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Current Concepts on the Etiology and Treatment Of Infectious arthritis

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ABSTRACT: *Infectious arthritis is an important joint infection in rheumatology emergency. Infection is usually hematogenously acquired during overt or occult bacteremia. Septic arthritis is an unusual complication of arthroscopy or arthroscopic reconstruction of knee surgery. Health care acquired infections are associated with higher mortality rate. Up to 50% of patients reporting decreased joint function or mobility. Any organism can cause infectious arthritis include: gonococcus, S.aureus, MRSA, streptococci, mycobacteria, fungi and virus. Diagnosis, treatment, prognosis of infectious arthritis mainly dependent on the identity of infecting pathogen and host factors. Therapy of infectious arthritis is with antimicrobials with ability to penetrate into synovial fluid, e.g. nafcillin, clindamycin, vancomycin, and cephalosprorins .Oral ciprofloxacin is the drug of choice for known susceptible pathogens. Antifungal include: amphotericin B, flucytocine, and newer extended spectrum triazole.*

KEYWORDS*: Infectious arthritis, Infecting organism, Arthroscopy, Treatment.*

I. INTRODUCTION

Infectious (septic) arthritis of single or multiple joints may be caused by any of a number of diverse microorganisms. Bacterial arthritis, also known as *suppurative pyogenic or septic arthritis,* is the most common, and arguably most important joint infection and is considered a rheumatologic emergency because of its potential for rapid joint destruction with irreversible loss of function [1]. The annual incidence of infectious arthritis in the general population is between 2 to 10 per 100,000, and is increasing because of a large number of at risk patients and surgical joint procedures in recent years [2]. Estimates of incidence in patients with rheumatoid arthritis are muchhigher, ranging from 28 to 38 per 100,000 per year. The published mortality rates of bacterial arthritis in adults vary between 7% and 15% and may be as high as 30% in those with significant comorbidity or underlying disease [3, 4]. Moreover, bone and joint infections that develop in a health caresetting are associated with significantly higher mortality rate, longer length of hospital stay, and greater financial cost than infections acquired in the community [5]. The morbidity of septic arthritis is considerable with up to 50% of patients reporting decreased joint function or mobility after infection [4]. Despite improved antimicrobial agents, adjunct treatment measures, and hospital care, the morbidity and mortality of septic arthritis have not changed appreciably in the past two decades [6]. Bacterial arthritis is usually hematogenously acquired during overt or occult bacteremia, including that due to endocarditis [7]. Normal, diseased and prosthetic joints are all susceptible to infection, although abnormal joint architecture greatly increases the risk. The extremely vascular synovial membrane of the joints lacks a limiting basement membrane and in particularly susceptible to the deposition of bacteria [2]. Septic arthritis is an unusual complication of arthroscopy or arthroscopic reconstructive surgery of the knee [8]. Therapy with anti- tumor necrosis factor agents and patients with human deficiency virus (HIV) infection patients may have a small increased risk of septic arthritis [9, 10]. An important source of hematogenously derived joint sepsis is skin disease or lesions with or without concomitant infection [2]. Almost any organism can cause septic arthritis; however certain bacteria are implicated in most cases. In the 15-40-year old group, gonococcus remains most common etiology [11]. In pediatric patients *S.aureus and H.influenzae*. Other bacteria involved in septic arthritis include: *S.aureus, MRSA*, Streptococcus, gram negative bacilli, mycobacteria, fungi and virus. Treatment of septic arthritis is mainly with antimicrobials that penetrate into the synovial fluid that would be adequate in therapy: nafcillin, clindamycin, vancomycin, and cephalosporin .Oral ciprofloxacin is a potential agent for susceptible pathogens [12, 13]. This paper reviews infections of joints with reference to infectious arthritis.

II. MICROBIAL ETIOLOGY OF SEPTIC ARTHRITIS

Nongonococcal arthritis

The most common etiology in adults is *S.aureus*, which is responsible for 37% to 65% of cases depending on geographic location, incidence of comorbid rheumatic disease, and proportion of infections involving native joints [2]. For patients with rheumatoid arthritis the proportion of septic arthritis due to *S.aureus* has been reported to be higher (approximately 75%). Methicillin resistant *Staphylococcus aureus*

(MRSA) is increasingly isolated from infected joints and previous colonization or infection of the patient by MRSA increases this risk [14]. Coincident with the rising prevalence of invasive infections due to community-acquired MRSA (Ca-MRSA) there are increasing reports of native joints infection due to this pathogen, particularly in children [5]. Septic arthritis due to Ca-MRSA is associated with increased suppurative complications and duration of fever and hospitalization compared to that caused by methicillin –susceptible *S.aureus* [15]. Vancomycin-intermediate *S.aureus* has been reported as cause of septic arthritis in patients with frequent exposure to health care facilities [16].

Streptococcus spp, are the bacteria next most frequently isolated from adults with native joints septic arthritis [17]. *Streptococcus pyogenes* and other beta streptococci from Lancefield groups C, F and G are important pathogens within this group. Group B streptococci are an increasing cause of bacterial arthritis in adults with diabetes, malignancy, and genitourinary structural abnormalities [18]. *Streococcus pneumonia*, traditionally thought of as a rare cause of hematogenous septic arthritis in the antibiotic era, was found to cause 6% of cases in a comprehensive systemic review [19]. *Streotococcus suis* an emerging zoonotic pathogen in China, Southeast Asia and to lesser extent Europe, has been reported to cause septic arthritis in people exposed to pigs or improperly cooked pork [20].

Gram-negative bacilli are cultured from approximately 5% to 20% of patients with bacterial arthritis, particularly from neonates, the elderly, intravenous drug users, and immunocompromised hosts [18]. The coliform bacteria are most commonly isolated, particularly in the elderly, immunocompromised, and comorbidly ill, and increasingly drug resistant [21]. *Pseudomonas aeruginosa* and important pathogen in intravenous drug users, has a particular affinity for fibro cartilaginous articular structures such as the pubic symphysis and sternoclavicular and sacroiliac joints [22]. For children younger than 4 years of age *Kingella kingae*, a resident of the normal oral flora has replaced *H.influenzae* as the principal *gram-negative cause of hematogenous* bacterial arthritis [23]. Joint infection due to *K.kignae* is often associated with stomatitis or upper respiratory tract infection, and sequel. Child to-child transmission of this communicable bacterium occurs; in child care center outbreak of *K. kignae* osteo articular infection has been reported [24]. Other nogonococcal bacteria identified in infected joints include: *Corynebacterium spp.*, *Salmonella spp.*, *Neisseria menigitidis*, *Listeria monocytoges*, *Brucella spp*., *Mycoplasma hominis*, and *Ureaplasma urealyticum*. Articular infection due to anaerobic bacteria is rarely reported [25]. Novel infections are caused by a variety of pathogens include: *Pasteurella multicida* and *Capnocytophyga spp*., infection after dog or cat bite, and in the case of human bite, *Eikenella corrodoens* and *Fusobacterium nucleatum* [26]. Important causes of bacterial arthritis in which pathogen is not isolated from blood or synovial fluid using conventional culture techniques are *Borrelia burgdorferi* and *Tropheryma whipplei*, agents associated with Lyme disease and Whipple's disease, respectively [27].

Gonococcal Arthritis

Gonococcus arthritis has markedly declined as the mucosal gonorrhea decreased by about 75% between 1975 and 2002. Gonococcal arthritis is one of the two clinical presentations of disseminated gonococcal infection (DGI) the other being a syndrome of tenosynovitis dermatitis, and polyarthralgia [28, 29]. There is overlap between the two conditions and in some patients DGI may progress from a bacteremic tenosynovitis-dermatitis syndrome to localized joint infection. Septic mono-or oligo articular arthritis occurs in 42% to 85% of patients with disseminated gonococcal infection [30]. DGI is about four times common in women than men and complicates 0.5% to 30% of persons with mucosal gonococcal infection. Epidemiologic characteristics associated with DGI consists of lower socioeconomic status, nonwhite ethnicity, men who have sex with men (MSM), multiple sexual partners, and illicit drug use [31, 32]. The incidence is markedly less in Europe than in North America and it is considerably higher in developing countries [32]. Gonococcal arthritis and DGI occur as a result of occult bacteremia secondary to mucosal infection of urethra, urine, cervix, rectum or oropharynx. A symptomatic mucosal infection is more likely to result in DGI than symptomatic infection may have been sexually contracted days to months before dissemination [31]. *N.gonorrhea* possesses several virulence factors, many of them cell surface proteins, which influence pathogenesis, and the ability of the organism to widely disseminate from infected mucosa [33]. *N.gonorrhea* also can resist the action of several antibiotics.

Mycobacterial Arthritis

Worldwide, about 10% to 11% of extra pulmonary tuberculosis (TB) involves the bone and joints, accounting for 1% to 3% of TB cases [34]. The incidence is high in the developing world and is increasing because of the escalating prevalence of HIV disease. In endemic regions of the developing world, TB arthritis is mostly a disease of children and young adults while in other regions, older adults and immunocompromised

hosts are predominantly afflicted. Risk factors for TB arthritis include age over 65 years, female sex, immigration from regions with high TB endemicity, a lower socioeconomic class, incarceration, alcohol abuse, debilitating illness, intravenous drug use, immunosuppressive drug therapy, HIV infection and preexisting joint disease [34]. *Mycobacterium tuberculosis* causes a chronic granulomatous monoarthritis that is usually a result of the hematogenous dissemination associated with primary tuberculosis [35].

Mycotic Arthritis

Mycotic arthritis may sometimes occur in healthy hosts. However in immunocompromised or chronically ill persons, a steadily increasing frequency of infection and diversity of infecting mycotic pathogens is apparent [36]. Although there is some overlap between the two groups the most common fungi pathogens isolated from infectious arthritis in healthy hosts residing in endemic regions for dimorphic fungi are *Blastomyces dermitidis*, *Coccidioides* spp., and *Sporothrix schenkii*; whereas in immunocompromised hosts Candida spp., *Cryptococcus*, and *Aspergillus* are more often observed. Joint infection in these cases usually results from hematogenous dissemination of the organism [36]. In noncompromised host, infection is typically introduced into joint via trauma or injury, sometimes associated with a penetrating foreign body [37].

Viral Arthritis

Arthritis or arthropathy due to viral agents is often acute, occurs concurrently with signs and symptoms of febrile systemic illness, and resolves along with other manifestation of illness. Viruses may cause arthritis directly by inflicting the synovium or indirectly through host immune-mediated responses, and much of pathogenesis is poorly understood [38]. Perhaps the most common form of viral arthritis in developed countries is caused by human parvovirus B19. In children, human parvovirus B 19 infection arises with fever, rash, coryza, headache, and malaise [39]. Viral arthritis may also be caused by other viruses include: Hepatitis B, Hepatitis C, enterovirus, HIV, Rubella, mumps, and dengue virus.

Chronic Infectious Arthritis

Chronic infectious arthritis consists of a constellation of monoarticular or less commonly oligoarticulate joints infections that are characterized by an insidious onset and indolent course, a paucity of symptoms and progressive joint destruction that may result in considerable loss of articular function. Many of these infections arise with few symptoms and signs of joint inflammation other than sub-acute or chronic joint swelling, with or without effusion, and stiffness during active range of motion. Inappropriate treatment (e.g. systemic or intra-articular steroids for a tentative diagnosis of rheumatoid arthritis) is not uncommon and can further delay diagnosis and /or lead to more rapid or severe joint destruction. Subacute chronic arthritis is usually caused by mycobacteria or fungi and occasionally by bacteria such as *B.burgdoferi* (Lyme disease). *T.whippleii* (Whipple's disease), *Treponema pallidum* (tertiary syphilis), and *Nocardia* [40-43].

CLINICAL MANIFESTATIONS

Nongonococca arthritis

Nongonococcal arthritis is monoarticular in 80% to 90% of cases, with knee being the site of infection in about 50% patients [2]. 0ther native joints which are frequently involved in adults include the hip, shoulder, wrist, and ankle. In children, hip infection predominate [2]. Infections of the peripheral joints of the hands are unusual except in the setting of trauma, particularly animal or human bites [44]. Septic arthritis of the small joints of the foot is most often secondary to contiguous spread from skin and soft tissue ulcerations or adjacent osteomyelitis and is most seen in diabetic patients [45]. Sterno clavicular or costochondral joints infections are uncommon except in intravenous drug users, and occasionally as a complication of occult bacteremia or subclavian vein cauterization [46]. Risk factors for septic arthritis of the pubic symphysis include female urinary incontinence surgery, participation in athletic, pelvic malignancy, and intravenous drug use [22]. Non gonococcal polyarticular bacterial arthritis is observed in 105 to 20% of patients especially in those with rheumatoid arthritis, immunosuppression, or prolonged or intense bacteremia and is usually caused by *S.aureus* [47]. Most patients with acute bacterial arthritis present with the cardinal symptoms of arthritis-pain and loss of function of one or more joints over 1- to 2- week period. In addition to intense pain and decreased range of motion, other symptoms of non gonococcal bacterial arthritis include swelling, redness, and increased warmth of the infected joints [48].

Gonococcal arthritis.

Patients with DGI typically present classical triad of dermatitis, tenosynovitis, and migratory polyarthalgia or polyarthritis [29]. Joints symptoms may be quite severe and are often asymmetric. Moderatefevers, chills, and general malaise are usually present. Lesions of dermatitis are seen in two thirds of DGI patients, are painless and nonpruritic, few in number, and may not be noticed by the patient [50]. Septic

gonococcal arthritis arising without tenosynovitis or skin lesions is less common than the so- called bacterimic form is clinically indistinguishable from bacterial arthritis due to other organisms. The knees wrists, and ankles are most commonly affected and monarthritis is more common than polyarthritis. For patients with DGI and gonococcal arthritis culture yield of *N.gonorrhoeae* is much higher from mucosal sites than from synovial fluid or blood. Culture is positive of uterine cervical swabs in 80% to 90% of women and of ureteral swabs in 50% to 70% of men [50].

Mycobacterial arthritis.

Mycobacterial and fungal arthritis is characterized by slow evolution of physical and radiographic findings [49]. Articular infection may remain latent for long periods before clinical presentation. It typically involves the knees, hip, and ankle, but can involve any joints [50]. The clinical presentation is that of chronic arthritis, indistinguishable from that with other infectious or noninfectious causes [51]. Coexisting pulmonary or other extra-articular infection may be evident, more than one half of cases it is not [52]. In order to prevent unacceptable delays in diagnosis and further joint destruction, a high index of suspicion for TB arthritis must be maintained [52]

Mycotic arthritis

Mycotic arthritis is seen mainly in immunocompromised patients. Evidence of disseminated disease is common. Among the fungi, sprotrichotic, candidal, and coccidiodal arthritis are the most common, but arthritis can also occur with blastomycosis, cryptococcosis, and histoplasmosis [52]. Bayer and Gauze reviewed fungal arthritis. Coccidiodes immitis monoarticular infection typically occurs in non-white immunocompromised men from endemic areas. Joint infection in patients with blastomycosis primarily spread from contiguous focus of osteomyelitis. [53]. Candadal infections of peripheral joints generally are of acute onset due to hematogenous spread [51].

Viral arthritis.

Although joint symptoms usually resolve within 2-weeks, persistent polyarticular arthritis may follow acute human parvovirus B 19 infection in up to 20% of female patients and in some individuals may last up to several months, occasionally longer [38].

Chronic Infectious Arthritis

Chronic Infectious Arthritis has the ability to mimic other inflammatory joint disorders such as rheumatoid arthritis and its ability to arouse little clinical suspicion, resulting in considerable delay in diagnosis. Moreover establishing a pathogen-specific diagnosis is difficult and response to treatment is slow and often incomplete [40, 41].

III. TREATMENT

Antimicrobial therapy

Instillation of antibiotics directly into the joints is unnecessary. Most antibiotic diffuse into the synovial fluid and intraarticular injections of antibiotics may induce a chemical synovitis [12, 13]. Parenterally administered antibiotics usually are indicated in the treatment of septic arthritis. Antibiotics of choice with penetration ability into synovial fluid include: penicillin G, ampicillin, nafcillin, carbenicillin, cephalothin, cefzolin, cefuroxime, clindamycin, chlsramphenicol, tetracycline, sulfonamides, vancomycin, gentamycin, amikacin, ceftriaxone, ceftazidime, aztreonam, imipenem [12, 13]. Vancomycin is indicated as empiric therapy for persons with gram positive cocci on a synovial fluid or as component of therapy for those with gram stain negative, due to high prevalence of health care-associated and Ca-MRSA joint infection. For patients with gram –negative rods on Gram-stain, an anti pseudomonal β-lectam antibiotic should be used unless there is previous or concurrent infection or colonization by an extended-spectrum β- lactamase producing pathogen, in which case a carbapenem antibiotic is preferred [54]. The current recommendations from CDC for the treatment of skeletal TB in adults without pulmonary tuberculosis are identical to that of extra pulmonary (including patients with HIV or other immunosuppressive state): isoniazid (INH), rifampin (RIF), ethambutol, and pyrazinamide for 8 weeks (ethambutol may be discontinued in isolates known to be without drug resistance); followed by INH and RIF to complete 6 months therapy. Directly observed therapy is advisable for most patients and adjuvant corticosteroids are generally not recommended [50]. Nontuberculous mycobacterial arthritis is usually caused by *Mycobacterium avium-intracellulare, M.Kansasi, M.marinum* and *M.terrae* from the environments e.g .soil, and water. Treatment varies depending on the identity of the isolated mycobacteria susceptibility testing can be performed in reference laboratories and is useful in directing therapy for some of these organisms [55]. In the past, most of the clinical experience with therapy for fungal arthritis was with amphotericin B with or without the addition of flucytosine. Recently, fluconazole, newer extended spectrum triazole (itraconazole,

voroconazole, and posaconazole), and the echinocanadin class antifungals (caspogungin, micafungin, and anidulagungin) have expanded the therapeutic options available for many fungal pathogens [56]. Viral arthritis that has been evident for less than 6 weeks is treated symptomatically. Nonsterioidal anti-inflammatory drugs (NSAIDs) are the mainstay to the patient that the symptoms are self-limiting and likely to develop into serious condition such as RA or cause joint destructions. The use of corticosteroids to be discouraged unless there are troublesome symptoms and contraindications to NSAIDs or where a brief course of low dose (<10mg prednisone daily) may be reasonable [57].

IV. CONCLUSIONS

Infectious arthritis is the common and most important joint infection with potential for joint destruction. The diagnosis, pathogenesis and treatment of infectious arthritis continue be challenging to rheumatologist.

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