Leading article – Tropical infection of the gastrointestinal tract and liver series

Salmonella typhi and other salmonellas

There is almost a north-south divide between the geographical prevalence of the two broad clinical syndromes caused by the organisms of the genus *salmonella*. The prolonged bacteraemic illnesses of typhoid and paratyphoid fevers, caused by the exclusively human pathogens, *Salmonella typhi* and *paratyphi* A, B, and C, are endemic only in the economically disadvantaged countries where poor sanitation and lack of safe drinking water permit the cases and carriers to disseminate the organisms widely. On the other hand, the acute diarrhoeal illnesses caused by the animal adapted *salmonella* serotypes are an important public health problem mainly in the affluent 'north' and this is related to the phenomenal growth in the animal food industry. In the developing countries, where large scale farming and processing of food animals are not yet the norm, salmonellas are not an important cause of community acquired diarrhoea. Salmonellosis is however an important cause of morbidity and mortality in many urban paediatric units in these countries and hospital cross infection is an important factor. Many strains are multidrug resistant and invasive illnesses, often with features of meningitis and septicaemia, are common.

Typhoid fever – the areas of concern

Despite the remarkable advances in effective treatments for typhoid fever since 1948, the continuing reports of high morbidity and mortality from many of the endemic areas has encouraged a belief in increased severity of typhoid fever in the developing countries.¹ These hospital based studies, however, do not reflect the true course of the illness as only seriously ill patients of meagre means are generally admitted to these state run hospitals, often late in their illness, having received either inadequate or inappropriate treatment. The main areas of concern for the developing countries are: a need for reliable and inexpensive diagnostic tests, the continued availability of cheap, orally effective antibiotics against the background of rapidly spreading multiresistant typhoid, and the provision of a cost effective prevention strategy.

Diagnosis

Definitive diagnosis of typhoid fever requires isolation of the organism from blood, bone marrow, faeces or urine, techniques that are not always practicable in the developing countries, particularly in the rural areas. The Widal serodiagnostic test, which is now rarely used in Britain because of its well known limitations,² continues to be widely used in these countries. More reliable serodiagnostic tests are badly needed. There is no shortage of published methods – how good these are in terms of reliability, cost, and simplicity remains to be assessed critically in field conditions. In a comparative study in India,³ an enzyme linked immunosorbent assay (ELISA) test proved superior to indirect haemagglutination and indirect fluorescent antibody test, but the study lacked adequate control groups of paratyphoid fever, invasive salmonellosis or other invasive enterobacterial illnesses. Measurement of IgG and IgM antibodies to *S typhi* lipopolysaccharide antigen by indirect ELISA is also promising⁴ but may not differentiate between typhoid and para-

typhoid A. Rapid antigen detection in blood is being explored – monoclonal antibodies against *S typhi* flagellin⁵ and Vi specific antigen DNA probes⁶ offer promising approaches.

The menace of multiresistant typhoid

In the therapeutic field, the recent emergence of multiresistant *S typhi* underscores yet again the continuing battle between humans and microbes. The dominance of chloramphenicol since its introduction in 1948 came to an end in the seventies with the wide scale emergence of plasmid mediated chloramphenicol resistant *S typhi* in Central/South America and Southeast Asia but co-trimoxazole and amoxycillin proved equal to the challenge. Since 1989, however, strains of *S typhi* that are simultaneously resistant to all three antibiotics have become widely prevalent in India,⁷ Pakistan,⁸ and China⁹ and have spread to the Middle East¹⁰ and South Africa.¹¹ Imported multiresistant typhoid is being encountered increasingly in Britain¹² and other Western countries¹³ and its possible spread to the endemic areas of Africa and America needs close monitoring.

Fortunately, the fluoroquinolone antimicrobials such as ciprofloxacin have proved highly effective in both sensitive¹⁴ and multiresistant typhoid⁷ and with their additional advantages of low relapses and convalescence carriage rates,^{14,15} they are now the preferred drugs for treatment of adult typhoid anywhere in the world.

Treatment of multiresistant typhoid in children presents a dilemma as the fluoroquinolones are not currently recommended for paediatric use because they cause cartilage damage in growing animals. The prototype quinolone, nalidixic acid, however, causes similar damage in animals but has not been associated with arthropathy despite its wide paediatric use. Also arthropathy has not been seen after ciprofloxacin use in children with cystic fibrosis.¹⁶ Thus, the use of ciprofloxacin to treat multiresistant typhoid would be justified. Alternatively, clinicians may use one of the third generation cephalosporins, for example, cefotaxime, ceftriaxone, and cefoperazone, which have a cure rate of 90%.¹⁷ The necessity of giving these drugs intravenously for a period of 10–14 days (although shorter courses may be effective) is an important disadvantage in the developing countries where typhoid is predominantly a disease of children. Not surprisingly, ciprofloxacin is being used widely in places like Calcutta (personal finding). The worry, of course, is the development of fluoroquinolone resistant strains and already one such strain has been encountered in Britain.¹²

Prevention strategy

Each year millions of travellers to the endemic countries are vaccinated against typhoid but is this ritual justified? How real is the threat of typhoid to an average 'package tour' traveller? Annually, around 200 cases of typhoid fever are currently seen in Britain, mostly in people visiting relatives or friends in the Indian subcontinent. The incidence of typhoid fever among those on short term package holidays in countries like Turkey, Tunisia, Morocco, Egypt, Kenya, Far

East, and South America is extremely low. Attention to personal, water, and food hygiene reduces the risk of typhoid to negligible values and the need for vaccination for additional protection should be based on the person's nature of travel and not just the country he travels to. Visitors on a low budget, back packing holiday or those who will be living close to local people should have the vaccine protection but the present large scale vaccination of anyone leaving for a warm country, is scarcely justified.

For those who need or want vaccine protection, there are now three choices: the long established heat killed 'whole cell' vaccine, the Vi capsular polysaccharide vaccine, and an oral vaccine containing live attenuated *S typhi* 21a in enteric capsules. The 'whole cell' and the Vi polysaccharide vaccines provide broadly similar protection rate of around 70% but the efficacy of the 3 dose schedule of oral vaccine as marketed in the United Kingdom is possibly poorer.¹⁸ The vaccine field trials have all been carried out among populations in whom low level pre-existing immunity is common through previous exposure (thus giving a booster effect to the vaccine immunogenicity) and the observed protection rates may not be applicable to travellers from a non-endemic country. Also, a high infecting dose (as found in contaminated food permitting multiplication) may break through the vaccine induced protection.¹⁹

The choice of a particular vaccine should depend on the traveller's preference based on the routes of administration, adverse effect profile, and cost. The oral vaccine is expensive, requires yearly boosting but is free of side effects. The 'whole cell' vaccine is inexpensive but a primary course requires two injections four to six weeks apart for protection lasting for three years and local and systemic side effects are common, whereas the single injection Vi polysaccharide will produce immunity of similar duration with minimal side effects at a reasonable cost. The oral vaccine is not suitable for children below 6 years and the polysaccharide vaccine, for children below 18 months.

In the endemic countries, the scourge of typhoid can only be eliminated through effective public health measures. Mass immunisation at repeated intervals will reduce the incidence of typhoid fever significantly (but not of paratyphoid fever). A sanitary improvement programme of safe drinking water, effective sewage disposal, and education on hygiene will achieve similar results but its effects will be long lasting and will emerge as the most cost effective strategy because of its influence on other enteric infections.²⁰

Salmonellosis and egg – a continuing problem

The dramatic rise in food poisoning caused by *S enteritidis* on both sides of the Atlantic can be attributed at least partly to consumption of hen eggs infected by vertical transmission. Although there is evidence of a decline in the incidence of poultry flocks infection in Britain after the introduction in 1989 of statutory measures of monitoring and slaughtering of infected flocks (Zoonoses order), the incidence of human infection has remained disappointingly high.²¹ Possible reasons are imported European eggs and flocks with low level of infection escaping detection under the Zoonoses order. Continued vigilance is therefore necessary regarding the use of eggs in meals. Contrary to belief, based on limited volunteer experiments that large inocula of salmonella are necessary to induce human infection, a very low infecting dose, possibly as low as 17, has caused outbreaks.²² Also, multiplication within eggs may occur during storage and conventional cooking does not necessarily destroy them.²³

Salmonellosis – diagnostic problems

The diarrhoea caused by salmonella infection is generally

sufficiently characteristic to point to an infective aetiology but occasionally diagnostic dilemmas may arise. Thus patients presenting with severe right iliac fossa tenderness (because of predominant ileal involvement) may undergo laparotomy as suspected cases of appendicitis before the stool culture reports become available. The finding of white and red cells in faecal smears often helps to differentiate such cases from appendicitis as intraluminal inflammation is absent in the second (personal finding).

Another, not infrequent diagnostic problem is the differentiation of severe primary salmonella colitis from acute inflammatory bowel disease with coincident salmonella infection. Underlying inflammatory bowel disease should be suspected if diarrhoea remains prominent beyond two weeks or even earlier if it is increasingly bloody despite an appropriate antibiotic, for example ciprofloxacin. Presence of toxic dilatation may compound the diagnostic problem.²⁴ Sigmoidoscopic and barium enema findings are not discriminatory at this stage but histological examination of rectal biopsy specimens is often helpful.²⁵ Distortion of crypt architecture and prominent mucus depletion are features of ulcerative colitis and are present rarely in salmonella colitis. When doubt remains, such patients should receive antibiotics and corticosteroids. If the diarrhoea settles very promptly, the diagnostic uncertainty can be resolved only by a further rectal biopsy six weeks later. In primary infective colitis, histological tests usually return to normal by this time but only rarely so in inflammatory bowel disease (personal finding). Toxic colonic dilatation in salmonella colitis usually resolves without recourse to surgery and the rare cases of perforation can usually be satisfactorily treated by exteriorisation of the perforation or simple closure.²⁴

Salmonellosis – to treat or not to treat

Traditionally, antimicrobial drugs have not been recommended for salmonella enterocolitis unless extraintestinal complications are present, as randomised controlled trials have shown that drugs like chloramphenicol,²⁶ ampicillin,²⁷ co-trimoxazole,²⁸ and neomycin,²⁹ do not shorten the duration of diarrhoea and may even prolong the period of convalescent faecal carriage.³⁰ With the introduction of fluoroquinolones, the time for a therapeutic rethink has come. Ciprofloxacin has excellent activity against salmonella and penetrates macrophages well.³¹ In vivo efficacy against invasive salmonellosis has been shown both in animals³² and humans.³³ It has also been shown to be effective in shortening the duration of diarrhoea in uncomplicated salmonella enterocolitis.³⁴ So, how widely should the drug be used in treatment of salmonellosis?

Although in most patients with salmonellosis, the diarrhoea is not severe and settles within two to three days, severe and prolonged diarrhoea is not at all uncommon – often leading to hospitalisation. Bacteraemia occurs in about 10% of hospitalised cases³⁵ and certain groups of patients are more prone to develop severe diarrhoea or invasive illness – that is, those who are immunocompromised, have other debilitating diseases, have endovascular abnormalities (atheroma, aneurysm or prosthesis) or gastric hyp acidity. A higher rate of bacteraemia and severe disease are also common in patients over 60 years of age.^{35 36}

There is a strong case of instituting early empiric ciprofloxacin treatment in all these 'high risk' patients with moderate to severe diarrhoea of 'infective' type as most will prove to have either salmonella, campylobacter or shigella infections, which all respond well to ciprofloxacin. Its role in younger, previously well subjects, is more contentious but those with continuing severe watery or bloody diarrhoea should also receive the benefit of ciprofloxacin.

Optimum treatment of salmonella enterocolitis in children

in the developed countries remains controversial. In view of the perceived high risk of invasive illness antibiotic treatment is often advocated in young infants below 3 months of age.³⁷⁻³⁹ The data on bacteraemic rate are conflicting however, with estimates ranging from 2 to 45%.^{35, 37-41} In a prospective study in infants under one year, Torre *et al.*⁴² found an incidence of 6.5%, which is no higher than the adult rates. Fear that the bacteraemia may lead to meningitis has been grossly exaggerated, perhaps based on the reports of high incidence of meningitis associated with hospital based outbreaks of multi-resistant *S. typhimurium* in the developing countries.⁴³ In fact, salmonella meningitis is a rarity in the West despite the high prevalence of salmonellosis. As salmonella accounts for only a small percentage of infantile diarrhoea and as there are no clinical or laboratory predictors of bacteraemia, there is no place for empiric antibiotic treatment in average cases of febrile diarrhoea. The child who looks ill and toxic will no doubt be investigated for 'septicaemia' and receive empiric antibiotic treatment, which will cover salmonella as well. Children with pronounced diarrhoea, particularly if the stools are bloody by the time of positive stool culture report, should also be treated with either ciprofloxacin or a third generation cephalosporin. A positive stool culture by itself is not an indication for treatment in a comparatively well child just because the age is below 3 months. All bacteraemic children should probably be treated as well, although there are no data as to whether treatment is necessary in children who are settling by the time of positive bacteriology.

Control of salmonellosis

The principles for controlling the routes of infection from the farm to the kitchen are already well established as summarised by McCoy⁴⁴: prevention of introduction of infection to flocks and herds through infected new arrivals and contaminated feeds; containment of infection once introduced; reduction of contamination of carcasses by intestinal contents during slaughtering; refrigeration to prevent growth; destruction of bacteria in food by pasteurisation, sterilisation or proper cooking; and the prevention of contamination after cooking.

In practice many of these measures are either difficult to implement or entail considerable cost and not surprisingly their implication has been slow and the problem of salmonellosis continues.

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