# *Salmonella* Arthritis

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Gabriel J. Tobón, Juan Esteban Garcia-Robledo, and Ivana Nieto-Aristizábal

## Abbreviations

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| DMARDs | Disease-modifying antirheumatic drugs |
| EFS | Enteric fever syndrome |
| LPS | Lipopolysaccharide |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| RA | Rheumatoid arthritis |
| ReA | Reactive arthritis |
| SA | Septic arthritis |
| SCV | *Salmonella*-containing vacuole |
| SPI-1 | *Salmonella* pathogenicity island 1 |

## Introduction

*Salmonella* spp. can affect joints by causing either reactive arthritis (ReA) or septic arthritis (SA). ReA is part of spondyloarthropathies [1], which are a large family of diseases recognised by sharing the presence of HLA-B27 [2]. It has been historically defined as a sterile joint inflammation [3], which is a consequence of gastrointestinal tract infections caused by enteric bacteria, including *Salmonella* [4]. Its classical manifestation is synovitis of the affected joints [5]. On the contrary, SA is known for being predominantly monoarticular and painful and for the presence of bacteria on synovial fluid analysis [3]. This chapter discusses the relevant aspects of ReA and SA.

G. J. Tobón (✉) · I. Nieto-Aristizábal
GIRAT (Grupo de Investigación en Reumatología, Autoinmunidad y Medicina Traslacional), Fundación Valle del Lili, Universidad Icesi, Cali, Valle del Cauca, Colombia

J. E. García-Robledo
GIRAT (Grupo de Investigación en Reumatología, Autoinmunidad y Medicina Traslacional), School of Medicine, Universidad Icesi, Cali, Valle del Cauca, Colombia

## Historical Aspects

During the nineteenth century, enteric fever syndrome (EFS), also known as typhoid fever, was an important cause of illness and mortality in the unsanitary and overcrowded urban conditions of Europe and the United States [6]. EFS is characterised by a severe systemic illness with fever, abdominal pain and diarrhoea. This underlying aetiology corresponds to the bacterium *Salmonella enterica* serotype *typhi* [6].

In 1880, German scientists Karl Joseph Eberth and Edwin Klebs competed to prove the aetiology of typhoid fever [7]. After performing 23 autopsies on patients who died because of typhoid fever, Eberth recovered '*Bacillus typhosus*' from the spleen in 12 of these patients and from Peyer's patches in 6 [8]. However, he did not identify this bacillus in the autopsies of patients without typhoid fever [7]. In 1881, Koch observed the bacillus in the kidney, spleen and liver of a dead patient. In 1884, Gaffky cultured the bacillus using newly developed techniques for bacterial solid culturing [7]. To satisfy Koch's criteria, Gaffky inoculated the grown bacillus in almost 60 animal species, without a positive result confirming salmonellosis as a human-specific disease. He also described its aetiology, mode of infection and prophylaxis [7]. The disease associated with *Salmonella* is typically a severe enteritis characterised by fever and gastrointestinal symptoms; however, the involvement of other tissues and organs, including joints, is possible [6]. Different cases of *Salmonella* arthritis have been reported in the literature since the last century [9]. Although ReA and SA are unusual, they are the main presentations of *Salmonella* joint involvement [10]. An important review published in 1990 reported different cohorts and reviews of patients with *Salmonella* arthritis [10]. David and Black reported a total of 84 cases of SA in 1960 following an exhaustive literature review in the pre-antibiotic era [11]. Another author reported a review of extra-intestinal cases of *Salmonella* in the antibiotic era until 1983, reporting a total of 44 cases of SA [12]. In 2013, a systematic review on ReA reported a total of 474 cases of *Salmonella*-associated ReA [13].



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## Epidemiology

In most cases, SA affects people in early or late stages of life [14]. It is predominantly monoarticular, and it occurs in large joints. The most affected areas are the knees, hips, shoulders, ankles and wrists [15, 16]. Its incidence varies depending on the population examined, with 4–10 per 100,000 inhabitants per year in the general population [14, 17]. Additionally, the mortality rate has been reported as 12% [15], with residual impairment of the affected joint in 61% of cases and complete recovery in 25% [15]. The majority of cases are reported in men [14, 15, 18]. The synovial fluid cultures of large cohorts of patients demonstrated that its presence is infrequent, comprising <1% of samples, compared with that of *Staphylococcus aureus*, which has been reportedly found in 62–100% of cases [15, 16, 19]. Some predictors of poor prognosis in bacterial arthritis have been described. Rheumatoid arthritis (RA) is the principal predictor, with an incidence of infectious involvement of 0.3–3% and a mortality rate of up to 20% over time in patients with RA where the involvement is monoarticular versus 71% when it is polyarticular. Other factors include the presence of a joint prosthesis, female gender and polyarticular involvement [15, 16].

Reports of studies conducted in the 1990s demonstrate that 2% of gastrointestinal infections caused by *Salmonella* were followed by joint involvement [16, 20]. Similarly, a retrospective study investigating the primary site of infection found that 13% of cases had a gastrointestinal origin, among other anatomical sources [15].

In developing countries, *Salmonella* is the cause of joint inflammation in one-third of the cases of ReA [21]. This gram-negative bacillus is likely to be present in adults aged >60 years, whereas it is rarely reported in children [22]. Of patients that develop ReA, 20% later develop ankylosing spondylitis [23].

## Basic Microbiology of *Salmonella*

Salmonellae are gram-negative, non-spore-forming, flagellated, facultatively anaerobic bacilli. Three antigens are important for its virulence and classification: antigen H or flagellar antigen, antigen O or somatic antigen and antigen Vi [24]. The cell envelope of *Salmonella* comprises a complex net of lipopolysaccharide (LPS), which can function as an endotoxin, being an important determinant of *Salmonella* virulence [24]. The two main species are *S. enterica* and *S. bongori*. *S. enterica* is subdivided into six subspecies, including ~2600 serotypes [25, 26]. *Salmonella* cells have a diameter of 0.7–1.5 μm and a length of 2–5 μm [27]. These bacilli are characterised for being chemotrophs; they obtain energy from organic sources by oxidation and reduction reactions [27]. *Salmonella* spp. are intracellular pathogens, and certain serotypes, known as typhoidal serotypes, are pathogenic [28]. The serotypes or serovars are classified according to the O and H antigens using the Kauffman–White classification [29].

*Salmonella* species have some important virulence factors. *Salmonella* pathogenicity island 1 (SPI-1) is present in almost all serovars of both *S. enterica* and *S. bongori*, and it plays a key role in the intestinal phase of *Salmonella* infections [30–32]. This genomic island is one of the oldest in *Salmonella* spp., and it is hypothesised that the acquisition of this pathogenicity island conferred *Salmonella* an enteric pathogen [33]. SPI-1 has a length of ~40 kb [34], and its expression is induced by certain environmental signals that are usually present in the intestinal environment. These genes are also repressed when *Salmonella* colonises an intracellular compartment [31, 35, 36].

## Pathogenesis

The first step in the pathogenesis of *Salmonella* accounts for the ingestion of the bacterial inoculum, usually via the faecal-oral route. Following the ingestion of the pathogen, the bacteria must survive the acidic environment in the stomach. *Salmonella* exhibit an increased tolerance for acid when exposed to moderately acidic environments (pH 4–5) [37]. Following survival and passage through the stomach, *Salmonella* bacilli must compete against normal flora to colonise [38, 39] and to survive and counteract host defence mechanisms, including bile salts, pancreatic enzymes, Paneth cell antimicrobial peptides and secretory IgA [40, 41].

Once the bacilli have colonised the intestine epithelium, adherence must occur, which is mediated by different genes that code for proteins, such as fimbriae [42, 43]. Invasion commences only after complete adherence and is regulated by genes in the invasion operon. Invasion mainly occurs in the epithelium that covers the Peyer's patches where M cells reside [44]. These cells are specialised in internalising the material from the lumen to the subepithelial space where antigen-presenting and T cells reside. *Salmonella* bacilli can also invade the subepithelium via enterocytes or dendritic cells present in the epithelium [45, 46].

When invasion is completed, the *Salmonella* bacilli that are internalised in phagosomes allow the expression of certain genes that modify these phagosomes, inducing the formation of the *Salmonella*-containing vacuole (SCV), where the bacilli express a type III secretion system to secrete all the virulent and structural proteins needed to survive, replicate and induce a potent inflammatory response. Once the bacilli are internalised, the risk for bacteraemia is high [47, 48].

## Reactive Arthritis

After *Salmonella* has invaded via the gastrointestinal tract, a majority of patients develop enteric fever (typhoid serovars) or self-limited gastroenteritis (non-typhoidal serovars). However, some can develop complications and extra-intestinal manifestations. ReA is one of these conditions; it develops 1–4 weeks following *Salmonella* infections, and the bacterium is not located in the joint [49]. The pathogens most closely associated with ReA are *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter* and *Chlamydia trachomatis*, which is the most common cause of ReA with a genital origin. It is important to know that all of these pathogens are gram-negative bacteria, which have LPS present in their outer membranes [50, 51].

The immunopathogenesis of ReA remains to be fully elucidated; however, it has been found that certain antigens from pathogens are present in the joints despite the bacterial cultures of synovial fluid being negative [52, 53]. This suggests the persistence of the bacilli outside the joints, mainly in the gut subepithelium, allowing monocytes to transport pathogenic antigens to the joints [54, 55]. The persistence of the pathogen in the gut or lymph nodes has been associated with certain patients having dysregulated cytokine production and/or function, which allows the persistence of the bacteria in the organism [56, 57].

A defective $CD4^+$ Th1 response has been proposed as patients with ReA reportedly present with low levels of tumour necrosis factor (TNF)-α and interferon (IFN)-γ [58, 59]. Conversely, the Th2 cytokine profile appears to be more active in ReA [60]. Reportedly, the Th17 profile [interleukin (IL)-17] plays the most important role in the pathogenesis of ReA as patients with this condition present with high levels of IL-17 in the synovial fluid [61, 62]. In patients with *C. trachomatis*-induced ReA, an increased percentage of $CD4^+$ T cells and IL-17 has been detected in the synovial fluid [63, 64]. *Salmonella* ReA in mice is suggested to be dependent on a Th17 profile response [21, 65].

## Septic Arthritis

In the case of SA, the pathogenesis is simpler. Joint invasion by pathogens occurs from haematogenous spread in a majority of patients. Trauma, surgery and infiltration can also be mechanisms of infection [66–68]. Once the bacteria have colonised the joints, they are able to rapidly proliferate and initiate an inflammatory acute response mediated mainly by IL-1ß and IL-6 [69, 70]. The innate response is mounted, and monocytes and neutrophils begin migrating to the synovial space, making inflammation worse [71] and activating an adaptive immune response of the Th1 profile [72], which in turn improves the bactericidal mechanisms of phagocytes, worsens inflammation and causes tissue destruction [73]. Figure 5.1 summarises the two pathological events.

## Clinical Manifestations

Joint infection has a pattern of clinical presentation regardless of the causative pathogen. Pain is the main symptom that is present in up to 85% of the cases, followed by joint swelling and fever with a temperature of up to 38.5 °C [74]. However, it is important to state that some patients may not

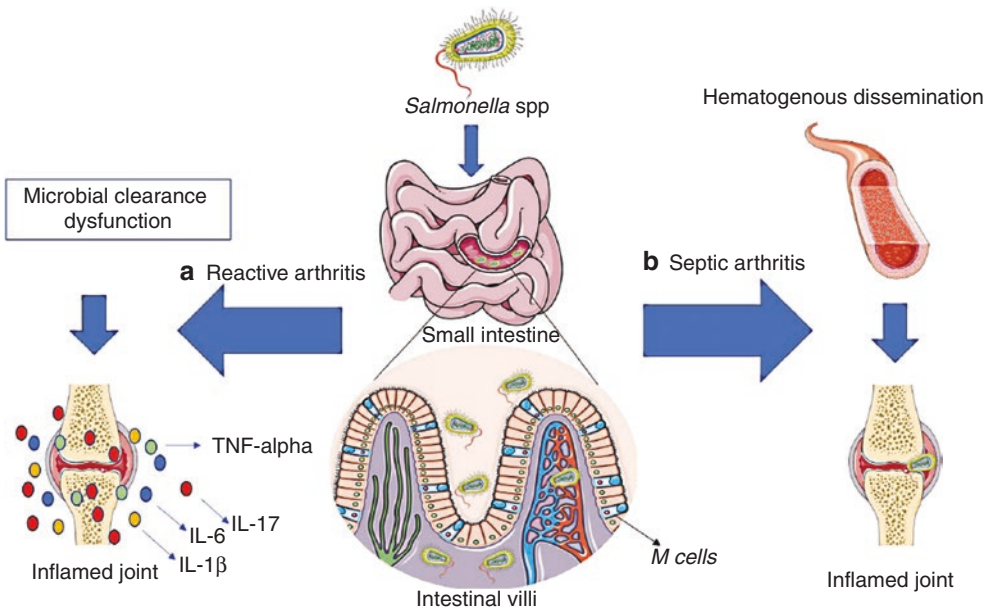


**Fig. 5.1** *Salmonella* arthritis pathophysiology.(**a**) After *Salmonella* intestinal colonisation and infection, a person with a genetic and environmental susceptibility related with factors that affect microbial clearance will probably develop reactive arthritis. (**b**) After *Salmonella* intestinal colonisation and infection, haematogenous dissemination might occur, allowing for joint seeding of *Salmonella* bacilli and the development of septic arthritis. Images are taken from SMART (Servier Medical Art), a free copyright website for medical and scientific illustrations; they are available at https://smart.servier.com

present with hyperthermia [10, 75, 76]. Movement limitation is also observed [74], and serum tests may reveal elevated erythrocyte sedimentation rates, C-reactive protein and leucocytosis [74, 75, 77].

Despite the wide range of recognised *Salmonella* serovars, *S. enterica* subspecies are recognised as the main serovars responsible for the development of human diseases. Therefore, the clinical presentation depends on the serovar involved [78]. In the United States, the *enteritidis* serovar is the most important cause of food-borne infection, whereas the *typhimurium* serovar is the main cause of typhoid fever [21, 79].

*Salmonella* arthritis is often associated with gastrointestinal tract infections, either as a sequela or as a coexisting condition. The former is more common than the latter; therefore, it is termed ReA [21]. In a study involving 97 patients with *Salmonella* arthritis, 38 presented with diarrhoea, abdominal pain and vomiting symptoms that lasted for an average of 11 days [5], 8 with urogenital symptoms and 3 with eye symptoms [5, 20]. Uveitis is the principal ocular manifestation of extra-articular involvement reported in the literature; dactylitis and enthesitis have also been described [76].

A cohort of 11 patients demonstrated that the time between intestinal infection and ReA was ~15–30 days [76, 77]; however, studies involving animal models have confirmed that there is a negative effect on the joint from day 5 of the initial gastrointestinal manifestation [21].

One of the characteristics that leads to the suspicion of reactive infection caused by *Salmonella* is the involvement of two or more joints [17, 76], which occurs more frequently in patients with comorbidities, including systemic lupus erythematosus, spondyloarthropathies and RA [17, 80].

In certain patients, symptoms can disappear within several weeks, whereas symptoms in others can persist over years [21]. In the latter, it is distinguished as a disease based on the chronic presence of immune complexes indicative of a long-lasting *Salmonella* infection [81]. In cases wherein sickle cell anaemia is underlying, the infection may last for >2 months, is periarticular and is associated with osteomyelitis [82].

## Diagnosis

Clinicians should always assess the complete clinical history to identify possible exposure to contaminated food or water [78]; previous infections and gastrointestinal and urogenital symptoms [76]; comorbidities involving connective tissue, autoimmune or autoinflammatory diseases or sickle cell anaemia [74, 80, 82]; joint surgery and replacement; trauma; and medications, including anti-TNF-α agents [77].

The clinical approach must take into account the above-mentioned features. Characterising the symptoms allows for an appropriate treatment approach; therefore, it is crucial to investigate whether there is monoarticular or polyarticular involvement and whether the symptoms are inflammatory or non-inflammatory [22]. Additionally, the presence of the classical signs of inflammation (swelling, tenderness, pain, movement limitation and redness) or synovitis increases the suspicion of a joint infection [10].

It is essential that the collection of aspirates from the involved joints, blood and stool cultures and Gram staining [17] are performed to confirm the isolation of *Salmonella* and permit a diagnostic confirmation [83]. It is important to state that gram-negative bacilli are positive in 50% of Gram stains, and joint cultures are positive in almost all cases of non-gonococcal bacterial arthritis [3]. Synovial fluid analysis provides detailed information to identify bacterial infection, including glucose consumption together with elevated lactate dehydrogenase; however, its specificity and sensibility to provide a diagnosis remain low [17]. In scenarios where the articular space is difficult to access, arthrocentesis may be guided by ultrasound [17].

There are key points enabling the differentiation between ReA and SA caused by *Salmonella*. In ReA, positive stool or blood cultures can be observed in addition to negative joint aspirates, whereas in SA, positive joint aspirates are observed. In terms of clinical presentation, ReA is defined as polyarticular and migratory, whereas SA is usually monoarticular [10].

Most of the serum inflammatory markers are unspecific. Conversely, procalcitonin has 93% sensitivity and specificity for SA compared with other acute phase reactants [84]. HLA-B27 supports the reactive form of infection due to *Salmonella*, and it is positive in 42–88% of patients. Studies suggest an important association between this marker and severe and long-lasting diseases rather than augmented susceptibility to the infection [5].

Imaging techniques, including simple radiography, computed tomography, magnetic resonance imaging and ultrasound, in the acute phases of the articular involvement are useful to identify evidence of effusion, osteomyelitis, arthritis and soft tissue oedema [3]. Gammagraphy also reportedly assists in the diagnosis of polyarticular involvement [85].

## Treatment

### Reactive Arthritis

ReA treatment focuses on providing symptomatic and supportive care. Antibiotics are not used usually; these are only indicated in ReA induced by genital pathogens when the infection is still active [86]. In the case of *Salmonella* infection, which is an enteric infection, evidence shows that the use of antibiotics does not improve the likelihood

of symptoms remission [87–91]. The mainstay of ReA treatment is the use of non-steroidal anti-inflammatory drugs (NSAIDs); however, the disease is usually self-limited, and the use of NSAIDs is directed to symptom relief only [49, 92].

When there is an inadequate response to NSAIDs treatment, intra-articular or systemic glucocorticoids can be used [49, 93, 94]. When the patient develops a chronic arthritis (≥6 weeks), non-biologic disease-modifying antirheumatic drugs (DMARDs), including sulfasalazine or methotrexate, can be used [95]. If there is no sufficient response, the use of biological therapy with TNF inhibitors has been reported [76, 96].

## Septic Arthritis

Antibiotic treatment is the mainstay of treatment for SA. In the case of gram-negative bacteria, including *Salmonella*, a third-generation cephalosporin is an ideal antimicrobial agent (ceftriaxone, ceftazidime or cefotaxime) [97, 98]. The antibiotic should be administered intravenously for at least 14 days, following which an oral course of fluoroquinolone must be administered of 14 days. Joint drainage is also recommended when there is a purulent collection [98, 99]. Providing symptomatic treatment is also encouraged [98].

## Future

Research on working towards the identification of early diagnostic essays has already commenced. HLA-B∗27:05 reportedly binds to the peptides of the outer membrane proteins of *Salmonella* and functions as stimulators of T cells [4]. A lack of highly specific and sensitive biomarkers for *Salmonella* arthritis still exists; therefore, continued investigations are required to achieve diagnosis in the early stages of the disease, ideally with less invasive procedures and faster results. In addition, although it is an infrequent condition, it can lead to complications and mortality. Therefore, enhanced warnings and prevention are required by clinicians to reduce its incidence.

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