Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial

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Summary

Background Children with complicated severe acute malnutrition (SAM) have a greatly increased risk of mortality from infections while in hospital and after discharge. In HIV-infected children, mortality and admission to hospital are prevented by daily co-trimoxazole prophylaxis, despite locally reported bacterial resistance to co-trimoxazole. We aimed to assess the efficacy of daily co-trimoxazole prophylaxis on survival in children without HIV being treated for complicated SAM.

Methods We did a multicentre, double-blind, randomised, placebo-controlled study in four hospitals in Kenya (two rural hospitals in Kilifi and Malindi, and two urban hospitals in Mombasa and Nairobi) with children aged 60 days to 59 months without HIV admitted to hospital and diagnosed with SAM. We randomly assigned eligible participants (1:1) to 6 months of either daily oral co-trimoxazole prophylaxis (given as water-dispersible tablets; 120 mg per day for age <6 months, 240 mg per day for age 6 months to 5 years) or matching placebo. Assignment was done with computer-generated randomisation in permuted blocks of 20, stratified by centre and age younger or older than 6 months. Treatment allocation was concealed in opaque, sealed envelopes and patients, their families, and all trial staff were masked to treatment assignment. Children were given recommended medical care and feeding, and followed up for 12 months. The primary endpoint was mortality, assessed each month for the first 6 months, then every 2 months for the second 6 months. Secondary endpoints were nutritional recovery, readmission to hospital, and illness episodes treated as an outpatient. Analysis was by intention to treat. This trial was registered at ClinicalTrials.gov, number NCT00934492.

Findings Between Nov 20, 2009, and March 14, 2013, we recruited and assigned 1778 eligible children to treatment (887 to co-trimoxazole prophylaxis and 891 to placebo). Median age was 11 months (IQR 7–16 months), 306 (17%) were younger than 6 months, 300 (17%) had oedematous malnutrition (kwashiorkor), and 1221 (69%) were stunted (length-for-age *Z* score <–2). During 1527 child-years of observation, 122 (14%) of 887 children in the co-trimoxazole group died, compared with 135 (15%) of 891 in the placebo group (unadjusted hazard ratio [HR] 0·90, 95% CI 0·71–1·16, p=0·429; 16·0 *vs* 17·7 events per 100 child-years observed (CYO); difference –1·7 events per 100 CYO, 95% CI –5·8 to 2·4]). In the first 6 months of the study (while participants received study medication), 63 suspected grade 3 or 4 associated adverse events were recorded among 57 (3%) children; 31 (2%) in the co-trimoxazole group and 32 (2%) in the placebo group (incidence rate ratio 0·98, 95% CI 0·58–1·65). The most common adverse events of these grades were urticarial rash (grade 3, equally common in both groups), neutropenia (grade 4, more common in the co-trimoxazole group), and anaemia (both grades equally common in both groups). One child in the placebo group had fatal toxic epidermal necrolysis with concurrent *Pseudomonas aeruginosa* bacteraemia.

Interpretation Daily co-trimoxazole prophylaxis did not reduce mortality in children with complicated SAM without HIV. Other strategies need to be tested in clinical trials to reduce deaths in this population.

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Introduction

Severe acute malnutrition (SAM) contributes to 1 million childhood deaths annually worldwide and its treatment is a key target for reducing childhood mortality.[1] Infectious disease is thought to be the main mediator of mortality in children with SAM. A short course of oral antibiotics given to children with uncomplicated SAM treated as outpatients reduced mortality and treatment failure in Malawi.[2] However, a short course of antibiotics had no effect on these outcomes in Niger,[3] although it did markedly reduce admission to hospital and improve early weight gain.

Children with SAM who have signs of infection or present with one or more Integrated Management of Childhood Illness danger signs,[4] or do not pass an appetite test are classified as having complicated SAM, and WHO recommends that they should be initially treated in hospital—empirical antibiotics, treatment of

Research in context

Evidence before this study

Children who are admitted to hospital with complicated severe acute malnutrition (SAM) are at greatly increased risk of mortality from common infections, including for a long period after discharge. Results from several randomised clinical trials in Africa have shown that daily co-trimoxazole reduces long-term all-cause mortality and readmissions to hospital among children who are susceptible to serious infections because of HIV. There is also evidence that antimicrobials improve growth. We aimed to investigate the efficacy of co-trimoxazole prophylaxis in children without HIV being treated for complicated SAM. We searched PubMed for randomised trials without date or language restrictions using the MeSH terms "child", "malnutrition", "mortality", "clinical trials as topic", "anti-infective agents", or "anti-bacterial agents". We identified two clinical trials of short-course antibiotic treatment in children with uncomplicated SAM treated as outpatients, but no previous clinical trials of longer-term antimicrobial prophylaxis to prevent mortality in children with complicated SAM after stabilisation. Generally, adequate evidence for the effectiveness of most interventions in children with SAM was absent or inconclusive.

Added value of this study

In our study, daily co-trimoxazole prophylaxis was well tolerated, but not effective at preventing mortality or morbidity, or improving nutritional recovery, in children aged 60 days to 59 months without HIV being treated for complicated SAM. However, some infections were prevented. Infants with complicated SAM had an especially high mortality during 1 year of follow-up, despite medical and nutritional care. Our results were different to those from trials of children with HIV, but similar to trials with children exposed to HIV but not infected. This outcome suggests that the interactions between antimicrobial prophylaxis, infections, and mortality depend on the specific immunopathology.

Implications of all the available evidence

SAM without HIV infection is not an indication for daily co-trimoxazole prophylaxis. To reduce mortality in children with complicated SAM will require a greater understanding of the condition and testing of other strategies in clinical trials.

specific medical conditions, and specialised therapeutic feeding are given.[5] Once complications have resolved and appetite returns, children continue therapeutic feeding as outpatients.

Complicated SAM is typically associated with a high inpatient mortality.[6,7] However, even after provision of recommended treatment, apparent stabilisation, and discharge from hospital, children with SAM still retain a markedly increased risk of death. In Malawi, despite the provision of recommended medical and nutritional therapy, 17% of children with SAM (and without HIV) died within 1 year.[8] In Bangladesh, among children with SAM and pneumonia, 9% died in hospital and a further 9% died within 3 months after discharge from hospital.[9] Increased mortality after hospital discharge also occurs outside the context of SAM and is a generally recognised occurrence that might exceed inpatient mortality in resource-poor settings.[10] In rural Kenya, children admitted to hospital had 7·7 times greater mortality in the year after discharge than community peers who were not admitted.[11]

Among children who are susceptible to infection because of HIV, daily co-trimoxazole prophylaxis reduced all-cause mortality and hospital admissions in two studies,[12,13] despite high levels of antimicrobial resistance being identified in vitro among invasive isolates at the study sites. Co-trimoxazole protected children with HIV against malaria, pneumonia, and sepsis.[14] In other contexts, co-trimoxazole prevented recurrent urinary tract infections,[15] pneumonia in children with measles,[16] and infections in children with specific immune deficiencies.[17] Co-trimoxazole is inexpensive, widely available, and has a known safety profile.[14]

Findings from a systematic review have shown beneficial effects of antimicrobials in children, including co-trimoxazole, on linear and ponderal growth, possibly by reducing nutrient diversion from subclinical infections and inflammation, and preventing or treating overt infections.[18] Antibiotics are also widely used in animal husbandry to promote growth. However, important potential harms might occur from the long-term use of antibiotics, including toxicity and exacerbation of antimicrobial resistance. Hence, for their use to be justified, major potential benefits such as a reduction in mortality in high-risk groups of children should be targeted.[19]

We therefore tested our hypothesis that daily co-trimoxazole prophylaxis would reduce mortality and morbidity, and improve nutritional recovery, in children without HIV being treated for complicated SAM.

Methods

Study design and participants

We did a two-arm, multicentre, double-blind, randomised, placebo-controlled trial in four hospitals in Kenya (two rural hospitals in Kilifi, one urban hospital in Mombasa, and one in Nairobi). The study protocol is available in the supplement to this Article. All the study hospitals provided inpatient care for SAM, and outpatient therapeutic and supplementary feeding clinics supported by UNICEF or Concern Worldwide. In Kenya, *Haemophilus influenzae* type b conjugate vaccine was introduced in 2001 and pneumococcal conjugate vaccine (PCV, 10-valent) was introduced during this trial in March, 2011.