

HIV-RELATED HEMATOLOGIC MANIFESTATIONS IN PEDIATRICS

I. INTRODUCTION

RECOMMENDATION:

A complete blood count with differential should be performed every 3 months to screen for hematologic abnormalities in HIV-infected children. Complete blood count may need to be obtained more often for children receiving bone marrow suppressive therapy or if abnormalities are identified.

Hematologic abnormalities are among the most common manifestations of HIV/AIDS infection in children. Of these abnormalities, anemia is the most common hematologic manifestation. In addition, hematologic toxicities comprise a significant proportion of the adverse events secondary to antiretroviral (ARV) therapy. Other hematological findings include neutropenia, thrombocytopenia, and coagulation abnormalities.

Several mechanisms are involved in the pathophysiology of these manifestations. Both impaired production of blood cells and autoantibody-mediated increased peripheral destruction may occur. Accelerated non-immune peripheral consumption presumably occurs in certain cases involving white cells and platelets but has not been well documented.

The etiologies for defective hematopoiesis (decreased blood cell production) include the following:

- **HIV-related bone marrow suppression:** The two main mechanisms by which HIV affects the marrow are 1) direct infection of the progenitor cells, or 2) indirect actions of infected accessory cells. The predominant mechanism varies from patient to patient and may vary in a given patient at different times. Megakaryocytes, for example, express CD4 and CCR5 receptors through which HIV enters these cells and creates a direct suppressive effect. Alternatively, infected T cells and macrophages secrete transforming growth factor- β (TGF- β), interferon- α , and/or tumor necrosis factor- α (TNF- α), which are all known to inhibit megakaryocytopoiesis. HIV may also infect the marrow stromal cells.
- **Drug therapy:** Single or multiple drug therapy with potentially myelosuppressive agents, such as zidovudine, trimethoprim-sulfamethoxazole, and ganciclovir, can cause defective hematopoiesis.
- **Opportunistic infections:** *Mycobacterium avium* complex, Parvovirus B19, cytomegalovirus, and other infectious agents can cause defective hematopoiesis.
- **Bone marrow infiltration by a malignancy:** HIV-related malignancies are rare in children, occurring in approximately 1.5% of infected children. Non-Hodgkin's lymphoma is the most common HIV-related malignancy in children.

A possible etiology for autoimmune-mediated peripheral destruction is the development of autoantibodies to platelets and, less commonly, to other blood elements, which can be triggered by HIV. Autoimmune destruction can occur in the marrow as well as the peripheral blood.

II. ANEMIA

Anemia, defined by hematocrit (Hct) <33% occurs in 16% to 94% of HIV-infected children¹ (see Table 1). A large epidemiological study of 32,867 HIV-infected adults and adolescents found that the risk of death was 170% greater for persons with persistent anemia (hemoglobin <10 gm/dL) compared with those whose anemia had resolved.² However, it is unknown whether severe or persistent anemia directly or indirectly causes mortality or merely serves as a marker of advanced HIV infection.

TABLE 1 ANEMIA COMMONLY ASSOCIATED WITH HIV					
Anemia	Iron	Total Iron-Binding Capacity	Mean Corpuscular Volume	Reticulocyte Count	Distinguishing Features
Anemia of chronic disease	Low	Normal or low	Normal or low	Low	By far the most common
Iron deficiency	Low	High	Low (if not masked by other causes)	Normal or decreased	Dietary—might be difficult to differentiate from anemia of chronic disease with low iron stores
Medication-induced hypoproduction (e.g., zidovudine, trimethoprim-sulfamethoxazole, amphotericin)	Normal	Normal	Normal to high	Normal or low	Develops within the first weeks of treatment
Medication-induced hemolysis (e.g., trimethoprim-sulfamethoxazole, dapsone)	Normal	Normal	Normal	High or normal	Elevated bilirubin, lactic dehydrogenase, low haptoglobin, smear; might be associated with G6PD deficiency
Infection-related hypoproduction (e.g., Parvo B19, MAC)	Normal	Normal	Normal to high	Decreased	Symptoms and signs of Fifth disease might be absent
Hypersplenism	Normal	Normal	Normal to high	Increased or normal	Splenomegaly, pancytopenia

In the general pediatric population, classification of anemia is often based on mean corpuscular volume (MCV) (microcytic vs. normocytic vs. megaloblastic) and on the mechanism of anemia (hemolytic vs. hypoplastic). However, MCV is not as useful a determinant for anemia classification in HIV-infected children because it may be falsely low as a result of anemia of chronic inflammation or falsely high in patients who are receiving zidovudine or who have other types of macrocytic anemia. Specific iron measurements are needed before diagnosing iron deficiency. Similarly, in HIV-infected children with hemolytic anemia, the reticulocyte count may be falsely low because of concomitant hypoproduction.

A. Types of Anemia

1. Microcytic Anemia

RECOMMENDATIONS:

The diagnostic evaluation for microcytic anemia in the HIV-infected child should include a careful nutritional history, review of systems (especially the gastrointestinal tract), and iron studies, specifically serum iron, total iron-binding capacity, transferrin saturation, and serum ferritin. If indicated by family history or if the anemia persists after a therapeutic trial of iron, hemoglobin electrophoresis with quantitative measurement of hemoglobin A2 and hemoglobin F should be performed.

Screening of lead levels should be performed yearly in all children and whenever toxicity is suspected.

The common causes of microcytic anemia in children with HIV include anemia of chronic disease with low iron levels, iron-deficiency anemia, thalassemia trait, and lead toxicity. Low serum iron levels have been reported in 48% of children with HIV and may be associated with intestinal malabsorption as well as poor intake.³ However, it is difficult to differentiate true iron deficiency from anemia of chronic inflammation with low iron levels. The increased range, frequency, severity, and chronicity of gastrointestinal infections in children with HIV may contribute to iron deficiency in several ways. Some infections, such as *Shigella* and amoebiasis, may lead to gastrointestinal bleeding. Others, including *Giardia* and *Cryptosporidium*, may cause malabsorption of iron. Chronic infection may also cause lactose intolerance, which itself may directly contribute to iron malabsorption.

Typically with iron deficiency, the serum iron and the transferrin saturation will be low with increased total iron-binding capacity (TIBC), whereas, in anemia of chronic disease, the TIBC will also be low. Serum ferritin is a marker of acute and chronic inflammation and will be elevated in the setting of HIV infection, thereby masking the decrease in ferritin that is characteristic of iron deficiency. Serum ferritin levels are also a marker of disease progression. One study found serum ferritin levels of more than 100 mg/mL in 93% of children with advanced disease, with increasing levels accompanying or closely preceding rapid disease progression.⁴

Other causes of microcytic anemia that are encountered in the general pediatric population, such as the thalassemias, including the thalassemia trait, should also be considered, especially if indicated by family history and ethnic background (i.e., Mediterranean, Hispanic, African American, Asian).

Lead toxicity, although rare, may be more common in patients with microcytic anemia because lead absorption is increased in the setting of iron deficiency. Screening of lead levels should be performed yearly in all children, and more frequently when toxicity is suspected.

2. Normocytic Anemia

Common causes of normocytic anemia in HIV-infected children include hypoplastic anemia caused by anemia of chronic disease or by infectious agents such as Parvovirus B19 or *Mycobacterium avium* complex. Hemolytic anemia caused by thrombotic thrombocytopenic purpura, drug toxicities, autoimmunity, or hypersplenism is also normocytic.

a. Hemolytic Anemia

RECOMMENDATION:

Evaluation for hemolysis should be performed in individuals with unusually high transfusion requirements or those with high reticulocyte count, low serum haptoglobin (only for intravascular hemolysis), presence of microspherocytes on the peripheral smear, indirect hyperbilirubinemia, or bone marrow erythroid hyperplasia.

Although a positive direct Coombs test is reported in 37% of anemic HIV-infected children, clinically significant hemolysis is rare.¹ Thrombotic thrombocytopenic purpura (TTP) has been reported to occur in HIV-infected pediatric patients. The syndrome is identified by the pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic signs and/or symptoms, and renal insufficiency (or hematuria alone). In addition, the serum lactate dehydrogenase is pathognomically increased to 5 to 10 times the normal level (almost always >700-1000 mg/dL; upper normal limit, 225 mg/dL). Several cases of TTP have developed in patients who had previously presented with HIV-associated immune thrombocytopenia.

Hemolytic anemia can also be caused by medications used in HIV management, such as trimethoprim-sulfamethoxazole and dapsone, particularly in G6PD-deficient individuals. Hemolytic anemia, or more commonly pancytopenia, can occur as a result of hypersplenism, especially in patients with advanced liver or systemic disease or because of coincident chronic hepatitis B or hepatitis C.

b. Hypoplastic Anemia

RECOMMENDATION:

If a patient presents with hypoplastic anemia in the presence of fever, weight loss, or new physical findings, opportunistic infections should be excluded. Appropriate cultures and bone marrow examination should be performed to help establish the diagnosis.

Anemia of chronic disease is the most frequent normocytic anemia in HIV-infected children. As in other forms of anemia of chronic disease, the reticulocyte response is suppressed. In addition to decreased responsiveness to erythropoietin, there is also blunted erythropoietin production in response to the degree of anemia. Serum immunoreactive erythropoietin levels were demonstrated to be elevated in patients with AIDS-related anemia, but the elevation was less than that seen in controls with anemia of comparable severity.⁵

Parvovirus B19 infection is more protracted in patients with HIV because they are immune compromised. Because this virus has tropism for erythroid progenitor cells, it can inhibit erythropoiesis for a prolonged period and can be the cause of severe anemia. Manifestations of Fifth disease (i.e., erythema infectiosum, “slapped cheek syndrome”) are generally absent but may become apparent after treatment with immune globulin. Diagnostically, Parvovirus B19 should be suspected in any persistently anemic patient, especially when the reticulocyte count is low and when the anemia is accompanied by other cytopenias. Parvovirus B19 DNA dot blot hybridization of the serum or polymerase chain reaction (PCR) examination can help in establishing the diagnosis; serology is not very useful. The presence of other systemic symptoms, such as persistent fever, weight loss, or abdominal pain in a severely immune deficient patient with anemia makes the diagnosis of an opportunistic infection more likely. Cultures for specific pathogens, including *Mycobacterium avium* complex and cytomegalovirus, may be useful. A bone marrow examination may be necessary both to examine for pathogens and to exclude other diagnoses, such as malignancies.

Amphotericin, trimethoprim-sulfamethoxazole, zidovudine, and ganciclovir can suppress erythropoietin production, causing normocytic anemia, and, although rare, it can affect the red blood cell membrane causing hemolysis.

3. Macrocytic Anemia

RECOMMENDATION:

If megaloblastic anemia cannot be explained by common causes, such as medications, including ARV drugs, evaluation should include liver and thyroid function tests, vitamin B₁₂ and folate levels, bone marrow aspiration, and biopsy to evaluate for the possibility of bone marrow failure or myelodysplasia.

Drug therapy is the most frequent cause of megaloblastic or macrocytic anemia in HIV-infected pediatric patients. Macrocytosis develops within weeks in most patients treated with zidovudine and can be used as a marker of adherence to zidovudine therapy. The incidence of anemia is related to the dose of zidovudine and to the stage of the HIV infection. Polypharmacy and other ARV drugs may contribute to macrocytosis.

Trimethoprim-sulfamethoxazole is commonly used for the prevention of *Pneumocystis carinii* pneumonia. It may result in megaloblastic anemia because of folate deficiency in patients with poor nutritional status. Hematologic toxicity of all kinds is much less likely at prophylactic doses of 5 mg trimethoprim/kg 3 days per week rather than at treatment doses of 20 mg trimethoprim/kg/day.

Although slightly decreased serum B₁₂ levels are not uncommon, clinical deficiency is rare. There is no evidence that replacement of B₁₂ improves the hematologic picture other than in rare cases of true deficiency.

B. Treatment of Anemia

RECOMMENDATIONS:

If endogenous erythropoietin levels are <500 mUnits/mL, erythropoietin therapy (50-200 iu/kg/dose 3×/week) should be administered to reduce the need for transfusion. Supplemental oral iron (3-6 mg/kg/day of elemental iron) and folate (1 mg/day) should be administered when erythropoietin is initiated.

If clinically significant anemia (i.e., hemoglobin <7 g/dL or cardiorespiratory compromise) develops within the first month of life and zidovudine prophylaxis, the use of erythropoietin or transfusion is recommended to allow sustained use of zidovudine until the diagnosis of perinatal infection has been established. The zidovudine dose should not be modified.

If severe anemia develops after the fourth week of zidovudine prophylaxis, zidovudine may be discontinued at that time rather than subjecting the neonate to blood transfusion or erythropoietin.

The necessity for blood transfusion should be evaluated carefully. Transfusions should be reserved for clinically significant, severe anemia. Irradiation and leukocyte reduction of blood according to standard protocols should be used for all transfusions.

The treatment of anemia should be directed to correct the underlying cause through nutritional support, iron supplementation for suspected iron deficiency, control of opportunistic infections, and control of ongoing hemorrhage tailored to the site of bleeding, as appropriate. Examples include humidification of air, possibly aminocaproic acid for epistaxis, and oral contraceptive pills for vaginal hemorrhage.

In general, after the neonatal period and early infancy, anemia attributable to ARV therapy is often mild and seldom requires cessation of therapy. At birth, special attention should be given to the hemoglobin of an infant born to an HIV-infected mother exposed to zidovudine. Hemoglobin levels tend to be slightly lower in neonates, with zidovudine-associated anemia evident at 3 weeks of age. Erythropoietin has been shown to be effective in HIV-related anemia, especially when it is caused by zidovudine or low endogenous erythropoietin levels.

The indications, risks, and benefits for red cell transfusions are similar to those of non-HIV-infected patients. However, when transfusing the HIV-infected patient, there are several special concerns that predate the availability of routine leuko-reduction. Studies have shown increased viral load 5 days after the transfusion,⁶ increased incidence of cytomegalovirus infection, and death in patients with advanced disease, although most of these studies were conducted in adults. The survival rate is possibly decreased in patients who are given transfusions compared with patients who have similar degrees of anemia and immunodeficiency who are not transfused. Irradiation and leukocyte reduction have greatly reduced the risk of infection and graft-versus-host disease related to transfusion.

III. THROMBOCYTOPENIA

A. Pathophysiology and Diagnosis

RECOMMENDATIONS:

If thrombocytopenia is identified, the differential diagnosis should be established according to the presence or absence of one or more of the following:

- **abnormalities in the physical examination, especially organomegaly or lymphadenopathy**
- **abnormalities in the non-platelet components of the complete blood count**
- **failure to respond to platelet-directed treatment.**

If physical examination abnormalities or multiple cell line deficits are present or if the platelet count does not respond to platelet-directed treatment, prompt investigation for infectious, toxic, or malignant causes should be performed.

A bone marrow examination should be performed in consultation with a hematologist/ oncologist when malignancy is suspected.

If thrombocytopenia is accompanied by other cytopenias or splenomegaly and is mild ($>50,000$ cells/ mm^3), hypersplenism caused by infectious causes or coincident liver disease should be suspected.

Thrombocytopenia can occur in 20% to 33% of pediatric patients with HIV at some time during the course of their disease.⁷ HIV directly causes thrombocytopenia in most patients. In patients with early stage HIV infection with intact CD4 counts, low viral load, no hepatosplenomegaly or adenopathy, and an otherwise normal complete blood count, HIV-associated immune thrombocytopenic purpura is the most likely diagnosis. With progression of the underlying HIV disease, secondary causes of thrombocytopenia should receive greater consideration.

The two major components of the pathophysiology of HIV-associated thrombocytopenia are 1) immune-mediated destruction of platelets, similar to that seen in immune thrombocytopenic purpura (ITP); and 2) a defect in bone marrow production as a result of the interaction between HIV and megakaryocytes through several pathways, which causes suppression of platelet production. Often both components can be present simultaneously.

Elevated levels of platelet-associated IgG and/or circulating immune complexes often indicate that immune-mediated destruction of platelets in HIV-infected children with thrombocytopenia is occurring. These children may have a marked increase of platelet-associated IgG, IgM, C3, and C4 levels. The immune complexes are thought to contain anti-HIV gp120 and anti-antibodies (anti-idiotypes) directed against the anti-HIV antibodies. In a few patients, cross-reactivity of antibodies against HIV gp120/gp160 with platelet glycoprotein GPIIb/IIIa has been shown.⁸ Because megakaryocytes are infected by HIV, the “anti-platelet” antibodies could also be directed against HIV proteins expressed on megakaryocytes or platelets. Although many patients have immune-mediated platelet destruction as an important or pre-

dominant cause of their thrombocytopenia, it is not thought to be helpful diagnostically to obtain “platelet antibodies” in the evaluation of a thrombocytopenic HIV-infected patient because the antibody tests have both high false-positive and false-negative rates.

The defect in bone marrow production can be caused by direct HIV-related suppression because human megakaryocytes can internalize HIV particles; this is presumably because megakaryocytes express both CD4 and CCR5 receptors. Other causes include infiltration by opportunistic infection or drug effect. In addition, viral infection of accessory cells may result in marrow inhibition. Antibodies to megakaryocytes could also mediate the marrow effect. The observation that zidovudine therapy increases platelet counts suggests that HIV causes direct or indirect suppression of platelet production.

HIV-related immune-mediated destruction of platelets is, however, the most common etiology of thrombocytopenia. A response to intravenous immunoglobulin (IVIg) or especially to IV anti-D is essentially diagnostic for immune-mediated destruction.

In children with advanced HIV disease, other causes of thrombocytopenia, such as opportunistic infections, medication side effects, and infiltrative malignancies, are more likely. This is particularly true when there are associated physical examination findings or other cell line deficits. Opportunistic infections can cause thrombocytopenia, especially histoplasmosis and cryptococcosis.

Medications used in the management of HIV that are most commonly associated with thrombocytopenia include ganciclovir (48%), pentamidine (18%), and trimethoprim-sulfamethoxazole (3%). Rifabutin, clarithromycin, zidovudine, and didanosine are less commonly associated with thrombocytopenia.

Although non-Hodgkin’s lymphoma is the most common HIV-related malignancy, it is still rare. Like other malignancies that infiltrate the bone marrow, it should be ruled out when there are suggestive signs from the physical examination, such as new or worsening adenopathy, organomegaly, or a palpable mass, and the thrombocytopenia is otherwise not readily explained. Malignancies usually occur in patients with advanced disease and can be associated with anemia and/or leukopenia.

Experimental tests with potential future use in the diagnosis of HIV-associated thrombocytopenia include the following:

- Measurement of thrombopoietin levels: Thrombopoietin levels are almost always normal in HIV-associated thrombocytopenic purpura unless the disease has progressed to a very late stage and the number of marrow megakaryocytes is decreased.
- Measurement of glycofibrinogen: Glycofibrinogen is the carbohydrate-rich portion of platelet membrane glycoprotein Ib- α , which has been reported to be increased when there is increased platelet turnover.
- Platelet reticulocyte counts: Platelet reticulocyte counts are thought to reflect the percentage of young platelets.

When these tests are available to the general practitioner, they may allow better estimation of the rate of platelet production.

B. Treatment of Thrombocytopenia

RECOMMENDATIONS:

Antiretroviral therapy should be the primary treatment of HIV-associated thrombocytopenic purpura unless 1) it has been previously demonstrated to be ineffective, 2) the count needs to be increased within 2 weeks, or 3) there are other reasons not to initiate it, such as refusal, intolerance, or limited antiretroviral susceptibility.

Treatment of asymptomatic, mild to moderate, HIV-associated thrombocytopenia is usually not necessary. When the platelet counts are <20,000 to 30,000 cells/mm³, treatment should be initiated in consultation with a hematologist. Treatment should be initiated in patients with bleeding tendencies such as hemophilia when the platelet count is <50,000 cells/mm³.

For most patients who need treatment for HIV-associated thrombocytopenia, the treatment of choice is intravenous anti-Rho immunoglobulin (IV anti-D), 50 µg/kg with premedications.

For patients unable to receive anti-D because they are either Rh(-), DAT(+), or have undergone a splenectomy, intravenous immunoglobulin (1 g/kg) is the next best treatment. Prednisone has also been effective in treating thrombocytopenia and may be administered once malignancy has been ruled out.

Zidovudine alone, in older data in adults, improved the platelet count in 40% to 60% of patients.⁹ Although other ARV therapy has not been formally studied, it seems clear that highly active antiretroviral therapy (HAART) has substantially reduced the rate of clinically significant HIV-associated thrombocytopenic purpura. Responses to treatment have been durable and occur in patients with all degrees of thrombocytopenia. The mechanism of action involves an increased rate of platelet production. If the viral load is high, it is more likely that there will be response to a treatment that suppresses the viral load. Conversely, a decreasing platelet count may be an early sign of viral resistance.

In the Rh+ patient with ITP, anti-Rho immunoglobulin (IV anti-D) has been shown primarily in adults to be superior to IVIg. It can also be combined with intravenous immunoglobulin, and its effectiveness increases as doses are increased from 50 to 75 µg/kg. IV anti-D has the advantage of rapid administration and is generally well tolerated; a single dose of prednisone and acetaminophen or diphenhydramine premedication is advised. Potential adverse effects of anti-D can include fever, headache, chills, signs of hypersensitivity, including anaphylaxis, or signs of intravascular hemolysis.

High-dose intravenous immunoglobulin (1 g/kg) infusions have been reported to cause prompt but transient remissions of HIV-related platelet destruction in a high proportion of patients. One study in children¹⁰ showed an increase from a mean pre-treatment count of 22,000 to a post-treatment count of 182,000, and 19 of 22 patients had an increase in platelet count of >50,000 cells/mm³. Maintenance therapy with repeated infusions of intravenous immunoglobulin can sustain responses in HIV-associated thrombocytopenia.

Although the response of HIV-infected patients to steroids is comparable to that of uninfected patients, it is not sustained in 60% to 80% of patients unless it is continued at a high dose, which may, however, increase the risk for secondary infections, such as *Candida* and *Aspergillus* infections.¹¹

Splenectomy could be considered for patients >5 years of age with refractory HIV-associated thrombocytopenia who have had the disease for >1 year and have a long life expectancy. There is no evidence that splenectomy accelerates the progression of HIV infection, and it often increases the CD4 count. Operative morbidity and mortality is comparable to that seen with classic, non-HIV ITP: <1% major morbidity and <1% major hemorrhage. Based on several studies in adults, the majority of patients have initial complete responses (platelet count >100,000 cells/mm³) with sustained response in as many as 70% to 90%, although with limited follow-up. Pediatric patients should be maintained on penicillin prophylaxis and should be appropriately immunized; prophylactic monthly intravenous immunoglobulin should be considered. Other treatments, including danazol, vincristine, and dapsone, may be useful in children with HIV-associated refractory thrombocytopenia but, because of limited experience in this population, they have not become a standard therapy.

IV. NEUTROPENIA

A. Diagnosis

Bone marrow failure is the most common mechanism of neutropenia in HIV-infected patients. Approximately 41% of HIV-infected pediatric patients will develop neutropenia, defined as an absolute neutrophil count (ANC) $<500 \mu\text{L}$. Although antibody-mediated neutropenia can occur, it is not common in HIV-infected children. It has been reported from several studies that the presence of granulocyte antibodies (5%-62%) will not necessarily correlate with the presence of neutropenia. HIV-infected infants and children seem to tolerate low ANCs with infrequent infectious complications. Few children with HIV sustain infectious complications as a result of neutropenia unless it is severe and prolonged.

If a child with HIV develops neutropenia, drug-related toxicity is the most likely cause. Zidovudine and other nucleoside analogues can cause a dose-dependent neutropenia. In these situations, when the ARV therapy is discontinued, the neutrophil count will often increase, but the platelet count may fall. This phenomenon may occur because undiagnosed HIV-associated thrombocytopenic purpura has been successfully treated with ARV therapy. Other medications causing neutropenia should be considered, such as ganciclovir (40%), trimethoprim-sulfamethoxazole (dose related; see Section II.A.3: *Macrocytic Anemia*), pentamidine, and dapsone.

Another major diagnostic consideration in the evaluation of HIV-related neutropenia is opportunistic infections, especially cytomegalovirus or *Mycobacterium avium* complex. Other infectious agents also can cause neutropenia, such as influenza A and B, respiratory syncytial virus, hepatitis A and B, measles, rubella, and bacterial infections such as *Staphylococcus aureus*, *Shigella sonnei*, or *Salmonella typhi*. In addition, a direct HIV effect on the myeloid progenitor cells may cause neutropenia.

Nutritional deficiencies may occur in HIV patients. Deficiencies of B₁₂, folic acid, and copper can cause neutropenia and megaloblastic anemia, but these deficiencies are rare. Defects in neutrophil function, including reduced bactericidal capacity, abnormal chemotaxis, and abnormal monocyte FcR expression, have been reported in patients with HIV.¹²

B. Treatment of Neutropenia

RECOMMENDATION:

If neutropenia is confirmed to be persistent and severe ($<500 \text{ cells/mm}^3$), rather than transient, consideration should be given to instituting granulocyte-colony stimulating factor (G-CSF). The initial dose is $5 \mu\text{g/kg/day}$ given subcutaneously. The G-CSF dosing required varies greatly from person to person; dosing frequency should be titrated to an individual's response. In children with multiple cell line deficits, G-CSF may exacerbate thrombocytopenia; therefore, platelet counts should be monitored. Bone marrow aspiration before initiating G-CSF therapy is not necessary unless there is also evidence of anemia, thrombocytopenia, new lymphadenopathy, or hepatosplenomegaly.

A series of single-arm trials have demonstrated that the myeloid colony stimulating factors, granulocyte-macrophage colony stimulating factor (GM-CSF) and G-CSF, given at relatively low doses can elevate the neutrophil count in HIV-infected patients receiving myelosuppressive medications. G-CSF, compared with GM-CSF, has the advantage of fewer side effects and more rapid increases in the leukocyte counts. Toxicity is rare but includes increase in spleen size, bone pain, and leukocytoclastic vasculitis. GM-CSF may also be associated with increase in the replication of HIV-1 and with eosinophilia. It can also cause fever, chills, myalgias, flu-like symptoms, nausea, rashes, and headache. The initial dose of G-CSF is $5 \mu\text{g/kg/day}$ given subcutaneously. Sometimes as little as 1 to $2 \mu\text{g/kg}$ is needed so that the G-CSF can be given as infrequently as once every 3 to 7 days. Conversely, if after 1 week of instituting the G-CSF, there is an insufficient response, the dose can be increased up to

10 µg/kg/day. When a response is seen, the dose may be decreased to maintain a neutrophil count >1000 cells/mm³.

V. COAGULATION ABNORMALITIES

A. Diagnosis

RECOMMENDATIONS:

The preoperative evaluation of bleeding tendency should include a medical history, physical examination, and, if indicated, basic hemostatic screening tests. The information obtained in the medical history should include the presence of abnormal bruising, both extensive or unexplained; gum bleeding; prolonged bleeding after laceration or surgery, such as circumcision, tonsillectomy, tooth extractions, or biopsies; epistaxis; menorrhagia; hematuria; and melena in the patient and in the family. In addition, information regarding liver or renal disease or changes in medication in the HIV-infected patient should be obtained.

Routine pre-operative bleeding screening tests, such as a partial thromboplastin time (PTT), prothrombin time (PT), fibrinogen platelet count, and thrombin time, should be reserved for patients with a positive assessment by history or those with a negative history who will be undergoing surgeries with a high risk of bleeding, such as tonsillectomy, central nervous system surgery, cardiac surgery, or scoliosis repair.

When a prolonged PTT is present, mixing studies (1:1 dilution with normal plasma) should be obtained. Failure to correct a prolonged PTT should be indicative of the presence of antiphospholipid antibodies (aPL) or specific factor inhibitors. If the mixing studies reveal correction, assays for factors VIII, IX, XI, and XII should be performed.

Primary hemostasis tests, including von Willebrand factor (vWF) studies, platelet aggregation, factors VIII, IX, XI, XIII, alpha 2-antiplasmin and plasminogen activator inhibitor (PAI), should be obtained for patients with normal PT, PTT, fibrinogen, and platelet count who are at high risk for bleeding based on history. Neither the bleeding time nor the Platelet Function Analyzer (PFA)-100 is recommended because of the absence of data to support that these tests predict bleeding.

Coagulation abnormalities in HIV may be caused by inherited factor deficiencies, acquired factor deficiencies, or acquired inhibitors. As a result of immune dysregulation, an increase in aPL and antibodies to other coagulation proteins has been reported in a significant proportion of HIV-infected adults and children. However, the clinical significance of these abnormalities is questionable. An increase in anticardiolipin antibodies and lupus anticoagulants has been reported without an increased frequency of thrombosis.¹³

Prolongation of PTT, and sometimes a PT, may be caused by aPLs. In general, the most common causes of prolonged PTT would be the presence of lupus anticoagulants, aPL, or mild factor XII deficiency, which are not usually associated with bleeding tendency. Isolated prolongation of PT in the absence of inhibitor would be suggestive of factor VII deficiency.

Acquired protein S deficiency results from autoantibodies directed against protein S and has been reported in children. In one study in which the protein S level was measured in 34 HIV-infected children with no previous history of thrombosis, decreased levels of protein S (total and functional) were found in 76.5% of the patients.¹⁴ These decreased levels of protein S were more prevalent in subjects with CD4 counts <200 cells/mm³. Long-term studies are needed to determine the cumulative risk of thrombotic complications caused by these abnormalities and to better describe the complete coagulation profile in these patients.

B. Treatment of Coagulation Abnormalities

RECOMMENDATION:

Treatment of HIV-associated coagulation abnormalities should be based on the specific diagnosis as well as bleeding history (see Table 2).

TABLE 2 GENERAL THERAPEUTIC OPTIONS FOR TREATING COAGULATION ABNORMALITIES IN HIV-INFECTED CHILDREN	
Coagulation Abnormality	Therapy
<ul style="list-style-type: none"> • Multifactorial coagulopathy • Factor replacement for known deficiencies associated with hemorrhage for which specific plasma derived or recombinant factor concentrates are unavailable • Correction of microvascular bleeding when PT or activated partial thromboplastin time (APTT) are $>1.5 \times$ normal 	Fresh frozen plasma (FFP, 10-20 mL/kg)
<ul style="list-style-type: none"> • Fibrinogen replacement • Factor XIII deficiency • Second-line therapy for von Willebrand disease or hemophilia A 	Cryoprecipitate (1 bag/10 lb)
<ul style="list-style-type: none"> • Hemophilia (mild) • von Willebrand disease-type I • Platelet function defects (other than Glanzmann's thrombasthenia) • Uremia • Liver disease • Cardiovascular surgery 	Desmopressin (0.3 mcg/kg IV)
<ul style="list-style-type: none"> • Prevention of oronasal mucosal bleeding of the upper respiratory tract • GI tract bleeding with hereditary or acquired hemostatic defects • Contraindicated in patients with genitourinary bleeding 	Antifibrinolytics [e.g., epsilon aminocaproic acid (EACA, 100 mg/kg, po or IV)]

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