Complicated enteric fever: challenges in identification, reporting and inclusion in global burden of disease estimates

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Abstract

**Background:** Enteric fever (typhoid fever and paratyphoid fever) remains an important public health problem in regions of the world where water and sanitation conditions are compromised, particularly in South Asia, East Asia and Africa. The clinical presentation of enteric fever varies from an acute non-complicated disease to a severe clinical form associated with intestinal or extra-intestinal manifestation. Currently available reports on the community-based burden of enteric fever have not included assessments of the severity and complications of enteric fever at a population-based level. Herein, we present a case of a patient with intestinal perforation and peritonitis caused by enteric fever. We also discuss the medical implications of typhoid fever including its persistent occurrence in high-risk areas, as well as the devastating medical and socioeconomic consequences that individuals and their families face. This case illustrates that there is an important burden of disease associated with complicated typhoid fever that it is often not captured in currently available assessments of the impact of this ancestral bacterial pathogen.

Introduction

*Salmonella enterica* infections are associated with three distinct clinical syndromes: a) enteric fever resulting from infection by the typhoidal *Salmonellae* (*Salmonella Typhi* and *Salmonella Paratyphi* A, B, and C); b) non-typhoidal *Salmonella gastroenteritis*; and c) non-typhoidal *Salmonella bacteremia* (invasive disease caused by non-typhoidal *Salmonellae*) [1]. Enteric fever (EF) is an acute systemic infection, representing two similar clinical illnesses, typhoid and paratyphoid fever, caused by different serotypes of the bacterium *Salmonella enterica*, serotypes Typhi (*S. Typhi*) and Paratyphi (*S. Paratyphi* A, B, and C), respectively. Combined morbidity and mortality caused by infections of *Salmonella enterica* serovars is considerable since this group of bacterial pathogens are responsible for a global toll of approximately one million deaths annually [2,3].

Case presentation

A twenty-two-year-old single male, youngest of four siblings, living in Karachi, Pakistan suffered from an illness consisting of fever, headache and myalgias. He works as a helper receiving daily wages with a local construction contractor. He continued having pain until the next morning when he noticed loss of appetite and nausea; and suffered an episode of vomiting. He was unable to work that day, and by the second day of his illness, his mother believed that his illness was caused by the “evil eye” and requested the services of the neighborhood healer who confirmed the “evil eye” effect. The local healer proceeded to read some “sacred” verses and to prescribe remedial water and powder; and also provided the patient with some written words in a piece of paper to be burnt. He experienced some limited improvement but by the next day he continued to experience the same symptoms and his cousin took him to a physician in the neighborhood. His initial diagnosis was “low blood pressure” and the patient received intravenous fluids and received a dose of an unknown intravenous medication. By the fourth day of his illness, an episode of high fever returned. Due to persistent fever, he visited the neighborhood physician for the second time. The physician prescribed intravenous fluids and an intramuscular injection (unknown medication). The patient experienced minimal improvement, and next day patient visited the physician for the third time due to the persistence of fever and abdominal pain. This time the doctor advised some laboratory tests and diagnosed him as having malaria (based on a “some” blood test) and prescribed medicine accordingly. Despite these interventions, the patient condition progressively deteriorated. The patient then visited another clinic at some distance despite financial challenges. This second physician consulted, recommended intravenous fluids and antibiotics; and despite these interventions, by the third day of treatment (ten days from the onset of symptoms), his condition became grave with severe abdominal pain and persistent vomiting. At this point, the patient was transferred to a regional clinic where a third physician evaluated him. By then, the patient was diagnosed with acute abdomen with associated hemodynamic instability and oliguria. He was diagnosed with typhoid fever and intestinal perforation; and was referred to a tertiary care hospital for appropriate management. At this center, the patient underwent exploratory laparotomy confirming the diagnosis of intestinal perforation for which the surgeon stated that it had the characteristic macroscopic signs of perforation peritonitis caused by typhoid fever. The patient required surgical closure of the

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perforation with an ileotransverse colostomy. The patient remained hospitalized for thirteen more days to receive supportive and specific antimicrobial therapy. The patient's mother and one of two cousins cared for him during his hospital stay. The patient and one of his cousins lost their jobs due to their inability to continue working during the illness. According to the patient, the out of pocket cost during the illness was approximately $100 USD in addition to the loss of productivity ($5 USD per day of the patient and his cousins). Transport cost to the tertiary care hospital was $10 USD per visit. Since the surgery took place in a public hospital, specific cost of surgery was not assessed. From a social support perspective, the patient restricted mingling with his friends, primarily due to the stigma of having a colostomy bag. The cost of supplies for colostomy bag was approximately of $20.00 USD per week.

Our team also met with the treating physician who was responsible for transferring the patient to the tertiary care hospital to obtain additional information about his experiences in managing cases of complicated enteric fever. The physician reported that the patient presented with severe abdominal pain, vomiting, and with high-grade fever (>103.5°F). On physical examination, his abdomen was tender, his blood pressure was low, and his urine output was significantly reduced. Based on his clinical course, his diagnosis was that of intestinal perforation caused by typhoid fever. He also reiterated that, on a daily basis, many febrile patients with a possible diagnosis of enteric fever seek care at his office. However, he is unable to perform confirmatory diagnostic testing for typhoid fever or else, of any other infectious disease contemplated supporting his provisional diagnosis. He further explained that blood culture testing is not performed locally and therefore patients and their families have to travel long distances. Furthermore, most patients evaluated at his office are extremely poor and are unable to afford the cost of any laboratory testing.

Discussion

This case illustrates that typhoid fever and its associated complications remain as an important public health problem in Pakistan. Typhoid fever is associated with a plethora of complications and sequelae that impose a substantial burden of disease in terms of the economic hardship to those affected. A constellation of factors can also be directly linked to poor clinical outcomes including inappropriate health seeking behavior of those affected with enteric fever, financial constraints, and misconceptions about the disease. From a healthcare standpoint, the undifferentiated clinical presentation of typhoid fever in conjunction with the unavailability of quality laboratory facilities to confirm the diagnosis in highly endemic settings often leads to unnecessary delays in diagnosis. These factors often result in burdensome complications and long-term sequelae such as in the case illustrated herein. These complications and the suffering caused by affected individuals and their families are not often captured in most of the estimates of disease burden. More importantly, complications of typhoid fever and it sequelae create a vicious cycle of destitution by affecting the already disenfranchised populations living in endemic settings without access to clean water and sewage.

The persistent burden of enteric fever

Across South and Southeast Asia, some areas in Latin America and Africa, typhoid fever remains the most commonly identified clinical syndrome caused by S. enterica [4]. Worldwide, it is most common in impoverished areas that are overloaded with poor access to sanitation. Non-epidemic incidence estimations suggest that south-central Asia, south-east Asia, and southern Africa are areas with high rates of S. typhi infection (more than 100 cases per 100,000-person years) [5]. Research conducted on enteric fever over the last decade in Asia, has also documented high disease incidence of enteric fever with elevated morbidity, particularly in the pediatric age group (<5 years) [6]. Recent reports too demonstrate a rising number of cases of S. Paratyphi A in South Asia with a presentation and severity similar to that of S. Typhi [7]. Studies to determine the burden of disease of typhoid fever in Asia have provided information on the incidence of the disease but little information has been added on severity, complications, and clinical outcomes such as mortality [8,9].

Many consider enteric fever a disease seen only in outpatient clinics and only requiring treatment with inexpensive and oral antibiotics. The reality for many individuals living in extreme poverty - those living in poorly constructed dwelling with limited to no access to clean water; with no available sewage disposal system, poor nutrition, and low education level - is that exposure to enteric pathogens is an inevitable fate of their biological and social destinies [10]. Furthermore, once they are infected, the prevailing inequalities (i.e., insufficient access to adequate health care services and insufficient financial resources to travel to seek care) and socio-cultural determinants, influence individuals’ health seeking behavior and thus grave consequences to the patients [11,12].

Available reports on typhoid fever have two dimensions; one that presents the population level typhoid fever incidence and is well documented through population-based studies, and the other that describes complicated/severe disease presenting to tertiary care hospitals as case reports and hospital-based studies. The severe cases reported by population-based studies are close to minimal, whereas hospital-based studies with a range of complicated cases fail to define a denominator and hence are unaccounted for in efforts to measure global burden of disease. The disadvantage thus, is that severity estimates are based on “expert opinion” resulting in less confidence by global scientific community. Historically when typhoid fever related hospitalizations and mortality were frequently reported, typhoid fever derived significant policy makers’ attention at national and international fora, and thus was a priority disease for control measures. For example, typhoid vaccine development and use during Anglo-Bohr war, as well as in Spanish-American war was a result of alarming case fatality rates [13-14]. In contrast since 2000 studies have repeatedly and regularly reported high typhoid and paratyphoid fever incidence in Asia and Africa with no minimal policy derive for typhoid vaccine use, instead finding reasons for delaying vaccine use in developing countries. Typhoid incidence is high [15], it affects all age groups with a peak incidence in children four to twelve years [16,17], cost of illness is very high [18], existing vaccines are efficacious with population impact [19], and a WHO pre-qualified vaccine is available and cost effective; public health use of typhoid vaccines and other control measures to combat enteric fever burden has been negligible [20]. Factors causing hindrance for the large-scale typhoid vaccine use have been differences in comparative lower incidence in rural areas, vaccine immune response in younger children (younger than five years), a clear vaccine delivery strategy and vaccine cost. Despite Gavi, the vaccine alliance’s commitment to support a typhoid vaccine, the above factors have played a major role in the absence of typhoid vaccine financing in typhoid endemic countries.

The two drivers of vaccine policy are disease specific mortality and severity resulting to a burden on health care system. Data on severe typhoid is not systematically collected and presented, and if it is, it comes from hospital-based case reports with many years of data. The above factors have thus resulted in minimal vaccine manufacturers’ interest in
vaccine development and production, and country licensure leading to WHO prequalification. In the presence of high antimicrobial resistance, global complication and mortality data are an under-estimate [21-23].

Discussion

The patient was diagnosed with complicated typhoid fever as perforation peritonitis with severe sepsis. Undifferentiated febrile syndromes in resource-poor settings usually in tropical or subtropical settings with prevailing low sanitation and insufficient access to safe water include a broad differential diagnosis of infectious diseases including enteric fever, dengue, tuberculosis, brucellosis, leptospirosis, rickettsiosis, chikungunya, and others [24]. Clinical judgment by the treating physician is often, the only way to care for patients, and therefore it is commonplace to institute concomitant empiric therapies for patient management. As this case illustrates, the true number of patients with severe and complicated enteric fever is difficult to ascertain in these communities where the lack of infrastructure, disorganized urban or peri-urban settlements leading to poor hygienic practices combined with lack of clean water result in a high rate of enteric transmitted illnesses including typhoid fever and paratyphoid fever [25-28]. The combination of undifferentiated febrile illnesses with often atypical clinical presentations; and insufficient availability of laboratories performing blood cultures converge with a plethora of social, cultural, and economic determinants to synergistically produce poor clinical outcomes. Therefore, we can conclude that at this point in time, the occurrence of complicated typhoid is almost exclusively seen in highly-endemic areas of enteric fever which not coincidentally, are communities living in extreme poverty.

Complications of Enteric Fever: Intestinal Perforation and Peritonitis

*S. Typhi* usually enters the human host through ingestion of contaminated water or food that subsequently survive the gastric acid milieu to then gain access to the micro-fold cells (M cells) of the intestinal epithelium through the activity of bacterial proteins delivered into host cells by a type III secretion system which is encoded the pathogenicity island SP-1 [29]. Subsequently, after forming an intracellular replicative niche, there is activation of a second type-III secretion system, but this time encoded by SPI-2. Some of the bacilli arrive into the lamina propria, where an influx of macrophages ingests the bacilli; and it is believed that typhoid bacilli reach the bloodstream mainly through lymph drainage from mesenteric nodes to then reaching the systemic circulation. As a result of this primary bacteremia, the pathogen reaches the intracellular sanctuary of the reticuloendothelial system where it replicates and spearheads to a secondary bacteremia that reaches the intracellular sanctuary of the reticuloendothelial system [26]. His description of cases of perforation demonstrated that it was usually a single perforation located in the ileum in the center of an ulcer. While intestinal perforation and mortality rates declined after the availability of chloramphenicol in 1949 and other antimicrobials afterwards, this condition continues to occur in highly endemic places among disenfranchised populations with prevailing health inequities and inequalities; and often leading to catastrophic consequences [27] as shown in this case. These complications are a result of undifferentiated febrile illness or non-specific clinical presentations, challenges with cost and unavailability of diagnostic techniques, and patient health seeking behavior [28]. A major challenge is the non-specific presentation of typhoid fever earlier during the course of the disease that makes it difficult to differentiate from other febrile illnesses [4]. In the current case report, we highlight the challenges in under reporting and difficulties that patients undergo as undifferentiated febrile illness leading to a complicated clinical course.

Enteric Fever is a Neglected Disease of Poverty

Case studies such as the one illustrated in this report provide information in assisting health practitioners in the clinical management of individuals with similar clinical presentations. However, its most important value resides in understanding the landscape of determinants of clinical outcomes at the individual level, at the community level, and at the healthcare level. Thus, these factors assist in designing surveillance studies to document the true burden of disease and hence guide population-based public health interventions. Certainly, this case of intestinal perforation highlights multiple issues ranging from individual behavior, household social and economic capacity, health care provider behavior, and health system performance. The purpose of reporting this case is to document the challenges involved in quantifying such information in large population-based studies. *Salmonella enterica* subspecies I include the most common bloodstream bacterial isolates in Asia and in Africa [33]. This patient would have been missed easily in a surveillance study even if there were surveillance activities in the area where the patient resided due to the following two factors: a) the patient was 22 years-old and typhoid fever is considered less common; b) the patient’s health care seeking ranged from “evil eye” healers to tertiary care hospital surgeons; and in the course of the disease (15-days) the patient was evaluated by five different “evil eye” healers to tertiary care hospital surgeons; and in the course of the disease (15-days) the patient was evaluated by five different health care providers. Therefore, this case study brings to the surface the importance of adapting surveillance efforts to the community-level and contemplating all potential scenarios of health seeking behaviors. In addition, information from these sources should be able identify unique cases, otherwise, cases like the one described may be counted more than once or not counted at all depending on participation of these health care providers with the surveillance system.
Public health implications

The availability of a limited number of prospective, community-based studies of febrile illness and blood culture-confirmed typhoid fever has often found few complications and long-term sequelae and limited case fatality from typhoid specifically and enteric fever in general [6-34]. As this case illustrates, there is a substantial hidden burden of disease that needs to be documented; and lack of useful estimates on enteric fever hospitalization, severity, complications, and mortality at a population-level needs comprehensive approach to burden of disease studies. However, there are significant challenges that remain in measuring complications and mortality data [8]. Positively, there is not a universally accepted definition of severe or complicated typhoid fever to assist in collecting standardized data. In many settings, given the increasing availability of safe and effective antimicrobials prescribed or given on an outpatient basis, hospitalization is therefore perceived as the main indicator of severity by many clinicians. Additionally, persistent and high-degree fever despite orally prescribed antimicrobials is also considered as a sign of clinical severity of enteric fever, often leading to hospitalization. In the presence of such ambiguities, community-based studies that collect information on clinical course of the disease will be guide future studies.

Nevertheless, information from existing case reports of hospital-based studies can provide a useful guide for enteric fever management and surveillance. In a study in Vietnam, 15.5 percent of all culture confirmed cases were classified as severe cases where 7.4 percent experienced gastrointestinal bleeding, 6 percent experienced intestinal perforation, 5 percent experienced hepatitis, and 2.6 percent experienced encephalopathy with an overall 0.5 percent case-fatality rate [35]. In addition, typhoid fever was found to be the second leading cause of perforation peritonitis in a case series in Delhi, India with a study in Pakistan reporting with similar results. In multiple outbreaks of typhoid fever in Arica, patients presented with intestinal perforation as a major complication of enteric fever [36-39]. To support the public health relevance of complicated enteric fever, a systematic review conducted from 1991 to 2011 identified a mortality rate of 15.5% in hospitalized cases of intestinal perforation [27]. These considerations illustrate the urgent need for focusing on severity of the disease and its associated complications and clinical outcomes in increasing the accuracy of burden of disease estimates that translate into effective policy-making and public health action.

In summary, currently available reports on the community-based burden of enteric fever have not included assessments of the severity and complications of enteric fever at a population-based level. There is evidence from hospital-based case series demonstrating that the forms of complicated enteric fever continue to affect population living in highly endemic areas. Therefore, the challenge is to be able to quantify the medical and socio-economic impact of complicated forms of enteric fever. Typhoid fever is an ancient infectious disease and the global public health response to this disease has been hampered by the insufficient surveillance efforts to systematically evaluate its complications, clinical outcomes, long-term sequelae, and socioeconomic impact.

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Conflicts of interest

None

References

20. Date KA, Bentsi-Enchill A, Marks F, Fox K (2015) Typhoid Fever vaccination strategies. Vaccine [Crossref]


