Quinolones and *Salmonella* Septic Arthritis

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Abstract

Salmonella septic arthritis is an infrequent infectious disease but can cause progressive joint destruction resulting in disability. The authors retrospectively reviewed cases with culture proved *Salmonella* septic arthritis in Srinagarind Hospital, Khon Kaen from 1994 to 2000. There were 23 episodes in 16 cases; all had underlying diseases and a history of steroid abuse or steroid and immunosuppressive therapy. Systemic lupus erythematosus was the most commonly found underlying disease (56%). *Salmonella* group D and group B were isolated in 13 and 3 cases.

Most first episodes had acute onset of monoarthritis. The antibiotics used as initial treatment of the first episodes were beta lactam, cotrimoxazole or quinolones.

There were 8 cases with disabled sequelae and 7 cases with relapse. For 13 evaluable first episodes, relapse occurred in 3 cases in the cephalosporin/penicillin and 4 cases in the cotrimoxazole treated group but none in the quinolones.

Six relapse cases were treated successfully with quinolones as well as one with cotrimoxazole. Although 5 relapse cases treated with quinolones had previous progressive joint destruction or avascular necrosis, there was no further joint damage after re-treatment with quinolones.

In conclusion, quinolones were more effective than beta-lactams and cotrimoxazole for the treatment of *Salmonella* septic arthritis to prevent relapse and progressive joint destruction.

Key word : *Salmonella*, Septic Arthritis, Quinolones

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Salmonella infection is common worldwide. Its manifestations include enteric fever, focal infection, disseminated infection, and chronic carrier (1). Septic arthritis is not a common manifestation but can occur in patients with both immunocompetent (2,3) and immunocompromised hosts(4-15). Certain conditions may predispose to Salmonella septic arthritis such as sickle cell disease(14-16) and thalassemia (16). In-patients with immunocompromised conditions such as autoimmune diseases(7-9), chronic steroid therapy, HIV(10-12), *Salmonella* can cause chronic and progressive diseases which require long-term antibiotic therapy. The drug of choice of this infection as well as the optimal duration of antibiotic treatment to prevent relapse has yet to be studied.

The authors retrospectively reviewed septic arthritis caused by *Salmonella* regarding its outcome and the antimicrobials used.

PATIENTS AND METHOD

Patients who had *Salmonella* septic arthritis admitted to Srinagarind Hospital from 1994 to 2000 were reviewed. All were culture proved. The demographic data, clinical findings and antimicrobials were collected. Cases were followed-up for at least one year.

For long-term outcome evaluation, successful treatment was defined as complete response without relapse for at least 1 year of follow-up and treatment failure as progressive joint destruction or relapse despite therapy.

Chi square test was used for statistical analysis.

RESULTS

There were 16 cases with 23 episodes, 16 first episodes and 7 relapses, of cultured proved *Salmonella* septic arthritis during the period of study. The average age of the patients was 28.6 years. All had underlying diseases, viz: SLE (9), nephrotic syndrome (2), rheumatoid arthritis (1), mixed connective tissue disease (1), osteoarthritis (1), gout (1), and aplastic anemia (1). All had a history of chronic steroid therapy or abuse with dosages of prednisolone ranging from less than 5 to 60 mg per day. Four patients also received concurrent immunosuppressive therapy with cyclophosphamide or azathioprine. The 20 episodes with long-term follow-up are shown in Table 1 and 2.

Of the 16 first episodes group, the onset of arthritis was acute in 62.5 per cent. Most of them were monoarticular, although 18.75 per cent had polyarthritis. The most commonly infected were knee and hip joints. The *Salmonella* group B and group D were identified in 3 and 13 cases respectively.

The initial antimicrobials given were cotrimoxazole (9), cephalosporin (5), ampicillin (1), and ciprofloxacin (1). Fifteen patients had parenteral antibiotics for the initial 2 weeks then changed to oral form or switched to other oral antibiotics including cotrimoxazole, ofloxacin, ciprofloxacin, and amoxycillin, pefloxacin and cefibuten. The duration of treatment was 6-12 weeks. Only one case received oral cotrimoxazole throughout the course. Thirteen cases had long-term follow-up, with 6 cases being cured and with no sequelae, whereas, 7 relapsed.

All relapse episodes presented with chronic progressive arthritis (Table 3). Most of them had relapse at the same joints previously infected but one had relapse at a new joint. Antibiotic treatments for relapse cases were ofloxacin (4), pefloxacin (1), ciprofloxacin (1) and cotrimoxazole (1). The duration of treatment was 12 –24 weeks. All responded well to treatment. No relapse occurred again during at least 1 year of follow-up.

When treatment results of 20 episodes including13 first and 7 relapse episodes, which had long-term follow-up were combined, they were successful in 65 per cent and failed in 35 per cent. There was no relapse in 9 patients who received quinolones as maintenance therapy. For 6 patients who had long-term cotrimoxazole treatment, 5 cases of first episodes and one of relapse, all 5 cases of first episode had relapses which were statistically significant ($p<0.05$). Three of five patients with long-term parenteral ampicillin or cephalosporin treatment also had relapses.

The sequelae of *Salmonella* septic arthritis that occurred in the present study were severe joint destruction which required joint replacement in one, chronic osteomyelitis in one, secondary osteoarthritis in two, and avascular necrosis of the involved joints in 4 cases. In 5 relapse cases with progressive joint damage or avascular necrosis, there was no further joint destruction after treatment with quinolones.

All patients also had either arthroscopic or surgical drainage during antibiotic therapy, especially infected hips.

DISCUSSION

Salmonella infections can occur in many organs, but the synovium is a common metastatic focus, comprising about 15-20 per cent of focal infec-

Table 1. Clinical findings, treatment of patients with *Salmonella* septic arthritis who had no relapse.

Pt No.	Age/sex	Underlying disease	Joint involved	Onset	*Salmonella* Group	Initial I.V. antibiotic	Subsequent oral antibiotic	Duration of treatment (wk)	Follow-up (mon)
1	14/F	Aplastic anemia	Left hip	Acute	D	Cefotaxime	No	6	38
2	49/M	Gout	Left knee	Acute	B	Ampicillin + Gentamicin	No	4	29
3	52/M	Rheumatoid arthritis, diabetes	Left knee	Acute	D	Ceftazidime + TMP/SMX*	Ofloxacin	8	29
4	28/M	Systemic lupus erythematosus	Both hips	Chronic	D	Ciprofloxacin	Ciprofloxacin	12	16
5	26/M	Systemic lupus erythematosus	Both knees/ankles	Acute	D	Ciprofloxacin	Ofloxacin	12	40
6	29/M	Nephrotic syndrome	Left hip	Acute	D	TMP/SMX	TMP/SMX	10	12

* Trimethoprim-sulfamethoxazole

Table 2. Clinical findings, treatment in *Salmonella* septic arthritis which relapse.

Pt No.	Age/sex	Underlying disease	Joint involved	Onset	*Salmonella* Group	Initial iv antibiotic	Subsequent oral antibiotic	Duration of treatment (wk)	Duration of treatment before relapse
7	21/M	Nephrotic syndrome	Both knees	Acute	D	TMP/SMX	TMP/SMX	12	4
8	27/F	Systemic lupus erythematosus	Left knee	Subacute	D	TMP/SMX	TMP/SMX	8	4
9	21/F	Systemic lupus erythematosus	Left knee	Acute	D	TMP/SMX	TMP/SMX	12	12
10	29/F	Systemic lupus erythematosus	Right hip	Acute	D	TMP/SMX	TMP/SMX	12	4
11	15/M	Systemic lupus erythematosus	Right knee	Acute	B	Cefotaxime	Amoxycillin	12	2
12	29/F	Systemic lupus erythematosus	Both hips	Chronic	D	Ceftriaxone	No	6	1.5
13	27/F	Systemic lupus erythematosus	Right hip	Subacute	B	Ceftriaxone	No	6	1.5

Table 3. Clinical findings, treatment and outcome of re-treatment of patients with relapsed *Salmonella* septic arthritis.

Pt No.	Joint involved	Onset	*Salmonella* Group	Initial I.V. antibiotic	Subsequent oral antibiotic	Duration of treatment	Follow-up (wk)	Outcome (mon)
7	Left knee	Chronic	D	No	Ofloxacin	24	24	Cure
8	Left knee	Chronic	D	No	Ofloxacin	12	48	Cure
9	Left hip	Chronic	D	Cefodizime	Pefloxacin	19	48	Cure
10	Right hip	Chronic	D	Ciprofloxacin	Ciprofloxacin	12	48	Cure
11	Right knee	Chronic	B	No	TMP/SMX	12	48	Cure
12	Both hips	Chronic	D	Cefodizime	Ofloxacin	14	36	Cure
13	Right hip	Chronic	B	TMP/SMX	Ofloxacin	12	12	Cure

tions[4]. The arthritis can be found in immunologically competent hosts, but most reported cases had underlying diseases such as autoimmune diseases particularly systemic lupus erythematosus (SLE) which required chronic steroid or immunosuppressive therapy, sickle cell disease and HIV. In the present report, all cases had either a history of steroid abuse or concurrent steroid or immunosuppressive treatment. Systemic lupus erythematosus is the most common underlying disease in the present series. There were a few reports on the susceptibility of SLE patients to *Salmonella* septic arthritis[7-9]. Chen et al also reported avascular necrosis was the most frequent articular factor[9].

Most of the presented cases with first episodes had acute onset but three had chronic onset that might be due to the anti-inflammatory effect of corticosteroid which masked the symptoms. All of the relapses had chronic progression.

Salmonella septic arthritis can present as polyarthritis or monoarthritis. In SLE, it is usually polyarticular involvement[9]. But in the present series, 80 per cent including SLE had monoarthritis and the joints usually infected were knee (56%) and hip (44%), either one or both sides in contrast to Chen's study in which hip joint was the most common. *Salmonella*, which caused septic arthritis in the present series, was group D and group B in 13 and 3 cases respectively. Ortiz-Neu et al[40 reported that *Salmonella* C1 serogroup was most commonly (67%) associated with septic arthritis in New York City. But a study in India by Lalitha et al[6] showed that *S. typhi* and *S. paratyphi*, were the most common, whereas, the study of Chen et al[9] from Singapore reported that *Salmonella* group B were the most common.

Salmonella septic arthritis is a destructive joint disease despite antibiotic therapy.

Although all *Salmonella* isolated of 13 first episodes of arthritis, which could be evaluated, were susceptible to antibiotics given initially, there were 8 cases with disabled sequelae. The initial treatment with beta lactam (3/5) or cotrimoxazole (3/5) resulted in 60 per cent of cases with joint destruction or avascular necrosis suggestive of insufficient efficacy. Avascular necrosis also occurred in one and secondary osteoarthritis in another of the three cases with ciprofloxacin as initial therapy. Habermann et al[16] reported avascular necrosis of the femoral head after hip joint infections of *Salmonella*. Ebong et al[13] reported that severe complications occurred in 76 per cent of sickle cell disease patients with *Salmonella* septic arthritis apparently due to a delay in diagnosis, severity of illness and hip joint infection. However, good response to treatment and minimal response damage were also reported by Neu et al[4].

Chen et al[9] reported a higher recurrence rate of arthritis in SLE patients. In the present study, there were 7 relapses. All but one had underlying SLE. Medina et al[8] suggested that *Salmonella* carrier state developed in SLE patients after septic arthritis and this increased the risk of relapse of infection by steroid or immunosuppressive drugs.

All relapses occurred in the beta-lactam or cotrimoxazole group but not in the quinolone group which was statistically different. This finding suggests that quinolone could be the antibiotic of choice. A few reports also showed that quinolone treatment of septic arthritis in immunocompromised host had a successful response[17,18]. The good response to treatment with quinolones is attributed to high intracellular concentration of quinolones[19]. The drugs are also bactericidal with very low minimal inhibitory concentration (MIC) for *Salmonella*[19]. The

quinolones were also reported to effectively eradicate chronic carrier state[20,21]. Although cotrimoxazole also has high concentration in cells, it seems to be bacteriostatic with a moderately high MIC level for *Salmonella*. This may explain the high relapse rate in cotrimoxazole treated patients. The 50 per cent relapse rate of patients treated with beta-lactam antibiotics may relate to their low intracellular drug level.

However, some patients had progressive joint destruction despite quinolone treatment since the beginning. The reason was not known. These patients might have had previous joint damage from their underlying disease or been infected with a more virulent *Salmonella* strain.

In the 6 relapse cases with previous joint damage treated with quinolones, no further joint damage was found during long-term follow-up.

The optimal duration of treatment of *Salmonella* septic arthritis is not well documented. Generally, salmonellosis in an immunocompromised host is usually treated for 2-3 weeks. Inappropriate therapy or an insufficient period of therapy was the most important factor of poor response[4]. Lim et al[7] also reported that surgical debridement and prolonged antibiotic therapy is essential for eradication in the treatment of septic arthritis. The duration of treatment in the present study ranged 4-12 weeks. There was no statistical difference of duration of treatment in the presented cases. Quinolones were associated with more favorable outcomes compared to other antimicrobials.

In conclusion, quinolone treatment of *Salmonella* septic arthritis were associated with better eradication of the organisms and termination of progressive joint destruction.

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ยากลุ่มควิโนโลนกับข้ออักเสบติดเชื้อ*ซัลโมเนลลา*

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ข้ออักเสบติดเชื้อ*ซัลโมเนลลา*เป็นโรคที่พบไม่บ่อย แต่ทำให้มีการทำลายข้อเรื้อรังและเกิดความพิการตามมา การศึกษานี้เป็นการศึกษาย้อนหลังผู้ป่วยที่มีโรคข้ออักเสบติดเชื้อ*ซัลโมเนลลา*ที่มีผลเพาะเชื้อยืนยันที่มารับการรักษาที่โรงพยาบาลศรีนครินทร์ จังหวัดขอนแก่นในระหว่างปี พ.ศ. 2537-2543 มีผู้ป่วยทั้งหมด 16 ราย ผู้ป่วยทุกรายมีโรคประจำตัวและมีประวัติการใช้ยาสตีรอยด์เองหรือได้รับสตีรอยด์หรือยากดภูมิคุ้มกันในการรักษา โรคที่พบบ่อยได้แก่ โรคลูปุส (56%) พบการเกิดข้ออักเสบติดเชื้อ*ซัลโมเนลลา* 23 ครั้ง เกิดจากเชื้อ *ซัลโมเนลลา* กลุ่มดี 13 รายและกลุ่มบี 3 ราย

ผู้ป่วยที่เกิดข้ออักเสบครั้งแรก 16 ราย ส่วนใหญ่ (13 ราย) มีอาการเป็นชนิดข้อเดี่ยวอักเสบเฉียบพลัน ยาปฏิชีวนะที่ใช้ในการรักษาช่วงแรกได้แก่ ยากลุ่มเบต้าแลคแตม ยาโคไทรม็อคซาโซล หรือยากลุ่มควิโนโลน ผลการรักษาพบว่าผู้ป่วย 8 รายเกิดภาวะแทรกซ้อนทำให้พิการ

ผู้ป่วยติดเชื้อข้ออักเสบครั้งแรกที่ติดตามผลการรักษาได้ 13 รายเกิดข้ออักเสบเป็นซ้ำในผู้ป่วยที่ได้ยากลุ่มเบต้า-แลคแตม 3 รายและยาโคไทรม็อคซาโซล 4 ราย แต่ไม่เกิดในกลุ่มที่ได้ยากลุ่มควิโนโลน

ผู้ป่วยที่กลับเป็นซ้ำ 7 ราย ได้รับการรักษาด้วยยากลุ่มควิโนโลน 6 รายและด้วยยาโคไทรม็อคซาโซล 1 ราย การรักษาได้ผลดีทุกรายและไม่เกิดการกลับเป็นซ้ำ ผู้ป่วย 5 รายที่มีข้อถูกทำลายร่วมด้วยและได้รับการรักษาด้วยยากลุ่มควิโนโลนพบว่าสามารถหยุดยั้งการทำลายได้

สรุป ยากลุ่มควิโนโลนมีประสิทธิภาพดีกว่ายากลุ่มเบต้าแลคแตมและโคไทรม็อคซาโซลในการรักษาข้ออักเสบติดเชื้อ*ซัลโมเนลลา*ในแง่การป้องกันการทำลายข้อและการกลับเป็นซ้ำ

คำสำคัญ : *ซัลโมเนลลา*, ข้ออักเสบติดเชื้อ, ยากลุ่มควิโนโลน

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