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MEDICAL MANAGEMENT OF HIV DISEASE IN CHILDREN

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Pediatric HIV infection in the United States has evolved from a rapidly progressive, fatal disease in the early years of the epidemic to a chronic infection with prolonged survival. Many children with perinatally acquired infection survive to 8 years of age and older. The development of highly active antiretroviral therapy (HAART), measurement of viral load, and availability of prophylactic medications to prevent certain opportunistic infections have dramatically altered the management of HIV infection. A total of 14 antiretroviral agents have been approved by the US Food and Drug Administration, 10 of which have been approved for use in pediatrics. Several new drugs are in various stages of development.

This article discusses special issues in the medical management of children with HIV infection, including routine care, immunization, and treatment of some of the more common organ-specific manifestations, disclosure of the HIV diagnosis, pain management, palliative care, and the management of infants born to HIV-seropositive women.

MANAGEMENT OF INFANTS AT RISK FOR HIV INFECTION

Obstetric standards and published guidelines strongly recommend offering HIV testing to all pregnant women.^{19, 66} In some states, offering HIV testing to pregnant women is mandated by law. This allows women to become informed about HIV, receive care for their disease, and participate in decision making regarding mode of delivery and chemoprophylaxis to reduce the risk for the

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perinatal transmission of HIV. These women and their families should be counseled about the schedule of care visits; diagnostic testing for HIV; and chemoprophylaxis with zidovudine (ZDV) and trimethoprim-sulfamethoxazole (TMP-SMX), which are recommended for at-risk infants (Table 1).^{2, 19} A DNA polymerase chain reaction for the detection of HIV is recommended before hospital discharge. Diagnostic tests for HIV in the infants detects 30% to 50% of infected infants at birth, with more than 95% diagnosed by 2 months of age, so physicians should follow up these infants closely during the first several months of life. Their mothers should be counseled against breast-feeding their infants because of the additional risk for transmission of HIV to infants.^{27, 65} At the authors' institution, the first postnatal visit is done at 14 days of life. At this visit, compliance with the ZDV regimen is assessed, dosing is adjusted as needed, and refills given to ensure that infants have a 6-week supply of ZDV. Also, feeding practices and nutrition are discussed. A complete blood count is recommended to monitor for hematologic toxicity, most commonly, anemia or leukopenia. If the HIV DNA PCR was not done at birth, it is performed at this visit. During the second visit, at 6 weeks of age, ZDV is discontinued if the HIV DNA PCR tests have been negative. At this visit, complete blood count, T-cell subsets, and DNA HIV PCR results are obtained. TMP-SMX is begun at a dose of 150 mg/m²/dose given three times a week for prophylaxis against *Pneumocystis carinii* pneumonia (PCP), and the first set of immunizations is given. PCP prophylaxis is started empirically in at-risk infants less than 1 year of age, independent of the CD4+ cell count and percentage, because HIV status may be uncertain and, in infected infants with rapid progression of disease, CD4+ cell counts can decrease precipitously in the first months of life, predisposing to PCP.^{68, 74}

At-risk infants are seen at 4 and 6 months of age for routine care and immunizations and appropriate immune and diagnostic tests. When an at-risk infant has had two negative HIV DNA PCR test results after 2 months of age and is clinically and immunologically normal, PCP prophylaxis is discontinued. These children are considered presumptively HIV negative, but an HIV enzyme-linked immunosorbent assay test is performed after 1 year of age to monitor for the disappearance of maternal antibody. If the HIV enzyme-linked immunosorbent assay and western blot are negative, the ELISA test is repeated and, if the result is negative, the child is considered uninfected and a seroreverter. Because many infants are born to HIV-infected women receiving combination antiretroviral therapy, physicians should carefully note drug exposure on these infants' charts and maintain follow-up on them as long as possible to determine any long-term effects of prenatal or postnatal exposure to these drugs. Also, any congenital anomalies or unusual illnesses occurring in these infants should be

Table 1. MANAGEMENT OF CHILDREN EXPOSED TO HIV IN UTERO

Age	Management
Birth	HIV DNA PCR; start zidovudine
2 wk	HIV DNA PCR; CBC (monitor for anemia)
6 wk	HIV DNA PCR; CBC; discontinue zidovudine; start PCP prophylaxis; start immunizations
4 mo	Continue PCP prophylaxis
6 mo	Discontinue PCP prophylaxis if tests for HIV remain negative
12-15 mo	HIV-1 ELISA

PCR = polymerase chain reaction, CBC = complete blood count, PCP = *Pneumocystis carinii* pneumonia; ELISA = enzyme linked immunosorbent assay.

reported to the Antiretroviral Pregnancy Registry (phone 800-722-9292, ext. 38465).

CARE OF HIV-INFECTED CHILDREN

A systematic approach to children with HIV infection is essential. These children should be assessed for symptoms related to HIV and the need for treatment and prophylaxis of opportunistic infections and other HIV-related conditions. Baseline laboratory tests should be performed to assess viral and immunologic status. A complete medical and immunization history should be obtained, with particular emphasis on the mode of transmission, exposure to antiretroviral agents during gestation and after delivery, timing of diagnosis of HIV, and family members who are aware of the diagnosis. The level of understanding of HIV should be assessed in children and their caregivers. If clinical trials are available, these should be discussed with these children and their families.

Children with HIV should receive routine pediatric care and monitoring of their HIV disease status. Experts recommend that HIV-infected children have consultation with an HIV specialist. In some cases, pediatricians provide routine care, with referral to an HIV specialist for monitoring of HIV status, whereas in other care settings, HIV specialists provide primary and specialty care. HIV-infected children should be seen at least every 3 months. At each visit, a complete physical examination should be done, with attention to signs and symptoms commonly associated with HIV infection. Growth and development should be evaluated at all stages of development through adolescence. The medications should be reviewed, doses adjusted for growth, and compliance assessed. Children should be assigned a classification (Tables 2-4), and laboratory studies done to monitor the immunologic and virologic status of the disease.

HIV infection is a multisystemic illness. Common clinical manifestations of pediatric HIV infection include generalized lymphadenopathy, hepatomegaly, splenomegaly, oral candidiasis, parotitis, recurrent or persistent diarrhea, failure to thrive, and developmental delay. Multiple organ system involvement is common, and the following HIV-associated conditions have been found: cardiomyopathy, lymphoid interstitial pneumonitis, nephropathy, encephalopathy, enteropathy, hepatitis, and malignancies. Skin manifestations caused by bacterial, viral, and fungal infections; atopic disease; hypersensitivity reactions; and pruritic papular reactions are common.

Table 5 outlines the clinical and laboratory studies and assessments that should be done at baseline and thereafter at periodic intervals. These studies are

Table 2. CLASSIFICATION OF PEDIATRIC HIV INFECTION

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Table 3. IMMUNOLOGIC CATEGORIES FOR CHILDREN WITH HIV

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Modified from Centers for Disease Control and Prevention: 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Morb Mortal Wkly Rep 43:4, 1994.

done to identify any acute problems and to assess the risk for opportunistic infections or other HIV-related complications and monitoring for medication side effects. Studies have shown that prognosis in children is related independently to viral burden and immune status.⁵⁹ Also, a direct relationship exists between the development of certain opportunistic infections and the degree of immune suppression.¹⁸

HIV-infected children should have baseline antibody titers obtained for toxoplasma, cytomegalovirus (CMV), Epstein-Barr virus, varicella-zoster virus, herpes simplex virus (HSV), and hepatitis viruses. The results provide information about these children's exposure and susceptibility to specific infections. For example, if a CMV-seronegative child requires a blood transfusion, then a CMV-negative donor blood is requested or, if unavailable, leukofiltered blood is used.

Each year, the following tests and services should be performed for HIV-infected children.

- **Chest radiography.** This test identifies mediastinal enlargement, lung lesions, lymphoid interstitial pneumonitis (LIP), and cardiomegaly. Patients with chronic lung disease should have oxygen saturation readings performed at every visit.
- **Baseline plain brain CT.** This scan may show changes such as basal ganglia calcifications and brain atrophy.¹²
- **A regular-strength tuberculin skin test** should be done yearly if a child lives in an area endemic for tuberculosis, because HIV-infected children are at increased risk for tuberculosis. As a control for anergy, candida, mumps, or tetanus toxoid is used, depending on a child's age and immunization status.
- **Visual screening** on children capable of cooperating with the examiner. Ophthalmology examination is performed each year, but children with immune category 3 need to be examined by an ophthalmologist every 6 months, especially if they are seropositive for toxoplasmosis or CMV, because they are at high risk for retinitis.
- **Psychometric testing** of children with suspected developmental delay or loss of acquired milestones to identify problems that can be treated early.^{29, 61}
- **Gynecologic examination.** Female adolescents should be referred to adolescent gynecologists or adolescent services. Baseline and annual gynecologic visits should be provided for female adolescents who are sexually active for cervical smears and screening for sexually transmitted diseases. All adolescents should be aware of their diagnoses and receive counseling regarding transmission of HIV, safe sex practices, birth control, the risk

Table 4. CLINICAL CATEGORIES FOR CHILDREN WITH HIV

Category N: not symptomatic

Category A: mildly symptomatic; two or more of the following conditions but none of the conditions listed in categories B and C

- Lymphadenopathy (≥ 0.5 cm at more than two sites; bilateral, one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: moderately symptomatic

- Anemia (< 8 g/dL), neutropenia ($< 1000/\text{mm}^3$), thrombocytopenia ($< 100,000/\text{mm}^3$) for ≥ 30 d
- Single episode of bacterial meningitis, pneumonia, or sepsis
- Thrush persisting > 2 mo in children > 6 mo of age
- Cardiomyopathy
- Cytomegalovirus (*onset* > 1 mo of age)
- Recurrent or chronic diarrhea
- Hepatitis
- Recurrent herpes stomatitis (> 2 episodes per year)
- HSV, bronchitis, pneumonitis, or esophagitis < 1 mo of age
- Shingles ≥ 2 dermatomes or ≥ 2 episodes
- Lymphoid interstitial pneumonitis (LIP)
- Nephropathy
- Nocardiosis
- Fever > 1 mo
- Toxoplasmosis < 1 mo of age
- Complicated chicken pox

Category C: severely symptomatic

- Severe bacterial infections, recurrent or multiple
- Candidiasis, esophageal, or pulmonary
- Coccidioidomycosis, disseminated
- Cryptosporidiosis or isosporiasis with diarrhea persisting > 1 mo
- Cytomegalovirus disease, onset > 1 mo of age
- Encephalopathy
- HSV infection causing mucocutaneous ulcer for > 1 mo; bronchitis, pneumonitis, esophagitis > 1 mo of age
- Histoplasmosis, disseminated
- Kaposi sarcoma
- Lymphoma
- Tuberculosis, disseminated or extrapulmonary
- Pneumocystis carinii* pneumonia
- Progressive multifocal encephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of the brain, onset > 1 mo of age
- Wasting syndrome

HSV = herpes simplex virus.

Modified from Centers for Disease Control and Prevention: 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Morb Mortal Wkly Rep 43:6-8, 1994.

for transmission of HIV to infants, and the consequences of perinatal infection.

- **Dental check up.** Annual visits to a dentist should be initiated early in life because cavities are common.⁷¹

Table 5. MEDICAL MANAGEMENT OF CHILDREN WITH HIV INFECTION

Evaluation	Interval
Complete history and physical examination	3 mo
Review of systems	3 mo
Immunization	See Table 7
Developmental examination	
0-12 mo	3 mo
1-3 y	6 mo
> 3 y	Annually
CT scan of the brain	Baseline and as indicated
Chest radiography	Annually
Laboratory values	
Complete blood count	3 mo
T-cell subsets	3 mo
HIV RNA PCR (quantitative)	3 mo
Liver enzymes	3 mo
Pancreatic enzymes	3 mo
Electrolytes, BUN, and creatinine	Baseline and as indicated
Quantitative immunoglobulins	6 mo
Urine analysis	Annually
Serology	
Cytomegalovirus	Baseline, annually if negative
Epstein-Barr virus	Baseline, annually if negative
Toxoplasmosis	Baseline, annually if negative
Rubella	Baseline
Varicella-zoster	Baseline
Herpes simplex	Baseline
Hepatitis B, C	Baseline
Tuberculin skin test and control	Annually*
Referrals	
Ophthalmologic examination	Annually†
Dental examination	6 mo
Cardiology (echocardiogram)	If clinically indicated
Gynecologic examination	Puberty, annually thereafter

*For control use mumps or tetanus antigen if the patient has already been immunized; otherwise use candida antigen.

†Every 6 mo if severely immunosuppressed.

PCR = polymerase chain reaction, BUN = blood urea nitrogen.

Referral to other specialty services depends on the medical status of patients. Ideally, specialists that participate in the care of these children should be aware of the problems affecting HIV-infected children and maintain communication with the primary care physician.

Because the care of HIV-infected children is complex, these children's caregivers should have ready access to health care providers to discuss medical problems. A coordinated family-centered comprehensive care team of physicians, nurses, case managers, and social workers facilitates the treatment of these patients and the work of the caregiver. In the authors' program, a case manager or social worker is assigned to each patient to provide community referrals for social services and psychosocial interventions. Home health agencies provide administration of parenteral medication at home, as well as instruction and supervision regarding the medications. A foster-care system is essential to meet the needs of at-risk infants who are abandoned or under protective custody and for HIV-infected children who have lost a parent or caregiver. Prescribed day

care that provides nursing services is important for the care of severely ill, medically complex children with HIV.

GROWTH AND NUTRITION

Assessment of growth is an integral part of the care of any pediatric patient. HIV-infected children should have careful monitoring of height, weight, and head circumference during infancy and childhood and evaluation of pubertal changes and growth during adolescence. Several measures of growth can be used in infants and children and include standardized growth charts, incremental growth curves, and computerized calculation of Z scores using the Epi Info Version 6 (Centers for Disease Control and Prevention). Growth delay is common in HIV-infected infants and may be the first sign of symptomatic HIV infection. At the other end of the spectrum of disease, weight loss and wasting may occur in older children and adolescents who have progression of HIV disease. The basal metabolism of children with HIV infection is increased compared with noninfected children, and when stressed, caloric needs increase, on average, 12% for each degree Celsius increase in temperature, 25% for acute diarrhea and 60% for sepsis.^{6, 57, 74}

For children who have growth delay or wasting, an evaluation should be done to determine potential causes. The goal is to treat the cause of the growth failure or weight loss and estimate energy needs for children to grow. The following formula can be used to estimate the energy needs of children who need a catch-up growth period⁶:

$$\text{Kcal/kg} = \frac{(\text{RDA Kcal for weight age}) \times (\text{ideal weight for age})}{\text{actual weight}}$$

where *RDA* is the recommended daily allowance, and weight age is the weight at which a patient's present weight would be at the 50th percentile.

Useful laboratory parameters for the assessment of nutritional status include albumin (to assess long-term visceral protein), prealbumin (to assess short-term visceral protein), iron, vitamin B₁₂ and folate studies, and micronutrients (i.e., zinc, magnesium, selenium, copper, carnitine, and other vitamin levels).

The management of nutritionally deficient children may include one or more of the following interventions: dietary instruction, vitamin supplementation, high-calorie formulas or alimentation using a nasogastric tube, or intravenous (IV) hyperalimentation. Nutritionists are invaluable in assisting the medical team with a dietary history, energy intake, and recommending appropriate interventions. Several high-energy nutritional supplements are available for use in the pediatric population. These formulas contain 4.2 to 6.3 Kcal/mL (1.0–1.5 Kcal/mL) but differ in their carbohydrate, fat, and protein contents; palatability; electrolytes; and solute load. Patients and their families should understand that supplements are not designed to be the only source of nutrition for patients.

If a child has a poor appetite or refuses alimentation, and when medical causes, such as oral ulcers or esophagitis, have been ruled out, physicians have two options: (1) tube feeding or (2) appetite stimulants. Nasogastric tube feedings are easy from a technical standpoint but may increase the risk for sinus infection and gastroesophageal reflux and, in the older children, may affect self-esteem. Gastrostomy tubes, although they require surgical placement, are easy to manage and do not pose a cosmetic problem or increase the risk for sinusitis,⁵⁸ but in the authors' experience, such tubes should be placed before significant

deterioration of the immune and nutritional status occurs because wound healing may be compromised. Two immunosuppressed children cared for at the authors' institution had delayed healing of the tissue around the gastrostomy site and required months of supportive therapy until it finally closed spontaneously. The authors recommend starting with 8-hour to 12-hour infusions of formula overnight at low rates and slowly increasing the volume. If vomiting develops, the tube may be advanced to the jejunum, bypassing the stomach.

Megestrol acetate is an orally administered, synthetic, progestational agent initially used to increase the appetite of patients with cancer. This product promotes weight gain but has the disadvantage of increasing fat deposition instead of lean body mass, thus altering the body habitus. An uncontrolled study of megestrol acetate in a small number of HIV-infected children demonstrated weight gain in most, with few other side effects.²² The usual dosage is 8 to 10 mg/kg/d, divided into two doses. Recombinant growth hormone has increased lean body mass in adults with HIV infection.

HEMATOLOGIC COMPLICATIONS

Anemia

Anemia in patients with HIV is multifactorial. The most common causes include nutritional deficiencies; iron; folic acid; and, less commonly, vitamin B₁₂; immune hemolysis; hemorrhage; drug toxicities; and bone marrow suppression caused by the HIV virus, other infectious agents, or malignancy.

The workup of anemic patients includes a complete blood count and reticulocyte count, iron level, total iron-binding capacity, transferrin level, vitamin B₁₂ level, folic acid level, and erythropoietin level. Sometimes a lead level is indicated. If hemolysis is suspected, a Coombs test is performed and the haptoglobin level is obtained.

An algorithm for the management of anemia is presented in Figure 1. Anemia with few or absent reticulocytes is common. When secondary to iron deficiency, iron sulfate at 6 mg/kg/d of elemental iron is usually sufficient to correct the hemoglobin level, but sometimes the solution is not that easy. If the erythropoietin level is less than 500 IU/L, a trial of erythropoietin at 100 U/kg/dose, three times a week, is suggested. A response usually occurs after 2 or 3 weeks of therapy. If the response is unsatisfactory, a higher dose may be given. The usual side effects are bone pain and polycythemia. Patients who are receiving erythropoietin should always receive iron supplementation because of increased utilization of iron.

On the other hand, if the erythropoietin is more than 500 IU/L, no evidence of iron, vitamin B₁₂ or folic acid deficiency is present, and the patient is reticulocytopenic, alternative diagnoses need to be investigated. Parvovirus B-19 infection can cause an aplastic anemia with a low or absent reticulocyte count and normal or high erythropoietin levels. If this infection is confirmed, IV immunoglobulin (IVIG), 1 g/kg/dose for 5 to 10 days, should be administered. The response is usually rapid and results in an increase in reticulocytes and hemoglobin levels and no further need of transfusion. This initial therapy is followed by monthly doses of IVIG at 400 mg/kg/dose. In the authors' limited experience, if IVIG is discontinued, a relapse of the aplastic anemia may occur. A case report of parvovirus B-19 anemia in an antiretroviral therapy-naïve patient showed resolution of the anemia with the initiation of HAART.

Another common opportunistic infection that causes bone marrow suppres-

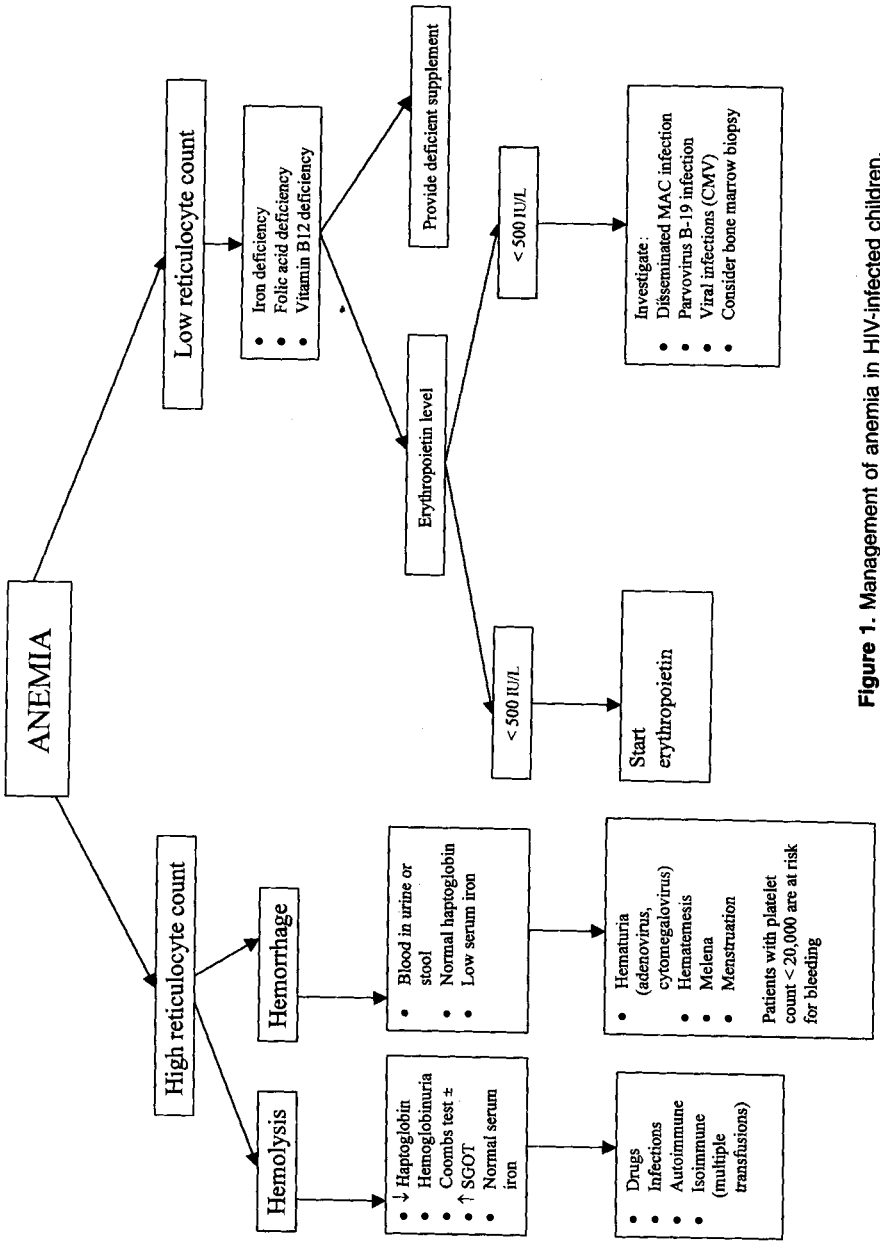


Figure 1. Management of anemia in HIV-infected children.

sion and anemia is disseminated infection with *Mycobacterium avium* complex (MAC) infection. When a specific cause for anemia cannot be elucidated, a bone marrow aspiration may be necessary.

Megaloblastic changes in the erythrocytes may result from antiretroviral therapy (i.e., ZDV, stavudine, and zalcitabine). Macrocytosis develops within weeks of commencing therapy with some antiretrovirals to a mean corpuscular volume of 110 cells/mL. Levels of vitamin B₁₂ and folic acid are usually within normal limits. In a few instances an intervention is needed, but if anemia is associated with the antiretroviral use, the options are to decrease the dose of the antiretroviral agent causing the anemia, or eliminating the drug and changing the treatment regimen. Megaloblastic anemia can also be caused by malabsorption or poor nutrition, and if the levels of folic acid and vitamin B₁₂ are diminished, the anemia must be re-evaluated after appropriate supplements are provided.

Anemia with an increased reticulocyte count can be secondary to hemorrhage or hemolysis. A decreased level of haptoglobin characterizes hemolysis. Treatment of this type of anemia is cause-specific and is beyond the scope of this article.

Neutropenia

Neutropenia is defined as an absolute neutrophil count of less than 1500 cells/mL. This is a common finding in HIV-infected children and may occur secondary to infection, nutritional deficiencies, or drug toxicity. Some drugs used to treat HIV infection, such as ZDV and TMP-SMX, are associated with the development of neutropenia. In some cases, neutropenia responds to initiation or a change of antiretroviral therapy. If the absolute neutrophil count is less than 500 cells/mL, a trial of granulocyte colony-stimulating factor starting at 5 to 10 µg/kg/dose is begun. Granulocyte colony-stimulating factor is a cytokine that increases circulating neutrophils and improves their functioning. Unlike erythropoietin, the response to granulocyte colony-stimulating factor is immediate, with demargination of the leukocytes, and the dose should be titrated to maintain an absolute neutrophil count of more than 1500 cells/mL.²⁵

Thrombocytopenia

Thrombocytopenia is a common problem among HIV-infected children. It may occur in the absence of other symptoms and, in some patients, is the initial presenting illness. Although a specific cause is usually not found, it should be investigated.⁷⁰ Antibodies against platelet glycoproteins have been identified in some HIV-infected patients with thrombocytopenia.²³

Intervention is not required, especially if the platelet count exceeds 50,000 platelets/mL. In some cases, the thrombocytopenia has responded to the initiation or change of antiretroviral therapy. ZDV has been shown to be beneficial in the treatment of patients with thrombocytopenia.³⁸ The role of other antiretroviral agents is less clear. When the platelet count is less than 20,000 platelets/mL or when bleeding is present, treatment should be instituted. Platelets are short-lived cells, and transfused platelets have even a shorter life span. The use of platelet transfusions is reserved for patients who are actively bleeding. IVIG has been beneficial in the treatment of immune thrombocytopenia. A total of 2 g/kg is administered over 2 to 4 days. If a response to the IVIG occurs, then this

is given at 3-week or 4-week intervals.^{10, 74} If a patient has maintained a normal platelet count for 6 to 12 months, the interval between doses is increased, and the treatment is eventually discontinued. RHo(D) immune globulin intravenous (WinRho SDF) is an alternative to IVIG, but hemolysis may result and is a significant side effect. Corticosteroids are another alternative treatment. Prednisone is usually started at a dose of 2 mg/kg/d for 2 to 4 weeks and then tapered and discontinued, but the thrombocytopenia may relapse when the steroids have been discontinued. Interferon alfa is reported to be effective in patients with severe thrombocytopenia that is resistant to antiretroviral therapy. Splenectomy is an option to consider if other treatments fail and usually results in the resolution of thrombocytopenia, but the lack of a spleen will predispose these children to encapsulated bacterial infections.^{55, 64} If splenectomy is considered, these children should be immunized with pneumococcal, *Haemophilus influenzae* type B, and meningococcal vaccines. A new approach is the use of recombinant thrombopoietin. Harker et al³⁵ experimentally treated three chimpanzees infected with HIV and thrombocytopenia with pegylated recombinant human megakaryocyte growth and development factor. The chimpanzees had a tenfold increase in platelet number, 30-fold increase in marrow megakaryocyte numbers, and fourfold increase in marrow megakaryocyte progenitor cells. On the other hand, Cole et al²³ found that thrombocytopenia in HIV-infected patients was caused by a shortening of platelet life span, increased splenic sequestration, and ineffective delivery of viable platelets and that levels of thrombopoietin were significantly higher than in control subjects.²³ The eventual role of this agent in the treatment of thrombocytopenia in children or adults infected with HIV is unclear.

GASTROINTESTINAL COMPLICATIONS

The occurrence of ulcers in the oral cavity presents a diagnostic dilemma because viral infections, such as HSV, CMV, and Coxsackie A infection, as well as bacteria, may be causative agents. Biopsy and culture of lesions that are persistent or increasing in size or number is recommended. Cultures are tested for viral, bacterial (aerobic and anaerobic cultures), mycobacterial, and fungal infection. If results are negative and the biopsy is not diagnostic, the authors assume that these are aphthous ulcerations and treat patients accordingly. Aphthous lesions may occur in the posterior pharynx, esophagus, perirectal area, and vulva. The treatment of these ulcers is by trial and error. Aphthous ulcers typically occur in severely immunosuppressed patients. For the treatment of oral aphthae, a mixture of viscous lidocaine, antacids (Maalox), diphenhydramine, and mycostatin to swish and swallow may relieve the symptoms. An alternative treatment is the use of clindamycin and steroids. Perirectal or vulvar lesions commonly respond to a mixture of equal parts of Aquaphor (Beiersdorf, S. Norwalk, CT) and cholestyramine. In one case at the authors' institution, fever, weight loss, and oral ulcers developed in an immunosuppressed 15-year old male adolescent. A culture grew CMV, and the patient responded well to treatment with ganciclovir, with a resolution of symptoms. Other alternatives are cimetidine, chlorhexidine, systemic steroids, and thalidomide.^{34, 39, 62, 71, 74}

Most cases of esophagitis are diagnosed by clinical symptoms and confirmed with a barium swallow study. In such cases, treatment is begun empirically for candida esophagitis, especially in the presence of oral candidiasis. Fluconazole is the drug of choice and is given at a dose of 6 mg/kg/d in one daily dose. The choice of inpatient versus outpatient treatment depends on the hydration and clinical condition of the patient and the reliability of the caregiver.

If a patient does not respond to empiric treatment after 3 days, then endoscopy with biopsy and culture of the esophageal mucosa should be done. If the biopsy results are compatible with fungal infection, parenteral amphotericin B is the drug of choice because some *Candida albicans* and *Torulopsis glabrata* and *Candida krusei* are resistant to fluconazole. Patients who receive recurrent courses or "prophylactic" regimens of fluconazole are at risk for resistant infections. In difficult-to-treat cases, therapy should be guided by antifungal susceptibility. A few children with recurrent severe oral thrush have developed resistance to most antifungals and are managed at the authors' center with IV amphotericin B infusions two or three times a week to control the pain and infection.

Esophagitis secondary to HSV is treated with IV acyclovir, 750 mg/m²/d divided into three doses. If CMV is the cause, then IV ganciclovir is used. Sometimes the cause of esophagitis is uncertain, even after biopsy. The management of these patients is controversial, and the same options discussed for treatment of aphthous ulcers apply. Patients with recurrent esophagitis are at risk for esophageal stenosis.

Development of chronic bilateral enlargement of the parotid glands may occur in as many as 15% of children with HIV infection and usually does not require any treatment, but sometimes parotid pain and fever develop in these patients. In this instance, infection is suspected, frequently with *Staphylococcus aureus*, although mouth flora may also be present. This complication is easily managed with a course of oral antibiotics, using antistaphylococcal agents. On the rare occasion when suppuration is suspected, an otolaryngologist should be consulted to evaluate the need for surgical treatment. Lymphomas and other tumors should be included in the differential diagnosis, especially in children with increasing parotid size.

Diarrhea is a common manifestation of HIV infection.⁴³ Although an infectious cause is frequently suspected, other important causes include side effects of medications, malignancies, and HIV enteropathy. Antibacterial agents are indicated in the treatment of diarrhea associated with enteric pathogens, such as shigellae, salmonellae, and campylobacter.^{9, 43} Adult patients commonly improve with fluoroquinolones, but in children, other alternatives (e.g., ampicillin, third-generation cephalosporins, or TMP-SMX) are used. HIV-infected patients, especially those with low CD4+ cell counts and frequent exposure to antibiotics, are at risk for diarrhea caused by *Clostridium difficile*. The treatment of choice is metronidazole with orally administered vancomycin used as an alternative drug. Relapse should not be considered a treatment failure because as many as 20% of patients relapse, and these patients should be retreated with metronidazole. Many viruses, including rotavirus, calicivirus, adenovirus, coronavirus, and astrovirus, can cause diarrhea. Specific treatment is available only for colitis associated with CMV (ganciclovir) or HSV (acyclovir). The management of parasitic and mycobacterial infections is discussed in the section on opportunistic infections. When pathogens cannot be identified, a consultation with a pediatric gastroenterologist is indicated for possible endoscopy and biopsy. Children who are immunosuppressed and have high viral loads benefit from HAART. Antiretrovirals which may cause diarrhea. In one series, 41% of patients receiving a protease inhibitor had diarrhea. Patients in whom a specific cause of diarrhea is identified may benefit from a lactose-free diet.

Abdominal distension with or without diarrhea is another common finding in HIV-infected children. In children without diarrhea, enlargement of the liver, spleen, or both may account for the distension. In patients with diarrhea, bacterial overgrowth of the upper gastrointestinal tract should be suspected. The distension worsens after meals and the breath test is abnormal, even before

challenge with carbohydrates. Cultures of the gastric and duodenal fluid commonly are positive, and the stomach pH has decreased acidity. Treatment consists of metronidazole, 30 mg/kg/d, divided into 3 or 4 doses, for 10 days. Some experts suggest using lactobacillus to restore normal bowel flora.

PULMONARY COMPLICATIONS

Lymphoid interstitial pneumonitis is a chronic lymphocytic infiltrative disease of the lung.^{5,40} The diagnosis of LIP in children is usually based on a typical chest radiograph with persistent reticulonodular bilateral infiltrates. In more severe cases, significant clubbing occurs. In asymptomatic children with LIP and normal oxygen saturation, a chest radiograph should be obtained at least once a year, and the oxygen saturation should be monitored using pulse oxymetry at each clinic visit. If a patient is hypoxic, steroids are indicated. Prednisone is given at a dose of 2 mg/kg/d for 2 to 4 weeks, with subsequent tapering to 1 mg/kg/d, and therapy is continued until the oxygen saturation becomes normal. Most children respond to this treatment within the first few weeks. In general, when an adequate response has occurred, the steroids may be weaned and discontinued. In some cases, repeated courses of steroids may be warranted. A few children with severe, advanced lung disease may not respond to steroid therapy, and if no response occurs after 4 to 6 months, the steroids should be discontinued. In addition, bronchodilators and chest physical therapy are helpful adjunctive therapies. The use of low doses of diuretics may also improve the respiratory status.⁷²

When dealing with suspected bacterial pneumonia, an aggressive approach should be taken in patients with chronic lung disease. When possible, the treatment should be directed to the specific pathogen causing the infection. Treatment is usually empiric because noninvasive diagnostic procedures, such as blood and sputum cultures, yield an organism in approximately 30% of cases. Therapy is directed at the usual pathogens (i.e., *Streptococcus pneumoniae*, *H. influenzae*, and *Staphylococcus aureus*), but in patients with chronic lung disease, gram-negative organisms, especially *P. aeruginosa*, must be considered potential pathogens. The authors have had good experience with the combination ticarcillin-clavulanic acid. The addition of aminoglycosides should be considered in immunocompromised patients and in those infected with resistant strains of gram-negative rods. Aminoglycosides can be delivered by nebulization (tobramycin, 80–160 mg three times a day) to decrease the risk for nephrotoxicity and improve delivery to the affected area. If a patient does not improve or his or her condition deteriorates on treatment, a bronchoalveolar lavage is indicated for diagnosis. The length of therapy is dependent on the cause and severity of the illness. Although the authors usually recommend 10 to 14 days of systemic antibiotic therapy, some children benefit from a longer course of treatment. In patients with chronic lung disease, pulmonary function tests may be beneficial at the onset of treatment and can be used as an indicator for length of therapy. If the pulmonary function tests continue to improve after 14 days of antibiotic therapy, treatment is continued until a return to baseline or a new plateau is reached.

Children with HIV infection who have bronchiectasis or frequent episodes of bacterial pneumonia may benefit from daily prophylaxis with TMP-SMX. If this is not successful in decreasing the frequency of infection, monthly infusions of IVIG at 400 mg/kg/d may be beneficial.

HIV NEPHROPATHY

HIV-associated nephropathy in children presents as a spectrum of disease that ranges from mild to moderate proteinuria that is persistent, hematuria, renal tubular acidosis, and end-stage renal disease (ESRD). Because a timed urine collection is difficult to perform in children, the authors use the ratio of urine creatinine and urine protein to calculate the degree of proteinuria. A normal creatinine-protein ratio is less than 0.2. A ratio more than 0.2 is abnormal and is consistent with nephrotic range proteinuria.¹ If this finding persists, it can lead to hypoalbuminemia and edema but without elevation of serum triglycerides as occurs in patients with idiopathic nephrotic syndrome. Renal function deteriorates more slowly in children than in adults. Renal sonography shows increased echogenicity and provides details of the function of the kidneys. Biopsy of the kidney usually shows focal segmental glomerulosclerosis or diffuse mesangial hyperplasia and, less frequently, minimal change or systemic lupus erythematosus-like nephropathy.

Renal tubular acidosis is corrected with alkalinizing agents. The authors use sodium or potassium citrate, depending on other electrolyte abnormalities. One milli-equivalent of citrate is equivalent to one milli-equivalent of bicarbonate. The authors start with 2 to 3 mEq/kg/d divided in 2 or 3 doses and adjust the dose to maintain a normal serum Ph. Patients with renal tubular acidosis may also need supplements of other minerals, such as calcium, magnesium, and phosphorus.

Therapy for patients with proteinuria is divided in two categories: (1) treatment of incipient renal disease to slow the progression to ESRD and (2) the treatment of ESRD.

Because the progression of disease in children is not as rapid as in adults, the first approach is to observe these patients over a period of time, monitoring electrolytes, blood urea nitrogen (BUN), and creatinine. Drugs commonly used in HIV Infection that need dose modification in patients with renal impairment include:

Antiretroviral agents

- Adefovir
- Didanosine (only on hemodialysis)
- Lamivudine
- Stavudine
- Zalcitabine
- ZDV

Others

- Acyclovir
- Aminoglycosides
- Amphotericin B
- Clarithromycin
- Ethambutol
- Foscarnet
- Fluconazole
- Flucytosine
- Ganciclovir
- Pentamidine
- TMP-SMX

The use of nephrotoxic agents should be avoided. Since the pathogenesis of the disease has been linked to immune complex deposition, an initial approach

has been to use immunosuppressive agents. Steroids represent another option. Several studies suggest that glucocorticoids might slow the progression of HIV-associated nephropathy in adults.^{63, 69} The use of steroids in children has not been as beneficial as in adults.

Diabetic patients with proteinuria benefit from treatment with angiotensin-converting enzyme inhibitors. Kimmel et al^{46, 47} compared the progression of renal insufficiency with ESRD in 18 patients with biopsy-proven HIV-associated nephropathy. Nine patients were treated with captopril, and nine patients did not receive an angiotensin-converting enzyme inhibitor. The mean survival of renal function in the captopril group was 156 ± 71 days versus 37 days in the control group. Gorritz et al³² described a 36-year-old white homosexual man with HIV-1 infection with nephrotic range proteinuria who was successfully treated with captopril,³² but because proteinuria may persist for long periods without progression in pediatric patients, the authors usually elect to follow these patients without specific treatment as long as they remain asymptomatic. As with every other manifestation of HIV infection, HAART may have a significant role in the prevention or treatment of nephropathy.⁷³

When ESRD has developed, a decision regarding dialysis must be made. The availability of HAART and the improved prognosis and extended survival time mandates an aggressive approach. At the University of Miami, several children with HIV-associated nephropathy have received long-term peritoneal dialysis and are managed in conjunction with the pediatric nephrology team.

CARDIOMYOPATHY

Cardiac involvement in AIDS was first reported in 1983 in a woman who had Kaposi's sarcoma involving the anterior cardiac wall. Since then, multiple reports have discussed the incidence, etiology, manifestations, and management of cardiomyopathy.^{7, 8, 51} The spectrum of cardiac disease ranges from clinically silent lesions to fatal disease, and the severity of disease correlates with the degree of immune suppression. Cardiomyopathy seems to affect survival in HIV-infected children.^{51, 56}

Autopsy studies in HIV-infected adults indicate that as many as 25% have dilated cardiomyopathy and as many as 52% had myocarditis at death.⁴ Depressed left ventricular function is common and progressive in children. Serial studies of 88 children with advanced symptomatic HIV infection showed that 21% had decreased left ventricular function and 34% had ventricular dilatation.⁴⁴ Every structure of the heart can be affected.^{49, 51, 52, 56, 75} Cardiac lesions described in patients with HIV include pericardial effusions; pericarditis; myocarditis; dilated cardiomyopathy; endocarditis; and vascular lesions, such as aneurysms, atherosclerosis, and pulmonary hypertension. Infiltrative neoplasm (i.e., Kaposi's sarcoma and lymphoma) has also been reported. The cause of cardiomyopathy is multifactorial. HIV has been found in the heart, but whether its role in pathogenesis is related to a direct effect on the myocardium or secondary to the immune response is a matter of controversy. Other factors that could be involved in the pathogenesis of cardiomyopathy include infections such as Coxsackie B virus, CMV, Epstein-Barr virus, toxoplasma and other opportunistic infections, pulmonary disease, wasting, nutritional deficiencies (i.e., selenium and carnitine),⁴⁵ pharmacotherapeutic agents (i.e., antiretrovirals, pentamidine, amphotericin B, foscarnet, interferon alfa, TMP-SMX, or steroids), and illicit drug use.^{4, 13, 21}

HIV cardiomyopathy starts early in life. In a multicenter study of lung and cardiac pathology in HIV-infected patients, fetal echocardiography was

performed in 174 fetuses of HIV-infected mothers. Fetuses of HIV-infected mothers had increased right and left ventricular wall thickness, decreased heart rates, and increased right and left ventricular outflow velocities. The postnatal phase of the study showed increased prevalence of structural heart disease (12.3%), but no significant difference in the prevalence of congenital cardiovascular malformations was found among HIV-infected and noninfected children.^{49, 51} Other studies showed a lower prevalence. The routine use of echocardiograms in children with HIV greatly influences the reported prevalence of HIV cardiomyopathy.

The most common clinical manifestation of cardiomyopathy is sinus tachycardia.⁵¹ Other associated manifestations include bradycardia, dysrhythmias, abnormal blood pressure (i.e., hypotension or hypertension), left ventricular hypertrophy, pulmonary hypertension, pericardial effusion, and congestive heart failure (CHF).

Evaluation of cardiac status includes a thorough history and physical examination followed by specific diagnostic tests when clinically indicated. Initial testing should include chest radiography and ECG. Chest radiography is useful in evaluating heart size and the presence of pulmonary disease (e.g., LIP, pneumonia, or pleural effusions) and other intrathoracic abnormalities. When patients are examined by ECG or during autopsy, cardiac abnormalities are detected more often than expected from physical examination. This raises the question of whether an ECG should be part of the routine examination of HIV-infected children, especially those with low CD4+ cell counts. Lipshultz⁵² prospectively followed up 196 HIV-infected children with baseline ECG at enrollment and every 4 months thereafter for 2 years. He found that subclinical cardiac abnormalities were not only common but also persistent and often progressive. Similar data are available on HIV-infected adults. Although introducing ECG as part of the routine care of HIV-infected children implies a significant cost and an additional workload, a periodic ECG assessment may be beneficial. Some centers recommend annual ECG for asymptomatic patients and every 8 months for symptomatic patients.⁶⁰ Other tests used in the assessment of cardiomyopathy include Holter monitoring and, rarely, cardiac catheterization and endomyocardial biopsy.

Noncardiac predictors of hemodynamic abnormalities are AIDS, wasting, LIP, recurrent bacterial infections, encephalopathy, anemia, positive CMV and Epstein-Barr virus serology, and age of less than 1 year.

Treatment of HIV cardiomyopathy starts with early detection. Specific therapy of infectious causes of HIV-associated heart disease, such as CMV, *Mycobacterium avium* complex disease, tuberculosis, toxoplasmosis, and salmonellosis, have significant effect on outcome. Problems such as anemia, nutritional deficiency, hypoxemia, and electrolyte deficiencies need correction. Nonpharmaceutical therapeutic measures include limitation of physical activity, restriction of salt and fluid intake, and oxygen support.³⁰

Pharmacologic treatment should be done in steps. The mildest manifestations of CHF are treated with angiotensin-converting enzyme inhibitors. The two most commonly used agents are enalapril and captopril. Most clinicians favor enalapril because of the advantage of once- or twice-a-day administration. Although the manufacturer does not specify a pediatric dose, two studies started patients on 0.1 mg/kg/d and titrated upward as tolerated to a maximum of 0.5 mg/kg/d. Renal function, serum electrolytes, and blood pressure must be monitored closely when using this class of drug. The next step is diuretics. Loop diuretics (e.g., furosemide) are preferred because thiazides are less potent and their efficiency decreases with decreased glomerular filtration rate. Patients who

remain symptomatic despite these measures may benefit from the use of digoxin. Antihypertensive and antiarrhythmic agents are prescribed when appropriate in conjunction with a pediatric cardiologist.

IVIG has been reported to be effective in patients with Kawasaki syndrome, CHF refractory to anticongestive therapy, and acute myocarditis. In one study, HIV-infected children on monthly infusions of IVIG seemed to have better left ventricular function and structure.⁵³ Anecdotal reports recommend the use of steroids and other immune suppressor agents in the management of patients with cardiomyopathy. Interferon alfa has also been associated with improvement of myocardial dysfunction in HIV-infected patients.²⁶

Because pericardial effusion is usually an incidental ECG finding, treatment depends on its severity and cause. When tamponade is present, pericardiocentesis is necessary. Pericardiocentesis is also indicated when bacterial infection is suspected. Nonsteroidal anti-inflammatory agents are useful in the management of patients with pain.⁷⁵ Steroids are not recommended.

Another issue is the management of patients with hypercholesterolemia and hypertriglyceridemia secondary to the use of protease inhibitors.¹⁴ In adults, the issue of whether the protease inhibitors cause coronary artery disease is debated.⁴² So far in pediatrics, no early coronary artery disease has been reported, but hyperlipidemia, lipodystrophy, insulin-resistance diabetes mellitus, and coronary artery disease have been reported in adults. The recommendation for the treatment of these side effects is modification of the diet and pharmacologic treatment with a lipid-lowering agent, if necessary. Some experts recommend the discontinuation of protease inhibitors if these measures are unsuccessful.^{31, 36, 37, 41, 48}

HIV ENCEPHALOPATHY

Progressive and static encephalopathy with cognitive, behavioral, and motor manifestations has been described in HIV-infected children.^{24, 29, 61} Although most children with neurologic impairment have no identifiable pathogen other than HIV, encephalopathy may occur as a result of opportunistic infections, inflammatory disease, vascular disease, or neoplastic changes. Evidence shows that HIV infection of the CNS is associated with typical neuropathologic changes.²⁸

According to the Centers for Disease Control and Prevention (CDC) Revised Classification System,¹⁶ the diagnosis of encephalopathy requires one of the following progressive findings present for at least 2 months in the absence of other identifiable causes:

- Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests
- Impaired brain growth or acquired microcephaly demonstrated by head circumference measurements, or brain atrophy demonstrated by CT or MR imaging, with serial imaging required in children less than 2 years of age
- Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia or gait disturbance

Estimates of the prevalence of HIV-related encephalopathy in children are much lower than those reported in the first decade of the pediatric AIDS epidemic. The Woman Infant Transmission Study prospectively followed up 128 HIV-

infected children. Of the 128 children, 27 (21%) were diagnosed with HIV encephalopathy. Encephalopathy was more common with advanced disease (89% of the children were category B or C, and 74% were category 2 or 3). The presence of encephalopathy increased the risk for death 28-fold. The presence of hepatomegaly, splenomegaly, or lymphadenopathy in the first 3 months of life and increased viral load was correlated with the presence of encephalopathy. A trend, although, not statistically significant, showed that children with a positive HIV culture in the first week of life were at higher risk for encephalopathy. Levels of HIV RNA in the cerebrospinal fluid may be an important predictor of encephalopathy. Encephalopathy in HIV-infected children can be secondary to HIV or other intercurrent illness, such as infection with other pathogens, neoplasm, and vascular or inflammatory disease.

The workup of children with HIV and encephalopathy is as follows.

1. **Evaluation by a pediatric neurologist**
2. **Developmental, audiology, and ophthalmologic evaluation**
3. **Imaging of the brain** by CT or MR imaging. Cerebral atrophy, attenuation of white matter, and cerebral calcifications are the most common findings. The CT scan can easily detect calcifications, but MR imaging is superior in detecting white-matter abnormalities and atrophy.
4. **Cerebrospinal fluid studies** for opportunistic infections and neoplasms. The value of monitoring HIV RNA viral load in cerebrospinal fluid is not yet well defined.⁶⁷
5. **Specific tests for expected pathogens** (i.e., *Cryptococcus neoformans*, *Toxoplasma gondii*, *Mycobacterium tuberculosis* and nontuberculosis, CMV, HSV, varicella zoster virus, and *Treponema pallidum*)
6. **Appropriate treatment of identifiable causes.** If no cause other than HIV is identified, then the treatment goal is to reduce the viral load. The antiretrovirals with most penetration across the blood-brain barrier are ZDV, stavudine, and nevirapine. Although protease inhibitors may not have good CSF penetration because of their high protein binding, one small study using MR imaging brain studies demonstrated improvement or no progression in white matter disease in 89% of adult patients on protease inhibitors versus worsening in 86% of the patients not using these agents.²⁸

Depending on the severity of disease, patients with encephalopathy need a strong support system. Physical therapy, braces, and even surgery are sometimes necessary to minimize contractures. Baclofen has a role in the treatment of hypertonicity. Seizures are treated with antiepileptic agents in conjunction with a neurologist. Because these patients may have a decreased appetite or may have problems swallowing, feeding tubes may be needed.

SPECIAL ISSUES IN IMMUNIZATION

HIV-infected children have a similar immunization schedule to that of HIV-noninfected children (Table 6) except for a few variations that are discussed in this section. The administration of some vaccines has led to a transient increase in HIV viral load, but this effect does not contraindicate the use of vaccines.¹¹

Table 6. IMMUNIZATION OF HIV-INFECTED CHILDREN

Rights were not granted to include this data in electronic media. Please refer to the printed journal.

IPV = inactivated poliomyelitis vaccine; OPV = oral polio vaccine; MMR = measles, mumps, rubella; BCG = bacille Calmette-Guérin vaccine.

Poliomyelitis

A series of three doses of inactivated polio vaccine at 2, 4, and 6 to 18 months of age, followed by a booster dose at 4 to 6 years, is recommended. Children who have HIV infection, are at risk for infection, or reside in households with immunocompromised hosts should not receive oral polio vaccine because the vaccine virus is shed through the gastrointestinal tract and could cause vaccine-associated paralytic poliomyelitis in susceptible hosts. In the early years of the AIDS epidemic, infected children in the United States received primary and booster doses of oral polio vaccine without complications, and in developing countries, oral polio vaccine continues to be administered, but because inactivated polio vaccine is readily available and a theoretic risk for vaccine-associated paralytic poliomyelitis exists, this is the recommended vaccine in the United States.

Measles

The measles-mumps-rubella vaccine is a live attenuated viral vaccine given between 12 and 15 months of age, with a booster dose at 4 to 6 years of age. In areas where a high prevalence of measles exists, monovalent measles vaccine is given between 6 and 12 months of age. In the early years of the AIDS epidemic, children with HIV who developed measles infection had a high risk for complications and death, suggesting that the benefits of administering this live viral vaccine outweighed the potential risks, but in one case report, a 21-year-old hemophiliac man infected with HIV was immunized with the measles-mumps-rubella vaccine, giant cell pneumonia developed 1 year later, and the patient died.¹⁷ The measles vaccine virus was isolated from postmortem specimens. Since this report, recommendations have been altered, and children with mild

or moderate immunosuppression (i.e., immune category 1 or 2) should receive the measles vaccine, but children with severe immunosuppression (i.e., immune category 3) should be excluded. Whether a child with severe immunosuppression who responds to HAART with an increase in the CD4+ T-cell count and percentage corresponding to immune category 1 or 2 should be immunized with measles vaccine is a matter of controversy. At this time, the functional capacity of the CD4+ T cells that have been restored is uncertain. Until a reliable, quantitative test is available to define the function of these restored cells, immunization with the measles vaccine is not recommended in these situations. Also, the antibody response to measles vaccination in HIV-infected children may vary in amount and duration, depending on the clinical and immune status of these children, so in the case of exposure to measles, HIV-infected children should receive prophylaxis with immunoglobulin, preferably within 72 hours after exposure. The dose recommended for children with symptomatic HIV infection is 0.5 mL/kg (maximum dose, 15 mL) and for asymptomatic children is 0.25 mL/kg, given intramuscularly. Children who have received IVIG therapy within 3 weeks of exposure do not need additional prophylaxis.

Influenza

A yearly influenza vaccine is recommended for infants and children with HIV infection who are 6 months of age or older. Only the subvirion, that is, split-virus, vaccine should be used in children less than 13 years of age because this minimizes fever and other adverse side effects. Children less than 9 years of age who have not been immunized previously should receive two doses of the vaccine given 1 month apart. For children previously immunized with this vaccine, one dose is adequate. Physicians should review the official recommendations for influenza vaccine yearly because the composition of the vaccine varies and the dosage for children aged 3 years or less may be different than for older children. The vaccine should be given in early autumn, before the onset of the flu season. In addition, household contacts of high-risk children should also be immunized.

Pneumococcal Vaccine

The incidence of infection with *Streptococcus pneumoniae* has increased in HIV-infected children. In addition, these organisms have an increasing pattern of resistance to penicillin and the cephalosporins. The currently available polyvalent pneumococcal polysaccharide vaccine should be given to all HIV-infected children who are aged 2 years or older. A booster dose is recommended after 5 years. A new protein-conjugated heptavalent pneumococcal vaccine is in development that shows safety and immunogenicity and reduces the incidence of otitis media and invasive disease secondary to *S. pneumoniae* infection in normal infants and children. Limited information on the use of these vaccines in HIV-infected children is available.¹¹

Varicella

Varicella infection has been associated with increased morbidity in children with HIV infection. In children with severe immunocompromization, recurrent herpes zoster virus or chronic varicella infection may develop. The Advisory

Committee on Immunization Practices does not recommend administering the varicella vaccine to persons with cellular immune deficiencies, but because of the increased risk for morbidity from varicella and herpes zoster, the Advisory Committee on Immunization Practices recommends that the varicella vaccine be considered for children with asymptomatic or mildly symptomatic HIV infection, CDC classification N1 or A1, with an age-specific CD4+ T-lymphocyte percentage of 25% or more.²⁰ The vaccine should be administered in two doses with a 3-month interval between doses for this group of children. This schedule differs from the vaccination schedule for healthy children. It is strongly recommended for HIV-negative siblings and children living in households with HIV-infected adults or children, but this vaccine should not be administered to children with HIV infection who have moderate or severe immunocompromization. Studies to evaluate the safety and tolerance of this vaccine in HIV-infected children are ongoing. In a study to determine the safety and immunogenicity of the Oka strain varicella vaccine, 42 HIV-infected children aged 1 to 8 years (stage N1 and A1) who had no history of varicella infection and had negative titers received two doses of the vaccine separated by 3 months. No severe adverse effects were reported. Fever occurred in 20% of the recipients after the first dose and in 5% after the second dose. Local reactions were similar to those seen in healthy children. After eight exposures, only one mild case of varicella occurred. Varicella-zoster virus antibody and specific lymphocyte proliferation were respectively detected in 48% and 63% of patients after the first and 56% and 82% of patients after the second dose.⁵⁰ Susceptible children with HIV infection exposed to varicella should receive passive immunization with varicella-zoster immunoglobulin given within 96 hours of exposure. If a child has received IVIG within the 3 weeks before exposure, then varicella-zoster immunoglobulin is not necessary.

Other Vaccines

Hepatitis B, diphtheria, pertussis, tetanus, and *H. influenzae* type b vaccine recommendations are the same for HIV-infected and noninfected children. Bacillus Calmette-Guérin vaccine is a live attenuated vaccine and is contraindicated for children with HIV living in the United States,^{15, 33} but the World Health Organization has continued to recommend the administration of this vaccine at birth in countries with a high prevalence of tuberculosis, even if a mother is known to have HIV infection. The rotavirus vaccine has not been evaluated in HIV-infected children and is not recommended for use in this population.

PALLIATIVE CARE AND PAIN MANAGEMENT IN HIV INFECTION

A wise physician said that medicine should not give more years to life but more life to years. Quality of life is an important issue when dealing with chronically ill patients, especially during the late stages of HIV infection. Palliative medicine focuses on the management of physical, psychological, and social aspects inherent in ultimately lethal diseases.^{3, 74}

Children with HIV infection may experience pain from their illness and the medical and surgical procedures done to alleviate their illness. An aggressive approach to pain management in children with HIV infection is recommended. The success of therapy is determined by self-reports from these children using age-specific scales. The type and dose of medication used depends on the degree

of pain experienced (Table 7). Certain principles apply to pain management. Opioid therapy is safe in infants and children. Therapy should be individualized, but around-the-clock therapy is preferred to intermittent dosing. Intramuscular and subcutaneous routes should be avoided, and oral and IV routes are preferred. The use of behavioral techniques also has a significant role.⁷⁴ From the beginning, an open and sincere relationship should exist between physicians, patients, and patients' families. When possible, pediatric patients should be involved in decision making that involves minimizing care and pain management.

If a physician believes that therapy would be futile or suffering would be too great, the issue of resuscitation should be discussed with the patient's family. A physician may have difficulty in determining the right time to bring up this issue but this conversation should precede a situation in which the patient requires artificial life support. Whether to include these children in the decision making depends on a child's age and maturity and the family's preferences. Psychiatric evaluation may be helpful to assess the level of maturity of these patients. Referrals to hospice for terminal care facilities are appropriate and provide support for families at this difficult time.

DISCLOSURE OF HIV STATUS

Children with perinatally acquired HIV are surviving longer than at the beginning of the pediatric AIDS epidemic. As children enter late childhood and

Table 7. SUGGESTED PROTOCOL FOR PHARMACOLOGIC MANAGEMENT OF PAIN IN HIV-INFECTED INFANTS AND CHILDREN

Rights were not granted to include this data in electronic media. Please refer to the printed journal.

po = by mouth, IM = intramuscularly, SC = subcutaneously, IV = intravenously.

Adapted from Working Group on Antiretroviral Therapy and Medical Management of HIV-infected Children: Antiretroviral therapy and medical management of pediatric HIV infection. Pediatrics 102:1008, 1998; with permission.

adolescence, they should be aware of their diagnoses. Children with other chronic diseases who know their diagnoses have been shown to cope better with their illness than those who do not know their diagnoses. In past years, families have been afraid to tell their children about their HIV infection because of the fear that these children will disclose to others and the family would be stigmatized or because of denial or guilt about transmitting the infection to their children, but an ongoing dialogue with the family regarding the importance of disclosure is important. The age, maturity, and social circumstance of these children must be taken into consideration, and disclosure should be done in a language and at a level that these children understand. Neuropsychological testing can guide the practitioner in determining the developmental age of a child. Simple, uncomplicated explanations can be given to children under 10 years of age, but older children and adolescents should have full disclosure, conveying an understanding of how the infection is transmitted, how to protect others from getting the infection, and a sense of responsibility for their health. These children should become active participants in their health care. As children reach adolescence, issues of compliance arise, and teenagers should be able to express opinions on the type of medication regimen they can accommodate, with full realization of the consequences of not taking their medication. Disclosure may occur through the family or guardian of the child or with assistance of the physician and the social worker. The counseling session should include a discussion of who must or should know about the diagnosis. The authors encourage telling siblings who are mature enough to handle the responsibility of knowing this information so that they can be supportive of the infected child. Physicians should answer questions openly and truthfully to prevent misconceptions about the illness. At each subsequent visit, physicians should allow the children to ask questions regarding the diagnosis. After disclosure, the children should be given the opportunity to speak with another infected child or attend a peer support group so they do not feel isolated.^{3, 54}

SUMMARY

Significant advances have been made in the understanding of the pathophysiology of HIV infection since the beginning of the epidemic. This knowledge has translated into the development of new therapies for HIV and opportunistic infections, laboratory advances in monitoring viral and immune status, and a better understanding of factors affecting patient outcome. Concomitantly, significant progress has been made in the medical management of children with HIV infection in the past 5 years. The number of children reported with AIDS in the United States is decreasing, and efforts are shifting from caring for children with advanced immunosuppression and severe opportunistic infections to early HAART, maintenance of the immune system, and prevention of opportunistic infections. Primary care physicians are now more involved and informed in the care of HIV-infected patients. Although published data are limited, physicians who have been working with this population have observed a dramatic improvement in the quality of life and length of survival of these patients. Unfortunately, this progress is not shared by developing countries where resources are minimal and antiretroviral agents are commonly unavailable. Although efforts to develop a vaccine to prevent HIV infection are ongoing, progress has been slow. Education and awareness continue to be the most powerful weapons against HIV.

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