Definitions

Meningitis: Inflammation of the meninges (abnormal number of white cells in CSF)
Bacterial meningitis: Meningitis + evidence of a bacterial pathogen in CSF
Aseptic meningitis: Meningitis + no bacterial pathogen in CSF on gram stain and routine culture

Causative Organisms

In bacterial meningitis, the organisms vary with age. In neonates, largely bacteria acquired at delivery (Gp B Strep., enterococci, E. coli, other gram neg enteric bacilli, Listeria). In older children, important bacteria are Strep. pneumoniae, N. meningitidis and H. influenzae type b (Hib). The incidence of Hib has fallen dramatically since the introduction of the vaccine.

Not all aseptic meningitis is viral. Consider an early or partially treated bacterial meningitis, a parameningeal focus (e.g. ear, sinus or cerebral abscess) with a “neighbourhood reaction” in the CSF, and tuberculosis. Other causes of aseptic meningitis are summarised in the appendix.

Pathogenesis

Most paediatric bacterial meningitis follows bacteraemia. The source of bacteraemia is seldom evident. Always look for multiple sites of infection. Rarely, infection may spread to the meninges directly from the sinuses, middle ear, mastoids, osteomyelitis of the skull or vertebral column, or through a connection to the outside world (skull fracture, dermoid sinus tract, meningocele).

Initial Assessment

- Level of consciousness - ideally Glasgow Coma Scale (GCS) - see Guideline on Coma
- Airway protective reflexes and adequacy of ventilation, especially if the level of consciousness is impaired (see note on respiratory acidosis below)
- Circulatory status, including heart rate, blood pressure and hydration
- Whether there are clinical signs of coagulopathy
Clinical Diagnosis

Symptoms and signs of meningitis vary with age, duration of illness and the child’s response to infection. Findings in neonates may be minimal, and in children less than 2 years neck stiffness may be absent. In the older child, fever, headache, photophobia, nausea and vomiting, mental confusion and lethargy, and/or excessive irritability are the usual initial symptoms.

- If there are localizing neurological signs, consider herpes encephalitis or cerebral abscess.
- Previous antibiotics make it difficult to exclude a partially treated bacterial meningitis.
- There are no clinical signs which reliably distinguish between bacterial and viral meningitis.

Some features may however support a viral aetiology: a well child with a mild illness, onset as part of a specifically viral illness (e.g. mumps), no alteration of level of consciousness, no features to suggest bacteraemia (in particular, no petechiae) and CSF findings consistent with a viral aetiology (WBC < 500, lymphocyte predominance with fewer than 35% polymorphs, normal protein and glucose, and no bacteria seen on microscopy).

Management of Shock / Hypoperfusion

It is important to maintain cerebral perfusion pressure (CPP), particularly where there is a possibility of cerebral oedema.

- Volume: normal saline (warmed in very small children), 10 - 20 ml/kg and repeat as necessary.
- Colloid (Gelofusine or 4% albumin) is a second-line option.
- Fresh frozen plasma may be required for clotting disturbance.
- Inotropes.

Initial Investigations

Lumbar puncture. This is not a priority if the child needs resuscitation. Antibiotics can begin without it. However, with increasing antimicrobial resistance, examination of the CSF is particularly important to guide therapy. Feigin states “early diagnosis and (appropriate) treatment in bacterial meningitis are imperative in reducing mortality and morbidity. A lumbar puncture should be performed unless there are specific contraindications”

<table>
<thead>
<tr>
<th>Contraindications to lumbar puncture (APLS Manual 3rd Ed 2002):</th>
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</thead>
<tbody>
<tr>
<td>Papilloedema</td>
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<tr>
<td>Septic shock or haemodynamic instability</td>
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<tr>
<td>Focal neurological deficits e.g. pupillary dilatation, ocular palsy, asymmetry</td>
</tr>
<tr>
<td>Signs of raised intracranial pressure (low HR, elevated BP, irregular breathing)</td>
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<tr>
<td>A bleeding diathesis or widespread purpura</td>
</tr>
</tbody>
</table>
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Other investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC, platelets, white cell differential count</td>
<td>Blood cultures</td>
</tr>
<tr>
<td>Serum Na+, K+, glucose, urea, creatinine</td>
<td>Coagulation studies if suspicion of coagulopathy</td>
</tr>
<tr>
<td>Capillary gas and oximetry, or arterial gas</td>
<td>PCR for N.meningitidis if pre-treated</td>
</tr>
</tbody>
</table>

Acidosis if metabolic will usually correct with treatment of shock, sepsis and seizures. If respiratory, consider hypoventilation, poor upper airway tone / airway obstruction or lung disease (aspiration).

The Cerebrospinal Fluid

The Normal Cerebrospinal Fluid (Pediatric Infectious Disease Journal, 1992;11:423-32)

<table>
<thead>
<tr>
<th></th>
<th>WBC / mm³</th>
<th>No. neutrophils</th>
<th>% neutrophils</th>
<th>Glucose mmol/l</th>
<th>CSF/blood glucose ratio</th>
<th>Protein g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prem neonate</td>
<td>9</td>
<td>0-29</td>
<td>7</td>
<td>0-66</td>
<td>2.8</td>
<td>1.3-3.5</td>
</tr>
<tr>
<td>Term neonate</td>
<td>8.2</td>
<td>0-22</td>
<td>61</td>
<td>2.8</td>
<td>2.8</td>
<td>1.9-6.6</td>
</tr>
<tr>
<td>0-4 wks</td>
<td>11</td>
<td>0-50</td>
<td>0.4</td>
<td>0-7.5</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>4-8 wks</td>
<td>7.1</td>
<td>0-50</td>
<td>0.18</td>
<td>0-2.1</td>
<td>2.9</td>
<td>0-42</td>
</tr>
<tr>
<td>&gt; 6 wks</td>
<td>2.3</td>
<td>0.68</td>
<td>0.35</td>
<td>3.4</td>
<td>2.5-3.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- Upper limit of normal (+ 2 SD) for CSF total WBC is 22/mm³ in term neonates, 35/mm³ age 0-4 weeks, 25/mm³ age 4-8 weeks and 5/mm³ in those older than 6 weeks.
- The absolute neutrophil count (ANC) = (total WBC x % neutrophils) x 10⁻². Only 5% of infants < 8 weeks have an ANC ≥ 1/mm³. Approximately 5% of all children older than 6 weeks of age have an ANC of up to 3/mm³, but 95% have no polymorphs in the CSF at all.
- In a bloody tap, the WBC:RBC ratio should not exceed the WBC:RBC ratio in the blood (usually 1:700 or more, although it may be as low as 1:250 in the presence of systemic leucocytosis).
- If there has been a bloody tap, subtract 0.01 g/l protein for every 1000 RBC / ml CSF.

Interpretation of CSF findings

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>WBC</th>
<th>Cytology</th>
<th>Glucose</th>
<th>Protein</th>
<th>Gram</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>200 - 5000</td>
<td>Polymorphs</td>
<td>Low</td>
<td>High</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Partly treated</td>
<td>200 - 5000</td>
<td>Mostly PMN</td>
<td>Low</td>
<td>High</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>100 - 500</td>
<td>Lymphocytes¹</td>
<td>Low²</td>
<td>High</td>
<td>-</td>
<td>+ (late)</td>
</tr>
<tr>
<td>Aseptic</td>
<td>100 - 700</td>
<td>Lymphocytes¹</td>
<td>Normal³</td>
<td>Slightly high</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In viral and Tb meningitis polymorphs may predominate early in the illness. In HSV, the CSF often contains many red cells. In viral meningitis, sugar may be low in up to 20% of patients. In Tb, it is usually < 50% blood glucose, but may be normal in up to 10% of patients.
Management

Admit all children who are unwell, have had a seizure or are less than 3 months old. Treat them as bacterial until CSF culture returns negative. A well child older than 3 months who has not received antibiotics and is thought to have viral meningitis may be followed as an outpatient.

Children where a clinical diagnosis of herpes simplex meningo-encephalitis is possible, should also be treated with IV Acyclovir. The dose is:
- 3 months – 12 years: 500 mg / m$^2$/ dose 8 hourly
- Over 12 years: 10 mg/kg/dose 8 hourly

General Management of Inpatients

- Quiet environment (if possible)
- Head-up positioning to reduce intracranial pressure (unless shocked)
- Frequent monitoring of: TPR, BP, Glasgow Coma Scale
- Measure head circumference daily in children < 2 years old
- Meticulous fluid balance. Monitor urine output in sick children by nappy weighing, or urethral catheter. Weigh the child once or twice daily.
- Oxygen is indicated for any patient at risk of hypoxaemia e.g. shock, seizures, decreased level of consciousness, intercurrent lung disease.
- SaO2 or PaO2 should be measured where supplemental O2 is being used
- Monitor serum [Na$^+$], looking for evidence of SIADH (see below)

Anticonvulsants

For any child who has fitted, is fitting or is likely to fit - unless there is a correctable biochemical abnormality (significantly low [Na$^+$], [glucose] or [Ca$^{2+}$]). Initial anticonvulsant therapy should be as below (see guidelines on convulsions - status epilepticus for more information).

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Loading Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>0.25 mg/kg</td>
<td>(max. 10 mg)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.5 mg/kg</td>
<td>(max. 10 mg)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20 mg/kg</td>
<td>(max. 1500 mg)</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>20 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

- Diazepam has only a short duration of effect. Ongoing anticonvulsant therapy should be instituted with Phenytoin.
- Phenytoin may produce an anti-SIADH effect which may be beneficial clinically.
- NB. Diazepam and Phenobarbitone given together can have additive respiratory depressant effects.

Pain relief

Regular Paracetamol (oral, NG or rectal: 10 – 15 mg/kg/dose (max. 1000 mg/dose) up to every four hours. For infants aged 1 to 3 months the total daily dose must not exceed 60mg/kg/day. Remember to prescribe a dose that is easy to measure and administer. Need for morphine is rare and may indicate other pathology. Patient needs careful review and discussion with consultant.
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Isolation
Respiratory isolation of bacterial meningitis caused by H. influenzae, N. Meningitidis or an unknown organism is necessary for the first 24 hours of therapy. S. pneumoniae does not require respiratory isolation, only contact precautions. Isolation of aseptic meningitis or encephalitis depends on the suspected aetiology (see Infection Control Manual: e.g. isolate mumps, measles, rubella, chicken pox, enterovirus but not HSV unless the child has skin lesions).

Maintenance Electrolyte and Glucose Requirements
- Sodium 2 - 3 mmol / kg / day if renal function is maintained
- Potassium 1.5 - 2 mmol / kg / day beginning after urine has been passed.
- Glucose 4 - 8g / kg / day (if possible despite fluid restriction).

Fluid management
Patients with meningitis require initial resuscitation as clinically indicated. Calculate usual rates of maintenance fluids, with appropriate adjustment for ongoing losses, while awaiting biochemistry. Fluid therapy should focus on avoiding both hypovolaemia and hypo-osmolality. Review the patient frequently, and check the serum [Na+] regularly (see “ongoing management” below).

Patients with meningitis are at high risk of developing hyponatraemia, and can be shown to have elevated levels of ADH. This is traditionally known as “inappropriate” ADH. However, there is good evidence that a key driver of ADH production is low blood volume. Many children with meningitis have unrecognised and under-treated hypovolaemia. In this situation, the raised levels of ADH are an appropriate attempt by the body to increase cerebral perfusion pressure.

Prevention of hyponatraemia
The best way to prevent hyponatraemia in meningitis is to ensure normovolaemia and to avoid excessive administration of free water. The best way to achieve this is by adequate resuscitation, treatment of the infection and appropriate volumes of isotonic maintenance fluids. Appropriate volumes of maintenance fluids can only be determined by close clinical observation of the patient.

There is disagreement about the volume of maintenance fluids required in meningitis. However, the fluid type should be 0.9% NaCl with 5% dextrose (10% may be required in infants) and KCl. Once you have resuscitated the patient, discuss the maintenance fluids with your consultant. In most cases, if the serum [Na+] is normal on admission, ordinary maintenance rates can be used.

Treatment of hyponatraemia
Hyponatraemia at presentation can usually be assumed to be dilutional, on the basis of elevated levels of ADH. This can be confirmed, if necessary, by a matched serum and urine osmolality. (A urine osmolality > 295 mosmol/kg simultaneous with a serum osmolality <270 is diagnostic). If serum osmolality is normal, an elevated urine osmolality has no diagnostic value.

If the serum [Na+] is low, ask: “Are there signs of HYPOVOLAEMIA that need correction?” If so, treat the hypovolaemia with 10 ml/kg boluses of normal saline. If hyponatraemia continues, discuss further management with your consultant. Fluid restriction may be required.
Severe Symptomatic Hyponatraemia - ADMIT TO PICU (especially if seizures), or [Na+] < 125.
In this situation:
- If normovolaemic, restrict fluids to as little as safely possible using 0.9% NaCl with 5% Dextrose (10% in infants) and monitoring blood glucose. Limit diluents for antibiotics and other medication.
- If normovolaemic, consider Frusemide 0.5 - 1 mg/kg IV
- Consider bringing the [Na+] up to 120 using hypertonic saline. The total dose (ml) required is (120-[Na+]) x wt x 4 / (% saline). Ideally the serum [Na+] should be increased by no more than 0.5 mmol/L/hr. However if the child is symptomatic the dose may need to be given faster. For example, 3% NaCl contains 517 mmol/l Na+ (≈0.5 mmol/ml). An infusion of 0.6 ml/kg/hr of 3% NaCl should raise the [Na+] by 0.5 mmol/hr.

Ongoing Management
- Frequent clinical review, including a careful assessment of volume status
- Check serum [Na+] 6 -12 hourly, depending on the initial [Na+], ongoing fluid losses, clinical status and whether there is a fluid restriction in place.
- NPM, or sips of water if fully conscious, thirsty and serum [Na+] normal. “Comfort” breast or bottle feeding on demand can begin when an infant is stable neurologically and wishes to feed.
- In a hyponatraemic child on fluid restriction, fluids can be increased slowly as condition improves and [Na+] normalises.

Specific Therapy for Bacterial Meningitis

Dexamethasone
All patients > 6 weeks old with presumed bacterial meningitis have Dexamethasone 0.15 mg / kg 6 hourly for 2 days. The first dose should be given 10 to 15 minutes before the first dose of antibiotic.

Antimicrobials (IV or IM)  Cefuroxime is not recommended

1. Suspected Pneumococcal Meningitis (Gram* cocci or gram* diplococci on CSF gramstain).

Add Vancomycin (15 mg / kg / dose, max. 500 mg/dose, IV over 60 minutes 6 hourly) to the regimen outlined below, and increase the dose of Cefotaxime to 75mg / kg / dose IV 6 hrly (max. 2000 mg/dose). Consider doing this in any very unwell child when LP is contraindicated but pneumococcus is strongly suspected. This covers the small possibility of penicillin-resistant pneumococci. Review at 48 hours when sensitivities are available.
2. Age Less Than One Month

<table>
<thead>
<tr>
<th>Birthweight</th>
<th>Antibiotic</th>
<th>Dose</th>
<th>Age (days)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2000g</td>
<td>Amoxycillin + Cefotaxime</td>
<td>50 mg / kg</td>
<td>0 - 7</td>
<td>12 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 - 28</td>
<td>6 hourly</td>
</tr>
<tr>
<td>&gt; 2000g</td>
<td>Amoxycillin</td>
<td>50 mg / kg</td>
<td>0 - 7</td>
<td>8 hourly</td>
</tr>
<tr>
<td></td>
<td>+ Cefotaxime</td>
<td></td>
<td>8 - 28</td>
<td>6 hourly</td>
</tr>
<tr>
<td>or</td>
<td>Amoxycillin + Gentamicin</td>
<td>50 mg / kg</td>
<td>0 - 7</td>
<td>8 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 - 28</td>
<td>6 hourly</td>
</tr>
</tbody>
</table>

Amoxycillin covers Listeria and Enterococci. Consider Cefazidime in a hospitalized LBW infant (possible nosocomial Pseudomonas infection).

3. Age One To Three Months

Amoxycillin 50 mg / kg / dose 6 hourly
+ Cefotaxime load 100 mg/kg then 50 mg / kg / dose 6 hourly

Amoxycillin and Cefotaxime or Ceftriaxone are required to cover both neonatal organisms and pathogens common in older children, especially Hib. Aminoglycosides have variable efficacy against Hib.

4. Age Greater Than Three Months

Cefotaxime Load 100 mg/kg then 50 mg/kg/dose (max. 2000 mg/dose) 6 hourly
Or
IM Ceftriaxone (If IV access unobtainable). Load 80-100 mg/kg, then 80-100 mg/kg/dose (max. 2000 mg/dose) every 24 hours starting 12 hrs after load

5. Continuing Therapy.

Once sensitivities are available, change to narrower spectrum monotherapy:

- **Hib (β lactamase negative)***
  - Amoxycillin 50 – 100 mg / kg / dose (max. 2000 mg/dose) 6 hrly IV 7-10 days
- **Pneumococcus***
  - Penicillin G 50 mg / kg / dose (max. 2400 mg/dose) 4 – 6 hrly IV 10-14 days
- **Meningococcus***
  - Penicillin G 50 mg / kg / dose (max. 2400 mg/dose) 4 – 6 hrly IV *

*Meningococcus treatment duration:
- For the uncomplicated child > 12 months: 4 days
- For those <12 months or with a more complicated course: 7 days minimum
**Indications for Admission to PICU**

- Inadequate airway protection
- Impaired level of consciousness, GCS < 13
- Signs suggestive of severe increase in ICP e.g. hypertension, bradycardia, papilloedema, pupillary changes
- Hypoventilation or respiratory failure
- Oxygen saturation < 90% in > 40% oxygen
- Uncontrollable or poorly controlled seizures
- Hypotension or tachycardia not responsive to fluid resuscitation
- Renal failure
- Serum [Na+] < 125 mmol/l (see above)
- Children with significant purpura or rapidly progressive petechiae
- Consider if still unstable after 40mls/kg resuscitation fluid

**Paediatric Infectious Diseases Team**

In Starship, patients with meningitis will usually be under the ID Team, though the initial management may be under the acute team of the day. The ID Team is available for consultation 24 hours a day 7 days a week. During working hours contact the registrar (93 4095), or on call consultant. After hours, contact the Paediatric Infectious Diseases consultant on call through the Auckland Hospital operator. The team likes to be consulted freely on children with meningitis, especially those with raised intracranial pressure or shock. Admissions to PICU for meningitis should be notified to the ID team.

**Notification to the Local Public Health Service**

Notify cases of Meningococcal and H. Influenzae type b disease to the Medical Officer of Health at the local Public Health Service as soon as possible. The Public Health Service will commence follow up of contacts of cases within 24 hours of notification, during daylight hours.

For cases in the Auckland region, call Auckland Regional Public Health Service on 09 623 4600 (ARPHS’ 24 hours per day, 7 days per week number).
Prophylaxis for N. Meningitidis and H. Influenzae Infection

This is vital to prevent disease in close contacts of the index case. A public health team is contracted to provide Rifampicin prophylaxis 7 days a week during daylight hours, within 24 hours of notification. **They prefer us not to dispense prophylaxis to relatives of cases in our care.**

Treatment with Cefotaxime or Ceftriaxone has been shown to eliminate the carriage of Haemophilus influenzae, so Rifampicin is not needed for the index case. The recommendations for prophylaxis (including recommendations for medical personnel) are detailed below.

Precautions for Rifampicin: liver disease, pregnancy (pregnant contacts receive Ceftriaxone). A contact who may be pregnant should have a pregnancy test before prophylaxis. Rifampicin turns urine red and can stain contact lenses red. It affects the metabolism of Chloramphenicol.

**Neisseria Meningitidis (Meningococcus)**
- **Who Receives Prophylaxis?** Household, day care centre and nursery contacts, also persons who have had contact with the patient’s oral secretions through kissing, sharing food or drink etc. Broadly, contacts who have eaten and/or slept with the index case. Prophylaxis is not recommended routinely for medical personnel except those who have had intimate exposure (such as mouth-to-mouth resuscitation, intubation or suctioning) before antibiotic therapy.
- **When Should They Receive It?** Preferably within 24 hours of diagnosis of index case, because 50% of secondary cases of meningococcal disease occur within 5 days of the index case.
- **What Is The Dosage Schedule?** Four doses over 48 hours (12 Hourly). Each dose is 10mg/kg, max. 600 mg/ dose. Some recommend reducing the dose for infants < 1 month old to 5mg/kg

**Haemophilus influenzae type b (all invasive disease)**
- **Who Receives Prophylaxis?** All household contacts, including adults, in households with at least one unvaccinated contact < 48 months. All members of a household with a child <12 months old (ie, with a child who has not yet received the 15 month vaccine dose) should receive Rifampicin prophylaxis, regardless of the vaccination status of the child. A household contact is defined in these circumstances as an individual residing with the index patient, or a non-resident who spent 4 or more hours with the index patient for at least 5 of the 7 days prior to the admission of the index patient. Prophylaxis of day care contacts is controversial.
- **When Should They Receive It?** As soon as possible. Do not delay to swab. Fifty-four percent of secondary cases occur in the first week after admission of the index case.
- **What Is The Dosage Schedule?** Four doses over 4 days. Each dose is 20 mg/kg to a maximum of 600 mg. The dose for infants less than 1 month old is not established. Some experts recommend lowering the dose to 10 mg/kg in these infants.
Appendix - Causes of Aseptic Meningitis

Infectious Agents and Diseases

Bacteria: Partially treated meningitis, Tb, parameningeal focus (brain abscess, epidural abscess), bacterial endocarditis, brucellosis
Viruses: Enteroviruses, mumps, lymphocytic choriomeningitis, Epstein-Barr, arboviruses, cytomegalovirus, herpes simplex, HIV
Rickettsiae: Rocky Mountain spotted fever
Spirochetes: Syphilis, leptospirosis, Lyme disease
Mycoplasma: M pneumoniae, M hominis (neonates)
Fungi: Candida albicans, Coccidioides immitis, Cryptococcus neoformans
Protozoa: Toxoplasma gondii, malaria, amoebas, visceral larva migrans
Nematode: Rat lung worm larvae (eosinophilic meningitis)
Cestodes: Cysticercosis

Non-infectious Diseases

Malignancy: Primary medulloblastoma, metastatic leukaemia, Hodgkins disease
Collagen-vascular disease: Lupus erythematosus
Trauma: Subarachnoid bleed, traumatic lumbar puncture, neurosurgery
Granulomatous disease: Sarcoidosis
Direct toxin: Intrathecal injections of contrast media, spinal anaesthesia
Poison: Lead, mercury
Drug induced: OKT3, Ig, isoniazid, sulfamethizole, cotrimoxazole, azathioprine
Auto-immune disease: Guillain-Barre syndrome

Unknown:

Multiple sclerosis, Mollaret's meningitis, Behcet syndrome, Kawasaki disease, steroid-responsive relapsing encephalomyelitis, Vogt-Koyanagi-Harada syndrome

References