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# Rare Cause of Septic Arthritis: *Salmonella*

Septik Artrit Nedeni: *Salmonella*

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## Abstract

Gram-positive pathogens, particularly *Staphylococcus aureus*, are more commonly isolated in septic arthritis cases. Compared to other Gram-negative pathogens, *Salmonella* spp. is a rarely encountered cause of septic arthritis. The aim of this study is to investigate the cases followed with the diagnosis of *Salmonella* septic arthritis at Ege University School of Medicine Hospital. This study aimed to retrospectively evaluate the clinical, laboratory, and treatment outcomes of patients with *Salmonella enterica* (*S. enterica*) growth in knee joint fluid cultures at Ege University Medical Faculty Hospital between April 2017 and April 2023. In four patients (one female, three males) [mean age 50.75±19.82 years, range 30-71 years] with a diagnosis of septic arthritis, *Salmonella enterica* spp. *enterica* was isolated. All four cases had a history of immunosuppressive drug use. They were successfully treated with surgical and medical interventions. *Salmonella* spp. commonly causes gastroenteritis. Bacteremia can occur, leading to localized infections. While Gram-positive pathogens are frequently isolated in septic arthritis, it should be considered that Gram-negative pathogens can also be responsible, and sampling from the joint fluid should be performed.

**Keywords:** Immunosuppressive agent, *Salmonella*, septic arthritis

## Öz

Septik artritlerde başta *Staphylococcus aureus* olmak üzere Gram-pozitif etkenler daha sık izole edilmektedir. Diğer Gram-negatif etkenlerle karşılaştırıldığında *Salmonella* spp. nadir rastlanılan bir septik artrit nedenidir. Bu çalışmada Ege Üniversitesi Tıp Fakültesi Hastanesi'nde *Salmonella* septik artrit tanısıyla takip edilen olguların irdelenmesi amaçlanmıştır. Bu çalışmada Ege Üniversitesi Tıp Fakültesi Hastanesi'nde Nisan 2017-Nisan 2023 yılları arasında diz ponksiyon sıvısı kültüründe *Salmonella enterica* (*S. enterica*) üremesi olan hastaların retrospektif olarak klinik, laboratuvar ve tedavi sonuçlarının değerlendirilmesi amaçlanmıştır. Septik artrit tanısı ile kültür alınan dört hastada (bir kadın üç erkek) [yaş ortalaması 50,75±19,82 (30-71) yıl] *Salmonella enterica* spp. *enterica* üremesi olmuştur. Dört olguda da immünsüpresif kullanım öyküsü bulunmaktadır. Cerrahi ve medikal tedavi ile başarılı bir şekilde tedavi edilmişlerdir. *Salmonella* spp. sıklıkla gastroenterit tablosuna sebep olmaktadır. Bakteriyemi ve takibinde lokal enfeksiyonlara rastlanabilmektedir. Septik artrit tablosunda sıklıkla Gram-pozitif patojenler izole edilmesine karşılık Gram-negatif etkenlerin de tabloya sebep olabileceği göz önünde bulundurulmalı ve eklem sıvısından örneklem yapılmalıdır.

**Anahtar Kelimeler:** İmmünsüpresif ajan, *Salmonella*, septik artrit

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## Introduction

*Salmonella* spp. are Gram-negative, motile, non-encapsulated, facultative anaerobic bacteria that are members of the *Enterobacteriaceae* family. *Salmonella* genus bacteria are taxonomically divided into two types: *Salmonella enterica* and *Salmonella bongori*. *Salmonella* subspecies are divided into serotypes and serovars according to somatic O and flagellar H antigen. Vi antigen is a polysaccharide antigen found in *Salmonella typhi* and some subspecies<sup>[1,2]</sup>.

Subspecies of *S. enterica* species can cause gastroenteritis, bacteremia, local infections, enteric fever and asymptomatic carriage. Transmission occurs via the fecal-oral route. Consumption of meat from infected animals, especially poultry, and consumption of water and food contaminated with feces cause transmission<sup>[3]</sup>. Since gastroenteritis caused by *Salmonella* may progress to systemic infection in children under five years of age, older patients, and immunosuppressed individuals, and antibiotic therapy is recommended for these groups<sup>[4]</sup>.

Enteric fever is a clinical condition characterized by fever, headache, abdominal pain and diarrhea, which may be caused by *Salmonella typhi*, *Salmonella paratyphi* A, B, C. While it is less common in developed and developing countries where infrastructure problems have been largely solved, it continues to be an important health problem in Asian, African and South American countries<sup>[5]</sup>.

Focal infections mostly develop following bacteremia. Risk factors such as sickle cell anemia, malignancy, congenital immunodeficiencies, HIV infection, and use of immunosuppressive agents increase the risk of developing bacteremia and focal infection<sup>[3]</sup>.

Septic arthritis is a clinical condition that occurs as a result of infection of the synovial joint space with viral, bacterial, mycobacterial or fungal factors. It mostly develops after bacteremia. The synovial membrane has a well-vascularized vascular structure but no barrier structure. There is no flow in the synovial space. Due to its barrier structure and lack of flow, it can easily grow after bacterial cultivation by hematogenous means. Gram-positive agents, especially *Staphylococcus aureus*,

are isolated more frequently in bacterial septic arthritis. In septic arthritis caused by gram-negative bacilli, *Pseudomonas aeruginosa* and *Escherichia coli* are the most frequently isolated agents. Compared to other Gram-negative agents, *Salmonella* spp. is a very rare cause of septic arthritis<sup>[6]</sup>. Third generation cephalosporins and quinolones are the first options in the treatment of *Salmonella* spp. infections. However, multi-drug resistant strains are also reported today<sup>[7]</sup>.

In this article, it was aimed to examine the patients followed up with the diagnosis of *Salmonella* septic arthritis in a tertiary university hospital.

## Case Report

Four patients, who were followed up at Ege University Faculty of Medicine Hospital between April 2017 and April 2023, and whose joint puncture fluid culture showed *Salmonella* spp. growth, were evaluated retrospectively through the electronic file system. All puncture samples were plated on eosin-methylene blue agar (BioMerieux, France) and Gram-negative enrichment medium (HAJNA), (Conda Lab., Spain) after direct microscopic examination. It was incubated in Gram-negative medium for 4–6 hours. Afterwards, they were subcultured onto Hektoen enteric agar (BioMerieux, France). It was evaluated after 24–48 hours of incubation at 37 °C. Biochemical tests were applied to colonies suspicious for *Salmonella* species and identification was made with VITEK-MS (BioMerieux, France). *Salmonella* isolates were identified at the serovar level using specific antisera (Denka Seiken Co, Japan). Susceptibility studies were carried out in accordance with EUCAST recommendations<sup>[8]</sup>. Ampicillin, cefotaxime, imipenem, meropenem, ciprofloxacin (pefloxacin screening) and trimethoprim-sulfamethoxazole disks were used for *Salmonella* isolates. The results were evaluated according to EUCAST criteria. Consent forms were obtained from all participants.

In our hospital, 3 of the 4 patients followed with the diagnosis of *Salmonella* septic arthritis between April 2017 and April 2023 were men. The average age of the patients was 50.75±19.82 (30–71) years (Table 1). Three of the patients were hospitalized in the Infectious Diseases and Clinical Microbiology service, and one patient was hospitalized in the Orthopedics and

**Table 1. Demographic characteristics of the patients, underlying diseases and immunosuppressive agents used**

Patient number	Age	Gender	Underlying diseases	Immunosuppressive agent
1	71	F	Hypertension, diabetes mellitus, asthma, chronic inflammatory polyneuropathy	Methylprednisolone
2	30	M	Glioblastoma	Temozolomide
3	38	M	Hypertension, bipolar disorder, polyangitis granulomatosis (Wegener's disease)	Cyclophosphamide
4	64	M	Diabetes mellitus, metastatic prostate cancer	Methylprednisolone

F: Female, M: Male

Traumatology service. It was observed that three of the patients were hospitalized after admitting to the outpatient clinic and one patient was admitted to the emergency room. The first symptom that developed in all patients was fever, and at the time of admission, there was pain, increased temperature, and a difference in diameter in one knee compared to the other knee. Two patients had symptoms of gastroenteritis one week before admission to the hospital. C-reactive protein elevation was observed in four cases, leukocytosis in two cases, and sedimentation elevation in two cases (Table 2). There was a history of immunosuppressive agent use in all patients. High-dose methylprednisolone was used for a long time in two patients, cyclophosphamide in one patient, and temozolomide in one patient. Two of the patients had a history of underlying malignancy (glioblastoma and metastatic prostate cancer) and chemoradiotherapy (Table 1). The joint involved in all patients was knee, and the culture of puncture fluids showed *S. enterica*

growth. In one patient, *S. enterica* growth was observed in simultaneous peripheral blood culture. Puncture fluid direct examinations and culture antibiograms are summarized in Table 3. Arthroscopic debridement was performed by the Orthopedics and Traumatology Clinic between days 1–14 (Table 3). Ampicillin/sulbactam was preferred as empirical initial treatment in three patients, and a combination of ceftriaxone and ciprofloxacin was preferred in one patient. When the specific treatments of the patients, arranged according to the culture antibiogram results, were examined, it was observed that two patients were given 21 days of meropenem treatment, one patient was given 14 days of ceftriaxone treatment, and one patient was given seven days of ciprofloxacin treatment. Sequential treatments are listed in Table 3. Three patients were discharged after improvement in clinical and/or laboratory results after treatment, and one patient was referred to another clinic for monitoring of underlying diseases after septic arthritis treatment.

**Table 2. The initial biochemistry parameters in the first referral**

Patient number	1	2	3	4
CRP (mg/L)	60.04	181.03	186.75	19.81
Leukocyte (10 <sup>3</sup> /μL)	22.26	7.67	14.46	7.88
Neutrophil (%)	91.1	45.5	58.1	95.3
Sedimentation	89	101	-	-

CRP: C-reactive protein

**Table 3. Direct examination of knee puncture fluid, antibiograms and treatments**

Patient	Leukocyte count (cell/μl) / PMNL (cell/μl)	Antibiogram			Empirical treatment	Specific treatment	Surgical treatment
		Quinolone	Third generation cephalosporin	Carbapenem			
1	36497/33292	R	S	S	Ampicillin/sulbactam 3x2 g (2 days)	Meropenem 3x1 g IV (19 days) + Ciprofloxacin 2x400 mg IV (14 days) Ciprofloxacin 2x750 mg PO (15 days)	Arthroscopic debridement (day 7)
2	30000	S	S	S	Ampicillin/sulbactam 3x2 g (1 day)	Ciprofloxacin 3x400 mg IV (7 days) Ciprofloxacin 2x750 mg PO (21 days)	Arthroscopic debridement (day 1)
3	38452/36680	S	S	S	Ampicillin/sulbactam 3x2 g (3 days)	Meropenem 3x1 g IV (14 days) Ciprofloxacin 2x400 mg IV (14 days)	Arthroscopic debridement (day 14)
4	300000	S	S	S		Ceftriaxone 2x1 g IV (14 days) Ciprofloxacin 2x500 mg PO (14 days)	Arthroscopic debridement (day 2)

IV: Intravenous, PMNL: Polymorphonuclear leukocytes

Discharged patients were called for a outpatient clinic check-up in the first month of the start of treatment. On-site consultations were evaluated at the clinic where the referred patient was admitted during the first month of treatment.

## Discussion

*Salmonella* septic arthritis is a rare complication encountered in 0.27% of *Salmonella*-infected patients<sup>[6]</sup>. *Salmonella enterica* spp. *enterica* subspecies was found to be the causative agent in the patients with *Salmonella* septic arthritis that we followed up in our hospital. According to CDC data, the most common strain isolated in cultures is *Salmonella enterica* spp. *enterica*<sup>[9]</sup>.

It is reported that most patients diagnosed as having *Salmonella* septic arthritis have an underlying history of trauma, prosthesis or immunosuppression<sup>[6]</sup>. None of the patients we followed up had a history of trauma or prosthesis. However, all of the patients were immunosuppressive.

It has been reported that bacteremia and local infections may develop at a rate of 5% after *Salmonella* gastroenteritis. HIV infection, sickle cell anemia, malignancy, congenital immunodeficiencies and use of immunosuppressive agents are risk factors for the development of bacteremia<sup>[3]</sup>. Two of the patients had symptoms of gastroenteritis before the complaint of fever, and it was noteworthy that there was a history of malignancy, a history of chemotherapy and the use of immunosuppressive agents. In one of the four patients, *S. enterica* grew in the blood culture, and in the other three patients, there was no growth in the blood culture.

Detection of 50,000/mm<sup>3</sup> leukocytes in the sample taken from the joint cavity by puncture is considered to be significant in terms of septic arthritis<sup>[10]</sup>. However, some authors consider the presence of >25,000/mm<sup>3</sup> leukocytes as significant<sup>[10]</sup>. Many factors, especially the conditions in which the puncture is performed, the waiting time for the sample taken, the competence of the person performing the direct examination, and technical defects in the counts made with the device, can affect the results. It is also reported that the use of corticosteroids can reduce the number of leukocytes in the fluid<sup>[11]</sup>. In this respect, it is important to culture samples taken from puncture fluid<sup>[6]</sup>. In our study, although less than 50,000/mm<sup>3</sup> leukocytes were found in the joint puncture fluid of all patients, *Salmonella* spp. was observed to grow. Consistent with the literature, all of the patients in our study were using immunosuppressive drugs, two of which were corticosteroids.

Third generation cephalosporins and quinolones are primarily preferred in the treatment of *Salmonella* septic arthritis. In recent years, quinolone resistance has reached 80% in Asia,

and multi-drug-resistant *Salmonella* spp. has been detected in countries such as Iraq and Pakistan. In our country, this rate is estimated to be lower, but current data are limited. A study reported from our hospital showed that there was a 16.5% decreased quinolone susceptibility in *S. enterica* strains examined between 1997 and 2005. In a study conducted in Kayseri, it was reported that 7.6% of *Salmonella* serovars were resistant to ciprofloxacin and 6.3% to cefotaxime in the samples examined between 2013 and 2016<sup>[7]</sup>. While one of the patients in our study had quinolone resistance, none of our patients had cefotaxime resistance.

Septic arthritis is among the orthopedic emergencies, so a puncture should be performed from the joint space as soon as possible. If septic arthritis is suspected based on clinical and laboratory findings, antibiotic therapy should be started as soon as possible. Debridement of the joint space is as important as antibiotic therapy in the treatment of septic arthritis<sup>[12]</sup>. It has been observed that surgical cleaning of the joint space improves the clinical course and increases the success of treatment<sup>[12]</sup>. Arthroscopic debridement was applied to the patients we followed up in our hospital by the Orthopedics and Traumatology clinic with a multidisciplinary approach. All patients were treated successfully.

When the patients with *Salmonella* septic arthritis reported in our country were examined, it was observed that *S. enterica* and *S. typhi* were isolated. Patients with sacroileac joint and knee joint involvement were reported in the literature. Published case reports included the use of immunosuppressive agents or underlying diagnoses causing immunosuppression, similar to the patients in our case series<sup>[13-16]</sup>. The reported patients were in the form of case reports and there was no *Salmonella* septic arthritis case series in the literature.

## Conclusion

It should be taken into consideration that *Salmonella* species may be the causative agent in septic arthritis that develops in immunosuppressed patients. It should be noted that high leukocyte counts may not always be detected in joint puncture fluid samples. Since there is increasing resistance in *Salmonella* spp. in the world today, culture and antibiogram should be performed and specific treatment should be arranged accordingly. Successful results are possible with appropriate antibiotic therapy and debridement of joint fluid.

## Ethics

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: M.B.Ö., D.B.E., M.E.K.B., B.A., M.I.T., Concept: M.B.Ö., M.I.T., Design: M.B.Ö., M.I.T., Data Collection or Processing: M.B.Ö., M.A.Ö., M.I.T., Analysis or Interpretation: M.B.Ö., M.A.Ö., M.I.T., Literature Search: M.B.Ö., D.B.E., M.I.T., Writing: M.B.Ö., D.B.E., B.A., M.I.T.

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