Fetal Infections: Rubella, HIV, HCV, HBV, and Human Parvovirus B19

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Abstract

Congenital rubella (CR) infection leads to damage in over 80% of fetuses during the first trimester of pregnancy, in 25–34% of cases in the second trimester, while no malformations occur in the third trimester CR syndrome is characterized by cardiac, ocular, and hearing defects, although any organ may be affected. All women of child-bearing age should have natural or vaccine-induced immunity to the virus. Mother-to-child transmission (MTCT) of HIV has decreased from 18% down to 1% in bottle-fed infants with adoption of preventive interventions. These include: prenatal antiretroviral (ARV) prophylaxis, administration of ARV during delivery and avoidance of breast feeding. An early combined ARV treatment of HIV-infected infants offers the great benefits of a longer asymptomatic period and of a prolonged survival. No interventions are currently available to prevent MTCT of HCV, that is estimated to be about 5%. The natural history of HCV infection is relatively benign in childhood. More than 90% of HBV exposed infants develop chronic infection. Administration of HBV vaccine and specific immunoglobulins at birth followed by the 3-dose vaccine series has reduced the MTCT rate by about 90%. Primary maternal infection with parvovirus B19 is associated with asymptomatic fetal infection, hydrops fetalis, intrauterine death, and birth defects. In the first and second trimester the MTCT rate is about 30%. In case of hydrops or signs of anemia, intrauterine trasfusions are recommended.

104.1 Salient Points

- Congenital rubella infection is most severe when transmission occurs in the first trimester of pregnancy, and it is characterized by the combination of cardiac, ocular, and hearing defects. To prevent the syndrome, it is important to determine maternal immune status.
- Transmission of HIV during pregnancy may occur in utero, during delivery, and through breast milk. Effective preventive interventions include the administration of prenatal antiretroviral prophylaxis, elective cesarean section, and the avoidance of breastfeeding.
- HCV is transmitted from mother to child in 5% of cases; spontaneous viral clearance occurs in at least one quarter of vertically infected children; the natural history of HCV infection in infancy and childhood is relatively benign.
- More than 90% of children perinatally exposed to HBV develop chronic infection. All term infants born to HbsAg-positive women should receive HBV vaccine and specific immunoglobulins at birth, followed by completion of three-dose vaccine series.
- Maternal infection with parvovirus B19 is associated with asymptomatic fetal infection, nonimmune hydrops fetalis, and intrauterine fetal death. No specific therapy is available; if there is hydrops and/or signs of fetal anemia, intrauterine erythrocyte transfusions are recommended.

104.2 Rubella Virus

104.2.1 Etiology and Pathogenesis

The importance of congenital rubella (CR) was recognized in the 1940s, and the etiological agent was discovered in the 1960s. Rubella epidemics occur at 6- to 9-year intervals and major pandemics every 10–30 years. Theoretically, universal immunization programs should eradicate rubella, but at least 100,000 cases of CRS still occur annually worldwide (Grant et al. 2015; Vynnycky et al. 2016).

The rubella virus, a member of the togavirus family, is composed of an icosahedral nucleocapsid containing a single-stranded RNA genome, surrounded by a lipid envelope. The mechanism by which the virus causes fetal damage is poorly understood. The virus spreads through the bloodstream, it can infect and replicate in the placenta, and it then reaches the fetus, where it persistently infects cells, inducing a decreased growth rate. In the first trimester of gestation, the fetus is unable to mount an adequate immune response, and the passive transfer of maternal antibodies is inefficient; thus the viral replication leads to altered organogenesis. From the second trimester of gestation, the risk of congenital rubella syndrome (CRS) decreases; in fact, changes in the placenta, the appearance of the immune response, and the passive transfer of maternal IgG result in a higher protection from viral damage. The virus can persist for over a year in target organs, where it can undergo recurrent replications. Late-onset CRS manifestations are due to persistent virus-driven tissue damage and scarring.

104.2.2 Transmission

Miscarriage, stillbirth, and a series of birth defects, such as low birth weight, congenital heart disease, and central nervous system damage, are possible sequelae of CRS. Fetal infection may occur at any stage of pregnancy. The outcome of infection depends on the gestational age. Primary maternal infection causes damage in more than 80% of the fetuses during the first trimester of pregnancy, in 25–34% in the second trimester, while no malformations occur in the third trimester. Rubella reinfection may occur both in vaccine-immune and, to a lesser extent, in naturally immune subjects. In these cases, the risk of CRS is estimated to be around 5% in the first trimester of pregnancy (Bouthry et al. 2014).

104.2.3 Clinical Aspects

Rubella infection spreads by droplets, and it is usually subclinical or paucisymptomatic in infants and children. Clinical manifestations (fever, nonconfluent maculopapular rash, headache, malaise, lymphadenopathy, usually involving suboccipital, postauricular, and cervical nodes) develop after 14–21 days of incubation.

CRS is typically characterized by the combination of cardiac, ocular, and hearing defects, although the virus can infect any organ (Table 1) (Duszak 2009; Neu et al. 2015).

104.2.4 Diagnosis

Amniotic fluid and fetal blood samples can be used to detect rubella infection by means of nested reverse transcriptase polymerase chain reaction (RT-PCR). Fetal blood, obtained by cordocentesis, can also be tested for specific IgM. Amniocentesis is less invasive than fetal blood sampling. Both tests should be performed 6–8 weeks after maternal infection; the best reliability is when the fetus is 22 weeks old.

Postnatally, CRS is diagnosed by detection of specific IgM, though both false negative and false positive results have been described, or by stable or increased titers of specific IgG over several months. IgG avidity testing may help to differentiate between recent and past infection (Best 2007; Lambert et al. 2015). Identification of the virus in urine, blood, or nasopharyngeal secretions by cultures or by RT-PCR may also confirm the diagnosis.

104.2.5 Prognosis

Children affected by CRS may require medical, surgical, educational, and rehabilitative

Table 1 Congenital rubella syndrome main defects (listed in order of decreasing frequency)

Early-onset manifestations
Deafness
Mental retardation
Cardiovascular defects affecting primarily the left atrium and the heart septa
Ocular defects (nuclear cataracts, microphthalmia, pigmentary retinopathy, glaucoma)
Thrombocytopenia
Hepatitis
Bone lesions
Dental defects
Hypospadias
Cryptorchidism
Inguinal hernia
Interstitial pneumonitis
Meningoencephalitis
Cerebral calcification
Splenic fibrosis
Nephrosclerosis
Nephrocalcinosis
Late-onset manifestations
The delayed manifestations (due to the altered immune system of CRS patients) underscore the importance of careful follow-up of these patients
Insulin-dependent diabetes
Thyroid dysfunction
Neurodegenerative disorders (panencephalitis)
Slow growth rate during preschool years
Smaller head circumference
Ocular defects (secondary glaucoma, strabismus)
Defects in the immune system (transitory hypogammaglobulinemia, especially ipoIgA, defects in cell-mediated immunity)

management. CRS must be managed as a dynamic rather than a static disease, requiring a multidisciplinary approach: for instance, early treatment is critical for hearing defects and psychomotor difficulties.

104.2.6 Therapy and Treatments

The prime strategy for the prevention of CRS is to ensure that all pregnant women are immune to rubella (CDC – Surveillance of congenital rubella syndrome 2014). In developed countries, vaccination programs are based on the universal immunization of infants at 12–15 months of age, plus a second vaccination at 5–6 years of age or before adolescence to achieve immunity in patients who did not receive the first dose or with primary vaccine failure. Furthermore, all women at childbearing age should be tested and vaccinated, if still susceptible. The RA 27/3 strain is used as a rubella vaccine. This is remarkably safe, has high efficacy (over 90%), and induces long-lasting protection. It is used as a component of the measles-mumps-rubella (MMR) vaccine or of the recent tetravalent vaccine (MMR plus varicella).

Vaccination programs have led to marked reduction in morbidity and mortality associated with CRS. Benefits of the vaccine far outweigh the costs of treatment and rehabilitation of affected children and adults.

104.3 Human Immunodeficiency Virus (HIV)

104.3.1 Etiology and Pathogenesis

More than 3.2 million children under 15 years are estimated to be living with human immunodeficiency virus type 1 (HIV-1) infection worldwide in 2013, mostly following mother-to-child transmission (MTCT) (UNAIDS 2016).

HIV is a retrovirus belonging to the subgroup of lentiviruses. The first step of its life cycle is characterized by the integration of the virion envelope glycoproteins (gp120 and gp41) with the cell surface CD4 molecule. After entering the cell, the virus is rapidly uncoated. Then, through reverse transcriptase, its viral RNA is transformed into linear DNA. This is circularized and transferred into the nucleus where it is inserted at random sites as a provirus. The provirus is activated by host cell responses to antigens, cytokines, or products of other viruses. Thousands of infectious particles can originate from a single infected cell, either chronically or as a single burst resulting in cell death. HIV infection leads to a profound qualitative and quantitative attrition of the immune system, particularly of cell-mediated immunity with a decrease in CD4+ cell count.

Immune-mediated damage presumably plays a key role in AIDS pathogenesis.

Two genetically distinct HIV types have been identified: HIV-1 and HIV-2; the latter is localized mainly in Western Africa and causes a less aggressive disease.

HIV infection results in a minimal risk of adverse pregnancy outcomes, such as spontaneous abortion, intrauterine growth restriction, and premature delivery (Sollai et al. 2015).

104.3.2 Transmission

HIV is a sexually transmitted infection that also spreads by contact with contaminated blood. After the screening of blood donors, MTCT has become the most common route of infection in children. MTCT ranges between 15 and 23% in bottle-fed infants. Prolonged breastfeeding may account for an additional 10–15% of infections. With the implementation of effective preventive measures, MTCT rate can be reduced to less than 1% in non-breastfed infants.

Maternal viral load is an independent risk factor for MTCT. Many other viral, maternal, obstetrical, fetal, and infant factors can influence the transmission rate (Table 2). Most children are infected perinatally, though intrauterine transmission may occur. An infant is considered to have been infected in utero when HIV-1 can be detected from peripheral blood within 48 h from birth. In contrast, a non-breastfed child is taken to have had intrapartum infection if he/she becomes viremic subsequently. Transmission due to household contacts is not documented.

Table 2 Maternal, obstetrical, and neonatal factors associated with increased HIV transmission rate

Pregnancy	Labor and delivery	Breastfeeding
High maternal viral load (new infection or advanced AIDS) and/or CD4 cell count $<200/mm^3$	High maternal viral load (new infection or advanced AIDS) and/or CD4 cell count $<200/mm^3$ at delivery	High maternal viral load (new infection or advanced AIDS) and/or CD4 cell count $<200/mm^3$
Viral, bacterial, or parasitic placental infections, such as malaria	Rupture of membranes (>4 h)	Duration of breastfeeding
Sexually transmitted infections	Invasive delivery procedures that increase contact with the mother' s infected blood or body fluids (e.g., episiotomy, artificial rupture of membranes)	Breast abscesses, mastitis, nipple fissures
	Chorioamnionitis (from untreated STI or other infections)	Oral disease in the baby (e.g., thrush or sores)
	Preterm delivery	

104.3.3 Clinical Manifestations

According to the infection status, an infant born to a seropositive mother is classified as exposed (E), infected (I), or seroreverted (SR) (see below). A breastfed infant is at risk of infection in the 6 months after interruption of maternal lactation.

HIV+ children are classified into mutually exclusive, progressive categories according to their clinical and immunological status (Table 3) (Centers for Disease Control and Prevention 1994). Once classified in a more severe category, a child cannot be reclassified in a less severe one, even if the clinical or immunologic situation improves.

HIV progression is more accelerated in children than in adults. HIV-infected newborns are usually asymptomatic, but they can become seriously ill within the first weeks/months of life. Growth delay is an early finding in untreated infected infants. Children more likely than adults have serious bacterial infections, and lymphoid interstitial pneumonia is almost entirely restricted to the pediatric age. P*neumocystis jirovecii* pneumonia (PJP) is the most common opportunistic infection (OI), with the highest incidence at 3–6 months of age.

The use of highly active antiretroviral therapy (HAART) has significantly improved the morbidity and mortality of HIV-infected children, though their rate of severe infections, particularly pneumonias, remains high (Berti et al. 2015).

Table 3 Classification system for HIV infection in children younger than 13 years of age

	Clinical categories			
Immune categories	No symptoms (N)	Mild symptoms (A)	Moderate symptoms (B)	Severe symptoms (C)
(Based on age-specific CD4+ cell count or percentage)				
1 – No suppression	N1	A1	B1	C1
0–11 months → > 1500 cells/μL (≥25%)				
1–5 years → > 1000 cells/μL (≥25%)				
> 6 years → >500 cells/μL (≥25%)				
2 – Moderate suppression	N2	A2	B2	C2
0–11 months → > 750–1499 cells/μL (15–24%)				
1–5 years → 500–999 cells/μL (15–24%)				
> 6 years → 200–499 cells/μL (15–24%)				
3 – Severe suppression	N3	A3	B3	C3
0–11 months → > < 750 cells/μL (<15%)				
1–5 years → > < 500 cells/μL (<15%)				
> 6 years → < 200 cells/μL (<15%)				

Modified from (Centers for Disease Control and Prevention 1994)

104.3.4 Diagnosis

Diagnosis of HIV infection in exposed infants is based on the detection of viremia in two separate determinations. Most uninfected children lose passively acquired maternal antibodies by 12–15 months of age, though in 2% these may persist up to 18 months. Criteria for diagnosis or exclusion of infection (Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children 2016) through detection of viremia are detailed in Table 4.

104.3.5 Prevention of MTCT

All pregnant women should be tested routinely for HIV during an early prenatal visit (first trimester) in order to adopt effective preventive strategies. These include:

- Administration of combined antiretroviral (cARV) therapy during pregnancy in order to reach a plasma viral load below the limit of detection.
- Prophylaxis with zidovudine (ZDV) during delivery can be considered, even if the additional benefit of intravenous (IV) ZDV in women receiving combination regimens has not been evaluated in randomized clinical trials.
- Elective cesarean section (CS), especially recommended in women with detectable viremia near the time of delivery despite antepartum cARV.
- ARV prophylaxis in the infant.
- Avoidance of breastfeeding.

104.3.5.1 Prenatal ARV Treatment

Prenatal ARV regimens with HAART, regardless of viral load and CD4 cell count, are recommended to all HIV-infected women to prevent MTCT as well as for their own health (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2015). In particular, women under ARV treatment should continue their therapy during pregnancy, while those who do not require treatment for their own health should receive a three-drug combination to prevent viral transmission to the offspring. ZDV prophylaxis

Table 4 Diagnosis of HIV infection in exposed children less than 18 months of age (Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children 2016)

Diagnosis of HIV infection (I)	Exclusion of HIV-1 infection (SR)
1. Positive results on two separate specimens (not including cord blood) from virologic assays that directly detect HIV; HIV antibody tests should not be used HIV RNA and HIV DNA nucleic acid tests are recommended as preferred virologic assays A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen	1. Definitive exclusion of HIV infection in non-breastfed infants is based on two or more negative virologic tests, with one obtained at age $\geq$ 1 month and one at age $\geq$ 4 months
2. Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages 14–21 days 1–2 months (preferably, 2–4 weeks after cessation of antiretroviral prophylaxis) 4–6 months	2. At least two negative HIV-1 antibody test results from separate specimens obtained at >6 months of age

alone is no more suggested. After the onset of labor or rupture of membranes (or approximately 3 h before an elective cesarean section), IV ZVD (2 mg/kg over the first hour, then 1 mg/kg per hour until delivery is complete) should be administered. However, IV ZVD is not strictly required in HIV-infected women receiving HAART and with undetectable viral load at delivery (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2015).

Although congenital abnormalities have been reported in animals treated with ARV drugs, results from registries and cohort studies do not confirm this association in human beings. Mitochondrial toxicity of clinical relevance has been described, albeit anecdotically, in Europe after in utero exposure to nucleoside analogues, but these findings still remain matter of debate, and the proven efficacy of maternal and infant ARV prophylaxis to prevent perinatal HIV transmission significantly outweighs these concerns. There is no evidence that exposure to antiretroviral drugs in utero or neonatally is associated with an increased risk of childhood cancer (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2015).

104.3.5.2 Elective Cesarean Section

The MTCT rate was reported lower in women who delivered by elective cesarean section than in those who delivered by emergency cesarean section or vaginal delivery (CDC – Surveillance of congenital rubella syndrome 2014). Thus, there was general agreement that elective C-section should be recommended at 38 weeks' gestation to all pregnant women with a viral load >1000 RNA copies per mL near the time of delivery.

Recently, several observational studies suggested no additional benefit from scheduled Cesarean delivery in women who received cARV for several weeks and who achieved virologic suppression (Kourtis et al. 2014; Briand et al. 2013). Furthermore, there is a persistently increased risk of maternal complications following CS compared to vaginal delivery (Kourtis et al. 2014). At present, in the great majority of industrialized countries, elective CS is recommended only when the maternal VL is not controlled by ARV therapy (Briand et al. 2013).

104.3.5.3 Infant ARV Prophylaxis

A 4–6-week course of ZDV prophylaxis is recommended for all exposed neonates and should be initiated as soon as possible after birth (Table 5). In certain situations (e.g., treated women with suboptimal viral suppression or only intrapartum ARV therapy or known ZDV-resistant virus), some experts suggest the addition of other ARV drugs (Sollai et al. 2015; Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2015; Chiappini et al. 2006).

Table 5 Zidovudine prophylaxis in HIV-exposed infants (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2015)

Gestational age at birth	Oral dose (mg/kg per dose)	Intravenous dose (mg/kg per dose)	Frequency	Weeks
≥35 weeks	4	3	Every 12 h	4–6
30 > weeks <35	2	1.5	Every 12 h advancing to 3 mg/kg/dose (or 2.3 mg/kg/dose IV) every 12 h at 2 weeks of age	6
<30 weeks	2	1.5	Every 12 h advancing to 3 mg/kg/dose (or 2.3 mg/kg/dose IV) every 12 h at 4 weeks of age	6

104.3.5.4 Breastfeeding

Although the risk of postnatal HIV transmission through maternal milk is well documented, the WHO recommends breastfeeding in the first 6 months of life in some developing countries, because such a risk is lower than that of death from diarrheal diseases and malnutrition. Conversely, in countries where formula feeding is affordable, feasible, acceptable, sustainable, and safe, breastfeeding should be discouraged (Sollai et al. 2015; Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission 2015; Chiappini et al. 2006).

104.3.6 Prognosis

The prognosis of perinatally acquired HIV infection was initially poor. Opportunistic infections (OIs), progressive neurological disorders, malignancies, severe bacterial infections, and wasting syndrome were the main causes of death (Tovo et al. 1992). However, morbidity and mortality due to AIDS-defining opportunistic infections have significantly decreased since the introduction of HAART in children. These can grow regularly, remain in good health for many years, and reach adulthood, and pregnant women can give birth to a second generation of HIV-1-exposed infants without additional risk factors for transmission (Calitri et al. 2014). However, severe pneumonia and fungal or bacterial sepsis still represent a problem. Furthermore, several noninfectious conditions related to chronic HIV infection and lifelong treatment, such as metabolic outcomes, renal abnormalities, cardiovascular complications, and non-AIDS-defining malignancies, are progressively emerging (Berti et al. 2015).

104.3.7 Therapy and Treatments

104.3.7.1 Antiretroviral Therapy

Initiation of ARV therapy is recommended in all HIV-infected infants in the first year of life, regardless of clinical and immunological conditions. Subsequently, the therapeutic options should be based on clinical, immunologic, and virologic findings. Whereas all children with severe HIV disease should start prompt treatment, asymptomatic subjects aged ≥1 year and those with mild to moderate clinical manifestations can take more time to fully assess, discuss, and address issues associated with adherence prior to initiating therapy. On the other hand, several studies highlight that initiation of ART at younger ages and higher CD4 values maximizes its potential benefit. The therapeutic regimen should contain at least three ARV drugs, from at least two distinct classes (Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children 2016).

104.3.7.2 Supportive Care

Every HIV-infected child should be protected from vaccine-preventable diseases (Figs. 1 and 2). In general, all inactivated vaccines can be administered safely, and usual doses and schedules are recommended. Children with HIV infection are at a high risk for complications of varicella zoster and measles. Bearing in mind the limited safety, immunogenicity, and efficacy of varicella and MMR vaccines in HIV-infected children, these

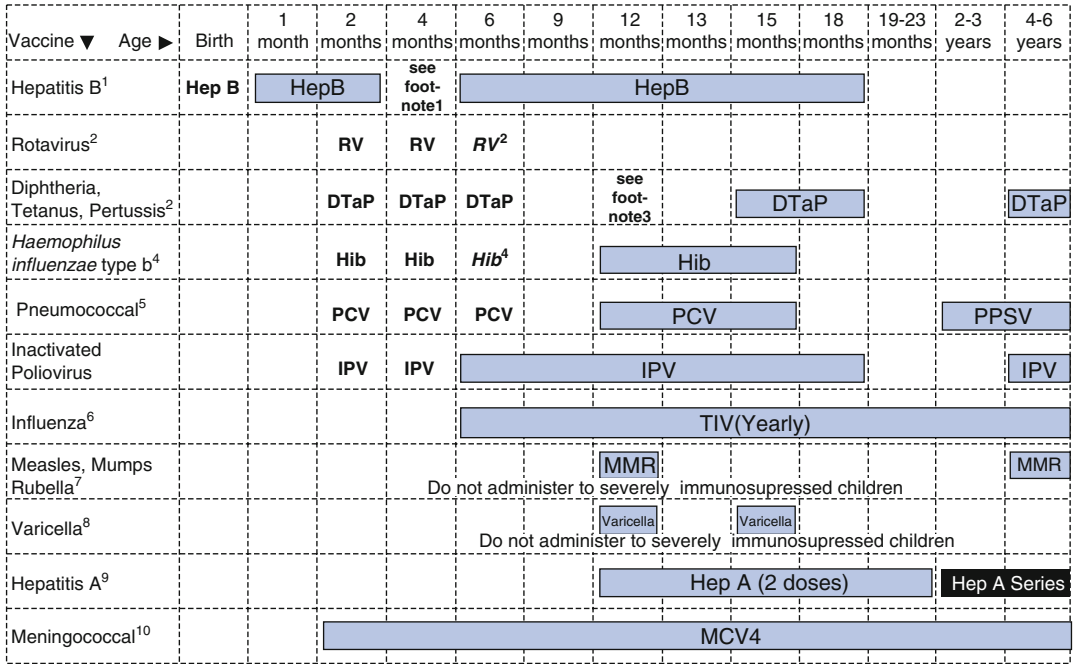


Fig. 1 Recommendations for routine immunizations in HIV-infected children aged 0–6 years. *HepB* hepatitis B vaccine, *RV* rotavirus vaccine, *DtaP* diphtheria and tetanus toxoids and acellular pertussis vaccine, *Hib Haemophilus influenzae* type B conjugate vaccine, *PCV* pneumococcal conjugate vaccine, *PPSV* pneumococcal polysaccharide vaccine, *IPV* inactivated polio vaccine, *TIV* trivalent inactivated influenza vaccine, *MMR* measles, mumps, and rubella vaccine, *Hep A* hepatitis A vaccine, *MCV4* meningococcal conjugate vaccine (Modified from Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children (2013))

should be administered only in subjects without severe immunosuppression (CD4+ cell percentage 15%).

Prophylactic measurements to prevent PJP pneumonia are detailed in Table 6 (Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children 2013).

104.4 Hepatitis C Virus (HCV)

104.4.1 Etiology and Pathogenesis

The hepatitis C virus (HCV) is the most common cause of chronic liver disease, with 115 million seropositive subjects (11 million children <15 years) worldwide (Gower et al. 2014). The prevalence of infection in children varies from 0.05–0.4% in developed countries to 2–5% in resource-limited settings. After the screening of blood donors, with consequent disappearance of posttransfusional hepatitis C, MTCT has become the most common route of infection in the pediatric population, at a rate of about 5%.

HCV is a small (50 nm in size), enveloped, single-stranded RNA virus. Six major genotypes exist; each genotype comprises hundreds to thousands of subtypes, referred to as quasi-species, resulting from the high viral mutation rates and reflecting the unique ability of the virus to continually alter its immunologically recognizable epitopes. HCV primarily enters hepatocytes, although other cell types, such as dendritic cells and B-cells, can also be infected. The virus is non-cytopathic by itself.

104.4.2 Transmission

Antenatal screening might be useful to identify infected children before the onset of symptoms and to offer post-pregnancy therapy to their

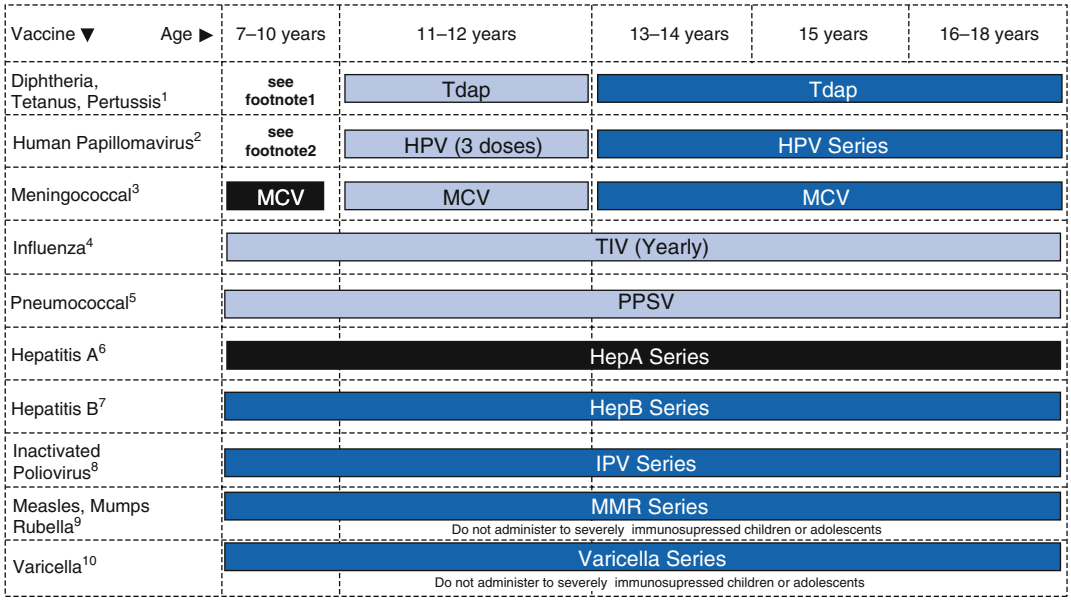


Fig. 2 Recommendations for routine immunizations in HIV-infected children aged 7–18 years. *Tdap* tetanus and diphtheria toxoids and acellular pertussis vaccine, *HPV* human papillomavirus vaccine, *MCV* meningococcal vaccine, *TIV* trivalent inactivated influenza vaccine, *PPSV* pneumococcal polysaccharide vaccine, *HepA* hepatitis A vaccine, *HepB* hepatitis B vaccine, *IPV* inactivated polio vaccine, *MMR* measles, mumps, and rubella vaccine (Modified from Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children (2013))

Table 6 Prophylaxis to prevent *Pneumocystis jirovecii* pneumonia in HIV-exposed infants or HIV-infected children

Pathogen	Indication	First choice	Alternative
Pneumocystis jirovecii	Exposed children From 6 weeks until exclusion of infection	TMP-SMX 2,5–5/12,5–25 mg/kg / dose orally twice per day and administered three times weekly on consecutive or alternate days	Dapsone (>1 month of age) 2 mg/kg orally daily or 4 mg/kg once weekly
	Infected children From 6 weeks until 1 year From 1 to 5 years if CD4 < 500 cells/mm^3 From 6 to 12 years if CD4 < 200 cells/mm^3 or percentage < 15%		Atovaquone: children aged 1–3 months and >24 months, 30–40 mg/kg, orally, once daily with food; children aged 4–24 months, 45 mg/kg, orally, once daily; children aged >13 years 1500 mg, orally, once daily
			Aerosolized pentamidine: >5 years, 300 mg every month

TMP trimethoprim, *SMX* sulfamethoxazole, *mon(s)* month(s), *yrs* years (Modified from Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children (2013))

mothers. However, because of the absence of effective preventive strategies, universal screening for HCV in pregnant women remains questionable, even if a routine screening and treatment program seem feasible and effective at a cost considered acceptable (Selvapatt et al. 2015). Indeed, antenatal screening is suggested in special circumstances: women positive for HIV or hepatitis B virus, a history of intravenous drug use, transplantation, hemodialysis, blood or blood product transfusion

prior to 1992, tattooing, or unexplained elevated liver enzymes (Pembrey et al. 2005).

HCV infection does not impair the course of pregnancy or increase the risk of spontaneous abortion or fetal death (Dunkelberg et al. 2014). The time of transmission remains unclear. The largest studies consistently estimate that 30–50% of HCV infections are acquired in utero, while the remainder occur in the late intrauterine/intrapartum period.

Several risk factors for MTCT have been identified (Table 7) (Tovo et al. 2016). However, none are modifiable and no preventive interventions can be adopted.

High viral load is associated with MTCT (Tovo et al. 2016; Cottrel et al. 2013). Thus, seropositive women with undetectable HCV RNA during pregnancy can be reassured that the risk of transmission to the offspring is very low, though it cannot be excluded. The new direct-acting antiviral agents (DAAs) can dramatically reduce the viral load in few weeks (Barth 2015). However, at present these drugs cannot be used in pregnant women because their effects on the fetus are unknown. An indirect decrease in the global number of vertical infections may derive from a widespread use of these agents in HCV-infected women of childbearing age.

Although the evidence is inconclusive, it is prudent to avoid obstetric procedures that may favor fetal exposure to contaminated maternal blood, such as amniocentesis or internal fetal monitoring. These procedures should only be used when indicated to avoid maternal or infant morbidity.

Most studies highlight that mode of delivery and type of feeding have no significant impact on the MTCT rate. Therefore, elective cesarean section should not be offered to HCV-infected pregnant women, and breastfeeding should not be discouraged.

Table 7 Potential risk factors for HCV mother-to-child transmission

Variable	Risk factor	Strength of the evidence
Maternal HCV/HIV coinfection	Yes	Strong
High maternal viral load	Yes	Strong
Cesarean section	No	Sufficient
Vaginal delivery	No	Sufficient
Breastfeeding	No	Sufficient
Genetic background	Yes	Sufficient
Amniocentesis	?	Insufficient
IV drug users	?	Insufficient
ALT levels during pregnancy	Yes	Insufficient
Internal fetal monitoring	Yes	Insufficient
Forceps deliveries	Yes	Insufficient
Perineal or vaginal lacerations	Yes	Insufficient
Episiotomy	No	Insufficient
Prolonged membrane rupture	Yes	Insufficient
Cigarette smoking	No	Insufficient
Alcohol intake	No	Insufficient
Maternal age	No	Insufficient
HCV genotype	No	Insufficient
Numbers of pregnancies	No	Insufficient
Prematurity	No	Insufficient
Girls gender	Yes	Insufficient

104.4.3 Clinical Aspects

The natural history of vertically acquired HCV infection is ill defined. Spontaneous disappearance of circulating HCV RNA occurs in at least one quarter of cases, mostly in preschool age (Garazzino et al. 2014). IL-28B polymorphisms have been associated with greater chance of viral clearance (Indolfi et al. 2014).

Infected children are asymptomatic at birth, and their general condition usually remains good during childhood with regular growth (England et al. 2005). Only a fraction develop minor abnormalities, such as hepatomegaly, or nonspecific symptoms and signs (European Paediatric Hepatitis C Virus Network 2005).

Alanine aminotransferase (ALT) activity is highest in the first 2 years of life, after which it declines, often assuming a fluctuating pattern. Viremia also fluctuates in a large proportion of infected children (Polywka et al. 2006).

Liver function tests are of little help in assessing the development of aggressive hepatitis and cirrhosis. Necrotic inflammation and fibrosis

are usually milder in children than in adults (European Paediatric Hepatitis C Virus Network 2005; Abdel-Hady et al. 2011). Progression of liver damage is not linear; cirrhosis and liver failure are rare in childhood (European Paediatric Hepatitis C Virus Network 2005; Abdel-Hady et al. 2011; Mack et al. 2012). Routine liver biopsy in infected children is not recommended.

HCV-associated extrahepatic manifestations and autoimmune diseases are rare in children with chronic infection, whereas non-organ-specific autoantibodies are frequently detected (Garazzino et al. 2014).

104.4.3.1 Diagnosis

The persistence of anti-HCV antibody beyond 15 months of age represents the "gold standard" for the diagnosis of vertically acquired HCV infection. Earlier diagnosis in an exposed child relies on the detection of HCV RNA by PCR. Children are taken to be infected if PCR is positive in at least two separate determinations. The test is highly specific, but its sensitivity is low at birth (22–33%), whereas it increases up to 85% after the first month of life (Mok et al. 2005).

Since a negative PCR might also reflect fluctuations in viremia, both antibody testing and the detection of serum HCV RNA have been suggested for definition of the infection status in exposed children (Fig. 3).

104.4.4 Therapy and Treatment

There are limited data for the management of children and adolescents with chronic HCV infection. The availability of DAAs with high pan-genotypic effectiveness has displaced the traditional treatments in HCV RNA-positive adults. At present, the combination of pegylated interferon-α and ribavirin remains the standard therapy for pediatric infections (Mack et al. 2012; Lee et al. 2015; Suzuki et al. 2016). However, clinical trials of interferon-free DAA regimens are in progress to verify safety and efficacy of these agents also in children with chronic infection (Ohmer and Honegger 2016). Indeed, since a significant liver damage is rare in preschool age, while during this period about a quarter of infected children show a spontaneous viral clearance, it seems reasonable to postpone any treatment beyond this age in most patients. HCV may however progress to hepatic failure, and liver transplantation has been performed in a few infected children (Mack et al. 2012).

Children with HCV should be immunized against hepatitis A and B.

104.5 Hepatitis B Virus (HBV)

104.5.1 Etiology and Pathogenesis

Two billion people worldwide are estimated to have acquired hepatitis B virus (HBV) and more than 350 million to be chronically infected (Schweitzer et al. 2015). In low-prevalence areas (chronic infection <2%), such as the USA and Western Europe, most new infections occur in young adults and are acquired sexually or through intravenous drug use, while in moderate- or high-prevalence areas (chronic infection 2–7% or >8%, respectively), perinatal and horizontal transmissions are the prevalent routes of infection.

HBV is a member of the Hepadnavirus family. The virus is divided into four major serotypes (adr, adw, ayr, ayw) and into eight genotypes (A–H) (Zhang et al. 2016).

Differences between genotypes affect the disease progression and the response to treatment. Hepatocytes are the primary target of HBV, but the kidney, pancreas, and mononuclear cells can also be infected. HBV is non-cytopathic by itself. The host's immune response causes both viral clearance and hepatocellular injury. The cytotoxic T-cell-mediated lysis of infected hepatocytes is the predominant mechanism of liver damage. Intrauterine exposure to HBV antigens may induce tolerance, accounting for the high rate of carriers among perinatally infected children.

104.5.2 Transmission

Possible routes of HBV transmission include unprotected sexual contact, blood transfusions, reuse of contaminated needles or syringes, and

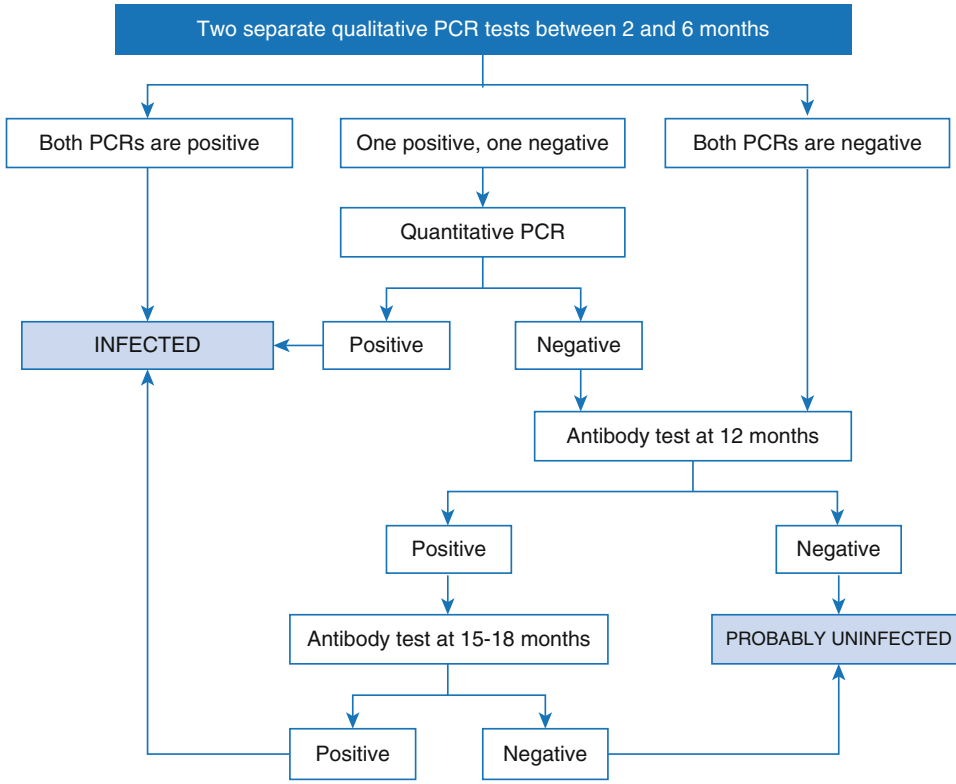


Fig. 3 Recommended follow-up schedule for early diagnosis of infection in infants born to HCV-infected women (Modified from (Pembrey et al. 2005))

MTCT. The vertical transmission rate is 70–90% in untreated infants of HB surface antigen (HbsAg)- and HBe antigen (HbeAg)-positive viremic women, while it decreases to 10–30% in the HBsAg carrier mothers who have anti-e antibody (anti-HBe) and are PCR negative. In utero infection is considered the most important reason for the failure of neonatal immunoprophylaxis in preventing MTCT; the exact mechanism of intrauterine transmission remains to be elucidated. Transmission to the offspring mostly occurs at delivery by microtransfusion or contact with contaminated body fluid. The mode of delivery (cesarean vs. vaginal) does not affect transmission, and breastfeeding is not an additional risk factor in infants treated with proper immunoprophylaxis (Gentile and Borgia 2014; Yi et al. 2016).

Acute HBV hepatitis or exacerbation of chronic disease may occur during pregnancy. However, these conditions increase neither maternal morbidity or mortality nor the risk of fetal complications, though a high number of preterm labors have been reported in women with acute hepatitis B.

104.5.3 Clinical Aspects

The age of HBV acquisition is roughly inversely correlated with the likelihood of developing a persistent infection. Neonates have >90% risk of developing chronic infection, as compared to 25–50% of older children and 5% of adult subjects.

104.5.3.1 Acute Infection

HBV-infected infants and children are usually asymptomatic. However, disease onset may be insidious. Symptoms and signs include anorexia,

malaise, nausea, vomiting, abdominal pain, and jaundice. MTCT is the most important route of transmission for acute or fulminating hepatitis in infancy. The incubation period ranges from 6 weeks to 6 months; the mortality rate of fulminating hepatitis is high (around 67%), and this may often require liver transplantation (Abdel-Hady and Kelly 2014).

Extrahepatic manifestations encompass skin rashes, membranous glomerulonephritis, arthralgias, and arthritis.

104.5.3.2 Chronic Infection

Chronic infection is defined as a persistence of HBsAg for >6 months. Affected children are usually asymptomatic with normal growth. In vertically infected children, the spontaneous clearance of HBV (i.e., loss of HBsAg and development of anti-HBs antibody) occurs at a rate of 0.6% per year over the first decade of life (Shah et al. 2009).

Most children who remain infected develop immune tolerance and have normal levels of hepatic transaminases. Chronic hepatitis B may exhibit various degrees of liver inflammation and fibrosis on biopsy. Levels of inflammation and fibrosis correlate with a worse prognosis. Less than 4% of infected children have persistent viral replication (HBeAg+) and elevated HBV DNA levels with ongoing liver inflammation and persistently or intermittently elevated transaminase levels (active hepatitis). Most concerns are focused on the latter patients, because they may develop cirrhosis and hepatocarcinoma (HCC) over a 20–30-year period.

104.5.3.3 Diagnosis

All pregnant women should be tested routinely for HBsAg during an early prenatal visit (first trimester) at each pregnancy, including women previously vaccinated or tested (Vodkin and Patton 2014; Ma et al. 2014).

Antigens and antibodies to be tested include HBsAg and specific antibody (anti-HBs), hepatitis B core antigen (HBcAg) and specific antibody (anti-HBc), and HBeAg and anti-HBe, bearing in mind that at least one serologic marker is present during the various phases of infection (Table 8). The presence of a confirmed HBsAg documents an ongoing infection. The detection of HBeAg and HBV DNA-positive PCR demonstrates viral replication. In general, these markers correlate with high infectivity. The appearance of anti-HBe means a loss of replicating virus, although reversion to HBeAg positivity may occur.

In exposed infants who undergo proper immunoprophylaxis, HBsAg and anti-HBs should be checked at 9–15 months of age or 1–3 months following completion of the primary immunization series to assess whether they are immune or infected.

Table 8 Interpretation of serologic tests for hepatitis B virus infection

Serologic markers				Interpretation
HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	
–	–	–	–	Never infected
+	–	–	–	Early acute infection, transient (up to 18 days) after vaccination
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Recovered from past infection and immune
+	+	–	–	Chronic infection
–	+	–	–	False positive (i.e., susceptible), past infection, "low-level " chronic infection, passive transfer to infants born to HBsAg-positive mothers
–	–	–	+	Immune if concentration is >10 mIU/mL, passive transfer after hepatitis B immune globulin administration

HBsAg hepatitis B surface antigen, *anti-HBc* antibody to HBV core antigen, *anti-HBs* antibody to surface antigen

104.5.4 Prevention

Prevention of MTCT of HBV is based on treatments for mothers during pregnancy and efforts for both newborns and their mothers after birth (Thio et al. 2015; Cheung et al. 2013).

Since high HBV DNA level and HBeAg-positive status in pregnant women are the most important risk factors for MTCT of HBV, antiviral therapies in highly viremic mothers can decrease the risk of transmission. Telbivudine, tenofovir, and lamivudine are three oral anti-HBV molecules whose use in pregnant women with chronic HBV infection did not result in increased adverse maternal or fetal outcome. Each drug showed improvement in maternal HBV DNA suppression at delivery and reduced the risk of MTCT (Brown et al. 2016).

All term infants born to HBsAg + women should receive hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) 12–24 h after birth, administered at different injection sites, followed by completion of the three-dose vaccine series.

This schedule prevents infection by 85–95%. Transplacental transmission cannot be interrupted by immunoprophylaxis and may account for the small percentage of unprotected infants.

Hepatitis B immunoprophylaxis for preterm infants differs slightly (Table 9).

104.5.5 Therapy and Treatments

Therapy for HBV infection has not been studied in neonates. Antiviral treatment is contraindicated in children under 1 year of age, given the adverse effects of interferon administered early in life. In general, children with normal ALT levels are not candidates for antiviral treatment.

104.5.5.1 Acute HBV Infection

There is no treatment of proven efficacy for children with acute HBV infection.

104.5.5.2 Chronic HBV Infection

General management of children with chronic infection includes (Ehrhardt et al. 2015; Haber et al. 2009):

Education and counseling of family members (including vaccination with hepatitis B vaccine).
Periodic clinical checks and laboratory investigations for liver disease.
Vaccination with hepatitis A vaccine.
Antiviral therapy, if appropriate.

No limitations in terms of school or other activities should be placed in children with chronic HBV infection.

The goals of chronic hepatitis B treatment are the cessation or reduction of viral replication, the normalization of aminotransferase levels, and the prevention of cirrhosis, hepatic failure, and HCC.

Treatment with two antiviral drugs (i.e., interferon (IFN)-α, adefovir, and lamivudine) (Table 11) is recommended for children over 1 year of age with evidence of chronic infection (i.e., detectable HBsAg for at least 6 months), active viral replication (i.e., presence of HBeAg and/or elevated HBV DNA levels), and increased ALT concentrations. HBV DNA is also essential to monitor response to antiviral therapy (Table 10). Elevated levels (>20,000 IU/mL or $>10^5$ copies/mL) after 24 weeks of therapy raise the highest concerns for liver health (Kurbegov and Sokol 2009; Ayoub and Keeffe 2011; Jonas et al. 2016; Jonas et al. 2010).

104.6 Human Parvovirus B19

104.6.1 Etiology and Pathogenesis

Parvovirus B19 (B19) is the only member of the family *Parvoviridae* to be pathogenic in humans. It may cause a wide spectrum of clinical manifestations; its seroprevalence increases with age and infection confers lifelong immunity.

B19 is a single-stranded non-enveloped DNA virus, genetically stable, resistant to heat and detergent inactivation, which can survive in blood products despite elimination procedures. It requires a mitotically active host cell for replication, such as erythroid precursors, fetal liver cells, or cord blood mononuclear cells. B19 infects these cells lytically.

Table 9 Hepatitis B immunization of term and preterm (<2000 g) infants by maternal hepatitis B surface (HBsAg) status

Newborn	Maternal HBsAg status	Drugs	Management dose	Age
Mature infants and preterm infants weighing >2000 g	Positive	Monovalent vaccine	1	Birth (<12 h)
		Monovalent vaccine	2	1 month
		Monovalent/ hexavalent vaccine	3	3 months
		Monovalent/ hexavalent vaccine	4	11–12 months
		HBIG	0.5 mL intramuscularly	Birth (<12 h)
	Unknown	Monovalent vaccine	1	Birth (<12 h)
		Monovalent vaccine	2	1 month
		Monovalent/ hexavalent vaccine	3	2 months
		Monovalent/ hexavalent Vaccine	4	11–12 months
		HBIG[a]	0.5 mL intramuscularly	<1 week of age[b]
Preterm infants weighing <2000 g	Positive	Monovalent vaccine	1	Birth (<12 h)
		Monovalent vaccine	2	1 month
		Monovalent/ hexavalent vaccine	3	2–3 months
		Monovalent/ hexavalent vaccine	4	6–7 months
		HIBG	0.5 mL intramuscularly	
	Unknown	As infants born to HbsAg-positive mother		
	Negative	Delay first dose of vaccine until 1 month of age or hospital discharge. Complete the vaccine series		

[a]If mother tested as soon as possible after admission for delivery is found to be HBsAg positive
[b]As soon as possible if HBsAg-positive status is confirmed

It uses at least three cellular receptors for cell attachment and entry. One of these, the glycolipid globoside (P-ag), is present on the placental trophoblasts, hematopoietic precursors, fetal myocytes, and endothelial cells. The presence of P-ag on these tissues may explain the congenital infection, the hematological disorders, the myocardial disease, and the vasculitis syndromes.

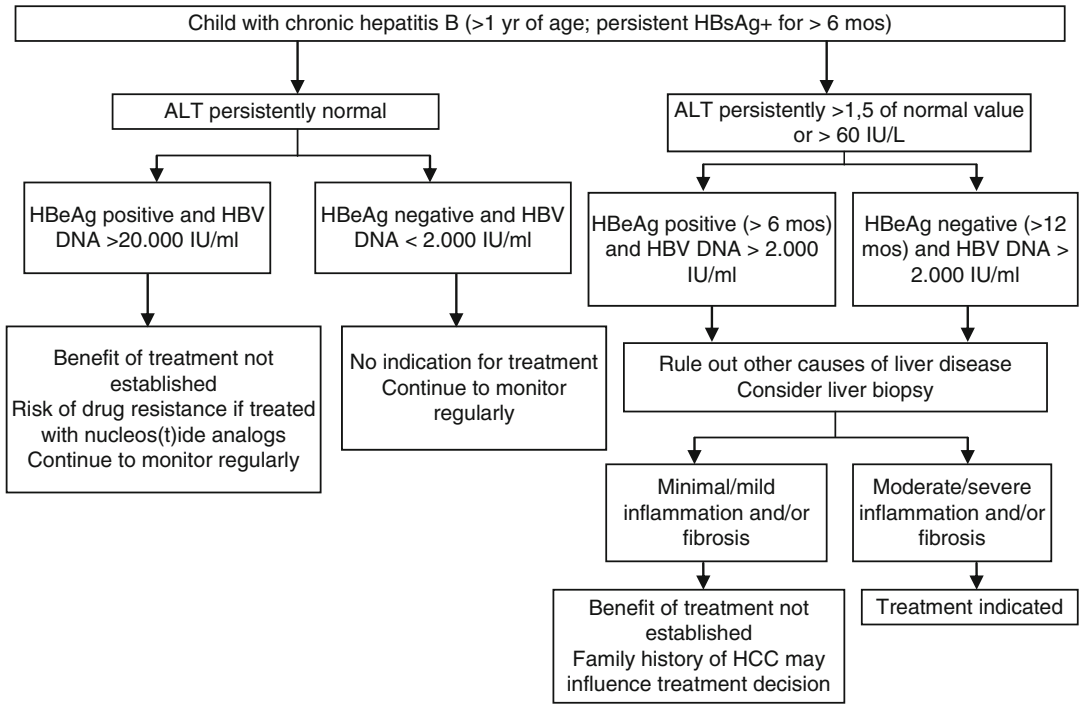
104.6.2 Transmission

Parvovirus B19 is transmitted by respiratory route and blood products and, vertically, from the mother to the offspring. About 30–50% of pregnant women are susceptible to B19 infection (Lamont et al. 2011). In the first and second trimester of pregnancy, the vertical transmission rate reaches 30%. Among vertically infected children, 5–10% presents an abnormal outcome. This risk is higher when maternal infection occurs in the first 20 weeks of pregnancy; about 3% of first trimester spontaneous abortions are estimated to be due to B19 infections. The inflammatory response of the placenta to the virus may lead to adverse fetal outcome even if the fetus is uninfected. Fetal infection is unpredictable, and discordant infections have been reported in twin pregnancies (Bekhit et al. 2009).

104.6.3 Clinical Aspects

Human parvovirus B19 infection may give rise to a large array of clinical manifestations, depending on the patient's immunological and hematologic

Table 10 Algorithm for selection of children for HBV antiviral treatment (Modified from Jonas et al. (2010))



status. In the normal host, the infection may be asymptomatic or give rise to erythema infectiosum (EI) and/or arthropathy. EI, also referred to as fifth disease or slapped cheek syndrome, usually affects school-aged children with low-grade fever, malaise, and the characteristic facial rash, involving the cheeks with relative circumoral pallor, that subsequently spreads to the trunk, back, and extremities. Arthralgia is more frequent in adults.

Patients with underlying hematological or immunological disorders are at risk for transient aplastic crisis, due to the block of erythropoiesis with a profound reticulocytopenia. Other manifestations associated with B19 infection are illustrated in Table 12.

Fetal infection is often asymptomatic, but it may give rise to:

Birth defects, particularly ocular and central nervous system abnormalities (long-term neurologic sequelae in infants with no signs at birth have been described).

Fetal hydrops, occurring in 1 out of 3000 births, with a mean interval of 6 weeks between the onset of maternal infection and fetal symptoms.

Intrauterine fetal death, more common in the first and second trimester, often unassociated with hydrops (de Jong et al. 2011).

Maternal clinical manifestations do not influence the pregnancy outcome.

104.6.3.1 Diagnosis

Diagnosis of B19 infection is based on detecting specific IgG and IgM or viral DNA in blood or tissue samples by PCR (Weiffenbach et al. 2012).

Specific IgM are present 10–12 days after infection; IgG appear shortly afterwards and mediate lifelong immunity. Caution is needed in interpreting serology in immunodeficient individuals or in pregnant women, because they are not always able to mount an adequate antibody response.

PCR analysis of B19 DNA in the serum, bone marrow (BM), and other tissues may integrate serology. In immunocompromised patients, a

Table 11 Treatment for chronic HBV infection

Drugs	Advantage	Disadvantage	Response in children
IFN-α[a]	No drug resistance	Parenteral administration	20–58% HBV DNA or HBeAg loss[b]
	Short duration of treatment	Adverse effects common	
PEG-IFN-2αa[c]	Administration once a week	Parenteral administration	HBV DNA disappearance in 6 out of 13 children without any side effect[c]
		Adverse effects common	
Lamivudine[d]	Minimal adverse effects	Drug resistance common (20%/years)	23–35% HBV DNA and HBeAg loss[e]
	Oral administration		
	Liquid formulation available		16–23% HBV DNA and HBeAg loss[f]
Adefovir[g]	Oral administration	Drug resistance less common than lamivudine	
	Minimal adverse effects		
	Effective in lamivudine resistance		
Entecavir[h]	Oral administration	Side effects in 9–10% of cases	55–82% ALT normalization in 48–52 weeks
	Effective in lamivudine resistance		

[a]Dosage in children >1 year of age: 5–10 MU/m^2 three times a week for 24 weeks
[b]From (Pawlowska and Halota 2007)
[c]In children there is only one preliminary report evaluating the rapid viral response of PEG-INF (100 μg/m^2/week) (Schwarz 2003). Not currently approved in chronic HBV infection in children
[d]Dosage in children >2 years of age: 3 mg/kg/day up to 100 mg/day for 52 weeks (Jonas et al. 2002)
[e]From (Schwarz 2003)
[f]From (Ayoub and Keeffe 2011)
[g]From (Ayoub and Keeffe 2011)
[h]Dosage in children 0.3–1 mg orally once a day. From (Clemente and Vajro 2016)

positive PCR test in blood indicates ongoing acute or persistent infection; in BM it may indicate either acute or previous infection. In cases of fetal complications, PCR analysis of amniotic fluid or cord blood may have a high priority for possible therapeutic interventions. Quantitative PCR allows the viral load concentration in different tissues to be quantified. However, further studies are needed to correlate the viral load with disease progression.

104.6.4 Prognosis

After intrauterine exposure to B19, the risk of fetal death is low (0.1–0.3%). Information on long-term outcomes of congenital infections is limited. However, severe sequelae including neurological disorders in survivors are well documented.

104.6.5 Therapy and Treatments

There is no specific therapy against B19 infection; some alternative interventions are however recommended, such as transfusion therapy to recover from aplastic crisis or intravenous IgG (0.4 g/kg × 5 days or 1 g/kg × 3 days) to facilitate the clearance of the virus in immunocompromised patients.

If maternal B19 infection is confirmed, weekly ultrasound examinations with Doppler

Table 12 Disorders associated with parvovirus B19 infection

Autoimmune disorders
Systemic lupus erythematosus
Systemic vasculitides
Rheumatoid arthritis
Production of autoantibodies to double-stranded DNA, antinuclear soluble antigens, cardiolipin, and rheumatoid factor
Increased bone marrow cell turnover
Transient aplastic crisis with severe anemia, resulting in congestive heart failure, cerebrovascular events, and acute splenic sequestration
Thrombocytopenia
Neutropenia
Pancytopenia
B19 persistence in immunocompetent patients
Persistent infection with potentially severe and chronic anemia, with various long-lasting symptoms such as fatigue, fever, arthralgia, and myalgia
Other associated disorders
Myocarditis and heart failure
Hepatitis
Kawasaki disease
Gloves and socks syndrome
Neurological disease
Fibromyalgia
Infection in immunocompromised individuals
Persistent BM suppression with chronic anemia (predisposing conditions are congenital immunodeficiencies, leukemia, lymphoma, myelodysplastic syndrome, BM and solid organ transplantation, chemotherapy, and infection with human immunodeficiency virus)
Infection-associated hemophagocytosis
Vertical transmission
Nonimmune fetal hydrops
Congenital anemia Thrombocytopenia Myocarditis Generalized edema Perivascular calcifications

measurement of middle cerebral artery flow velocity up to 20 weeks postexposure are appropriate to monitor the fetus (Dijkmans et al. 2012). If hydrops and/or signs of anemia appear, intrauterine erythrocyte transfusions can reduce the mortality rate and improve outcome (Lindenburg et al. 2014), though neurodevelopmental impairment may occur also in children treated with intrauterine transfusions.

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