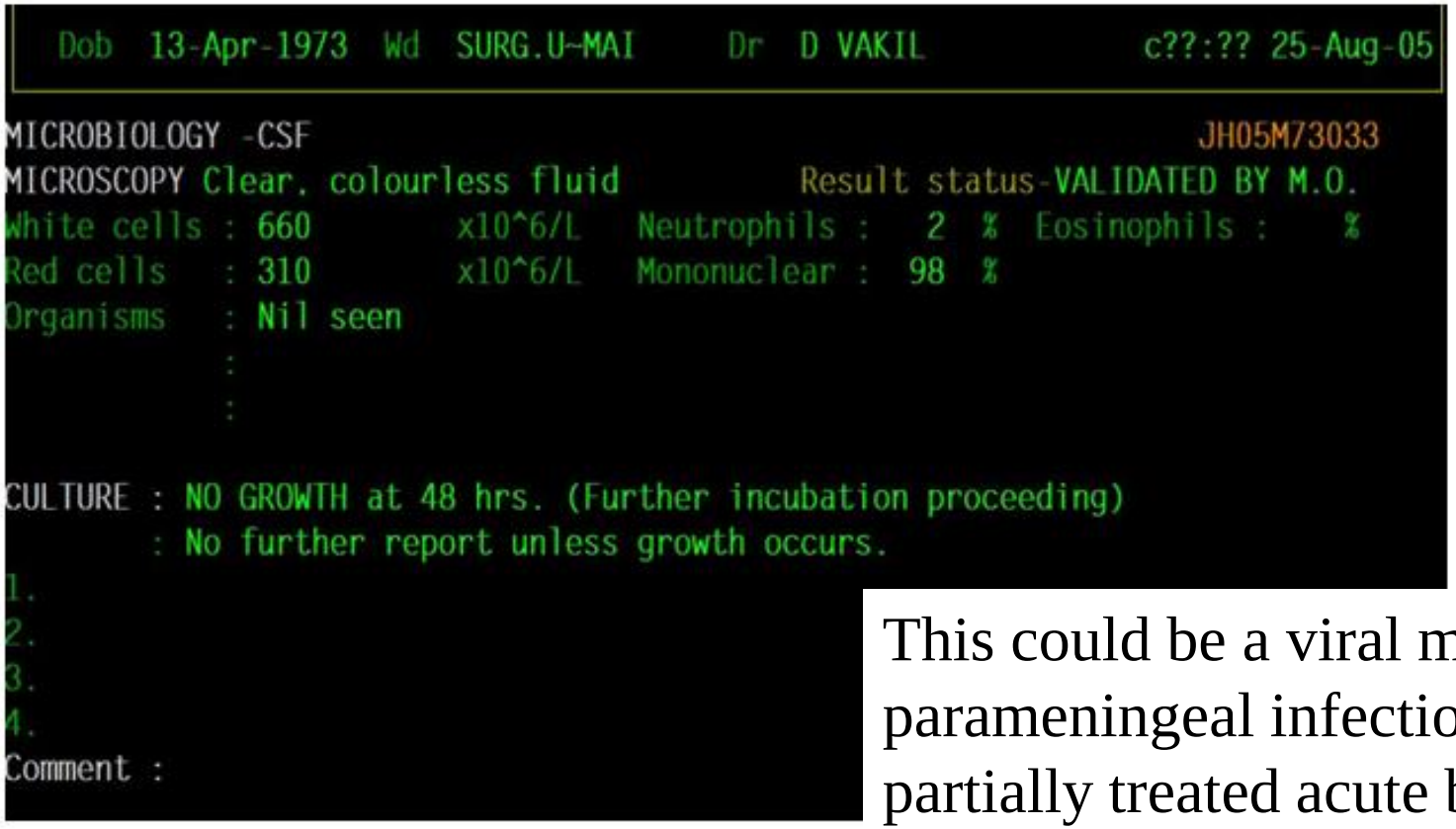
- Turbid (=cloudy) CSF with white cells (neutrophils), raised protein and usually low glucose. Differential diagnosis:
  - Bacterial meningitis
  - Rupture of cerebral abscess into the sub-arachnoid space
  - Spinal epidural abscess (LP needle has entered the abscess cavity!)
  - Parameningeal focus (as with case 3 above- glucose normal)

Blood stained CSF

- Bloody (traumatic) tap : normal wc to rbc ratio is 1:400. In acute meningitis, the number of WC far exceed the number of red cells
- Subarachnoid haemorrhage
- Trauma

Usually 3 tubes of CSF are collected sequentially. The last tube is used for the cell count so that any blood in the needle has time to be washed out first in to the first 2 tubes.

CNS case 4: 48 hr h/o fever, headache, neck stiffness and back stiffness



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  Dob  13-Apr-1973  Wd  SURG.U~MAI     Dr  D VAKIL            c??:?? 25-Aug-05

MICROBIOLOGY -CSF                                                JH05M73033
MICROSCOPY Clear, colourless fluid          Result status-VALIDATED BY M.O.
White cells : 660        x10^6/L   Neutrophils :   2  %  Eosinophils :    %
Red cells   : 310        x10^6/L   Mononuclear :  98  %
Organisms   : Nil seen
            :
            :

CULTURE : NO GROWTH at 48 hrs. (Further incubation proceeding)
        : No further report unless growth occurs.
1.
2.
3.
4.
Comment :
```

CSF glucose 2.8 (Normal)
CSF protein 0.74g/L (elevated)

This could be a viral meningitis, a parameningeal infection, a partially treated acute bacterial meningitis or even TB meningitis. All would depend on the clinical story and other investigations.

Am J Trop Med Hyg. 2012 Feb;86(2):240-245.

Predictors of Acute Bacterial Meningitis in Children from a Malaria-Endemic Area of Papua New Guinea.

Laman M, Manning L, Greenhill AR, Mare T, Michael A, Shem S, Vince J, Lagani W, Hwaiwhanje I, Siba PM, Mueller I, Davis TM.

Papua New Guinea Institute of Medical Research, Madang and Goroka, Papua New Guinea; School of Medicine and Pharmacology, University of Western Australia, Fremantle Hospital, Fremantle, Western Australia, Australia; Department of Pediatrics, School of Medicine and Health Sciences, University of Papua New Guinea, Port Moresby, Papua New Guinea; Department of Pediatrics, Goroka Base Hospital, Goroka, Eastern Highlands Province, Papua New Guinea; Infection and Immunity Division, Walter and Eliza Hall Institute, Parkville, Victoria, Australia; Centre de Recerca en Salut Internacional de Barcelona, Barcelona, Spain; Family Health Services, National Department of Health, Port Moresby, Papua New Guinea.

Abstract

Abstract. Predictors of acute bacterial meningitis (ABM) were assessed in 554 children in Papua New Guinea 0.2-10 years of age who were hospitalized with culture-proven meningitis, probable meningitis, or non-meningitic illness investigated by lumbar puncture. Forty-seven (8.5%) had proven meningitis and 36 (6.5%) had probable meningitis. Neck stiffness, Kernig's and Brudzinski's signs and, in children < 18 months of age, a bulging fontanel had positive likelihood ratios (LRs) ≥ 4.3 for proven/probable ABM. Multiple seizures and deep coma were less predictive (LR = 1.5-2.1). Single seizures and malaria parasitemia had low LRs (≤ 0.5). In logistic regression including clinical variables, Kernig's sign and deep coma were positively associated with ABM, and a single seizure was negatively associated (P ≤ 0.01). In models including microscopy, neck stiffness and deep coma were positively associated with ABM and parasitemia was negatively associated with ABM (P ≤ 0.04). In young children, a bulging fontanel added to the model (P < 0.001). Simple clinical features predict ABM in children in Papua New Guinea but malaria microscopy augments diagnostic precision.

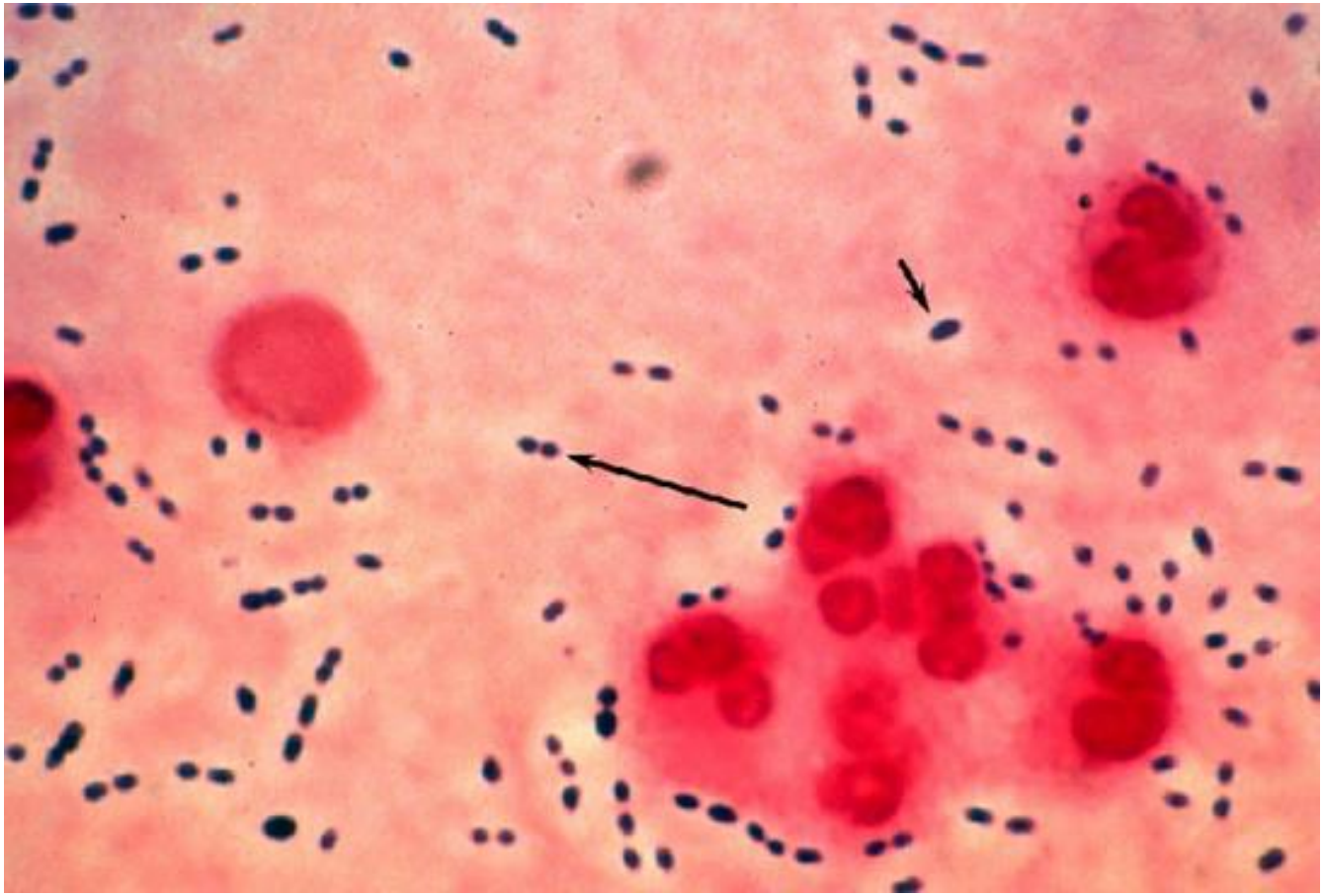
Kernig and Brudzinski signs are a reliable predictor of meningitis in infants in PNG!

Meningitis due to *S. pneumoniae*

- Turbid CSF usual
- [Traditional latex antigen tests are poor – no better than a Gram stain
- [BINAX pneumolysin-C antigen detection card works very well on CSF- much more sensitive than latex test

Gram positive diplococci – *S. pneumoniae*

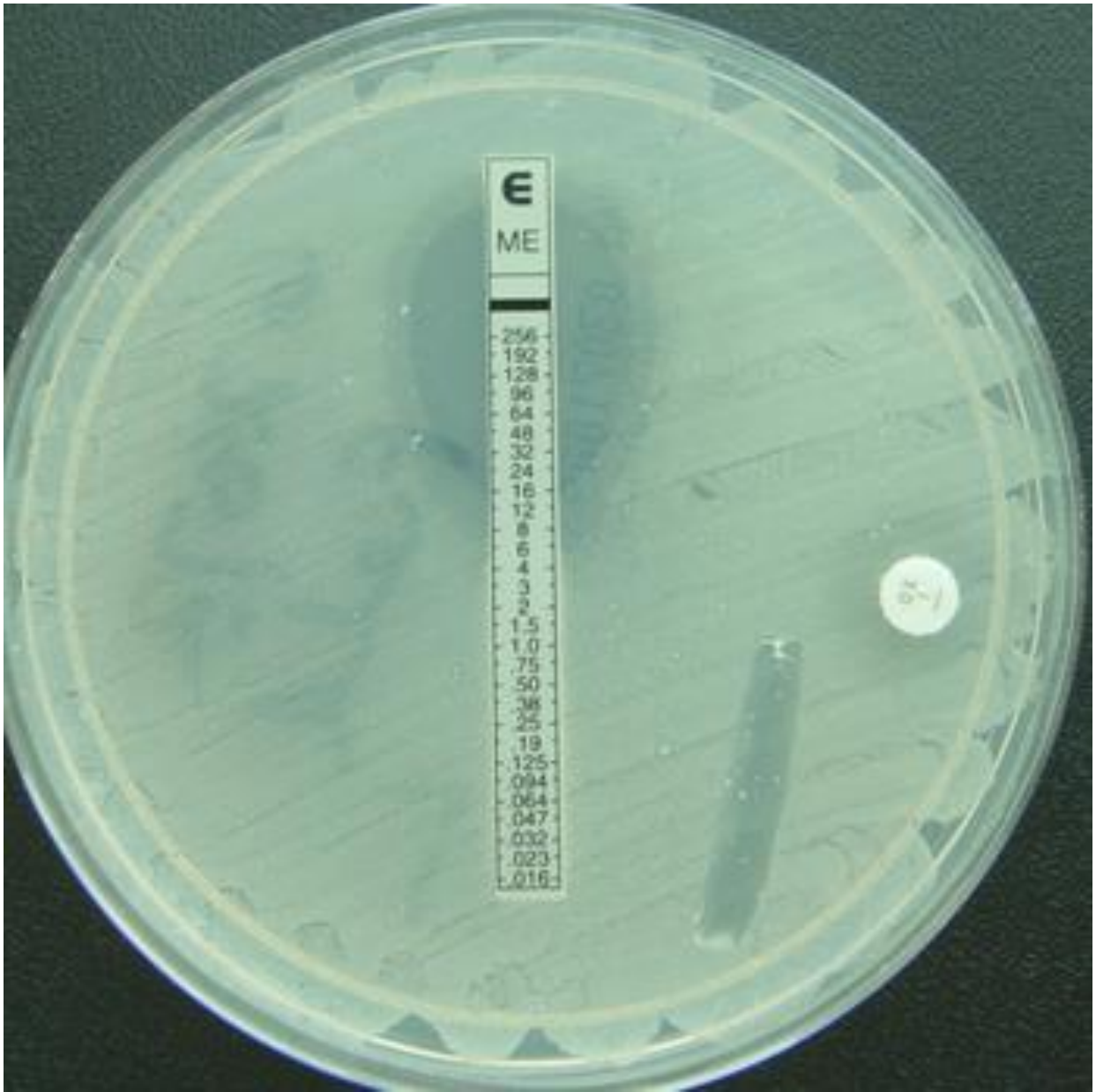
NB. These organisms may be quite sparse and a careful look is required to find them



Antibiotic resistance in pneumococcus

- Screen pneumococci from CSF with 1 microgram oxacillin disc test. Fully susceptible strains (MIC $\leq$0.12mg/L) have an oxacillin zone >=20mm.
- Strains with reduced susceptibility to penicillin cause penicillin to fail for treatment of meningitis; these strains may also be tolerant to chloramphenicol causing treatment failure
- **Ceftriaxone high dose is recommended for treatment due to the risk of penicillin resistance**
- [The laboratory can check the penicillin and ceftriaxone susceptibility in cases of pneumococcal meningitis – the E-test is used

E-test


ME
256
192
128
96
64
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16
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6
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3
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1.5
1.0
.75
.50
.38
.25
.19
.125
.094
.064
.047
.032
.023
.016

Management options: pneumococcal meningitis where penicillin MIC is elevated

- Third generation cephalosporin (ceftriaxone) works provided that MIC < 1mg/L for ceftriaxone
- IF E-test MIC for ceftriaxone >=1mg/L then it may also fail
  - Options are to give ceftriaxone AND either vancomycin (iv) or rifampicin for synergy

Chloramphenicol

- Bactericidal activity (MBC) against many penicillin-resistant strains of pneumococcus is poor, despite “susceptibility” on basis of MIC testing

- S. Africa: **33**% (children with pen-res, chlor-s meningitis treated with chloramphenicol) survived without deficit vs **59%** (pen-s meningitis treated with penicillin)

Chloramphenicol or ceftriaxone, or both, as treatment for meningitis in developing countries? Goroka, PNG.

METHODS: An observational study with a retrospective control group nested within a randomised trial of fluid management for bacterial meningitis where clinical care was standardised. Chloramphenicol is standard treatment for bacterial meningitis in Papua New Guinea. In the first 150 cases we used chloramphenicol and only changed treatment to ceftriaxone if chloramphenicol resistance for cerebrospinal fluid isolates was proved. After finding 20% of *Haemophilus influenzae* were resistant to chloramphenicol, and that most affected children had poor outcomes, we changed to an alternative strategy. In the next 196 cases first line treatment was ceftriaxone and treatment was changed to chloramphenicol if the isolated bacteria were found to be susceptible.

RESULTS: When chloramphenicol was used as first line treatment for meningitis followed by ceftriaxone when in vitro resistance was shown, there was invariably a very poor outcome in chloramphenicol resistant disease (71% of children died or had severe neurological complications). **Using ceftriaxone as first line treatment was effective in reducing mortality and neurological sequelae from chloramphenicol resistant *Haemophilus influenzae* type (71% v 9%, relative risk 0.13; 95% CI 0.02 to 0.87; p = 0.013).** Changing to chloramphenicol if there was no evidence of in vitro resistance was less than half the cost of empirical use of ceftriaxone for a full course for all children with meningitis.

Arch Dis Child. 2003 Jun;88(6):536-9.

Accuracy of initial clinical diagnosis of acute bacterial meningitis in children from a malaria-endemic area of Papua New Guinea.

The diagnosis of acute bacterial meningitis (ABM) is challenging in resource-limited settings where cerebral malaria and viral encephalitis are also common. METHODS: To assess the accuracy of an initial clinical diagnosis of ABM in a malaria-endemic area of Papua New Guinea (PNG), a retrospective chart review of hospitalized children aged 2 months to 10 years was conducted. RESULTS: Of the 481 eligible children, 240 had an initial clinical diagnosis of ABM that was confirmed independently by trained research staff under standardized conditions, with laboratory support in only 84 (17.5%; 84/481). When compared with the final laboratory-confirmed diagnosis, an initial diagnosis of ABM had a sensitivity, specificity, positive predictive value and negative predictive value of 76% (95% CI 66-85%), 56% (95% CI 51- 61%), 27% (95% CI 21-33%) and 92% (95% CI 87- 95%), respectively. There was discordance between initial and final diagnosis of ABM in 196 children; 176 initially considered to have ABM had an alternative diagnosis, while 20 without an initial diagnosis of ABM were confirmed to have ABM. **CONCLUSION: These data show that initial misdiagnosis of ABM is common in a malaria-endemic area of PNG.** A diagnostic algorithm using standardized assessment for meningeal irritation, coma and malaria parasitological testing needs further evaluation in this setting.

Trans R Soc Trop Med Hyg 2014