Pediatric HIV Infection

by Mark W. Kline, M.D.

2. Clinical Manifestations

Infants with vertically acquired HIV infection usually are clinically normal during the neonatal period. A congenital HIV syndrome, encompassing microcephaly, a prominent box-like forehead, flattened nasal bridge, short nose with flattened columella, well formed triangular philtrum and patulous lips with prominent upper vermilion border, has been described, but its specificity for HIV infection is poor.

The CDC AIDS case definitions for adults and children are similar, with several exceptions. Lymphoid interstitial pneumonia/pulmonary lymphoid hyperplasia (LIP/PLH) and multiple or recurrent serious bacterial infections are AIDS defining only for children. Several other conditions, including certain types of cytomegalovirus and herpes simplex virus infections and toxoplasmosis of the brain, are AIDS defining only for adults and for children greater than one month of age. The expanded definition for AIDS in adolescents and adults, which became effective in 1993, does not apply to children (less than 13 years old).

The AIDS case definition is used for purposes of surveillance and reporting. The CDC has developed a separate classification system to describe the spectrum of HIV disease, including HIV exposed infants with undetermined infection status. The system employs two axes to indicate severity of clinical signs and symptoms and degree of immunosuppression (Tables 1 and 2). Clinical categories include N, for no signs or symptoms, and A, B and C, for mild, moderate and severe signs or symptoms. All AIDS defining conditions with the exception of LIP/PLH are included in category C. Several studies indicate that the prognosis of children with LIP/PLH is better than that of children with other AIDS defining conditions. As a consequence, LIP/PLH was separated from the other AIDS defining conditions and placed in category B along with many infectious complications and organ dysfunctions (e.g. cardiomyopathy and nephropathy).

Immunological categories outlined in the revised classification system include the following: 1, no evidence of suppression; 2, moderate suppression; and 3, severe suppression. Degree of immunosuppression is defined on the basis of age adjusted CD4+ lymphocyte counts and percentages.

Table 1. 1994 Revised human immunodeficiency virus pediatric classification system: immune categories based on age-specific CD4+ T-lymphocyte count and percentage*

	less than 12		

	mos		1-5 yrs		6-12 yrs	
Immune Category	No./ L	(%)	No./ L	(%)	No./ L	(%)
Category 1-no suppression	≥1,500	(≥25%)	≥1,000	(≥25%)	≥500	(≥25%)
Category 2-moderate suppression	750-1,499	(15%-24%)	500-999	(15%-24%)	200-499	(15%-24%)
Category 3-severe suppression	<750	(<15%)	<500	(<15%)	<200	(<15%)

*Modified from CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(no. RR-12):1-10.

Table 2. 1994 Revised human immunodeficiency virus pediatric classification system: clinical categories*

Category N: Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A: Mildly Symptomatic

Children with 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

Children who have symptomatic conditions other than those listed for category A or category C that are attributed to HIV infection. Examples of conditions in clinical category B include but are not limited to the following:

Anemia (<8 gm/dL), neutropenia (<1,000/mm^3), or thrombocytopenia (<100,000/mm^3) persisting ≥30 days
Bacterial meningitis, pneumonia, or sepsis (single episode)
Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months
Cardiomyopathy
Cytomegalovirus infection with onset before age 1 month
Diarrhea, recurrent or chronic
Hepatitis
Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)
HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
Leiomyosarcoma
Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia (PLH) complex
Nephropathy
Nocardiosis
Fever lasting >1 month
Toxoplasmosis with onset before age 1 month
Varicella, disseminated (i.e., complicated chickenpox)
Category C: Severely Symptomatic
Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP (which is a category B condition).

*Modified from CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(no. RR-12):1-10.

Use of the revised classification system is relatively straightforward. For example, a 3-month-old infant with *Pneumocystis carinii* pneumonia and a CD4+ lymphocyte count less than 750 μl^{-1} has a classification code of C3 to indicate severe signs or symptoms and severe immunosuppression. An asymptomatic 6-month-old infant with CD4+ lymphocyte count and percentage of at least 1500 μl^{-1} and 25%, respectively, is

classified N1 to indicate no signs or symptoms and no evidence of immunosuppression.

These new clinical and immunological classification categories are mutually exclusive. Once classified, an infant or child may not be reclassified in a less severe category even if improvement in clinical or immunological status occurs in response to antiretroviral therapy or other factors. An infant with HIV vertical exposure and indeterminate (unconfirmed) infection status has>E= (for vertically exposed) placed as a prefix to the appropriate classification code (e.g. EN1).

The clinical manifestations of HIV infection in infants and children are varied and often non-specific. Lymphadenopathy, often in association with hepatosplenomegaly, can be an early sign of infection. During the first year of life, oral candidiasis, failure to thrive, and developmental delay are other common presenting features of HIV infection.

Table 3 lists the most common AIDS defining conditions observed among American children with vertically acquired HIV infection. *P. carinii* pneumonia accounts for about half of all AIDS defining conditions diagnosed during the first year of life; the median age at diagnosis of *P. carinii* pneumonia in children in one series was five months. Affected children usually have progressive respiratory distress and hypoxemia. Fever may be absent. In young infants in particular, the clinical course may be fulminant. The chest radiograph may demonstrate bilateral interstitial infiltrates, but any pattern of findings, including a completely normal radiograph, can be observed early in the course of illness. Diagnosis of *P. carinii* pneumonia is best accomplished by bronchoalveolar lavage or open lung biopsy.

Table 3. Common AIDS defining conditions in children

Pneumocystis carinii pneumonia
Lymphoid interstitial pneumonia/pulmonary lymphoid hyperplasia
Recurrent bacterial infections
Wasting syndrome
Candida esophagitis
HIV encephalopathy
Cytomegalovirus disease
Pulmonary candidiasis
Cryptosporidiosis
Herpes simplex disease
Mycobacterium avium-intracellulare complex infection

Infants and children with *P. carinii* pneumonia usually are treated with intravenous trimethoprim-sulfamethoxazole or pentamidine. Adjunctive corticosteroid therapy is recommended for adults with AIDS and *P. carinii* pneumonia. Limited information suggests that corticosteroid therapy may be beneficial in pediatric patients, as well.

LIP/PLH affects a somewhat older group of children than *P. carinii* pneumonia , with a median age at diagnosis of about 14 months. The onset of LIP/PLH generally is insidious. Cough and tachypnea often are noted. Examination of the chest reveals few auscultatory abnormalities. Frequently there is marked generalized lymphadenopathy, hepatosplenomegaly and salivary gland enlargement. Digital clubbing may be observed in advanced cases. Chest radiography typically reveals symmetric bilateral reticulonodular interstitial infiltrates, sometimes in association with hilar adenopathy. Confirmation of the diagnosis is made by open lung biopsy. Histopathology and immunocytochemistry reveal a mononuclear interstitial infiltrate composed of immunoblasts, plasma cells and CD8+ lymphocytes. The pathophysiology of LIP/PLH is unknown, although Epstein-Barr virus has been implicated as a cofactor in its development.

The clinical course of LIP/PLH is variable. Spontaneous clinical remission sometimes is observed. Exacerbation of clinical signs and symptoms may occur in association with intercurrent viral respiratory illnesses. In severe cases of LIP/PLH there is progressive hypoxia and respiratory failure. The management of children with LIP/PLH is largely supportive. Some patients require intermittent or continuous supplemental oxygen. Anecdotal reports suggest that some children with progressive hypoxemia respond to corticosteroid therapy.

Bacterial infections occur commonly in children with HIV infection. *Streptococcus pneumoniae, Salmonella* species, *Staphylococcus aureus* and *Haemophilus influenzae* type b are the bacteria isolated most frequently. Risk factors for bacterial infection in HIV infected children have not been defined precisely, but young children with vertically acquired HIV appear to be at particularly great risk.

The majority of children with HIV infection have central nervous system abnormalities. Progressive HIV encephalopathy, which may include developmental delay or regression, spastic weakness of the extremities, microcephaly, seizures and, by computerized tomography, cerebral atrophy and basal ganglia calcification, occurs less commonly. There is evidence that encephalopathy results from central nervous system involvement by HIV itself. The virus has been cultured from cerebrospinal fluid, intrathecal synthesis of anti-HIV antibody has been demonstrated, and HIV nucleotide sequences have been identified in brain tissue at autopsy. Inflammatory lesions, reactive gliosis, and white matter degenerative changes are some of the neuropathological findings noted in the brains of HIV-infected children.

Central nervous system infection by HIV generally is restricted to monocytes, macrophages, and their derivatives. It is hypothesized that activation of these cells by HIV can result in overproduction of certain cytokines, arachidonic acid metabolites and quinolinic acid, which, in turn, may produce some of the neuropathological

changes observed. Elevated serum concentrations of tumor necrosis factor (TNF) have been associated with progressive encephalopathy in children with HIV infection, and TNF can produce white matter destruction similar to that observed in children with progressive encephalopathy. Furthermore, platelet activating factor and products of arachidonic acid metabolism may precipitate central nervous system injury, possibly through upregulation of TNF or other cytokines.

A wide variety of other clinical manifestations of pediatric HIV infection has been described. Hematological findings, including thrombocytopenia, anemia, and leukopenia, are particularly common. Common dermatological manifestations include fungal, bacterial and viral infections of the skin, as well as severe seborrheic dermatitis, vasculitis, and drug eruptions. Oral findings include infections, aphthous ulcers, and parotid gland swelling. Cardiomyopathy, pericardial effusion, myocarditis, and cardiac dysrythmias are potentially lethal conditions observed commonly among HIV infected children. Finally, renal disease, with proteinuria, nephrotic syndrome and renal insufficiency, has been reported.