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Short Communication

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Risk Factors for Bacteremia in Severely Malnourished Pneumonic Children and their Outcome

Bacteremia is quite common in Severe Acute Malnourished (SAM) children with pneumonia, who often experience a fatal outcome, especially in developing countries. There is limited information in the medical literature on the risks of bacteremia in SAM children with pneumonia. We have examined the factors associated with bacteremia and their outcome in under-five children who were hospitalized for the management of pneumonia and SAM.

Methods: In this unmatched case-control study, SAM children of either sex, aged 0-59 months, admitted to the Dhaka Hospital of the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) with cough or respiratory distress and radiological pneumonia during April 2011 to July 2012 were enrolled (n=405). Those with pneumonia as well as bacteremia constituted the cases (n=18) and randomly selected SAM children with pneumonia without bacteremia constituted controls (n=54). A wide range of bacterial pathogens were isolated among the cases of which 13 (72%) were Gram negatives. Death rate was higher among the cases than the controls (28% vs. 9%) but the difference was not statistically significant (p=0.111). In logistic regression analysis, after adjusting for potential confounders, such as the lack of DPT/oral polio/HIV/hepatitis vaccination, measles vaccination, vomiting and clinical dehydration (some/severe) the SAM children with pneumonia as well as bacteremia more often had the history of lack of BCG vaccination (95% CI=1.17-29.98) and had diastolic hypotension (<50 mm of Hg) (95% CI=1.01-12.86) not only after correction of dehydration but also in its absence.

Keywords

Diarrheal Disease Research, Severe Acute Malnourished

Back Ground

Severely acutely malnourished children have traditionally been treated with broad-spectrum antibiotics at presentation even in the absence of overt infection. The rationale for this is that (i) malnourished children frequently have bacterial infections (including bacteraemia); (ii) diagnosing infection in malnourished children is difficult because clinical manifestations of infection (e.g. fever) may not be apparent; and (iii) malnourished children have bacterial overgrowth in their small bowel. However, while this approach has a sound and rational basis, there has been very little evidence of its effectiveness until recently. In

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2013, a study from Malawi powerfully demonstrated the importance of antibiotic provision to children with SAM without clinical features of infection: 2,767 children with SAM eligible for outpatient care and aged 6–59 months were randomised to 7 days treatment with oral amoxicillin (80–90 mg/kg/day), cefdinir (an oral third-generation cephalosporin at 14mg/kg/day), or placebo. The 12-week mortality rates were 4.8% (amoxicillin), 4.1% (cefdinir), and 7.4% (placebo), giving relative risks for mortality for placebo compared to amoxicillin of 1.55 (95% CI 1.07-2.24), and for placebo compared to cefdinir of 1.80 (95% CI 1.22–2.64). Differences in mortality and recovery between the amoxicillin and cefdinir arms were not statistically significant.4

This substantial mortality reduction in children without overt infection and eligible for outpatient treatment in a rural area suggests that the provision of antibiotics should remain routine (and critically important) in all settings where SAM is managed outside of hospitals, regardless of the presence of features of infection. In this population the rates of HIV and kwashiorkor were high, but we consider that the burden is on demonstrating with trial evidence the safety of deviating from this management strategy (which is currently recommended by WHO) in other populations and settings, rather than considering that implementation can be postponed.

Which antibiotic is most appropriate for outpatient care?

Ideally, choice of antibiotics should be guided by knowledge of which organisms need to be treated and their likely resistance profile, informed by microbiologic assessment for reference in cases of treatment failure and to provide local population resistance data. However, in areas where malnutrition is common, microbiologic services tend to be weak and treatment choice is influenced by cost, availability and ease of administration, as much as by effectiveness. In practical terms, while the Malawian study described above suggested possible advantages of cefdinir over amoxicillin, in the absence of further more definitive evidence of increased efficacy compared to readily available antibiotics, oral third-generation cephalosporins are unlikely to become widely used due to cost.4 Indeed, in assessing the potential benefit of any policy move towards widespread cephalosporin usage, improvements in efficacy will need to be weighed against the risk of promoting community-based third-generation cephalosporin resistance. In our setting in rural Kenya, increasing unregulated use of ceftriaxone in the community appears to be driving high levels of resistance to multiple antibiotics identified in bacteria isolated from community carriage (literally, where it is possible to identify the presence of microbes on skin/mucosal surfaces without direct evidence of them causing disease) and infection studies (unpublished). Data from Médecins Sans Frontières in Niger showed alarmingly high rates of carriage of highly resistant enteric bacteria in children with SAM in the community.

Currently, WHO guidelines (which pre-date the Malawi study) recommend provision of co-trimoxazole as the 'broad spectrum antibiotic' for treatment of children with SAM in the community.6 Amoxicillin and co-trimoxazole have similar spectra of activity and are both widely used so may have similar problems of antibiotic resistance. Despite a widespread view that co-trimoxazole is less effective than amoxicillin in treating small intestinal bacterial overgrowth, in fact they have both been used with some success for this indication – though neither is as effective as other agents, like amoxicillin-clavulanic acid, metronidazole, or rifixamin.7,8 There are no published studies on the use of co-trimoxazole in

severely acutely malnourished children treated in the community, whereas amoxicillin use is now supported by the Malawian trial. Amoxicillin reaches therapeutic plasma levels in acutely malnourished children when given orally, and is considered to be reasonably safe with few side-effects.9,10 Therefore, pending further studies or significant changes in the availability of oral third-generation cephalosporins, current evidence suggests that amoxicillin 80–90 mg/kg/day in two divided doses for 7 days is the most appropriate treatment. While other dosages and regimens have been quoted previously, this is now the one with the strongest evidence base. For children already taking daily co-trimoxazole prophylaxis because of HIV, this should be continued at the usual dose throughout their management, but an additional antibiotic (e.g. amoxicillin) should be given at presentation as well. Where strong programmes of active early case-finding for acute malnutrition in the community are present, most malnourished children will be referred for care before the onset of complications, will be clinically well and have retained appetite. Such can be safely managed in outpatient care and do not require hospital admission. However, children who are severely unwell, fail an appetite test (unable to take or tolerate sufficient RUTF), or who have evidence of severe or systemic infection require at least a period of inpatient-based stabilisation prior to transfer for outpatient management of SAM. The mortality rates for such children are often very high, and invasive infection is often present. In a case series at our centre, a rural district hospital in Kenya, laboratory-proven bacteraemia occurred in 12% - the true proportion with bacteraemia is likely to have been much higher because the inherent sensitivity of blood cultures is low. These, and other data provide a clear rationale for the routine provision of antibiotics to children with SAM requiring inpatient care. WHO recommends ampicillin (parenterally for 2 days followed by enteral amoxicillin/ampicillin for a further 5) and gentamicin (parenterally for 7 days), though it is notable that the efficacy of this particular combination and schedule has never been tested in this population in a randomised controlled trial.

Conclusion: The results of our study suggest that history of lack of BCG vaccination and presence of diastolic hypotension in absence of dehydration on admission are the independent predictors of bacteremia in SAM children with pneumonia. The results indicate the importance of continuation of BCG vaccination to produce benefits beyond the primary benefits.

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