Septic arthritis due to Salmonella Typhi in children—A case series

Rakesh Kumar Mahajan¹, Jyoti Chaudhary¹, Priyanka Chaskar¹, Rajinder Kumar Arya², Nandini Duggal¹, Charoo Hans¹

¹: Department of Microbiology, 2: Department of Orthopaedics, Dr Ram Manohar Lohia Hospital & PGIMER, New Delhi-110001, India

*Corresponding author: Rakesh Kumar Mahajan, M.D., Department of Microbiology, Dr Ram Manohar Lohia Hospital & PGIMER, New Delhi-110001 (Email: rks.mahajan@gmail.com; Tel: 9968307899)

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Salmonella enterica serotype Typhi has been considered a rare cause of septic arthritis. This case series represents four cases of septic arthritis over a period of about one year in which S. Typhi was isolated and three of them were unrelated to prior enteric fever. These findings point to this cause and effect relationship either being overlooked before and elsewhere, or its emerging virulence potential. A thorough search for the causative agent in all such cases and to look for involvement of Salmonella Typhi is strongly warranted.

Keywords: Salmonella Typhi, arthritis, children

**Abstract:** Salmonella enterica serotype Typhi has been considered a rare cause of septic arthritis. This case series represents four cases of septic arthritis over a period of about one year in which S. Typhi was isolated and three of them were unrelated to prior enteric fever. These findings point to this cause and effect relationship either being overlooked before and elsewhere, or its emerging virulence potential. A thorough search for the causative agent in all such cases and to look for involvement of Salmonella Typhi is strongly warranted.

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During a period of about one year, four cases of Salmonella Typhi septic arthritis were noticed. Clinical profile of all four subjects, whose joint aspirates yielded Salmonella Typhi has been presented briefly. Of the four children, three were females and one male, in the age range between three to twelve years.

**Case 1.** A female child, twelve year old, HIV positive, was admitted in the paediatrics ward with complaints of pain in the left knee and high grade fever for fifteen days. There was history of preceding trauma fifteen days back, when the child had slipped and developed pain and swelling in knee. She was given analgesics for pain relief. At time of admission, the knee was swollen and tender with rise in local temperature. X-ray of knee joint showed features of soft tissue swelling and osteopenia compatible with pyogenic pathology. The patient was referred to Orthopaedics department for further work up. Diagnostic and therapeutic arthrotomy was undertaken and about 10ml of pus drained and submitted to Microbiology department for culture and sensitivity. The pus showed Gram negative rods on smear and grew Salmonella Typhi in pure culture. Blood, stool and urine cultures were sterile, total leukocyte count (TLC) was 13000/mm³ and biochemical parameters were within normal biological range. CD4+ count


$\text{S. enterica}$ serotype Typhi is a pathogen specific only to humans and is one of the most extensively studied bacterial pathogens. However, it is not adequately understood in respect of its ability to establish persistent infections, which serve as reservoirs for disease transmission and associated morbidity and mortality.[1] The global burden of Typhi infections has been estimated at twenty million cases and two hundred thousand deaths each year [2]. Organisms commonly associated with septic arthritis include Staphylococcus aureus, Haemophilus influenzae, Streptococci, Gram negative rods like Klebsiella spp., gonococci, Spirochaetes like Borrelia burgdorferi, some Mycoplasma and several viruses [3]. Salmonella has never been considered an important cause of septic arthritis and whenever associated, it has invariably been a metastatic extension of non-typhoidal salmonella illness [3, 4]. Association of Salmonella Typhi with septic arthritis is an extremely rare clinical entity but data presented in this study seem to indicate that either salmonella arthritis is less noticed or this entity is an emerging phenomenon.

**Cases:**

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was recorded as 590/µl.

**Case2.** A female child of five years reported to the orthopaedics outpatient department with complaints of fever, pain in left hip, and difficulty in standing and walking. The presenting features appeared about ten days after the child was pushed down during play and had had severe pain in the hip area. A diagnosis of infective arthritis was made and a needle aspirated sample was sent for culture; meanwhile the child was put on ampicillin and gentamicin. The pus sample yielded a pure growth of *Salmonella Typhi*. The report was communicated to the treating surgeon but it was informed that parents of the child had taken discharge against medical advice. The child was brought back after about one week without any relief. Arthrotomy was done for joint lavage and debridement as the child had developed swelling at the site of initial aspiration. Second sample taken at this time also yielded *Salmonella Typhi*. She was treated with ceftriaxone and ofloxacin and during next follow up after three weeks, the child was afebrile and able to walk around comfortably.

**Case3.** A three year old female child had trauma while playing, had severe pain in the hip and could only get up with difficulty. Afterwards, the child did not have any problem for about ten days. This was followed by high grade fever, pain around hip joint and inability to walk. She was treated by a private practitioner for about seven days but without any relief. A referral to the orthopaedics department of our hospital found features of septic arthritis like, raised local temperature and marked restriction in movements on left side. X-ray hip joint revealed increase in the joint space and soft tissue swelling. *Salmonella Typhi* was found to be the causative agent in the sample collected during arthrotomy.

**Case4:** A 6 years old male child, admitted to the orthopaedics emergency department with one month history of fever and one week complaint of pain and swelling in the left thigh without any preceding history of trauma. The child showed features of toxicity and MRI of the hip joint showed moderate effusion in the left hip joint and oedema of left femoral neck and metaphysis. There was left groin lymphadenopathy. Arthrotomy was performed and a diagnosis of osteomyelitis of metaphysis was made with the pus yielding *Salmonella Typhi* on culture.

### Table 1. Clinical & demographic profile

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age &amp; Sex</strong></td>
<td>3 yrs. Female</td>
<td>5 yrs. Female</td>
<td>6 yrs. Male</td>
<td>12 yrs. Female</td>
</tr>
<tr>
<td><strong>Socio-economic status</strong></td>
<td>Low income group</td>
<td>Low income group</td>
<td>Low income group</td>
<td>Low income group</td>
</tr>
<tr>
<td><strong>Joint involved</strong></td>
<td>Hip joint (Left)</td>
<td>Hip joint (Left)</td>
<td>Hip joint (Left)</td>
<td>Knee joint (Left)</td>
</tr>
<tr>
<td><strong>History of fever prior to joint involvement</strong></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>History of trauma prior to joint involvement</strong></td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Pus Culture</strong></td>
<td><em>Salmonella Typhi</em></td>
<td><em>Salmonella Typhi</em></td>
<td><em>Salmonella Typhi</em></td>
<td><em>Salmonella Typhi</em></td>
</tr>
<tr>
<td><strong>Antimicrobial Sensitivity</strong></td>
<td>S- Co, Ac, Ci, Cf, Of, C R-A, Na</td>
<td>S-Co, Ac, Ci, Cf, Of, C R-A, Na</td>
<td>S-Co, Ac, Ci, Cf, Of, C R-A, Na</td>
<td>S-Co, Ac, Ci, Cf, Of, C R-A, Na</td>
</tr>
<tr>
<td><strong>Blood, urine, stool culture</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>8.3 gm%</td>
<td>9.2 gm%</td>
<td>8.8 gm%</td>
<td>7.8 gm%</td>
</tr>
<tr>
<td><strong>Polymorphs</strong></td>
<td>65%</td>
<td>68%</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>11,000</td>
<td>11,500</td>
<td>15,000</td>
<td>13,000</td>
</tr>
<tr>
<td><strong>HIV Status</strong></td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

*Ac- Augmentin, Ci- Ceftriaxone, Cf- Ciprofloxacin, Of- Ofloxacin, C- Chloramphenicol, A- Ampicillin, Co- Co-trimoxazole, Na- Nalidixic acid, S- Sensitive, R- Resistant*
results are shown in the Table 1

Pus samples received from all the cases were processed as per standard microbiological protocols [5]. The samples were inoculated on to MacConkey’s and blood agar and also into brain heart infusion broth (BHI). A microscopic examination of a Gram stained smear and following conventional biochemical characterization, a provisional identification of *Salmonella* Typhi was made. Detailed analysis by Micro Scan automated identification system (Siemen’s MicroScan WalkAway 40plus) and slide agglutination with Denka Seiken specific Salmonella antisera confirmed the diagnosis. Antimicrobial sensitivity was performed by Kirby Bauer’s method as per CLSI (clinical laboratory standards institute) guidelines. All the isolates were sensitive to co-trimoxazole(Co), augmentin(Ac), chloramphenicol(C), ceftriaxone(Ci), ciprofloxacin(Cf) and ofloxacin(Of), and resistant to Ampicillin(A) and nalidixic acid (Na) [6]. All the children were successfully treated with ofloxacin and ceftriaxone for 2 weeks duration, who had responded with improvement in features of septic illness and physiological functions of the affected joints.

**Discussion:**

The pathophysiological mechanism involved in typhoidal *Salmonella* infection includes entering the host system primarily through distal ileum. Specialized fimbriae that adhere to epithelium over clusters of lymphoid tissue (Peyer Patches) in ileum are the main relay point for macrophages travelling from gut into lymphatic system. It has been hypothesized that typhoidal salmonellae express certain virulence mechanisms allowing them to down regulate a pathogen recognition receptor (PRR) mediated host response in intestinal mucosa that results in the absence of neutrophilic infiltration. [7] Bacteria then induce their host macrophages to attract more macrophages. It co-opts the macrophage cellular machinery for their own reproduction before disseminating to other organs. After a brief period of bacteremia, they re-infect Peyer patches. [8]

In the present case series of four cases, there was only one case where joint involvement appeared secondary to clinical illness compatible with features suggestive of enteric fever. The child was treated by a private doctor for about one week before reporting to our hospital for treatment of fever and pain in the leg. Remaining three cases had approached with primary complaints of features of joint involvement following trauma, without any prior history of febrile illness. The cause of latency is definitely a debatable issue but it is hypothesized that typhoid bacilli could have been surviving in a state of latency in the bone marrow during which the patient remained asymptomatic. The inability to contain spread to bones and immune incompetence was definitely apparent in all the cases.

Age, nutrition, low socio economic status, HIV infection etc are attributed as underlying high risk host factors which may favour the accessibility and persistence of this organism. Evidence in literature states that certain infections may not become clinically apparent in severely malnourished e.g. malarial infection in famine stricken areas may not induce fever but once nutrition improves; clinical malaria develops [9]. In our series, some element of under nutrition may have been there since all the patients were children and were from low income families. Joint infection is uncommon in HIV positive patients but where it is found, it is often associated with a CD4 count less than 250/µl [10]. However in the present series, one of the cases was HIV positive with a CD4+ count of 590 /µl.

Septic arthritis represents invasion of joint space by various micro-organisms including bacteria, viruses, mycobacteria and fungi. A few cases of arthritis occur because of direct inoculation of bacteria into the joint space through injury or animal bites in rural community [11] or by iatrogenic causes but majority of cases occur by internal dissemination of bacteria [12]. Bacteria may reach the joint via blood stream or direct spread from adjacent structures but may not necessarily cause septic arthritis [13]. In hip and shoulder, part of metaphyseal shaft is intra-articular and osteomyelitis of femoral or humoral shaft may spread to adjacent joint. Although any infectious agent may cause arthritis, bacterial pathogens are the most common causes and significant in terms of frequency of morbidity associated with these pathologies. Of the bacterial pathogens, *Salmonella* arthritis occurs very infrequently, accounting for only about 1% of all cases and even that usually represents metastatic extension of non-typhoidal *Salmonella*. Septic arthritis is an extremely rare complication of typhoidal *Salmonella* [14].

On literature search, we came across seven reports of septic arthritis due to *Salmonella* Typhi from India and abroad [15, 16, 17, 18]. It is likely that there is a combination of other factors involved in addition to the presence of bacteria and it is also very likely that trauma is one of these factors. In three of the four cases in the present series, there was evidence of preceding trauma and that could have acted as trigger for joint involvement. The exact infectious dose and time to reach the threshold for bacteremia for causing specific extra-intestinal infectious complications is unknown. It has been hypothesized by Perry [19] that capillary stasis reduces oxygen tension as a result of trauma and creates a nidus of infection locally that may develop into septic arthritis. In a study on rabbits, Onley’s work supports that microtrauma in the presence of bacteremia renders joints susceptible [20].

Traumatic and non-traumatic introduction of *Salmonella* seem to have the propensity for persistence in the host. The form in which persistent bacilli exists and the mechanism that establishes persistence are the subject of a larger enquiry but
the linkage between persistence and arthritis can be speculated upon. An intracellular pathogen trapped in an ecological niche not conducive for normal existence through binary fission and proliferation has the option of long term persistence in a stealthy form without provoking inimical immune recognition [21]. This necessarily involves immune modulation including immune escape, MHC modulation, improper antigen presentation and other factors. Together with nuanced cytokine/chemokine alterations either qualitative, or quantitative, or temporal measure that may interfere with their production or action and can have clinical consequences. One such afebrile consequence is arthritis with a pronounced immunological bias. Arthritis may be an intrinsic aspect of natural history of salmonellosis associated with persistence and increasing antigenic load due to slow multiplication of the bacillus cowering in an aggressive immunological nids; if it had not been glaring so far, it could be the result of extreme reduction in antigenic load attendant with pharmacological intervention; consequent immune reactivity might be so fleeting and clinically irrelevant.

Septic arthritis especially in children is a potential cause of damage to epiphysis and diaphysis thereby making its diagnosis and early treatment an emergency. In countries like, India where enteric fever is endemic, children reporting for remedy of joint related issues, more so if the joint involvement is subsequent to some injury, a thorough retrospective history of febrile illness should be explored and probability of typhoidal salmonella as a cause requires to be entertained. Gold standard for diagnosis of septic arthritis would remain microbiological but the culture results are usually not available before 48 hours and even molecular techniques require time. Empirical antimicrobial treatment that could take care of both gram positive and negative organism and in line with anti microbial susceptibility pattern of that area should be immediately instituted. Therapy also includes adequate joint drainage, antibiotic therapy, and analgesics. Repeated joint aspirations, arthroscopic washout, or open surgical drainage are the other alternatives.

Conclusion:

Septic arthritis due to Salmonella Typhi is rare and involvement of joints without preceding history of bacteremic illness is being reported for the very first time. Trauma appears to have acted as precipitating factor in the pathogenesis. In countries where enteric fever is endemic, and children report with features of septic arthritis, possibility of Salmonella Typhi as one of the causative agents needs to be entertained even if history of febrile illness is not traceable in the recent past.

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