

# Acute Cholelithiasis with Calculous Cholecystitis and Impending Perforation: A Rare Presentation of *Salmonella* Typhi

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## Abstract

Cholelithiasis is a common biliary condition with substantial morbidity, often progressing to acute calculous cholecystitis when complicated by gallstone obstruction. While the typical pathogens implicated in biliary infections are enteric Gram-negative bacilli, *Salmonella enterica* serovar Typhi (*S. Typhi*) is a rare etiological agent, particularly in immunocompetent individuals, and can present without any systemic typhoid features.

**Case Presentation:** This case report describes a young female presenting with right upper quadrant pain and radiological evidence of acute cholecystitis with impending gallbladder perforation. Intraoperative findings included a phlegmon with pus, inflammation, and the presence of gallbladder perforation, with microbiological culture of these fluids revealing the pathogen as *S. Typhi* resistant to ciprofloxacin, ampicillin, and tetracycline. Histopathology confirmed the findings. The case underscores the emerging prevalence of drug-resistant *S. Typhi* in endemic regions such as India and highlights the importance of routine culture in severe cholecystitis cases, even in the absence of overt enteric fever. It also emphasizes the need for vigilance in endemic settings where typhoid complications may present atypically.

**Key words:** Cholecystectomy, Cholecystitis, Typhoid fever

## INTRODUCTION

Cholelithiasis is the development of gallstones within the gallbladder. They are usually formed due to the accumulation of bile components (cholesterol, bilirubin, and calcium salts). Globally, about 10–20% of adults carry gallstones,<sup>[1]</sup> and though a significant proportion of gallstone cases are clinically silent, approximately 10% progress symptomatically within 5 years and 20% within 20 years of diagnosis. Gallstone occurrence escalates with advancing age, with over one-fourth of women above 60 years affected. In India as well, several studies have been done in regards to these abdominal diseases, with prevalence ranges between 2% and 29% depending on region and demographic factors.<sup>[2]</sup> If the disease worsens, acute cholecystitis is the more prevalent consequence of cholelithiasis.

Cholecystitis is mainly caused by biliary system blockage due to the presence of these gallstones that obstruct the same. Typically, this obstruction to normal flow causes distention,

decreased biliary outflow (owing to a lack of bile flow to and from the gallbladder), inflammation, and gallbladder infection.<sup>[3]</sup> Such patients often present with unremitting right upper quadrant pain, vomiting, fever, and anorexia. The majority of these cases, i.e., 95%, present with gallstones (calculous cholecystitis), one of the main causes of the cystic duct blockage, while the remaining 5% lack gallstones (acalculous cholecystitis).<sup>[4]</sup>

To prevent complications such as gangrenous cholecystitis, gallbladder perforation, gallstone ileus, and ascending cholangitis, which can ultimately lead to sepsis and multi-organ failure, surgical intervention is necessary, with early

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Received: ???

Revised: ???

Accepted: ???

laparoscopic cholecystectomy (done within 72 h) being recommended for acute calculous cholecystitis to reduce complication risk, conversion rates, and length of hospital stay.<sup>[5,6]</sup>

The collection of bile in the gallbladder serves as a hotspot for microbial pathogens to grow. Approximately 20% of these cases develop secondary bacterial infections, predominantly caused by enteric organisms such as *Escherichia coli* and *Enterococcus faecalis*.<sup>[7]</sup> On occasion, pathogens outside of the normal flora of the human body environment can also infect the organ. *Salmonella enterica* serovar Typhi (*S. Typhi*) is a rare etiological agent of biliary tract infections, particularly in immunocompetent individuals without presentation of any systemic symptoms of typhoid in the afflicted patients. This report discusses a unique case of *S. Typhi* isolated from gallbladder pus in a patient undergoing surgery for acute cholecystitis with cholelithiasis.

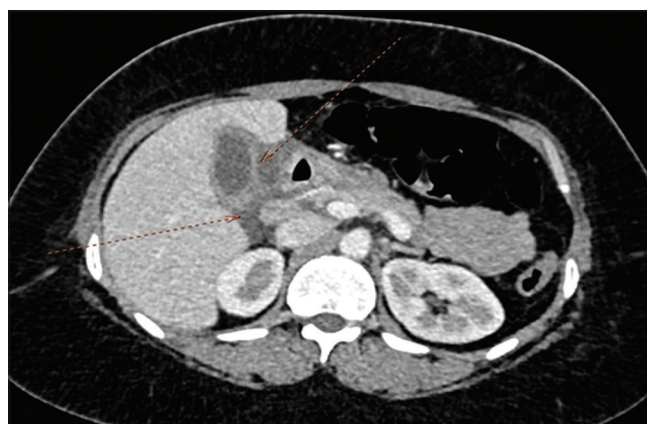
## CASE PRESENTATION

A woman in her mid-20s presented to the emergency room with upper abdominal pain for 5 days and vomiting for 2 days. The pain was slow in onset, moderate in severity, radiating to the right flank region, and not relieved with analgesics. About 4–5 episodes of vomiting were seen every day, with the vomitus consisting mainly of food particles, and often occurring after food intake. She had no prior history of similar illness or comorbidities such as diabetes, immunosuppression, or chronic liver disease. On examination, there was mild tachycardia (pulse 98 beats/minute). Tachypnea (respiratory rate was 18 breaths/minute) and blood pressure were 100/70 mmHg. On checking the patient's temperature, she was febrile at 99°F (37.2°C) with tenderness present over the right hypochondriac and right flank region, with normal bowel sounds and no gross organomegaly. The patient was admitted, and relevant investigations were done.

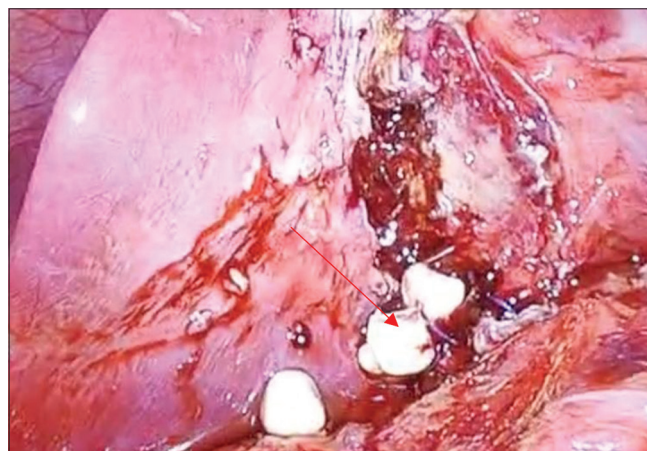
Hemoglobin was 10 g/dL, platelet count was 174,000/μL, and white blood cell count was 1790/μL (neutrophils 60%, lymphocytes 23%). Liver function test, renal function test, serum electrolytes, serum albumin, and coagulation profile were in the normal range. The Widal tube agglutination test showed high reactivity to the O and H antigen at over 1:320, with interpretation reported as highly suggestive of Enteric fever. Complete urine examination showed ketonuria and proteinuria. No air was visualized under the diaphragm in the chest X-ray. Contrast enhanced computed tomography of the abdomen was also done and it identified the presence of acute calculous cholecystitis with pericholecystic collection in close proximity to fundus along with substantial reactive inflammatory changes and impending perforation, with a well-defined thickening of the gallbladder wall (4.5 mm) and a hypodense collection of 4.5 cc volume in close proximity to the fundus of the gallbladder, [Figure 1] with corresponding

ultrasound of the abdomen also confirming the findings of at least gallbladder calculi measuring 1.2 cm in size.

In view of the progressing gallbladder inflammation likely to worsen into gallbladder perforation, the patient was planned for emergency laparoscopic cholecystectomy after obtaining pre-anesthetic fitness. Surgery was performed under general anesthesia. Upon laparoscopy, the peritoneal cavity revealed no free intraperitoneal fluid. The peritoneal surfaces appeared macroscopically unremarkable, with no visible lesions. A phlegmonous inflammatory mass involving the gallbladder was identified. This mass contained pus along the fundus, adherent to the omentum and hepatic flexure of the colon region. Within this, copious purulent material was present in the gallbladder fossa. Perforation was also identified at the fundus on the hepatic surface. The gallbladder was also notably contracted, with a thickened, congested wall in the remaining mucosa. Five faceted cholesterol gallstones were removed during the procedure, including a calculus lodged at the junction of Hartmann's pouch and the cystic duct. [Figure 2] The pus sample in the gallbladder inflammatory



**Figure 1:** Contrast-enhanced computed tomography abdomen showing cholecystitis through gallbladder wall thickening (top arrow facing down-left) and hypodense fluid collection around the fundus of the gallbladder (bottom arrow facing up-right)



**Figure 2:** Intraoperative laparoscopic view of gallbladder with multiple cholesterol stones (red arrow)

mass was collected intraoperatively and sent for bacterial culture and sensitivity, whereas the cut-open cholecystectomy specimen was sent for histopathological examination.

The pus sample was cultured on three different agars: Blood, chocolate, and MacConkey. On blood agar, non-lytic gray moist colonies were detected; however, on MacConkey agar, non-lactose fermenting colonies appeared. Preliminary tests were performed to identify the organism in these colonies, and it was discovered to be a motile gram-negative bacillus that was catalase positive but oxidase negative. Biochemical identification was performed, and incubated overnight, wherein it was found to produce hydrogen sulphide in triple sugar iron agar and ferment glucose and mannitol. It did not produce indole, utilize citrate, nor hydrolyze urea. Slide agglutination with antisera to somatic antigen D (serogroup 9) confirmed it to belong to *Salmonella enterica* subspecies *enterica* serotype Typhi in the VITEK® 2 COMPACT (bioMérieux, Inc., Hazelwood, MO) with 99.9% probability. It was discovered to be susceptible to ceftriaxone, chloramphenicol, cotrimoxazole, and azithromycin, but resistant to ciprofloxacin, ampicillin, and tetracycline (As per the Clinical and Laboratory Standards Institute standards). Blood and urine cultures were discovered to be sterile. Histopathological examination was done, wherein microscopic examination revealed extensive ulceration of the gallbladder mucosa, accompanied by dense infiltration of the lamina propria by a mixed inflammatory infiltrate predominantly composed of lymphocytes, neutrophils, and eosinophils – consistent with acute-on-chronic inflammatory activity. Notably, Rokitsansky–Aschoff sinuses were present within the muscularis layer, a classic hallmark of chronic cholecystitis.<sup>[8]</sup> Serosal surface demonstrated areas of hemorrhage and vascular congestion, reflecting acute inflammatory exudation extending beyond the gallbladder wall. Impression of the given sample was reported as exhibiting features of acute chronic cholecystitis.

Physical examination	<ul style="list-style-type: none"> <li>• Mild tachycardia (98 beats/min), tachypnea (18 breaths/min), febrile: 99°F (37.2°C), blood pressure: 100/70 mmHg</li> <li>• Tenderness in the right hypochondriac and right flank region, normal bowel sounds, no gross organomegaly</li> </ul>
Radiological findings	<ul style="list-style-type: none"> <li>• Contrast-enhanced computed tomography abdomen: Acute calculous cholecystitis with pericholecystic collection (4.5 cc), impending perforation, gallbladder wall thickening (4.5 mm)</li> <li>• Hypodense collection near the fundus</li> <li>• Gallbladder calculi (1.2 cm) on ultrasound</li> <li>• Chest X-ray: No free air under the diaphragm</li> </ul>
Surgical findings	<ul style="list-style-type: none"> <li>• No free intraperitoneal fluid</li> <li>• Phlegmonous inflammatory mass with pus near the fundus, adherent to omentum and</li> </ul>

	<ul style="list-style-type: none"> <li>hepatic flexure, perforation at the fundus on the hepatic surface</li> <li>• Copious pus in the gallbladder fossa</li> <li>• Gallbladder: Contracted, thickened, congested wall</li> <li>• Five-faceted cholesterol gallstones; one lodged at Hartmann's pouch–cystic duct junction</li> </ul>
Laboratory findings	<ul style="list-style-type: none"> <li>• Hemoglobin: 10 g/dL, platelets: 174,000/μL, white blood cells: 1,790/μL (neutrophils 60%, lymphocytes 23%)</li> <li>• Liver function test, renal function test, electrolytes, albumin, coagulation: Normal</li> <li>• Widal test: High reactivity to O and H antigen (&gt;1:320)</li> <li>• Urine: Ketouria, proteinuria</li> <li>• Blood and urine cultures: Sterile</li> </ul>
Microbiological findings	<ul style="list-style-type: none"> <li>• Pus culture: Gray moist colonies (blood agar), non-lactose fermenting colonies (MacConkey)</li> <li>• Gram-negative bacillus, motile, catalase positive, oxidase negative</li> <li>• Biochemical: H<sub>2</sub>S positive, glucose and mannitol fermentation, indole negative, citrate negative, urease negative</li> <li>• Slide agglutination: <i>Salmonella</i> serogroup D</li> <li>• VITEK® 2: <i>Salmonella enterica</i> serovar Typhi (99.9%)</li> <li>• Susceptible: Ceftriaxone, chloramphenicol, cotrimoxazole, azithromycin</li> <li>• Resistant: Ciprofloxacin, ampicillin, tetracycline</li> </ul>
Histopathology	<ul style="list-style-type: none"> <li>• Extensive mucosal ulceration</li> <li>• Lamina propria: Dense mixed inflammatory infiltrate (lymphocytes, neutrophils, eosinophils)</li> <li>• Rokitsansky–Aschoff sinuses in the muscularis layer</li> <li>• Serosa: Hemorrhage and congestion</li> <li>• Diagnosis: Acute-on-chronic cholecystitis</li> </ul>

Following confirmation from the culture results, the patient was treated with intravenous injection of xone (Ceftriaxone) 1 g twice daily for 3 days, analgesics for the post-operative pain, and anti-emetics for nausea. Following treatment, the patient demonstrated marked improvement, and her fever resolved. She was discharged on post-operative day 4 with instructions to return for a surgical follow-up after 7 days and prescribed azithromycin 500 mg orally, twice daily, for 5 days.

## DISCUSSION

*E. coli*, *Salmonella* spp., *Helicobacter* spp., *Bacteroides fragilis*, *Enterococcus* spp., *Staphylococcus aureus*, *Proteus*

spp., *Pseudomonas aeruginosa*, and *Acinetobacter* spp. have all been found in the gallbladders of patients suffering from cholecystitis and cholelithiasis, with these acute hepatobiliary conditions being a known but uncommon consequence of *S. Typhi* and *Salmonella* Paratyphi. An infection. 2-5% of infected individuals develop a protracted gallbladder infection with shedding in the stool, even resulting in a carrier status.<sup>[3]</sup> Typhoid fever is a systemic infection characterized by bacteremia and caused by the ingestion of *S. Typhi* or *S. Paratyphi A*. It is transmitted primarily through the faeco-oral route. The incubation period ranges from 5 to 30 days. This acute illness commonly presents with non-specific symptoms such as fever, malaise, abdominal pain, headache, lethargy, and diarrhea.<sup>[9]</sup> The process by which these bacteria can enter the organ can be explained through their pathogenesis when invading the gastrointestinal system. Upon penetrating the intestine, the bacteria are engulfed by macrophages in the lymphoid tissue. This process triggers secondary bacteremia, commonly observed during the acute phase. Through this bacteremia, the biliary system becomes infected, either via the portal blood supply or by retrograde movement through the biliary passages.<sup>[9]</sup>

Gallbladder colonization by *S. Typhi* is well-documented in chronic carriers, particularly in endemic regions, and especially in the presence of gallstones, which is mainly due to the formation of biofilms on the cholesterol gallstone surfaces.<sup>[8,10]</sup> However, symptomatic gallbladder infection with *S. Typhi* in non-carriers, especially in young adults without systemic illness, remains sporadic. In a review of 6250 cases of salmonellosis, only five were confirmed as acute calculus cholecystitis due to the bacteria, confirming that gallbladder involvement – especially with stones – is exceptionally rare.<sup>[11]</sup> In the presented case, the presence of *S. Typhi* in a patient without a history of typhoid fever or chronic biliary disease points toward the development of asymptomatic biliary colonization precipitated by gallstone-related obstruction. Such cases underline the importance of a routine culture of intraoperative specimens in suspected cholecystitis, especially in endemic regions. Isolation of the bacteria in blood cultures, along with radiological studies identifying the presence of gallbladder inflammation, is commonly used to confirm a diagnosis.<sup>[12]</sup> Bone marrow aspirate culture is more sensitive, but it is seldom used due to the risks associated with performing the procedure. Isolation from stool cultures can assist validation of diagnosis in people with histories indicating infection but still demonstrating negative blood cultures.<sup>[13]</sup>

The overall frequency of occurrence of these cases of *Salmonella* bacteria in locations outside of their usual placement in the gastrointestinal tract occurs most commonly in endemic areas, wherein typhoid is prevalent. In typhoid-endemic regions – particularly South Asia and sub-Saharan Africa – the burden of typhoid fever remains strikingly high, including countries such as Ethiopia, Ghana, Madagascar, Nigeria,<sup>[14]</sup> Indonesia, China,<sup>[15]</sup> Nepal, Pakistan, Bangladesh,

and India.<sup>[16,17]</sup> In 2021, India accounted for almost 58% of global cases, totaling almost 5.4 million of the population. Pakistan (8%) and Bangladesh (5%) came in second and third, respectively.<sup>[18]</sup> One geographic pattern study done in India found that the incidence was higher in southern and western states (Maharashtra and Tamil Nadu), as well as urban centers in the north (Chandigarh and Delhi), whereas it was lower in rural northern states (Arunachal Pradesh and Himachal Pradesh).<sup>[19]</sup> Across these endemic areas, children and adolescents bear the greatest burden, with especially high rates in urban and densely populated environments.

Disease progression is determined by a combination of factors, such as the presence of metabolic disorders, such as diabetes, insulin resistance, dyslipidemia, obesity, and diets containing heavy amounts of saturated fat and sugar but low in fiber quantity. A sedentary lifestyle, along with factors such as rapid weight reduction or prolonged periods of fasting, contributes to impaired gallbladder contractility and elevated biliary cholesterol release.<sup>[20]</sup> Women also show a higher preponderance of the disease than men, due to the presence of elevated estrogen. Studies indicate that females in their reproductive years or using estrogen-containing oral contraceptives face a twofold increase in gallstone formation.<sup>[21]</sup>

This specific isolate exhibited resistance to ciprofloxacin, ampicillin, and tetracycline, and among *Salmonella* isolates, the development of this trend has emerged as a significant cause of global public health concern, driven by widespread misuse of antibiotics and the dissemination of resistance genes through plasmids. A 2022 global systematic review and meta-analysis, including nearly 35,000 *S. Typhi* isolates, reported pooled resistance rates of 38.8% for ampicillin, 15.0% for ciprofloxacin, and 40.7% for tetracycline. These resistance patterns have been associated with the acquisition by the pathogen of plasmid-encoded beta-lactamases such as *bla*<sub>TEM</sub>, quinolone-resistance genes (*gyrA*, *parC* mutations), and efflux pumps such as AcrAB-TolC. Through horizontal gene transfer, *S. Typhi* can acquire antimicrobial resistance genes from non-related organisms through mobile genetic elements, including plasmids and transposons, enabling interspecies gene exchange.<sup>[22,23]</sup> In India, following a four-center characterization of antimicrobial resistance in *Salmonellae* during 2014–2015, surveillance showed ciprofloxacin resistance exceeding 90% in *S. Typhi* isolates and ampicillin resistance ranging from 27% to 85%.<sup>[24]</sup> More recently, the SEFI surveillance project (2021–2024) identified *S. Typhi* strains in Ahmedabad resistant to multiple frontline drugs – ampicillin, ciprofloxacin, and ceftriaxone – some linked to plasmid-mediated resistance.<sup>[25]</sup>

Other gallbladder-associated infections due to *Salmonella*, though rare, have also been reported. For instance, a rare case of a patient with acute acalculous cholecystitis caused by *Salmonella* compounded with a pancolitis was reported in the University of California.<sup>[26]</sup> A near-fatal intestinal

hemorrhage and acute acalculous cholecystitis due to fluoroquinolone-insensitive *S. Typhi* infection were reported in China, wherein early cholecystectomy was required to prevent further complications.<sup>[27]</sup> Although the disease is almost always seen in adults, rare pediatric manifestations can also occur. As of 2022, the occurrence of pediatric acalculous cholecystitis caused by *S. Typhi* is rare, with only six case reports or series documented in the literature.<sup>[28]</sup>

Non-typhoidal *Salmonella* spp. commonly results in gastroenteritis, though in some instances, individuals may persist as chronic carriers of the pathogen in their gallbladder. A case of *Salmonella Enteritidis cholecystitis* presented in a patient with chronic granulomatous disease, a rare hereditary disease that suppresses bactericidal ability and thereby allows the pathogen to translocate from the gut to the gallbladder and establish infection.<sup>[29]</sup> Another case report in 2019 described a rare case of non-typhoidal salmonellosis (identified as *Salmonella enterica* subsp. *Salamae*) leading to acute calculus cholecystitis.<sup>[30]</sup> Acute calculus cholecystitis due to these water-borne pathogens is an extremely rare clinical picture and has only, alongside the case from Guinea, been reported in a young child,<sup>[31]</sup> and in an intensive therapy unit patient.<sup>[32]</sup> In all these cases, the development of these infections is seen most commonly in endemic areas.

The prevalence of comorbidities such as HIV, differences in antimicrobial resistance patterns, low quality antibiotic preparations, availability of over-the-counter antibiotics, lack of pipe-borne drinkable water, lack of community awareness regarding the risk factors of this infection, and a lack of efficiency in the overall health system functionality all contribute to the differences seen in disease spectrum, complications, and mortality across regions.<sup>[33]</sup> Furthermore, publications have theorized that age plays an important impact, with some research indicating higher morbidity and mortality in younger children, whereas others claim much better outcomes in this age group. The introduction and subsequent rise in single- and multidrug-resistant typhoidal *Salmonella* have been associated with reported sickness severity changes.<sup>[34,35]</sup> This has reduced the therapeutic alternatives in high-burden countries, as well as increased treatment costs, sickness severity, and higher case fatality rates.<sup>[36]</sup>

## CONCLUSION

Because enteric fever occurs in low-income groups with limited access and awareness to diagnostic services, the disease burden is difficult to analyze, and policymakers lack the data required to make decisions on the distribution of enteric fever preventative measures and vaccines. Typhoid fever poses a major public health burden in India, with urban centers reporting comparatively higher incidence. Experts recommend strengthening policies that enhance public awareness and accessibility of typhoid vaccination programs

to effectively combat the burden of typhoid fever in India. As the trend of multidrug-resistant and more virulent forms of *Salmonella* infection continues to rise in these endemic areas, it is inevitable that more of these rarer complications of enteric fever, such as cholecystitis, will become more frequent. This case highlights the need for high clinical suspicion and routine microbiological examination in acute cholecystitis, especially when surgical outcomes indicate serious infection or perforation. Although uncommon, *S. Typhi* should be regarded as a biliary pathogen in endemic locations, even if systemic typhoid symptoms do not appear.

## ACKNOWLEDGMENTS

The authors have to acknowledge all co-authors for this work.

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**Source of Support:** Nil. **Conflicts of Interest:** None declared.

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