Cotrimoxazole as a Prophylaxis for HIV Positive Malnourished Children

Summary of review

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The WHO (2004) estimates that Pnuemoncystis Carinii (PCP) accounts for about 20% of cases of severe pneumonia in HIV infected children and over one third of all HIV related deaths in infancy. Severe malnutrition may predispose patients to PCP. PCP can be prevented by cotrimoxazole prophylaxis. Despite explicit guidelines from WHO/UNAIDS on prophylactic cotrimoxazole (see box), and near universal use in developed countries, usage of cotrimoxazole for prophylaxis against opportunistic infections in children was only 1% in Africa in 2001. A recent review, conducted by Action Against Hunger (AAH) in Malawi, has examined the evidence for using cotrimoxazole as a prophylaxis for HIV positive malnourished children.

Current WHO/UNAIDS guidance on cotrimoxazole prophylaxis

The World Health Organisation (WHO) and the joint United Nations programme on HIV and AIDS (UNAIDS) now recommend that all children of HIV positive mothers receive prophylactic cotrimoxazole against PCP from 6 weeks of age and continue this therapy until exposure through breast milk ceases-and the infant is confirmed HIV negative (rarely before one year of age).

Cotrimoxazole should be offered to all HIV exposed infants from six weeks of age using the following criteria:

- Any child born to an HIV infected woman irrespective of whether the woman received antiretroviral therapy in pregnancy.
- Any child who is identified as being HIV infected within the first year of life by PCR, HIV serology or by clinical diagnosis of HIV infection (according to WHO/national guidelines).
- Children older than 15 months who have had a PCP event, have symptomatic HIV disease, an AIDS defining illness, or have CD4 percentage less than 15.

Provisional WHO/UNAIDS recommendations on the use of cotrimoxazole prophylaxis (trimethoprim and sulfamethoxazole) in adults and children living with HIV/AIDS in Africa state that cotrimoxazole should be used for prophylaxis in adults and children living with HIV/AIDS in Africa as part of a minimum package of care.
Evidence for the use of cotrimoxazole

There is an increasing body of evidence of the benefits of cotrimoxazole prophylaxis. Studies of cotrimoxazole prophylaxis in African adults, and of the recent CHAP (Children with HIV Antibiotic Prophylaxis) trial amongst Zambian children aged 1-14 years, have shown improved survival in people with HIV infection. In Cote d'Ivoire, daily administration of cotrimoxazole to adult patients who were both HIV positive and smear positive to TB significantly lowered, by almost half, the rates of death (46% decrease in risk of mortality, p<0.001) and admission to hospital (43%).

The Zambian CHAP trial has observed an overall reduction in mortality of 43% in children receiving cotrimoxazole as part of a placebo controlled trial, and reduced hospital admission by 23%. This has led to WHO, UNAIDS and UNICEF modifying current recommendations for cotrimoxazole prophylaxis. Interim recommendations endorse continued cotrimoxazole prophylaxis (due for expert technical review in early 2005).

Amongst African adults, PCP may be a less important opportunistic pathogen than TB and other infectious diseases that feature at an earlier stage of AIDS disease progression. Cotrimoxazole can particularly reduce bacterial disease and malaria, with potential benefit to uninfected infants as well as infants with HIV infection.

Problems and evidence of contraindications for cotrimoxazole

There are a number of potential/hypothetical drawbacks to mass cotrimoxazole prophylaxis, which include:

1. The efficacy of sulphonamide containing antimalarials could be reduced by mass cotrimoxazole prophylaxis.
2. Given its antimalarial activity, cotrimoxazole prophylaxis could impede the acquisition of natural malaria immunity by infants.
3. Further investigation is required into whether or not extensive use of cotrimoxazole accelerates resistance to cotrimoxazole and cross resistance to other drugs of some pathogens in the community, and the complexities of any such interactions.

Cotrimoxazole prophylaxis based solely on HIV exposure, without confirmation of HIV infection status, is likely the only option in resource poor settings and remains a trade off between possible benefit to the infant, versus the risk of resistance to antibiotics and antimalarials.
Adaptations based on evidence for and against

Infants under six months

The current guidelines in Malawi for the use of cotrimoxazole in children, recommend that cotrimoxazole prophylaxis should be administered to all infants born to HIV infected mothers from 6 weeks until 6 months of age (MOH 2004, based on WHO guidelines, 2002).

Infants over six months

Cotrimoxazole prophylaxis for HIV exposed and HIV infected children beyond age 6 months is a separate issue. PCP is less common in infants over six months and young children, and prophylaxis in this group might lead to substantial, and negative, effects on successful management of malaria and common bacterial infections. However due to difficulties with HIV diagnosis in infancy and the contributing risk of postpartum transmission of HIV, PCP could present before diagnosis of HIV can be confirmed. There is, therefore, a rationale for prophylaxis to all those who are HIV exposed.

Influence of testing on prophylaxis

CD4 testing, ideally used to decide on prophylaxis, is likely impractical in resource limited settings, while total lymphocyte count has not been proven as an accurate indicator of immune status in children. There is evidence that, in the African context, an HIV antibody test could be highly specific for infection as early as 6 months of age but this requires further research.

Malnutrition

No studies were identified by the review on the use of cotrimoxazole prophylaxis in HIV positive malnourished children. Follow-up anthropometric data collected in the CHAP trial has not yet been reported.

Cotrimoxazole has long been recommended as a prophylaxis for HIV positive severely malnourished children who are susceptible to serious invasive bacterial diseases and opportunistic infections such as PCP, and are prone to broken down or infected mucocutaneous surfaces and skin areas (the latter in kwashiorkor, especially). However, cotrimoxazole is likely to benefit those in the earlier rather than advanced stages of HIV disease.

Current Malawian guidelines for the management of severe malnutrition include systematic antibiotic treatment but do not include cotrimoxazole - experiences have found it to be no longer effective against established serious infection, resistance to cotrimoxazole is common, and bacteria causing small bowel bacteria overgrowth are better targeted by amoxicillin. However, the reviewed evidence suggests that it may still work as a prophylaxis, even when ineffective as a treatment but should not replace the systematic antibiotics use in therapeutic feeding.

Discussion

In many areas where 3 by 5 is being implemented, children will have limited access to ARVs. Although for an individual patient, prophylaxis of opportunistic infections does not confer the survival advantage of antiretroviral therapy, prophylaxis could have an important impact because of its low cost and ease of implementation.

From the CHAP trial and the Cote d'Ivoire study, there is a growing body of evidence that would suggest that all severely malnourished children who are found to be HIV positive should be on cotrimoxazole prophylaxis, and
the child should remain on cotrimoxazole indefinitely after discharge from therapeutic feeding. However, it remains to be seen whether cotrimoxazole prophylaxis is still indicated should the child gain access to antiretroviral therapy (ART) and show an improvement in their condition.

Recommendations As ACF is a leading organisation in the fight against severe malnutrition, and evidence has shown that HIV and severe malnutrition are inextricably linked, they should take the lead initiative in the integration of HIV care into the treatment of severe malnutrition.

In resource limited settings, emphasis should be placed on the demonstrated benefits of cotrimoxazole prophylaxis. ACF-International should initiate guidelines for the provision of cotrimoxazole to HIV positive malnourished children, through integrating HIV counselling and testing into TFCs and NRUs in high HIV prevalent countries. In order to ensure continued HIV care, links should be established with local health structures for continued provision of this drug and other services for the prevention and treatment of HIV related infections and severe malnutrition. By using TFCs/NRUs as an entry point and strengthening referral systems, services such as prevention of mother to child transmission (PMTCT), ART provision and community home based care (CHBC) can be utilised to maximum benefit to help prevent the vicious cycle of HIV infection and severe malnutrition.

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1 Cotrimoxazole as prophylaxis for HIV positive malnourished children, Action Against Hunger, January 2005, Malawi. By Susan Thurstans. This research was funded by the National AIDS Commission of Malawi


4 These have since been updated since the CHAP trial (ref:footnote 5).


8 See footnote 5

9 At the time of writing this article (March 2005), the Malawi guidelines were in the process of change which should be in place at time of print (May 2005). The revised guidelines recommend that all HIV exposed and infected children will receive cotrimoxazole indefinitely from six weeks of age, or in the case of the exposed, until a negative HIV result >18 months of age. Adults will start cotrimoxazole indefinitely if HIV +ve (stage 3 or 4) or CD4 count <500.

11 Since the revised Malawi guidelines (see footnote 8) support treating all exposed infants, testing will not be so much of an issue for this age-group in Malawi.


13 Global initiative of the World Health Organization and UNAIDS to provide antiretroviral therapy to 3 million people with HIV/AIDS in developing countries by the end of 2005.

14 See footnote 5