Antibiotics Cut Death Rates in Children with Malnutrition

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Study Overview

Objective. To determine the therapeutic efficacy of antibiotics when added to ready-to-use therapeutic food (RUTF) in the treatment of uncomplicated severe acute malnutrition (SAM) in pediatric outpatient populations.

Design. Randomized, double-blind, placebo-controlled trial.

Settings and participants. Researchers enrolled children with uncomplicated cases of SAM at 18 feeding clinics in rural Malawi. Children presenting to the clinics were measured for weight, height, and mid-upper arm circumference. Eligible patients were 6 to 59 months of age presenting with kwashiorkor (edema), marasmus (weight-for-height z score of less than –3), or both (marasmic kwashiorkor) and able to receive outpatient treatment (assessed on their ability to successfully consume a 30-g test feeding of RUTF). Eligible patients were enrolled upon written and oral consent from their caretakers.

Intervention: All patients received 175 kcal of RUTF per kilogram of body weight daily. Study personnel provided extra allotments of RUTF if the household included a healthy child with whom the food might be shared. In addition, subjects were randomized using computer-generated block randomization to receive one of the following study drugs during the first 7 days: 80 to 90 mg/kg/day of amoxicillin suspension, 14 mg/kg/day of cefdinir suspension, or placebo. Caretakers were counseled to deliver the medication in a plastic syringe marked for a rounded amount of the calculated dose twice daily.

Children received a 2-week supply of RUTF and were scheduled for follow-up visits every 2 weeks for up to 6 follow-up visits, at which time study personnel repeated anthropomorphic measurements and asked caretakers about the child's history since the last visit and adherence to the intervention. Community health workers and a member of the study team visited the homes of those who did not return for follow-up visits. Children without bipedal pitting edema and with weight-for-height z scores of –2 or higher were considered to have recovered and completed the study while those that continued to have edema and a z score below –2 at follow-up visits remained in the study and received an additional 2-week supply of RUTF until the next follow-up assessment. Children whose condition worsened or were still malnourished after 6 follow-up visits were referred for inpatient care.

Main outcome measures. Nutritional recovery and mortality rates were the main outcome measures and

were assessed using intention-to-treat analyses. Secondary outcomes included weight and length gains, adverse events, and time to recovery. A planned subgroup analysis explored the interaction between types of SAM and interventions on the main outcome measures.

Results. Out of 3212 children identified, 2767 met the inclusion criteria. Mean age was 20.1 months, and 70.3% had kwashiorkor, 20.9% had marasmus, and 8.8% had marasmic kwashiorkor. Baseline characteristics in the 3 treatment arms were similar with regards to age, mother as primary caretaker, breast-feeding status, type of SAM, height-for-age z score, and HIV status. Caretakers reported less frequent cough from children who received amoxicillin vs. placebo (25% for amoxicillin vs. 35% for placebo, $P = 0.001$) while children who received cefdinir vs. placebo had lower rates of diarrhea (32% for cefdinir vs. 40% for placebo, $P < 0.001$). Caretakers also reported higher rates of cough and diarrhea at the first follow-up visit from children who received placebo vs. those who received antibiotics. The majority (88.3%) of study participants recovered from severe acute malnutrition while 11.7% did not recover during the study; of those, 1.9% remained acutely malnourished, 2.2% dropped out, 2.3% were hospitalized, and 5.4% died. The mortality rate was higher in children receiving the placebo vs. amoxicillin (relative risk 1.55; 95% CI 1.07–2.24) and placebo vs. cefdinir (relative risk 1.80; 95% CI 1.22–2.64). Similarly, treatment failure was higher in younger children receiving placebo vs. amoxicillin (relative risk 1.32; 95% CI 1.04–1.68) and placebo vs. cefdinir (relative risk 1.64; 95% CI 1.27–2.11). No significant difference was found in mortality between the 2 antibiotic groups ($P = 0.53$ for death by logistical regression).

Children who received cefdinir were much more likely to gain weight from enrollment to the second follow-up visit and had greater increases in mid-upper-arm circumference than those in the other treatment arms. Three adverse events presumed to be from antibiotic reactions were reported (generalized papular rash from amoxicillin and thrush and bloody diarrhea from cefdinir). The average recovery time was 29 ± 19 days and did not differ significantly between intervention arms. The type of malnutrition was associated with weight gain and mortality rates; children with marasmic kwashiorkor gained weight more slowly than children with kwashiorkor or marasmus. The study found no interaction between type of SAM and intervention group for either mortality or nutritional recovery.

Conclusion. Children with SAM treated with antibiotics and RUTF had less treatment failure and lower levels of mortality when compared with children treated with RUTF alone in the outpatient setting.

Commentary

Mortality rates due to severe acute malnutrition are high; more than 1 million children die from SAM annually [1]. RUTF, an energy-dense paste of peanuts, milk powder, oil, sugar, and a micronutrient supplement, is easy and safe to use in resource-limited settings and has transformed the treatment of malnutrition. Research has shown RUTF to be effective for the treatment of SAM in several populations and settings including in home-based rehabilitation of severely malnourished children in emergency situations [2]. Given the high rates of infection seen in malnourished children, treatment guidelines recommend the addition of antibiotics to RUTF in the treatment of SAM [3]. However, it was previously unclear if antibiotics reduced mortality and whether the benefits outweighed the potential risks of adverse reactions and antibiotic resistance seen globally [4].

This large, well-designed, randomized controlled study demonstrated a significant mortality benefit with few adverse outcomes, thus supporting the addition of antibiotics to RUTF for the treatment of SAM. While a previous smaller study showed no benefit of routine amoxicillin therapy in addition to RUTF in outpatient SAM treatment, differences in baseline characteristics between the treatment and control groups may have confounded the results [5]. However, longitudinal studies are needed to gauge the long term effects of antibiotic exposure in this population.

The mechanism of action of antibiotics in this study needs to be examined further. While antibiotics are often given in conjunction with RUTF to treat presumed bacterial co-infections, antibiotics may also have a metabolic impact mediated by the changes in the microbiome. There is emerging evidence of a relationship between host physiology and microbiota [6] involving gut metabolism and energy harvesting [7,8]. For over half a century, farmers have given low doses of antibiotics to animals in order to increase their ability to

absorb nutrients and gain weight [9]. Infant antibiotic exposure has also been associated with increased body mass during early childhood [10]. A study of identical twins in Malawi showed divergence for kwashiorkor despite similar diets [11]. Furthermore, researchers have observed that transplantation of fecal microbiota of Malawian children with kwashiorkor into germ-free mice, in combination with the typical Malawian diet, cause symptoms of malnutrition in the mice. Meanwhile, mice that receive fecal microbiota from kwashiorkor patients who are then fed RUTF do not suffer from malnutrition [11]. Germ-free mice that receive microbiota from healthy samples show no symptoms. This growing body of evidence suggests that lack of food is not the sole cause of malnutrition and implicates a causal role of gut microbiota in kwashiorkor. Thus, the antibiotics used in this study potentially impact SAM by changing a child's microbiome. Further investigation is needed to better understand the pathophysiology of malnutrition, the potential role of microbiota, and the mechanisms by which antibiotics may help to mitigate this epidemic.

Applications for Clinical Practice

This study supports the use of antibiotics in conjunction with RUTF in the treatment of malnutrition in children. Further studies are needed to explore long-term effects of antibiotics in uncomplicated cases of severe acute malnutrition and the mechanisms by which antibiotics exert their therapeutic effect.

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