Parvovirus Infections

Chapter 202 | Part 5: Infectious Diseases | Part 5 – Infectious Diseases: Viral (incl. HIV) | DETAILED EDITION

KEY CLINICAL POINTS

1. Parvovirus B19 (B19V) has narrow tropism for erythroid progenitors in bone marrow, causing cessation of red cell production.
2. Erythema infectiosum (fifth disease) is the classic presentation in children, characterized by a 'slapped-cheek' facial rash and lacy reticular rash on trunk/extremities.
3. Transient aplastic crisis (TAC) occurs in patients with hemolytic disorders (e.g., sickle cell) due to B19V-induced cessation of red cell production.
4. Pure red cell aplasia (PRCA) develops in immunocompromised patients unable to mount a neutralizing immune response.
5. Diagnosis relies on IgM seroconversion or quantitative PCR; PCR alone is not diagnostic for acute infection due to persistent DNA in healthy tissues.
6. Hydrops fetalis occurs in fetuses infected before 20 weeks gestation; risk of fetal loss is ~9% if maternal infection occurs before week 20.
7. Treatment for TAC/PRCA involves IVIG (400 mg/kg daily for 5–10 days) or blood transfusions; no antiviral drugs are available.
8. B19V DNA can persist in tissues (heart, liver, synovia) for decades without causing disease in immunocompetent individuals.
9. No vaccine is currently approved for B19V prevention; phase 1 trials were discontinued due to adverse side effects.
10. Rash in erythema infectiosum may recur for weeks with exercise or sunbathing, but the child is no longer infectious.

FIGURES IN THIS CHAPTER

1. DEFINITION & OVERVIEW

• Parvoviruses are members of the large family Parvoviridae.

• They are small (diameter ~22 nm), nonenveloped, icosahedral viruses with a linear single-stranded DNA genome of ~5000 nucleotides.

• The family includes viruses infecting many different animal hosts, from mammals to insects.

• Five main groups of parvoviruses infect humans: parvovirus B19 (B19V), adeno-associated viruses (AAVs), parvovirus 4 (parv4), human bocaviruses (HBoVs), and human protoparvoviruses (bufavirus and

cutavirus).

• B19V belongs to the genus Erythroparvovirus, so named due to its narrow tropism of erythrocyte precursors in the bone marrow.

• B19V is divided into three genotypes (1, 2, and 3), with similar antigenic, pathogenic, and biological properties.

• Harrison's defines this as: B19V belongs to the genus Erythroparvovirus, so named due to its narrow tropism of erythrocyte precursors in the bone marrow.

1.1 Viral Structure & Genome

• Diameter: ~22 nm.

• Structure: Nonenveloped, icosahedral.

• Genome: Linear single-stranded DNA (~5000 nucleotides).

• Host Range: Humans (B19V), various animals (AAVs, parv4, HBoVs, bufavirus, cutavirus).

1.2 Genotypes

• Genotype 1: Currently predominant worldwide.

• Genotype 2: Nowadays rarely causes active infections.

• Genotype 3: Most diverse, appears to be more common in the western parts of Africa.

2. EPIDEMIOLOGY

• B19V exclusively infects humans.

• Infection is common in virtually all parts of the world.

• Outbreaks of B19V infection, causing childhood rash (erythema infectiosum), are most common in schools and day-care centers.

• Outbreaks occur as epidemics a few years apart, in temperate climates, mostly in winter and spring.

• Within households, schools, and day-care centers, infection rates approach 50%.

• The risk of infection increases in proportion to the number of children.

• Transmission occurs primarily via the respiratory route and occurs before the onset of rash or arthralgia.

• By the age of 15 years, ~50% of children have detectable IgG antibody to B19V.

• Seroprevalence may rise to 80% among the elderly.

• Especially in patients with a hemolytic disorder or compromised immune system, the viral load of B19V in blood can be extremely high (up to 10^14 particles/mL).

• Transmission can also occur via transfusion, particularly of pooled blood products.

• Plasma pools are nowadays screened for B19V DNA, and high-titer pools are discarded.

• B19V is quite resistant to both heat and solvent-detergent inactivation.

2.1 Seroprevalence Trends

• Age 15 years: ~50% of children have detectable IgG antibody.

• Elderly: Seroprevalence may rise to 80%.

• Genotype 1: Predominant worldwide.

• Genotype 2: Rarely causes active infections.

2.2 Transmission Dynamics

• Route: Respiratory.

• Timing: Before onset of rash or arthralgia.

• Settings: Schools, day-care centers, households.

• Viral Load: Up to 10^14 particles/mL in immunocompromised.

• Blood Products: Pools screened for B19V DNA; high-titer pools discarded.

3. ETIOLOGY & PATHOPHYSIOLOGY

• B19V replicates in erythroid progenitors.

• This specificity may be due in part to a limited tissue distribution of the yet unknown primary B19V receptor that is recognized by the N-terminal unique region of B19-virus protein 1 (VP1u).

• Another important receptor, the blood group P antigen (globoside), recognized by the common VP region, VP2, is needed at a later intracellular step.

• Individuals who lack this P antigen are naturally resistant to B19V infection.

• Infection leads to high-titer viremia, with 10^4-12 virus particles/mL detectable in the blood at the apex.

• Virus-induced cytotoxicity results in cessation of red cell production.

• The viral load will, however, quickly drop, leaving very low-level B19V DNA in the blood for months and even years after the acute infection.

• B19V DNAemia in nonacute infections has, however, also been shown to be due to nonencapsidated naked DNA being released from injured tissues.

• In immunocompetent individuals with normal hemopoiesis, the arrest of erythropoiesis is transient, with only a minimal drop in hemoglobin levels, which resolves as the immune response is mounted.

• In individuals with increased erythropoiesis (especially with hemolytic anemia), the cessation of red cell production can induce a transient crisis with severe anemia.

• If an individual (or a fetus) does not induce neutralizing antibodies to halt the lytic infection, erythroid production is compromised, and chronic anemia develops.

• In immunocompetent individuals, the immune-mediated phase of illness, which begins 2–3 weeks after acute infection as the IgM response peaks, manifests as the rash of erythema infectiosum or fifth disease alone or together with arthralgia and/or frank arthritis.

• If immunocompromised patients with Parvoviruses are given immunoglobulins, they may also present with a rash, which is due to antigen-antibody complexes in skin.

• Even if B19V requires erythroid precursor cells for its replication, it can also enter nonpermissive cells, such as B cells, monocytes, and endothelial cells, by antibody-dependent enhancement (ADE), and remain presumably dormant for life in multiple tissues, such as the heart, liver, kidneys, synovia, brain, and even bones.

• This persistent presence of B19V DNA in our tissues does not generally seem to complicate normal health but may nevertheless be responsible for some disease presentations in predisposed individuals, as has been suggested in myocarditis, for example.

3.1 Receptor Biology

• Primary Receptor: Unknown primary B19V receptor recognized by N-terminal unique region of VP1u.

• Secondary Receptor: Blood group P antigen (globoside) recognized by common VP region, VP2.

• Timing: P antigen needed at a later intracellular step.

• Resistance: Individuals lacking P antigen are naturally resistant.

3.2 Pathogenesis Cascade

• Step 1: Replication in erythroid progenitors.

• Step 2: High-titer viremia (10^4-12 particles/mL).

• Step 3: Virus-induced cytotoxicity -> cessation of red cell production.

• Step 4: Viral load drop -> low-level DNA persists for months/years.

• Step 5: Immune response (IgM peak 2-3 weeks) -> rash/arthralgia in immunocompetent.

• Step 6: Chronic infection in immunocompromised -> PRCA.

4. CLINICAL FEATURES

• Most B19V infections are asymptomatic or exhibit only a mild nonspecific illness.

• The main manifestation of symptomatic B19V infection is erythema infectiosum, also known as fifth disease or slapped-cheek disease.

• Infection may begin with a minor febrile prodrome ~7–10 days after exposure, but it is often absent.

• The classic facial rash develops suddenly several days later.

• After 2–3 days, the erythematous maculopapular rash may spread to the trunk and extremities in a lacy reticular pattern.

• Its pattern, intensity, and distribution vary, and B19V-induced rash is difficult to clinically distinguish from other viral exanthems.

• Typically, the rash may recur for weeks when exercising or sunbathing, but the child is no longer infectious and can go to school.

• Adults typically do not exhibit the 'slapped-cheek' appearance but present with arthralgia, with or without a macular rash.

• In children, arthritis and encephalitis are rare complications.

• Polyarthropathy Syndrome: Although uncommon among children, arthropathy occurs in ~50% of adults and is more common among women than among men.

• The distribution of the affected joints is often symmetrical, with arthralgia affecting the small joints of the hands and occasionally the ankles, knees, and wrists.

• Resolution usually occurs within a few weeks, but recurring symptoms can continue for months.

• The illness may mimic rheumatoid arthritis, and rheumatoid factor can often be detected in serum.

• However, the mere presence of B19V DNA in synovia is not enough to prove a causative relation, since healthy individuals also may exhibit viral DNA in their synovia.

• Transient Aplastic Crisis: Asymptomatic transient reticulocytopenia occurs in most individuals with B19V infection.

• However, in patients who depend on continual rapid production of red cells, infection can cause a transient aplastic crisis (TAC).

• B19V is the predominant cause of TAC in individuals with hemolytic disorders, hemoglobinopathies, red cell enzymopathies, and autoimmune hemolytic anemias.

• Patients present with severe to life-threatening anemia and a low reticulocyte count.

• Bone marrow examination reveals characteristic giant pronormoblasts and an absence of erythroid precursors.

• However, reticulocytopenia in sickle-cell patients with acute worsening of anemia is diagnostic without bone marrow examination.

• Patients are often febrile and very ill, often including other complications.

• Pure Red Cell Aplasia (PRCA)/Chronic Anemia: Chronic B19V infection has been reported in a wide range of immunocompromised patients who are unable to mount a neutralizing immune response.

• Includes those with certain congenital immunodeficiencies, AIDS, lymphoproliferative disorders (especially acute lymphocytic leukemia), and transplantation.

• PRCA patients have persistent anemia with reticulocytopenia, absent or low levels of B19V IgG, extremely high titers of B19V DNA in serum, and typically scattered giant pronormoblasts on bone marrow examination.

• Nonerythroid hematologic lineages are rarely affected, but transient neutropenia, lymphopenia, and thrombocytopenia (including idiopathic thrombocytopenic purpura) have been observed.

• B19V occasionally causes a hemophagocytic syndrome.

• Hydrops Fetalis: B19V infection during pregnancy can lead to hydrops fetalis and/or fetal loss, due to either miscarriage (before 22 weeks of gestation) or fetal death (after 22 weeks of gestation).

• B19V probably causes 10–20% of all cases of nonimmune hydrops, which is characterized by gross edema and severe anemia.

• The risk of transplacental fetal infection is ~30%, and the excess risk of fetal loss (when the mother is infected before gestational week 20) is ~9%, but very low thereafter.

• Although B19V does not appear to be teratogenic, rare cases of eye damage, central nervous system (CNS) abnormalities, and congenital anemia have been reported.

• Unusual Manifestations: B19V infection may rarely cause hepatitis, vasculitis, myocarditis, glomerulosclerosis, or meningoencephalitis.

• A variety of other cardiac manifestations, CNS diseases, and autoimmune diseases have also been reported in conjunction with B19V infection.

4.1 Erythema Infectiosum (Fifth Disease)

• Presentation: Classic facial rash ('slapped-cheek').

• Progression: Spreads to trunk/extremities in lacy reticular pattern after 2-3 days.

• Prodrome: Minor febrile illness ~7-10 days after exposure (often absent).

• Recurrence: Rash may recur for weeks with exercise or sunbathing.

• Infectiousness: Child is no longer infectious when rash recurs.

• Adult Presentation: Arthralgia with or without macular rash (no 'slapped-cheek').

• Complications: Arthritis (rare in children), encephalitis (rare in children).

4.2 Polyarthropathy Syndrome

• Demographics: ~50% of adults, more common in women than men.

• Joint Distribution: Symmetrical, small joints of hands, ankles, knees, wrists.

• Duration: Resolution within few weeks; recurring symptoms can continue for months.

• Mimics: Rheumatoid arthritis.

• Serology: Rheumatoid factor often detected in serum.

• Caveat: Presence of B19V DNA in synovia does not prove causation.

4.3 Transient Aplastic Crisis (TAC)

• Hosts: Patients with increased erythropoiesis (hemolytic disorders, hemoglobinopathies, red cell enzymopathies, autoimmune hemolytic anemias).

• Presentation: Severe to life-threatening anemia, low reticulocyte count.

• Bone Marrow: Giant pronormoblasts, absence of erythroid precursors.

• Diagnosis: Reticulocytopenia in sickle-cell patients with acute worsening of anemia is diagnostic without bone marrow examination.

• Clinical Status: Patients often febrile and very ill.

4.4 Pure Red Cell Aplasia (PRCA)

• Hosts: Immunocompromised patients (congenital immunodeficiencies, AIDS, lymphoproliferative disorders, transplantation).

• Presentation: Persistent anemia, reticulocytopenia.

• Serology: Absent or low levels of B19V IgG.

• Viral Load: Extremely high titers of B19V DNA in serum.

• Bone Marrow: Scattered giant pronormoblasts.

• Other Findings: Transient neutropenia, lymphopenia, thrombocytopenia (including ITP).

• Complications: Hemophagocytic syndrome.

4.5 Hydrops Fetalis

• Timing: Infection during pregnancy.

• Outcome: Hydrops fetalis and/or fetal loss.

• Gestational Age: Miscarriage before 22 weeks; fetal death after 22 weeks.

• Incidence: B19V causes 10-20% of all cases of nonimmune hydrops.

• Characteristics: Gross edema and severe anemia.

• Risk Factors: Maternal infection before gestational week 20 (excess risk of fetal loss ~9%).

• Teratogenicity: Does not appear teratogenic; rare cases of eye damage, CNS abnormalities, congenital anemia reported.

5. DIFFERENTIAL DIAGNOSIS

• Erythema Infectiosum: Difficult to clinically distinguish from other viral exanthems.

• Polyarthropathy: Mimics rheumatoid arthritis.

• Transient Aplastic Crisis: Other causes of hemolytic anemia exacerbation.

• PRCA: Other causes of pure red cell aplasia in immunocompromised hosts.

• Hydrops Fetalis: Other causes of nonimmune hydrops.

5.1 Rash Differential

• Viral exanthems: B19V-induced rash is difficult to clinically distinguish.

• Recommendation: Laboratory test should be used when a definite diagnosis is necessary (e.g., pregnant women).

5.2 Arthropathy Differential

• Rheumatoid Arthritis: Illness may mimic rheumatoid arthritis.

• Rheumatoid Factor: Often detected in serum.

• Differentiation: Mere presence of B19V DNA in synovia is not enough to prove causative relation.

6. INVESTIGATIONS & DIAGNOSIS

• Diagnosis of B19V infection in immunocompetent individuals is generally based on detection of B19V antibodies.

• IgM: Can be detected by indirect enzyme immunoassay (EIA) at the time of the rash in erythema infectiosum and by the third day of TAC in patients with hematologic disorders.

• IgM Duration: May remain detectable for ~3 months or longer.

• IgG: Detectable by the seventh day of illness and persists throughout life.

• IgG Significance: IgG positivity marks immunity.

• Acute Infection Criteria: Serum samples taken 2 weeks apart that show seroconversion or a four-fold or greater increase in IgG titer are considered diagnostic for acute infection.

• IgG Quality: Modern serology can further measure the quality of IgG; as the immune response matures with time, the initially low avidity of IgG gradually increases within 6 months and can be measured with a denaturing EIA.

• Epitope-Type-Specific (ETS) EIA: Another way of timing the B19V infection is by comparing the IgG responses toward linear versus conformational B19V VP2 epitopes.

• Both avidity and ETS EIAs differentiate between acute and past infection and thus increase the specificity of the diagnosis.

• PCR: Detection of B19V DNA in serum (or amniotic fluid) by PCR provides further help, especially in pregnancy, TAC, or chronic anemia.

• Viral Load Thresholds: In acute infection at the height of viremia, B19V >10^12 B19V DNA IU/mL of serum can be detected.

• Viral Load Persistence: The viral load falls rapidly within a few days but can remain detectable by PCR for months or even years after acute infection, even in healthy individuals.

• Tissue PCR: In tissue material, PCR alone should not be used to establish a B19V etiology because viral DNA remains in healthy bodies for decades.

• Bone Marrow: Examination reveals characteristic giant pronormoblasts and an absence of erythroid precursors in TAC/PRCA.

• Table 202-1: Diseases Associated with Human Parvovirus B19 Infection and Methods of Diagnosis.

Table 1 Table 202-1: Diseases Associated with Human Parvovirus B19 Infection and Methods of Diagnosis

DISEASE	HOSTS	IgM	IgG	PCR	QUANTITATIVE PCR
Fifth disease	Healthy children	Positive	Positive	Positive	>10^4 IU/mL
Polyarthropathy syndrome	Healthy adults (more often women)	Positive within 3 months of onset	Positive	Positive	>10^4 IU/mL
Transient aplastic crisis	Patients with increased erythropoiesis	Negative/positive	Negative/positive	Positive	Often >10^12 IU/mL, but rapidly decreases
Persistent anemia/pure red cell aplasia	Immunodeficient or immunosuppressed patients	Negative/weakly positive	Negative/weakly positive	Positive	Often >10^12 IU/mL, but should be >10^6 in the absence of treatment
Hydrops fetalis/congenital anemia	Fetuses (of mothers infected <20 weeks)	Negative/positive	Positive	Positive amniotic fluid or tissue	n/a

6.1 Serology

• IgM: Detected by indirect enzyme immunoassay (EIA).

- Timing: At time of rash (erythema infectiosum) or third day of TAC.
- Duration: ~3 months or longer.
- IgG: Detectable by seventh day of illness.
- Immunity: IgG positivity marks immunity.
- Acute Infection: Seroconversion or four-fold increase in IgG titer over 2 weeks.
- IgG Avidity: Increases within 6 months; measured with denaturing EIA.
- ETS EIA: Compares IgG responses toward linear vs conformational VP2 epitopes.

6.2 PCR & Viral Load

- Indication: Pregnancy, TAC, chronic anemia.
- Acute Viremia: >10^12 B19V DNA IU/mL of serum.
- Persistence: Detectable for months/years after acute infection.
- Tissue PCR: Not diagnostic for etiology due to persistence in healthy bodies.

6.3 Bone Marrow Findings

- TAC/PRCA: Characteristic giant pronormoblasts.
- Erythroid Precursors: Absence.

7. MANAGEMENT & TREATMENT

- No antiviral drugs against B19V are available for patient use.
- Treatment of B19V infection often targets symptoms only.
- Cidofovir, and its lipid conjugate brincidofovir, as well as hydroxyurea, seem to inhibit B19V replication in vitro.
- TAC caused by B19V frequently necessitates treatment with repeated blood transfusions.
- In patients receiving chemotherapy, temporary cessation of treatment may result in an immune response and resolution.
- If this approach is unsuccessful or not applicable, commercial immunoglobulin can cure or ameliorate chronic B19V infection in immunosuppressed or otherwise immunocompromised patients.
- Generally, the intravenous IgG (IVIG) dose is 400 mg/kg daily for 5–10 days.
- The patient should be monitored for relapses.
- Administration of IVIG is not beneficial for the immune-mediated erythema infectiosum or B19V-associated arthropathies, which generally are self-limited.
- Intrauterine blood transfusion can prevent fetal loss in some cases of fetal hydrops; however, the risks need to be evaluated.
- Exposed seronegative mothers should undergo tests for B19V infection.
- If found positive, they should be monitored regularly throughout pregnancy.
- Most fetal infections resolve themselves, but sometimes intrauterine red cell transfusions are needed.

7.1 Symptomatic Management

- Erythema Infectiosum: Self-limited; IVIG not beneficial.
- Arthropathy: Self-limited; IVIG not beneficial.

7.2 Transient Aplastic Crisis (TAC)

- Treatment: Repeated blood transfusions.

• Immunosuppression: Temporary cessation of chemotherapy may result in immune response and resolution.

• IVIG: Not beneficial for TAC in immunocompetent hosts.

7.3 Pure Red Cell Aplasia (PRCA)

• Treatment: Commercial immunoglobulin (IVIG).

• Dose: 400 mg/kg daily for 5–10 days.

• Monitoring: Monitor for relapses.

• Etiology: Immunocompromised patients unable to mount neutralizing immune response.

7.4 Pregnancy Management

• Screening: Exposed seronegative mothers should undergo tests for B19V infection.

• Monitoring: If positive, monitor regularly throughout pregnancy.

• Fetal Infection: Most resolve themselves.

• Intervention: Intrauterine red cell transfusions if needed.

• Hydrops Fetalis: Intrauterine blood transfusion can prevent fetal loss; risks need evaluation.

8. PROGNOSIS & COMPLICATIONS

• In immunocompetent individuals, the arrest of erythropoiesis is transient, with only a minimal drop in hemoglobin levels, which resolves as the immune response is mounted.

• Lifelong immunity follows resolution of TAC.

• In immunocompromised patients, chronic anemia develops if neutralizing antibodies are not induced.

• B19V DNA can be detected by PCR for life in many tissues; therefore, this finding is of no known clinical significance, but its interpretation may cause confusion regarding B19V disease association.

• B19V-infected immunocompetent individuals seldom show PRCA or chronic anemia.

• Co-infection with Plasmodium and B19V has been suggested to play a role in the development of severe anemia in young children with malaria.

• Unusual Manifestations: Hepatitis, vasculitis, myocarditis, glomerulosclerosis, meningoencephalitis, cardiac manifestations, CNS diseases, autoimmune diseases.

8.1 Immunocompetent Hosts

• Erythema Infectiosum: Self-limited.

• TAC: Resolves with cessation of cytopathic infection; lifelong immunity follows.

• PRCA: Seldom occurs in immunocompetent individuals.

8.2 Immunocompromised Hosts

• Chronic Anemia: Develops if neutralizing antibodies not induced.

• Treatment: IVIG can cure or ameliorate chronic B19V infection.

• Viral Load: Extremely high titers of B19V DNA in serum.

• Persistence: B19V DNA detectable for life in tissues.

9. SPECIAL CONSIDERATIONS

• Pregnancy: Risk of transplacental fetal infection ~30%.

• Fetal Loss: Excess risk ~9% if maternal infection before gestational week 20.

- Pediatrics: Erythema infectiosum common in children; polyarthropathy uncommon.
- Elderly: Seroprevalence rises to 80%.
- Immunocompromised: PRCA, chronic anemia, hemophagocytic syndrome.
- Hemolytic Disorders: TAC risk.

9.1 Pregnancy

- Screening: Exposed seronegative mothers should undergo tests.
- Monitoring: Regular monitoring throughout pregnancy if positive.
- Fetal Outcome: Most infections resolve; intrauterine transfusions needed sometimes.
- Hydrops: Gross edema and severe anemia.

9.2 Immunocompromised

- Conditions: Congenital immunodeficiencies, AIDS, lymphoproliferative disorders, transplantation.
- Manifestation: PRCA, chronic anemia.
- Treatment: IVIG, cessation of immunosuppression.

10. KEY PEARLS & CLINICAL TRAPS

- Rash recurrence: Rash may recur for weeks when exercising or sunbathing, but the child is no longer infectious.
- PCR Interpretation: PCR alone should not be used to establish a B19V etiology because viral DNA remains in healthy bodies for decades.
- Synovial DNA: The mere presence of B19V DNA in synovia is not enough to prove a causative relation, since healthy individuals also may exhibit viral DNA in their synovia.
- Viral Load: In immunocompromised patients, viral load can be extremely high (up to 10^14 particles/mL).
- IVIG Dosing: Generally, the intravenous IgG (IVIG) dose is 400 mg/kg daily for 5–10 days.
- Vaccine Status: No vaccine has been approved for the prevention of B19V infection; phase 1 trials were discontinued because of adverse side effects.

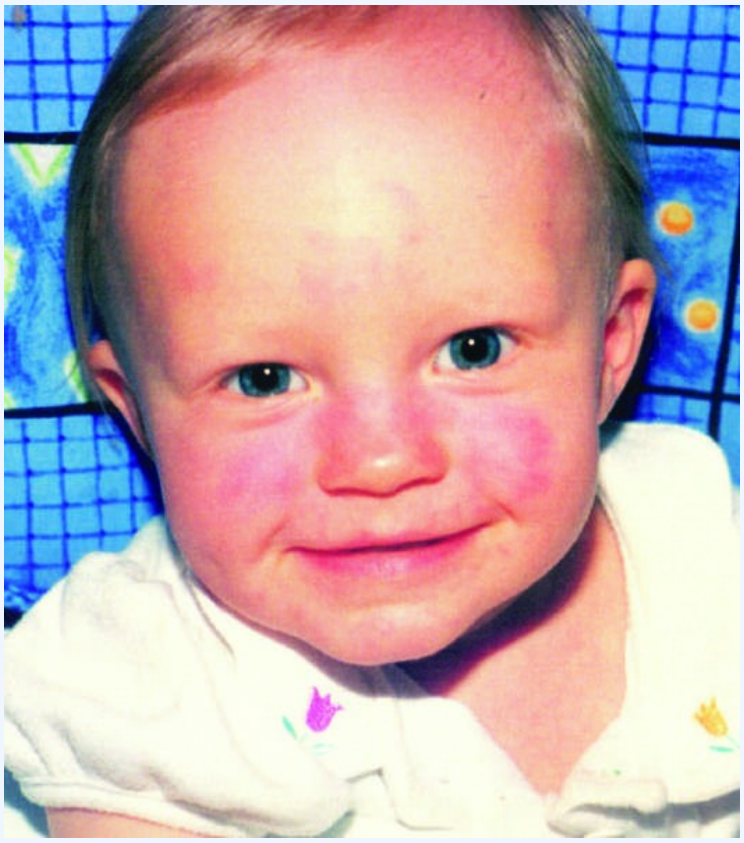
10.1 Diagnostic Pitfalls

- PCR Persistence: Viral DNA remains in healthy bodies for decades.
- Synovial DNA: Presence does not prove causation.
- Clinical Signs: Rash difficult to distinguish from other viral exanthems.

10.2 Treatment Pearls

- IVIG: Beneficial for PRCA/TAC in immunocompromised.
- IVIG: Not beneficial for erythema infectiosum/arthropathy.
- Transfusion: Repeated blood transfusions for TAC.

FIGURES & ILLUSTRATIONS — FROM HARRISON'S



Harrison's 22e · Figure 1

FIGURE 202-1 Schematic of the time course of parvovirus B19 infection in (A) normals pure red cell aplasia (PRCA). (From The New England Journal of Medicine, Parvovirus Reprinted with permission from Massachusetts Medical Society.) — Figure 202-1: Schematic of the time course of parvovirus B19 infection in (A) normals (erythema infectiosum), (B) transient aplastic crisis (TAC), and (C) chronic anemia/pure red cell aplasia (PRCA). The figure illustrates viral load, IgM/IgG antibody kinetics, and hemoglobin/reticulocyte levels over days post-inoculation.