Antibiotics as part of the management of severe acute malnutrition

Summary of published research

Mothers receive instruction on how to administer antibiotics

Location: Malawi

What we know already: There is a high prevalence of clinically significant infections among children hospitalised for severe malnutrition (complicated cases).

What this article adds: Routine inclusion of antibiotics as part of the outpatient management of children with uncomplicated severe acute malnutrition at high infection risk (HIV prevalent) is warranted. Further investigation of longer term outcomes and high risk groups is needed.

International consensus guidelines now recommend the use of ready-to-use therapeutic food (RUTF) in outpatient settings as the preferred management for uncomplicated cases of severe acute malnutrition (SAM). Despite the markedly better outcomes observed with this revised outpatient regimen, 10-15% of children still do not recover, even in the context of rigorously controlled clinical trials. Even modest improvements in recovery and mortality rates could mean thousands of lives saved annually. Many studies, but not all, have shown a high prevalence of clinically significant infections among children hospitalised for severe malnutrition. This observation has led to treatment guidelines recommending the use of routine antibiotic agents even for children treated as outpatients, although outpatients are presumably much less likely to have a systemic infection than are patients with complicated cases that require inpatient care. This recommendation for the use of routine antibiotics is based on expert opinion and has not been directly tested in a clinical trial.

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A paper has recently been published on a prospective clinical trial to determine whether the routine administration of oral antibiotics as part of the outpatient management of SAM in children in Malawi was associated with improved outcomes.

The study enrolled children from December 2009 through January 2011 at 18 feeding clinics in rural Malawi. Each child’s weight, length, and mid-upper arm circumference (MUAC) were measured. Children who were 6 to 59 months of age, with oedema (indicative of kwashiorkor), a weight-for-height z score of less than -3 (indicative of marasmus) or both (marasmic kwashiorkor), were eligible for enrolment. Each eligible child was given a 30g test feeding of RUTF under the supervision of a nurse to verify that the child was an appropriate candidate for outpatient therapy. Children who were too ill to consume the test dose in the clinic were hospitalised for inpatient management.

The study was a randomised, double-blind, placebo-controlled clinical trial which compared nutritional and mortality outcomes among children with uncomplicated SAM who received treatment as outpatients with or without antibiotics. One intervention group received 80 to 90 mg of amoxicillin suspension per kg per day, divided into two daily doses; a second intervention group received approximately 14 mg of cefdinir suspension per kg per day, divided into two daily doses. The dose to be given to each child was based on a rounded amount that could be given by the field research pharmacist using the markings on a plastic syringe. The control group received placebo twice daily. Caregivers were instructed to administer the study drug in addition to RUTF during the initial seven days of therapy. Baseline characteristics of the enrolled children were similar among the three groups.

A total of 924 children were randomly assigned to the amoxicillin group, 923 to the cefdinir group, and 920 to the placebo group. Caregivers for more than 98% of the children reported that the child completed the entire 7-day course of the study regimen.

**Findings**

Overall, 88.3% of the children enrolled in the study recovered from SAM. Children with marasmic kwashiorkor recovered less frequently and had higher mortality rates than children with either kwashiorkor or marasmus. The proportion of children who recovered was significantly lower among those who received placebo than among those who received either amoxicillin (3.6 percentage points lower; 95% confidence interval [CI], 0.6 to 6.7) or

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cefidine (5.8 percentage points lower; 95% CI, 2.8 to 8.7). Deaths accounted for the largest proportion of children who did not recover in each study group and for each type of SAM. The overall mortality rate was 5.4%, but the rate was significantly higher among children who received placebo than among those who received either amoxicillin (relative risk, 1.55; 95% CI, 1.07 to 2.24) or cefdinir (relative risk, 1.80; 95% CI, 1.22 to 2.64). No significant differences in the causes of death, as reported by verbal autopsy (i.e., a structured investigation of events leading to the death), were identified among the three study groups. Although the point estimates for nutritional recovery were higher and those for death were lower among children who received cefdinir than among those who received amoxicillin, these differences were not significant (P = 0.22 for recovery and P = 0.53 for death, for the comparison of amoxicillin and cefdinir by logistic regression).

Kaplan–Meier survival analysis for all children in the study showed that the time to recovery was shorter in the cefdinir group than in the amoxicillin group or the placebo group and was shorter in the amoxicillin group than in the placebo group. Similarly, children who received an antibiotic agent survived longer than those who received placebo.

Weight gain from enrolment until the second follow-up visit (or until the one follow-up visit for children with only one) was significantly higher among children who received cefdinir than among those who received placebo. Children who received either antibiotic agent also had greater increases in MUAC than did those who received placebo.

As compared with children who did not recover, those who recovered were significantly older and were more likely to have their father alive and still in the home. Among children with marasmus or marasmic kwashiorkor, those with the MUAC and the lowest weight-for-height z score at enrolment were most likely to have treatment failure or to die. Children with the lowest height-for age z score were least likely to recover. Although only 874 of 2765 children (31.6%) were tested for HIV, those who were known to be HIV-seropositive, especially if not receiving antiretroviral therapy, had the highest risks of treatment failure and death. Acute infectious symptoms and poor appetite both at enrolment and at the first follow-up visit were also associated with an increased risk of treatment failure.

The amoxicillin used in this study cost an average of $2.67 per child. The cost of cefdinir was $7.85 but presumably would be lower if it were used on a large scale.

The results suggest that children with uncomplicated SAM who qualify for outpatient therapy remain at risk for severe bacterial infection and that the routine inclusion of antibiotics as part of their nutritional therapy is warranted. Further studies are needed to evaluate long-term outcomes of routine antibiotic use in children with uncomplicated SAM and to determine whether a specific high-risk target population can be better defined.


Taken from Field Exchange 45

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