e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(2); 1604-1612

Original Research Article

# Routine Amoxicillin for UncomplicatedSevere Acute Malnutrition in Children in MTC (Malnutrition Treatment Center) Government Medical College Chittorgarh

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**Received: 25-11-2023 / Revised: 23-12-2023 / Accepted: 26-01-2024**
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**Conflict of interest: Nil**

**Abstract:**

**Background:** High-quality evidence supporting a community-based treatment protocol for children with severe acute malnutrition, including routine antibiotic use at admission to a nutritional treatment program, remains limited. In view of the costs and consequences of emerging resistance associated with routine antibiotic use, more evidence is required to support this practice.

**Methods:** In a double-blind, placebo-controlled trial in MTC (Malnutrition treatment center) GMC Chittorgarh. We randomly assigned children who were 6 to 59 months of age and had uncomplicated severe acute malnutrition to receive amoxicillin or placebo for 7 days. The primary outcome was nutritional recovery at or before week 8.

**Results:** A total of 2412 children underwent randomization, and 2399 children were included in the analysis. Nutritional recovery occurred in 65.9% of children in the amoxicillin group (790 of 1199) and in 62.7% of children in the placebo group (752 of 1200). There was no significant difference in the likelihood of nutri- tional recovery (risk ratio for amoxicillin vs. placebo, 1.05; 95% confidence interval [CI], 0.99 to 1.12; P = 0.10). In secondary analyses, amoxicillin decreased the risk of transfer to inpatient care by 14% (26.4% in the amoxicillin group vs. 30.7% in the placebo group; risk ratio, 0.86; 95% CI, 0.76 to 0.98; P=0.02).

**Conclusions:** We found no benefit of routine antibiotic use with respect to nutritional recovery from uncomplicated severe acute malnutrition in MTC (Malnutrition treatment center) GMC Chittorgarh.

**Keywords:** Children 6 months to 59 months, uncomplicated SAM, Amoxicillin.



## Introduction

Severe acute malnutrition affects approximately 19 million children under 5 years of age worldwide and contributes substantially to mortality and the disease burden among children. [1] To reduce the risk of death from severe acute malnutrition, specialized nutritional and medical intervention is required. Bacterial infection can complicate advanced cases of severe acute malnutrition, [2-9] and the risk of nosocomial infection in inpatient settings can be high. Therefore, in 1999, when all children with severe acute malnutrition were treated as inpatients, the World Health Organization (WHO) recommended routine use of broad-spectrum antibiotics for the management of severe acute malnutrition, irrespective of clinical indications. [10]

Infection remains one of the most important causes of death in children with SAM, both during the initial management and in the months following completion of treatment. In an attempt to reduce this high mortality, antibiotics are routinely given to children admitted to hospital with complicated SAM and are also recommended for children receiving outpatient treatment.

However, more recent developments have changed the nutritional and clinical profile of children treated for severe acute malnutrition. In 2006, the development of the WHO Child Growth Standards led to a substantial advance in the measurement of nutritional status, and the number of children classified as having severe acute malnutrition is now 4 to 5 times as high as the number before the introduction of the standards, depending on the context; since implementation of the standards, the weight-for- height z scores are higher and medical complications are fewer. [11,12] In 2007, the WHO and the United Nations endorsed a community-based model for the management of malnutrition,

in which children with uncomplicated severe acute malnutrition are treated at home with ready-to- use therapeutic food (RUTF). [13] Community-based treatment emphasizes community mobilization and the finding of active cases, with the goal of reaching greater numbers of malnourished children before clinical complications arise.

## Methods

### Study Site and population

The study was conducted at MTC (Malnutrition treatment center) GMC Chittorgarh. All children presenting to the study centers who were candidates for outpatient treatment of severe acute malnutrition were eligible for inclusion if they lived within 15 km of the center, were available for the 12-week study period, had not been admitted to a nutritional program within the previous 3 months or received any antibiotic within the previous 7 days, had no clinical complications requiring antibiotic treatment, and had no congenital abnormalities. Written informed consent was obtained from each child's parent or legal guardian. The criteria for outpatient treatment of severe acute malnutrition were an age between 6 and 59 months; a weight-for-height z score of less than −3 according to the 2006 WHO Growth Standards, a mid-upper-arm circumference of less than 115 mm, or both; sufficient appetite according to a test feeding of RUTF; and an absence of clinical complications requiring hospitalization, including bipedal edema.

### Study Design and Interventions

This study was a randomized, double-blind, placebo-controlled trial with the primary aim of examining the effect of routine antibiotic use, as compared with placebo, on nutritional recovery from uncomplicated severe acute malnutrition. Amoxicillin was chosen as the active study medication in accordance with current national guidelines.

Children were randomly assigned, in a 1:1 ratio and in computer-generated blocks of six, to receive amoxicillin (80 mg per kilogram of body weight per day, divided into two daily doses) or placebo for 7 days. The randomization codes were created with a computerized random number generator according to site; kept inside opaque, sealed, consecutively numbered envelopes; and opened by a study physician in numerical order. A study nurse administered the first dose of the study medication at the health center and instructed the caregiver in administration of the remaining doses at home. Adherence was evaluated at the first weekly visit through direct questioning of the caregiver and review of a pictorial calendar recording home administration of the study medication. Amoxicillin and placebo were indistinguishable in color and packaging. All clinical and research staff members were unaware of the treatment assignments.

### Study procedures

All children received standard care for outpatient treatment of uncomplicated severe acute malnutrition, as specified in national guidelines. In brief, at the time of admission to the nutritional program, children received RUTF (170 kcal per kilogram per day) and routine medicines. Follow-up in the nutritional program was conducted weekly at the health center for a minimum of 3 weeks. During these visits, a medical history was obtained, and a physical examination and anthropometric assessment were performed. [16] Children were transferred to inpatient care if they had any clinical complication requiring inpatient management, weight loss of more than 5%, or both between two consecutive visits or if they had no weight gain after 2 weeks. Weekly follow-up data were censored at the time of transfer to inpatient care, but vital status was assessed 2 weeks and 4 weeks after the date of transfer. Children were seen at the study health centers at 4, 8, and 12 weeks after study enrollment, regardless of their status in the nutritional program; physical examination, history taking, and anthropometric assessment were repeated at these follow-up visits.

### Laboratory Testing

We collected stool, urine, and blood samples at admission to the nutritional program. In light of the low prevalence of bacterial infection and the relatively high burden of biologic sampling among young children, the data and safety monitoring board recommended obtaining samples from a subset of 1000 children over a period of 12 months. Samples were transported to Sri Sawaliyaji Govt District Hospital, Chittorgarh Laboratory, and plated on culture medium for incubation on the day of collection. [17] Pathogenic bacteria were identified with the use of standard biochemical techniques, and antimicrobial susceptibility was assessed by means of disk diffusion. [18]

Bacteremia and bacteriuria were defined as positive blood and urine cultures, respectively. Bacterial gastroenteritis was defined as a stool culture that was positive for a known pathogen and diarrhea. Results of confirmed bacteremia or bacteriuria were made available to the clinical teams within 1 to 3 days. A home visit was made the same day or the next day to determine the clinical status of the child, and appropriate treatment was provided.

### Study Outcomes

The primary outcome was nutritional recovery by 8 weeks. Nutritional recovery was documented at or after 3 weeks if a child had a weight-for- height z score of −2 or higher on two consecutive visits and a mid-upper-arm circumference of 115 mm or

greater; if there was no acute complication or edema for at least 7 days; and if the child had completed all antibiotic and anti-malarial treatments at the time of discharge from the nutritional program.

Secondary outcomes included non-response at 8 weeks, death from any cause, default (defined as three or more consecutive missed weekly visits), and transfer to inpatient care. Non response was documented if a child did not meet the criteria for nutritional recovery at 8 weeks.

**Statistical Analysis**

We calculated that a sample of 1005 children in each group would provide the study with 80% power at a two-sided alpha level of 0.05 to detect a between-group difference in nutritional recovery of at least 5%, assuming an 80% likelihood of nutritional recovery in the amoxicillin group. Allowing for a 20% rate of loss to follow-up, we estimated that we would need to include 1206 children in each group. With an observed likelihood of recovery of 63%, the study had 73% power to detect a 5% difference between groups. All analyses were based on the intention-to-treat principle.

Risk ratios and 95% confidence intervals for each secondary outcome were calculated by means of unadjusted log-binomial regression.19 Between-group comparisons of time to recovery, transfer to inpatient care, and death among children without a response were performed with the use of t-tests. We assumed that the pharmacologic effect of amoxicillin would be greatest in the first 2 weeks after administration and there- fore calculated the intervention effect on the likelihood of nutritional recovery and transfer to inpatient care within 2 weeks after admission to the nutritional program. We also assumed that the pharmacologic effect of amoxicillin would be greatest among children with bacterial infection at admission to the nutritional program; therefore, we calculated the intervention effect on the likelihood of nutritional recovery and transfer to inpatient care among children with laboratory-confirmed infection.

In additional post hoc analyses, we used a likelihood-ratio test to determine whether the intervention effect varied according to age at baseline (<24 months vs. ≥24 months) and sex.

Intervention effects on additional secondary outcomes, including individual signs of infection and gains in weight, height, and mid-upper-arm circumference, were assessed at weeks 1 and 2. Signs of infection included diarrhea (≥3 loose stools in the previous 24 hours), vomiting, fever (axillary temperature >38.5°C), cough, tachypnea, and malaria with fever. We estimated average differences between the groups for gains from baseline (i.e., admission to the nutritional program) in weight, height, and mid-upper-arm circumference at weeks 1, 2, and 4 and at the time of discharge from the nutritional program. The intervention effect was compared between groups with the use of a t-test for weight gain; linear regression, adjusted for baseline anthropometric data, for gains in height and mid-upper-arm circumference; and unadjusted binomial regression for signs of infection. Intention-to-treat analyses were used; all tests were two-sided, with no adjustments for multiple comparisons.

**Results**

**Study patients**

Between October 2022 and November 2023, a total of 16,421 children presented at the four health centers (Fig. 1). A total of 2412 children were randomly assigned to a study group, 13 were subsequently excluded for protocol violations, and 2399 children (1199 in the amoxicillin group and 1200 in the placebo group) were included in the final analysis. Baseline characteristics were similar in the two groups, with no clinically relevant differences (Table 1). All caregivers received voluntary HIV counseling and testing; 1 child was confirmed to be HIV-positive and was included in the study. Program outcome was attributed to all children at 8 weeks after admission to the nutritional program. The rate of reported adherence, defined as completion of all 7 days of the study regimen, was 99% and did not differ significantly between the two groups (P>0.05).

**Primary Outcome**

Overall, 64% of the children enrolled in the study (1542 of 2399) recovered from severe acute malnutrition. There was no significant between-group difference in the likelihood of nutritional recovery (risk ratio with amoxicillin vs. placebo, 1.05; 95% confidence interval [CI], 0.99 to 1.12) (Table 2). Among children who recovered, the time to recovery was significantly shorter with amoxicillin than with placebo, with a mean treatment duration of 28 days versus 30 days (P<0.001). Amoxicillin had no significant effect among children with a confirmed bacterial infection at admission to the nutritional program (Table S1 in the Supplementary Appendix) and the effect did not vary significantly according to age or sex (P>0.05 for interaction).

**Secondary Outcomes**

The risks of non-response at 8 weeks, default, and death were similar in the two groups (Table 2). There was a significant interaction of age in the risk of death (P= 0.04 for interaction); amoxicillin tended to reduce the risk of death among children who were 24 months of age or older (risk ratio0.24; 95% CI, 0.03 to 2.12) but not among children

younger than 24 months of age (risk ratio, 3.04; 95% CI, 0.61 to 15.01). A total of 13 children died during treatment (7 in the amoxicillin group and 6 in the placebo group) (Table 2); the time to death did not differ significantly between the groups (29 days in the amoxicillin group and 18 days in the placebo group, P= 0.40). Amoxicillin significantly decreased the over- all risk of a transfer to inpatient care and the risk of a transfer within the first 2 weeks (Table 2, and Table S2 in the Supplementary Appendix). There was no significant between-group difference in the meantime to a transfer to inpatient care (25 days in the amoxicillin group and 24 days in the placebo group, P = 0.62). We found no intervention effect among children who were transferred to inpatient care for weight loss or lack of weight gain, but amoxicillin significantly reduced the risk of a transfer for clinical complications in general (by 31%) and for acute gastroenteritis in particular (by 33%). The study intervention had no effect on the risk of a transfer to inpatient care among children with any bacterial infection, and there was no evidence of a heterogeneous effect according to age or sex. No cases of severe allergy or anaphylaxis were identified. None of the clinical complications or deaths were reported to be related to the study drug. Amoxicillin significantly accelerated early gains in weight and mid-upper-arm circumference, with no significant effect on height gain during treatment (Table 3). The frequency of diarrhea was lower in the amoxicillin group than in the placebo group at week 1, with no significant effect of amoxicillin on the incidence of other clinical symptoms. The overall prevalence of bacterial infection in blood, urine, and stool from children with diarrhea was low (Table 4). The likelihood of resistance to amoxicillin was 35% for enterobacteria isolated from stool in children with diarrhea and 66% for enterobacteria isolated from blood.

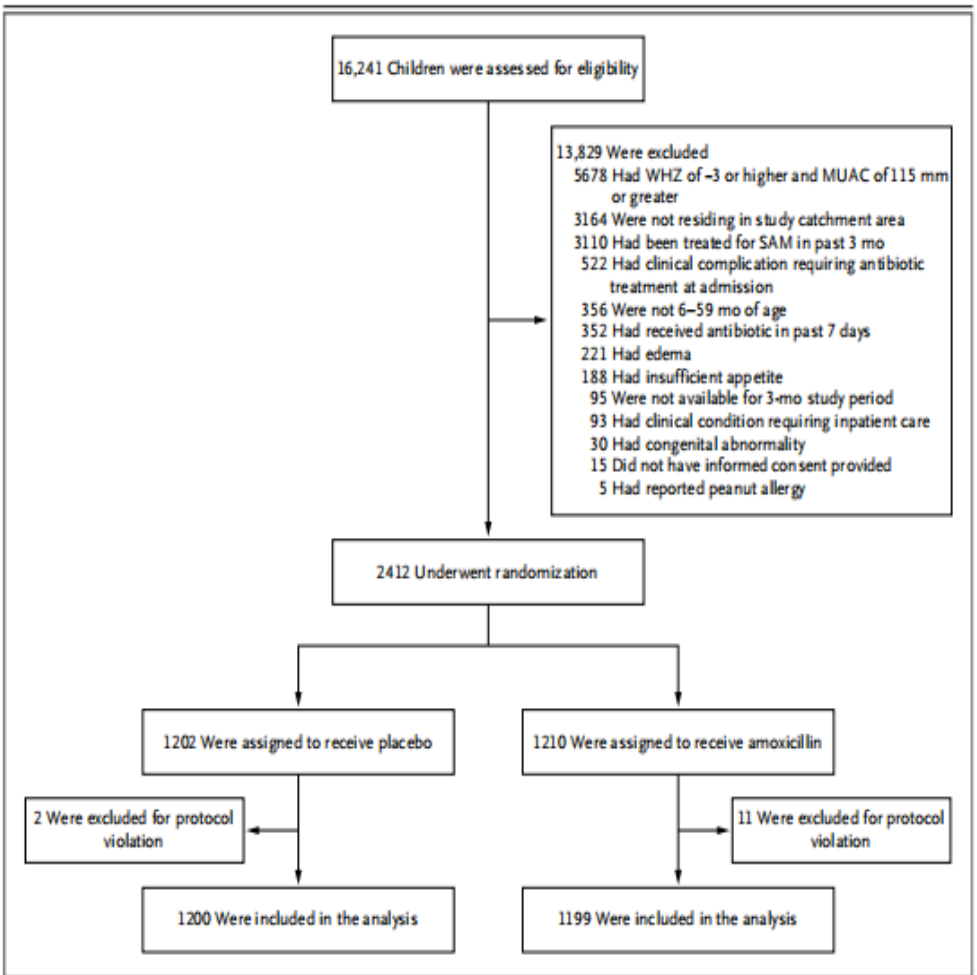


Figure 1. Numbers of Children Who Were Assessed for Eligibility, Randomly Assigned to a Study Group, and Included in the Analysis.

MUAC denotes mid-upper-arm circumference, SAM severe acute malnutrition, and WHZ weight-for-height z score.

**Figure 1:**

**Table 1: Baseline Characteristics of the Study Participants**

| Characteristic | Total (N = 2399) | Amoxicillin (N = 1199) | Placebo (N = 1200) |
|---|---|---|---|
| **Sociodemographic characteristics** | | | |
| Age | | | |
| Child — mo | 16.7±8.6 | 16.8±8.4 | 16.6±8.7 |
| Mother — yr | 26.8±6.7 | 26.6±6.6 | 27.1±6.9 |
| Female sex — no. (%) | 1196 (49.9) | 600 (50.0) | 596 (49.7) |
| Maternal level of education ≥6 yr — no. (%) | 50 (2.1) | 34 (2.8) | 16 (1.3) |
| No. of household members | 7.3±3.8 | 7.2±3.8 | 7.4±3.8 |
| **Anthropometric data** | | | |
| Weight-for-height z score | | | |
| Mean score | −3.1±0.6 | −3.1±0.6 | −3.1±0.6 |
| Score below −3 — no. (%) | 1469 (61.2) | 733 (61.1) | 736 (61.3) |
| Mid-upper-arm circumference | | | |
| Mean circumference — mm | 112±5 | 112±5 | 112±4 |
| Circumference <115 mm — no. (%) | 1869 (77.9) | 929 (77.5) | 940 (78.3) |
| Height-for-age z score | | | |
| Mean score | −3.0±1.2 | −3.0±1.2 | −3.0±1.3 |
| Score below −2 — no. (%) | 1897 (79.1) | 956 (79.7) | 941 (78.4) |
| **Clinical characteristics and medical history** | | | |
| Hemoglobin <11.0 g/dl — no. (%) | 1747 (72.8) | 869 (72.5) | 878 (73.2) |
| Rapid diagnostic test positive for malaria — no. (%) | 1327 (55.3) | 652 (54.4) | 675 (56.2) |
| Axillary temperature >38.5°C — no. (%) | 112 (4.7) | 63 (5.3) | 49 (4.1) |
| Signs of infection in previous 24 hr — no. (%) | | | |
| Diarrhea | 759 (31.6) | 385 (32.1) | 374 (31.2) |
| Vomiting | 138 (5.8) | 71 (5.9) | 67 (5.6) |
| Cough | 387 (16.1) | 208 (17.4) | 179 (14.9) |
| Seen at health facility in previous 30 days — no. (%) | 509 (21.2) | 250 (20.9) | 259 (21.6) |
| Child currently breast-feeding — no. (%) | 1510 (62.9) | 751 (62.6) | 759 (63.2) |
| **Bacteriologic findings at admission to nutritionalprogram** | | | |
| Bacterial gastroenteritis — no./total no. (%) | 114/1090 (10.5) | 56/544 (10.3) | 58/546 (10.6) |
| Bacteremia — no./total no. (%) | 41/1087 (3.8) | 22/541 (4.1) | 19/546 (3.5) |
| Bacteriuria — no./total no. (%) | 26/789 (3.3) | 12/380 (3.2) | 14/409 (3.4) |

*Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the twostudy groups except for maternal level of education (P=0.01).

**Table 2: Treatment Outcomes According to Study Group**

| Outcome | Amoxicillin Placebo (N = 1199) (N = 1200) No. (%) | | Risk Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| Nutritional recovery | 790 (65.9) | 752 (62.7) | 1.05 (0.99–1.12) | 0.10 |
| Nonresponse at 8 wk | 72 (6.0) | 64 (5.3) | 1.13 (0.81–1.56) | 0.48 |
| Death | 7 (0.6) | 6 (0.5) | 1.17 (0.39–3.46) | 0.78 |
| Default† | 14 (1.2) | 10 (0.8) | 1.40 (0.62–3.14) | 0.41 |
| Transfer to inpatient care‡ | 316 (26.4) | 368 (30.7) | 0.86 (0.76–0.98) | 0.02 |
| Weight loss or no weight gain | 285 (23.8) | 320 (26.7) | 0.89 (0.78–1.02) | 0.10 |
| Clinical complication | 90 (7.5) | 130 (10.8) | 0.69 (0.54–0.90) | 0.01 |
| Acute gastroenteritis | 53 (4.4) | 79 (6.6) | 0.67 (0.48–0.94) | 0.02 |
| Respiratory infection | 17 (1.4) | 21 (1.8) | 0.81 (0.43–1.53) | 0.52 |
| Severe malaria | 7 (0.6) | 7 (0.6) | 1.00 (0.35–2.84) | 1.00 |
| Other§ | 19 (1.6) | 26 (2.2) | 0.68 (0.38–1.21) | 0.19 |
| Transfer to inpatient care <2 wk after admissionto nutritional program | 41 (3.4) | 66 (5.5) | 0.62 (0.42–0.91) | 0.01 |

* Risk ratios and 95% confidence intervals are based on unadjusted binomial regression.

† Default was defined as three or more consecutive missed weekly visits.

‡ Children were transferred to inpatient care if they had weight loss or no weight gain, a clinical complication, or both.
§ Other clinical complications included skin infections, the nephrotic syndrome, injuries, and urinary tract infections, viral in- fections, anemia, and worsening of clinical state.

**Discussion**

In this double-blind, randomized, placebo controlled trial; we found that routine provision of amoxicillin was not superior to placebo for nutritional recovery in children with uncomplicated severe acute malnutrition.

This finding challenges the view that routine antibiotic therapy is always necessary or beneficial. Considering the burden of infection and limitations in the local capacity for adequate medical follow-up, eliminating routine antibiotic use could represent an important simplification of treatment, resulting in substantial cost savings with respect to drugs, staff, and systems for delivery and encouraging expanded service provision and responsible antibiotic stewardship. Driven by numerous factors, including imprudent antibiotic use, resistance to antibiotics can result in infections that are especially difficult and costly to treat. [20,21] Our study showed that amoxicillin reduced the risk of a transfer to inpatient care by 14%, as compared with placebo. Further review revealed three important insights. First, 53% of children transferred to inpatient care according to the study protocol (49% in the amoxicillin group and 56% in the placebo group) were admitted to a hospital (Table S2 in the Supplementary Appendix).

Owing to multiple considerations, including operational constraints such as limited capacity, only 50% of children who were eligible for inpatient care because of weight loss or lack of weight gain were admitted. Amoxicillin reduced the risk of hospitalization, potentially a more specific and generalizable secondary end point than a transfer to inpatient care, by 24%, as compared with placebo (risk ratio, 0.76; 95% CI, 0.62 to 0.92). Second, among hospitalized children, there were no significant between-group differences in the mean length of stay (4.9 days in the amoxicillin group and 4.4 days in the placebo group, P= 0.32) or the rate of recovery (94% and 96%, respectively).

Children in both groups recovered quickly, suggesting that adequate inpatient care may mitigate any risk associated with the absence of routine antibiotic use. Third, amoxicillin specifically reduced the risk of transfers to inpatient care for clinical complications due to gastroenteritis.

This was an unexpected finding, since the viruses and parasites primarily responsible for gastroenteritis in young children are not sensitive to amoxicillin. [23] A possible explanation is that poor mucosal integrity in malnourished children allows the translocation of bacteria across compromised intestinal surfaces, resulting in bacteremia. [2,24,25]

Alternatively, oral antibiotics may reduce excessive proliferation of small- bowel flora, [26] modifying the composition and function of the gut microbiome.

**Table 3: Anthropometric Data and Signs of Infection According to Study Group**

| Variable | Amoxicillin | Placebo | Mean Differenceor Risk Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| **Anthropometric data** | | | | |
| Weight gain after admission to nutritional program (g/kg/day) | | | | |
| Week 1 | 11.1±7.7 | 7.3±7.6 | 3.8 (3.1–4.4) | <0.001 |
| Week 2 | 7.0±4.3 | 5.7±4.4 | 1.2 (0.9–1.6) | <0.001 |
| Week 4 | 5.0±2.5 | 4.5±2.6 | 0.5 (0.3–0.7) | <0.001 |
| Program discharge | 4.9±3.9 | 4.0±4.1 | 0.9 (0.5–1.2) | <0.001 |
| Gain in length or height after admission (mm/day) | | | | |
| Week 1 | −0.01±0.38 | 0.01±0.32 | −0.02 (−0.04–0.01) | 0.29 |
| Week 2 | 0.01±0.17 | 0.01±0.14 | 0.00 (−0.01–0.01) | 0.95 |
| Week 4 | 0.16±0.20 | 0.16±0.19 | 0.01 (−0.01–0.02) | 0.38 |
| Program discharge | 0.11±0.16 | 0.11±0.15 | 0.00 (−0.01–0.01) | 0.86 |
| Gain in mid-upper-arm circumference after admission (mm/day) | | | | |
| Week 1 | 0.57±0.49 | 0.36±0.46 | 0.21 (0.17–0.25) | <0.001 |
| Week 2 | 0.39±0.31 | 0.31±0.31 | 0.08 (0.05–0.10) | <0.001 |
| Week 4 | 0.32±0.20 | 0.28±0.20 | 0.04 (0.02–0.05) | <0.001 |
| Program discharge | 0.30±0.27 | 0.24±0.28 | 0.06 (0.04–0.08) | <0.001 |
| **Signs of infection** | | | | |
| Diarrhea — no./total no. (%) | | | | |
| Week 1 | 38/1180 (3.2) | 78/1185 (6.6) | 0.49 (0.33–0.71) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Week 2 | 78/1151 (6.8) | 68/1140 (6.0) | 1.14 (0.83–1.56) | 0.43 |
| Vomiting — no./total no. (%) | | | | |
| Week 1 | 15/1180 (1.3) | 28/1185 (2.4) | 0.54 (0.29–1.00) | 0.05 |
| Week 2 | 15/1151 (1.3) | 22/1140 (1.9) | 0.67 (0.35–1.30) | 0.24 |
| Cough — no./total no. (%) | | | | |
| Week 1 | 84/1180 (7.1) | 108/1185 (9.1) | 0.78 (0.59–1.03) | 0.08 |
| Week 2 | 91/1151 (7.9) | 105/1140 (9.2) | 0.86 (0.66–1.12) | 0.27 |
| Tachypnea — no./total no. (%)† | | | | |
| Week 1 | 14/1180 (1.2) | 9/1185 (0.8) | 1.56 (0.68–3.60) | 0.29 |
| Week 2 | 9/1151 (0.8) | 4/1140 (0.4) | 2.23 (0.69–7.22) | 0.18 |
| Fever — no./total no. (%) | | | | |
| Week 1 | 15/1180 (1.3) | 25/1185 (2.1) | 0.60 (0.32–1.14) | 0.12 |
| Week 2 | 28/1151 (2.4) | 22/1140 (1.9) | 1.26 (0.73–2.19) | 0.41 |
| Malaria with fever — no./total no. (%) | | | | |
| Week 1 | 8/1173 (0.7) | 16/1179 (1.4) | 0.50 (0.22–1.17) | 0.11 |
| Week 2 | 20/1147 (1.7) | 16/1137 (1.4) | 1.24 (0.65–2.38) | 0.52 |

*Plus–minus values are means ±SD. Mean differences and 95% confidence intervals are shown for gains from baseline (i.e., admission to the nutritional program) in anthropometric data.

Gains were calculated with the use of t-tests (for weight gain) or linear regression adjusted for baseline data (for gains in height and mid-upper-arm circumference). Risk ratios and 95% confidence intervals are shown for signs of infection and are based on unadjusted binomial regression.

† Tachypnea was measured in children who were 6 to 11 months of age as a respiratory rate of more than 50 breaths per minute and in children who were 12 to 59 months of age as a rate of more than 40 breaths per minute. The values shown are the average of the two mean.

**Table 4: Bacteriologic Status and Antibiotic Resistance at Admission to Nutritional Program**

| **Bacteriologic Status** | **Total** | **Amoxicillin Resistance number/total number (percent)** | **Amoxicillin–Clavulanate** |
|---|---|---|---|
| Bacterial gastroenteritis* | 114/1090 (10) | | |
| Enterobacteria | 66/114 (58) | 40/114 (35) | 10/114 (9) |
| Campylobacter | 55/114 (48) | 5/114 (4) | 0/114 |
| Bacteremia | 41/1087 (4) | | |
| Enterobacteria | 34/41 (83) | 27/41 (66) | 6/41 (15) |
| Pneumococcus | 4/41 (10) | 0/41 | 0/41 |
| Staphylococcus species other than S. aureus | 3/41 (7) | 0/41 | 0/41 |
| Bacteriuria | 26/789 (3) | | |
| Enterobacteria | 24/26 (92) | 21/26 (81) | 4/26 (15) |
| Pseudomonas aeruginosa | 1/26 (4) | 1/26 (4) | |
| Enterococcus | 1/26 (4) | 0/26 | |

* The total number of children infected by type-specific bacteria is greater than the total number of children with bacterialgastroenteritis, because multiple types of bacteria were identified in seven children.

We found that routine amoxicillin use provided some benefit over placebo in terms of short-term weight gain. The greater early weight gain in the amoxicillin group appeared to contribute to a slightly faster time to recovery (mean, 2 days). However, without evidence of longer-term effects on weight or height, the early growth-promoting benefits of routine antibiotic use may be limited.

Our study has several key limitations. First, we assumed a likelihood of nutritional recovery of 80%, which was not achieved, and we cannot rule out the possibility that amoxicillin had a protective effect of 12% or a harmful effect of 1% on nutritional recovery. Second, although the study was not designed to estimate the effect on mortality, mortality was lower than expected and previously reported. Third, the study was limited to one regimen, which was consistent with the national protocol. We therefore leave unanswered the question of whether alternative antibiotic regimens, such as a regimen with a dosage that accounts for altered pharmaco kinetics in severely malnourished children [28,29] or a regimen that minimizes the emergence of resistant strains, could have maximized recovery. Finally, the study interventions were performed by well-trained and supervised medical personnel and there was close follow-up, features that may not be generally

representative of standard care provided in many nutritional programs. Our findings should be confirmed in studies designed to reflect real-life contexts.

In conclusion, we found no significant benefit of routine amoxicillin use with respect to nutritional recovery among children with un- complicated severe acute malnutrition in MTC (Malnutrition treatment center) GMC Chittorgarh. Our findings provide useful information for public health authorities and their implementing partners regarding the routine use of antibiotics in the treatment of uncomplicated severe acute malnutrition.

## References


1. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013; 382:427-51.
2. Bachou H, Tylleskär T, Kaddu-Mulind- wa DH, Tumwine JK. Bacteraemia among severely malnourished children infected and uninfected with the human immuno- deficiency virus-1 in Kampala, Uganda. BMC Infect Dis 2006; 6:160.
3. Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. N Engl J Med 2005; 352:39-47.
4. Brent AJ, Ahmed I, Ndiritu M, et al. In- cidence of clinically significant bacteraemia in children who present to hospital in Ke- nya: community-based observational study. Lancet 2006; 367:482-8.
5. Hill PC, Onyeama CO, Ikumapayi UN, et al. Bacteraemia in patients admitted to an urban hospital in West Africa. BMC Infect Dis 2007; 7:2.
6. Hossain MI, Dodd NS, Ahmed T, et al. Experience in managing severe malnutri- tion in a government tertiary treatment fa- cility in Bangladesh. J Health Popul Nutr 2009; 27:72-9.
7. Noorani N, Macharia WM, Oyatsi D, Revathi G. Bacterial isolates in severely malnourished children at Kenyatta Na- tional Hospital, Nairobi. East Afr Med J 2005; 82:343-8.
8. Friedland IR. Bacteraemia in severely malnourished children. Ann Trop Paediatr 1992; 12:433-40.
9. Wolf BH, Ikeogu MO, Vos ET. Effect of nutritional and HIV status on bacteraemia in Zimbabwean children who died at home. Eur J Pediatr 1995; 154:299-303.
10. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva: World Health Organization, 1999.
11. Isanaka S, Villamor E, Shepherd S, Grais RF. Assessing the impact of the in- troduction of the World Health Organiza- tion growth standards and weight-for- height z-score criterion on the response to treatment of severe acute malnutrition in children: secondary data analysis. Pe- diatrics 2009; 123(1):e54-9.
12. WHO child growth standards and the identification of severe acute malnutrition in infants and children: a joint statement by the World Health Organization and the United Nations Children's Fund. Geneva: World Health Organization, 2009.
13. Community-based management of se- vere acute malnutrition. Geneva: World Health Organization, the World Food Pro- gram, the United Nations System Standing Committee on Nutrition, and the United Nations Children's Fund, 2007.
14. Guideline: update on the manage- ment of severe acute malnutrition in in- fants and children. Geneva: World Health Organization, 2013.
15. Trehan I, Goldbach HS, LaGrone LN, et al. Antibiotics as part of the management of severe acute malnutrition. N Engl J Med 2013; 368:425-35.
16. The WHO Child Growth Standards. Geneva: World Health Organization (http:// www.who. int/childgrowth/standards/en).
17. Page AL, de Rekeneire N, Sayadi S, et al. Infections in children admitted with com- plicated severe acute malnutrition in Niger. PLoS One 2013;8(7):e68699.
18. Comité de l'Antibiogramme de la So- ciété Française de Microbiologie Recom- mandations 2012. Paris: Société Française de Microbiologie, 2012.
19. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005; 162:199-200.
20. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis 2013; 13:1057-98.
21. Laxminarayan R, Heymann DL. Chal- lenges of drug resistance in the developing world. BMJ 2012; 344:e1567.
22. Annual medical report. Madarounfa District, Niger: Ministry of Health, 2014.
23. Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in de- veloping countries (the Global Enteric Mul- ticenter Study, GEMS): a prospective, case- control study. Lancet 2013; 382:209-22.
24. Blomberg B, Manji KP, Urassa WK, et al. antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study. BMC Infect Dis 2007; 7:43.
25. Graham SM, English M. Non-typhoi- dal salmonellae: a management challenge for children with community-acquired in- vasive dis-

ease in tropical African coun- tries. Lancet 2009; 373:267-9.
26. Laterza L, Ianiro G, Scoleri I, et al. Ri- faximin for the treatment of diarrhoea-pre- dominant irritable bowel syndrome. Expert Opin Pharmacother 2015; 16:607-15.
27. Alcoba G, Kerac M, Breysse S, et al. Do children with uncomplicated severe acute malnutrition need antibiotics? A systematic review and meta-analysis. PLoS One 2013; 8(1):e53184.
28. Oshikoya KA, Senbanjo IO. Pathophysiological changes that affect drug disposi- tion in protein-energy malnourished chil- dren. Nutr Metab (Lond) 2009; 6:50.
29. Seaton C, Ignas J, Muchohi S, Kokwaro G, Maitland K, Thomson AH. Population pharmacokinetics of a single daily intra- muscular dose of gentamicin in children with severe malnutrition. J Antimicrob Che- mother 2007; 59:681-9.