Does Routine Antibiotic Therapy Benefit Children With Severe Acute Malnutrition?

Source Citation: Isanaka S, Langendorf C, Berthé F, Gnegne S, Li N, Ousmane N, *et al.* Routine amoxicillin for uncomplicated severe acute malnutrition in children. N Engl J Med. 2016; 374:444-53.

Section Editor: Abhijeet Saha

Summary

In this double-blind, placebo-controlled trial, the authors randomly assigned children (age 6-59 mo) with uncomplicated severe acute malnutrition (SAM) to receive amoxicillin or placebo for 7 days. The primary outcome was nutritional recovery at or before week 8. A total of 2412 children were randomized, 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 (RR 1.05; 95% CI 0.99, 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; RR 0.86; 95% CI 0.76, 0.98; *P*=0.02). The authors found no benefit of routine antibiotic use with respect to nutritional recovery from uncomplicated SAM, and concluded that 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.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: Traditional teaching and clinical practice advocate prescribing a course of antibiotic therapy in children with severe acute malnutrition (SAM) even without confirmation of the presence of bacterial infection(s). This is because of concerns of heightened risk of severe bacterial infections on account of diminished immunity in such children. However, the evidence base for such practice may be limited by methodological quality, changes in overall child survival patterns, and better management of SAM and/or its complications. For these reasons, Isanaka, *et al.* [1] revisited the issue of whether routine antibiotic therapy actually benefits children with severe acute malnutrition.

Critical appraisal: ***Table* I** summarizes the trial and ***Table* II** presents a critical appraisal of the study [1]. Overall, this is an excellent trial (as noted above). However, there are some important issues that need consideration. The absence of beneficial effect of amoxicillin could be interpreted as the authors have done; but it is also possible that amoxicillin may not be the most appropriate antibiotic in such children. The clinical data suggest that about one-third of children had diarrhea at presentation and over 10% children had bacteria in stool culture. Amoxicillin is unlikely to be the appropriate antimicrobial in such settings. Further, some children had bacteremia and bacteriuria – which also may not respond to amoxicillin in the clinical setting of SAM. Therefore it is important to be able to identify such children at presentation (*i.e* even before culture results become available). Although this was not a focus of this study, such data would likely be available, and can contribute to clinical decision-making.

Inexplicably, adverse effects of the interventions have not been documented. This is especially pertinent as amoxicillin itself can cause diarrhea and its frequency in children in the study would have been helpful to balance the benefits reported for some outcomes. It would also have been useful to assess whether amoxicillin-induced diarrhea led to in-patient care subsequently. It is also odd that the group receiving Amoxicillin developed diarrhea less frequently than those who received placebo. Since the content and nature of the placebo was not described, this could be related to the placebo itself. Another unusual finding is that although 55% children in this study had malaria, fever (>38.5°C) was present in only about 5%. This reflects either low grade fever in children with malaria (which is unusual/unlikely) or faulty test kits. The concern is that if 55% children had malaria, a proportion of these could progress to severe/complicated malaria, requiring

TABLE I OUTLINE OF THE TRIAL

Hypothesis	There is limited evidence supporting the traditional practice of empiric antibiotic therapy in all children with severe acute malnutrition (SAM).
Research question	Does a course of oral Amoxicillin (*I=Intervention)* administered to children with uncomplicated severe acute malnutrition (SAM) *(P=Population)*, affect nutritional recovery (*O=Outcome)*, compared to placebo *(C=Comparator)*?
Study design	Randomized controlled trial
Study setting	Rural setting in a single district in Niger. The area has previously been recorded to have high prevalence of SAM in children.
Participants	*Inclusion criteria*: Children (6 mo to 5y) with SAM defined as (*i*) weight-for-height z score <-3, or (*ii*) mid-arm circumference (MAC) <11.5 cm, or (*iii*) both; without complications such as edema and/or any indication necessitating in-hospital care. *Exclusion criteria:* (*i*) Residence >15 km from the health facility, (*ii*) prior nutritional interventions within 3 months, (*iii*) antibiotic intake in the preceding week, (*iv*) congenital malformations, and (*v*) stated inability to follow-up for the duration of the study.
Sample size	*A priori* calculation assuming that 80% children would achieve the primary outcome of interest yielded a total sample size of 2010; 20% additional enrollments were made to account for attrition. Post hoc analysis revealed a power of 73% as the nutritional recovery rate was only 63%.
Intervention	Amoxicillin @40mg/kg twice daily x 7 days
Comparator	Placebo (nature, dose, and duration not described)
Study procedures	All enrolled children were administered standard care for SAM as per national guidelines. This included a commercial ready-to-use formula @170 kcal/kg/day, vitamin supplementation, anti-helminth therapy, catch-up vaccination, etc.Weight (least count 100 g); length/height (least count 0.1 cm); MAC (least count 0.1 cm) were recorded at enrollment and thereafter weekly. Indications for hospitalization were: occurrence of clinical condition/complication requiring admission and/or loss of weight >5% between visits or failure to gain weight after 2 weeks. Laboratory assessments included hemoglobin, HIV serology, rapid test for malaria, bacterial culture of blood, urine and stool samples (in a sub-group).
Follow-up protocol	Enrolled children were assessed weekly for at least 3 weeks. They were also followed up 4, 8 and 12 weeks following admission.
Outcomes	*Primary outcome*: Nutritional recovery (weight-for-height z score >-2 on two sequential visits, and MAC >11.5 cm) by 8 weeks. *Secondary outcomes*: Failure of nutritional recovery at 8 weeks; Mortality (all-cause); Transfer to in-patient care including hospitalization
Statistical methods	Detailed statistical methods have been described. Data were analyzed by intention-to-treat.

hospitalization. Such data are not presented in this study.

Extendibility: As mentioned above, it is relatively easy to extend the study findings to diverse health-care settings, including our own. However, we need to carefully consider whether the findings are a 'flash in the pan' or can be consistently demonstrated and thereby applied. In this light, some trials have demonstrated that severe pneumonia in children (traditionally hospitalized and treated with parenteral antibiotics) could be managed with oral antibiotic therapy [2-4] even without hospitalization [5]. Likewise, recent data suggest that oral antibiotics may be as effective as parenteral antibiotics in children with febrile neutropenia [6]. However, in both situations, a sub-group would exist (in real-world settings) that would require the conventional treatment (although these may not be detected in clinical trials). Failure to identify these could result in adverse clinical outcomes at the individual level despite apparent success at the group level. Similarly, there may be a sub-cohort of children with uncomplicated SAM who would require antibiotic therapy. Future studies should concentrate on early identification of these children.

Conclusion: Routine amoxicillin therapy does not appear to benefit nutritional recovery in children with uncomplicated severe acute malnutrition. However, it may reduce the need for in-hospital care in some children.

REFERENCES

1. Isanaka S, Langendorf C, Berthé F, Gnegne S, Li N, Ousmane N, *et al* . Routine amoxicillin for uncomplicated

TABLE II CRITICAL APPRAISAL OF THE TRIAL

Parameter	*Description and assessment*
Methodology	
Randomization	The sequence was generated using a computer program, off-site, by personnel unconnected with this study. Fixed block sizes of six were used. The procedure is judged as Adequate.
Allocation concealment	Allocation was concealed using serially numbered, opaque, sealed envelopes (SNOSE). The procedure is judged as Adequate.
Blinding (masking)	The intervention and comparator were similar in colour and packaging.The study team members were blinded to the allocation. However, if a child developed complications requiring antibiotics, the allocation code could be broken to facilitate clinical management. The procedure is judged as Adequate.
Incomplete outcome reporting	All participants who were enrolled are accounted for in the data analysis. The procedure is judged as Adequate.
Selective outcome reporting	Relevant outcomes have been considered, and a priori listed outcomes have been presented. However, adverse effects associated with amoxicillin/placebo have not been considered. Barring this, the procedure is judged as Adequate.
Other sources of bias	No obvious additional sources of bias
Overall assessment of methodological quality	Low risk of bias
Results	
Similarity of groups at baseline	The randomized infants were similar in terms of age, gender distribution, maternal characteristics, nutritional status (weight-for-age, MAC, height/length for age), hemoglobin, presence of malaria, fever, symptoms/signs of infection, and prior visits to health facilities. The bacterial culture of blood, urine and stool showed similar results in both groups.
Salient Results (Amoxicillin *vs* Placebo)	Nutritional recovery: 790/1199 *vs* 752/1200 (RR 1.05, 95% CI 0.99, 1.12); Mortality (all-cause): 7/1199 *vs* 6/1200 (RR 1.17, 95% CI 0.39, 3.46); Failure of nutritional recovery at 8 weeks: 72/1199 *vs* 64/1200 (RR 1.13, 95% CI 0.81, 1.56); Transfer for in-patient care: 316/1199 *vs* 368/1200 (RR 0.86, 95% CI 0.76, 0.98). Adverse events (AE) have not been reported. Subgroup analyses showed that the beneficial effect on "need for in-patient care" existed for acute diarrhea only, and not for other indications including failure to gain weight, respiratory tract infection, or severe malaria. There was a statistically significant benefit on transfer to in-patient care within 2 weeks of the start of the intervention. There were also some statistically (but perhaps not clinically) significant differences in the pattern of gain in weight and MAC.
Interpretation of results	The data suggest that amoxicillin therapy did not have beneficial effect on nutritional recovery (compared to placebo), but reduced the need for in-patient care in some children.
Overall impression	*Validity*: Well-designed and well-conducted RCT with a low risk of bias. *Results*: Clinically important results reported. *Applicability*: The results can be applied across a broad range of settings. However, there are some caveats to generalizability, as described in the text.

severe acute malnutrition in children. N Engl J Med. 2016;374:444-53.
2. Agweyu A, Gathara D, Oliwa J, Muinga N, Edwards T, Allen E, *et al.* Severe Pneumonia Study Group. Oral amoxicillin versus benzyl penicillin for severe pneumonia among kenyan children: A pragmatic randomized controlled non-inferiority trial. Clin Infect Dis. 2015;60:1216-24.
3. Soofi S, Ahmed S, Fox MP, MacLeod WB, Thea DM, Qazi SA, *et al.* Effectiveness of community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Matiari district, rural Pakistan: A cluster-randomized controlled trial. Lancet. 2012; 379:729-37.
4. Addo-Yobo E, Anh DD, El-Sayed HF, Fox LM, Fox MP, MacLeod W, *et al.* Multicenter Amoxicillin Severe pneumonia Study (MASS) Group. Outpatient treatment of children with severe pneumonia with oral amoxicillin in four countries: the MASS study. Trop Med Int Health. 2011;16:995-1006.
5. Bari A, Sadruddin S, Khan A, Khan IU, Khan A, Lehri IA, *et al.* Community case management of severe pneumonia

with oral amoxicillin in children aged 2-59 months in Haripur district, Pakistan: a cluster randomized trial. Lancet. 2011; 378:1796-1803.
6. Vidal L, Ben Dor I, Paul M, Eliakim-Raz N, Pokroy E, Soares-Weiser K, *et al.* Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. Cochrane Database Syst Rev. 2013;10:CD003992.

JOSEPH L MATHEW
Department of Pediatrics, PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

Pediatrician's Viewpoint

Facility-based management spearheaded the fight against acute malnutrition in children until a few years ago. But it was increasingly being felt that a significant number of children even with severe acute malnutrition (SAM) did not require hospital admission and could be managed in the community. In 2007, WHO and UNICEF endorsed the community-based management of acute malnutrition. This is based on a community outreach model and aims at management of children aged more than 6 months with SAM who have no medical complications and a good appetite with ready to use therapeutic foods (RUTF). The Government of India (GOI) and the National Health Mission (NHM) have not yet adopted the program, and we are largely restricted to the facility-based approach except in some pockets [1]. But there is a growing consensus on the community based model and the Indian Academy of Pediatrics in 2013 issued a Consensus Statement on Integrated Management of SAM stressing on the need for a home-based management [2].

Apart from the nutritional rehabilitation, a routine use of amoxicillin for 7 days to all the children with uncomplicated SAM is recommended by the WHO. High prevalence of bacteremia, urinary tract infections and other bacterial infections have been shown in children with malnutrition but there are no such data available for the children with uncomplicated SAM, and therefore there is no clear rationale for routine use of amoxicillin in these children [3]. In a retrospective study on the effect of amoxicillin on the recovery rate of children with SAM, Trehan, *et al.* [4] documented no significant difference in the rate of nutritional recovery of children at 12 weeks (84% in amoxicillin group *vs* 86% in the group with no amoxicillin). The death and default rates were also comparable. In a double blind placebo controlled trial by the same group of authors, significantly higher risk of treatment failure with placebo in comparison to amoxicillin (RR 1.32, 95% CI 1.04, 1.68) was documented [5]. The risk of death was also higher with placebo (RR 1.55, 95% CI 1.07, 2.24). A meta-analysis done by Alcoba, *et al*. [6] concluded that there is little evidence to continue with the routine amoxicillin therapy in children with uncomplicated SAM, especially in low HIV prevalence populations.

This study is a well-designed randomized controlled trial (RCT) with low risk of bias. They have used amoxicillin in a dose of 80 mg/kg/d, which is the upper range of the recommended dosage. A lower dose of 50 mg/kg/d could have been used. The secondary outcome of non-response at 8 weeks does not hold too much relevance as the primary outcome as nutritional recovery was already taken. Only one child was found to be HIV positive whereas in the study done by Trehan, *et al*. [5], the prevalence of HIV was 22%. This could explain the contradiction in the results of the two studies. HIV-positive children with SAM are likely to be more immune-deficient, and therefore may benefit with the routine use of antibiotics. The authors have reported a significantly shorter time to recovery in the amoxicillin group (28 d *vs* 30 d). This reduction of 2 days may be statistically significant but may not translate into clinical significance. Rapid diagnostic test for malaria was positive in 55.3% of the total study population although only 4.7% had fever. This points needs to be highlighted in the discussion.

There is a need to review the policy of routine amoxicillin in children in uncomplicated SAM, but before that we need to have well designed RCTs from different parts of the world including India which should include stratification of the participants according to the HIV status. Routine use of amoxicillin is associated with the possibility of emergence of bacterial resistance, toxicity and allergies, and also adds to the cost and complexity of treatment. But routine use of amoxicillin may benefit those children who may be falsely labelled as uncomplicated, and may actually be harbouring a complication. Therefore, if we do away with the use of amoxicillin, we must also be able to ensure that even the grass root level health worker is well trained in identification of danger signs and early referral.

REFERENCES

1. Burza S, Mahajan R, Marino E, Sunyoto T, Shandilya C, Tabrez M, *et al*. Community-based management of severe acute malnutrition in India: New evidence from Bihar. Am J Clin Nutr. 2015;101:847-59.
2. Dalwai S, Choudhury P, Bavdekar SB, Dalal R, Kapil U, Dubey AP, *et al.* Consensus statement of the Indian Academy of Pediatrics on integrated management of severe acute malnutrition. Indian Pediatr. 2013; 50:399-404.
3. Lazzerini M, Tickell D. Antibiotics in severely malnourished children: Systematic review of efficacy,

safety and pharmacokinetics. Bull World Health Organ. 2011;89:594-607.
4. Trehan I, Amthor RE, Maleta K, Manary MJ. Evaluation of the routine use of amoxicillin as part of the home-based treatment of severe acute malnutrition. Trop Med Int Health. 2010;15:1022-8.
5. Trehan I, Goldbach HS, LaGrone LN, Meuli GJ, Wang RJ, Maleta KM, *et al.* Antibiotics as part of the management of severe acute malnutrition. N Engl J Med. 2013;368:425-35.
6. Alcoba G, Kerac M, Breysse S, Salpeteur C, Galetto-Lacour A, Briend A, *et al.* Do children with uncomplicated severe acute malnutrition need antibiotics? A systematic review and Meta-Analysis. PLoS One. 2013;8:e53184.

RUCHI RAI
Department of Neonatology,
Superspecialty Pediatric Hospital &
Post Graduate Teaching Institute, Noida, India.
ruchiraialld@gmail.com