Congenital infection: Diagnosis and management

Overview:

- Infections transmitted and acquired in utero.
- Most as a result of primary infection of mother during pregnancy, some organisms such as Cytomegalovirus (CMV) and Herpes simplex virus (HSV), can also occur following reactivation during pregnancy.
- For some infections, specific measures exist (e.g. Rubella immunisation programme); however, prevention largely consists of general hygiene advice such as good hand-washing, keeping food preparation surfaces clean, and the avoidance of undercooked meats and unpasteurised dairy products.
- Antenatal diagnosis challenging and requires high index of suspicion. Mother usually entirely asymptomatic, or experience only mild ‘flu-like’ illness.
- IgG positive indicates a previous infection but not useful in determining timing. Not always present in early infection.
- IgM positive indicates recent infection. Will persist at least a month but usually longer. Can also be detected when a latent infection reactivates, e.g. CMV.
- Potential clues: maternal rash, miscarriage, premature birth, anomalies on foetal USS, history of maternal contact with a disease. In these instances, screening serology to demonstrate seroconversion in mother may be helpful.

Relative frequency of features in CMV, Syphilis and toxoplasmosis:

Use clinical pattern of disease as a guide to specific testing. Previously requested ‘TORCH’ screen is now obsolete.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Syphilis</th>
<th>CMV</th>
<th>Toxoplasmosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcephaly</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>+</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Calcification</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Deafness</td>
<td>-</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cataracts</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepatosplenomegaly (HSM)</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Purpura</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>-</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Bony involvement</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Classic features</td>
<td>Rash on palms and soles, persistent snuffles, HSM, interstitial keratitis, hydrops</td>
<td>Jaundice, petechiae, HSM</td>
<td>HSM, petechiae, eye defects, intracranial calcifications</td>
</tr>
</tbody>
</table>
Congenital Cytomegalovirus

Background:

- Most common congenital infection.
- May occur following either primary or recurrent maternal infection (1-4% of susceptible women acquire CMV during pregnancy, with reactivation occurring in 10% of seropositive women).
- Risk of both transmission and of clinical sequelae is higher after primary infection, particularly if acquired at earlier gestations.
- Most infants asymptomatic, but CMV is the most significant cause of non-genetic sensorineural hearing loss (SNHL) and can cause significant neurological impairment.

The approximate composition of congenital CMV babies in the UK:

Who to screen: infants with unexplained IUGR, unexplained thrombocytopenia, or with >1 of the above neonatal features. If positive, check mother’s current serology and if possible compare with serology earlier during pregnancy.

How to screen / diagnosis: Virus isolation (culture or PCR) from urine or saliva or within first 3 weeks of life. Retrospective diagnosis from Guthrie possible but high false negative rate, so early testing essential if suspect CMV.

Who to treat: Current best evidence suggests treatment should be limited to those with:

- symptomatic CNS disease: microcephaly (if in combination with other signs), radiological abnormalities on MRI or CrUSS, abnormal csf parameters or a positive CMV csf PCR, chorioretinitis, or a sensorineural hearing loss diagnosed by brain stem evoked responses (BSER).
- severe focal organ disease: hepatitis, bone marrow suppression – ie anaemia, neutopenia, thrombocytopenia, colitis or pneumonitis.

Weekly monitoring for neutropenia, thrombocytopenia and anaemia is required. Treatment should be discontinued (but discussed with infectious disease consultant) if neutrophil count drops to <0.5 x 10^9/l or platelets drop to < 50 x 10^9/l. It can be recommenced if values improve to > 0.75 x 10^9/l or > 50 x 10^9/l respectively. Weekly monitoring of LFTs and renal function are also required.
Suggested management and follow-up protocol (to be adapted locally based on resource availability)

Confirmed diagnosis within first 21 days of life (any of):
- CMV PCR on saliva / urine
- Retrospective diagnosis on dry blood spot

Investigations

Bloods (FBC, U+E, LFTs); auditory assessment, ophthalmology assessment; CRUSS +/- MRI

Asymptomatic / no focal organ or CNS disease

No treatment

If investigations normal and asymptomatic (or no focal organ / CNS symptoms), no treatment is advised

Symptomatic focal organ or CNS disease

Treat – dosing + monitoring

- Ganciclovir 6mg/kg IV BD 6 weeks (or Valganciclovir 16mg/kg/dose BD PO 6 weeks).
- Treat at least 6 week but may be longer in severe disease
- FBC, LFT, U+E weekly
- Viral load weekly
- Therapeutic drug monitoring

Follow up

- Paediatric clinical at 12 months
- Audiology 3-6 monthly until 3 years old then annually until 6 years old

- Paediatric clinical at 6 + 12 months
- Audiology 3-6 monthly until 3 years old then annually until 6 years old
- Neurodevelopmental assessment at 1 year
- Ophthalmology annually until 5 years old

UK CMV expert:
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Congenital Syphilis

Background:

- caused by a spirochete bacterium, *Treponema pallidum*, which, if not treated promptly, can result in serious short and long-term morbidity. Incidence has been increasing over the past five years in the United Kingdom.
- syphilis may be transmitted via the placenta, at any stage of pregnancy, and may result in miscarriage, pre-term labour, stillbirth, hydrops and congenital syphilis.

Who and how to screen:

- all pregnant women offered screening. Women with syphilis positive results should be referred to a GUM or Sexual Health Service specialist for treatment and follow up.
- a referral letter should be sent to a paediatrician with an interest in infectious diseases by the obstetrician/antenatal screening coordinator to ensure a birth plan is made and follow up plans for the neonate.
- all infants born to seropositive mothers should be considered exposed to Syphilis unless good evidence of complete treatment and response in mother. The paediatrician should be informed, if possible, before or immediately following the delivery and postnatal/neonatal clotted and EDTA samples taken.
- a 5ml plain tube from the mother and a neonatal sample of at least 0.5ml venous blood (not cord blood) should be taken and sent together to the laboratory. These samples need to be taken on the same day and ‘linked’ to ensure that the laboratory is aware of the connection; they require testing in parallel.
- NPA (nasopharyngeal aspirate) from the neonate for syphilis PCR may also be indicated and requires discussion with the virology consultant/microbiology consultant prior to being sent.

Neonatal management:

- evaluate as per figure 1 below. Treatment of the neonate should commence only after discussion with consultant Neonatologist / paediatrician consultant in medical microbiology or virology.
- further investigations should include FBC, LFT and renal function. CSF analysis (cells, protein, serology), Ophthalmology review, and x-ray of long bones (lesions found in up to 20% of asymptomatic, and most symptomatic) are also indicated.

Treatment: Benzyl penicillin 30mg/kg BD IV if in first 7 days of life, and then 30mg/kg 8 hourly after 7 days of life. Total duration of treatment is 10 days.

*Figure 1: Management of infants at risk of congenital syphilis*

Symptomatic infant

- Infant RPR titres 4 fold higher than maternal titres or EIA IgM positive
- Mother inadequately treated (less than 3 fold fall in RPR titres) or treatment uncertain
- Mother treated < 4 weeks prior to delivery
- Treated with non-penicillin regimen
- Follow-up of infant uncertain

Treat as congenital Syphilis

Maternal reactive RPR + Treponemal tests

Paired maternal + infant blood
EIA IgG + IgM, TPHA, RPR

Mother treated > 4 weeks prior to delivery AND with penicillin based regimen with no evidence of relapse

Mother treated prior to pregnancy with no changes in titres of serology tests

Serology follow-up: 0, 3, 6, 12 months or until all negative

Treat as congenital Syphilis if rising titre or if symptoms develop

Asymptomatic infant
Congenital Toxoplasmosis

Background:
- causative organism is the parasite *Toxoplasma Gondii*. Acquired by ingestion of cyst-containing tissues in undercooked meat, or of oocysts excreted by cats which contaminate soil or water.
- vertically transmitted to foetus and can lead to inflammatory lesions affecting the brain, retina and choroid which can cause permanent neurological and visual sequelae and, rarely, foetal or postnatal death.
- UK Seroprevalence around 8%, incidence of congenital infection around 3 per 100,000.
- the risk of maternal-fetal transmission increases with advancing gestational age at time of maternal infection (from around 5% in the first trimester, to 80% just prior to delivery), with overall transmission rates being about 25%. Conversely, the risk of clinical sequelae is highest if transmitted in the early stages of pregnancy (60-80% in first trimester).

Who and how to screen:
- routine antenatal and neonatal screening for Toxoplasmosis is not performed in UK because of low prevalence of disease, relatively high false positive screening results, and limited evidence of the benefit of prenatal treatment in reducing transmission of infection from mother to foetus.
- if antenatal infection is detected, mother may be treated with spiramycin in an attempt to reduce transmission of infection, and/or severity of its impact on the foetus/newborn.
- screen infants if mother thought to be affected or if clinical signs (>90% asymptomatic, more common signs include prematurity, IUGR, jaundice, hepatosplenomegaly, petechiae, cataract and microphthalmia).
- serological tests during pregnancy for evaluation of maternal infection are interpreted as shown below. In addition, PCR analysis of amniotic fluid is possible. Foetal ultrasound looking for typical, but non-specific findings including hydrocephalus, brain or hepatic calcifications, splenomegaly and ascites also offer diagnostic clues.

Maternal Serology:

<table>
<thead>
<tr>
<th>IgG negative</th>
<th>IgM negative</th>
<th>No evidence of infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG negative</td>
<td>IgM positive</td>
<td>False positive IgM or early infection – repeat test, if same probably false positive IgM</td>
</tr>
<tr>
<td>IgG positive</td>
<td>IgM positive</td>
<td>Suggests acute / recent infection</td>
</tr>
<tr>
<td>IgG positive</td>
<td>IgM negative</td>
<td>Previous infection</td>
</tr>
</tbody>
</table>

- postnatal diagnosis is challenging. Detection of neonatal IgM and IgA by enzyme immunoassay and/or by immunosorbent agglutination assay is considered diagnostic of neonatal infection.
- however, current assays often fail to detect IgM in neonatal serum, and passively acquired IgG makes interpretation of routine serology difficult. Therefore, where primary maternal infection during pregnancy cannot be excluded, serial infant specimens should be analysed over the first 12 months of life.
- passive infection will lead to disappearance of IgG by 1 year of age. Persistence confirms congenital infection.

Management:
- treatment of congenitally infected children should always be initiated after detailed discussion with microbiologist and a paediatric infectious disease specialist.
- optimum treatment regimen and duration are not well established but most standard regimens consist of a combination of pyrimethamine and a sulphonamide (sulphadiazine or sulphadoxine).
- these treatment regimens can cause bone marrow toxicity (hence folic acid given) and at least twice monthly FBC is advised to monitor for neutropenia, and thrombocytopenia.
## Treatment regimens

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic / mildly affected&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Severely affected&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pyrimethamine</strong></td>
<td>1mg/kg/d for 2 months then 0.5-1mg/kg 3 times per week for 10 months</td>
<td>1mg/kg/d for 6 months then 0.5-1mg/kg 3 times per week for 6 months</td>
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<tr>
<td><strong>and</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Sulphadiazine</strong></td>
<td>100mg/kg/d for 1 year</td>
<td>100mg/kg/d for 1 year</td>
</tr>
<tr>
<td><strong>and</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Folinic acid</strong></td>
<td>50mg once weekly</td>
<td>50mg once weekly</td>
</tr>
<tr>
<td><strong>Pyrimethamine / sulphadoxine</strong> combination (25/500mg) – Fansidar and <strong>Folinic acid</strong></td>
<td>1.25mg/kg &amp; 25mg/kg every 15 days for 1-2 years</td>
<td>1.25mg/kg &amp; 25mg/kg every 7 days for 1-2 years</td>
</tr>
</tbody>
</table>

<sup>a</sup> - ≤ 1 ocular lesion and/or ≤ 3 intracerebral calcifications

<sup>b</sup> - neurological signs and/or > 1 ocular lesion and/or > 3 intracerebral calcifications

### Follow-up:

No specific guidance is available and will depend on the nature and extent of organ involvement. As a minimum the child should have regular follow up with:

- **ophthalmology**: when actively investigated, retinocchoroiditis and/or intracranial lesions (e.g. calcifications, hydrocephalus, epilepsy) are detected in 17% of infected infants in the postnatal period. Further eye lesions can appear at any stage of life as a result of reactivation of latent cysts in the retina and choroid. Progression to severe neurological impairment is rare (less than 5%), but the extent of milder neurodevelopmental problems is uncertain.
- **neuro-developmental paediatrician**.
- **paediatrician with a special interest in infectious diseases**.

### References:


Chakraborty R, Luck S. Syphilis is on the increase: Implications for child health. *Arch dis child* Feb 2008; 93(2):105-9


Robert-Gangneux F, It is not only the cat that did it: How to prevent and treat congenital toxoplasmosis, *J Infect* (2013), http://dx.doi.org/10.1016/j.jinf.2013.09.023

UK national screening committee. *Screening for toxoplasmosis* January 2011.

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