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Case management of HIV-infected severely malnourished children: challenges in the area of highest prevalence

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Malnutrition is an important contributing factor to 5·6 million of the 10 million child deaths a year, with severe malnutrition the cause of more than 1·5 million of these deaths.^{1,2} The *Lancet* Child Survival Series presented the clinical context and successful interventions for the most common causes of child deaths worldwide,³ but the case management of severely malnourished children was not addressed.³ As global efforts to achieve Millennium Development Goals 4 and 6 gather pace, and antiretroviral therapy (ART) becomes increasingly available, we have to respond to the additional challenge of severe malnutrition in the context of HIV infection. Working in child-health services in sub-Saharan Africa, we are seeing greater numbers of critically and chronically ill, severely malnourished children than before—higher than the numbers suggested recently.⁴ In the ideal situation, use of WHO therapeutic guidelines for management of severe malnutrition⁵ and a continuum of care for malnourished children⁶ through community therapeutic care programmes would successfully improve survival in children without HIV infection. An alarming consequence of the HIV epidemic is an increase in the need by severely malnourished, seriously ill children for facility-based treatment. Ready-to-use therapeutic foods that facilitate effective home-based therapy have resulted in recovery rates for uncomplicated severe malnutrition of more than 90%, with reported case-fatality rates of less than 5%;⁷ however, in sub-Saharan Africa mortality is three times higher in HIV-infected children with severe malnutrition than in non-infected children.^{8,9} The HIV pandemic in sub-Saharan Africa has substantially altered the epidemiology, clinical presentation, pathophysiology, case management, and survival of severely malnourished children. Case-fatality rates range from 20% to 50%, despite the use of WHO guidelines. Furthermore, severe erosion of health systems means that current guidelines are difficult to apply. New therapeutic guidelines, based on evidence from the region of highest HIV prevalence, are urgently needed.

The varied clinical presentation of HIV-uninfected children with malnutrition is determined by the complex interactions between specific nutrient deficiencies, infections, and stress within each individual. Decrease in food intake leads to wasting, with associated reduced function of body organs and systems, and an increased susceptibility to environmental perturbations or stress.¹⁰ In sub-Saharan Africa, HIV affects a wide age range of children, rendering them susceptible to infection and malnutrition. Although many of the metabolic responses are described in severe malnutrition, the responses in

HIV-infected malnourished children are largely unknown.¹¹

In the past, nutrition rehabilitation units typically admitted sick severely malnourished children during periods of food insecurity or in the post-weaning period (6–36 months old).⁶ In sub-Saharan Africa we now admit many HIV-infected malnourished children outside this range. Young HIV-infected severely malnourished infants are either perinatally infected with HIV, or inadequately fed, or both.¹² These infants present with multiple pathology and many have (persistent) diarrhoea, pneumonia, *Pneumocystis jirovecii* pneumonia, extensive skin infections, and oral thrush.¹³ Additionally, young children aged 3–6 years are often admitted with persistent diarrhoea. In such children, especially those presenting with profuse diarrhoea, case fatality is high and their response to management as set out in current guidelines is poor.¹⁴ Also, extremely wasted and stunted young adolescents, previously rarely admitted outside the setting of famine, are now admitted for nutritional recovery and present with chronic HIV-related multisystem disease.¹¹

Severe malnutrition and HIV infection often occur in a social milieu of extreme poverty and food insecurity, with the result that a high HIV infectious pressure affects even uninfected children because of their mothers' or caretakers' chronic disease and through children becoming orphaned. In Zambia and Malawi, more than half of patients admitted to many nutrition rehabilitation units are HIV positive, with case-fatality rates of 40% or higher.⁸ The percentage of readmissions is increasing. Hence, a dichotomy emerges in our patient population: the HIV-uninfected and HIV-infected children both present with severe malnutrition and comorbidity but have different pathophysiology, case-management, and referral pathways, presenting us with challenging therapeutic and care pathways, including palliative care.

In 2007, 50 clinical and child-health researchers and practitioners from various regions within sub-Saharan Africa gathered in Blantyre, Malawi, and established the Blantyre Working Group, which collectively care for more than 100 000 severely malnourished children per year; many have been trainers on WHO therapeutic guidelines. The group concluded that severe malnutrition in the HIV-infected child is a different clinical, in many cases chronic, entity, and has started to document geographic and regional variations in this new clinical spectrum. We identified five key areas for multicentre studies to establish a new evidence base for guidelines in their child-health systems in sub-Saharan Africa. We also recommended that, to improve prevention and treatment

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outcomes, and to update the currently outdated WHO therapeutic guidelines, substantial research on clinical and health services is needed to understand better the complex pathophysiological, metabolic, and pharmacological interactions.^{3,5,15}

Case fatality in severe malnutrition is high because of the concurrence of multiple infections^{16,17} and metabolic adaptations.¹⁰ When this synergism is compounded by HIV infection the case-fatality rate increases many times. Since early in-hospital mortality is high, improvements in initial treatment strategies will depend on improved knowledge of the cause of infection and antimicrobial susceptibilities,¹⁷ pharmacokinetics in malnourished children, and complex drug interactions and toxicities (eg, ART and therapy for tuberculosis). There are also currently inadequate data on the optimum regimen of supportive care (eg, for shock) in the malnourished child who has adapted to a reduced body mass and organ and system function.¹⁶ Antimicrobial sensitivity to first-line antibiotic treatment varies between centres, and currently recommended second-line antimicrobials might not be ideal.¹⁷ The effects of wide use of co-trimoxazole in HIV-infected populations is not yet certain.^{18,19} In South Africa, among children with community-acquired lower respiratory tract infection, tuberculosis was identified 22 times more often among HIV-infected children than in HIV-uninfected children;¹⁹ new approaches to diagnosis and treatment of tuberculosis are urgently needed.²⁰ In these children, tuberculin skin testing is insensitive, radiological appearances are non-specific, lymphocyte stimulation tests do not distinguish active from latent disease, sputum samples are difficult to obtain, and culture facilities are expensive and rarely available.²⁰

The introduction of therapeutic diets and appropriate rehydration fluids, including F₇₅, F₁₀₀, ReSoMal,¹⁵ and ready-to-use therapeutic foods^{3,7} has improved the rehabilitation process and shortened hospital stays of HIV-uninfected severely malnourished children and have addressed micronutrient and macronutrient deficiencies.²¹ However, the metabolic and nutrient needs of HIV-infected children should be made clear.²² In HIV-uninfected malnourished children, appetite is useful to assess nutritional recovery but this seems not to be the case in HIV-infected children, in whom persistent anorexia is common. Suitable feeding regimens are needed for severe diarrhoea, which is often associated with high case-fatality rates.^{14,23} Appropriate diets are also needed for the increasing number of severely malnourished infants under age 6 months, because unmodified F₇₅ and F₁₀₀ are unsuitable for them.¹⁵ The poor socioeconomic environments in which many such patients live contraindicate the safe use of commercial formulae.²⁴

Diarrhoea, often severe with rapid shifts in fluids and electrolytes, can be life threatening.²³ It is associated with gram-negative infections, zinc deficiency, malabsorption, enteropathy, and changes in intestinal flora.²⁵ In

HIV-uninfected children, adequate treatment regimens were developed to reduce diarrhoeal incidence, induce catch-up growth,²⁵ and improve outcome.²⁶ The spectrum of organisms associated with septicaemia²⁷ supports the importance of bacterial translocation in the pathogenesis of systemic septicaemia. Severe wasting makes clinical assessment of dehydration difficult, so the presence of metabolic acidosis and lethargy often point to the need for resuscitation.¹⁶

There are few prospective studies on the long-term outcomes of children with severe malnutrition,⁶ and almost none of severe malnutrition complicated by HIV. The role of ART in improving nutritional status is increasingly recognised. Although wasting can be treated in HIV-uninfected children with nutritional therapy alone, effective regimens for HIV-infected children need development.²⁸ The use of high-energy therapeutic feeds (eg, F₁₀₀ or ready-to-use therapeutic foods) is part of standard care for HIV-infected severely malnourished children, but mortality within 4–6 weeks remains unacceptably high (38%).⁸ Whether it is better to start ART before or after nutritional rehabilitation is unclear. Many children will gain weight with nutrition support alone. When available, CD4-cell count would help to identify those requiring treatment, since up to a quarter of severely malnourished children in food insecure settings will be above the threshold for initiation of ART.^{9,29} Those without WHO stage 3 or 4 HIV disease should be started on co-trimoxazole, but CD4-cell counts do not seem to rise after nutritional rehabilitation³⁰ and will continue to fall with disease progression. Immune reconstitution syndromes, recognised on recovery from severe malnutrition, tuberculosis, and HIV infection,³¹ are as yet poorly defined and present within a few weeks of starting treatment with clinical deterioration that can be fatal. Hence, the need for pharmacokinetic studies during recovery from malnutrition to confirm or establish the correct ART dosing and timing.

Community therapeutic care methods,³ strengthened by local production of ready-to-use therapeutic foods, require fewer staff to run programmes and ensure compliance; the HIV epidemic however has generated a new group of children requiring nutrition rehabilitation unit-based care. To develop regionally appropriate local child-health systems for maintaining this continuum of care, resources, treatment, the staff, salaries, and their education (higher education and on-the-job training) should be secured. These are important tasks for national health services and medical schools and nursing colleges, which require up-to-date learning materials and sufficient and appropriately qualified staff.¹⁵

The Blantyre Working Group recommends that studies be done on the optimum timing and dosing of ART, on the definition of the best therapeutic feeding regimens, and on the better understanding of the basis for treatment of acute and chronic infection and the metabolic changes in HIV-infected severely malnourished children. To

improve our understanding and to develop evidence-based guidelines for the management of severely malnourished children in areas of high HIV prevalence, child survival initiatives³² must be supportive. What is needed is a critical mass of collaborating interested clinical scientists (within a recognised scientific and educational network), well-equipped educational institutions, and support and funds to maintain this quest for child survival.³³ Much of this success will depend on local capacity building in the developing world and the generation of new evidence in this population. A call to action is urgently needed to defeat the scourge of HIV and severe malnutrition,³⁴ the commonest causes of child death in a large part of sub-Saharan African communities.

Blantyre Working Group

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References

- Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet* 2003; **361**: 2226–34.
- Collins S, Dent N, Binns P, et al. Management of severe acute malnutrition in children. *Lancet* 2006; **368**: 1992–2000.
- Briend A, Prudhon C, Weise Prinzo Z, et al. Putting the management of severely malnutrition back on the international health agenda. In: SCN Nutrition Policy paper no. 21: WHO, UNICEF, and SCN informal consultation on community-based management of severe malnutrition in Children. *Food Nutr Bull* 2006; **27**: S3–5.
- Black RE, Allan LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008; **371**: 243–60.
- WHO. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva: WHO, 1999.
- Heikens GT. Rehabilitation of sick malnourished children: environment, requirements, prognosis and feasibility. Amsterdam: University Press, Rozenberg Publishers, 2003.
- Manary MJ, Ndekha MJ, Ashorn P, et al. Home based therapy for severe malnutrition with ready-to-use food. *Arch Dis Child* 2004; **89**: 557–61.
- Bunn J, Kerac M. Excess mortality risk associated with HIV in a large Malawi nutritional rehabilitation unit. *Malawi Med J* 2007; **19**: 95.
- Chinkumbha J, Tomkins AM, Banda T, M Kangama K, Fergusson P. The impact of HIV on mortality during inpatient rehabilitation of severely malnourished children in Malawi. *Trans R Soc Trop Med Hyg* (in press).
- Jackson AA, Golden MHN. Chapter 8: severe malnutrition. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford textbook of medicine. Oxford: Oxford University Press, 1987: 12–28.
- Heikens GT. How can we improve the care for severely malnourished children in Africa? *PLoS Med* 2007; **4**: e45.
- Kafulafula G, Hoover DR, Taha TE, et al. Gastroenteritis-associated mortality with early weaning in HIV-1-uninfected children born to HIV-infected women in Malawi. www.medcol.mw/com/Abstracts.pdf (accessed March 17, 2008).
- Kessler L, Daley H, Malenga G, Graham SM. The impact of the human immunodeficiency virus type 1 on the management of severe malnutrition in Malawi. *Ann Trop Paediatr Int Child Health* 2000; **20**: 50–56.
- Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet* 2002; **360**: 1375–80.
- WHO. Severe malnutrition: report of a consultation to review current literature. Geneva: WHO, 2005.
- Maitland K, Berkley JA, Shebbe M, et al. Children with severe malnutrition: can those at highest risk of death be identified with the WHO protocol. *PLoS Med* 2006; **3**: e500.
- Abirekere-Iriso E, Musoke P, Kekitiinwa A. Bacteraemia in severely malnourished children in an HIV-endemic setting. *Ann Trop Paediatr Int Child Health* 2006; **26**: 319–28.
- Zar HJ, Hanslo D, Hussey G. The impact of HIV infection and trimethoprim-sulphamethoxazole prophylaxis on bacterial isolates from children with community-acquired pneumonia in South Africa. *J Trop Pediatr* 2003; **49**: 78–83.
- Madhi SA, Petersen K, Madhi A, et al. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. *Clin Infect Dis* 2000; **31**: 170–76.
- Marais BJ, Pai M. New approaches and emerging technologies in the diagnosis of childhood tuberculosis. *Paediatr Resp Rev* 2007; **8**: 124–33.
- Hsu JWC, Pencharz PB, Mcallan, Tomkins A. Macronutrients and HIV/AIDS: a review of current evidence. 2005. http://www.who.int/nutrition/topics/Paper_1_Macronutrients_bangkok.pdf (accessed March 19, 2008).
- Ciliberto MA, Sandige H, Ndekha MJ, et al. Comparison of home based therapy with ready-to-use therapeutic food with standard therapy in the treatment of malnourished Malawian children: a controlled, clinical effectiveness trial. *Am J Clin Nutr* 2005; **81**: 864–70.
- Amadi B, Kelly P, Mwiya M, et al. Intestinal and systemic infection, HIV, and mortality in Zambian children with persistent diarrhoea and malnutrition. *J Pediatr Gastroenterol Nutr* 2001; **32**: 550–54.
- Andresen E, Rollins NC, Sturm AW, et al. Bacterial contamination and over-dilution of commercial infant formula prepared by HIV-infected mothers in a prevention of mother-to-child transmission (PMTCT) programme, South Africa. *J Trop Pediatr* 2007; **53**: 409–14.
- Heikens GT, Schofield WN, Christie CD, et al. Morbidity in malnourished children given metronidazole and a high energy supplement during rehabilitation in the community. *Eur J Clin Nutr* 1993; **47**: 174–91.
- Chhagan MK, Kauchali S. Co-morbidities and mortality among children hospitalized with diarrheal disease in an area of high prevalence of human immunodeficiency virus infection. *Pediatr Infect Dis J* 2006; **25**: 333–38.
- Brent AJ, Oundo JO, Mwangi I, Ochola L, Lowe B, Berkley JA. salmonella bacteraemia in Kenyan children. *Pediatr Infect Dis J* 2006; **25**: 230–36.
- Miller TL, Evans SJ, Orav EJ, Morris V, McIntosh K, Winter HS. Growth and body composition in children infected with HIV-1. *Am J Clin Nutr* 1993; **57**: 588–92.
- WHO. Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV related disease in adults and children. Geneva: WHO, 2006.
- Hughes S, Amadi B, Mwiya M, Nkamba H, Goldblatt D, Tomkins A. CD4 counts of severely malnourished children: their relationship to clinical syndromes and response to nutritional rehabilitation. *Arch Dis Child* 2006; **91** (suppl 1): A15.
- Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. *Int J Tuberc Lung Dis* 2007; **11**: 417–23.
- Victoria CS, Black RE, Bryce J. Learning from new initiatives in maternal child health. *Lancet* 2007; **370**: 1113–14.
- Heikens GT, Molyneux E, Broadhead RL, Rollins N, Adhikari M. Research challenges to improve maternal and child survival. *Lancet* 2007; **369**: 2159.
- Heikens GT, Amadi BC, Manary M, Rollins N, Tomkins A. Nutrition interventions need improved operational capacity. *Lancet* 2008; **371**: 181–82.