

CASE REPORT

Unusual *Salmonella typhi* periprosthetic joint infection involving bilateral knees: management options and literature review

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SUMMARY

A 70-year-old Indian woman, who had undergone primary bilateral total knee arthroplasty (TKA) for rheumatoid arthritis 10 months prior, presented with 10 days history of pain, swelling and erythema over both knees with pus discharging from the right knee. She had type 2 diabetes mellitus and was on long-term steroid, leflunomide and antitumour necrosis factor therapy for rheumatoid arthritis. Her clinical and laboratory features were suggestive of a haematogenous periprosthetic joint infection (PJI). The final diagnosis of bilateral *Salmonella typhi* PJI was made based on culture reports. Considering her underlying immunosuppression, a bilateral two-stage revision TKA was done with complete remission of symptoms and good functional recovery at last follow-up after 18 months. *S. typhi* infection of prosthetic joint has not been reported in the literature. Patients presenting with gastrointestinal complaints and PJI should alert the clinician to the possibility of infection with such atypical organisms endemic to the region.

BACKGROUND

The incidence of periprosthetic joint infection (PJI) is around 0.3%–1.7% following a primary total hip arthroplasty (THA) and 0.8%–2% after a primary total knee arthroplasty (TKA).^{1–2} *Staphylococcus* species (*Staphylococcus aureus* and coagulase-negative species like *S. epidermidis* and *S. saprophyticus*) account for more than 50% of the cases. PJI due to Gram-negative bacilli account for less than 6% of cases,² *Escherichia coli* and *Pseudomonas* being the most common organisms identified. *Salmonella*, a Gram-negative bacilli, belonging to the genus Enterobacteriaceae is a rare cause of PJI (42 cases with 44 joints reported to date) and is mostly seen in patients with underlying immunosuppression.³ *Salmonella* PJI (S-PJI) of the hip is commoner (32 cases reported) than that of the knee (11 cases with 12 knees reported to date) and is almost always unilateral. Non-typhoid *Salmonella* (NTS) strains are the causative organism in 98% (43/44) of these cases. *Salmonella enteritidis* and *S. typhimurium*, both belonging to the NTS group account for 61% (27/44) of S-PJIs reported in literature. Despite its endemicity affecting a large subgroup of the world population, *Salmonella typhi*, the causative organism for typhoid fever, is an extremely rare cause of PJI. In fact, to our knowledge, no case of *S. typhi* PJI (St-PJI) has been reported in the literature.

We report a case of St-PJI involving bilateral knees 10 months after bilateral TKA in a 70-year-old Indian woman with rheumatoid arthritis and type 2 diabetes mellitus. Unique characteristics of *Salmonella* and its implications in deciding the mode of treatment of such cases are discussed.

CASE PRESENTATION

A 70-year-old Indian woman presented with sudden onset of pain, swelling and restricted movements over both the knees for the past 10 days. She had undergone bilateral single-stage cemented TKA 10 months prior to this and her postoperative period was uneventful. She developed intermittent episodes of fever with chills, abdominal distension and loose stools over the previous 1 month and had taken a 5-day course of norfloxacin–tinidazole 2 weeks prior to the onset of joint symptoms. She had rheumatoid arthritis diagnosed for the past 15 years which had been treated with 5 mg prednisolone and 10 mg leflunomide once a day along with 40 mg adalimumab injection once a week for the past year. Other significant medical history includes type 2 diabetes mellitus controlled with oral hypoglycaemics (latest haemoglobin A1c 5.8), hypothyroidism since 10 years (on daily 100 µg thyroxine) and recently diagnosed hypertension treated with diltiazem (calcium channel blocker) 90 mg daily.

Physical examination revealed local warmth, tenderness and erythema over both the knees with active pus discharge and erythema was noticed over the proximal third of the right knee incision site. The range of motion was severely restricted to 30°–40° in both knees. She was febrile with a temperature of 37.5°C. The patient was hospitalised.

INVESTIGATIONS

Fresh radiographs of both the knees showed radiolucent lines under the tibial base plate on both the sides (figure 1). Haematological examination revealed a haemoglobin of 11.1 g/dL, white cell count (WCC) of $15.8 \times 10^9/L$ with 76% neutrophils and 16% lymphocytes, low total serum protein 5.5 g/dL (reference value: 6.4–8.2 g/dL) and albumin 2.9 g/dL (reference value: 3.4–5 g/dL), erythrocyte sedimentation rate (ESR) 85 mm/hour and C reactive protein (CRP) 96 mg/L (normal <6 mg/L).

On aspiration of both the knee joints, a seropurulent slightly reddish fluid was obtained from both the knees with a WCC of $13.2 \times 10^9/L$ with



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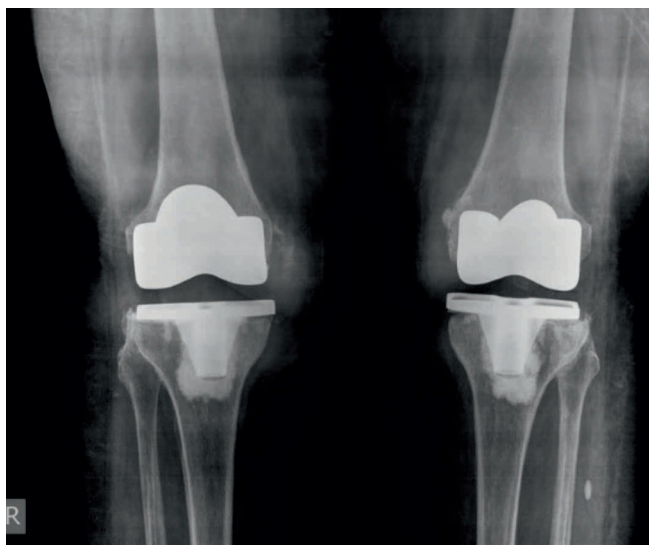


Figure 1 Bilateral peri-prosthetic joint infection following total knee arthroplasty due to *Salmonella typhi*—radiographs showing relatively well-fixed components with radiolucent lines under the tibial base plate.

94% neutrophils on the right and $11.5 \times 10^9/L$ with 90% neutrophils on the left. Gram staining revealed Gram-negative bacilli which after 2 days of culture was reported to be *S. typhi*, which was sensitive to cephalosporins, trimethoprim-sulfamethoxazole, chloramphenicol and fluoroquinolones. Stool and blood cultures were negative. Ultrasound examination of the abdomen was unremarkable with no hepatosplenomegaly and normal gallbladder.

TREATMENT

A two-staged revision with aggressive local debridement and removal of the previous implant was done. The right knee was operated first followed by the left knee after 2 days. The prosthesis was found to be well-fixed with no evidence of loosening on both the sides. An antibiotic-impregnated static cemented spacer (containing gentamicin) was used for both the sides and was kept in situ for 5 weeks. Five intraoperative samples were collected from each side including the joint fluid and biopsy samples from synovial tissue, granulation tissue under the femoral and tibial components and deep tibial intramedullary tissue. *S. typhi* was detected from three samples from the right and two from the left. The patient was kept on injectable third-generation cephalosporins (injection ceftriaxone 2g for every 24 hours and oral ciprofloxacin (500mg for every 12 hours) for 4 weeks. The surgical wounds were healthy with no evidence of local infection. Her ESR and CRP showed a decreasing trend and were 9 mm/hour and 2 mg/L at 5 weeks, respectively. The second stage of revision was carried out using a condylar constrained prosthesis (Legacy Constrained Condylar Knee LCKK; NexGen, Zimmer) 5 weeks after the first stage of revision (figure 2). Intraoperative frozen tissue biopsy revealed neutrophil count <5 cells/high power field. Culture from tissue samples obtained during the second stage did not detect any organism. Oral ciprofloxacin was continued for 6 weeks postoperatively.

OUTCOME AND FOLLOW-UP

The patient recovered well from the surgery and was able to ambulate using a walking stick after 3 months postoperatively. At her last follow-up at 18 months, there was no local warmth over the knees and the swelling and erythema had subsided

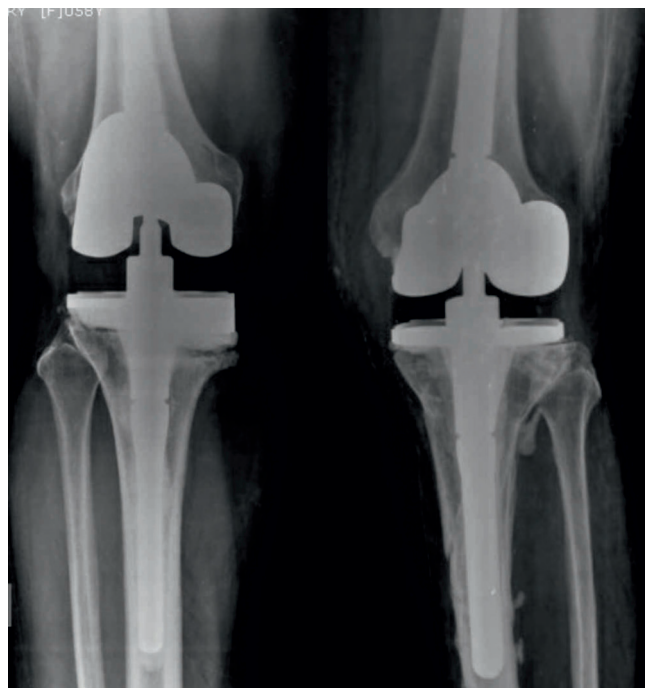


Figure 2 Postoperative radiographs of both knees following two-stage revision total knee arthroplasty.

completely. She was capable of independent ambulation and stair-climbing with a flexion range of 0° – 100° on both knees. The patient died at 20 months after the second-stage revision due to an unrelated cardiovascular event.

DISCUSSION

Salmonella infection of the prosthetic joints is a rare entity. The genus is classified as typhoid *Salmonella* (causative agents of enteric fever, includes *S. enterica* serovar Typhi and *S. enterica* serovar Paratyphi A, B, C) and non-typhoid *Salmonella* (NTS, which includes the rest of the strains).⁴

S-PJI is a rare entity. Literature review has revealed 32 cases of S-PJI following THA and 11 cases (with 12 knees) following TKA.^{5,6} NTS are the most common and almost exclusive causative organisms. Seventeen (11 hip and 6 knees) out of a total of 44 S-PJIs have been caused by the NTS strain of *S. enterica* serovar *enteritidis* while *S. typhimurium* was isolated from 6 (five hip and one knee) of the 44 cases. To the best of our knowledge, no case of *S. typhi* has been reported in the literature to date. S-PJI usually affects a single joint and bilateral involvement is extremely rare with only one case of unilateral hip and knee affection⁵ and one case of bilateral knee⁷ involvement reported in literature. The higher frequency of NTS strains causing PJI may be due to its global distribution and the fact that bacteraemia and extraintestinal manifestations are more common with NTS (seen in 5% of infected cases).^{4,8}

A few important characteristic features of the bacteria deserve mention in order to understand its pathogenicity to guide further management. *Salmonella* is a Gram-negative enteroinvasive bacilli and a facultative anaerobe capable of intracellular survival within macrophages. The ability of the bacteria to invade non-phagocytic cells (including the intestinal epithelium) enables it to cause haematogenous seeding of distant organs.⁴ Involvement of the musculoskeletal system in salmonellosis is seen in the form of reactive arthritis (ReA, most common joint manifestation), abscess formation, osteomyelitis

Table 1 Reported cases of *Salmonella* PJI involving the knee in the literature

Study	Age/sex	Underlying diseases	Age of prosthesis at presentation	Species of <i>Salmonella</i> detected	Treatment	Duration of follow-up	Outcome
Rae <i>et al</i> ²⁷ (1977)	67/F	RA	5 years	<i>S. typhimurium</i>	Chloramphenicol and amoxicillin with retention of prosthesis, followed by chronic antibiotic suppression with amoxicillin	NS	Required chronic antibiotic suppression
Boland <i>et al</i> ²⁹ (1999)	51/F	RA on methotrexate and azathioprine	NS	<i>S. enteritidis</i>	Multiple closed drainage with needle aspiration and intravenous ceftriaxone for 4 weeks	1 year	Uneventful follow-up
Madan <i>et al</i> ²⁰ (2001)	75/F	RA on long-term oral steroids	8 years	<i>S. enteritidis</i>	Ciprofloxacin for 6 weeks—flaring up of symptoms after 15 months with detection of <i>Salmonella</i> —ciprofloxacin continued for 3 months	NS	Asymptomatic until last follow-up*
Day <i>et al</i> ²⁸ (2002)	55/M	OA, type 2 DM	12 days	<i>S. enteritidis</i>	Open debridement, poly-exchange and retention of prosthesis followed by 6 weeks of ceftriaxone therapy	6 years	No recurrence
Musante <i>et al</i> ³¹ (2004)	63/F	OA, history of gout	8 weeks	<i>S. typhimurium</i>	Open irrigation and debridement with poly-exchange followed by 6 weeks of ceftazidime	15 months	Cured
Miron <i>et al</i> ³² (2006)	75/M	NS	NS	<i>S. enteritidis</i>	Open debridement, prosthesis retention followed by 3 weeks of intravenous ceftriaxone and 3 months of oral ciprofloxacin	NS	Cured
Kobayashi <i>et al</i> ⁷ (2008)	71/F	RA on steroids, methotrexate, HCQ, azathioprine	Bilateral knee involvement Right—11 years, Left—6 years	<i>S. enteritidis</i>	Open debridement and poly-exchange with long-term antibiotic suppression with continuing oral ciprofloxacin until last follow-up	30 months	Persistent warmth over joints, no other evidence of infection
Kenichi <i>et al</i> ²⁴ (2009)	61/M	RA on long-term steroids, methotrexate and etanercept	5 weeks	<i>S. enteritidis</i>	Arthroscopic debridement, implant retention followed by intravenous meropenem and oral levofloxacin for 2 weeks and oral minocycline for 3 months	3 years	Cured, etanercept resumed 12 months after surgery
Carlile <i>et al</i> ³³ (2010)	71/M	NS, revision surgery done for PJI after 3 years (no organism isolated), pyoderma gangrenous on long-term steroids	2 years after revision surgery	<i>S. choleraesuis</i>	Two-stage revision surgery followed by intravenous cefotaxime for 1 week and oral ciprofloxacin for 3 weeks	1 year	Cured
De la Torre <i>et al</i> ⁵ (2012)	72/M	RA, on prednisone and methotrexate	10 months	<i>S. enteritidis</i>	Two-stage revision at first. Recurrence of infection after 9 months with simultaneous hip prosthetic joint involvement. Two-stage hip and knee revision carried out.	3 ½ years	Cured
Gupta <i>et al</i> ⁶ (2014)		RA, bladder cancer	3 years	<i>S. enteritidis</i>	Initially aspiration followed by oral TMP-SMX for 12 weeks—failed treatment in 3 months—open debridement, prosthesis removal and arthrodesis	15 years	Cured

DM, diabetes mellitus; F, female; HCQ, hydroxychloroquine; M, male; NS, not specified; OA, osteoarthritis; PJI, prosthetic joint infection; RA, rheumatoid arthritis; TMP-SMX, trimethoprim-sulfamethoxazole.

and *Salmonella* septic arthritis (SSA) of the native or prosthetic joint.⁴ An important property of *Salmonella* is the ability to form biofilm which helps in survival in the outside environment by adhering to plants, abiotic surfaces such as metal (prosthesis), plastics or glass and other food products.⁹ Chronic carrier state is said to be 1%–4% and one reason is due to the ability to survive by biofilm formation.⁴ The biofilm forms are more resistant to antibiotic therapy in vivo though they may demonstrate susceptibility in the laboratory. Hence, retention of implant may lead to persistence of infection in S-PJIs. Addition of biofilm-active drugs such as fluoroquinolones¹⁰ may be necessary. Widmer *et al*¹¹ have reported a case where a PJI of hip due to *Salmonella dublin* failed prolonged treatment with oral co-trimoxazole and was eventually cured after addition of oral ciprofloxacin though recurrence was seen after 9 years.

S. typhi infection is a notifiable disease and humans are the only reservoir. Case reports of *S. typhi* infection of native joints causing SSA, usually in young children and immunocompromised adults,^{12–14} have been well reported.

The patient in our report belonged to India which is endemic for *S. typhi*. The incidence of *S. typhi* is estimated to be approximately 100 cases for 100 000 inhabitants per year in Southcentral and Southeast Asia.^{4,15} In a recent systematic review, the pooled estimate of typhoid burden in India was found to be 377 (178–801) per 100 000 person-years for typhoid.¹⁶ The incidence is significantly lower in the developed countries with a reported incidence of 0.31 cases per 100 000 in the year 2014 in the European Union countries, and predominantly acquired during travel to endemic countries particularly South Asia.¹⁷

As in the rest of the world, the numbers of TKA surgeries are increasing exponentially in India. PJI is the second most common cause of revision as reported in the Indian Joint Registry accounting for 26% of the cases of revision.¹⁸ This case study demonstrates the importance of recognising the fact that as the number of total knee replacements increase in the Indian subcontinent, investigations for causative organisms for PJI should include the effort to look for atypical tropical organisms endemic to this region, such as *S. typhi*. It is important to recognise that a part of the population undergoing a joint replacement in this community may be carriers for and prone to infection with the said organism. Also, with a rise in arthroplasty cases in the region, the population at risk for haematogenous PJI with *S. typhi* is also subject to increase, a possibility that should be kept in mind. Hence, preceding episodes of diarrhoea with fever and abdominal symptoms in the setting of immunosuppression should alert the clinician about the possibility of PJI with enteric bacteria such as *S. typhi* as one of the uncommon and rare causative organism. Other differential diagnoses include PJI due to *Campylobacter*, *Clostridium difficile* and *Yersinia enterocolitica* which may present with a similar picture.⁶

It is important to differentiate between ReA and SSA as the management differs—symptomatic treatment with anti-inflammatory medications and rest for ReA while aggressive approach is necessary in SSA or S-PJI. Oral and long-term antibiotics have less role in treating the former condition¹⁹ and association with HLA-B27 is seen in about 40%–90% of cases in some reports.^{20 21} The incidence of ReA following *Salmonella* gastroenteritis is reported to be between 1.2% and 7.3%,^{20 22} most commonly due to *S. typhimurium* (60%) and *S. enteritidis* (25%),²⁰ is due to an immunogenic phenomenon and may present with slight arthralgia to severe disabling disease. The diagnosis is by the detection of specific antibodies from joint fluid using agglutination tests (Widal test), enzyme immunoassay, immunofluorescence or immunoblotting techniques.

SSA and S-PJI is most commonly seen in patients with history of immunosuppression due to underlying disease (diabetes mellitus, HIV) or following immunosuppressive treatment (eg, for rheumatoid arthritis, renal transplant recipients, connective tissue or haematological disorders, etc).⁵ Patients on anti-tumour necrosis factor (TNF) alpha therapy, such as infliximab,²³ etanercept²⁴ and certolizumab,²⁵ are particularly susceptible due to reduction in the ability to kill the intracellular pathogens. The patient in our case report had been on adalimumab (Humira), a chimeric monoclonal anti-TNF antibody. A high degree of suspicion and the possibility of extraintestinal salmonellosis should be kept in mind while dealing with patients with PJI receiving anti-TNF therapy.

There is no consensus regarding the ideal treatment modality in case of S-PJI. Such cases are rare and varied outcomes following treatment have been reported. Cohen *et al*²⁶ have reported better outcomes with *Salmonella* septic arthritis than with other Gram-negative organisms. Among the 11 cases (12 knees) of S-PJI involving TKA (table 1), three were treated with open debridement and antibiotic therapy with implant retention, another three underwent exchange of the polyethylene component, one with arthroscopic debridement with implant retention, one treated with only long-term antibiotics, two underwent a two-stage revision surgery and one case following failure of antibiotic therapy underwent prosthesis removal and subsequent arthrodesis. Failure was seen in the case treated with only antibiotics²⁷ and chronic antibiotic suppression was required in the case reported by Kobayashi *et al*⁷ with bilateral knee prosthesis involvement treated with debridement and poly-exchange.

Learning points

- ▶ The possibility of *Salmonella typhi* prosthetic joint infection (St-PJI) should be kept in mind and investigated for in patients belonging to endemic regions or with history of recent travel to endemic countries. The likelihood increases in those with history of immunosuppression and/or with preceding gastrointestinal symptoms.
- ▶ The ideal treatment in cases of *Salmonella* PJI should be individualised based on the duration of symptoms, age of the patient and systemic comorbidities and also if there is associated loosening of the implant. Open or arthroscopic debridement is usually not sufficient in these cases with higher rates of recurrences.
- ▶ In patients with lesser duration of symptoms (<3–4 weeks), open debridement with exchange of polyethylene component can be attempted. The risk of persistence of infection and the need for prolonged antibiotic therapy should be explained to the patient.
- ▶ The susceptibility of *Salmonella* species to antibiotics should be identified since strains with reduced susceptibility to first-line drugs and multidrug resistance is increasingly prevalent in the developing countries.
- ▶ Considering the virulence of *Salmonella* and its ability to form biofilms with reports of late recurrences occurring upto 9 years postrevision,¹¹ a two-stage revision should be considered as the gold standard of treatment and should be attempted as the definitive modality of treatment.

Earlier, Day *et al*²⁸ have reported that 9 out of 12 patients with S-PJI involving the hip (10 cases) and knee (2 cases) required removal of at least one or more components of the prosthesis to achieve favourable outcomes. In an extensive literature review of S-PJI, de la Torre *et al*⁵ have shown that the outcome following removal of part of prosthesis or complete replacement was uniformly favourable. They reported a case of recurrent knee PJI following two-stage revision with concomitant hip PJI with *S. enteritidis*. They advocated that an aggressive approach and two-stage revision should be undertaken especially in patients with compromised immune status. Gupta *et al*⁶ identified six patients with S-PJI from a 44-year study period of which five were following THA and one following TKA. They noted that all four patients treated without removal of implant failed treatment within a median time of 2.5 months (range 2–11) following commencement of treatment. They concluded that prosthesis removal was associated with higher rates of cure and implant retention and debridement alone had higher failure rates.

Among all the 42 cases (44 joints) of S-PJI reported to date, a documented two-stage revision was carried out in only nine cases. Of this, only one patient undergoing two-stage revision had recurrence of symptoms.⁵ A two-stage revision using antibiotic spacer yielded good result bilaterally in our case with no recurrence of symptoms and good functional outcome.

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Competing interests None declared.

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