

Comments on the paper “Antibiotics as part of management of severe acute malnutrition” and on the interpretation by the New York Times, “Malnourished gain lifesaver in antibiotics”

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Background

The paper by Trehan et al (1) intended to assess the value of adding antibiotics to nutritional therapy to increase recovery rates and decrease mortality among malnourished children treated in the community. The authors report enrolling 2,767 children aged 6-59 months with severe acute malnutrition (SAM) and assigning them to three different groups: amoxicillin, cefdinir and placebo (in addition to receiving ready-to-use-therapeutic-food, RUFT). Although only 871 (31.5%) children were tested for HIV, prevalence of HIV infection was 21.6% (188/871). Fever, cough or diarrhea were reported in 2,308 (83.4%) of the subjects in the two weeks previous to enrollment. The children received the antibiotic or the placebo during the initial seven days of therapy and were followed for 12 weeks by home visits every two weeks. One hundred and fifty children died during the 12 week follow-up period, 4.8% of the amoxicillin group, 4.1% of those in the cefdinir group and 7.4% in the placebo group. The rates of treatment failure of those surviving were 1.5%, 1.7% and 2.4%, in the three groups, respectively. The authors conclude that the routine inclusion of antibiotics as part of the nutritional therapy is warranted.

The New York Times published a note by Denise Grady (2) stating that the studies “reveal that severe malnutrition often involves more than lack of food, and that feeding alone may not cure it”. Also, that “malnourished children are prone to infections and the drugs ... were so helpful that researchers said medical practice should change immediately to include an antibiotic in the routine treatment of severe malnutrition”.

Comments

It is important to consider that HIV infection among the study subjects (21.6%) and their mothers (18.8%) was high. The difference in rates may be associated with sampling since all the children were probably infected *in utero*. The fact that 83.4% of them were reported to have had signs and symptoms of infections in the two weeks prior to enrollment should also be taken into consideration for assessing the implications of the study.

Figure 1 in the article (1) is central for understanding the progression of both nutritional recovery and mortality. Four weeks after initiation of treatment (follow-up visit 2) nutritional recovery was identical in the three groups and it was not until eight weeks that the placebo group started to lag behind the two antibiotic groups (Fig 1A). Furthermore, nutritional recuperation among children in the amoxicillin group was delayed and the recovery rate did not reach the same level as that seen in cefdinir group before week 12. The question is how do the authors explain the absence of an intervention effect five weeks after termination of the antibiotic treatment, when 83% of the children showed signs of infection during the two-week period prior to receiving the antibiotic? Additionally, during the study period diarrhea was observed more commonly among the placebo group, a fact that would induce delays in nutritional

recuperation. Even with that consideration, at the end of the 12 week-observation period, there were only seven children in the placebo group that would have recovered had they received antibiotics (the difference between 1.5% treatment failure in the amoxicillin group and 2.4% in the placebo group).

On the other hand, Figure 1B shows that mortality rates were identical among children in the placebo and amoxicillin groups up to four weeks after initiation of treatment. After week six (follow –up visit 3) there were no more deaths among the amoxicillin group, but they continue to occur in the placebo and the cefdinir groups. The numbers in the bottom of Fig1B show that there were 28 children lost to follow up in the amoxicillin group, 12 in the cefdinir group and 19 in the placebo group. The question here is how do the authors explain the continued mortality among the cefdinir group as compared the group receiving amoxicillin? Was the RUFT treatment appropriate? Were the signs or symptoms of infection during the study period more common among children who died? Was a cause of death identified (for example, severe pneumonia or dehydrating diarrhea? Were children who were HIV positive more likely to have signs of infection and to die?

We believe that the authors should have discussed the implications of previous infections, age and breast feeding history on both the nutritional recovery and the mortality of the children for the following reasons:

The interactions between infection, nutrition and immunity have been documented for many years now (3-5). Field studies in developing countries have clearly shown that infectious diseases, especially diarrhea and respiratory infections, have a negative effect on nutritional status both in terms of weight and length (6-8). Clinical, symptomatic infections usually precede and precipitate acute malnutrition and its associated immune deficiencies (9, 10). Nevertheless, the magnitude of the immune depression seen among malnourished children does not necessarily correlate with nutritional indicators (11). The obvious effects of HIV infections on immune mechanisms, added morbidity and weight loss provide additional evidence of the interactions.

Breast feeding has been shown to protect breast fed children from infections and infectious illnesses (12, 13). Breast milk contains multiple factors that prevent infections, promote growth of harmless bacteria in the intestine and induce the maturation of the children's own immune system (14-16). Furthermore, studies from Africa have shown that breast feeding prevents death among children born from HIV-infected mothers (17).

The use of ready to use supplementary food was associated with 73% recovery rates among malnourished children aged 6 to 60 months in Ethiopia (18). In the case of Malawi (1) the recovery rates in all groups, even among those receiving placebo, were above 85%. Additionally, multiple micronutrient supplementation of 6-24 month old malnourished children results in fewer episodes of fever or fever and cough (19).

Lastly, a recent analysis of 45 articles showed that the evidence that may support the current WHO recommendation to give routine antibiotics to children with severe acute malnutrition, even in the absence of obvious clinical infectious illnesses, is weak (20).

We, therefore, believe that antibiotics should not be given routinely to treat malnutrition. They should, instead, be used to treat infection, and ideally should be targeted as much as possible to the pathogen involved and avoid, whenever possible, the use of broad spectrum drugs. Antibiotics should not be an excuse not to diagnose and document infection for which appropriate drugs can be selected. Routine use of antibiotics is a formula for more rapid selection of resistance, a phenomenon already all too prevalent around the world.

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