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>Microcephaly</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Hydrocephaly</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Calcification</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Deafness</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Eyes</td>
<td>Microphthalmia</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Chorioretinitis</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Cataracts</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.

Who to screen: infants with unexplained IUGR, unexplained thrombocytopenia, unexplained ventriculomegaly 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, neutropenia, 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
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

- Oral Valganciclovir 16mg/kg/dose BD
- Ganciclovir 6mg/kg IV BD if not tolerating oral treatment
- Treatment will usually be for 6 months
- FBC, LFT, U+E at 0, 2 and 4 weeks, then monthly
- Viral load at 0, 1 and 6 months

**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

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)
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, fetal 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 immunosorbert 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</th>
<th>Severe affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimethamine</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>
</tr>
<tr>
<td>and Sulphadiazine</td>
<td>100mg/kg/d for 1 year</td>
<td>100mg/kg/d for 1 year</td>
</tr>
<tr>
<td>and Folinic acid</td>
<td>50mg once weekly</td>
<td>50mg once weekly</td>
</tr>
<tr>
<td>Pyrimethamine / sulphadoxine combination (25/500mg) – Fansidar and Folinic acid</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>

**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, retinochoroiditis 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.

NB: Folinic acid is a derivative of folic acid and given to negate the side effects of Pyrimethamine which impairs folic acid metabolism.
**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 (Dr Jennifer Evans, based at UHW, in South Wales) by the obstetrician/antenatal screening coordinator to ensure a ‘Syphilis birth plan’ (see below) is made with 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.
- it is important to explain to mother the implications of any positive testing, to include treatment options and any further monitoring they may be required.
- you must ensure results are chased. Any insufficient samples need to be repeated and discuss any positive results or uncertainty with consultant neonatologist / consultant paediatrician with infectious disease expertise.

**Neonatal management:**

- where available, review the ‘Syphilis birth plan’ in mother’s notes.
- treatment of the neonate should commence only after discussion with consultant Neonatologist / paediatrician and consultant in medical microbiology or virology.
- investigations, treatment and follow-up guidance is detailed in the syphilis birth plan (below)

**Treatment:** Benzyl penicillin 25mg/kg BD IV if in first 7 days of life, and then 25mg/kg 8 hourly after 7 days of life. Total duration of treatment is 10 days.

**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
SYPHILIS BIRTH PLAN
To Midwife / Obstetric Team

No need to contact on-call paediatric team from syphilis viewpoint □
Contact on-call paediatric team when baby is delivered □
Send placenta for histology and PCR if treatment indicated for infant □

Mother's name .............................................................. Mother's DOB ..............................................................
Mother's address ..............................................................
Mother's hospital number ...................................................... Mother's GUM number ......................................................
Mother's consent to record GU number in hospital records: □
Mother's phone numbers: Mobile ..............................................
Landline ..............................................................
Estimated date of delivery ..............................................................

MATERNAL SYphilis DIAGNOSIS:
Adequately treated before this pregnancy □
Early latent □
Late latent □
Other examples:
primary □
secondary □
Inadequately treated/treatment not documented □
Possibility of re-infection from untreated partner □
Unbooked □

GUM ADVICE TO PEDIATRICIANS
Infant requires no physical examination above routine. No syphilis serology □
Assess infant clinically; if no physical signs of syphilis check 'initial blood tests' (see page 2) □
Treat infant at birth after clinical assessment, 'initial blood tests' and 'further tests' (see page 2) □

Please discuss all infant blood test results with GUM & Paediatric infectious diseases team. Out of hours, contact the GUM or infectious diseases registrar on call via switchboard

Signed .............................................................. (GUM Consultant) .............................................................. Date ..............................................................

COPIES (of pages 1–4 only) TO CONTACTS: Matron, Delivery Suite; .................................................. Neonatal consultant,
GP gets copy of page 1 only
Pediatric ID Consultant .................................................. Obstetric Consultant,
Screening Midwife ..............................................................
PHYSICAL SIGNS OF EARLY CONGENITAL SYPHILIS

- Jaundice, anaemia, generalised lymphadenopathy, hepatosplenomegaly, non-immune hydrops, pyrexia, failure to move an extremity (pseudoparalysis of Parrot), low birth weight.
- Skin rash (usually maculo-papular but almost any form of rash is possible); palms and soles may be red, mottled and swollen. Vesicles or bullae may be present.
- Condylomata lata (flat, wart-like plaques in moist areas such as perineum)
- Osteochondritis, periostitis (elbows, knees, wrists)
- Ulceration of nasal mucosa, rhinitis (‘snuffles’ usually after the first week of life)

Approximately half of all neonates with congenital syphilis are normal on initial examination

INITIAL BLOOD TESTS

Send a venous blood sample for serum RPR and treponemal IgM (take blood from the neonate, not the umbilical cord).

ADDITIONAL TESTS ON INFANT IF LESIONS PRESENT (see page 4)

1. T pallidum polymerase chain reaction (PCR) test
2. Dark ground microscopy (DGM)

FURTHER TESTS IF TREATMENT INDICATED (see below)

1. FBC, U+E, LFT, ALT/AST
2. HIV antibody
3. Lumbar puncture for CSF WCC, VDRL or RPR, TPPA, protein
4. Long bone X-rays for osteochondritis and periostitis
5. Chest X-ray for cardiomegaly
6. Cranial U/S scan
7. Ophthalmology assessment for interstitial keratitis
8. Audiology for 8th nerve deafness

INDICATIONS FOR FURTHER TESTS AND TREATMENT

1. Mother inadequately treated (GUM consultant will advise, see above)
2. Infant has clinical signs consistent with syphilis
3. Infant’s RPR/VDRL titre 4x mother’s on two occasions (e.g. mother’s RPR 1:4, infant’s RPR 1:16). Sample from mother to be taken no greater than 4 weeks before that of infant.
4. Infant has positive treponemal IgM test together with corroborative history, clinical signs. GUM consultant will advise.
5. Infant has positive dark ground microscopy
6. Infant has positive T pallidum PCR test together with corroborative history, clinical signs. GUM consultant will advise.

TREATMENT OF NEWBORN

Benzylpenicillin 25 mg/kg i.v. hourly IV for 7 days, then 8 hourly on days 8, 9 and 10 (total of 10 days)
INFANT FOLLOW-UP

Ideally, this should be done in liaison with consultant colleague in genitourinary medicine.

1. Infants treated for syphilis at birth
   Months 1 and 2: check RPR and treponemal IgM.
   Month 6: check RPR.
   Month 12: check RPR. Discharge if RPR has achieved sustained 4x drop from peak level.

2. Infant not treated for syphilis
   RPR <4 x mother’s. IgM negative at birth
   Month 3: check RPR and treponemal IgM.
   Month 6: check RPR. if negative discharge, if positive repeat at 12 months.
   Month 12: RPR negative, no further follow-up.
   Month 12: RPR still positive, discuss with GUM colleague.

(Nota: the RPR is usually negative by six months).

3. Infant not treated for syphilis and RPR and IgM negative at birth
   Month 3: repeat RPR and IgM and discharge if still negative.
   Month 3: RPR and/or IgM positive - discuss with GUM colleague.

Neonatal RPR should be negative by 6 months of age and the TPPA by 18 months of age when they are reactive as a result of passive transfer of maternal antibodies.

SIBLINGS FOR SCREENING

None: ☐

Name(s): ___________________________________________ DOB: ___________ Sex: ___________

__________________________________________

__________________________________________

__________________________________________

__________________________________________

__________________________________________
GUIDE TO INFANT LABORATORY TESTS

Treponemal IgM
A positive treponemal IgM test is supportive of a diagnosis of congenital syphilis, but must be interpreted in conjunction with the history, clinical signs and results of other syphilis blood tests. A negative IgM test does not exclude infection as the IgM response may be delayed or suppressed.

Rapid plasma reagin (RPR) or Venereal disease research laboratory (VDRL) test
The RPR and VDRL are different versions of the same test and availability will vary between laboratories. Passive trans-placental transfer of maternal IgG antibodies may cause a false positive RPR/VDRL test in the newborn but these usually revert to negative by 6 months. A positive RPR/VDRL titre at a titre four-fold or more that of the mother (e.g. mother’s t: 4, infant t: 16) supports a diagnosis of congenital syphilis, and should be repeated. Ideally, maternal and infant tests should be timed as closely as possible and no greater than one month apart.

A neonatal RPR/VDRL titre less than four-fold that of the mother’s (e.g. mother t:16, infant t:8) does not exclude congenital syphilis. Please discuss all neonatal test results with GUM and Paediatric ID consultant.

Full blood count
May show non-haemolytic anaemia, leucocytosis or leucopenia, thrombocytopenia, polychromasia, or erythroblastaeemia.

Liver function tests/transaminases
Syphilitic hepatitis may cause elevated levels of alkaline phosphatase, AST/ALT, bilirubin.

U+E, creatinine
Syphilis can cause glomerulonephritis resulting in uraemia.

Polymerase chain reaction (PCR) testing
Ulcers, nasal discharge, mucous membrane lesions or moist skin rashes can be swabbed and the sample sent in viral transport medium (to Clinical Virology, Manchester Royal Infirmary) for T pallidum PCR testing.

Dark ground microscopy (DGM)
Ulcers, nasal discharge, mucous membrane lesions or moist skin rashes can be sampled and used to directly visualise T pallidum. However, specimen collection and microscopy require prior training. Microscopy should take place as soon as possible after the specimen is obtained. Call GU Medicine if you wish to perform DGM.

Placenta
The syphilitic placenta may appear macroscopically normal. If the fetus is severely affected by syphilis the placenta may appear paler, larger and thicker than normal. Histology of the placenta and cord (with special staining) may provide evidence of congenital infection.

Radiology
Most bone lesions in congenital syphilis are not clinically apparent. However, osteochondritis, periostitis and osteomyelitis are frequently present, most often in the long bones and ribs. Periostitis of the skull can produce frontal bossing on x-ray.
FOR GU MEDICINE USE

MATERNAL FACTORS

DECREASING NEONATAL RISK
- Treatment completed
- Treated with penicillin
- Treatment completed >30 days pre-delivery
- Late syphils
- 4x drop in RPR achieved
- Final RPR titre <1 in 2 (VDRL I in 1)
- HIV negative

INCREASING NEONATAL RISK
- Partial or no treatment*
- Treated with non-penicillin*
- Treatment <30 days before delivery*
- Early syphilis
- 4x drop in RPR not achieved
- Final RPR titre >1 in 4 (VDRL >1 in 2)
- HIV positive

*The presence of any one of the ‘bold’ (asterisk) factors above constitutes inadequate maternal treatment and requires treatment of the infant at birth.

Congenital syphils can still occur despite the absence of any of the three ‘bold’ factors.

Copy pages 1–4 to those on circulation list. Copy pages 1–5 to be retained in GUM notes.