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Multidrug-Resistant Bovine Salmonellosis Predisposing for Severe Human Clostridial Myonecrosis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Patient: Female, 23
Final Diagnosis: Clostridial myonecrosis
Symptoms: Diarrhea • fever • muscle pain • sepsis
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course

Background: The overuse of antibiotics in animals promotes the development of multidrug-resistance predisposing for severe polymicrobial human infections.

Case Report: We describe a case of spontaneous clostridial myonecrosis due to ulcerative colonic infection with multidrug-resistant *Salmonella enterica* subsp. *enterica*, serotype 4,[5],12: i: –. Serotyping of the colonic *Salmonella* isolate in the index case and the bovine farm outbreak isolates from where the patient worked indicated they were both serotype I 4,[5],12: i: –, which is linked with a multitude of large reported disease outbreaks. Further analysis revealed that they are highly genetically related and antibiotic susceptibility testing indicated that they are phenotypically identical.

Conclusions: Enteritis due to human acquisition of multidrug-resistant *Salmonella* from cattle led to the invasion and dissemination of *Clostridium septicum* resulting in devastating myonecrotic disease. This highlights the ramifications of co-existence and evolution of pathogenic bacteria in animals and humans and lends support to reducing the use of antibiotics in animals.

MeSH Keywords: *Clostridium septicum* • Multi-Drug Resistance • *Salmonella* Infections • Zoonoses

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/913472

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Background

The use of antibiotics in agriculture is widely practiced but has deleterious consequences, the most important of which is the breeding of multidrug-resistant enteric bacteria. The close interaction of humans and animals, as well as handling and the consumption of contaminated animal meat, represents a direct threat to human health. Such is the case for members of the bacterial genus *Salmonella,* a diverse group of pathogenic intracellular gram-negative bacteria responsible for large foodborne outbreaks of enteric diseases of humans and animals. Non-typhoidal *Salmonella*, such as *S. enterica*, serotype Typhimurium, is chiefly responsible for diarrheal outbreaks in bovine species [1]. The related human *S. enterica*, serotype I 4,[5],12: i: –, is increasingly associated with livestock-associated outbreaks of human disease, and antibiotic use in animal feed has been linked to multidrug-resistant (MDR) phenotypes [2,3]. Here, we present a devastating case of atraumatic *Clostridium septicum* myonecrosis in an otherwise healthy person. The development of this infection was likely through the acquisition of multidrug-resistant *Salmonella* through direct animal contact on a farm utilizing antibiotics in feed. This resulted in invasive enteric salmonellosis, which led to the sequelae of disseminated clostridial infection. Analysis of bovine and human isolates showed their genetic relatedness and identical antibiotic-resistance profiles, confirming transmission. This case highlights the hazards of antibiotic use in livestock and its associated impact on health and disease.

Case Report

A 23-year-old previously healthy woman from a rural location in the midwestern United States presented with a 2-day history of watery, non-bloody diarrhea, and 12-h of subjective fever, and left leg and right forearm pain. There was no accompanying nausea or vomiting and her remaining review of systems were negative. She lived and worked on a beef-producing cattle farm where there had been a diarrheal outbreak 1 week prior to her illness. She denied consumption of beef produced on the farm and reported no ill family members or co-workers. On hospital arrival she was febrile (102.3°F [39°C]) and had a pulse of 140 beats/min and a blood pressure of 98/55 mm Hg. She had severe mottling, tenderness, discoloration, and crepitus of her right medial mid-forearm and the left thigh. Her left lower extremity was cold, firm, and insensate. Her laboratory exam revealed evidence of disseminated intravascular coagulation and severe rhabdomyolysis. Her WBC count was 1.4 k/mL (normal: 3.5–11.5 k/mL), platelet count was 0.42 k/mL (normal: 1.5–4.5 k/mL), and prothrombin time was elevated at 23.4 s (normal: 12.1–14.4 s). Her CK was 18,328 U/L (normal: 30–184 U/L) and lactate was 5.9 mmol/L (normal: 0.5–1.6 mmol/L). Blood cultures for aerobic, anaerobic, and fungal organisms were negative at multiple times throughout the clinical course. Cardiac echocardiography was negative for valvular abnormalities. She was started on broad-spectrum antibiotics and intravenous immunoglobulin. Within the first 24 h there was rapid progression of necrosis of the involved extremities and worsening septic shock associated with acute renal failure. She underwent emergent surgery, and intraoperative findings revealed extensive muscle necrosis and presence of gas in multiple compartments of her left thigh. She required left hip disarticulation with extensive debridement of the muscle, skin, and soft tissues of the left lower abdomen and right arm to control infection. Histopathologic analysis indicated extensive myonecrosis and abundant rod-shaped hematoxylin-staining bacteria infesting the muscle and connective tissue, with a scant neutrophilic infiltrate (Figure 1, upper panel A, B). Anaerobic cultures of the tissue revealed *Clostridium septicum* that was susceptible to penicillin and metronidazole. To control the infection, multiple debridements of the involved arm and pelvis were required, along with a diverting colostomy. Eventually, the patient recovered and completed a 2-week course of piperacillin-tazobactam and clindamycin followed by an additional 2 weeks of intravenous penicillin. Sepsis and associated fevers resolved within 24–48 h of debridement of the affected limbs. On the third week of her admission, she developed lower gastrointestinal bleeding, and emergent colonoscopy revealed 3 shallow ulcers in the right lower colon, with 1 actively bleeding cecal ulcer (Figure 1, upper panel C). Histopathology of biopsy specimens showed infectious colitis with underlying microabscesses (Figure 1, upper panel D, E). Cultures of biopsy grew *Salmonella enterica* serotype I 4,[5],12: i: – which was resistant to ampicillin, cephalothin, ceftriaxone chloramphenicol, kanamycin, tetracycline, TMP/Sulfa, and sulfisoxazole but susceptible to ciprofloxacin, gentamicin, and nalidixic acid (Table 1). The patient denied receiving any antibiotics prior to her hospitalization. The patient's *Salmonella* colitis was successfully treated with a 2-week course of oral ciprofloxacin and she was subsequently discharged home in stable condition with outpatient follow-up. Retrospective history revealed that the livestock on this patient's farm were routinely administered antibiotics to facilitate growth and infection prophylaxis. Co-incident with the hospital course of this patient, *Salmonella* was determined to be the etiology of the bovine diarrheal outbreak; cultures of the gastrointestinal and gallbladder samples of the deceased animals were positive for *Salmonella enterica* serotype I 4,[5],12: i: – (isolate codes: E2016000770 and E2016000771, in Figure 2A).

The co-incident finding of invasive colonic lesions harboring *Salmonella enterica* in our patient and the cultivation of *Salmonella* from bovine tissues harvested as part of an outbreak investigation were suspicious for a causal link between the episodes. To determine the link, both human and bovine isolates were sent to the Centers for Disease Control (CDC)

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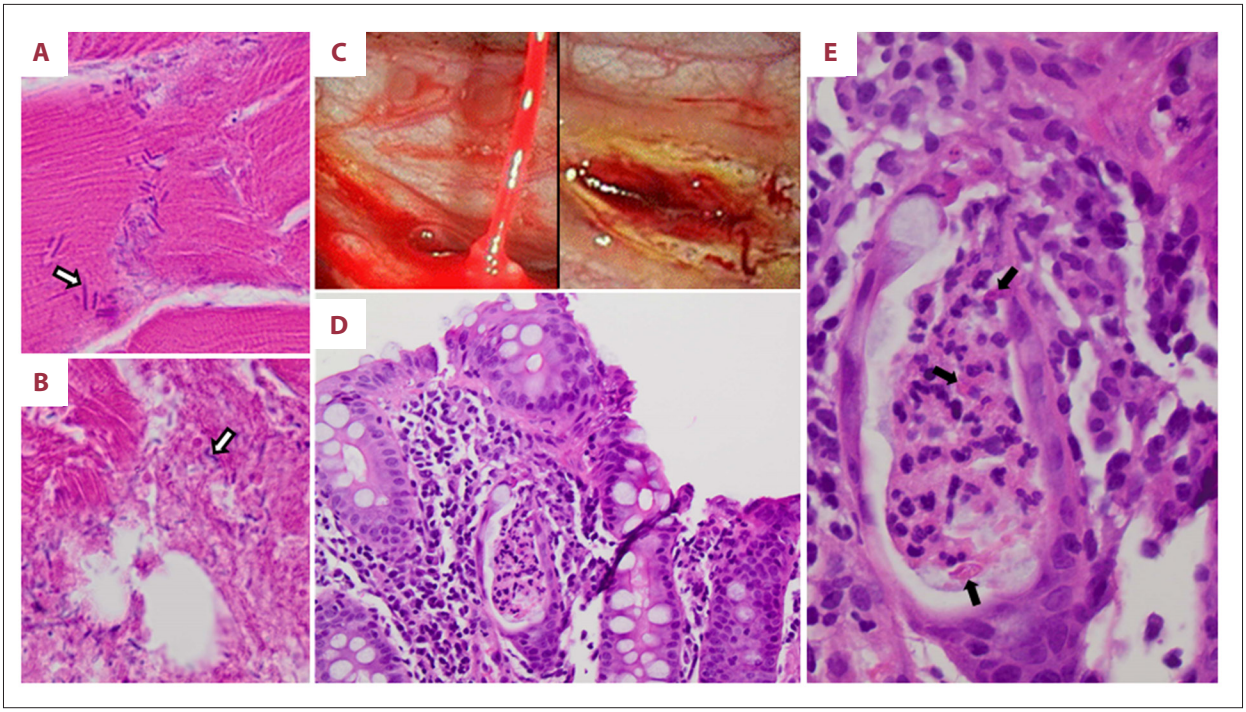

Figure 1. Histopathologic and colonoscopic analysis of patient. A&B) Histopathologic sections of H&E-stained muscle (**A**) and connective tissue (**B**) tissue from the debrided left extremity, showing numerous bacilli throughout both tissues (white arrows). (**C**) Colonoscopic evaluation for gastrointestinal bleeding demonstrate an actively bleeding ulcer (**left panel**), and after cauterization (**right panel**). (**D, E**) Histopathologic analysis of mucosal lesions taken during colonoscopy (in **C**) shows the ulcerative lesions associated with a microabscess. Higher magnification (in **E**) shows intracellular inclusions (black arrows) containing possible bacteria. Cultures taken of tissue biopsies where positive for multidrug-resistant *S. enterica*, serotype I 4,[5],12: i: –.

Table 1. Antibiotic susceptibilities of human and bovine *Salmonella enterica* isolates.

Antibiotic	Susceptibility	
	Human isolate (2015K-0414)	Bovine isolate (E2016000770)
Ampicillin	Resistant	Resistant
Cephalothin	Resistant	Resistant
Ceftriaxone	Resistant	Resistant
Chloramphenicol	Resistant	Resistant
Kanamycin	Resistant	Resistant
Tetracycline	Resistant	Resistant
TMP/Sulfa	Resistant	Resistant
Sulfisoxazole	Resistant	Resistant
Gentamicin	Susceptible	Susceptible
Ciprofloxacin	Susceptible	Susceptible
Nalidixic acid	Susceptible	Susceptible

Susceptibility assays were performed in tandem under the same conditions using MicroScan (Siemens Healthcare Diagnostics).

for further analysis. Serologic analysis of the animal isolates revealed it was *Salmonella enterica,* serotype I 4,[5],12: i: – (Figure 2A). The human colonic isolates (isolate codes: 2015K-0414 and 2015K-0415) were typed as *Salmonella enterica* serotype I 4,[5],12: i: – a close variant of serotype *Typhimurium*. These isolates were highly similar to isolates found elsewhere in other zoonotic disease outbreaks (Figure 2A, isolate codes: PNUSAS000603 PNUSAS000710).

To further characterize the isolates, purified DNA of the 4 isolates were subjected to restriction enzyme PFGE, which revealed dissimilar patterns between the *Salmonella* isolated from the colonic lesion of the patient and that from the stool (Figure 2B). The PFGE pattern of isolate in the human colonic lesion was identical to that of the animal isolates from the outbreak (Figure 2A). This demonstrates that the patient harbored at least 2 genetically different *Salmonella* isolates with the same serotype and that the isolate from the colonic biopsy was identical to the PFGE pattern found in animals on the same farm. Both geographically-linked human and bovine *Salmonella* isolates were tested for antibiotic susceptibilities using a panel of diverse antibiotics. The results (Table 1) show identical patterns to antibiotic resistance to all antibiotics tested.

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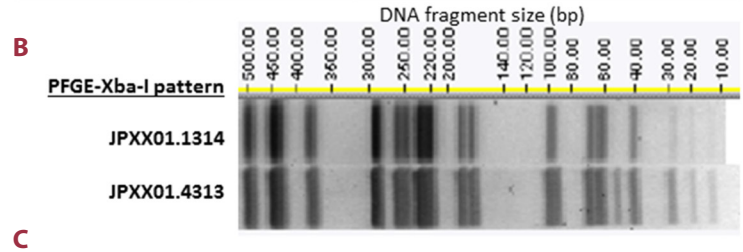
A

Isolate code	Serotype	PFGE-XbaI-pattern	Specimen source	Specimen site	Date isolated
E2016000770	Typhimurium	JPXX01.1314	Animal	Mes. lymph node	4/1/2015
E2016000771	Typhimurium	JPXX01.1314	Animal	Small intestine	4/1/2015
2015K-0414	4,[5],12:i:-	JPXX01.1314	Human	Intestinal ulcer	4/27/2015
2015K-0415	4,[5],12:i:-	JPXX01.4313	Human	Stool	4/29/2015
PNUSAS000603	4,[5],12:i:-	JPXX01.1314	Human	Stool	6/16/2015
PNUSAS000710	4,[5],12:i:-	JPXX01.1314	Human	Stool	7/6/2015

B



C

	2015K-0414	2015K-0415	E2016000770	E2016000771	PNUSAS000603	PNUSAS000710
2015K-0414	-	1	1	1	34	21
2015K-0415	1	-	0	0	31	17
E2016000770	1	0	-	0	33	20
E2016000771	1	0	0	-	32	18
PNUSAS000603	34	31	33	32	-	6
PNUSAS000710	21	17	20	18	6	-

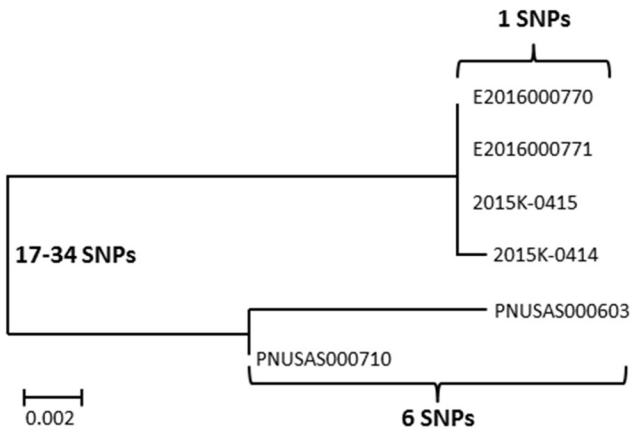


Figure 2. Molecular characterization of *Salmonella* isolates from animals and humans. (**A**) Table listing the characteristics of *Salmonella* isolates. (**B**) Comparison of Xba 1-restricted DNA pulse field gel electrophoresis (PFGE) patterns of indicated human and animal isolates from the same farm. (**C**) **Left**, table of the number of single-nucleotide polymorphisms (SNPs) from total chromosomal sequencing of indicated isolates; **right**, phylogenetic relatedness of isolates based on the number of SNPs identified. PFGE was performed following the standardized PulseNet USA protocol [18]. Restriction patterns were uploaded to the national *Salmonella* PFGE database and named according to the standardized PulseNet USA nomenclature [19]. Genomic DNA was extracted using the DNAeasy Blood and Tissue Kit (Qiagen, Valencia, CA). DNA libraries were prepared using the NexteraXT (Illumina, Inc., San Diego, CA) library preparation kit and sequenced on the Illumina MiSeq using the 2×250 bp (v2) chemistry to a minimum average coverage of 30x and average quality (Phred) score of 30. Whole-genome high-quality single-nucleotide polymorphism (hqSNP) analysis was performed with Lyve-SET version 1.1.4e (*http://github.com/lskatz/Lyve-SET*) on the raw reads, which were trimmed with Computational Genomics Pipeline (CGP) (*http://github.com/lskatz/CG-Pipeline*). SNPs were filtered using Lyve-SET with the following options: ≥20× coverage, 95% read support, >5bp flanking SNP distance. In-house closed PacBio sequence of the strain 2013K-0676 with the same PFGE pattern as the study strains was used as a reference for SNP calling without phage masking. Phylogenetic tree was constructed using RAxML (*https://github.com/stamatak/standard-RAxML*). Informed consent was obtained for use of patient clinical data and characterization of human and animal isolates.

To determine whether the human and bovine isolates were identical, we completely sequenced the genomic DNA from each of the 4 isolates (2015K-0414, 2015K-0415, E2016000770, and E2016000771) and differences were determined using single-nucleotide polymorphisms (SNPs) (Figure 2C). These were compared to recently characterized isolates with similar PFGE patterns and serotypes (PNUSAS000603 and PNUSAS000710). Both isolates from the index patient and the 2 outbreak isolates

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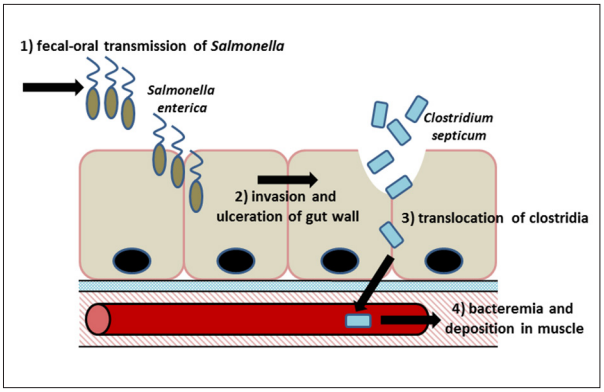

Figure 3. Probable steps in the pathophysiology of salmonellosis leading to clostridial myonecrosis. Diagram illustrates the lining of the gut lumen infected by *Salmonella* via fecal-oral transmission (step 1), breakdown of the epithelial layer and subsequent ulceration of the gut lining (step 2), translocation of luminal clostridia into the microcirculation in the submucosa (step 3), and metastasis of bacteria and deposition into muscle leading to myonecrosis (step 4). *Salmonella* are in brown and *Clostridium* in blue (as indicated); mucosa in dotted blue and submucosa (containing blood vessels) in red stripes.

from cattle were highly genetically related, having 0 to 1 SNP differences. These were genetically distant from the geographically unrelated isolates, which contained between 17–34 different SNPs (Figure 2C, left and right panels). These results further support that the isolates from the index case originate from the cattle in the outbreak.

Discussion

This is a novel case of human spontaneous (nontraumatic) *Clostridium septicum* myonecrosis associated with ulcerative intestinal lesions due non-typhoidal *Salmonella* enteritis. Such reported systemic severe clostridial infections leading to myonecrosis are found in those with gastrointestinal or hematologic malignancies and in those who are immunosuppressed or who have severely uncontrolled diabetes [4–6] none of which were present in our index patient. The patient did not report consumption of beef produced on the farm and likely acquired *Salmonella* from animal fecal-to-oral contaminative transmission. Intestinal salmonellosis likely led to ulcerations in the colonic wall, which facilitated the translocation of *Clostridium septicum*, present in the colonic lumen, across the gut wall into the blood, leading to transient bacteremia and deposition in the muscle and thus leading to myonecrosis. The probable steps in the pathophysiology in this case are shown in Figure 3.

The histology of the colonic lesions revealed microabscesses and the biopsy cultures grew *Salmonella*, supporting the diagnosis of invasive salmonellosis as the cause of the colonic lesions. The close proximity of the bovine *Salmonella* outbreak and the diarrheal episode in our patient is a significant epidemiological clue for the animal-to-human transmission of this entero-invasive pathogen. This is strongly supported by the matching PGFE patterns of both the human colonic and bovine isolates. The whole-genome sequencing (WGS) showed that all 4 isolates (2 human and 2 bovine) were highly related. Our data also identified both human and cattle isolates as serotype I 4,[5],12: i: – of *Salmonella enterica*, which is a monophasic variant of *Salmonella Typhimurium* that has lost the ability to express phase 2 flagella. This serotype has worldwide distribution and is among most common non-typhoidal serotypes associated with human infections in a number of countries, including the United States, with increasing prevalence [7]. It has been implicated in multiple nationwide foodborne outbreaks [8,9] and these isolates are typically multidrug-resistant, as was noted in our patient [3].

As a group, *Salmonella spp.* contains an array of genes and mutations that confer antibiotic resistance. These are due to the presence of drug resistance genes either within the chromosome or those encoded on transmissible plasmids. In addition, point mutations present in chromosomal genes encoding protein drug antibiotic targets are also responsible for resistance. Despite this, there are relatively few reports of the precise mechanisms of antibiotic resistance found in *Salmonella enterica*, serotype I 4,[5],12: i: –. Multidrug-resistant (MDR) isolates are more commonly found in Europe, and pan-susceptible isolates predominate in North and South America and in Asia. It is likely that the MDR isolates described in this study are related to the presence of plasmids containing multiple resistance genes, such as IncA/C plasmids carrying bla_{CMY} genes encoding extended-spectrum cephalosporins predominantly found in cattle [2]. Our isolates were susceptible to fluoroquinolones and nalidixic acid, resistance to which are mostly related to chromosomal point mutations in gyrase or topoisomerase, but plasmid-mediated quinolone resistance has been described in serotype I 4,[5],12: i: – isolates [10]. It is unknown what specific virulence genes are expressed in our isolates, but the presence of plasmids conferring MDR-phenotypes in the I 4,[5],12: i: – serotype have been postulated to carry virulence genes [3]. These genes can confer increased invasiveness in this serotype, and *Salmonella enterica* serotype *Typhimurium* can cause deep cecal ulcers and massive gastrointestinal hemorrhage, similar to what happened in our patient [11].

This case represents a convergence of events leading to a disastrous outcome and is an example of the real threat of the development and transfer of multidrug-resistant bacteria from animal to human populations. Animal-to-human multidrug-resistant *Salmonella* isolates have been associated with zoonotic transmission [12,13]. Widespread animal antibiotic use and

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development of multidrug-resistant commensal *Escherichia coli* in livestock is another example with significant ramifications for public health [14,15]. Antibiotic use has also increased among livestock, with 60% of the antibiotics used belonging to the 'medically important' category [16]. The isolates in our case were multidrug-resistant, thus we surmise that this arose due to the routine use of antibiotics in the animals, a practice that is common in the livestock industry, as well as the farm where our patient lived and worked. In Sept 2014, the Office of the President of the United States released the "National action plan for combating antibiotic resistant bacteria", which calls for the reduced use of antibiotics in agriculture to try to mitigate the development and spread of such pathogens [17]. This case highlights, in real terms, the need for the implementation in this plan.

Conclusions

We describe a case of spontaneous clostridial myonecrosis in a human due to ulcerative colonic infection with multidrug-resistant *Salmonella enterica*, serotype 4,[5],12: i. Serotyping- and PFGE-analyses, and whole-genome sequencing link invasive enteritis to human acquisition of *Salmonella* from a bovine disease outbreak support the direct link between development of drug resistance in pathogenic bacteria in animals and their transmission to humans, predisposing for serious super-infection. This highlights the need for judicious use of antibiotics in animal populations and recognition of the hazards of animal-to-human disease transmission.

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Conflicts of interest

None.

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