Infection and Arthritis

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Infection is one of the important causes for the inflammation of the joint (arthritis). Microorganisms which include bacteria, viruses, fungi and parasites can cause arthritis, which can be acute or chronic. Acute arthritis is generally caused by pyogenic bacteria and termed as septic arthritis. Chronic arthritis is generally caused by mycobacteria and fungi. In reactive arthritis and other forms of spondyloarthropathies, arthritis can be secondary to infection elsewhere in the body. Infection can be a triggering factor in some chronic inflammatory conditions, which affect joints e.g. rheumatoid arthritis. On the basis of bacterial infection, arthritides have been classified into infective, reactive and inflammatory arthritis. Some microbes can cause infective as well as reactive arthritis. The type of arthritis is determined by microbial factors as well as host factors.

**Microbial Factors**

Virulence of the microbes, production of toxic substances, degradability of microbial components and tissue tropism are some important microbial factors.

*Staph. aureus* and *Neisseria gonorrhoea* appear to have a predilection for joint cavity and target a joint during bacteraemic phase. They have an enhanced ability to adhere to synovial tissue or produce toxins that facilitate colonisation during bacteraemic phase.1,2

Strains of *N. gonorrhoea* associated with disseminated disease (DGI) differ biologically from those associated with symptomatic localised disease. They are more resistant to killing by factors present in the serum and express specific cell surface proteins. The strains which cause asymptomatic localised infection do not provoke local inflammation and thus are not limited to mucosa and seed into the blood stream.3 Dissemination from local mucosal site also represents a failure of local inflammatory response to eradicate the bacteria due to production of IgA protease by some strains of gonococci.4

Certain strains of Group A streptococci are particularly rheumatogenic.5 Virulence of streptococci has been linked to the presence of M protein as well as large hyaluronic acid capsule.

Organisms which cause reactive arthritis related to gastro-intestinal or genito-urinary tract infection, share some similarities. They are either facultative or obligate intracellular pathogens. They have lipopolysaccharide and are capable of establishing stable infection of host mucosa. These organisms and Group A streptococci can also cause damage to the joint because of antigenic similarities between the bacteria and self (HLA molecule or other articular structures).

**Host Factors**

Age, sex, genetic susceptibility, immune status of the individual as well as the diseased status of the joints are some of the important host factors which determine the establishment of infection and clinical manifestation of arthritis.

Age of the patient and the underlying medical condition provide important clue to the probable infectious agent. Staphylococci are the most common bacterial cause of septic arthritis particularly in adults whereas in neonates Group B streptococci and Gram-negative organisms are generally associated. *Haemophilus influenzae* are most commonly found in children under 2 years of age, but account for only about 2% of cases in adults.6,7,8

There is greater incidence of gonococcal arthritis in women who are particularly susceptible to gonococcal bacteraemia during pregnancy, post-partum and during the first week of menstrual cycle. Rubella arthritis occurs primarily in post-pubertal women. Mumps arthritis occurs in post-pubertal men.9

The clinical manifestation of different forms of spondyloarthropathies and chronic inflammatory arthritis such as rheumatoid arthritis appear to be determined by specific genes mostly represented in the major histocompatibility complex. Some genes are necessary for disease susceptibility and others act as modifiers responsible for severity of disease. HLA B27 (HLA class I antigen) positive individuals are more prone to develop ankylosing spondylitis or any other form of spondyloarthropathy. Severe forms of rheumatoid arthritis are associated with HLA DR B1 alleles.

Complement deficiency especially of the terminal components such as C5-C8 appears to be a risk factor for the development of neisserial infection.10

Exposure to infectious agents when the immune system is developing may be a cause for poly arthritis. Recent evidences suggest that an influenza A2 epidemic caused an intra uterine infection that predisposed children to the development of a subtype of juvenile chronic arthritis.11

Local factors and systemic factors predispose to the development of arthritis. Staph aureus is the primary pathogen recovered from primary septic arthritis as well as septic arthritis following trauma, intra articular injection, under lying debilitating illness like diabetes mellitus, rheumatoid arthritis and SLE.

*Staph epidermidis* is the most common bacterial species associated with infection complicating articular prosthesis.12

Salmonella arthritis is a rare complication of salmonellosis. But patients with sickle cell anaemia and SLE are at an increased risk for salmonella arthritis because chronic salmonella carrier status is more common in these conditions due to impaired clearance by reticulo endothelial system.13,14

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Joint infection is a relatively common complication of immuno deficiency status particularly primary hypoglobulinaemia (X-linked agamma-globulinaemia and common variable immunodeficiency) and in majority of cases it has been shown to be due to mycoplasma infection.15,16

Gram negative enteric organisms, coagulase negative Staph species, methicillin resistant S. aureus and fungi must be considered in chronically hospitalised patients.

**Mode of spread of microbes to the joint**

1. **Haematogenous seeding** is the most common route for the entry of microbes into the joint. The primary focus of bacteraemia could be an infected wound of the skin, abscess, tooth infection, or respiratory infection. The organism may be transported within immune complex (Yersinia triggered reactive arthritis) macrophage (enterobacteria), polymorphonuclear leucocytes (elementary bodies of chlamydia) or the microbial structures such as lipopolysaccharide alone may be transported to the joints. But most bacteraemic episodes do not result in septic arthritis and some bacteria that are frequent causes of bacteraemia are rare causes of joint infection. Certain factors appear to predispose such seeding of bacteria to the joints.
   a. Joints affected by a variety of chronic arthritides (Rheumatoid arthritis, osteoarthritis, gout and prosthetic joints) are at increased risk for seeding of the bacteria.
   b. General condition of the patients is another deciding factor for the seeding of bacteria. They include altered immunity due to congenital or acquired immuno deficiency states, chronic debilitating diseases such as cancer, diabetes, patients on steroids and immunocompromised patients.

2. **Spread from an adjacent focus of infection** e.g., from osteomyelitis in adults due to an anastomosis between the metaphysis and synovial vascular bed, allowing direct entry of bacteria.17

3. **Direct introduction of bacteria into the joint** - penetrating trauma usually by dirty objects, animal or human bites and surgical procedures such as arthroplasty, arthroscopy, joint replacement surgery or intraarticular injection.

**Mechanism of Tissue Damage**

Damage to the articular tissue can be mediated by different mechanisms.

1. Products of infection mediated inflammation can directly cause damage. The initial site of infection in septic arthritis is the synovium. Once the infection is established, bacteria multiply and spread throughout the synovium and eventually into synovial fluid. The organisms are phagocytosed by polymorphs resulting in the release of chemotactic factors, activation of complement and recruitment of additional phagocytic cells, thus setting up classic inflammation. Prolonged inflammation damages joint capsule, articular cartilage, bone and tendon consequent to a) synovial ischaemia from markedly increased intra synovial fluid pressure and compression of blood vessels, b) phlogistic products of invading organisms and c) host defense mechanisms.

In animal models, the proteoglycan content of the cartilage is reduced by 40% within 48 hours of induction of joint infection. Within 2-3 weeks significant loss of cartilage develops. This underscores the need for prompt diagnosis and treatment of septic arthritis.18 Bacterial superantigens (Staph enterotoxin) cause toxic shock syndrome and septic arthritis as a result of production of large quantities of inflammatory cytokines.19

II. **Immune response mediated inflammation:** Immune response, directed against a pathogen or fragments of organism cause inflammation and much of the tissue injury is caused by immune complexes. In gonococcal infection, after an acute arthritis, synovitis may persist in response to the constituents of gonococcal cell wall such as LPS and manifest as sterile chronic synovitis. This has been proved in animal models. Both killed gonococci as well as purified LPS can induce a purulent synovitis after an intra-articular injection.20 Effusion may be caused and maintained by host immunological mechanism. Immune complex have been demonstrated in blood as well as in SF of patients with DGI.21

Lyme disease caused by *Borrelia burgdorferi* manifests as acute arthritis. But in some susceptible individuals, joint inflammation may persist even after the by PCR (DNA) genetically has become negative.22 The development of serological immune response against outer surface proteins has been linked to the development of chronic arthritis.23 In rubella arthritis, onset of rash and arthritis coincides with the antibody production, suggesting a role for either antibody or immune complex in synovium.24 In hepatitis B infection, arthritis and urticaria may precede jaundice due to the formation of immune complex containing hepatitis B antigen and specific antibodies.25 Arthritis due to parasitic infestation is rare but can occur with *Dracunculus medinensis* (Guinea worm) in an endemic area like Tamilnadu. It can manifest as a result of localisation of parasite in the joint or as a reaction to the presence of parasite in neighbouring tissue. Septic arthritis can very rarely occur secondary to bacterial infection of the parasite in the subcutaneous lesions.26,27,28

III. A third mechanism which involves autoimmune-mediated damage in addition to infection-mediated inflammation and immune response mediated inflammation may also be involved. A classic example is seen in rheumatic fever which causes damage to the heart and may cause migratory polyarthritis as sequelae to an infection in the throat. The immune response mounted against Group A β haemolytic streptococci is directed against self due to antigenic similarity between some streptococcal antigens and cardiac and/or articular tissue. Similar mechanism of molecular mimicry has been implicated in the pathogenesis of rheumatoid arthritis because of sharing of same aminoacid sequences in specific portions of certain HLA DR molecules (HLA DR B1*04) and Epstein Barr virus.

A strong association between HLA B 27 and several forms of spondyloarthropathies particularly ankylosing spondylitis has been reported from almost all ethnic populations.29,30,31 Apart from molecular mimicry that is reported to exist between *Klebsiella pneumoniae* and HLA B 27, other mechanisms have also been proposed for the pathogenesis. Some studies suggest that
HLA B 27 enhances the intracellular survival of the microbes and make them more arthritogenic or alter the immune response to produce more proinflammatory chemokines.32,33

Since HLA molecules determine the nature of peptides to be presented to the T lymphocytes, the strong association between HLA molecules and certain immunoinflammatory diseases can be very well understood.

Several viruses have been associated with arthritis. Rubella, hepatitis B and C viruses, mumps and a parvovirus B19 are most commonly associated and may cause arthritis through a combination of mechanisms. Viruses may directly infect the synovial cell and cause death of the cell by classic necrosis or programmed cell death. Death may be mediated by cytotoxic T cells when they recognise the virally encoded antigens on the cell surface. Immuno-inflammatory damage can be mediated through cytokines by transactivation of host gene by viral products. Humoral immune response may generate antibodies that deposit immune complex either locally or systemically with deposition of immune complexes in the synovium. Molecular mimicry between host and viral antigens may break immune tolerance and autoimmune mediated tissue injury follows.34

Additional mechanisms may be involved in Human Immunodeficiency virus mediated spondyloarthropathies. Progressive depletion of CD4 T cells may allow establishment of persistent infection and/or greater invasiveness of gut microbes by diminishing help for B cell dependent bacterial clearance mechanisms.35,36

**CLINICAL FEATURES**

Septic arthritis is a medical emergency. The outcome is favourable if detected during first 2-3 days. A delay in diagnosis particularly septic arthritis of hip in children often results in joint destruction.

The clinical presentation varies with age. In neonatal period and up to 1 year of age, the symptoms are usually systemic rather than local and are more of sepsis rather than local arthritis.37 In adults, the symptoms are localised and most commonly affect the lower extremities.38

The joint capsule is distended, warm, reddened and oedematous. But localisation of pain and tenderness may be common. The incidence of fever in acute bacterial arthritis varies from 25%-90%.39-42 Therefore, while the presence of fever in patients with acute arthritis should always raise the suspicion of pyogenic infection, absence of fever does not exclude the diagnosis. Typically, pyogenic arthritis is monoarticular and affect knee (50%) followed by hip (20%). Approximately 20% bacteremic episodes can lead to polyarthritis.43,44 10% rheumatoid arthritis patients are at risk for the development of pyogenic arthritis of the affected joint.45,46

Arthritis is the most common presenting symptom of rheumatic fever and has been recorded in 45-65% of affected children and teenagers.44,45 Arthritis is migratory and it is unusual for acute rheumatic fever to involve one joint like knee or wrist joint for a period longer than 1-2 weeks. In such cases, other possible causes of arthritis such as juvenile chronic arthritis or septic arthritis should seriously be considered.46

The general clinical characteristics of Brucella arthritis are similar to that of infectious arthritis due to other organisms. Large peripheral joints, sacroiliac joint and spine are the usual joints involved.47

Disseminated gonococcal infection can affect skin, joint and less commonly heart and meninges. Arthritic lesions in disseminated gonococcal infection (DGI) has been classified according to the presence or absence of purulent effusion.34,48 In group I, two-thirds of the patients present with acute illness, migratory polyarthritis with non purulent effusion and predilection for upper extremities. Though blood culture may be positive, SF culture is negative. Group II patients present with purulent mono arthritis affecting knee and SF culture will be positive. Osteoarticular tuberculosis can manifest as spondylitis (Pott’s disease) in 50%, peripheral arthritis in 20%, osteomyelitis, tenosynovitis or Poncelet’s disease which is an acute articular involvement without bacteriological evidence for the joint involvement.49 Peripheral arthritis more commonly occurs in joints of lower extremities. Usually single joint is affected. Hip, knee, ankle, sacroiliac joint are affected in that order.40,51

Majority of viral arthritis are acute and self-limited illnesses, usually accompanied by fever, distinct cutaneous manifestation and other clinical features. The most common arthritogenic viruses are rubella and hepatitis B and C viruses and also a variety of mosquito borne viral infections causing epidemics. Chronic polyarthritis mimicking RA especially in adults may occur with parvo virus B19 infection,52 hepatitis B and C infections. In rubella infection, joint complaints are common in adults especially in women. Joint involvement is usually symmetrical and may be migratory and occur 1 week before or after the onset of rash. Arthritis normally resolves over a few days to 2 weeks. In some patients it may persist for several months or years.53,54

Arthritis in Hepatitis B infection is immune complex mediated and is usually sudden in onset and often severe. Several joints are involved simultaneously and may be migratory or additive. Arthritis and urticaria may precede jaundice by days to weeks and usually subside soon after the onset of clinical jaundice.55

Acute onset poly arthritis in rheumatoid like distribution may occur in HIV infection. In spite of gross immunodeficiency, only a very low incidence of septic arthritis has been reported.56,57 The most frequently encountered condition in HIV infected individuals is spondyloarthropathies. Reiter’s syndrome may occur in 11% of HIV infected individuals.58,59 In contrast to HIV negative Reiter’s, cutaneous manifestations are very conspicuous and sustained. Involvement of the musculoskeletal system (spondyloarthropathies) and skin (psoriasiform disease) are distinctive clinical markers for advanced HIV infection.60

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