Royal Devon University Healthcare NHS Foundation Trust

Title:

Meningitis & Encephalitis Guidelines / Pathway

Reference Number: RDF1318-23
Date of Response: 09/03/2023

Please be aware that the Royal Devon University Healthcare NHS Foundation Trust (Royal Devon) has existed since 1st April 2022 following the integration of the Northern Devon Healthcare NHS Trust (known as Northern Services) and the Royal Devon and Exeter NHS Foundation Trust (known as Eastern Services).

Further to your Freedom of Information Act request, please find the Trust's response(s) below: Please also see attached – The Trust's Paediatric Team use a national guideline (attached). There is guidance about which specific antibiotics are to be used for children and adults.

Also attached are the Microbiology guidelines for the Northern service which expand into some broader guidance around CSF collection.

1. Of the following, which guidelines does your Trust follow for the diagnosis and treatment of meningitis/encephalitis: (Please answer: Yes/No)
• NICE Guidelines (CG102) - Bacterial meningitis in under 16s: recognition, diagnosis, and management. YES.
• UK Joint Specialist Societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults (published 2016) No.
• Association of British Neurologists and British Infection Association National Guidelines – Management of suspected viral encephalitis in adults (published 2011) No.
• Association of British Neurologists and British Paediatric Allergy, Immunology, and Infection Group National Guidelines – Management of suspected viral encephalitis in children (published 2011) No.

2. Does your Trust have any locally developed/adapted guidelines for the diagnosis and treatment of meningitis/encephalitis in both adults and paediatric patients?
If yes, please state which guidelines have been adapted and please provide a copy of your local guidelines. No.

3. What are the top 3 roles in your Trust, in order of involvement, that are responsible for the development of local pathways and guidelines for meningitis/encephalitis?
Neurology Clinical Lead Paeds Clinical Lead AMU Clinical Lead

4. Does your Trust typically take samples of blood cultures from patients with suspected meningitis/encephalitis within: (Please select answer) –
The Trust is unable to respond to this question as this information is not audited. To provide you with the information requested would require the manual extraction and manipulation of information from various sources. To carry out this work would

exceed the appropriate cost limit as set out in Section 12 (1) of the Freedom of Information Act 2000 and is therefore exempt.

Under the Freedom of Information Act 2000 Section 12 (1) and defined in the Freedom of Information and Data Protection (Appropriate Limit and Fees) Regulations 2004, a public authority is not obliged to comply with a request for information if it estimates that the cost of complying would exceed the appropriate limit. The limit of £450 represents the estimated cost of one person spending two and a half days in determining whether the Trust holds the information, locating, retrieving, and extracting that information.

We target blood cultures and treatment within 1 hour for a septic patient.
• 1 hour of admission?
• 2-4 hours of admission?
• 4-8 hours of admission?
• 8> hours of admission?

5. Does your Trust consistently carry out lumbar punctures in patients with no contradictions who have suspected meningitis/encephalitis? (Yes/No)
If yes, who performs the lumbar puncture? (Please specify job role) Trainee Doctor –

- In medicine typically IMT grade and above without supervision.
- A trained ACP (advanced care practitioner) is able to perform LP without supervision.
- Foundation trainees however under supervision.

6. Does your Trust consistently take cerebrospinal fluid (CSF) samples via lumbar puncture from patients with suspected meningitis/encephalitis within: (Please select answer) – Please see response for question 4.

We aspire to take CSF prior to starting antibiotics. A delay in getting the LP done should not delay prompt antibiotic treatment
• 1 hour of admission?
• 1-2 hours of admission?
• 2-4 hours of admission?
• 4-8 hours of admission?
• 8-12 hours of admission?
• >12 hours of admission?

7. Does your Trust administer antibiotics to patients where appropriate prior to taking blood culture and CSF samples? (Yes/No)

8. Does your Trust consistently administer antibiotics to patients with suspected meningitis/encephalitis within: (Please select answer) - As for question 4 and 6.
• 1 hours of admission?
• 2-4 hours of admission?
• 4-8 hours of admission?
• 8> hours of admission?

Questions for lab team(s):

9. Which of the following guidelines does your Trust follow for the microbiological investigation of meningitis/encephalitis: (Please select: Yes/No)

• UK Standards for Microbiology Investigations – Meningoencephalitis (published 2014)
• UK Standards for Microbiology Investigations – Investigation of Cerebrospinal Fluid (published 2017) Yes - this is SMI 27 as below.

The below comes from Microbiology at The Eastern service and would also apply in the Northern area of the Trust.

10. Does your Trust have any local adaptations or amendments to the two UK Standards for Microbiology Investigations listed in the above question?
If yes, please provide a copy of your local amendments. SMI 27

11. Following lumbar puncture on a patient with suspected meningitis/encephalitis, how long are the turnaround times from point of receiving specimen to result on the following tests: (Please select answer for each result)
a) Cell count (<1 hour, 1-2 hours, 2-4 hours or >4 hours)
b) Gram staining (<1 hour, 1-2 hours, 2-4 hours or >4 hours) n/a
c) Bacterial culture (<1 hour, 1-2 hours, 2-4 hours or>4 hours)
d) PCR (<1 hour, 1-2 hours, 2-4 hours or >4 hours)

12. Where does your Trust process CSF samples? Microbiology for above tests

13. Does your Trust perform PCR testing to test samples from patients with suspected meningitis/encephalitis? (Yes/No)

14. If PCR testing is carried out in your Trust, which bacterial and viral pathogens are tested for? (Please separate your answer by bacterial and viral pathogens)
Viral only: HSV,1, HSV 2, Enterovirus, VZV, Parecho

Management of Bacterial Meningitis in Children and Young People

Incorporates NICE Bacterial Meningitis and Meningococcal Septicaemia Guideline CG102. Distributed in partnership with NICE

2nd Edition

Meningitis Research Foundation

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Meningococcal Disease Algorithm www.meningitis.org

Symptoms and signs of bacterial meningitis?

YES

Check airway, breathing and circulation; gain vascular access

Signs of raised intracranial pressure (RICP) or shock?

YES

NO

Perform diagnostic tests BM1 **Correct any dehydration**

Contraindication to Lumbar Puncture? BM2

NO → **Perform Lumbar Puncture**
Do not await CSF results before starting antibiotics

YES

<3 months old?

YES

Empiric antibiotics for suspected meningitis
IV Cefotaxime + either Amoxicillin or Ampicillin (can replace Cefotaxime with Ceftriaxone if no contraindication BM3)
DO NOT DELAY ANTIBIOTICS

NO

Empiric antibiotics for suspected meningitis
IV Ceftriaxone unless contraindicated BM3
DO NOT DELAY ANTIBIOTICS

Add Vancomycin if recently overseas, or prolonged or multiple antibiotic exposure within last 3 months.

LP results available?

NO

YES

Lumbar puncture suggests meningitis?
- In neonates (<28 days old), ≥ 20 cells/µl
- In older children > 5 cells/µl or > 1 neutrophil/µl

(if lower cell count, still consider bacterial meningitis if other symptoms and signs suggest the diagnosis especially in neonates).

NO → **NICE feverish illness guideline CG160** www.nice.org.uk/guidance/cg160

YES

- **Consider TB meningitis** If raised CSF WBC count and risk factors for TB. If TB meningitis in differential diagnosis refer to NICE TB CG117 for appropriate antibiotic treatment
- **Consider Herpes simplex meningoencephalitis**. If HSV in differential diagnosis give Aciclovir.

Steroids: Dexamethasone 0.15 mg/kg to a max dose of 10 mg, qds x 4 days for children ≥ 3 months old IF ≤ 12h from first antibiotics and LP shows:
- frankly purulent CSF
- CSF WBC count > 1000/µl
- raised CSF WBC count and protein > 1 g/L
- bacteria on Gram stain.

Steroids should not be used in developing countries.
If TB meningitis in the differential diagnosis, refer to NICE CG117 before administering steroids.

Reduced or fluctuating conscious level or focal neurological signs? BM4

YES → **Perform CT Scan**

NO

- Full-volume maintenance fluids: enteral feeds if tolerated or isotonic IV fluids e.g. 0.9% Saline or 0.9% Saline with 5% Glucose
- Do not restrict fluids unless there is evidence of increased anti-diuretic hormone secretion or RICP
- Monitor fluid administration, urine output, electrolytes and blood glucose
- See Meningococcal Disease Algorithm to treat seizures.

- Close monitoring for signs of Raised ICP, Shock & repeated review

Go to Meningococcal Disease Algorithm if signs are found and consult a paediatric intensivist, anaesthetist, or intensivist

- Perform delayed LP if no longer contraindicated BM2
- If LP contraindicated, perform delayed LP when no longer contraindications.

Specific pathogen identified?

YES

Antibiotics for confirmed meningitis
- Meningococcus: IV Ceftriaxone for 7 days
- *H influenzae*: IV Ceftriaxone for 10 days
- *S pneumoniae*: IV Ceftriaxone for 14 days, add Vancomycin if resistant strain.
- Group B Strep: IV Cefotaxime for ≥ 14 days
- *L monocytogenes*: IV Amoxicillin or Ampicillin for 21 days in total, plus IV Gentamicin for at least the first 7 days
- Gram-negative bacilli: IV Cefotaxime for ≥ 21 days (unless alternative directed by local antimicrobial resistance patterns or specific sensitivities)

Unless directed otherwise by antibiotic sensitivities. Duration may be dictated by clinical response – discuss with infectious disease specialist.

NO → **Antibiotics for unconfirmed meningitis**

<3 months old?

YES → IV Cefotaxime (or Ceftriaxone unless contraindicated BM3) + either Amoxicillin or Ampicillin IV for ≥ 14 days.

NO → IV Ceftriaxone for ≥10 days.

Notify public health, prophylaxis see MD11 **on Meningococcal disease algorithm; Long-term management** BM7

BM1 Diagnostic and other laboratory tests:
Take bloods for Blood gas (bicarb, base deficit), Lactate, Glucose, FBC, U&E, Ca++, Mg++, PO_4, Clotting, CRP, Blood cultures, Whole blood (EDTA) for PCR, X-match. Take Throat swab. If limited blood volume, prioritise blood gas, lactate, glucose, electrolytes, FBC, clotting.

BM2 Contraindications to Lumbar Puncture
- Clinical or radiological signs of raised intracranial pressure
- Shock
- After convulsions until stabilised
- Coagulation abnormalities
  - Clotting study results (if obtained) outside the normal range
  - Platelet count below 100 x 10^9/L
  - on Anticoagulant therapy
- Local superficial infection at LP site
- Respiratory insufficiency.

Perform delayed LP in children with suspected bacterial meningitis when contraindications no longer present

BM3 Contraindications to Ceftriaxone
Premature neonates with corrected gestational age < 41 weeks and other neonates <1 month old, particularly those with jaundice, hypoalbuminaemia, or acidosis; or receiving concomitant treatment with intravenous calcium.

BM4 Indications for CT scan in children with suspected bacterial meningitis
CT scan cannot reliably detect raised intracranial pressure. This should be assessed clinically.
Perform a CT scan to detect other intracranial pathologies if GCS ≤8 or focal neurological signs in the absence of an explanation for the clinical features.
Do not delay treatment to undertake a CT scan.
Clinically stabilise the child before CT scanning.
Consult a paediatric intensivist, anaesthetist, or intensivist.

BM5 Indications for tracheal intubation and mechanical ventilation
Threatened or actual loss of airway patency (e.g. GCS ≤8, response to pain only).
- Need for any form of assisted ventilation e.g. bag–mask ventilation.
- Clinical observation of increased work of breathing
- Hypoventilation or Apnoea
- Features of respiratory failure, including
  - Irregular respiration (e.g. Cheyne–Stokes breathing)
  - Hypoxia (saturation <94% in air, PaO_2 < 13 kPa or 97.5mmHg), hypercapnoea ($PaCO_2$ > 6 kPa or 45 mmHg)
- Continuing shock following 40ml/kg of resuscitation fluid
- Signs of raised intracranial pressure
- Impaired mental status
  - GCS drop of ≥ 3, or score ≤ 8, or fluctuation in conscious level
  - Moribund state
- Control of intractable seizures
- Need for Stabilisation for brain imaging or for transfer to PICU.

Should be undertaken by a health professional with expertise in paediatric airway management, Consult PICU. (See MD4)

BM6 Repeat LP in neonates after starting treatment if:
persistent or re-emergent fever, new clinical findings (especially neurological findings), deteriorating clinical condition, or persistently abnormal inflammatory markers

BM7 Long-term management: Before discharge consider need for after care, discuss potential long-term effects with parents, arrange hearing test. Refer children with severe or profound deafness for cochlear implant assessment ASAP. Use MRF discharge checklist **http://www.meningitis.org/assets/x/56050**. Provide 'Your Guide' and direct to meningitis support organisations **www.meningitis.org/recovery** or **www.meningitisnow.org/recovery**. Offer further care on discharge as needed. Paediatrician to review child with results of their hearing test 4-6 weeks after discharge from hospital considering all potential morbidities and offer referral. Inform GP, health visitor or school nurse.

Based on NICE CG102 www.nice.org.uk/guidance/CG102

Authors AJ Pollard (GDG chair), A Cloke, SN Faust, L Glennie, C Haines, PT Heath, JS Kroll, M Levin, I Maconochie, S McQueen, P Monk, S Nadel, N Ninis, MP Richardson, MJ Thompson, AP Thomson, D Turner.

Further copies from www.meningitis.org or 080 88003344.

Management of Meningococcal Disease in Children and Young People

Incorporates NICE Bacterial Meningitis and Meningococcal Septicaemia Guideline CG102. Distributed in partnership with NICE 8th Edition

Meningitis Research Foundation

ENDORSED

Royal College of Paediatrics and Child Health

RECOGNITION

May present with predominant **SEPTICAEMIA (with shock)**, **MENINGITIS (with raised ICP)** or **both**. **Purpuric/petechial non-blanching rash is typical**.
Some may have neither shock nor meningitis. Rash may be atypical or absent in some cases.

Call consultant in Emergency Medicine, Paediatrics, Anaesthesia or Intensive Care
Initial assessment looking for shock/raised ICP
Do not perform Lumbar Puncture yet

Give IV Ceftriaxone (80 mg/kg od) without delay
Do not use Ceftriaxone at the same time as calcium-containing solutions:
in this situation use Cefotaxime (50 mg/kg qds)

Bacterial meningitis algorithm www.meningitis.org

SIGNS OF SHOCK? MD2

- Tachycardia
- Capillary refill time > 2 seconds
- Cold hands/feet; pale or blue skin
- Respiratory distress/ oxygen saturation <95% in air
- Altered mental state/decreased conscious level
- Decreased urine output (<1 ml/kg/hr)
- Hypotension (late sign)
- Hypoxia on arterial blood gas
- Base deficit (worse than -5 mmol/l)
- Increased lactate (>2 mmol/l)

NO

YES

Do not perform Lumbar Puncture; Nil by mouth

- ABC & High flow Oxygen (minimum 10 l/min) by face mask
- Insert 2 large IV cannulae (or intraosseous); Take bloods, see MD3
- Take blood gas (including lactate). Measure glucose.

VOLUME RESUSCITATION

- Immediate bolus of 20 ml/kg of 0.9% Saline over 5-10 minutes and reassess immediately
- If shock persists immediately give second bolus of 20 ml/kg of 0.9% Saline or of 4.5% Human Albumin over 5-10 minutes and reassess immediately
- Observe closely for response/deterioration
- Consider Urinary catheter to monitor output

After **40 ml/kg fluid** resuscitation – **STILL SIGNS OF SHOCK?**

NO — Repeated review

YES

WILL REQUIRE URGENT ELECTIVE INTUBATION AND VENTILATION MD4

D/W Paediatric intensivist and Call anaesthetist

- Immediate bolus of 20 ml/kg of 0.9% Saline or 4.5% Human Albumin over 5-10 minutes and reassess immediately; Continue boluses if necessary with repeated clinical and laboratory assessments including blood gas measurements. Fluid resuscitation should be guided by lactate, tachycardia, perfusion, hepatomegaly to avoid fluid overload and determine need for inotropes.
- Start peripheral inotropes (Dopamine); if IO access start Adrenaline MD5
- ET Tube (Cuffed if possible) and CXR
- Anticipate pulmonary oedema ensure adequate PEEP (≥5cm H_20)
- Central venous access
- Urine catheter to monitor urine output
- Start Adrenaline infusion (central) if continuing need for Volume resuscitation & Inotropes
- For warm shock: warm peripheries, bounding pulses and low diastolic pressure, give Noradrenaline (central)

Anticipate, monitor and correct:

- Hypoglycaemia MD6
- Acidosis MD7
- Hypokalaemia MD8
- Hypocalcaemia MD9
- Hypomagnesaemia MD10
- Anaemia
- If bleeding or performing invasive procedure (i.e.central line insertion) treat coagulopathy with FFP/Cryoprecipitate/platelets

RAISED INTRACRANIAL PRESSURE?

- Reduced (GCS ≤8) or fluctuating level of consciousness
- Relative Bradycardia and Hypertension
- Focal neurological signs
- Abnormal posture or posturing
- Seizures
- Unequal, dilated or poorly responsive pupils
- Papilloedema (late sign)
- Abnormal 'doll's eye' movements

YES

Do not perform Lumbar Puncture; Nil by mouth

- ABC and Oxygen (minimum 10 l/min) by face mask
- Insert 2 large IV cannulae (or IO); Take bloods, see MD3
- Take blood gas (including lactate). Measure glucose.
- Treat shock if present

Call anaesthetist and contact PICU

- Intubate and ventilate to control $PaCO_2$ (4-4.5 kPa)
- Urinary catheter and monitor output, NG tube

Do not perform Lumbar Puncture

NEUROINTENSIVE CARE

- 30° head elevation, midline position
- Avoid internal jugular lines
- Repeat Mannitol or 3% Saline if indicated
- Sedate (muscle relax for transport)
- Cautious fluid resuscitation (but correct coexisting shock)
- Monitor pupillary size and reaction
- Avoid hyperthermia
- Once patient is stabilised, consider CT scan to detect other intracranial pathology if GCS ≤8, fluctuating conscious level or focal neurological signs

Do not restrict fluids unless there is evidence of:
- raised intracranial pressure, or
- increased antidiuretic hormone secretion

STEPWISE TREATMENT OF SEIZURES

- IV Lorazepam (0.1 mg/kg) or Midazolam (0.1 mg/kg) bolus
- Consider Paraldehyde (0.4 ml/kg PR)
- Phenytoin (18 mg/kg over 30 min IV with ECG monitoring)

If persistent seizures:

- Thiopental (thiopentone) 4 mg/kg in intubated patients (beware of hypotension)
- Midazolam/Thiopental infusion

Perform delayed LP when stable and no contraindications

GO TO BACTERIAL MENINGITIS ALGORITHM

NO

YES

CLINICAL FEATURES OF MENINGITIS?

NO

Take bloods, see MD3
Close monitoring for signs of
- Raised ICP
- Shock

Perform LP if no contraindication
DO NOT DELAY ANTIBIOTICS

Repeated Review
Children with MD can deteriorate rapidly.
Deterioration detected?

Transfer to Intensive Care by Paediatric Intensive Care Retrieval Team

Notify public health, prophylaxis see MD11; Long-term management: see BM7 on Bacterial Meningitis Algorithm

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MD1 Estimate of child's weight (1–10 years)
Weight (kg) = 2 x (age in years + 4)

MD2 **Observe HR, RR, BP, perfusion, conscious level**
Cardiac monitor & pulse oximetry.

Conscious Level
Alert
Responds to **V**oice
Responds to **P**ain
Unresponsive

Normal Values

Age	Heart Rate/min	Resp Rate/min
<1	110-160	30-40
1-2	100-150	25-35
2-5	95-140	25-30
5-12	80-120	20-25
Over 12	60-100	15-20

Normal systolic blood pressure = 80 + (age in years x 2)
N.B. Low BP is a pre-terminal sign in children

MD3 Take bloods for Blood gas (bicarb, base deficit), Lactate, Glucose, FBC, U&E, Ca++, Mg++, PO_4, Clotting, CRP, Blood cultures, Whole blood (EDTA) for PCR, X-match. Take Throat swab. If limited blood volume, prioritise blood gas, lactate, glucose, electrolytes, FBC, clotting.

MD4 **Intubation** (call anaesthetist and consult PICU) see BM5
Consider using: Atropine 20 mcg/kg (max 600 mcg) AND Ketamine 1-2 mg/kg in shock or Thiopental (thiopentone) 3-5 mg/kg in RICP AND Suxamethonium 2 mg/kg (caution, high potassium). ETT size = age/4 + 4, ETT length (oral) = age/2 + 12 (use cuffed ET tube if possible). Then: Morphine (100 mcg/kg) and Midazolam (100 mcg/kg) every 30 min.

MD5 **Inotropes**
Dopamine at 10-20 mcg/kg/min. Make up 3 x weight (kg) mg in 50 ml 5% dextrose and run at 10 ml/hr = 10 mcg/kg/min. (These dilute solutions can be used via a peripheral vein).
Start Adrenaline via a central or IO line only at 0.1 mcg/kg/min.
Start Noradrenaline via a central or IO line only at 0.1 mcg/kg/min. for 'warm shock'.
Adrenaline & Noradrenaline: Make up 300 mcg/kg in 50 ml of normal saline at 1 ml/hour = 0.1 mcg/kg/min.

MD6 **Hypoglycaemia** (glucose < 3 mmol/l) 2 ml/kg 10% Dextrose bolus IV.

MD7 **Correction of metabolic acidosis** pH < 7.2
Give half correction bicarb IV.
Volume (ml) to give = (0.3 x weight in kg x base deficit ÷2) of 8.4% bicarb over 20 mins, or in neonates, volume (ml) to give = (0.3 x weight in kg x base deficit) of 4.2% bicarb.

MD8 **If K^+< 3.5 mmol/l**
Give 0.25 mmol/kg over 30 mins IV with ECG monitoring.
Central line preferable. Caution if anuric.

MD9 **If total Calcium < 2 mmol/l or ionized Ca^{++}< 1.0**
Give 0.1 ml/kg 10% $CaCl_2$ (0.7 mmol/ml) over 30 mins IV (max 10 ml) or 0.3 ml/kg 10% Ca gluconate (0.22 mmol/ml) over 30 mins (max 20 ml). Central line preferable.

MD10 **If Mg^{++}< 0.75 mmol/l**
Give 0.2 ml/kg of 50% $MgSO_4$ over 30 mins IV (max 10 ml).

MD11 Urgently **notify** public health of any suspected case of meningitis or meningococcal disease
Prophylaxis of household contacts of MD
www.gov.uk/government/publications/meningococcal-disease guidance-on-public-health-management
- Preferred: Ciprofloxacin single dose <5yrs 30 mg/kg up to max 125 mg; 5-12yrs 250 mg; >12yrs 500 mg *or*
- Rifampicin bd for 2 days: <1yr 5 mg/kg; 1-12yrs 10 mg/kg; >12yrs 600 mg *or*
- Ciprofloxacin, ceftriaxone *or* azithromycin may be used for pregnant and breast-feeding contacts of cases

For index case not treated with Ceftriaxone, prophylaxis when well enough.
Hib: prophylaxis may be indicated – consult public health

MD12 **Antibiotics** for confirmed and unconfirmed (but clinically suspected) meningococcal disease: IV Ceftriaxone for 7 days unless contraindicated BM3 (see bacterial meningitis algorithm for antibiotics against other pathogens)

Based on Early Management algorithm, Dept Paediatrics, Imperial College at St Mary's Hospital as described in Arch Dis Child 1999;80:290 & 2007;92:283 & on NICE CG102
www.nice.org.uk/guidance/cg102

Authors AJ Pollard (GDG chair), A Cloke, SN Faust, L Glennie, C Haines, PT Heath, JS Kroll, M Levin, I Maconochie, S McQueen, P Monk, S Nadel, N Ninis, MP Richardson, MJ Thompson, AP Thomson, D Turner.

Search...

Lumbar puncture is contraindicated in the following:

Signs of severe sepsis or rapidly evolving rash	Focal neurological signs †
Respiratory or cardiac compromise	Presence of papilloedema*†
Anticoagulant therapy/known thrombocytopenia	Continuous or uncontrolled seizures†
Infection at the intended site of LP	GCS ≤12**†

*inability to see the fundus is not a contraindication to LP

** LP may be safe at lower levels of consciousness
†Neuroimaging should be performed before LP for these indications. Once the patient is stable and if meningitis is likely (with or without sepsis) an LP may still be diagnostically useful, even after several days.

Strong predictors of bacterial meningitis from LP include:

- Opening pressure >30cm
- Neutrophils (polymorphs) >1200 cells/mL, leukocytes (all) >2000 cells/mL.
- Protein usually raised >2.2g/L
- CSF glucose is less than 60% of the peripheral glucose, or <1.9mmol/L.