

ORIGINAL ARTICLE

Routine Amoxicillin for Uncomplicated Severe Acute Malnutrition in Children

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ABSTRACT

BACKGROUND

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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 Niger, 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 nutritional 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 Niger. In regions with adequate infrastructure for surveillance and management of complications, health care facilities could consider eliminating the routine use of antibiotics in protocols for the treatment of uncomplicated severe acute malnutrition. (Funded by Médecins sans Frontières Operational Center Paris; ClinicalTrials.gov number, NCT01613547.)

N Engl J Med 2016;374:444-53.

DOI: 10.1056/NEJMoa1507024

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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

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.

Although such changes affected the absolute number and clinical profile of children with severe acute malnutrition, high-quality evidence to support the use of the same medical protocol for community-based treatment remains limited.¹⁴ Only one previous randomized trial has examined the routine use of antibiotics in the community-based treatment of severe acute malnutrition. The findings from that well-conducted trial in Malawi, reported in 2013, added important evidence to inform international guidance, but the high-risk study population, characterized by a high burden of kwashiorkor and human immunodeficiency virus (HIV) infection, makes it difficult to generalize the findings.¹⁵ The pro-

grammatic costs and public health consequences of emerging antibiotic resistance associated with routine antibiotic use require more evidence to support continued practice. We present the results of a randomized, double-blind, placebo-controlled trial in Niger that assessed the effect of routine amoxicillin use on nutritional recovery in children with severe acute malnutrition.

METHODS

STUDY SITE AND POPULATION

The study was conducted at four health centers in the rural health district of Madarounfa, Niger. 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. Detailed descriptions of the study population and methods are provided in the Supplementary Appendix and protocol, available with the full text of this article at NEJM.org.

STUDY OVERSIGHT

The study protocol was approved by the Comité Consultatif National d'Éthique, Niger, and Comité de Protection des Personnes, Île-de-France XI, Paris. An independent data and safety monitoring board reviewed study progress and safety events. All authors vouch for the accuracy and completeness of the data and analyses reported. The first, third, and last authors vouch for the fidelity of the study to the protocol.

STUDY DESIGN AND INTERVENTIONS

This study was a randomized, double-blind, placebo-controlled trial with the primary aim of



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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 in Niger.

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 (obtained at cost from the Investigational Drug Service, Perelman School of Medicine, University of Pennsylvania) 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 the guidelines of Médecins sans Frontières and the government of Niger. In brief, at the time of admission to the nutritional program, children received RUTF (170 kcal per kilogram per day; Plumpy'Nut, Nutriset) 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 the Epicenter laboratory in Maradi, Niger, 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 antimalarial treatments at the time of discharge from the nutritional program.

Secondary outcomes included nonresponse at 8 weeks, death from any cause, default (defined as three or more consecutive missed weekly visits), and transfer to inpatient care. Nonresponse 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 therefore 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 circumfer-

ence; 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

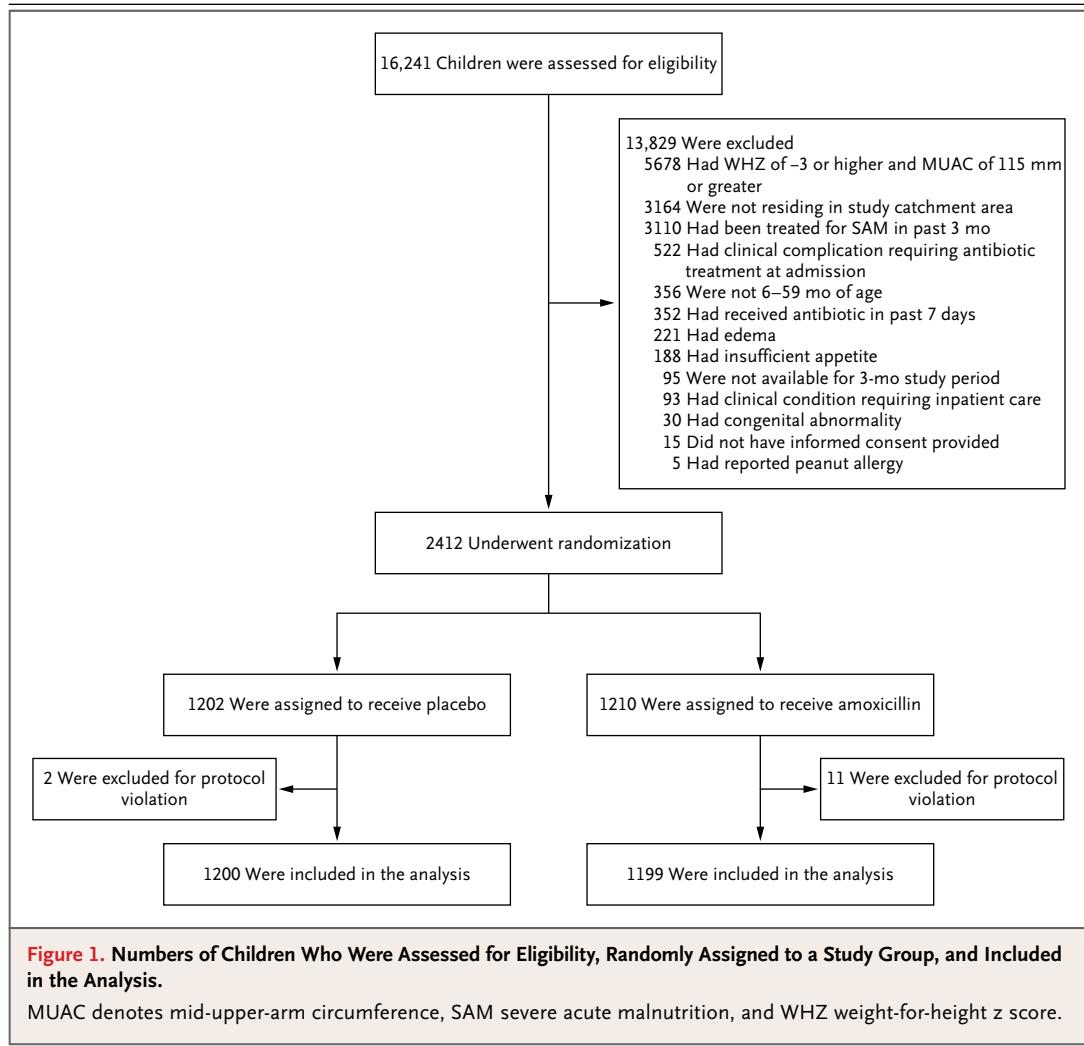
Between October 2012 and November 2013, a total of 16,421 children presented at the four health centers (Fig. 1). A total of 2412 children were randomly assigned to a study group, 13 were subsequently excluded for protocol violations, and 2399 children (1199 in the amoxicillin group and 1200 in the placebo 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 nonresponse 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 ratio,



0.24; 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 overall 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 mean time 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 signifi-

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 nutritional program			
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 two study groups except for maternal level of education (P=0.01).

cant 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.

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

Table 2. Treatment Outcomes According to Study Group.

Outcome	Amoxicillin (N=1199)	Placebo (N=1200)	Risk Ratio (95% CI)*	P Value
	<i>no. (%)</i>			
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 admission to 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, urinary tract infections, viral infections, anemia, and worsening of clinical state.

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} Ministry of Health data from the Madarounfa Health District suggest that the routine use of antibiotics for the treatment of severe acute malnutrition accounts for 15% of all antibiotic use among children younger than 5 years of age.²²

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, result-

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

Variable	Amoxicillin	Placebo	Mean Difference or 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 measures.

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

Bacteriologic Status	Total	Amoxicillin Resistance	Amoxicillin–Clavulanate Resistance
		number/total number (percent)	
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 <i>S. aureus</i>	3/41 (7)	0/41	0/41
Bacteriuria	26/789 (3)		
Enterobacteria	24/26 (92)	21/26 (81)	4/26 (15)
<i>Pseudomonas aeruginosa</i>	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 bacterial gastroenteritis, because multiple types of bacteria were identified in seven children.

ing 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.

One other randomized study, from Malawi, evaluated the effect of routine antibiotic therapy for uncomplicated severe acute malnutrition.¹⁵ In that study, amoxicillin significantly reduced the risk of treatment failure (by 24%) and death (by 36%), as compared with placebo. The authors concluded that antibiotics should continue to be used routinely in areas where kwashiorkor and HIV infection are prevalent. Children with HIV infection, however, were not assessed separately, and it was not possible to confirm a benefit among children without HIV infection. In our study in Niger, malnutrition was predominantly due to marasmus, and the prevalence of HIV infection was low. Differences in study findings may therefore be due to differences in study populations, as well as in the level of ancillary care and in the frequency of follow-up.

Contrary to previous reports of infection in inpatient settings,^{2-9,27} the prevalence of infection among uncomplicated cases in our study was low. This new evidence raises fundamental questions about our understanding of the pathophysiology of illness in cases of uncomplicated severe acute malnutrition. Among children with laboratory-confirmed bacterial infection, there

was no evidence that routine use of amoxicillin, as compared with placebo, had a significant effect on nutritional recovery, although the available sample size was limited.

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. In Malawi, cefdinir, but not amoxicillin, was associated with increased weight gain, as compared with placebo.¹⁵

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 pharmacokinetics 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 uncomplicated severe acute malnutrition in Niger. 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.

Supported by Médecins sans Frontières Operational Center Paris.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the families and children who participated in this study; our field research teams; Lynda Woi-Messe and Aimé Makimere, coordinators of our field research center; Dr. Kenneth Rockwell at the Investigational Drug Service, Perelman School of Medicine, University of Pennsylvania, for assistance with the study intervention and randomization tools; André Munger, Greg Elder, and Brigitte Vasset at Médecins sans Frontières Operational Center Paris; Emmanuel Baron at Epicentre; and the members of the data and safety monitoring board: Elizabeth Ashley (chair), Philippe Guerin, and Derek Cummings.

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