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Nontyphoidal salmonellae: a management challenge for children with community acquired invasive disease in tropical African countries

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Nontyphoidal salmonellae (NTS) have long been a common but relatively neglected cause of invasive disease in children living in tropical Africa especially during rainy seasons¹. NTS bacteraemia has consistently been associated with young age (most cases present between 6 months and 3 years of age), anaemia, malnutrition and more recently with HIV infection, with reported case-fatality rates of over 20%.¹⁻⁶ NTS are also a common and frequently fatal cause of meningitis.⁷ Reports of the burden of disease from the region include sick children presenting to rural district facilities as well as urban-based hospitals.¹⁻⁹ As immunisation with *Haemophilus influenzae* type b (Hib) conjugate vaccine becomes more widely available, NTS together with *Streptococcus pneumoniae* are the major causes of severe bacterial disease in African children from 2 months to 5 years of age.^{2,3} Future implementation of pneumococcal conjugate vaccines is likely to further emphasise their relative importance as a pathogen amongst an increasingly diverse pattern of aetiological agents causing childhood bacteraemia and pneumonia.¹⁰

It is important to consider the role of NTS in the presentation of acute childhood pneumonia in tropical Africa as pneumonia incidence and mortality are very high.¹¹ While it is unlikely that NTS commonly *cause* pneumonia, at least pneumonia with a pattern of well defined consolidation on chest radiograph, from a practical standpoint this is irrelevant if they are commonly found in children with a clinical presentation mimicking pneumonia and if these children commonly die. Although a lung aspiration study from The Gambia¹² where NTS bacteraemia is known to be prevalent^{2,8} did not isolate NTS from lungs of children with pneumonia, clinical overlap appears to be common. Cough and tachypnoea are common features in children with NTS bacteraemia^{1,2} and studies from West, Central and East Africa found NTS to be the commonest or second commonest (after pneumococcus) isolate from children with a diagnosis of pneumonia.^{8,9,13,14} These studies were conducted before Hib vaccine was routine and relied on blood culture for aetiological diagnosis but clearly

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Conflict of interest

None

showed, even then, the importance of NTS amongst a group with invasive disease and a high risk of death likely to be treated empirically for severe or very severe pneumonia.

The practical question then becomes whether treatment aimed at suspected septicaemia or pneumonia requiring hospitalisation will be effective against invasive NTS disease? At present health workers in Africa are trained to follow simple clinical guidelines in selecting antibiotic therapy for children aged 2 months to 5 years with severe illness.¹⁵ It is suggested that those with severe pneumonia should receive penicillin alone and those with a sign of very severe pneumonia (or disease) either parenteral chloramphenicol or gentamicin in combination with penicillin or ampicillin. In the Kenyan studies NTS represented 20% and 6% of blood culture isolates from children meeting these criteria respectively.¹³ For the child with acute fever who is severely ill but lacks an obvious focus of infection resulting in a diagnosis of 'suspected septicaemia' current guidelines recommend penicillin in combination with chloramphenicol.¹⁵ NTS are reported as the cause of 'suspected septicaemia' in 40% and 28% of cases from Malawi and Kenya respectively.^{1,13} Although national adaptation of these WHO guidelines to take account of the local epidemiology of disease is recommended, at present few countries have the data that would allow them to do this and the tendency is to follow generic WHO advice.

Penicillin is ineffective against NTS and gentamicin is not ideal because of poor extravascular penetration. Unfortunately there are also now reports from across tropical Africa, including from rural-based populations, of high levels of resistance among NTS isolates to other widely available, currently recommended antibiotics: ampicillin (48% to >90%), chloramphenicol (15% to >90%) and gentamicin (25% to 35%).^{2,9,16-18} Where NTS can be identified fluoroquinolones such as ciprofloxacin or cephalosporins such as ceftriaxone are increasingly relied upon for treatment.¹⁶ However, their role in formal treatment guidelines has yet to be defined in part because the data on antibiotic resistance vary considerably over time and region and are as yet inadequate to draw general conclusions. Ciprofloxacin in generic form is now more widely available and can be relatively cheap as an oral formulation. Such a formulation is problematic for those with very serious illness who are not able to drink and would not be recommended alone as first-line therapy for pneumonia or septicaemia because of relatively poor activity against pneumococcus.

Ceftriaxone is an attractive alternative first-line therapy for severe invasive bacterial infections including septicaemia, pneumonia and meningitis in children in tropical Africa. Ceftriaxone is active against pneumococcus, Hib and NTS as well as other Gram negatives which can be relatively common especially in children with HIV infection or malnutrition. It can also be administered just once daily and has become more affordable. Its broad spectrum activity, perceived superiority against pneumococci with *in vitro* penicillin resistance and ease of administration have made ceftriaxone a common choice as empiric first-line therapy for severe childhood pneumonia or suspected severe sepsis in resource-rich countries, in Asia and increasingly in major 'opinion-leading' hospitals in Africa. Although some observational data support this approach, for many this represents a complete failure of the move to evidence-based practice as there are to date no high quality clinical trials demonstrating its benefit over alternative combinations.¹⁹

While ceftriaxone is an apparently attractive alternative particularly in the light of the data on NTS, specific evidence of its potential value and possible risks is required before its widespread use for the empiric management of severe pneumonia or sepsis in tropical Africa. Broad spectrum cephalosporins readily induce resistance in organisms as happened in Asia with *S. typhi* and the generally poor state of environmental hygiene and associated high risks of nosocomial infection in many African hospitals make the potentially

widespread use of broad spectrum cephalosporins as first-line therapy for common illnesses a major cause for concern. This does not preclude making ceftriaxone more widely available as first-line therapy for meningitis as effective treatment requires high levels in the cerebrospinal fluid of an antibiotic effective against all the major bacterial causes including NTS. Selection pressure for development of resistance would be much lower in this context because meningitis is much less common than pneumonia or suspected septicaemia.

Another important reason for advocating an evidence-based approach is that changing empiric antibiotic therapy for pneumonia or septicaemia on the basis of *in vitro* susceptibility data may not have a significant impact on overall outcomes. In a *post-hoc* analysis in Kenyan children, fatal outcome did appear more likely, but not significantly so, in those with bacterial infections with antibiotic resistance to recommended treatment (OR 1.2; 95% CI 0.78-1.92).¹³ In contrast, there is strong evidence that penicillin is still effective for pneumonia (not meningitis) due to pneumococci that show intermediate resistance *in vitro* because levels achieved in the blood at recommended dosages are high enough to overcome an intermediate level of resistance.²⁰ Another important reason why a child hospitalised with pneumonia or bacteraemia due to NTS may not always benefit from changing to an antibiotic to which the organism is susceptible *in vitro* is because the high NTS associated case-fatality rate is often confounded by co-morbidities. In a prospective study of bacteraemia in Malawian children with severe malaria, clinical features indicating severity of malaria but not NTS bacteraemia were significantly associated with death on multivariate analysis.⁵ Other common co-morbidities such as severe malnutrition or HIV infection increase the risk of bacterial infection (including NTS), antibiotic resistance and death which complicates analysis of the association between resistance and outcome.^{3,17} A study of Ugandan children with severe malnutrition found that bacteraemia alone was not significantly associated with mortality except in those who were also HIV-infected.⁶

Therefore, while choice of antibiotic therapy in an individual will be guided by blood culture data when available, the benefits of generalising these data to the population treated empirically may be less than expected. Efficacy of alternative antibiotics is best measured by comparing to standard recommended antibiotics as was done in two recent studies of child pneumonia^{21,22} now influencing WHO case-management guidelines for the non-HIV endemic setting. However, these studies did not include or excluded at an early stage children hospitalised with pneumonia in tropical Africa, the region with the highest pneumonia case-fatality rates and where invasive NTS disease as well as malnutrition and HIV infection are much more prevalent than elsewhere.

The burden of disease due to NTS in African children requires an improved understanding of epidemiology and a far greater effort towards vaccine development.^{1,4} The more immediate problem is how to manage children with severe forms of pneumonia or presumed sepsis reaching hospitals when we know NTS bacteraemia is common and increasingly resistant to currently recommended first-line antibiotics. We have argued that while a change to a more broad-spectrum antibiotic would seem logical, research is urgently required to provide evidence of benefit. Research should be of a scale that allows *a priori* sub-group analysis for children with common co-morbidities and should measure the effect on inducing further antibiotic resistance. This will demand greater capacity in Africa for the conduct of large, multi-centre pragmatic trials and long term, linked, microbiological and clinical surveillance.

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