

# Salmonella Typhi – a Quiet Bacteria with a Loud Message: An ICU Case Report



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## ABSTRACT

Typhoid fever, caused by *Salmonella enterica*, serovar *Typhi*, is restricted to humans as its host and evades the human immune system with ease. This quality has been one of the many reasons why it is commonly found as an endemic bacterium in emerging economies. Also, due to a remarkably low yield from blood cultures (median of 1 CFU/mL of blood), *Salmonella* septicemia is uncommon. New evidence gathered together with clinical investigations

have provided insight into the mechanisms that underlie the pathogenesis of typhoid, host restriction as well as antibiotic and vaccine susceptibility. However, very little has been done to curb the persistence of disease and emergence of resistant strains. We discuss a case of *Salmonella* Septic Shock in the Intensive Care Unit (ICU) that takes us through various aspects in diagnosis, the treatment potential and the problems surrounding prevention.

**Keywords:** typhoid, fever, *Salmonella*, serovar

**Cite This Article:** Adu-Gyamfi, R., Hoosain, F., Chetty, S. 2019. *Salmonella Typhi – a Quiet Bacteria with a Loud Message: An ICU Case Report*. *Bali Journal of Anesthesiology* 3(2): 129-132. DOI:10.15562/bjoa.v3i2.161

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## INTRODUCTION

Typhoid fever (enteric fever) is a gastrointestinal infection caused by *Salmonella enterica*, serotype *Typhi* or serotypes Paratyphi A, B or C. Humans are the only hosts and transmission occurs through the fecal-oral route. With the world becoming a global village, it is incumbent on health professionals to become more knowledgeable regarding the effects of this disease on human health. Understanding the burden of enteric fever helps with decision-making at all levels of healthcare and could also serve as a guide for travelers. The bacteria are present in many Southeast Asian countries as well as in Africa, Central and South America, and Western Pacific countries, where water and sewage sanitation is poor. Flood or drought phenomena in endemic regions also cause the rapid spread of the bacteria.<sup>1</sup>

Typhoid fever is not as well understood in Africa as elsewhere; largely due to the poor resources for laboratory diagnostics and insufficient infrastructure to support epidemiological and clinical studies. These problems are manifestations of the challenges faced by a continent already riddled with numerous chronic conditions and infectious diseases. The inability of governments to provide safe food and potable water is a key reason for the high prevalence of this disease.<sup>2</sup>

Despite the genetic similarity of *Salmonella typhi* (SALTY) and *Salmonella typhimurium* (90% of their genes are shared), there remains a poor understanding of the genetic differences that underlie the ability of SALTY, but not *Salmonella typhimurium*, to cause enteric fever.<sup>3</sup> Even though SALTY resides

(for most of its lifecycle) in the biliary and gastrointestinal tract, intestinal inflammation is generally uncommon in enteric fever due to the bacteria's ability to evade the immune system. Additionally, blood-borne infection leading to systemic sepsis is even more rare, for the same reason.

## CASE REPORT

We report the case of a 28 years-old male with no known co-morbidities who presented with septic shock after a ten-day history of abdominal pain, malaise, vomiting, and diarrhea. Associated symptoms included night sweats, chills, and rigors, lethargy, light-headedness, and cough. His abdominal pain was initially peri-umbilical, colicky, and persisted for more than 24 hours.

By day 4 the patient had become constipated with worsening weakness, abdominal distension, nausea, and vomiting. He was referred to a tertiary healthcare facility, in a delirious state, 6 days after the onset of symptoms. An abdominal CT scan revealed right iliac fossa fluid collections with a possible ruptured appendix necessitating an emergency laparotomy. Intra-operative findings indicated peritoneal inflammation, primarily in the right iliac region, involving a severely inflamed, thickened terminal ileum, dilated colon, and multiple mesenteric lymph nodes. The appendix was located but was only mildly inflamed with no perforation or necrosis. There was frank pus found in the dissected abdominal lymph nodes, but no evidence of necrosis or perforation of the small bowel. An

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appendectomy and a transverse loop colostomy were performed.

The patient had to be transferred to the intensive care unit (ICU) on adrenaline because of hemodynamic instability. The admission blood chemistry indicated hyponatremia, hypokalemia, and uraemic; fulfilling the criteria for acute renal injury. He also had leucocytosis and thrombocytopenia. Other blood tests indicated deranged liver functions, low calcium, magnesium and inorganic phosphate levels with elevated C-reactive protein (CRP), admission APACHE II of 31 and SOFA score of 10.

The blood and intra-abdominal specimens submitted for analysis showed gram-negative bacilli subsequently identified as SALT sensitive to ciprofloxacin. The patient's antibiotic therapy was changed appropriately. He came off inotropes within 24 hours and was discharged by day 3 to the general ward. He was managed in isolation for 1-week post op and discharged to a step-down facility, then discharged home to complete 21 days of oral ciprofloxacin. A follow-up blood culture and stool samples 6 weeks after admission showed no growth for SALT. On six months follow-up, the patient's stoma has been reversed and he has resumed normal activity.

## DISCUSSION

The Kaufmann-White scheme classifies SALT as Group D with O-antigen type O9-12, phase-1 flagellin type H:d, and Vi capsule positivity. Humans are the only known hosts of SALT, however, the organism can survive for several days in both freshwater and seawater, and for prolonged periods (up to several months) in contaminated foods. The infectious dose has been determined in human challenge studies to be around 10,000 organisms, but may vary between individuals and in different settings. Recent studies indicate it may actually be lower.<sup>4</sup>

The Vi capsule has anti-inflammatory properties, limiting the deposition of complement component CR3 onto the bacterial cell surface, restricting immune activation and increasing resistance to serum killing. It is also postulated to modulate interactions between LPS and TLR4 and increase the local concentrations of the immune-regulatory cytokine interleukin 10 (IL-10) in the infected tissues.<sup>5</sup>

The bacteria invade the intestinal mucosa potentially through microfold (M) cells (in the gut-associated lymphoid tissue (GALT) of the Peyer's patches in the small intestine) and establish an initially clinically undetectable infection involving significant systemic dissemination and transient primary bacteremia.<sup>6</sup> The pathogen in some cases, cause necrosis of the Peyer's patch, appearing

macroscopically as ulcerations commonly seen on the anti-mesenteric mucosal lining of the terminal ileum. In untreated cases, perforation can occur.

Mostly, however, it does not trigger a rapid inflammatory or diarrheal response. This lack of mucosal inflammatory response is what makes SALT disease distinct from most disease caused by non-typhoidal Salmonella (NTS) serovars. The average incubation period after infection is 10 to 14 days (range 5 to 21 days). This may not be followed by clinical symptoms. Those who go on to develop disease become fatigued with a classical stepwise manner fever. If left untreated, the temperature may remain high (>39 °C) and associated symptoms generally, include coughing, vomiting, headache, and relative bradycardia or tachycardia.<sup>6</sup>

Typhoid can be difficult to distinguish clinically from other systemic and abdominal conditions, such as malaria, appendicitis, abdominal tuberculosis, Crohn's disease or even respiratory tract infections. However, a well-trained clinician with knowledge of other febrile diseases may observe particular clinical patterns, including a spiking temperature or Rose spots on the chest.<sup>7</sup> Our patient manifested a broad range of symptoms which are usually rare. These included diarrhea (considered to be more frequent in children and HIV-infected adults), pulmonary, cardiovascular, central nervous system manifestations, and septicemia.

As occurred in our patient, hepatic damage can also occur during the acute stage. The life cycle of SALT in the human host makes culture yields from the blood samples remarkably low, with a median of 1 colony-forming unit (CFU)/mL of blood, explaining why SALT septicemia is a rare occurrence.<sup>8</sup> Intestinal inflammation is generally not regarded as a feature of typhoid due to the organisms' ability to evade immune response in the mucosa.<sup>5</sup>

However, histological examinations of perforation sites have identified a combination of acute and chronic inflammation close to the perforation site. In our patient, there were both macroscopic and histological features of inflammation. This may indicate that there could have been an impending perforation of the bowel. A key feature of typhoid is the human carrier state. Individuals in this state can shed high levels of SALT while being outwardly asymptomatic and leading a normal life. The molecular mechanisms involved in establishing the carrier state are not completely understood, but colonization of the gallbladder is key to SALT. The carrier state is also associated with intestinal re-entry from the gall bladder and this can lead to reinfection and subsequent clinical manifestations. Gallbladder damage and gallstones can potentially contribute to carrier risk.

Various studies have found that between 2% and 4% of individuals in endemic regions can be carriers. Individuals in typhoid endemic regions who have never reported having typhoid have been found to have elevated anti-Vi antibody levels.<sup>9-11</sup> Mortality rates in untreated typhoid fever can be as high as 26%.<sup>12</sup> Some studies had shown mortality rates of 10% or lower, however, these studies were done in carefully managed patients and do not represent the reality of managing typhoid in the developing world.

The introduction of chloramphenicol (in 1948), ampicillin (1961), co-trimoxazole (1970s), and third-generation cephalosporins and fluoroquinolones (1980s) reduced the mortality associated with typhoid fever considerably. However, resistant strains to all three first-line antimicrobial drugs emerged prior to the introduction of the latter two agents in the 1980s, followed by strains resistant to the fluoroquinolones in the 1990s. Extended-spectrum  $\beta$  lactamase-producing organisms (ESBLs) have been increasingly noted in recent times.<sup>13</sup> Fluoroquinolones are a treatment of choice for typhoid even in the light of resistance in some cases.

SALTY induces pathogen-associated molecular patterns (PAMPs), via lipopolysaccharide (LPS), flagella, and peptidoglycan. There is a drop in systemic zinc concentration, the levels of circulating platelets and lymphocytes, as well as hemoglobin levels.<sup>14</sup> Levine MM, et al<sup>15</sup> have shown that protection can be induced by a variety of different vaccines (live attenuated, live and Vi). There are a number of live oral vaccines such as Ty21a that have been developed from attenuated mutants of SALTY. There is both Vi-dependent and Vi-independent protective mechanisms in mounting immunity against SALTY.<sup>15</sup>

Evidence has shown that previous SALTY infection is not protective in the long term and that people can be re-infected within weeks or months of a primary episode. Relapse may be a consequence of either recrudescence by the same strain from tissues or reinfection from an environmental source. Like other resource-constrained countries, typhoid fever is endemic within South Africa but with an unknown local burden. The epidemic potential of typhoid fever has been demonstrated in 1993 and 2005 when repeated outbreaks were observed in Delmas (Mpumalanga) affecting over 1 000 cases, and over 400 suspected cases and three deaths respectively.

According to the 2015 National Typhoid and Paratyphoid Fever Prevention and Control Guidelines, South Africa observes a mixed pattern of endemic disease and sporadic cases not only in the rural setting but also within more developed

areas of the country. Travelers, both local and international, returning from areas with endemic transmission are suspected to account for a large proportion of cases in South Africa but very little is done to screen these individuals. Furthermore, clinicians are likely to make a diagnosis of the other differentials of typhoid fever. All these factors contribute to *missed* cases, especially in the carrier population. Our patient lived in the Eastern Cape for 6 months before only presenting 2 weeks after returning to Cape Town. The possibility remains that the patient was a chronic carrier of SALTY who developed the recrudescence illness, or alternatively that he was newly infected from a recent contact. Questions also remain as to whether the unprecedented drought in the Western Cape in 2016-2018, could have contributed to the risk infection and if so how many other people have also been infected.

## CONCLUSION

There has been enormous progress in our understanding of the molecular pathogenesis, evolution, epidemiology, and immunology of Salmonella infections in recent decades. However, our patient presented with an array of clinical features which hitherto were considered rare. It might, therefore, signify that we may be dealing with a mutated species and this should be a matter of concern. Instituting measures such as screening of tourist/travelers, education of clinicians and the general populace, provision of clean water, vaccination and provision of needed facilities and infrastructure to aid in clinical and epidemiological studies on SALTY has become even more necessary especially with the emergence of resistant species. If this becomes widespread, treatment options could become severely scarce and very expensive. In the end, not only would cost of management be high, but more lives will be lost. SALTY, survives poorly in the environment and is trapped in the human population. If emerging economies, including South Africa, were to put the right measures in place, the control and even elimination of the disease can be a possibility.

## ACKNOWLEDGMENT

The authors report no conflict of interests.

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