Complete Summary

GUIDELINE TITLE

HIV-related hematologic manifestations in pediatrics.

BIBLIOGRAPHIC SOURCE(S)

New York State Department of Health. HIV-related hematologic manifestations in pediatrics. New York (NY): New York State Department of Health; 2003. 12 p. [14 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating
 Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified
 healthcare professionals of revised boxed warnings and other safety-related
 product labeling changes for erythropoiesis-stimulating agents (ESAs) stating
 serious adverse events, such as tumor growth and shortened survival in
 patients with advanced cancer and chronic kidney failure.
- December 04, 2007, Desmopressin Acetate (DDAVP, DDVP, Minirin, & Stimate): New information has been added to the existing boxed warning in Desmopressin's prescribing information about potential increased risk for severe hyponatremia and seizures.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT ** SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infection
- Anemia (microcytic, normocytic, macrocytic)
- Thrombocytopenia
- Neutropenia
- Coagulation abnormalities

GUIDELINE CATEGORY

Diagnosis Evaluation Management Screening Treatment

CLINICAL SPECIALTY

Allergy and Immunology Family Practice Hematology Infectious Diseases Pediatrics

INTENDED USERS

Health Care Providers Physician Assistants Physicians Public Health Departments

GUIDELINE OBJECTIVE(S)

To develop guidelines to reduce human immunodeficiency virus (HIV)-related hematologic manifestations in pediatric patients

TARGET POPULATION

INTERVENTIONS AND PRACTICES CONSIDERED

Screening

- 1. Complete blood count with differential every 3 months; more frequent complete blood counts as indicated in the guideline
- 2. Lead levels every year, and when toxicity is suspected

Diagnosis/Evaluation - refer to Major Recommendations for context

Anemia

- 1. Nutritional history
- 2. Review of systems (especially the gastrointestinal tract)
- 3. Iron studies, specifically serum iron, total iron-binding capacity, transferrin saturation, and serum ferritin
- 4. Hemoglobin electrophoresis with quantitative measurement of hemoglobin A2 and hemoglobin F, if indicated
- 5. Evaluation for hemolysis (e.g., direct Coombs test, serum lactate dehydrogenase, medication list, splenomegaly)
- 6. Exclude opportunistic infection: cultures, bone marrow examination
- 7. Liver and thyroid function tests, vitamin B12 and folate levels, bone marrow aspiration and biopsy

Thrombocytopenia

- 1. Physical examination, especially organomegaly or lymphadenopathy
- 2. Consideration of non-platelet components of the complete blood count
- 3. Consideration of response to platelet-directed treatment
- 4. Bone marrow examination in consultation with specialist when malignancy is suspected

Coagulation Abnormalities

Preoperative evaluation of bleeding tendencies by medical history, physical examination, and, basic hemostatic tests (e.g., partial thromboplastin time [PTT], prothrombin time [PT], fibrinogen platelet count, and thrombin time), if indicated

Treatment

Anemia

- 1. Erythropoietin therapy with supplemental oral iron and folate
- 2. Blood transfusion with irradiated and leukocyte-reduced blood products

Thrombocytopenia

1. Antiretroviral therapy

- 2. Intravenous anti-Rho immunoglobulin (IV anti-D) with premedications; intravenous immunoglobulin as an alternative
- 3. Prednisone (after malignancy excluded)

Neutropenia

Granulocyte-colony stimulating factor (G-CSF)

Coagulation Abnormalities

- 1. Fresh frozen plasma (FFP)
- 2. Cryoprecipitate
- 3. Desmopressin
- 4. Antifibrinolytics (e.g., epsilon aminocaproic acid [EACA])

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Human Immunodeficiency Virus (HIV) Guidelines Program works directly with committees composed of HIV Specialists to develop clinical practice guidelines. These specialists represent different disciplines associated with HIV care, including infectious diseases, family medicine, obstetrics and gynecology, among others. Generally, committees meet in person 3-4 times per year, and otherwise conduct business through monthly conference calls.

Committees meet to determine priorities of content, review literature, and weigh evidence for a given topic. These discussions are followed by careful deliberation to craft recommendations that can guide HIV primary care practitioners in the delivery of HIV care. Decision making occurs by consensus. When sufficient evidence is unavailable to support a specific recommendation that addresses an important component of HIV care, the group relies on their collective best practice experience to develop the final statement. The text is then drafted by one member, reviewed and modified by the committee, edited by medical writers, and then submitted for peer review.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Screening for Hematologic Abnormalities

A complete blood count with differential should be performed every 3 months to screen for hematologic abnormalities in human immunodeficiency virus (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.

Anemia

Types of Anemia

Microcytic Anemia

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.

Normocytic Anemia

Hemolytic Anemia

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.

Hypoplastic Anemia

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.

Macrocytic Anemia

If megaloblastic anemia cannot be explained by common causes, such as medications, including antiretroviral (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.

Treatment of Anemia

If endogenous erythropoietin levels are <500 mUnits/mL, erythropoietin therapy (50-200 iu/kg/dose 3 times/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.

Thrombocytopenia

Pathophysiology and Diagnosis

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/mm³), hypersplenism caused by infectious causes or coincident liver disease should be suspected.

Treatment of Thrombocytopenia

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 micrograms/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.

Neutropenia

Treatment of Neutropenia

If neutropenia is confirmed to be persistent and severe (<500 cells/mm³), rather than transient, consideration should be given to instituting granulocyte-colony stimulating factor (G-CSF). The initial dose is 5 micrograms/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.

Coagulation Abnormalities

Diagnosis

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.

Treatment of Coagulation Abnormalities

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

Table: General Therapeutic Options for Treating Coagulation Abnormalities in HIV-infected Children

Coagulation Abnormality	Therapy
 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)
 Fibrinogen replacement Factor XIII deficiency Second-line therapy for von Willebrand disease or hemophilia A 	Cryoprecipitate (1 bag/10 lb)
 Hemophilia (mild) von Willebrand disease-type I Platelet function defects (other than Glanzmann's thrombasthenia Uremia Liver disease Cardiovascular surgery 	Desmopressin (refer to the original guideline document for dosing information)
 Prevention of oronasal mucosal bleeding of the upper respiratory tract Gastrointestinal tract bleeding with hereditary or acquired hemostatic defects 	Antifibrinolytics [e.g., epsilon aminocaproic acid (EACA, 100 mg/kg, po or IV)]

Coagulation Abnormality	Therapy
Contraindicated in patients with genitourinary bleeding	

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of HIV-related hematologic manifestations in pediatrics including anemia, thrombocytopenia, neutropenia, and coagulation abnormalities.

POTENTIAL HARMS

- Risks associated with red cell transfusion. The indications, risks, and benefits for red cell transfusions are similar to those of non-human immunodeficiency virus (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 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.
- Adverse effects of intravenous anti-Rho immunoglobulin (IV anti-D). Potential adverse effects of anti-D can include fever, headache, chills, signs of hypersensitivity, including anaphylaxis, or signs of intravascular hemolysis.
- Risks associated with steroids. 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.
- Adverse effects of granulocyte-colony stimulating factor (G-CSF). Toxicity is rare but includes increase in spleen size, bone pain, and leukocytoclastic vasculitis. G-CSF may also exacerbate thrombocytopenia.

CONTRAINDICATIONS

CONTRAINDICATIONS

Antifibrinolytics are contraindicated in patients with genitourinary bleeding.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Following the development and dissemination of guidelines, the next crucial steps are adoption and implementation. Once practitioners become familiar with the content of guidelines, they can then consider how to change the ways in which they take care of their patients. This may involve changing systems that are part of the office or clinic in which they practice. Changes may be implemented rapidly, especially when clear outcomes have been demonstrated to result from the new practice such as prescribing new medication regimens. In other cases, such as diagnostic screening, or oral health delivery, however, barriers emerge which prevent effective implementation. Strategies to promote implementation, such as through quality of care monitoring or dissemination of best practices, are listed and illustrated in the companion document to the original guideline (*HIV clinical practice guidelines*, New York State Department of Health; 2003), which portrays New York's HIV Guidelines Program. The general implementation strategy is outlined below.

- Statement of purpose and goal to encourage adoption and implementation of guidelines into clinical practice by target audience.
- Define target audience (providers, consumers, support service providers)

Are there groups within this audience that need to be identified and approached with different strategies? (e.g., HIV Specialists, family practitioners, minority providers, professional groups, rural-based providers)

Define implementation methods

What are the best methods to reach these specific groups (e.g., performance measurement consumer materials, media, conferences)?

- Determine appropriate implementation processes
 - What steps need to be taken to make these activities happen?
 - What necessary processes are internal to the organization (e.g., coordination with colleagues, monitoring of activities)?
 - What necessary processes are external to the organization (e.g., meetings with external groups, conferences)?
 - Are there opinion leaders that can be identified from the target audience that can champion the topic and influence opinion?
- Monitor Progress

What is the flow of activities associated with the implementation process and which can be tracked to monitor the process?

- Evaluate
 - Did the processes and strategies work? Were the guidelines implemented?
 - What could be improved in future endeavors?

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about <u>availability</u>, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

New York State Department of Health. HIV-related hematologic manifestations in pediatrics. New York (NY): New York State Department of Health; 2003. 12 p. [14 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003

GUIDELINE DEVELOPER(S)

New York State Department of Health - State/Local Government Agency [U.S.]

SOURCE(S) OF FUNDING

New York State Department of Health

GUIDELINE COMMITTEE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the <u>New York State Department of Health AIDS</u> Institute Web site.

Print copies: Available from Office of the Medical Director, AIDS Institute, New York State Department of Health, 5 Penn Plaza, New York, NY 10001; Telephone: (212) 268-6108.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

 HIV clinical practice guidelines. New York (NY): New York State Department of Health; 2003. 36 p.

Electronic copies: Available from the <u>New York State Department of Health AIDS</u> Institute Web site.

Print copies: Available from Office of the Medical Director, AIDS Institute, New York State Department of Health, 5 Penn Plaza, New York, NY 10001; Telephone: (212) 268-6108.

This guideline is available as a Personal Digital Assistant (PDA) download from the New York State Department of Health AIDS Institute Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was prepared by ECRI on January 21, 2004. This summary was updated by ECRI on January 31, 2006, following release of a public health advisory from the U.S. Food and Drug Administration regarding the use of WinRho SDF (Rho(D) Immune Globulin Intravenous [Human]). This summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on December 7, 2007, following the U.S. Food and Drug Administration advisory on Desmopressin Acetate. This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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Date Modified: 11/3/2008

