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**Severe infection with multidrug-resistant *Salmonella choleraesuis* in a young patient with primary sclerosing cholangitis**

Ferstl PG *et al.* Severe infection with multidrug-resistant *Salmonella choleraesuis*

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**Author contributions:**Ferstl P was in charge of medical care for the patient as long as admission had lasted; Upon discharge, he compiled relevant patient data, wrote the manuscript and conducted literature research; Reinheimer C and Jozsa K conducted literature research and took part in writing the manuscript on behalf of the microbiological topics; Zeuzem S, Kempf V and Waidmann O were involved in the critical review of the manuscript; Grammatikos G was supervising patient care during hospital admission. He compiled most of the relevant patient data, and was responsible for critical review of the manuscript.

**Institutional review board statement:** Since medical treatment was conducted according to highest clinical standards, the present case report is not of experimental character and does not require an ethical committee statement.

**Informed consent statement:** Patient data and dates of treatment were anonymized prior to writing the case report. The patient provided informed written consent prior to report submission.

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**Abstract**

Massive global spread of multidrug-resistant *Salmonella* spp. expressing extended-spectrum beta-lactamase (ESBL) and additional resistance to fluoroquinolones (MDR) has often been attributed to high international mobility as well as excessive use of oral antibiotics in livestock farming. However, MDR *Salmonella* spp. has not been mentioned as a widespread pathogen in clinical settings so far. We demonstrate the case of a 25-year-old male with primary sclerosing cholangitis tested positive for MDR *Salmonella enterica* serotype Choleraesuis expressing ESBL and fluoroquinolone resistance. The pathogen was supposedly acquired during a trip to Thailand, causing severe fever, cholangitis and pancreatitis. To our knowledge, this is the first report of *Salmonella enterica* serotype Choleraesuisin Europe expressing such a multidrug resistance pattern. ESBL resistance of *Salmonella* *enterica* spp. should be considered in patients with obstructive biliary tract pathology and travel history in endemic countries.

**Key words:** Biliary physiology; Infectious disease; Multi-drug resistance; Primary sclerosing cholangitis; Salmonella choleraesuis

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**Core tip:**We report a case of aggressive infection with a multi-drug resistant strain of *Salmonella choleraesuis* in a patient with primary sclerosing cholangitis. Successful treatment involved repetitive ultrasound and endoscopic intervention, as well as multiple adjustments of the antibiotic regimen. This is the first case report addressing MDR salmonellosis in patients with predisposing biliary disease in Europe. It illustrates how close interdisciplinary cooperation between clinicians and microbiologists is warranted in an era of emerging antibiotic resistance.

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**INTRODUCTION**

Among a variety of pathogens that are known for colonizing the gallbladder, *Salmonella* spp. seem to benefit from its prevailing conditions in particular[1]. Bile has bactericidal properties, which *Salmonella* spp. manage to escape by several mechanisms[2]. Thus, the biliary system serves as a favorable reservoir and *Salmonella* spp. might bloom particularly well if passage into the intestine is impaired. In case of inflammation, the bile’s constitution alters, supporting infection of the biliary tree with pathogenic gram-negative organisms, *e.g.,* *Salmonella* spp.[3]. Up to now, this phenomenon has mostly been attributed to gall stones[4], which have been known to be a common cause for infectious cholangitis. However, only few case reports of patients suffering from primary hepatobiliary diseases such as Caroli’s syndromeand shedding *Salmonella* are available up to now[5]. In case of severe cholangitis and acute pancreatitis in patients with cholestatic predisposition, *Salmonella* spp. should be considered as causative pathogen. Since cases of infectious pancreatitis due to *e.g.*, *Salmonella enterica* serotype Typhimuriumhave been reported earlier[6], we demonstrate here an infection with *Salmonella enterica* serotype Choleraesuis. Immunocompromising diseases, *e.g.,* cirrhosis or inflammatory bowel disease, might promote invasive salmonellosis and bloodstream infection and lead to severe courses of infections[7].

**CASE REPORT**

A 25-year old male student presented at the emergency department of the University Hospital Frankfurt. The patient had suffered from watery diarrhea with a frequency of ten stools per day, concomitant cramps in the lower abdomen and fever up to 40 °C for six days. He was diagnosed with primary sclerosing cholangitis and ulcerative colitis in 2005 and was on long-term medication with mesalazine and ursodesoxycholic acid. He had returned from a backpacking holiday to Thailand 16 days ago, which ended without any medical complaints or symptoms.

On admission, blood tests showed serum levels of bilirubin at 1.7 mg/dL, alkaline phosphatase (AP) at 276 U/L, alanine aminotransferase (ALT) at 56 U/L, lipase at 501 U/L, c-reactive protein (CRP) at 9.2 mg/dL and 15.000 leucocytes/mL. Abdominal ultrasound showed an enlarged gall bladder of 11cm diameter without any signs of cholecystitis or acute pancreatitis. Blood and stool cultures were taken and intravenous antibiotic therapy with ciprofloxacin 500 mg and metronidazole 400 mg three times daily was initiated. Stool cultures yielded detection of a non-typhoidal *Salmonella* spp., hence antibiotic therapy was switched to ceftriaxone 2 g daily. Despite the adaptation of the antibiotic regimen the patient´s general condition worsened and he reported increasing abdominal pain located in the epigastrium. Fever continued and diarrhea suspended.

Repeated ultrasound of the abdomen displayed a mildly bloated pancreas with peripancreatic edema. Liver function tests showed rising bilirubin, ALT, AP, leucocytes and CRP kept increasing. Antibiotic therapy was switched to imipenem 500 mg four times daily. Subsequently, an isolate of *Salmonella* group C with ESBL and additional resistance to fluoroquinolones was detected in stool cultures. Due to ongoing elevation of cholestatic enzymes and ultrasound evidence of a distended common bile duct (CBD), endoscopic retrograde cholangiopancreatography (ERCP) was performed, showing a high-grade stricture of the distal CBD (Figures 1 and 2). A 3mm small stone and pus were extracted, and a stent was applied to the CBD. Fever ceased immediately and pain was easing during the following week. Gall cultures yielded detection of the same bacterial strain as were detected in the stool. Culture isolates were sent to the national reference center for salmonellosis in Wernigerode, Germany, in order to determine the exact species’ serotype. Imipenem was administered for 14 d and the patient was discharged with mild residual abdominal complaints. The following week, the reference center confirmed detection of *Salmonella enterica* serotype Choleraesuis [6,7,(c)1,5]. On readmission for planned stent extraction, the patient was free of symptoms and any *Salmonella* spp. in stool cultures. Thoracoabdominal magnetic resonance imaging showed no signs of mycotic aortic aneurism, which is frequently observed in *Salmonella* groupC and Dinfections[7].

Patient data and dates of treatment were anonymized prior to writing the case report. The patient provided informed written consent prior to report submission.

**DISCUSSION**

The rising global burden of MDR non-typhoidal *Salmonella* spp. has been attributed to increasing tourism to South-East Asia, where MDR non-typhoidal *Salmonella* spp. are endemic[8-10]. The prevalence of MDR non-typhoidal *Salmonella* spp. has been increasing worldwide for several years[7]. The global spread of these pathogens has been linked to use of antibiotics in livestock farming[11], consumption of raw or insufficiently cooked meat and vegetables, global food trade as well as travel to endemic areas[12,13]. The first case of serotype Choleraesuisresistant to both 3rd generation cephalosporines and fluoroquinolones has been reported in 2004[14]. Therefore, MDR *Salmonella* spp. are an issue of growing public health concern in Europe[11,13]. While antibiotic treatment is not recommended in asymptomatic shedders of *Salmonella* spp*.* or in uncomplicated gastroenteritis[15,16]{}, MDR resistant *Salmonella* is likely to have a critical impact in patients with obstructive biliary tract pathology and altered bile constitution. Since global burden of MDR *Salmonella* spp. keeps rising, this alarming development is reflected by our case report on travel-associated salmonellosis with serotype Choleraesuis expressing ESBL and additional resistance to fluoroquinolones.

We conclude that salmonellosis due to MDR *Salmonella* spp. should be considered in patients with immunosuppression or with hepatobiliary diseases, who develop severe and complicated courses. Empiric treatment with carbapenems should be initiated in these patients upon clinical deterioration on common antibiotic regimes like fluoroquinolones and cephalosporins. Carbapenems cover MDR *Salmonella* spp., achieve higher concentrations within the pancreatic tissue and thus reduce bacterial count[17]. Antibiotic treatment should be reserved for symptomatic patients. From the first day of treatment on, structured microbiological surveillance and close interdisciplinary cooperation between clinicians and microbiologists are warranted for best patient care.

**COMMENTS**

***Case characteristics***

A 25-year old male with known primary sclerosing cholangitis and ulcerative colitis presented to our emergency ward with watery diarrhea at a frequency of ten stools per day, concomitant cramps in the lower abdomen and fever up to 40 °C.

***Clinical diagnosis***

The authors diagnosed a case of severe salmonellosis due to an isolate of *Salmonella choleraesuis* expressing ESBL and fluoroquinolone resistance, which could be detected in both bile and stool cultures.

***Differential diagnosis***

Initial differential diagnoses were infectious gastroenteritis, an atypical acute attack of ulcerative colitis, and obstructive cholangitis with febrile cholecystitis and pancreatitis.

***Laboratory diagnosis***

Blood tests showed serum levels of bilirubin at 1.7 mg/dL, alkaline phosphatase (AP) at 276 U/L, alanine aminotransferase (ALT) at 56 U/L, lipase at 501 U/L, c-reactive protein (CRP) at 9.2 mg/dL and 15.000 leucocytes/mL.

***Imaging diagnosis***

Ultrasound of the abdomen displayed a distended gall bladder, a mildly bloated pancreas with peripancreatic edema and a distended common bile duct (CBD), while endoscopic retrograde cholangiopancreatography (ERCP) showed a high-grade stricture of the distal CBD with discharge of a small stone and pus.

***Treatment***

Upon unsuccessful antibiotic treatment with ciprofloxacin/metronidazole and later with ceftriaxone, the patient’s condition and laboratory values improved rapidly under therapy with imipenem, which was administered for 14 d in total.

***Experiences and lessons***

ESBL resistance of *Salmonella* *enterica* spp. should be considered in patients with obstructive biliary tract pathology and travel history in endemic countries.

***Peer-review***

From an interdisciplinary perspective, this case report illustrates the features of MDR non-typhoidal salmonellosis in patients with primary sclerosing cholangitis, it explains diagnostic pathways, and it summarizes treatment recommendations for these patients.

**REFERENCES**

1 **Verdier J**, Luedde T, Sellge G. Biliary Mucosal Barrier and Microbiome. *Viszeralmedizin* 2015; **31**: 156-161 [PMID: 26468308 DOI: 10.1159/000431071]

2 **Merritt ME**, Donaldson JR. Effect of bile salts on the DNA and membrane integrity of enteric bacteria. *J Med Microbiol* 2009; **58**: 1533-1541 [PMID: 19762477 DOI: 10.1099/jmm.0.014092-0]

3 **Vaishnavi C**, Singh S, Kochhar R, Bhasin D, Singh G, Singh K. Prevalence of Salmonella enterica serovar typhi in bile and stool of patients with biliary diseases and those requiring biliary drainage for other purposes. *Jpn J Infect Dis* 2005; **58**: 363-365 [PMID: 16377868]

4 **Crawford RW**, Rosales-Reyes R, Ramírez-Aguilar Mde L, Chapa-Azuela O, Alpuche-Aranda C, Gunn JS. Gallstones play a significant role in Salmonella spp. gallbladder colonization and carriage. *Proc Natl Acad Sci U S A* 2010; **107**: 4353-4358 [PMID: 20176950 DOI: 10.1073/pnas.1000862107]

5 **Waldram R**, Vahrman J, Williams R. Salmonella heidelberg infection in Caroli's syndrome. *Gastroenterology* 1975; **68**: 151-153 [PMID: 1116657]

6 **Rombolà F**, Bertuccio SN. [Typhoid fever and acute pancreatitis: two cases]. *Infez Med* 2007; **15**: 63-65 [PMID: 17515678]

7 **Chiu CH**, Su LH, Chu C. Salmonella enterica serotype Choleraesuis: epidemiology, pathogenesis, clinical disease, and treatment. *Clin Microbiol Rev* 2004; **17**: 311-322 [PMID: 15084503]

8 **Suwantarat N**, Carroll KC. Epidemiology and molecular characterization of multidrug-resistant Gram-negative bacteria in Southeast Asia. *Antimicrob Resist Infect Control* 2016; **5**: 15 [PMID: 27148448 DOI: 10.1186/s13756-016-0115-6]

9 **Vlieghe ER**, Phe T, De Smet B, Veng CH, Kham C, Bertrand S, Vanhoof R, Lynen L, Peetermans WE, Jacobs JA. Azithromycin and ciprofloxacin resistance in Salmonella bloodstream infections in Cambodian adults. *PLoS Negl Trop Dis* 2012; **6**: e1933 [PMID: 23272255 DOI: 10.1371/journal.pntd.0001933]

10 **Su LH**, Teng WS, Chen CL, Lee HY, Li HC, Wu TL, Chiu CH. Increasing ceftriaxone resistance in Salmonellae, Taiwan. *Emerg Infect Dis* 2011; **17**: 1086-1090 [PMID: 21749777 DOI: 10.3201/eid/1706.101949]

11 **Liebana E**, Carattoli A, Coque TM, Hasman H, Magiorakos AP, Mevius D, Peixe L, Poirel L, Schuepbach-Regula G, Torneke K, Torren-Edo J, Torres C, Threlfall J. Public health risks of enterobacterial isolates producing extended-spectrum β-lactamases or AmpC β-lactamases in food and food-producing animals: an EU perspective of epidemiology, analytical methods, risk factors, and control options. *Clin Infect Dis* 2013; **56**: 1030-1037 [PMID: 23243183 DOI: 10.1093/cid/cis1043]

12 **Bae D**, Cheng CM, Khan AA. Characterization of extended-spectrum β-lactamase (ESBL) producing non-typhoidal Salmonella (NTS) from imported food products. *Int J Food Microbiol* 2015; **214**: 12-17 [PMID: 26210532 DOI: 10.1016/j.ijfoodmicro.2015.07.017]

13 **Burke L**, Hopkins KL, Meunier D, de Pinna E, Fitzgerald-Hughes D, Humphreys H, Woodford N. Resistance to third-generation cephalosporins in human non-typhoidal Salmonella enterica isolates from England and Wales, 2010-12. *J Antimicrob Chemother* 2014; **69**: 977-981 [PMID: 24288030 DOI: 10.1093/jac/dkt469]

14 **Chiu CH**, Su LH, Chu C, Chia JH, Wu TL, Lin TY, Lee YS, Ou JT. Isolation of Salmonella enterica serotype choleraesuis resistant to ceftriaxone and ciprofloxacin. *Lancet* 2004; **363**: 1285-1286 [PMID: 15094275 DOI: 10.1016/S0140-6736(04)16003-0]

15 **Marzel A**, Desai PT, Goren A, Schorr YI, Nissan I, Porwollik S, Valinsky L, McClelland M, Rahav G, Gal-Mor O. Persistent Infections by Nontyphoidal Salmonella in Humans: Epidemiology and Genetics. *Clin Infect Dis* 2016; **62**: 879-886 [PMID: 26740515 DOI: 10.1093/cid/civ1221]

16 **Onwuezobe IA**, Oshun PO, Odigwe CC. Antimicrobials for treating symptomatic non-typhoidal Salmonella infection. *Cochrane Database Syst Rev* 2012; **11**: CD001167 [PMID: 23152205 DOI: 10.1002/14651858.CD001167.pub2]

17 **Lankisch PG**, Lerch MM. The role of antibiotic prophylaxis in the treatment of acute pancreatitis. *J Clin Gastroenterol* 2006; **40**: 149-155 [PMID: 16394877]

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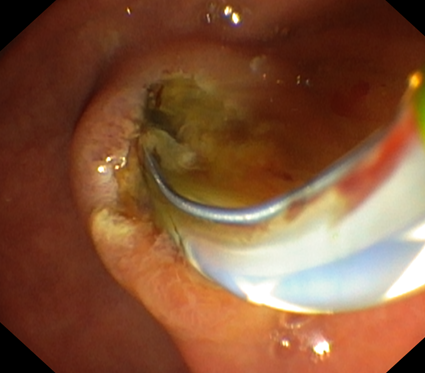
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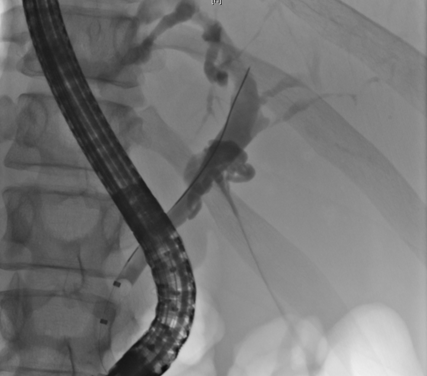
Grade C (Good): C, C, C

Grade D (Fair): 0

Grade E (Poor): 0



**Figure 1 Endoscopic image of purulent discharge of the papilla of Vater.**



**Figure 2 Endoscopic retrograde cholangiopancreatography with high-grade stricture of the distal common bile duct.**