NOTES
PERINATAL INFECTIONS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Infections during pregnancy, birth
  - Teratogenic/other adverse effects on fetus, neonate
  - Congenital infections cross placenta, infect fetus *in utero*
  - Neonatal infections shortly before, during, after delivery

RISK FACTORS

- Maternal infection

COMPLICATIONS

- Premature birth; intrauterine growth restriction; tissue damage, related sequelae

SIGNS & SYMPTOMS

- Self-limiting to life-threatening conditions

DIAGNOSIS

- Maternal prenatal, delivery history; neonatal physical examination
- Imaging

LAB RESULTS

- Culture, serology testing

TREATMENT

- Address complications

MEDICATIONS

- Antimicrobials

CONGENITAL CYTOMEGALOVIRUS INFECTION

osms.it/congenital-CMV-infection

PATHOLOGY & CAUSES

- Clinical syndrome affects developing fetus, neonate
  - Caused by *Cytomegalovirus* (CMV) perinatal infection
  - *Herpesvirus* family
- Enveloped, double-stranded linear DNA, icosahedral viral capsid
  - Toxoplasmosis, other (syphilis, *Varicella zoster*, parvovirus B19), rubella, CMV, herpes (TORCH) infection
  - Tends to become latent, reactivate
- Highly-prevalent virus; not very contagious
  - Infects all ages
  - Approx. one-third of children are infected with CMV by age five
  - > half of adults are infected by age 40
- Virus spreads to fetus transplacentally/may be acquired via maternal genital contact during delivery/through breastmilk

Maternal infection

- Direct infectious body-fluid contact (e.g. saliva, urine, sexually transmitted); blood transfusions; transplanted organs; household contact, close contact with young infected children (e.g. daycare centers)
  - Usually asymptomatic in adults

RISK FACTORS

- Maternal infection

COMPLICATIONS

- Fetal/neonatal
  - Sensorineural hearing loss (SNHL), chorioretinitis, microcephaly, neurodevelopmental disability, seizure, anemia (hemolytic), pneumonitis, dental irregularity

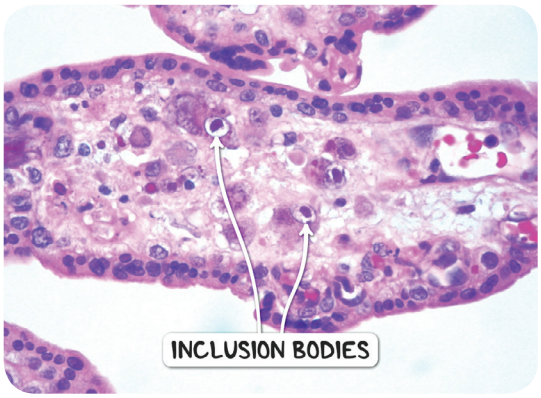

Figure 131.1 Histological sections of chorionic villi demonstrating nuclear inclusions seen in congenital cytomegalovirus infection.

SIGNS & SYMPTOMS

- Birth
  - May be asymptomatic
- Small for gestational age, petechial rash, "Blueberry muffin" rash, hypotonia, weak suck, hepatosplenomegaly, jaundice

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan/MRI

- Neuroimaging
  - Intracranial calcification, ventriculomegaly, white matter disease, periventricular leukomalacia, corpus callosum dysgenesis, cerebellar hypoplasia

Auditory brainstem response (ABR)

- Hearing deficit

Ultrasound

- Suggestive prenatal fetal diagnostic findings
  - Growth restriction, ventriculomegaly, microcephaly, periventricular calcification, hepatic calcification, hydrops/ascites, echogenic bowel

LAB RESULTS

- Maternal prenatal, delivery history; positive maternal CMV immunoglobulin G (IgG), CMV immunoglobulin M (IgM) antibody; neonatal examination

Microbe identification

- Positive culture (urine, saliva)
- Polymerase chain reaction (PCR) (blood, urine, saliva)
- CMV antigens (pp65) in peripheral leukocytes

Blood studies

- ↑ liver transaminases
- ↑ direct, indirect serum bilirubin
- ↓ white blood cells (WBCs), ↓ platelets, ↓ red blood cells (RBCs)

TREATMENT

- Address complications

MEDICATIONS

- Antiviral therapy
  - Intravenous (IV) ganciclovir/oral (PO) valganciclovir

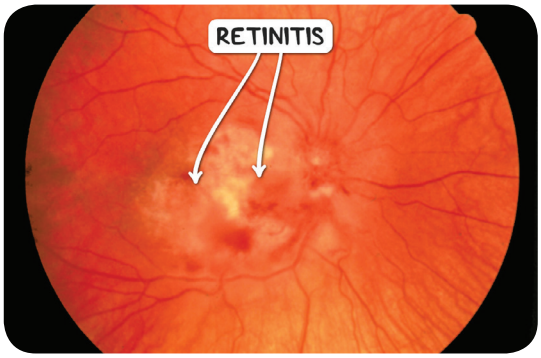

Figure 131.2 Retinal photograph demonstrating the necrotizing retinitis of CMV infection. The retinitis will typically spread in a "brush fire" pattern.

CONGENITAL RUBELLA SYNDROME

osms.it/congenital-rubella-syndrome

PATHOLOGY & CAUSES

- Syndrome caused by fetal rubella virus infection
  - Enveloped, positive-sense, single-stranded RNA virus
  - *Rubivirus* in *Togaviridae* family
  - Humans are only natural hosts

Maternal infection

- Occurs through droplet inhalation/direct infectious nasopharyngeal secretion contact → maternal viremia → hematogenous transplacental spread to fetus → persistent fetal infection throughout gestation → virus-induced impaired cellular division, direct cytopathic effects
- Maternal–fetal transmission, congenital defect risk varies in accordance with maternal infection timing
  - ↑ ↑ *risk*: inoculation occurs during first ten gestational weeks
  - ↑ *risk*: cardiac, eye defects if inoculation occurs before eight gestational weeks
  - ↑ *risk*: hearing deficits if inoculation occurs up to 18 gestational weeks
  - ↓ *risk*: inoculation occurs after 18–20 gestational weeks

RISK FACTORS

- Maternal non-immunized status, infection

COMPLICATIONS

- Fetal growth restriction
- Hemolytic anemia, thrombocytopenia

Neurological, sensory defects

- Sensorineural hearing loss
- Cataracts, congenital glaucoma, pigmentary retinopathy, microphthalmia
- Microcephaly, meningoencephalitis, intellectual disability

Congenital heart defects

- Patent ductus arteriosus
- Pulmonary artery stenosis
- Coarctation of aorta

Vascular defects

- Intimal fibromuscular proliferation, arterial sclerosis, systemi345c hypertension (related to renal disease)
- May result in adult coronary, cerebral, peripheral vascular disease

Late complications

- Diabetes, thyroid disease, growth hormone deficiency, progressive rubella panencephalitis

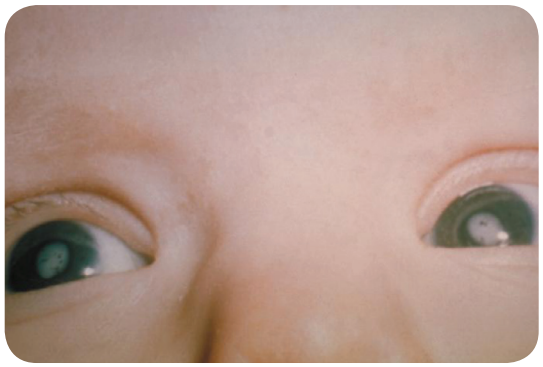

Figure 131.3 Bilateral cataracts in a newborn baby as a consequence of congenital rubella infection.

SIGNS & SYMPTOMS

- "Blueberry muffin" rash
  - Purpuric rash indicates cutaneous hematopoiesis
- Small for gestational age; low birth weight
- Hepatosplenomegaly
- Jaundice
- Complications present (e.g. cataracts, heart defects)

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Head
  - Periventricular calcifications; demyelination
- Long bones
  - Radiolucent bone lesions; irregular, alternating longitudinal light, dark bands of density ("celery stalk" appearance)

LAB RESULTS

Viral identification

- Nasopharyngeal swabs, blood/cord blood, placenta, urine, cerebrospinal fluid (CSF)
  - *PCR/culture*: rubella-specific IgM (usually present at birth); persistent IgG

Prenatal diagnosis

- Viral isolation from amniotic fluid

OTHER DIAGNOSTICS

Maternal prenatal history

- Rubella exposure
- Neonatal exam

TREATMENT

- No specific treatment
- Address complications

Prevention

- Maternal MMR vaccination before conception

CONGENITAL SYPHILIS

osms.it/congenital-syphilis

PATHOLOGY & CAUSES

- Congenital infection caused by *Treponema pallidum* (spirochete bacterium causes syphilis)

Maternal infection

- Sexually
  - Direct infectious lesion contact → enters via microscopic abrasions → crosses placenta easily → fetal spirochetemia → widespread dissemination (almost all fetal organs) → congenital syphilis

RISK FACTORS

- Maternal infection → vertical (transplacental) → fetal transmission

COMPLICATIONS

- Stillbirth
- Premature birth
- Nonimmune hydrops
- Neurological
  - Sensorineural hearing loss, intellectual disability, seizures
- Hematologic
  - Hemolytic anemia, thrombocytopenia
- Renal
  - Nephrotic syndrome (immune complex mediated)
- Ophthalmologic
  - Chorioretinitis, uveitis, cataract, glaucoma, optic atrophy
- Gastrointestinal
  - Necrotizing enterocolitis, ileus, malabsorption
- Skeletal
  - Long-bone abnormalities, pathologic fractures

Treatment-related complications

- Benzathine penicillin G
  - *Jarisch–Herxheimer reaction:* release of endotoxin-like compounds during penicillin-mediated lysis of *T. pallidum* → fever/chills, hypotension

SIGNS & SYMPTOMS

Early congenital syphilis

- General
  - Low birthweight, fever, hepatomegaly, jaundice, lymphadenopathy, pain-related ↓ extremity movement (pseudoparalysis)
- Mucocutaneous
  - Vesicular (pemphigus syphiliticus)/maculopapular rash
  - Contagious, wart-like lesions (condylomata lata)
  - Syphilitic rhinitis ("snuffles")
- Umbilical cord
  - Necrotizing funisitis ("barber-pole" appearance)

Late congenital syphilis

- Onset after two years old
- Facial features
  - Frontal bossing, saddle nose, short maxilla, protuberant mandible
- Sensory
  - Impaired vision/hearing
- Oropharynx
  - Hutchinson teeth (widely-spaced; notched incisors); mulberry molars (small, defective molars; cusps covered with globular enamel growths)
- Cutaneous
  - Gummas
- Skeletal
  - Anterior tibia bowing (saber shins), Higouménakis' sign (sternoclavicular portion of clavicle enlargement), painless arthritis (Clutton's joints), scaphoid scapula

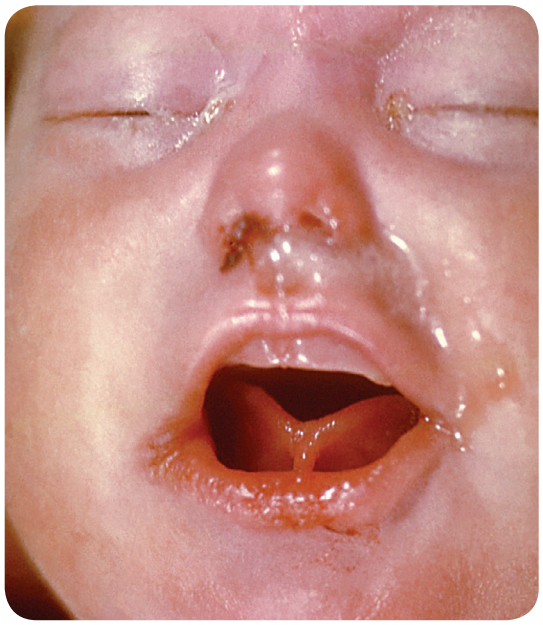

Figure 131.4 A newborn baby with a saddle nose malformation and snuffles, both of which are signs of congenital syphilis infection.

DIAGNOSIS

DIAGNOSTIC IMAGING

Long-bone radiographs

- Multiple anomalies
  - E.g. metaphyseal lucent bands, metaphyseal "sawtooth" serration (Wegener sign), "moth-eaten" appearance

Chest X-ray

- Diffuse infiltrate/opacification of both lung fields ("pneumonia alba")

LAB RESULTS

- *T. pallidum* identification
  - Dark field microscopy
  - Direct fluorescent antibody (DFA) staining (nasal secretions, placenta, umbilical cord, autopsy tissue)
  - Reactive venereal disease research laboratory (VDRL), rapid plasma reagin (RPR)
- Blood studies
  - ↓ platelets, ↑ ↓ WBCs
- CSF analysis
  - Reactive VDRL, pleocytosis, ↑ protein, *T. pallidum* DNA presence (identified by PCR)

TREATMENT

MEDICATIONS

- Intramuscular (IM) benzathine penicillin G

Prevention

- Screening at first prenatal visit
  - IM benzathine penicillin G

OTHER INTERVENTIONS

Prevention

- Characteristic fetal congenital infection features detectable via ultrasound
  - 18–22 weeks of gestation

GROUP B STREPTOCOCCUS (GBS) INFECTION

osms.it/group-b-strep-infection

PATHOLOGY & CAUSES

- Serious neonatal infection caused by *Streptococcus agalactiae*
  - Gram-positive, encapsulated diplococcus
  - Commonly colonizes maternal gastrointestinal, genital tracts
  - Produces complete (beta hemolysis) on blood agar plates
- Acquired via intra-amniotic infection, ascending infection after amniotic membrane rupture/during birth canal passage

Classification

- GBS onset timing
  - *Early-onset GBS*: presents between 24 hours to six days post-delivery (most common)
  - *Late-onset GBS*: 4–5 weeks post-delivery
  - *Late, late-onset GBS*: presents in infants > three months (most common in infants with immunodeficiency history/born < 28 gestational weeks)

RISK FACTORS

- GBS-positive intrapartum nucleic acid amplification test (NAAT)
- Chorioamnionitis
- Preterm labor
- Premature membrane rupture ≥ 18 hours

Maternal presentation

- Delivery time
  - Intrapartum fever ≥ 38°C/100.4°F
  - Delivery < 37+0 gestational weeks
  - GBS bacteriuria in current pregnancy

Demographic risk factors

- Young maternal age
- Biologically-female individuals of African descent

COMPLICATIONS

- Bacteremia
- Sepsis; septic shock
- Pulmonary hypertension (PPHN)
- Focal infections
  - Meningitis, pneumonia, endocarditis septic arthritis, osteomyelitis, cellulitis, adenitis
- ↑ preterm infant mortality

SIGNS & SYMPTOMS

- Lethargy/irritability; poor feeding
- Temperature instability
- Respiratory symptoms
  - E.g. tachypnea, grunting, retractions, apnea, hypoxemia/↓ oxygen saturation
- Hypotension
- Bulging fontanel, nuchal rigidity (GBS meningitis)
- ↓ extremity movement/pain with manipulation GBS bone/joint infection

DIAGNOSIS

DIAGNOSTIC IMAGING

Chest X-ray

- Diffuse alveolar infiltrates, pleural effusion indicate GBS pneumonia

LAB RESULTS

Neonatal blood studies

- ↑ ↓ absolute neutrophil count
- ↓ platelet count
- Positive blood culture

- ↑ C-reactive protein (CRP)

Neonatal CSF analysis

- ↑ protein level, WBC count
- ↓ glucose level
- Positive Gram stain, culture results

Urinalysis

- Gram stain, culture
  - Presence of nitrates, leukocyte esterase, bacteria

TREATMENT

MEDICATIONS

- Antibiotics
  - Penicillin G, ampicillin, nafcillin

Prevention

- *Vaginal-rectal culture*: 35–37 gestational weeks
  - If positive culture →intrapartum antibiotic prophylaxis
  - Penicillin, ampicillin, cefazolin

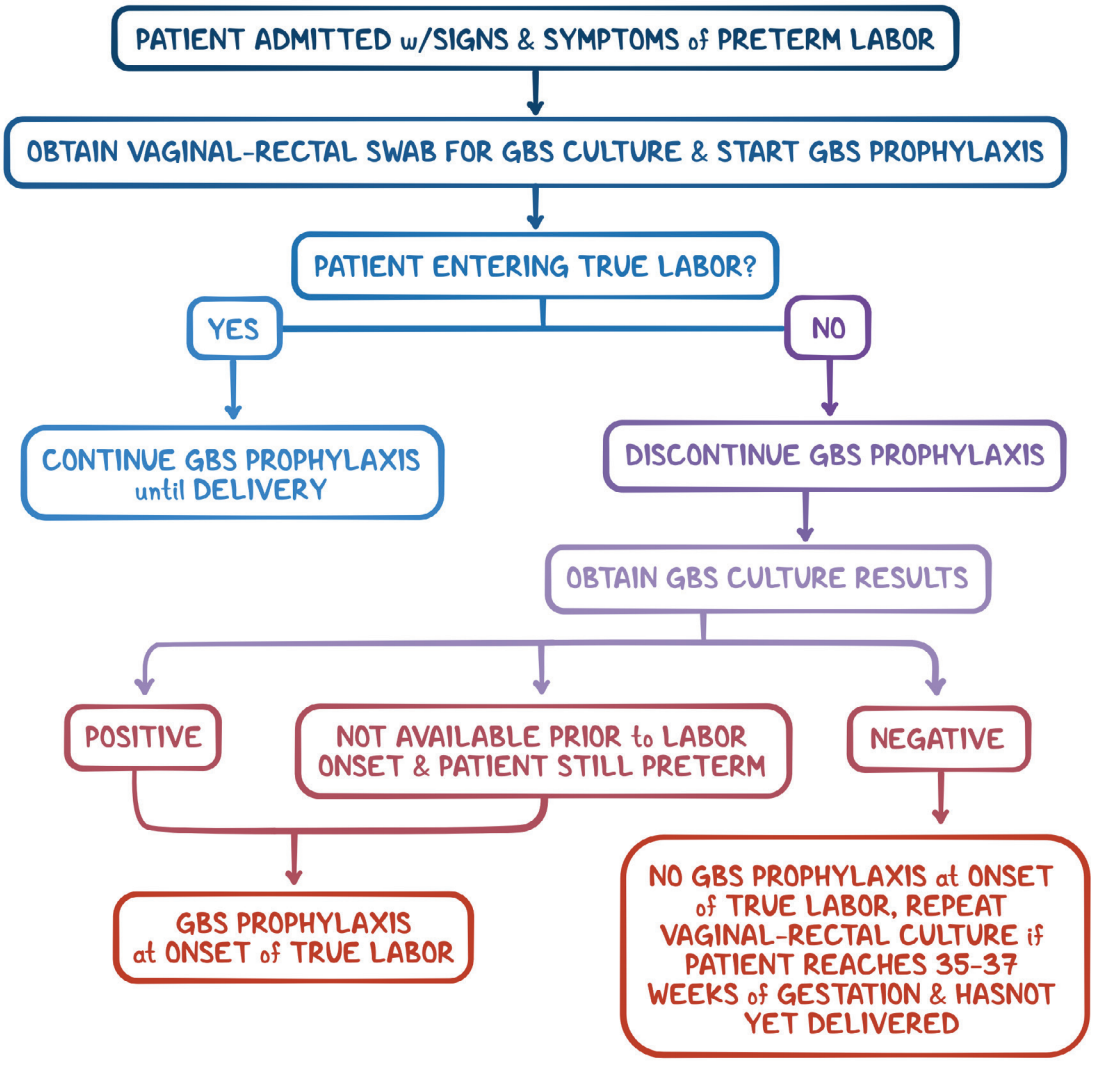

Figure 131.5 Algorithm for GBS screening and prophylaxis.

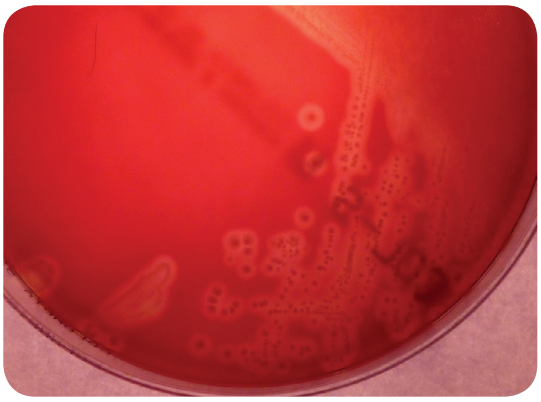

Figure 131.6 Group B *streptococcus* colonies cultured on blood agar.

NEONATAL CONJUNCTIVITIS

osms.it/neonatal-conjunctivitis

PATHOLOGY & CAUSES

- Clinical infection manifestation occurs within first four weeks of life, AKA ophthalmia neonatorum
  - Most commonly caused by *Neisseria gonorrhoeae*/*Chlamydia trachomatis* (coinfection with both microbes common)
  - Rarely, herpetic conjunctivitis caused by herpes simplex virus (HSV)
  - *Staphylococcus*, *Streptococcus* may also be implicated in some conjunctival infections

Transmission

- Primarily via exposure to mother's infected genital flora during vaginal birth
- Ascending infection in case of premature membrane rupture

RISK FACTORS

- Maternal infection

COMPLICATIONS

- Corneal ulceration, scarring
- Vision impairment, blindness
- Systemic sequelae of infection
- *HSV*: keratitis, keratouveitis

SIGNS & SYMPTOMS

- Eyelid swelling, watery/mucopurulent discharge, chemosis, micropannus (granulation tissue membrane)

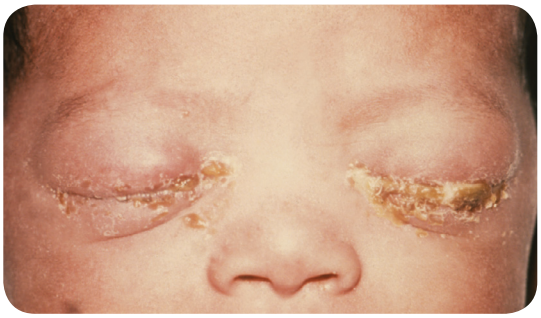

Figure 131.7 The clinical appearance of severe neonatal conjunctivitis.

DIAGNOSIS

LAB RESUTS

Microbe identification

- Conjunctival, nasopharyngeal specimens
  - Culture
  - Gram stain
  - Nucleic acid amplification test (NAAT)
  - Polymerase chain reaction (PCR)
  - Direct fluorescent antibody (DFA), enzyme immunoassay (EIA) tests
  - *HSV*: Giemsa stain, PCR

CBC

- ↑ eosinophil count

OTHER DIAGNOSTICS

- Maternal history
- No prenatal care; untreated *C. trachomatis*/*N. gonorrhoeae* infection; neonatal examination

TREATMENT

- Antibiotics
  - *Gonococcal disease:* IV/IM ceftriaxone
  - *Chlamydial disease*: oral erythromycin, azithromycin
  - *HSV*: acyclovir

Prevention

- Gonococcal conjunctivitis
  - Routine neonatal prophylaxis with erythromycin 0.5% ointment

OTHER INTERVENTIONS

- Treat neonate's mother, sexual partner
- Maternal prenatal screening

NEONATAL HERPES SIMPLEX

osms.it/neonatal-herpes-simplex

PATHOLOGY & CAUSES

- Uncommon, serious neonatal infection caused by herpes simplex virus (HSV-1, HSV-2)
- Enveloped, double-stranded DNA virus
  - *HSV-2*: most neonatal cases
  - TORCH infection

Transmission

- Intrauterine/transplacentally is rare
- *Intrapartum*: ascending infection from maternal genitals during delivery/mother's infected genital flora exposure
  - Most maternal HSV infections are clinically inapparent
- Postnatal via close contact

Inoculation

- 2–21 day incubation
- Skin, eyes, mouth (SEM) disease
- Central nervous system (CNS) disease
- Disseminated disease
  - Multiple organs (e.g. lungs, liver, adrenal, CNS, skin, eye, mouth)

RISK FACTORS

Maternal infection

- ↑ transmission risk with vaginal delivery, prolonged membrane rupture, delivery instruments that disrupt fetal skin barrier

COMPLICATIONS

- Recurring skin lesions throughout childhood

- CNS HSV
  - Meningoencephalitis
- Disseminated HSV
  - Hepatitis, disseminated intravascular coagulation (DIC), hemorrhagic pneumonitis
  - High mortality

SIGNS & SYMPTOMS

- May be asymptomatic initially
- SEM
  - Mucosal vesiculopustular eruption
- CNS HSV
  - Temperature instability, irritability/lethargy, bulging fontanelle, seizure
- Disseminated HSV
  - Temperature instability, lethargy, poor feeding, jaundice, hepatosplenomegaly, respiratory distress

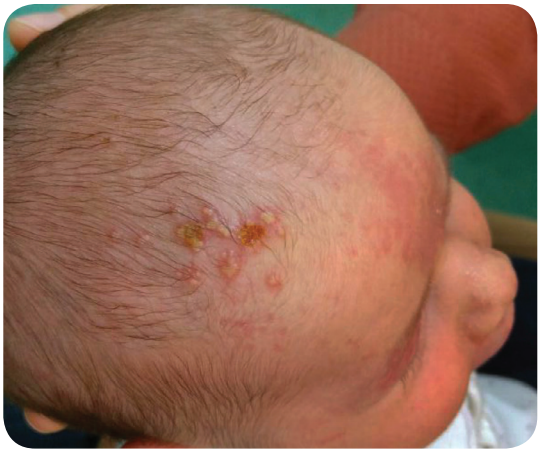

Figure 131.8 A neonate with herpes simplex vesicles on the scalp.

DIAGNOSIS

LAB RESULTS

- Microbe identification
  - Culture (blood, CSF, urine, mucous membrane fluid)
  - PCR
- CNS analysis
  - CSF ↑ protein, ↑mononuclear pleocytosis
- Lesion analysis
  - Multinucleated giant cells visualized with Giemsa/Wright stain

TREATMENT

MEDICATIONS

- IV acyclovir

OTHER INTERVENTIONS

- Also treat mother, mother's partner

NEONATAL MENINGITIS

osms.it/neonatal-meningitis

PATHOLOGY & CAUSES

- Severe neurological infection complication
  - High morbidity, mortality rate
  - Most often occurs during first week of life
  - Bacterial, viral, fungal infections
- Usually caused by variety of bacteria (e.g. GBS, *E. coli*, *S. pneumoniae*, *Enterococcus*, *coagulase-negative staphylococci*, *S. aureus*, *L. monocytogenes*, *H. influenzae*)

RISK FACTORS

- Premature birth, low birthweight, maternal infection, sepsis

COMPLICATIONS

- Cerebral edema/abscess, hydrocephalus, intraventricular hemorrhage, encephalomalacia, cerebral palsy, seizure disorder, auditory/visual sensory deficits

SIGNS & SYMPTOMS

General

- Temperature instability, lethargy, poor feeding, vomiting, diarrhea

Neurological

- Irritability, hypotonia, tremors, seizures, full/bulging fontanelle; may have nuchal rigidity

Respiratory

- Tachypnea, retractions nasal flaring, grunting, apnea

DIAGNOSIS

DIAGNOSTIC IMAGING

Cranial sonography

- Assess ventricular size
  - Detect ventricular hemorrhage, ventriculitis, extracerebral fluid collections

MRI/CT scan

- Detects cerebral edema, infarction/abscess area, CSF obstruction, encephalomalacia, atrophic tissue (cortical, white matter)

LAB RESULTS

- Microbe identification
  - CSF
  - Gram stain, culture, PCR, NAAT
  - Blood culture (may be negative)
  - Urine culture
- Blood studies
  - ↑↓ WBC count, left shift, ↓ platelets
- CSF
  - ↑ WBCs, ↑ protein, ↓ glucose

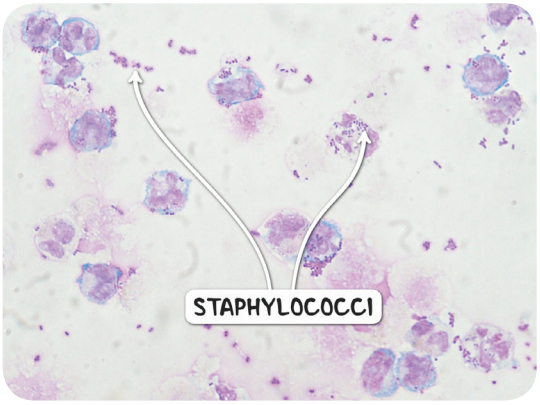

Figure 131.9 A sample of cerebrospinal fluid from a neonate with meningitis. There are neutrophils present, denoting an acute inflammatory process as well as cocci arranged in groups and pairs. Culture grew *Staphylococcus capitis*.

TREATMENT

MEDICATIONS

- Antimicrobials
  - usually ampicillin + gentamicin + third-generation cephalosporin
- Anticonvulsants
- IV fluids, vasopressors

NEONATAL SEPSIS

osms.it/neonatal-sepsis

PATHOLOGY & CAUSES

- Serious infection; presents within neonate's first 30 days; characterized by bacteremia/meningitis
- Characterized by onset
  - *Early-onset sepsis*: occurs with first 3–7 days
  - *Late-onset sepsis*: occurs between 7–30 days
- May be bacterial (most common), viral, fungal (more common in preterm infants) → vertical transmission before/during labor/delivery

RISK FACTORS

- Low birthweight
- Preterm birth
- Low Apgar score at five minutes
- Prolonged membrane rupture
- Chorioamnionitis
- Maternal GBS colonization (inadequate intrapartum treatment)
- Inborn metabolism errors
- Maternal age ≤ 20

COMPLICATIONS

- Meningitis, pneumonia, multi-organ failure, necrotizing enterocolitis (NEC), high mortality rate

SIGNS & SYMPTOMS

- May be initially nonspecific
- Fever, temperature instability

General signs

- Lethargy, irritability, poor suck, hypotonia

Respiratory distress signs

- Tachypnea, grunting, nasal flaring, retractions, apneic periods, cyanosis

Hemodynamic instability

- Tachycardia/bradycardia, prolonged capillary refill time, hypotension, pallor

DIAGNOSIS

- Maternal, intrapartum, neonatal history
- Compatible clinical presentation

LAB RESULTS

- Blood, CSF culture
  - Identify causative microbe
- CBC
  - Neutropenia (due to small neutrophil storage pool)
- CSF analysis
  - ↑ WBCs; protein, glucose may also be ↑

TREATMENT

MEDICATIONS

- Antibiotics
- Vasopressors

OTHER INTERVENTIONS

- Supplemental oxygen, mechanical ventilation
- IV fluids

TOXOPLASMOSIS

osms.it/toxoplasmosis

PATHOLOGY & CAUSES

- Congenital infection
  - Caused by protozoa *Toxoplasma gondii*
  - TORCH infection
- Obligate intracellular parasite
- Transplacental transmission to fetus

Biphasic life cycle

- Sexual cycle
  - Occurs exclusively in felines (definitive host)
- Asexual cycle
  - Occurs in other animals, including humans

Maternal infection routes

- Cats consume infective form (cysts) from prey (e.g. intermediate hosts—rodents, birds) → replication within intestines → oocyst formation → fecal excretion → maternal infection via cat fecal exposure (soil, litter box)
- Wild game/animals bred for human consumption (e.g. cattle) may ingest environmental oocytes → infection → maternal consumption of raw/undercooked meat, contaminated water/vegetables → maternal infection

RISK FACTORS

- Maternal infection
  - Primary infection during pregnancy/reactivation in immunocompromised host

COMPLICATIONS

- ↑ congenital effect severity when infection occurs early in gestation
  - *Classic triad:* chorioretinitis, hydrocephalus, intracranial calcification
  - Sensorineural hearing loss, microcephaly, intellectual disability, motor/cerebellar dysfunction, growth delay, seizure, pneumonitis, anemia, thrombocytopenia

SIGNS & SYMPTOMS

Subclinical infection

- Routine assessment reveals no anomalies
- Focused examination may reveal infection signs (e.g. ophthalmologic, CNS imaging)

Clinically apparent disease

- During neonatal period/first few months of life
  - May be mild/severe, CNS/ocular complications, purpuric rash ("blueberry muffin" rash), fever, jaundice, hepatosplenomegaly, lymphadenopathy, microphthalmia, hypotonia

Late infancy, childhood, adolescence

- Undiagnosed/untreated infection emergence/relapse
  - Complication developments (e.g. chorioretinitis, neurosensory hearing loss)
  - Growth delay, endocrine abnormalities secondary to hypothalamic, pituitary dysfunction

DIAGNOSIS

DIAGNOSTIC IMAGING

ABR

- Sensorineural hearing loss

CT scan

- Neuroimaging
  - Intracranial calcifications, hydrocephalus (ventriculomegaly), cortical atrophy

LAB RESULTS

Confirmatory diagnostics

- With any of following
  - Positive IgG with positive IgM (after five days of life), IgA (after ten days of life) + confirmed maternal serology
  - Positive CSF PCR + confirmed maternal *T. gondii* infection during pregnancy, characteristic neonatal clinical findings
  - Positive IgG beyond 12 months of age demonstrates anti-*Toxoplasma* IgG persistence

Ophthalmic examination

- Chorioretinitis

Neurologic examination

- Lumbar puncture
  - ↑ protein, mononuclear pleocytosis

Blood studies

- CBC
  - ↓ RBCs ↓ platelets, ↑ eosinophils
- Liver function tests
  - Possible ↑ aspartate aminotransferase; alanine aminotransferase; total, direct bilirubin

Cytologic placental examination

- *T. gondii* cyst/tachyzoite presence

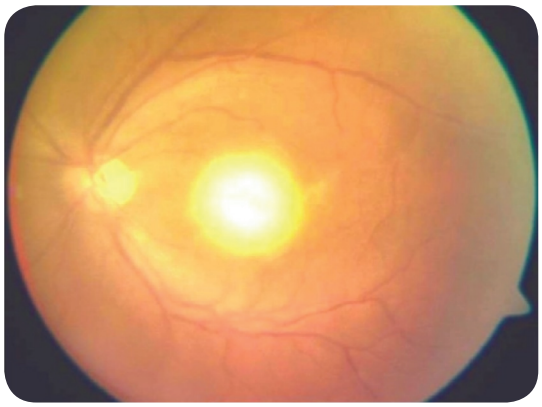

Figure 131.10 Retinal photograph demonstrating the characteristic "headlight in the fog" appearance of toxoplasma retinitis.

TREATMENT

MEDICATIONS

Neonatal treatment

- Antiparasitic therapy
  - Pyrimethamine + sulfadiazine + folinic acid
- Prednisone if ↑ CSF protein

Prevention

- Maternal antiparasitic therapy
  - Positive amniotic fluid PCR before 18 gestational weeks
- Pyrimethamine + sulfadiazine plus folinic acid until delivery