Re: Antibiotics for severe malnutrition

Malnutrition is contributes to the mortality of about a fifth of children who die before the age of five. Those that are sickened but not killed by malnutrition are more likely to be debilitated by infectious disease and their physical and cognitive development is often impaired. Retrospective studies on children malnourished in the 1966-69 Biafra war reveal that even when malnutrition does not persist, it predisposes the previous sufferer poor overall health that can be life-long (14). In Bangladesh, malnourished girls that survive to adulthood frequently continue to be undernourished and bear children at risk from undernutrition (1). All of these factors emphasize the importance of effectively preventing and properly treating malnutrition. In spite of long-standing documentation of the problems of childhood malnutrition in resource-limited settings, progress in treatment has been slow with the most successful intervention being fortified peanut-paste and milk powder-based Ready-to-Use Therapeutic Food (RUTF) (6). RUTF alone however does not guarantee cure and treatments to augment this therapy are sorely needed.

Trehan et al (25) recently reported that a home-based course of beta-lactam antibiotics reduced mortality from and increased recovery of malnourished children in Malawi. While positive results were not seen in all antibiotic-treated patients, the overall improvement in treated children versus placebos was statistically significant, with cefdinir producing slightly better results than amoxicillin. Antibiotics are recommended for patients that are hospitalized due to severe malnutrition, who almost invariably have symptomatic infections. Following the results of their study, Trehan et al (25) suggest that antibiotics should be used more generally in severe malnutrition, for outpatients, irrespective of concomitant infectious disease. While the investigators acknowledge that antibiotic use selects for resistance and that resistant bacteria represent a specific risk for undernourished children, they "believe that the routine use of antibiotics is worth serious consideration because of the observed benefits".

The results of the Trehan et al (25) study point to the potential that certain bacterial species may exacerbate or even cause Kwashiokor, one of the worst and most deadly manifestations of undermalnutrition. This finding is consistent with recent data from microbiome research (performed by some of the same investigators(24)) and offers promise that specific factors associated with poor outcomes for treated malnutrition may be identified soon, and targeted directly. Given that research along these lines has shown considerable progress, it is possible that an effective and sustainable solution to malnutrition therapy may be in sight. Until such a treatment is available, given the burden from severe malnutrition and the long-term consequences of childhood malnutrition, the stop-gap therapy administering antibiotics to in-patients with severe malnutrition is justifiable in spite of the resultant selective pressure for drug resistance. Is more widespread use of antibiotics in malnutrition warranted? In addition to the results of this study, what are the other factors that policy-makers responsible for the "consideration" recommended by Trehan et al (25) should take into account.

All antimicrobial use, irrespective of how strongly justified, selects for resistance. Therefore the decision to use an antibiotic in a given condition must be weighed against the cost of resistance to the community. As up to 50% of children are malnourished in some settings, routine outpatient administration of antibiotics represents significant selective pressure that could result in unforeseen consequences. Evolutionary theory and recent experience predict that a policy that requires antimicrobial use in a significant fraction of these children will eventually obliterate its own usefulness and compromise the treatment of life-threatening infectious diseases in resource-limited settings where these are the commonest cause of illness and death. Unfortunately, Trehan et al (25) did not monitor drug resistance in any way in their study and the potential for New York Times Op-Ed columnist Denise Grady's (30 Jan 13) suggestion that based on the Trehan et al (25) findings, "medical practice should change immediately to include an antibiotic in the routine treatment of severe malnutrition" to cause irreversible harm has not been assessed.

The study itself opens an important, and unaddressed, question. Why was third generation cephalosporin, Cefdinir, slightly more effective than amoxicillin? Could this be because resistance to amoxicillin is widespread and resistance to Cefdinir is not? (Those patterns have been documented in

among deadly pathogens in Malawi (11)). If so, as resistance of the unknown target(s) to both drugs becomes more common, antibiotic therapy will become less useful. Trehan et al (25) stated idea that mass use of the more expensive but more effective cefdinir in severely malnourished children would fall if the treatment were used more broadly is flawed. The immediate cost of cefdinir would indeed drop but the cost of treating conditions for which drugs belonging to this class (including severe malnutrition) would rise because resistance will evolve. This is not speculation, it has happened for other conditions.

A handful of broad-spectrum antimicrobials, namely tetracycline, the aminopenicillins, cholramphenicol as well as sulphonamides with and without trimethoprim were the mainstay of bacterial infections in Africa in the latter half of the 20th century. These drugs remain effective against susceptible bacteria but justified or questionable therapeutic and preventive use combined with unsanctioned use in the informal health sector has provided the selective pressure for present-day resistant strains that have all but replaced the susceptibles. This selection accounts for the situation today in which previously easy-to-treat infections are costly or impossible to treat in many patients. Resistance has undermined the outcome of bacillary dysentery and cholera and has become a common feature among bacteria implicated in persistent childhood diarrhea and pneumonia that for many patients, operate in a mutually detrimental cycle with malnutrition (22). Newer, more expensive drugs such as the fluoroquinolones and third-generation cephalosporins are not accessible to many poor patients who die or are disabled by treatable infections. These relatively expensive medicines represent the last resort for most African countries which have no alternatives even though resistance to them is already common-place (16, 19).

In resource-limited African settings, rising rates of beta-lactamase-producing organisms are cause for concern. Following multiple reports of multidrug resistant *Salmonella* Concord in Ethiopian adoptees in Europe, Beyene et al (3) established that *S.* Concord resistant to a range of antibiotics, including ampicillin and third generation cephalosporins, were the predominant cause of *Salmonella* infections at three locations in Ethiopia. Research in other African countries, including Malawi where this study was performed, intense antimicrobial use has resulted in the evolution of new lineages of invasive non-typhoidal *Salmonella* that are deadly to young children, particularly those that are malnourished (9, 17, 23). Recent research uncovering this evolutionary event in a subcontinent where laboratory support for infectious disease is weak was only initiated after mortality clusters determined that there was a problem; that is, after thousands of individuals had died of resistant bacterial infections. Third generation cephalosporins like Cefdinir are the last resort life-savers for this condition. Likely continent-wide dissemination of resistance genes on conjugative plasmids and transposable elements has been seen in parallel (18, 23). Devastation from antimicrobial resistance is neither a hypothetical or minor problem in resource-limited settings and use of ampicillin and cefdinir by outpatients in countries where these pathogens are endemic could well predispose them and their contacts to infections by these and other resistant strains.

The degree of selection that could occur due to more widespread use of beta-lactam antibiotics in malnutrition is considerable. Because relapse is common in treated malnourished patients (5), meeting Trehan et al's (25) recommendations will require repeated antimicrobial therapy, which could add up to a lot of selective pressure. It is important to acknowledge there is no proposal to administer antibiotics to children with moderate malnutrition. However, due to uncontrolled access to antibacterials in most African countries and well-documented unsanctioned patterns of drug use in these communities (7, 12, 26), policy makers may not be able to prevent this from occurring. In addition to studies on the evolution, ecology and epidemiology of resistance, anthropological studies of drug use must also precede any policy suggestion broad use of antimicrobials for severe malnutrition. The available data suggest that there may be public health value to antibiotic use in severe acute malnutrition but they are insufficient to inform a policy that would broaden the use of antimicrobials in this condition, particularly as only a fraction of malnourished children benefit from this therapy.

In far too many situations interventions viewed as simple or cheap are advocated for resource-limited settings, which must later bear the true cost of their ruse (2, 10, 15, 17). These new findings and recommendations come fast on the heels of what are now being admitted as previous misjudgments in the face of a true Tragedy of the Commons(13). The risks and benefits of antibiotic use cannot be assessed

by quantifying cure rates alone. Like malnutrition, which is the principal underlying risk factor for an underestimated proportion of childhood deaths, resistance is a hidden threat because its victims are documented as dying from disease rather than resistance. The threat from antimicrobial resistance is less well recognized or acknowledged but it is also less well studied experimentally than nutrition. As a consequence, crises arising from resistance are identified when it is too late to intervene. A pertinent example come from cholera. In African countries, where antimicrobials have had front row seats in front of water, sanitation, vaccination and rehydration, cholera control has been least effective (4, 8, 20-22). In recent epidemics, false reassurance from antimicrobial use has actually exacerbated epidemic size and case-fatalities but this has not altered practices in many African countries even though *Vibrio cholerae* isolates are resistant. Following over three decades of research, cholera policy-makers are finally coming to the realization that comparatively costly vaccines are in fact more cost-effective than antibiotics (World Health Assembly resolution WHA64.15 in May 2011). It will take years to move this realization to policy and then practice.

There are no vaccines for severe acute malnutrition today, nor are their likely to be specific treatments other than RUTF for some time. As the new data show that antibiotics can be life-saving and more specific targets are yet to be uncovered, it makes sense for now to maintain policies that recommend their use in special and supervised situations, most notably for in-patients with severe malnutrition. Our collective research agenda must be to identify therapies for malnutrition that are more effective and less costly to public health than broad-spectrum antibiotics. And while we are not yet in a position to reduce antibiotic use for this condition, any policy recommendations for broader use must be based on an assessment of the likely costs – in lives – of increasing selective pressure for precious beta-lactam resistance at this precarious time.

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