Typhoid fever in young children

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ABSTRACT

Typhoid fever is a waterborne and food borne disorder. Unlike most other gastrointestinal infections, which predominantly affect children aged 6 months to 3 years, the incidence of typhoid fever peaks between 5 and 12 years.

Interpretation Our findings challenge the common view that typhoid fever is a disorder of school-age children and of adults. Typhoid is a common and significant cause of morbidity between 1 and 5 years of age. The optimum age of typhoid immunization and the choice of vaccines needs to be reassessed.

This article will briefly review the changes in the Typhoid fever cases that will focus on a practical approach to the care of patients with Typhoid fever. Therefore, this review is intended to serve as a practical guide for clinicians who are caring for children with Typhoid fever. and choice of pharmacologic agents to treat this cases.

In summary, it is important to consider the diagnosis of typhoid fever in children with prolonged fever. Antibiotic resistance patterns of S. typhi isolates from children who live in areas that are not endemic parallel those seen in areas of endemicity. Cases oftyphoid fever should be promptly reported to the local health department so that contacts and sources of infection can be investigated, thus further reducing transmission of this illness.

INTRODUCTION

Typhoid fever is an infection that spreads across the body caused by Salmonella enterica serotype Typhi (S. typhi) (1) in developing countries, the disease continues to be a major public health problem. In 2000, it was documented that over 2.16 million incidents of typhoid occurred globally, resulting in 216 000 deaths, with Asia accounting for more than 90% of this morbidity and mortality. While improved water quality and sanitation are the long-term solutions to this issue, (2) WHO recommend vaccination in high-risk areas as a possible short-to-intermediate-term control strategy. Typhoid fever was a leading cause of hospitalization and death in Europe and the United States' overcrowded and filthy cities. (3) The implementation of safe drinking water and sanitation systems led to a significant reduction in the incidence of typhoid. (4) Today, the majority of the disease burden is seen in developed countries with inadequate sanitary conditions (5).

Infections with *Salmonella enterica* serovar Typhi (*S.* Typhi) or *S.* Paratyphi A, B, or C (*S.* Paratyphi), referred to respectively as typhoid and paratyphoid fever and collectively as enteric fever, are important causes of morbidity and mortality among international travelers (6). Typhoid and paratyphoid fever are common in many resource-limited countries, with an estimated global burden of 10.9 million cases (116,800 deaths) and 3.4 million cases (19,100 deaths), respectively in 2017 [7].

Despite improvements in global control since the 1990s, enteric fever remains a major challenge to health systems, affecting predominantly young children in endemic countries in Asia and Africa. The recent development of new-generation typhoid conjugate vaccines (TCVs) that will allow effective immunization of infants (>6 months of age) and young children, led the World

Health Organization (WHO) to recommend typhoid vaccination program implementation in countries with a high disease burden [8].

Enteric fever in high-income countries is largely related to international travel (>85% of cases), with most cases imported from South Asia by travelers who visited friends or relatives (VFRs) [9]. The parenteral Vi-polysaccharide (Vi-PS) or oral attenuated Ty21a vaccines are recommended for travelers to countries where typhoid fever is endemic [10].

The protective efficacy against typhoid fever has been estimated to be 50–80%; while there is no vaccine for paratyphoid fever, Ty21a may have some protective efficacy against *S.* Paratyphi B [11].

METHODS

The internet database was searched for English language studies and guidelines relating to Typhoid fever in young children. The following search terms were used alone and in combination: Typhoid, paratyphoid, children, enteric fever and young . Results were reviewed and selected for inclusion based on relevance to the topic. Additional articles were identified by manually searching reference lists of included articles.

Typhoid fever:

Enteric (typhoid) fever remains a problem in low- and middle-income countries that lack the infrastructure to maintain sanitation and where inadequate diagnostic methods have restricted our ability to identify and control the disease more effectively. As we move into a period of potential disease elimination through the introduction of typhoid conjugate vaccine (TCV), we again need to reconsider the role of typhoid diagnostics in how they can aid in facilitating disease control. Recent technological advances, including serology, transcriptomics, and metabolomics, have provided new insights into how we can detect signatures of invasive *Salmonella* organisms interacting with the host during infection. Many of these new techniques exhibit potential that could be further explored with the aim of creating a new enteric fever diagnostic to work in conjunction with TCV. We need a sustained effort within the enteric fever field to accelerate, validate, and ultimately introduce 1 (or more) of these methods to facilitate the disease control initiative. The window of opportunity is still open, but we need to recognize the need for communication with other research areas and commercial organizations to assist in the progression of these diagnostic approaches. The elimination of enteric fever is now becoming a real possibility, but new diagnostics need to be part of the equation and factored into future calculations for disease control.

Enteric (typhoid) fever is a clinical syndrome caused by ingestion of the gram-negative bacteria *Salmonella enterica* serovar Typhi (*S*. Typhi) or *Salmonella enterica* serovar Paratyphi (*S*. Paratyphi) A, B, or C. Despite the availability of good antimicrobial treatment regimens and new-generation conjugate vaccines for preventing *S.* Typhi infection (TCVs), enteric fever continues to cause a significant degree of morbidity and mortality
worldwide; current estimates suggest approximately 13.5– 26.9 million new cases of *S.* Typhi and *S.* Paratyphi A (the focus of this review) each year [12]. The uncertainty around these estimates is, in part, due to the limitations in availability and performance of current diagnostic tools. Enteric fever is

associated with a broad spectrum of clinical disease, ranging from asymptomatic to severe symptoms, such as fever, malaise, headache, and complications of ileal ulceration including perforation and profuse hemorrhage.

Furthermore, some individuals who are exposed to *S*. Typhi or *S*. Paratyphi A will go on to become long-term carriers, where the organisms are retained in the gallbladder and occasionally at other sites including the kidney. Why different individuals present with differing clinical symptoms is not understood, but laboratory models and human challenge with virulent organisms have revealed a highly complex natural history of infection resulting from the co-evolution of bacteria with humans. The result is that both *S*. Typhi and *S*. Paratyphi A are exquisitely adapted to transit almost effortlessly throughout the human body, triggering a cascade of events that result in symptomatic disease in some, and long-term asymptomatic carriage in others. Consequently, diagnosing enteric fever remains an enigma, with symptomatic infections mimicking various aspects of many other infectious diseases. These factors are especially relevant in settings with the limited resources found in low- and middle-income countries (LMICs), where differential diagnostic tests (many of which have their own inherent limitations) for febrile disease are often not available, and diagnosis is performed purely on the clinical judgment of an attending healthcare worker [13].

Inaccurate diagnosis of enteric fever (and other common febrile diseases) results in the under or over diagnosing of infectious pathologies and frequently unsuitable treatment.

How is it caused?

Enteric fever encompasses typhoid fever, caused by infection with bacteria Salmonella Typhi (S Typhi), and paratyphoid fever, caused by Salmonella Paratyphi A and B. S Typhi is estimated to cause 76% of enteric fever globally. Paratyphoid fever is mostly seen in parts of South Asia and China. Ingestion of food or water contaminated by infected human faeces causes infection.5 Who gets enteric fever? Poor access to clean drinking water and inadequate sanitation and hygiene increase the risk of transmission (14). Enteric fever is most common in South Asia (incidence >500 per 100 000 population); South-East Asia, sub-Saharan Africa, and Oceania (>100 per 100 000 population); and Latin America and Caribbean (1-10 per 100 000 population). Children and young adults are more commonly affected. Among travellers, enteric fever is more common in adults after a visit to endemic areas. Use of proton pump inhibitors increases susceptibility to enteric fever by reducing gastric acidity, as per a systematic review. The role of HIV infection as a risk factor is unclear, but it may contribute to disease severity. A case series reported neonatal sepsis due to S Typhi and Paratyphi in babies born to infected mothers (15).

How do patients present?

Patients present with a gradual onset of fever which typically rises to a plateau of 39-40°C (102-104°F) towards the end of a week.8 -10 This slow rise in fever contrasts with the intermittent high fever and rigors seen in malaria. Abdominal symptoms such as diarrhoea, nausea, vomiting, and abdominal pain are common as per a systematic review on clinical profile of enteric fever (16)). Abdominal pain is diffuse and poorly localised but occasionally intense in the right iliac fossa, mimicking appendicitis. Patients may also have headache, cough, and malaise. Children under 5 years old frequently present with only fever, and the diagnosis may be missed unless they have complications.9 Symptoms start 7-14 days after exposure (range 3-60 days). Paratyphoid fever has a shorter incubation period (4-5 days), but symptoms are indistinguishable from those of typhoid fever (17).

How is it diagnosed?

Enteric fever is mainly a clinical diagnosis based on history and examination. A gradual onset of fever, particularly with one or more abdominal symptoms, should raise suspicion of enteric fever in endemic areas. Ask about travel to endemic regions. Physical findings are often non-specific. Soft tender hepatosplenomegaly, abdominal distension, mild ascites, and a diffuse or localised tenderness may be noticed on abdominal examination. Hepatitis and hepatomegaly are more common in children under 5 years old and are seen in 30-50% of children with enteric fever.9 Scattered wheezes or crepitations in the chest might suggest bronchitis. A bradycardia relative to the height of the fever may be noted. Rose spots, blanching erythematous maculopapular lesions on the trunk, were considered characteristic of typhoid fever, but are now rarely reported. If the disease progresses beyond the first week the patient often becomes impassive and unresponsive (18).

What are the investigations?

Request a complete blood count and blood culture. The total white cell count is usually within, or just below, the normal range in enteric fever. Leucocytosis (raised white cell count) may suggest intestinal perforation or another diagnosis such as a pyogenic infection or leptospirosis. A mild normochromic or hypochromic anaemia, mild thrombocytopenia, and mild elevation of liver transaminases with a normal bilirubin are common(19). The C reactive protein (CRP) is usually elevated in enteric fever. Blood culture is the optimum method to confirm the diagnosis by isolating the organism and testing antimicrobial sensitivity. It takes two to three days for a result, and empirical antimicrobial treatment is required in the interim. It has a sensitivity of 61% (95% CI 52 to 70) (see supplementary table 2 on bmj.com). A negative blood culture does not exclude enteric fever. Antibiotic pre-treatment, low sample volume, and low circulating bacterial load in the blood result in this low sensitivity. Bone marrow culture gives a higher yield, but it is rarely performed. Faeces, urine, or bile aspirate may be cultured, but a positive result may indicate chronic faecal carriage rather than acute infection (20). Serological tests, including the Widal test and newer rapid diagnostic tests, are not confirmatory in the acute phase of illness. The Widal test measures antibodies against O and H antigens of S Typhi and S Paratyphi A. It is cheap and simple but lacks sensitivity and specificity. A single measurement in the acute phase of the illness may be false negative or false positive. Other commercially available, point-of-care rapid diagnostic tests detect IgM antibodies against S Typhi antigens. These are insufficiently accurate to be useful in diagnosis. In a diagnostic accuracy review, the TUBEX test (14 studies) had an average sensitivity of 78% (95% CI 71% to 85%) and specificity of 87% (82% to 91%). The Typhidot test had an average sensitivity of 66% (59% to 73%) with a specificity of 81% (58% to 93%) across a number of versions. Novel assays to detect antibodies, antigens, and DNA in blood are being developed (21). In endemic areas and returning travellers, rule out malaria and dengue fever with testing. Consider other causes of acute fever based on local disease patterns such as scrub and murine typhus, leptospirosis, brucellosis, influenza, chikungunya, and covid-19 and other viral conditions (22)

What are the complications?

Severe disease usually manifests in the second or third week of illness with continuing fever, increasing weakness, anaemia, weight loss, persistent vomiting, or a clouded mental state. Delayed treatment, the virulence of the bacterial strain, and host factors contribute to disease severity (23). In a pooled analysis (13 studies, 2554 patients), 27% (95% CI 21% to 32%) of patients with enteric fever experienced complications (25). Encephalopathy, gastrointestinal bleeding, nephritis, and hepatitis are common complications seen in 5-7% of hospitalised patients. Intestinal haemorrhage or colitis and intestinal perforation can occur. These present with signs of acute peritonitis or more insidiously with increasing restlessness, a diffusely tender abdomen, hypotension, tachycardia, and shock (26). The mean case fatality rate with enteric fever is 2.49% (95% CI 1.65% to 3.75%), and 4.45% (2.85% to 6.88%) in hospitalised patients as per a recent systematic review (44 studies, 41 723 patients). Between 5% and 10% of patients experience a relapse with a second episode of fever two to three weeks after initial recovery. This usually responds to the original treatment (27).

How is it treated?

Initial treatment and referral Patients can usually be managed at home if they have no complications. Referral to a hospital is necessary if the patient is vomiting and unable to take oral medication, is clinically unstable has developed complications, or if the diagnosis is uncertain (29). Typhoid fever is treated with antibiotics that kill the bacteria. It's important to take the medicine for the whole time that the doctor prescribes, even if your child feels better. If you stop it too soon, some bacteria could remain (30).

Most kids start feeling better within 2 to 3 days of beginning treatment. Offer your child plenty of fluids to prevent dehydration. Kids who are severely dehydrated due to diarrhea might need to get IV (intravenous) fluids in a hospital or other medical care facility(31).

CONCLUSION AND RECOMENDATION

Typhoid fever remains a significant health problem in developing countries. The incidence admission is high and therefore effort at providing clean potable drinking water, health education on personal hygiene, environmental sanitation and proper sewage disposal could be a preventive measure. In addition the availability of appropriate well equipped laboratory facilities for the diagnosis of typhoid fever by culture would enable the institution of appropriate treatment. It is in our opinion that the use of widely test should be evaluated properly in Iraq and see if the test should be abandoned. This will save the patients a lot of financial resources. It will also save gross abuse of antibiotics and on the long run prevent antibiotic resistant.

Our study concludes that typhoid fever is endemic with the highest incidence occurring in children (both girls and boys) of age 5–10 years, especially after rainfall months. Facility-based surveillance missed a significant proportion of potential cases raising the need for even more extensive surveillance systems. There is also a need to conduct studies on the healthcare-seeking behavior of the population, and practices of the healthcare providers, so that more precise studies can be designed to capture true incidence. This will ultimately be required in order to take the decision for the use of mass scale vaccination against typhoid fever in high-risk age groups

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