






REVIEW ARTICLE

Salmonella Osteomyelitis in Adults: A Systematic Review

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The aim of this systematic review was to characterize the clinical features of adults with Salmonella osteomyelitis and summarize diagnosis and treatment methods to provide guidance for clinicians. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We conducted a literature search in the PubMed, EMBASE, and Cochrane Library databases. Article screening and data extraction were performed by two reviewers individually. All the included studies were independently evaluated by two reviewers using the Methodological Index for Non-Randomized Studies (MINORS) criteria. A total of 67 articles published between 1970 and 2019 were selected, which include 69 patients with an average age of 47.5 years (range, 18–79). The majority of cases (47.76%) occurred in immunocompetent adults without common risk factors. Aspiration and biopsy cultures were all positive in Salmonella osteomyelitis patients who underwent aspiration or biopsy. All infections were monomicrobial, and a total of 12 different serotypes were identified. The three most commonly reported Salmonella serotypes were Salmonella typhi (19 cases), Salmonella typhimurium (12 cases), and Salmonella enteritidis (11 cases). Only 12 of the 67 cases in our data (17.91%) had diarrhea symptoms, and 44 of the 67 cases (65.67%) had fever symptoms. Fifty-nine of the 67 cases (88.06%) had local inflammatory manifestations, such as erythema, swelling, and tenderness in the affected area. The commonly reported involved sites were the vertebrae, femur, and tibia. Antibiotic therapy alone was utilized in 30 cases, and 24 patients (80.00%) were eventually cured. In total, 75.68% of patients achieved satisfactory results after treatment with surgery and antibiotics. Third-generation cephalosporins were most commonly utilized, and antibiotic treatment was administered for an average of 11.3 weeks (95% CI, 8.31–14.37 weeks). Salmonella osteomyelitis should be considered in patients without any common risk factors. Aspiration or biopsy can facilitate the identification of pathogens to guide antibiotic choice. Empirical therapy with a third-generation cephalosporin is recommended until the susceptibility of the strain is determined.

Key words: Adults; Osteomyelitides; Osteomyelitis; Salmonella; Systematic review

Introduction

Osteomyelitis is a common orthopaedic disease caused by infectious organisms. Despite current health-care advantages, osteomyelitis is a challenging condition for physicians and patients with recurrent and persistent infection. *Staphylococcus aureus* and *Staphylococcus epidermidis* are responsible for most cases due to their presence in the normal skin flora. In contrast, other relevant bacteria, such as Salmonella, have rarely been reported and account for only 0.45% of all the causative agents of osteomyelitis¹.

Salmonella osteomyelitis is most common in children with hemoglobinopathies such as sickle cell anemia and it

remains a significant cause of morbidity and mortality in this population². An association between Salmonella osteomyelitis and sickle-cell anemia has been previously recognized, including impaired splenic function, defects in complement activation, genetic factors, deficiencies in micronutrients, and the presence of infarcted or necrotic bone³. Sickling events may lead to microscopic infarctions in the intestinal mucosa and bone and create a permissive environment for both bacterial entry from the gut to the blood stream, followed by seeding of damaged bone by blood-borne bacteria. Immune compromise due to dysfunction of liver and spleen and abnormal complement function may suppress clearance from the blood stream^{4,5}.

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Furthermore, *Salmonella* osteomyelitis is also seen in individuals with diabetes mellitus, systemic lupus erythematosus, and immune deficiency, and involves mainly infants and neonates^{6–8}. In addition, some investigators have confirmed that *Salmonella* osteomyelitis also has a predilection for immunocompetent adults, and common risk factors for *Salmonella* infection are frequently absent^{9, 10}.

Salmonella osteomyelitis is often overlooked, causing misdiagnoses and delays in diagnosis¹¹. A preceding history of gastrointestinal infection is not usual¹². The cardinal symptoms include fever, pain, and soft tissue swelling and are not indicative of the causative agent. Serology for *Salmonella* and culture are helpful but can produce false-negative results. Imaging examinations such as X-ray and computed tomography (CT) scans are often delayed and cannot differentiate pathogens. In addition, no surgical procedures or standardized antibacterial therapy regimens are available thus far. At present, most of the studies on *Salmonella* osteomyelitis are case reports, and previous systematic reviews mainly focused on children¹³.

This study compiled multiple studies with the aim of: (i) characterizing the etiology of *Salmonella* osteomyelitis in adults; and (ii) summarizing diagnosis and treatment methods for *Salmonella* osteomyelitis to provide clinical practice guidance.

Materials

Literature Search

We conducted the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We conducted a literature review in multiple databases, including PubMed, EMBASE, and the Cochrane Library. The MeSH terms “Osteomyelitis” and its corresponding synonyms were designated keywords, and the term “*Salmonella*” was combined in “AND” form in the search strategy. The search was restricted to studies

involving only humans over 18 years of age and limited to articles written in English with the application of the filters (Table 1). The aforementioned procedures were performed by two reviewers individually. Any disagreement was settled by discussion.

Selection Criteria

All the retrieved studies met the following inclusion criteria: (i) the original study topic involved adults (> 18 years old) with *Salmonella* osteomyelitis; (ii) the necessary information of clinical outcomes, diagnosis, and treatment methods of patients was sufficient; (iii) the study was a randomized controlled trial, non-randomized clinical trial, prospective or retrospective cohort study, case-control study, cross-sectional study, case report, or case series.

The exclusion criteria were as follows: (i) the study was published in a non-English language or was a nonhuman study; (ii) the study included a duplicate population.

Quality Assessment

The quality of the studies was evaluated by two reviewers independently using the Methodological Index for Non-Randomized Studies (MINORS) criteria¹⁴, which has been validated for assessing the quality of non-randomized surgical studies. Finally, the quality of the study was categorized in accordance with the total score of each study: poor (0–5), moderate (6–10), or good (11–16).

Data Extraction

Two independent researchers extracted the relevant information from all the eligible studies. General information included the first author, publication year, and study design. Demographic information included country of residence, age, sex, primary diagnosis, and history of immunosuppressant use. Clinical information included the affected sites, systemic and local symptoms and signs, laboratory test results, pathogen types, antibiotic types, administration routes, duration, operations, and treatment outcomes. The definition of success after treatment is: (i) infection eradication, characterized by no symptoms and signs of infection, and no infection recurrence caused by the same organism strain; (ii) no subsequent surgical intervention; and (iii) no death caused by a condition directly linked to *Salmonella* osteomyelitis.

Statistical Analysis

Categorical variables were analyzed by Student's *t*-test or Mann–Whitney *U*-test, and continuous variables were analyzed by chi-square test or Fisher's exact test. SPSS v25.0 (SPSS, Inc., USA) was used to perform the analyses, and $P < 0.05$ was considered statistically significant.

Results

Literature Search Results

Details of the literature search process are shown in Fig. 1. A total of 392 publications were obtained from the literature

TABLE 1 Electronic search strategies

Database	Search strategy
PubMed	(((("Osteomyelitis"[Mesh]) OR "Osteomyelitis"[Title/Abstract]) OR "Osteomyelites"[Title/Abstract]) AND Humans [Mesh] AND English[lang])) AND (((("Salmonella"[Mesh]) OR "Salmonella"[Title/ Abstract]) Filters applied: Humans; English; Adult: 19+ years No limitation on publication date
Embase	('salmonella'/exp. OR 'salmonella') AND ('osteomyelitis'/exp. OR 'osteomyelitis' OR 'osteomyelites') Filters applied: English, Human, Adult: 19+ years No limitation on publication date
Cochrane Library	salmonella AND (osteomyelitis OR osteomyelites) Filters applied: English, Human, Adult: 19+ years No limitation on publication date

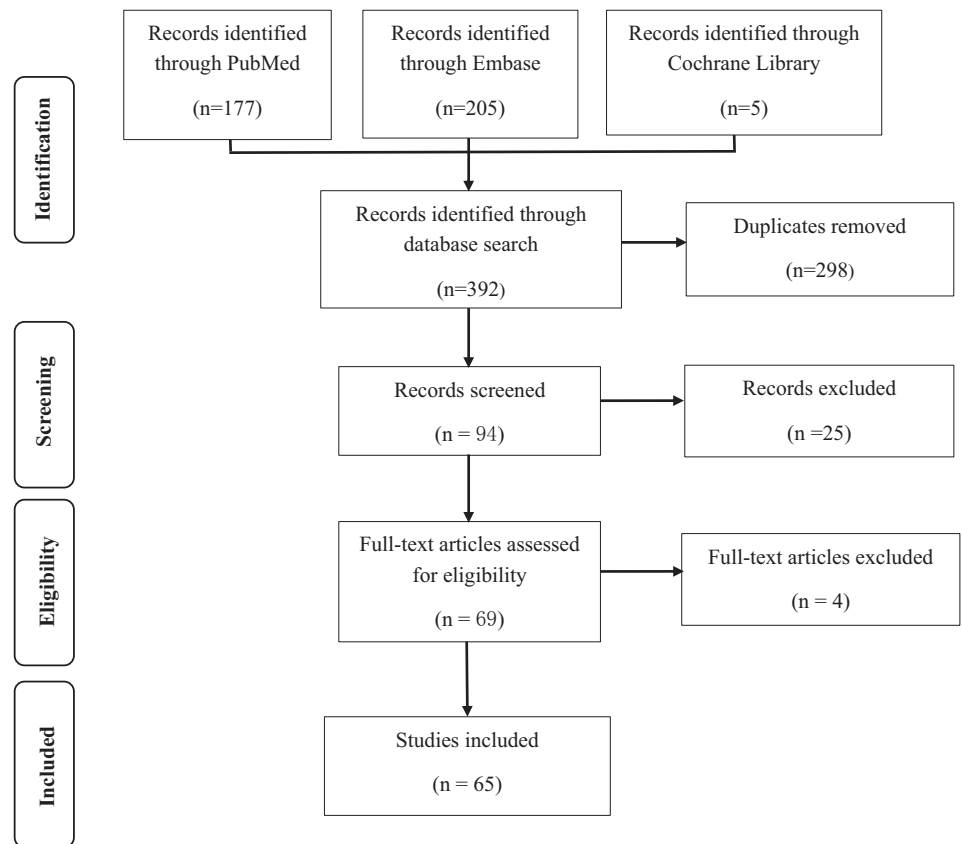


Fig. 1 Flow diagram of the systematic literature search.

search. By excluding duplicates ($n = 298$) and scanning titles and abstracts ($n = 25$), 69 articles were enrolled for full-text review. Finally, a total of 65 articles were selected for quality (Additional file 2). Information of 67 cases of Salmonella osteomyelitis are shown in Additional file 3.

Demographic Information

The major clinical features of the cases reported in the literature are summarized in Table 2. Sixty-five articles including 67 different cases met the inclusion criteria. They were published between 1970 and 2019, with 42 articles published after 2000. Twelve publications originated from the United States, 12 from India, nine from the United Kingdom, six from China, five from Austria, and three from Turkey. Three other countries contributed two reports each, and 13 other countries contributed one report each. In the studies, the mean patient ages ranged from 18 to 79 years (median: 47.5 years). The studies included 45 males (47%) and 23 females (53%).

Etiology and Pathogenesis

The majority of cases (47.76%) occurred in immunocompetent adults without common risk factors. In total, 26.87% of patients were immunocompromised by malignancy, an

TABLE 2 Clinical features in cases of salmonella osteomyelitis

Feature	Value
Age (years)	
Range	18–79
Mean	47.5
Sex [cases(%)]	
Male	45(67.16)
Female	23(34.33)
Predisposing factor [cases(%)]	
Diabetes	14(20.90)
Autoimmune diseases	12(17.91)
Haemoglobinopathies	6(8.96)
Splenectomy	1(1.49)
Chronic alcoholism	1(1.49)
Symptom [cases(%)]	
Fever	44(65.67)
Diarrhea	12(17.91)
Focal symptoms	46(68.66)
Site [cases(%)]	
Vertebra	27(40.30)
Femur	14(20.90)
Tibia	7(10.45)
Rib	7(10.45)
Pevis	5(7.46)
Skull	5(7.46)
Radius	4(5.97)
Others	5(7.46)

immunodeficiency disease, or a history of immunosuppressant use. Common underlying conditions included diabetes (20.90%), autoimmune diseases (17.91%), hemoglobinopathies (8.96%), splenectomy (1.49%), and chronic alcoholism (1.49%).

All infections were monomicrobial, and a total of 12 different serotypes were identified. The three most commonly reported Salmonella serotypes were Salmonella typhi (19 cases), Salmonella typhimurium (12 cases), and Salmonella enteritidis (18 cases). In addition, there were 12 cases of unknown Salmonella infection (6.0%). Regarding the Salmonella serogroup, the proportion of group D Salmonella was the highest. Of the 67 cases, 32 cases (47.76%) involved group D Salmonella infection, 17 cases (25.37%) involved group B Salmonella infection, five cases (7.46%) involved group C1 Salmonella infection, three cases (4.48%) involved group A Salmonella infection, and three cases (4.48%) involved group C2 Salmonella infection.

Clinical Features

Only 12 of the 67 cases in our data (17.91%) had diarrhea symptoms, and 44 of the 67 cases (65.67%) had fever symptoms. Fifty-nine of the 67 cases (88.06%) had local inflammatory manifestations, such as erythema, swelling, and tenderness in the affected area. The commonly reported involved sites were the vertebrae, femur, and tibia. The vertebra was the most commonly reported bone location, accounting for 40% of all the reported bones (27/67 total bones). The femur was reported in 14 cases, whereas the tibia was reported in seven cases. Twenty-nine patients (43.28%) developed multifocal osteomyelitis. However, 13 patients suffered from suppurative complications of the bone (19.40%).

Clinical Test Results

The clinical test results in cases of Salmonella osteomyelitis are summarized in Table 3. White blood cell counts were recorded in 47 patients, with an average of $11195.12 \pm$

$10804.99 \times 10^6/L$ (95% CI, 8022.64–14367.57 $\times 10^6/L$). In addition, neutrophil percentages were recorded in seven patients, with an average of $75.14 \pm 11.95\%$ (95% CI, 64.09%–86.20%). Serum C-reactive protein (CRP) was detected in 22 patients, with an average of 138.32 ± 106.76 mg/L (95% CI, 90.98–185.65 mg/L), and the erythrocyte sedimentation rate (ESR) was detected in 33 patients, with an average of 72.52 ± 36.55 mm/1 h (95% CI, 59.56–85.47 mm/1 h). All of these laboratory results were higher than the normal ranges.

All 52 reported aspiration and biopsy cultures isolated Salmonella (100%), whereas only 25 of 37 reported blood cultures isolated Salmonella (67.57%). In addition, stool culture was positive in 28% of cases. Ten patients underwent all three culture methods. All of the cases were positive by aspiration and biopsy culture, while only five (50.00%) cases were positive by blood culture and three (30.00%) by stool culture. In addition, 14 cases underwent serological testing, and 11 (78.57%) were positive. Seven studies reported antibiotic resistance (Additional file 2), and great variation in the antimicrobial susceptibility of the reported strains was observed. Multidrug resistance was detected in 71.43% of Salmonella spp. Salmonella typhi presented the highest resistance (42.86%) and multidrug resistance (38.10%) rates, respectively.

Treatment and Clinical Outcomes

Antibiotic therapy alone was utilized in 30 cases, and 24 patients (80.00%) were eventually cured. The other 37 cases were treated with surgical intervention in addition to antibiotics; 28 patients (75.68%) eventually achieved good outcomes after being treated with antibiotics for Salmonella infection (Additional file 2). The overall cure rate was 77.61%.

With regard to therapy, ciprofloxacin was reported in 24 cases. Third-generation cephalosporins were utilized in 21 cases, ampicillin in 11, chloramphenicol in eight, ofloxacin in five, trimethoprim-sulfamethoxazole in four, and fusidic acid in three. The duration of treatment for four patients who were cured was not recorded. Treatment was continued for an average of 11.3 weeks (95% CI, 8.31–14.37 weeks).

Discussion

Salmonella is a gram-negative bacillus that can cause a broad spectrum of human infections, such as gastroenteritis, typhoid fever, and bacteremia, and an asymptomatic carrier state can occur. Osteomyelitis is an extremely rare complication of Salmonella infection and occurs in approximately 0.8% of all Salmonella infections¹⁵. We compiled multiple studies published between 1970 and 2019, and only 67 cases could be found. Perhaps the disease is underreported or underdiagnosed. Among the 67 cases of Salmonella osteomyelitis, there was a male preponderance, with a sex ratio of nearly 2:1. The rate of osteomyelitis due to Salmonella typhi was the highest, but osteomyelitis due to Salmonella typhimurium and Salmonella enteritidis was also common. These results were consistent with those of Salmonella osteomyelitis in children¹³.

TABLE 3 Clinical test results in cases of salmonella osteomyelitis

Finding	No. of patients with finding/total no. (%)
WBC count > 9500/mm ³	22/47(46.81)
ESR > 20 mm/h	31/34(91.18)
CRP > 8 mg/L	21/22(95.45)
Positive blood culture	25/37(67.57)
Positive tissue culture	52/52(100)
Positive stool culture	7/25(28)
Salmonella serotype isolate	
S.typhi	19/67(28.36)
S.typhimurium	12/67(17.91)
S.enteritidis	11/67(16.42)
S.choleraesuis	3/67(4.48)
S.newport	2/67(2.99)
Others	9/67(13.43)
Not typed	12/67(17.91)

Etiology

In our systematic review, we defined patients with malignancies, AIDS, or other immunodeficiency diseases or a history of immunosuppressant use as immunocompromised, as indicated in previous literature¹⁶. Salmonella osteomyelitis is common in immunocompromised patients. Salmonella osteomyelitis also occurs in patients with diabetes, autoimmune diseases, and hemoglobinopathies; this has been well recognized³⁻⁵. However, immunocompetent adults without common risk factors accounted for the largest proportion of cases, which is in complete contrast with a previous study. This is an indication that Salmonella osteomyelitis should be considered even if no predisposing factor is found.

Clinical Features

The clinical presentation of Salmonella osteomyelitis is often nonspecific and insidious, and it shares several features similar to pyogenic osteomyelitis due to other causes. The usual clinical signs include fever, bone pain, tenderness, and soft tissue swelling. Only a minority of patients have diarrhea or a recent history of diarrhea. This is probably due to a long incubation period and nonintestinal entry routes of infection^{17, 18}. Initial investigations include WBC counts, ESRs, and imaging tests. The usual laboratory findings include leukocytosis, an elevated ESR, and bone erosion on radiograph or CT imaging.

However, the relevant inflammatory markers and radiographic examination findings are common in osteomyelitis patients and cannot differentiate Salmonella osteomyelitis from other types of infectious osteomyelitis.

Diagnosis

Serology tests and the culture of Salmonella is useful in aiding diagnosis. The sensitivity of the Widal test for osteomyelitis is higher than that for gastroenteritis, presumably because the immune system has sufficient time to mount an antibody response. However, titers can be increased due to prior exposure, so the definitive diagnosis can only be confirmed by a positive culture¹⁹. In our review, the culture from an aspiration or biopsy sample was valuable for diagnosis, as they were positive for all Salmonella osteomyelitis patients. Notably, stool cultures and blood cultures may or may not be positive in infected patients.

The emergence of antibiotic resistance is the most alarming issue with respect to Salmonella infection. Salmonella was commonly treated with ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, resulting in a high prevalence of antimicrobial resistance. Due to good oral bioavailability and strong macrophage penetration, fluoroquinolones have become alternative antimicrobial agents¹¹. However, fluoroquinolones are failing because resistance has become increasingly common^{20, 21}. Consequently, third-generation cephalosporins were the most common agents of choice in our review. However, the emergence of resistance to third-generation cephalosporins has also been reported^{22, 23}. Thus, empirical therapy with a third-

generation cephalosporin is recommended until the susceptibility of the strain is detected.

Treatment

The optimal antibiotic treatment duration is of great importance, as failure and recurrence can occur if treatment is provided for an insufficient duration. However, no data on failure and recurrence were available, and most of the included cases that achieved favorable results were treated for 6 to 8 weeks. Santos and Sapiccro recommend a therapy duration of 2 months for uncomplicated osteomyelitis. In chronic or complicated infections, therapy should be administered for a minimum of 3 months¹¹. The termination of antibiotics should be decided according to the therapeutic effect of the antibiotics. Furthermore, clinical trials should be conducted to determine the ideal length of treatment.

There are no randomized or case-control studies that report standardized antibacterial therapy regimens or surgical procedures, so optimal individualized management is crucial for the treatment of patients. When antibacterial treatment failed or the infected implants required debridement or removal, the surgical procedures were only indicated, and surgery was required in more than half of the cases in our review. Carlson and Dobozi consider that surgical debridement is not adequate and radical debridement of the lesion is recommended¹⁵. Finally, most patients with Salmonella osteomyelitis achieved good outcomes, with a cure rate of 77.61% in our literature review, which is consistent with the results of Salmonella osteomyelitis in children¹³.

Limitations

Admittedly, our systematic review had several limitations. First, the included studies were all case series, and the quality of the original studies was limited. In addition, the small sample size may have resulted in biased results. The differences in disease severity, postoperative care protocols, length of follow-up, and other confounding factors might have led to study heterogeneity, and the effects of different treatments could not be compared. Finally, we did not attempt to identify unpublished literature; thus, potential publication bias may lower the validity of the results. Therefore, the suggestions in this systematic review should be interpreted with caution.

Salmonella is a non-spore-forming gram-negative bacillus that can cause a broad spectrum of human infections. Salmonella osteomyelitis is an extremely rare complication but it shares many features with infectious osteomyelitis due to other causes that are difficult to correctly diagnose and eventually cause persistent infection. Aspiration or biopsy can be utilized for the identification of pathogens to guide antibiotic choice. Empirical therapy with a third-generation cephalosporin is recommended until the susceptibility of the strain is detected. When antibiotic treatment fails, surgery combined with antibiotics is required to achieve the desired results, and optimal individualized management is crucial for the treatment of patients.

References

1. Rayan F, Mukundan C, Shukla DD. A case of relapsing salmonella osteomyelitis in a thalassaemia trait patient. *J Orthop Traumatol*, 2009, 10: 31–33.
2. Almeida A, Roberts I. Bone involvement in sickle cell disease. *Br J Haematol*, 2015, 129: 482–490.
3. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. *Int J Infect Dis*, 2010, 14: e2–2e12.
4. Adeyokunnu AA, Hendrickse RG. Salmonella osteomyelitis in childhood. A report of 63 cases seen in Nigerian children of whom 57 had sickle cell anaemia. *Arch Dis Child*, 1980, 55: 175–184.
5. Anand AJ, Glatt AE. Salmonella osteomyelitis and arthritis in sickle cell disease. *Semin Arthritis Rheum*, 1994, 24: 211–221.
6. Gondusky JS, Gondusky CJ, Helmers SW. Salmonella osteomyelitis in new-onset diabetes mellitus. *Orthopedics*, 2009, 32: 690–693.
7. Matheson N, Kingsley RA, Sturgess K, et al. Ten years experience of salmonella infections in Cambridge, UK. *J Infect*, 2010, 60: 21–25.
8. Sy AM, Sandhu J, Lenox T. *Salmonella enterica* serotype Choleraesuis infection of the knee and femur in a Nonbacteremic diabetic patient. *Case Rep Infect Dis*, 2013, 2013: 506157.
9. Shrestha P, Mohan S, Roy S. Bug on the back: vertebral osteomyelitis secondary to fluoroquinolone resistant salmonella typhi in an immunocompetent patient. *BMJ Case Rep*, 2015, 2015: bcr2015212503.
10. Hashimoto K, Nishimura S, Iemura S, Akagi M. Salmonella osteomyelitis of the distal tibia in a healthy woman. *Acta Med Okayama*, 2018, 72: 601–604.
11. Santos EM, Sapico FL. Vertebral osteomyelitis due to salmonellae: report of two cases and review. *Clin Infect Dis*, 1998, 27: 287–295.
12. Deysine M, Isenberg HD, Steiner G. Chronic haematogenous osteomyelitis: studies on an experimental model. *Int Orthop*, 1983, 7: 69–78.
13. Gill AN, Muller ML, Pavlik DF, et al. Non-Typhoidal Salmonella Osteomyelitis in Immunocompetent Children without Hemoglobinopathies: a case series and systematic review of the literature. *Pediatr Infect Dis J*, 2017, 36: 910–912.
14. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*, 2003, 73: 712–716.
15. Sanchez AA, Mazurek MT, Clapper MF. Salmonella osteomyelitis presenting as fibrous dysplasia. *A Case Report. Clin Orthop Relat Res*, 1996, 330: 185–189.
16. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the Immunocompromised population. *Clin Microbiol Rev*, 2004, 17: 208–217.
17. Collazos J, Mayo J, Blanco MS. Muscle infections caused by salmonella species: case report and review. *Clin Infect Dis*, 1999, 29: 673–677.
18. Ramos JM, Garcia-Corbeira P, Aguado JM, Alés JM, Soriano F. Classifying extraintestinal non-typhoid salmonella infections. *QJM*, 1996, 89: 123–126.
19. Arora A, Singh S, Aggarwal A, Aggarwal P. Salmonella osteomyelitis in an otherwise healthy adult male—successful management with conservative treatment: a case report. *J Orthop Surg (Hong Kong)*, 2003, 11: 217–220.
20. Cotter L, Mushtaq M, Gonzalez A. A case of vertebral osteomyelitis due to quinolone-resistant salmonella paratyphi a. *BMJ Case Rep*, 2009, 2009: bcr07.2008.0400.
21. Raveendran R, Wattal C, Sharma A, Oberoi J, Prasad K, Datta S. High level ciprofloxacin resistance in *Salmonella enterica* isolated from blood. *Indian J Med Microbiol*, 2008, 26: 50.
22. Saha S. A highly ceftriaxone-resistant salmonella typhi in Bangladesh. *Pediatr Infect Dis J*, 1999, 18: 387.
23. Robert-Jan H, Goessens WHF, Wilfrid VP, et al. Salmonella subtypes with increased MICs for azithromycin in travelers returned to The Netherlands. *Emerg Infect Dis*, 2014, 20: 705–708.