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1995 Revised Guidelines for Prophylaxis Against *Pneumocystis carinii* Pneumonia for Children Infected with or Perinatally Exposed to Human Immunodeficiency Virus

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1995 Revised Guidelines for Prophylaxis Against *Pneumocystis carinii* Pneumonia for Children Infected with or Perinatally Exposed to Human Immunodeficiency Virus

Summary

Pneumocystis carinii *pneumonia (PCP) is the most common opportunistic infection in children who have acquired immunodeficiency syndrome (AIDS). Despite the publication of guidelines for prophylaxis against PCP for children infected with human immunodeficiency virus (HIV) in 1991 (*1*), ongoing AIDS surveillance has detected no substantial decrease in PCP incidence among HIV-infected infants. Studies indicate that this continued incidence is associated with failure to identify HIV-infected children before PCP occurs and with limitations in the ability of CD4+ measurements to identify children at risk for PCP. In March 1994, the National Pediatric & Family HIV Resource Center,* in collaboration with CDC, convened a working group to review additional data about the occurrence of PCP among HIV-infected children and to reevaluate the 1991 PCP prophylaxis guidelines for children. This report summarizes these new data and presents revised PCP prevention guidelines that recommend a) promptly identifying children born to HIV-infected women and initiating regular diagnostic and immunologic monitoring of such children; b) beginning PCP prophylaxis at 4–6 weeks of age for all children who have been perinatally exposed to HIV; c) continuing prophylaxis through 12 months of age for HIV-infected children; and d) making decisions regarding prophylaxis for HIV-infected children ≥12 months of age based on CD4+ measurements and whether PCP previously has occurred.*

INTRODUCTION

In 1991, guidelines for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) for children infected with human immunodeficiency virus (HIV) were developed by a working group convened by the National Pediatric & Family HIV Resource Center (*1*). These guidelines addressed the need for prompt identification of infants born to HIV-infected women (i.e., HIV-exposed infants), measurement of such infants' CD4+ T-lymphocyte counts (CD4+ counts) and percentage of total lymphocytes (CD4+ percentage) first upon identification and then serially thereafter, and initiation of PCP prophylaxis based on age-associated CD4+ measurement values. In addition, the guidelines recommended that all children who had had a previous episode of PCP be maintained on prophylaxis, regardless of their CD4+ measurement values.

Since publication of these guidelines, additional data have been collected that address a) the specificity and sensitivity of CD4+ count thresholds for indicating risk for PCP, b) changes in CD4+ counts preceding an episode of PCP, c) correlation of CD4+ counts with CD4+ percentages, d) medications used for prophylaxis, and e) factors underlying the continued incidence of PCP among children. In March 1994, the

* Until September 1994, this organization was named the National Pediatric HIV Resource Center.

National Pediatric & Family HIV Resource Center, in collaboration with CDC, convened a working group to review this new information and to reevaluate the 1991 PCP prophylaxis guidelines for children. This report summarizes that information and presents the group's recommendations for PCP prophylaxis for children <13 years of age.

BACKGROUND

Identification of Children at Risk for PCP

Among children with perinatally acquired HIV infection, PCP occurs most often in infants 3–6 months of age (*2*). PCP in infants (i.e., children <12 months of age) is often acute in onset and results in a poor prognosis. Effective prevention of PCP among HIV-infected infants requires that exposure to HIV be identified either before or immediately following birth so that prophylaxis can be initiated before 2 months of age (the age at which the risk for PCP begins to increase dramatically) (*2*). The recent demonstration of the efficacy of zidovudine in lowering the rate of perinatal HIV transmission emphasizes the importance of identifying pregnant women with HIV infection as early as possible (*3*). Thus, through prenatal HIV counseling and voluntary testing, pregnant women who are infected with HIV can be offered interventions to a) maintain or improve their own health, b) reduce the risk for transmitting HIV infection to their children, and c) prevent PCP in their children if they also become infected.

At present, however, many HIV-exposed children are not identified early enough to be offered prophylaxis before the period of highest risk for PCP. Studies have indicated that only 35%–55% of HIV-exposed children have been identified by their health-care providers (*4–6*). A study of HIV-infected children diagnosed with PCP in the United States during 1991–1993 indicated that 59% of the children who had not received prophylaxis had not been identified as being at risk for HIV infection soon enough for prophylaxis to be initiated (*7*). Failure to identify and evaluate pregnant women with HIV infection and HIV-exposed children by early infancy substantially limits the effectiveness of any PCP prophylaxis strategy in preventing PCP among HIV-infected children.

CD4+ Count and PCP Among HIV-Infected Children

Data available when the 1991 prophylaxis guidelines were published indicated that approximately 10% of children diagnosed with PCP at <12 months of age had CD4+ counts of ≥1,500 cells/μL, the threshold for prophylaxis in this age group as defined in the 1991 guidelines. Recently published data, however, suggest that this percentage may be even higher among HIV-infected infants diagnosed with PCP at ≤6 months of age, the age at which most cases of PCP occur (*7–9*). Moreover, CD4+ counts can drop rapidly in infants during the few months preceding PCP diagnosis. For example, in one study of children with PCP, 26% of children <6 months of age had CD4+ counts of ≥1,500 cells/μL at the time of PCP diagnosis (Table 1) (*7*). In the same study, among 129 infants <1 year of age who had CD4+ counts measured before or at the time of PCP diagnosis, the estimated decline of CD4+ counts during the 3 months preceding the PCP diagnosis was 967 cells/μL (95% confidence interval=724–1,210 cells/μL) (*7*). Because HIV-infected infants <1 year of age are at risk for PCP even with CD4+ counts of ≥1,500 cells/μL and because these infants might have counts that drop to this level or

lower between measurements, the usefulness of CD4+ counts in determining the need for prophylaxis among infants in this age group is limited.

Few data are available regarding CD4+ counts at the time of PCP diagnosis for children >1 year of age. In three previously published studies of children who had PCP, one (5%) of 18 children 1–5 years of age had a CD4+ count of ≥500 cells/μL, and two (22%) of nine children 6–12 years of age had counts of ≥200 cells/μL (*10–12*). In a recent study, three (16%) of 19 children 1–5 years of age had CD4+ counts of ≥500 cells/μL at the time of PCP diagnosis; each of these three children had CD4+ counts that declined rapidly at approximately the time of PCP diagnosis (Table 1) (*7*). Also, all seven of the children ≥6 years of age who developed PCP had CD4+ counts of <200 cells/μL (Table 1).

Correlation of CD4+ Counts with CD4+ Percentages

Measurements of CD4+ percentages may be subject to less variation than those of CD4+ counts (*13*); thus, some clinicians prefer using CD4+ percentage to monitor immunosuppression in HIV-infected children. In the 1991 guidelines (*1*), the prophylaxis threshold of <20% that had been recommended previously for adolescents and adults (*14*) was also recommended for children. However, the potentially low sensitivity of this threshold for the risk for PCP among young children was recognized. Recently revised recommendations for PCP prophylaxis among adolescents and adults no longer include CD4+ percentage as a criterion for prophylaxis (*15*).

Data correlating CD4+ counts and percentages among HIV-infected children have been collected since 1991. These data have been used to develop a revised classification system for HIV infection among children that utilizes both CD4+ counts and percentages to categorize children by their level of immunosuppression (*16*) (Table 2).

TABLE 1. Number of children* with definitively diagnosed *Pneumocystis carinii* pneumonia (PCP), by age at PCP diagnosis and CD4+ T-lymphocyte count†§

CD4+ T-lymphocyte count (cells/μL)	Age (mos) at PCP diagnosis				
	0–5	6–11	12–23	24–71	≥72
≥1,500	*22*	*0*	*1*¶	*0*	*0*
750–1,499	22	5	*1***	*0*	*0*
500–749	8	4	0	*1*††	*0*
200–499	13	6	2	3	*0*
<200	21	5	3	8	7
Total	**86**	**20**	**7**	**12**	**7**

* Numbers in italics refer to children with CD4+ T-lymphocyte counts that exceed the threshold for prophylaxis in the 1991 guidelines (i.e., CD4+ counts of <1,500 cells/μL for children 1–11 months of age, <750 cells/μL for children ages 12–23 months, <500 cells/μL for children 24 months to 5 years of age, and <200 cells/μL for children ≥6 years of age).

† Measurements were taken within 2 months of PCP diagnosis.

§ CDC, unpublished data.

¶ A child 12 months of age who had a CD4+ count of 1,662 cells/μL when first measured (at the time of PCP diagnosis) and a CD4+ count of 832 cells/μL 3 months later.

** A child 18 months of age who had a CD4+ count of 1,010 cells/μL at the time of PCP diagnosis, preceded 5 months earlier (which was the most recent measurement) by a CD4+ count of 3,120 cells/μL.

†† A child 30 months of age who had a CD4+ count of 530 cells/μL at the time of PCP diagnosis, preceded 21 months earlier (which was the most recent measurement) by a CD4+ count of 3,514 cells/μL.

Correlation of these measurements has also allowed for determination of a CD4+ percentage level that is more indicative of severe immunosuppression in children.

Diagnosis of HIV Infection Among Children

HIV infection can be diagnosed among children ≥18 months of age by using standard HIV IgG antibody tests. However, because maternal IgG can be present in children <18 months of age, standard HIV-IgG serologic assays cannot be used to diagnose HIV infection in this age group. Advances in the development of viral detection assays, however, have made diagnosing HIV infection possible in nearly all infants by 4–6 months of age (*17*). The sensitivity of HIV culture or polymerase chain reaction (PCR) among infants is ≤50% during the first week after birth, but increases to >90% by age 3 months and to nearly 100% by 6 months of age (*17–20*). The use of these assays has been recommended for HIV-exposed children who are ≥1 month of age (*21*) because results of these assays can be used to diagnose HIV infection among infants (*16*).

Both the standard p24 antigen-capture assay and the immune-complex–dissociated, p24 antigen-capture assay are highly specific and can be used to diagnose HIV infection among infants (*16*). The sensitivity of the standard p24 antigen-capture assay, however, is low (i.e., <50%) in all age groups and therefore cannot be used to exclude HIV infection. Modification of the p24 antigen-detection assay by pretreating serum samples to dissociate antigen-antibody complexes has increased the sensitivity of this assay (*21,22*). However, because data concerning the sensitivity of this assay in early infancy are limited, use of this assay alone is not currently recommended to exclude HIV infection.

RECOMMENDATIONS

The revised guidelines for PCP prophylaxis for children who are infected with or perinatally exposed to HIV are based on similar considerations as the 1991 guidelines, including the age distribution of PCP among children, the rapid onset of PCP (especially among infants), the high mortality rate associated with PCP, and data regarding CD4+ counts and percentages among HIV-infected children. Based on these considerations and more recent data, the following guidelines are recommended for PCP prophylaxis among children <13 years of age.

TABLE 2. CD4+ T-lymphocyte counts and percentage of total lymphocytes corresponding to moderate and severe immunosuppression in human immunodeficiency virus (HIV)-infected children,* by age at CD4+ measurement (*16*)

Age at CD4+ measurement	Level of immunosuppression	
	Moderate	Severe
CD4+ count (cells/μL)		
≤11 mos	750–1,499	<750
1– 5 yrs	500–999	<500
6–12 yrs	200–499	<200
CD4+ percentage		
<13 yrs	15%–24%	<15%

*Persons <13 years of age.

Identifying Infants at Risk for HIV Infection

- Infants born to HIV-infected women should be identified promptly so that prophylaxis can be initiated before these infants are at risk for PCP. Diagnosing HIV infection among women before or during pregnancy is the most beneficial way to accomplish this goal. Early diagnosis not only allows for prompt evaluation of the need for PCP prophylaxis among the infants of HIV-infected women, but also gives such women the opportunity to access interventions that could a) maintain or improve their own health status and b) reduce the risk for transmitting HIV infection to their children (e.g., through antiretroviral therapy and avoidance of breastfeeding).
- If maternal HIV infection is not identified prenatally, pediatric health-care providers should identify infants born to HIV-infected women as soon as possible after birth so that PCP prophylaxis can begin promptly. Availability of and access to health care for both HIV-infected women and their newborns are essential to the implementation of an effective PCP prophylaxis strategy.

Diagnostic and Immunologic Monitoring of HIV-Exposed Infants

- All infants born to HIV-infected women should be monitored to determine their HIV infection status; the use of HIV culture or PCR is the preferred method for diagnosing HIV infection among infants (*21*). These assays should be performed at least twice: once at ≥1 month of age and once at ≥4 months of age. If the result of any test is positive, testing should be repeated to confirm diagnosis of HIV infection.
- Although the use of CD4+ counts and percentages is no longer recommended for determining the need for PCP prophylaxis among HIV-exposed infants <1 year of age (see Initiating PCP Prophylaxis Among HIV-Exposed Infants), other clinical considerations for such infants rely on these measurements. These include the assessment of such infants' immune status, risk for disease progression, and need for continued PCP prophylaxis after 1 year of age (see PCP Prophylaxis for HIV-Infected Children ≥12 Months of Age). Therefore, CD4+ counts and percentages should be measured in all HIV-exposed infants at 1 and 3 months of age (Table 3). CD4+ monitoring is not necessary after HIV infection has been reasonably excluded (see PCP Prophylaxis for Infants 4–12 Months of Age). For infants who have been diagnosed as HIV-infected and for those whose infection status has not yet been determined, CD4+ values should be monitored at 6, 9, and 12 months of age.

Initiating PCP Prophylaxis Among HIV-Exposed Infants

- All infants born to HIV-infected women should be started on PCP prophylaxis at 4–6 weeks of age, regardless of their CD4+ count (Table 3). Infants who are first identified as being HIV-exposed after 6 weeks of age should be started on prophylaxis at the time of identification. These recommendations are based on the following considerations: a) most cases of PCP among HIV-infected children occur in the first year of life; b) the risk for PCP begins to increase dramatically at age 2 months (when HIV infection cannot yet be reasonably excluded) (see PCP Prophylaxis For Infants 4–12 Months of Age); and c) the reliability of CD4+

counts in predicting which infants are at risk for PCP is relatively low during infancy—particularly among infants ≤6 months of age, the age at which the peak incidence of PCP occurs.

PCP prophylaxis should not be administered to infants <4 weeks of age because a) they are at low risk for PCP and b) the use of sulfa drugs among infants at this age is not advised because of the potential for adverse drug effects resulting from immature bilirubin metabolism. Additionally, the concurrent use of sulfa drugs among HIV-exposed infants who are receiving zidovudine during the first 6 weeks of life to prevent perinatal HIV transmission could potentially exacerbate the anemia that some children receiving zidovudine experience (*3*). Therefore, to avoid the potential for additional toxicity in such children, prophylaxis should be started at 6 weeks of age, the age at which zidovudine is discontinued.

PCP Prophylaxis for Infants 4–12 Months of Age

- All HIV-infected infants and infants whose infection status has not yet been determined should continue prophylaxis until 12 months of age.
- PCP prophylaxis should be discontinued among infants in whom HIV infection has been reasonably excluded on the basis of two or more negative viral diagnostic tests (i.e., HIV culture or PCR), both of which are performed at ≥1 month of age and one of which is performed at ≥4 months of age. In some clinical centers, these viral diagnostic tests are not available. For children who do not have

TABLE 3. Recommendations for PCP prophylaxis and CD4+ monitoring for human immunodeficiency virus (HIV)-exposed infants and HIV-infected children, by age and HIV-infection status

Age/HIV-infection status	PCP prophylaxis	CD4+ monitoring
Birth to 4–6 wks, HIV exposed	No prophylaxis	1 month
4–6 wks to 4 mos, HIV exposed	Prophylaxis	3 mos
4–12 mos		
HIV infected or indeterminate	Prophylaxis	6, 9, and 12 mos
HIV infection reasonably excluded*	No prophylaxis	None
1–5 yrs, HIV infected	Prophylaxis if: CD4+ count is <500 cells/μL or CD4+ percentage is <15%[§¶]	Every 3–4 mos[†]
6–12 yrs, HIV infected	Prophylaxis if: CD4+ count is <200 cells/μL or CD4+ percentage is <15%[¶]	Every 3–4 mos[†]

*HIV infection can be reasonably excluded among children who have had two or more negative HIV diagnostic tests (i.e., HIV culture or PCR), both of which are performed at ≥1 month of age and one of which is performed at ≥4 months of age, or two or more negative HIV IgG antibody tests performed at >6 months of age among children who have no clinical evidence of HIV disease.

†More frequent monitoring (e.g., monthly) is recommended for children whose CD4+ counts or percentages are approaching the threshold at which prophylaxis is recommended.

§Children 1–2 years of age who were receiving PCP prophylaxis and had a CD4+ count of <750 cells/μL or percentage of <15% at <12 months of age should continue prophylaxis.

¶Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PCP, such as children with rapidly declining CD4+ counts or percentages or children with Category C conditions (*16*). Children who have had PCP should receive lifelong PCP prophylaxis.

access to such testing, prophylaxis should be continued until 12 months of age unless HIV infection has been excluded on the basis of two or more negative HIV- antibody tests performed at ≥6 months of age (*16*).

PCP Prophylaxis for HIV-Infected Children ≥12 Months of Age

- All HIV-infected children ≥12 months of age should continue to have regular CD4+ monitoring to determine their need for PCP prophylaxis (Table 3).
- HIV-infected children and children whose infection status has not been determined should be evaluated at 12 months of age to determine their need for continued PCP prophylaxis.

  PCP prophylaxis should be continued after 12 months of age for HIV-infected children who have had any CD4+ measurement during the first 12 months of life indicating severe immunosuppression (i.e., a CD4+ count of <750 cells/μL or a CD4+ percentage of <15%). Prophylaxis should be discontinued at 12 months of age for HIV-infected children whose CD4+ measurements have been adequately monitored (Table 3) and have remained higher than these levels. PCP prophylaxis should also be discontinued for any child who is diagnosed as not being infected with HIV (*16*).
- Children who have received PCP prophylaxis from 12 to 24 months of age should be evaluated again at 24 months of age, and prophylaxis should be continued for those children who have had any CD4+ measurement indicating severe immunosuppression (i.e., a CD4+ count of <500 cells/μL or a CD4+ percentage of <15%). Prophylaxis should be discontinued at 24 months of age for HIV-infected children whose CD4+ measurements have been adequately monitored (Table 3) and have remained higher than these levels.
- HIV-infected children ≥12 months of age who are not receiving prophylaxis (e.g., those children whose infection was not identified previously or whose PCP prophylaxis was discontinued) should begin PCP prophylaxis if their CD4+ measurement indicates severe immunosuppression (Table 2).
- Initiation or continuation of prophylaxis should also be considered on a case-by-case basis for HIV-infected children ≥12 months of age who might otherwise be at risk for PCP, such as children with rapidly declining CD4+ counts or percentages or children with severely symptomatic HIV disease (i.e., Category C conditions [*16*]).

Prophylaxis Against PCP Recurrence

- HIV-infected children who have had an episode of PCP should receive lifelong PCP prophylaxis to prevent recurrence—regardless of CD4+ measurement or clinical status.

Recommended Chemoprophylaxis Regimens

- The recommended PCP chemoprophylaxis regimen for children is trimethoprim/sulfamethoxazole (TMP-SMX) (Box 1). When initiating TMP-SMX prophylaxis, a baseline complete blood count, differential count, and platelet count should be

obtained. These measurements should be repeated monthly while the child is receiving prophylaxis.

If TMP-SMX is not tolerated, alternative regimens should be followed. On the basis of recently compiled pharmacokinetics data, the revised recommended dosage of dapsone as an alternative regimen is 2 mg/kg/day. These data indicate that peak serum concentrations for children receiving chronic dosing of dapsone at 1 mg/kg/dose average 1.84 μg/mL, compared with average peak concentrations of 4.65 μg/mL for adults receiving the standard dose of 100 mg/day (*23,24*). The increased dose of dapsone is recommended so that peak concentrations will approach concentrations achieved at dosages recommended for adults (*15*).

PCP prophylaxis is an approved labeling indication by the U.S. Food and Drug Administration for oral TMP-SMX but not for the various other alternative regimens for PCP prophylaxis.

TMP-SMX has been shown to substantially reduce the risk for PCP among HIV-infected children (*25*). However, clinicians should be aware that some children have developed PCP despite the use of recommended prophylaxis (*26*).

BOX 1. Drug regimens for PCP prophylaxis for children ≥4 weeks of age

Recommended regimen:

Trimethoprim/sulfamethoxazole (TMP-SMX) 150 mg TMP/M^2/day with 750 mg SMX/M^2/day administered orally in divided doses twice a day (b.i.d.) 3 times per week on consecutive days (e.g., Monday-Tuesday-Wednesday).

Acceptable alternative TMP-SMX dosage schedules:

- 150 mg TMP/M^2/day with 750 mg SMX/M^2/day administered orally **as a single daily dose** 3 times per week on consecutive days (e.g., Monday-Tuesday-Wednesday).
- 150 mg TMP/M^2/day with 750 mg SMX/M^2/day orally divided b.i.d. and **administered 7 days per week.**
- 150 mg TMP/M^2/day with 750 mg SMX/M^2/day administered orally divided b.i.d. and administered 3 times per week on **alternate days** (e.g., Monday-Wednesday-Friday).

Alternative regimens if TMP-SMX is not tolerated:

- **Dapsone***

  2 mg/kg (not to exceed 100 mg) administered orally once daily.
- **Aerosolized pentamidine*** (children ≥5 years of age)

  300 mg administered via Respirgard II inhaler monthly.

*If neither dapsone nor aerosolized pentamidine is tolerated, some clinicians use **intravenous pentamidine** (4 mg/kg) administered every 2 or 4 weeks.

Education and Counseling

- Providing HIV counseling and voluntary testing to all pregnant women and providing comprehensive pediatric care for infants born to HIV-infected women are likely to be the most effective steps toward preventing PCP in children. The U.S. Public Health Service is recommending voluntary HIV counseling and testing of all pregnant women because of the prevention opportunities these services provide for women and their infants (*27*). For uninfected women, such counseling is intended to initiate or reinforce HIV risk-reduction behavior. For infected women, knowledge of their HIV infection status allows for more informed reproductive decisions, opportunities to reduce the risk for perinatal HIV transmission, and early diagnosis and treatment for themselves and their HIV-exposed infants. Early identification of HIV-exposed infants also allows for education of parents or other caregivers regarding treatment considerations, including PCP prophylaxis.
- An optimal PCP prophylaxis strategy requires consistent adherence to the chemoprophylaxis regimen by the child's parent or other caregiver. Such adherence is likely to be enhanced if the caregiver is knowledgeable about PCP and its prevention. Therefore, parents and other caregivers of HIV-exposed children should be provided information that addresses
  - how HIV infection is diagnosed among infants, including types and sensitivities of available tests;
  - the relatively high risk for PCP among young infants;
  - the frequently sudden onset and high mortality of PCP among infants;
  - drug regimens for PCP chemoprophylaxis, including efficacy and the frequency and nature of potential adverse effects;
  - the importance of starting prophylaxis in all HIV-exposed infants at 4–6 weeks of age, even when the diagnosis of HIV infection has not been established; and
  - the rationale for having different prophylaxis strategies for adults and children.

  Additionally, health-care providers should review the various acceptable alternative dosing schedules with the child's caregiver and make every effort to tailor the dosing regimen to fit the caregiver's schedule.

FUTURE NEEDS

These recommendations were developed on the basis of currently available data. Other strategies for prophylaxis might need to be considered in the future. Factors that might influence the need to modify these guidelines include the extent to which a) the incidence of PCP decreases following implementation of these recommendations and those for HIV counseling and testing of pregnant women; b) improvements in the sensitivity and availability of HIV diagnostic tests allow for diagnosis and exclusion of HIV infection in most HIV-exposed infants before the age of greatest risk for

PCP; and c) reduction in mother-to-infant HIV transmission through zidovudine therapy results in an increased number of HIV-exposed but uninfected infants receiving PCP prophylaxis.

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