"A STUDY ON THE CLINICAL FEATURES OF REACTIVE ARTHRITIS AND ITS OUTCOME"

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CERTIFICATE

This is to certify that this dissertation "**A study on the Clinical features of Reactive Arthritis and its outcome"** presented here is the original work done by Dr.M.Hema, D.M Postgraduate in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai 600003 in partial fulfilment of the university rules and regulation for the award of D.M. Branch IX - Rheumatology, under my guidance and supervision during the academic period from 2011-2014.

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DECLARATION

I, Dr.M.HEMA hereby solemnly declare that this dissertation entitled "**A study on the Clinical features of Reactive Arthritis and its outcome"** was done by me in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai 600003 during January 2013 to January 2014 under the guidance and supervision of Dr.S.Rajeswari M.D., D.M. This dissertation is submitted to the Tamil Nadu Dr.M.G.R.Medical University towards the partial fulfilment of requirement for the award of D.M. degree in Rheumatology.

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Place:

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INDEX

ABBREVIATIONS

ReA	:	Reactive arthritis
USpa	:	Undifferentiated Spondyloartropathy
SPA	:	Spondyloarthropathy
CRP	:	C reactive protein
ESR	:	Erythrocyte sedimentation rate
MOMP	:	Membrane outer membrane protein
LPS	:	Lipopolysaccharide
YOP	:	Yersinia outermembrane protein
YAD		Yersinia adherence protein
Ct	:	Chlamydia trachomatis
Cpn	:	Chlamydia pneumonia
PCR	:	Polymerase chain reaction
DNA	:	Deoxyibonucleic acid
ELISA	:	Enzyme linked immunosorbent assay
TNF	:	Tumour necrosis factor
IL	:	Interleukin
HLA	:	Human Leukocyte antigen
PBS	:	Phosphate buffer saline
TMB	:	Tetramethyl benzidine
DMARD	:	Disease modifying anti-rheumatic drugs
XLD	:	Xylose lysine deoxycholate.
IBA	:	Inflammatory back ache
CT	:	Computerised Tomogram
CREA	:	Chronic Reactive Arthritis
MVPS	:	Mitral Valve Prolapse Syndrome
LVH	:	Left Ventricular Hypertrophy
AML	:	Anterior Mitral Leaflet
PML	:	Posterior Mitral Leaflet
OD	:	Odds Ratio
B/L	:	Bilateral

INTRODUCTION

Reactive arthritis (ReA) is a spondyloarthropathic group of disorders characterized by inflammation of the joints occurring either after a genitourinary or gastrointestinal infection. Its is a sterile synovitis associated with infection at a distant site without evidence of sepsis at the affected joint and often associated with urethritis, conjunctivitis and occurrence of other extraarticular manifestations. Time interval between the onset of infection and joint symptoms should be between 1 week to a of maximum 4 weeks .

Clinical features are classically characterized by axial arthritis, oligoarthritis and enthesitis accompanied by extraarticular manifestations. Musculoskeletal symptoms are often acute associated with systemic features such as fatigue, weight loss and fever. Extraarticular symptoms include mucocutaneous, ocular and cardiac manifestations. Men and women are equally affected and the common age group is 20 to 40.Different bacterial species are associated with reactive arthritis. Commonest enteric pathogens are Salmonella, Shigella, Campylobacter and Yersinia. Chlamydia trachomatis is the commonest genitourinary pathogen.

Factors contributing to etiopathogenesis include alternation in cytokine profile leading to impaired elimination of microbes , persistence of the microbe and trafficking of their antigenic peptides to the joint leading to pathological immune response. Genetic factors play a role leading to susceptibility and 65-85% of reactive arthritis patients are positive for HLA-B27 .The disease is more severe and chronic in patients positive for HLA-B27.

Diagnosis of Reactive arthritis is made on the basis of classification criteria and laboratory parameters. Treatment is rest , non-steroidal anti-inflammatory drugs and intra-articular steroids. In chronic reactive arthritis DMARD therapy is indicated. Role of antibiotic treatment is controversial.

Reactive arthritis is usually a self limiting disorder, however 15-30% may progress to chronic reactive arthritis (>6 months).Prognosis is less favourable in patients with HLA-B27 positivity.

AIM AND OBJECTIVE

1) To study the clinical features of Reactive arthritis.

2) To study the outcome of Reactive arthritis.

   a. To study the association of disease activity of Reactive arthritis and its outcome .

   b. To correlate the association between HLA B27 and the outcome of Reactive arthritis

   c. To correlate the serum levels of IL 17A levels and disease activity of Reactive arthritis.

   d. To study the radiological outcome of Reactive arthritis.

REVIEW OF LITERATURE

Reactive arthritis(ReA) is an inflammatory arthritis which arises either after a gastrointestinal or genitourinary tract infection. It belongs to the spondyloarthropathy group of disorders and displays a strong interplay between host and environment. Classic triad includes symptoms of urethra, conjunctiva and synovium. In general there are two forms of reactive arthritis post dysentery and post venereal.

HISTORY

Many people attribute that, the description of reactive arthritis was first by Hans Reiter in 1916,[1] when he described the clinical triad of arthritis, nongonococcal urethritis, and conjunctivitis in a German soldier after an episode of bloody diarrhea. The syndrome was also described by two French physicians Fiessinger and Leroy[2] in the same year and hence Fiessinger-Leroy syndrome has also been used. But the description of reactive arthritis dates back to 460 B.C ,when Hippocrates wrote "A youth does not suffer from Gout until sexual intercourse.[3]'' Christopher Columbus developed ReA in 1494, after a bout of dysentery[4].Several cases were described in literature by many persons . Pierre van Forest's description of a case of ''secondary arthritis and urethritis'' in 1507[5], Thomas Sydenham's association of arthritis with diarrhea in 1686[6], Stoll's documentation of arthritis following dysentery in 1776[7], and Yvan's description of a French captain who developed "ophthalmia" and inflammatory arthritis primarily of the lower extremities 15 days after a venereal infection[8]. The classic triad of ReA was first described in 1818 by Brodie[9] .He documented five patients who had triad of urethritis,

arthritis, and conjunctivitis, and the second was in 1897 by Launoi's when he distinguished septic from aseptic arthritis[10].In 1824, Cooper proposed the relationship between venereal infections and arthritis, predominantly of lower extremities[11].In 1942 two researchers , Bauer and Engelmann from Harvard recognized the symptoms of ReA as a syndrome again. But in their literature review they found that this syndrome was already described by Hans Reiter in 1916, so they coined the term as Reiter's syndrome[11].A thorough search of history reveals that Sir Hans Reiter was the first to describe this syndrome to have an infectious etiology, though he described it due to spirochaetal infections (spirochetosis arthritica). Since Hans Reiter performed medical experiments on prisoners during the world war, people argued against using the term Reiter's syndrome. The term Reiter's syndrome is no longer used now. Many clinicians are reluctant to diagnose Reiter's syndrome in the absence of the complete triad of symptoms, thereby missing a majority of cases. The term Reactive arthritis has now become the most appropriate terminology.

Table-1: Proposed Criteria for Reactive Arthritis in Literature

Ahvonen et al 1969	Arthritis that develops soon after or during infection elsewhere in the body but in which the microorganism does not enter the joint cavity
Olhagen, 1980	Uroarthritis and enteroarthritis are rheumatic conditions developing in association with urogenital and enteric infections, respectively.
Willkens et al, 1981	Reiter's syndrome consists of an episode of peripheral arthritis of more than 1-month duration in association with urethritis and/or cervicitis.

Calin 1984	Seronegative asymmetric arthropathy (predominantly lower extremity) plus one or more of the following: • Urethritis / Cervicitis • Dysentery • Inflammatory eye disease • Mucocutaneous disease (balanitis, oral ulceration, keratoderma)and exclusion of other rheumatic diseases such as ankylosing spondylitis and psoriatic arthropathy
Pacheco-Tena et al, 1999-	Probable reactive arthritis • Musculoskeletal symptoms (arthritis, oligoarthritis, polyarthritis or arthropathy) • Clinical features of infectious disease (diarrhea or urethritis) but no bacterial identification preceding musculoskeletal symptoms by 4 to 6 weeks Definite ReA triggered by bacteria • Bacterial identification of an infectious disease preceding musculoskeletal symptoms • Bacterial identification in a recent onset (4 to 6 weeks) episode of musculoskeletal symptoms • Bacteria associated undifferentiated oligoarthritis or spondyloarthritis

Modified ACR criteria for Reactive Arthritis-2004

Arthritis for longer than 1 month with uveitis or cervicitis.

Arthritis for longer than 1 month and other, urethritis or cervicitis or bilateral conjunctivitis.

Episode of arthritis and conjunctivitis.

Episode of arthritis of more than 1 month, urethritis, and conjunctivitis.

For a definite diagnosis of Reactive arthritis, evidence of Arthritis with urethritis or cervicitis need to be present. No need for laboratory confirmation.

Third International Workshop diagnostic criteria for Reactive Arthritis – 1996 (European Criteria)[12]

Typical peripheral arthritis

- Predominantly lower limb, asymmetric oligoarthritis

  Plus

- Evidence of preceding infection
  - Where clear clinical diarrhoea or urethritis within preceding four weeks, laboratory confirmation is desirable but not essential
  - Where no clear clinical infection, laboratory confirmation of infection is essential

Exclusion Criteria

Patients with other known causes of mono/oligoarthritis, such as other defined spondyloarthropathies, septic arthritis, crystal arthritis, Lyme disease, and streptococcal ReA, should be excluded.

The diagnosis of ReA does not require the presence of HLA-B27 or extraarticular features of Reiter's syndrome (conjunctivitis, iritis, skin lesions, non-infectious urethritis, cardiac and neurological features) or typical spondyloarthropathic features (inflammatory back pain, alternating buttock pain, enthesitis, iritis) but these, if present, should be recorded.

Laboratory tests For preceding infection

Stool culture

Helpful if positive; should be routine if previous diarrhoea; stool culture in absence of diarrhoea rarely positive.

Urethral culture

Urethral culture often positive in absence of symptoms; need to interpret in light of local asymptomatic carriage rate.

Urine/urethral PCR

These tests can be used, where available, instead of urethral culture or urethral immunofluorescence for bacteria.

Serology

Chlamydial IgG is of no value because of high prevalence in community. A rising titre of IgA antibodies is useful in presence of non-specific urethritis history.

Yersinia, Salmonella, and Campylobacter antibodies by ELISA: IgG antibodies-a fourfold change in titre or a strongly raised titre (difficult to specify; depends on local situation); IgA or IgM antibodies-may be more specific; useful if >2 standard deviations above control populations.

Haemagglutination (Widal) tests for Yersinia or Salmonella are specific for recent infection but insensitive, especially for Salmonella.

Shigella serology is of no use because of cross reactivity with Escherichia coli.

The following tests should currently be regarded as research tools:

Immunofluorescence for bacteria in synovium and proliferation of synovial lymphocytes

These tests are labour intensive and technically difficult tests whose sensitivity and specificity is uncertain. They are unlikely ever to be suitable for routine diagnostic use.

PCR for chlamydial DNA in the joint

A potentially valuable test which could be practicable for routine use. Its sensitivity and specificity are being further investigated. This approach cannot currently be used for enteric ReA because it is uncertain whether DNA from enteric organisms reaches the joint

Preliminary Classification Criteria for Reactive Arthritis Modified from Braun et al., 2000

Major criteria

1) Arthritis, with 2 of 3 of the following findings

   a. Asymmetric

   b. Mono or oligoarthritis

   c. Affection predominantly in lower limbs

2) Preceding symptomatic infection, with 1 or 2 of the following findings

   a. Enteritis (diarrhoea for at least 1 day, 3 days to 6 weeks before the onset of arthritis)

   b. Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis)

Minor criteria, at least 1 of the following

1) Evidence of triggering infection

   a. Positive nucleic acid amplification test in the morning urine or urethral/cervical swab for Chlamydia trachomatis

   b. Positive stool culture for enteric pathogens associated with ReA

2) Evidence of persistent synovial infection (positive immunohistology or PCR for Chlamydia)

Definition of reactive arthritis

Definite ReA	Both major criteria and a relevant minor criterion
Probable ReA	1) Both major criteria, but no relevant minor criteria or 2) Major criteria 1 and one or more of minor criteria

Exclusion Criteria

Other causes for acute arthritis

EPIDEMIOLOGY

The incidence and prevalence of ReA depends on the prevalence of causative pathogens and on the geographic region .Incidence is estimated to be 5 - 14/100,000 patients, aged 18 - 60 years[14]. It is more common in Caucasians affecting men and women equally. Most patients are aged 20- 40 yrs[13].A population based study in OREGON – MINNESOTA[14] reported an incidence of 0.6 to 3.1 cases per 100,000, following documented enteric bacterial infections, range depending upon the organism.0-22% infected persons subsequently developed reactive arthritis following Yersinial

infection according to a study by M.Vasala et al on the frequency of reactive arthritis after Yersinia infection[15]. A study done by E.Collantes-et-al on the disease pattern of spondyloarthropathies in Spain suggested that 1.2-1.4%of the patient with spondyloarthropathy had reactive arthritis[16]. A recent epidemiological study by Buschiazzo, Emilio-et-al in Argentina informed that among 402 patients with spondyloarthropathy aged 38.3 - 58 years, 6.2%patients had ReA[17].

HLA-B7 is found in 30-70% of patients with reactive arthritis. Patients with HLA –B27 positivity had more extra-articular manifestations and more commonly progressed to chronic stage[18].

TRIGERRING MICROBES

Bacteria associated with the development of reactive arthritis.

Enteric infections

Salmonella

Various serovars

Shigella

S. flexneri

S. dysenteriae

S. sonnei

Yersinia

Y. enterocolitica (especially O:3 and O:9)

Y. pseudotuberculosis

Campylobacter

C. jejuni

C. coli

Clostridium difficile

Escherichia coli

Diarrhogenic strains

Urogenital infections

Chlamydia trachomatis

Ureaplasma urealyticum

Mycoplasma genitaliuma

Respiratory infections

Chlamydia pneumoniae

Group A beta-hemolytic Streptococcus

Other infections

Borrelia

Brucella

Mycobacterium

Staphylococcus

Viruses

Various parasites

Ascaris

Giardia lamblia

Filarial worms ,Schistosoma , Strongyloides stercoralis and Taenia saginata.

Though different bacterial species are associated with reactive arthritis, the classical enteric pathogens involved in the trigerring of reactive arthritis belong to Salmonella, Shigella, Yersiniae and Camplyobacter species. Chylamdia trachomatis is the most common urogenital pathogen.

SALMONELLA

It is a rod shaped motile bacterium most commonly involved in reactive arthritis. Salmonella typhimurium and Salmonella enteritidis are the subtypes commonly involved. Attack rates range from 6-30%.[19,20] Causcians are more likely to develop reactive arthritis after Salmonellosis than Asians. Children are less commonly affected than adults. Buxton JA, et al, Hannu T, et al, Inman RD et al and Lee AT etal[21-24] reported that the attack rate of reactive arthritis ranged from 6-15% after an outbreak of Salmonella typhimurium in three different countries The prevalence of HLA-B27 in these affected individuals ranged from 17-50%.After an outbreak of salmonella enterides in four different countries attack rate of ReA ranged from 7-29%[25,26].The prevalence of HLA-B27 was reported to be 33% in one of these outbreaks. A Denmark based study by Schiellerup P-etal, compared different enteric pathogens in the trigerring of reactive arthritis and found that Salmonella was the second most common organism next to Campylobactrium and second most common arthritogenic[27] . Reactive arthritis was reported in 12% of patients after an outbreak of Salmonella bovismorbificans[28].

SHIGELLA

The first bacteria implicated in the cause of reactive arthritis was Shigella [29]. However it is a rare cause of ReA in developed countries[30]. It is

caused by all four species of Shigella such as Shigellla sonnei, Shigella flexneri, Shigella dysenteriae and Shigella boydi of which Shigella flexneri and Shigella dysenteriae are the common organisms implicated. Shigella sonnei is a rare cause[31].DNA of Shigella have been demonstrated in the synovial tissue of patients with ReA. A study from Finland in 2005 revealed cases of reactive arthritis due to Shigella in which Shigella sonnei was the most common cause[31].The attack rate of reactive arthritis in this study was 7%.36% were HLA-B27 positive among those who developed reactive arthritis in this study.

CAMPYLOBACTER JEJUNI

ReA is caused both by Campylobacter jejuni and Campylobacter coli. It usually causes mild arthritis, either oligoarthritis or polyarthritis. Inflammatory back pain is uncommon compared to other types of reactive arthritis. A Finland based study in 2002 by Hannu T et al found that 7% of the campylobacter positive stool culture positive patients developed reactive arthritis[32].In their study they could not find an association with HLA B27. A review study by Pope JE et al suggested that the attack rate of ReA after campylobacter jejuni infection is 1-5%. It does not have a significant association with HLA-B27[33].

YERSINIA

Among the three species of Yersinia,only Yersinia enterocolitica and Yersinia pseudotuberculosis have been implicated in the causation of reactive arthritis. Compared to other organisms in the etiology of reactive arthritis Yersinia is very arthritogenic. A DENMARK study suggested that it is the

most common organism causing reactive arthritis[27].Yersinia pseudotuberculosis outbreak occured in two different places in 1998, one at Finland due to serovar 0:3 and the other at Canada due to serovar 1b and the joint symptoms occured subsequently in 12% of these affected individuals.[34,35]

CHLAMYDIA

Chlamydia trachomatis is the most common urogenital pathogen causing reactive arthritis. Chlamydia is the most common bacterium involved in sexually transmitted diseases and Trachomas. The ocular stains are A, B, C whereas the urogenital infections are caused by D-K serovars. In a review of Chlamydia induced reactive arthritis, contrary to the assumption that urogenital serovars are the ones to be seen in synovial tissue, it was the ocular serovar which was identified using the PCR technique[36]. If so, are the ocular serovars more arthritogenic than genital serovars? The question remains to be answered.

Possible explanations are

1) The ability of the ocular serovar to disseminate is much more than the urogenital serovar

2) If the initial inoculum of urogenital infection contains a small portion of ocular serovar the situation leads to an active arthritis episode.

Chlamydial DNA has been demonstrated by PCR in the synovial tissue of patients with reactive arthritis.50% of patients develop reactive arthritis following symptomatic infection[37].Chlamydia induced ReA is largely under diagnosed because most Chlamydial infections are asymptomatic and the

clinical triad is not expressed fully.In 2008, a study which analysed Chlamydial PCR positivity by Carter JD et al in patients with undifferentiated spondyloarthropathy ,found that 62% of patients had PCR positivity suggesting,Chamydia could be an etiologic agent for undifferentiated SPA.[38]

PATHOGENENSIS OF REACTIVE ARTHRITIS

The pathogenesis of reactive arthritis is contributed by three factors.

1) The presence of bacterial products in joints which is evident from the table below[39]

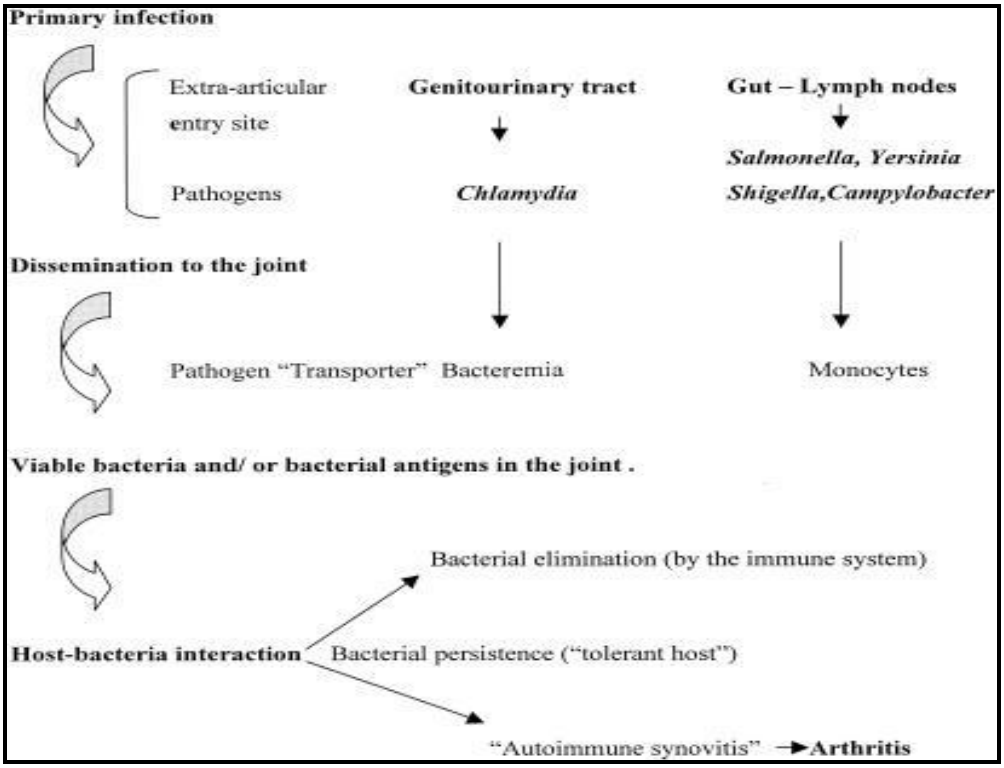
Bacterium	Presence in joint of bacterial products			
	Antigens	DNA	RNA	Culture
C. trachomatis	+	+	+	±
Y. enterocolitica	+	+	ND	−
Y. pseudotuberculosis	+	−	+	−
S. flexneri and S. sonnei	+	+	ND	−

ND-Not Done

2) The host bacterial interactions

3) Local immune response

The interaction between the bacterial products and the host immune system is shown below[39]



PATHOGENESIS OF ENTERIC REACTIVE ARTHRITIS

In enteric form of ReA, the bacteria survive outside the synovium such as gut mucosa and lymphatics, from which it is carried to the synovium by monocytes and macrophages and binds to the synovial blood vessels and the bacterial products persist in the synovium and elicit an inflammatory response[40-42].

A Study conducted to study the pathogenic mechanism of enteric pathogens such as Salmonella, Shigella and Yersinia found that after invasion of synovial cells by these bacteria, they undergo slow metabolic activity leading to the disappearance of bacterial cytosol leaving only bacterial products.[43-44] Survival of Yersinia is provided by many virulence

factors such as cytotoxin, invasin and adhesion .These factors prevent the microbiocidal action of neutrophils and its adhesion to host cells by adherence factors YOP B and D. A cationic protein 19kDa urease 3 subunit shown to induce arthritis in mice, sticks to the cartilage and elicits an inflammatory response. 14kDa ribosomal protein also plays an important role.

Regarding Shigella it causes apoptosis of the invading cell, hence its DNA is rarely found in synovial cells except when it is encoded by plasmid such as PSD2 which is arthrogenic.[45,46]

PATHOGENESIS OF CHLAMYDIA INDUCED ARTHITIS

Chlamydia trachomatis is an obligate intracellular parasite implicated and studied in reactive arthritis extensively. Newer developments in genetics and molecular biology have helped in understanding the pathogenesis of Chlamydia induced reactive arthritis. Following urogenital infections, the pathogenic substances are found in synovial fluid many years after initial infection. The organisms after entering into the synovial fluid reside in the monocytes, and display new characteristics quite different from their normal activity in urogenital tissues.

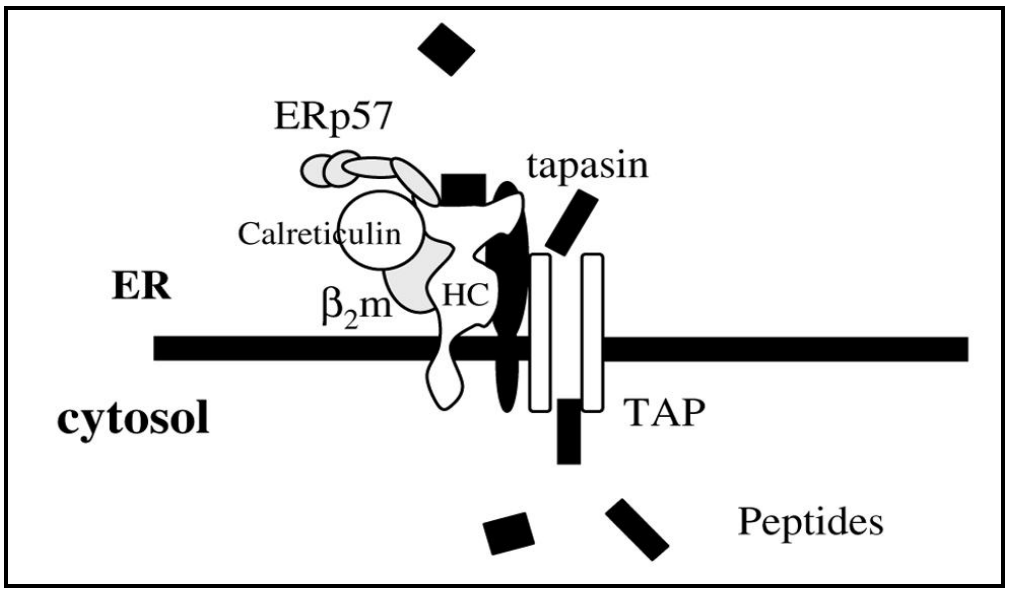
Chlamydia reaches the joint either during bacteremia or by monocytes.[47] Chlamydia has an elementary body. Initially, the extracellular form (elementary body) attaches itself to the host cell and when taken inside the cell, stays in the membrane bound vesicle, forming the inclusion body. This develops into an active form called the reticulate body. This reticulate body undergoes cycles again and almost 80% get back to their original elementary bodies, which are capable of infecting. The elementary bodies are

released by cell lysis or exocytosis. Such replications incite significant inflammatory responses inside the human body. Within the joint cavity factors such as decreased apoptosis of host cells or down regulation of antigen presentation leads to the persistence of infection.[48,49] Chlamydia survive within the synovial tissue rather than fluid in an altered elementary form leading to escape from immune surveillance. It also upregulates HSP 60 protein which is immunogenic. Studies have found the presence of three open reading frames coding heat shock protein HSP 60, Ct 110, Ct604 and Ct755. Of the three frames Ct604 is increased in persistent inflammatory models and Ct 755 is reduced[50].Chlamydia also induces upregulation of proinflammatory cytokines such as IL1,IL6 and TNF α.[21,22] The major target antigen in Chlamydia induced reactive arthritis is a 57 kDa heat shock protein. Further studies of the same has found no epitope recognition or cross reactivity. Other antigenic targets recognized are 18kDa histone protein and a 30 kDa antigen. Their relevance has not been fully studied. In Chlamydia induced urethritis, Outer Membrane Protein (OMP)of Chlamydia has been found to have a pathgenetic role. However this OMP is not found in increased levels in joints of patients with reactive arthritis. This suggests that different immunogenetic responses happen in reactive arthritis.

HLA B27

HLA B27 is a Major Histocompatability Complex (MHC-I) molecule, formed in endoplasmic reticulum as a glycoprotein. It contains the heavy chain, β2 microglobulin and an aminoacid peptide. After synthesis, the heavy chain undergoes glycosylation, it binds to β2 microglobulin and get chaperoned to form a heterodimer. It interacts with tapasin, calreticulin and

Erp57. A stable heavy chain – β2 microglobulin complex is needed for trafficking of signals to the cell surface achieved with help from chaperones.[51] However HLA B27 is characterized by two unusual properties. The folding rate of this molecule is very slow allowing the formation of unstable and misfolded molecules and forms aberrant disulphide bonded dimers.[52] B pocket of MHC class I molecule plays an important role in selection of peptides. It is the composition of B pocket which plays an important role in folding of HLA B27. Mutations in the B pocket and an unpaired cysteine residue at 67 allows the dimerisation of HLA B27.[53,54] The aminoacids allowing the dimerisation of HLA B27 are present in almost all cases of reactive arthritis with HLA B27 positivity suggesting that they play a dynamic role in its pathogenesis as well.



Accumulation of misfolded peptides evokes endoplasmic reticulum stress response, an Unfolded Protein Response (UPR). This unfolded protein response upregulates chaperones and improves the folding capacity of

endoplasmic reticulum. This applies to misfolded HLA B 27, evoking a stress response and in turn an inflammatory reaction also.

ROLE OF HLA B27 IN THE PATHOGENENSIS OF REACTIVE ARTHRITIS

HLA-B27 is composed of 25 glycoproteins (2701-2725).It belongs to MHC Class I molecule, the function of which is antigenic presentation to CD 8+ cytotoxic T cells. HLA B27 has the strongest genetic association with reactive arthritis .The prevalence of reactive arthritis is five times more in patients with HLA B 27 positivity. After the role of HLA B27 has been identified in Ankylosing spondylitis, its role in Reactive arthritis has also been studied extensively. Published data analysis from Gambia suggested that not all subtypes of HLA B27 predispose to spondyloarthropathy. HLA-B2703 is not associated with any of the spondyloarthropathies.

HLA-B2705 subtype was associated with Ankylosing spondylitis and reactive arthritis in the European population. HLA-B2706, found in Thailand, has not been described in association with AS, but this again may be due to any other reason as the population is not susceptible for reactive arthritis. T cell receptor and other co-transporters have not been identified in the pathogenesis of reactive arthritis. Apart from HLA B27, MHC class II allele could also be associated. Though there are various explanations for association of HLA B27, none has been universally accepted. In AS, more than 90% of the patients are HLA B27 positive, whereas the proportion is not so high in reactive arthritis.

The frequency of HLA B27 positivity is high in hospital admissions with reactive arthritis suggesting the fact that its association increases the disease severity and chronicity rather than being an inciting feature itself. Its positivity is also associated with iritis, sacroilitis and enthesitis .Inman et al suggested that HLAB27 positive cell lines are resistant to invasion by Salmonella and Yersinia, hence acute synovitis is rare.

The most popular theory associating reactive arthritis with HLA B27 is the arthritogenic peptide theory. Accordingly, HLA B27 which is expressed in MHC I cells, presents an arthritis inducing peptide to CD8+ cytotoxic T cells. The peptide is usually derived from the infecting bacterium and in chronic cases this may be incited by an autoantigen. Bowness identified 60 peptides associated with Chlamydia which will bind HLA B27 and simulate an arthritic attack, one of which is HSP 70(heat shock protein)[55]. Marker et al has identified bacteria specific, HLA-B27 restricted CD8+ T cell clones from the synovial fluid of patients with enteric reactive arthritis. [56].

Mouse models developed by Hammer gave us newer insights on the arthritogenic peptide theory in which, neither mouse in pathogen free environment failed to develop arthritis even with HLA B27 positivity[57] nor do nude mice without T cells, suggesting the need for T cells in the pathogenesis of reactive arthritis. Transgenic mice for the human HLAB27 and human B2 microglobulin genes, develop arthritis, gut inflammation, epididymitis, and skin lesions which strongly resembles spondyloarthropathy of humans. However a high copy of B27 gene is needed to bring in those

symptoms seen in human Spondyloarthropathy. Apart from the above theory, HLA B27 invokes an inflammatory response by the following process also.

Heavy chains of HLA-B27 have an unpaired cysteine at position 67 in the B pocket of the peptide binding groove which leads to the formation of heterodimers and homodimers, which are recognised by NK cells and T cells. This unusual dimer stimulates $CD4^+$ T cell when bound by peptides. Transgenic mice develop arthritis only when B2 microglobulin is lacking since its presence inhibits HLA B27 expression.

HeLa cells transfected with HLA-B27 respond to in vitro bacterial invasion whereas controls don't. HLA B27 improves bacterial survival by alteration in protein folding which when done in endoplasmic reticulum is slower. Protein misfolding is also common resulting in formation of proinflammatory cytokines and activation of Nuclear Factor kappa B.

Presence of HLA B 27 reduces the ability of a cell to eliminate the infected macrophages normally. This results in prolonging the cellular survival of pathogens prolonging the inflammatory incitation and signals. Studies show that adhesion molecules of Yersinia and Salmonella use HLA-B27 as a ligand to attach to cells of the synovial environment.

Summarising the role of HLA B27

1) Binds to an antigenic (self) peptide

2) Unfolded Protein Response

3) Homodimer formation resulting in recognition by NK cell receptors

4) Altered intracellular killing in certain infections, suggesting that infection or immune response may act as a trigger.

HLA B27 may influence the human microbiome. Change in microbiome predisposes to AS. Bacteria implicated in causing reactive arthritis are not often cultured nor demonstrated in synovial samples. However bacterial products like lipopolysacchrides are found in the affected joints. They are highly antigenic and trigger an inflammatory reaction resulting in arthritis. Lipopolysacchrides can activate tumour necrosis factor α, which has been known to be the major cytokine in reactive arthritis. Genetic polymorphisms of TNF α can itself trigger a spondyloarthritis.[585,9] TNF α production is controlled by Nuclear Factor kappa B and Mitogen Activated Protein Kinases. HLA B27 affected cell lines reduces the inhibition of NFkappa B and thereby increases the TNF α production.[60]

NON-ANTIGEN-PRESENTING EFFECTS OF HLAB27

Apart from the above described antigen presenting models of HLA B 27 affected cell lines there is evidence suggesting a role of non antigenic presenting effects also, in that it induces altered inflammatory response. It was shown in an experimental mouse model that mice expressing HLA B27 positivity lacking B2 microglobulins developed arthritis. Therefore it was said that rather than presence of HLA B27 HC dimers, absence of β2 microglobulin results in developing arthritic symptoms after an initial trigger.

ROLE OF AUTO ANTIGENS

Once reactive arthritis becomes chronic and persistent the pathogenesis shifts from an infectious process to an autoimmune process. As like in

ankylosing spondylitis, whether autoantigens like collagen II or proteoglycans play a role has to be further explored.

HLA B27 AND SALMONELLA INFECTIONS

Patients with reactive arthritis due to a preceding Salmonella infection have elevated Immunoglobulin IgM, IgG and IgA concentrations when compared to people without joint symptoms after the infection.[61,62] These immunoglobulins last longer and are often persistent. In patients with Yersinia infection IgA levels are persistently elevated suggesting that the antigenic stimulation is from an enteric source. Antigenic products of the infective organism stay in white blood cells for many years after an initial infection[63]. This phenomenon is often observed in patients with HLA B 27 positivity.

The bacteria involved in reactive arthritis are capable of surviving intracellularly. HLA B27 has been studied to have a role in modulation of intracellular survival of pathogens. Monocytes and macrophages form the first line of defence against Salmonella, However HLA B27 affected monocytic cells and fibroblast cells showed reduced elimination of Salmonella after the initial infection. But the intestinal survival of Salmonella is not affected by HLA B27 positivity. Cells expressing HLA B27 will allow the intracellular replication of Salmonella.[64]

HLA B27 does not influence the pathogenesis of Chlamydial ReA. It neither influences the invasion nor replication of Chlamydia trachomatis infection in cell line.

CYTOKINES IN REACTIVE ARTHRITIS

Analysis of cytokine profile in ReA states that the TH1 cytokines such as TNF α and IFN-γ are low in patients with acute ReA. Normally TH1 cytokines mediate a protective against intracellular pathogens. Elevated IL12 level leads to the suppression of TNFα and IFNγ. This imbalance resulting in elevated TH 2 cytokines leads to decreased bacterial clearance and disease persistence. However enhanced production of TNF α and IFN-γ is observed in chonic ReA.

IL 17 IN REACTIVE ARTHRITIS

Th17, a third cell line in the subset of helper T cells plays an important role in many autoimmune and inflammatory diseases, of which most studies are in the group of spondyloarthritis. It also plays a pathogenetic role in primary Sjogren's syndrome, Multiple sclerosis and Rheumatoid arthritis.[65,66] In mouse cell lines Th17 cells depend on transforming growth factor β1 and Interleukin 6 for their differentiation. In humans it depends on Interleukin 1 and interleukin 6.[67] An expansion of Th17 cells need IL 23 which is common both to mouse and human cell lines. IL-23, a heterodimeric cytokine is made of a unique p19 subunit which is linked to a common p40 chain.[67] Importantly p40 is associated with a p35 chain and forms IL-12, a cytokine which plays a role in Th1 differentiaition.[68] Yersinia infected mice with $p40^{5}$developed acute reactive arthritis whereas ones with $TNFRp55^{-}$ developed chronic arthritis.[69] A study from India has demonstrated an increased level of various cytokines(1L 17,IL 6, IFN γand TGF β) in the plasma and in synovial fluids of patients with reactive arthritis.[70] Recent data suggest that IL 17 plays an important role in the spectrum of spondyloarthritis.[71]

CLINICAL FEATURES

Reactive arthritis occur in the second to fourth decades of life. The male to female ratio following urogenital infection is 9:1 and 1:1 following enteric infection[72,73]. It has articular, enthesopathic and extraarticular features. It not only affects the joints but also has systemic features. Gastrointestinal symptoms appear before 1 month in postdysenteric ReA and urogenital symptoms appear 1-6 weeks before articular manifestations. It has both acute symptoms (6 months) and chronic symptoms (>6months).

ARTICULAR MANIFESTATION

It includes both axial and peripheral joints.

Peripheral joints are the most commonly affected joints. It presents as an asymmetric non erosive oligoarthritis. Sensitivity and specificity of oligoarthritis distribution is 44% and 95%.Knee, ankle and hip joints are commonly involved. Elbows, shoulders and wrist joints can also be involved. Polyarticular forms can also occur which include interphalangeal joints of toes, metatarsophalangeal joints and subtalar joints.[74,75] Axial joints frequently affected are the sacroiliac joints and lumbar spine. Thoracic and cervical spine are affected in chronic reactive arthritis. Sternoclavicular and costosternal joints can also be affected. Frequency of inflammatory back pain due to sacroilitis is 14-49% (with sensitivity and specificity of 71% and 77% respectively), spondylitis 12-26% and ligamentous insertion inflammation of ischial tuberosity in 15-30%.Chronic recurrent arthritis occurs in 15-30% of cases and occurs most commonly in Chlamydial infection.Dactylitis occur in 16% of cases of ReA and is very distinct with a specificity of 99%.[76,77]

ENTHESOPATHIC SYNDROME

Enthesitis is very specific for reactive arthritis. Commonly involved sites are the plantar fascia and Achilles tendon. Frequency of enthesitis is about 30%.

MUCOCUTANEOUS SYNDROME

Keratoderma blenorrhagicum or palmoplantar pustulosis is the typical skin lesion of reactive arthritis which commonly occurs over the palms and soles and the frequency is 5-30%.[78]Circinate balanitis which occurs over the glans penis is seen in 4-20% of cases. Oral ulcers over the gingivae, hard palate, cheeks and tongue occur in 5-10% of patients.6-12% of patients may have nail dystrophy. Yersinia Induced reactive arthritis can have erythema nodosum in 15% of cases.[79] Erythema Nodosum is not associated with the presence of HLA-B27.

OCULAR MANIFESTATIONS

Conjunctivitis occurs in 30% of patients with Shigella, Salmonella and Campylobacter infections, 35% of Chlamydial infections and 10% of Yersinial infections. It can be unilateral or bilateral with a mucopurulent discharge. Its course is often transient and mild[80]. Acute anterior uveitis occurs in 5% of patients. Among these 50% can have HLA-B27 positivity.It is usually acute, painful and unilateral.[81,82]. Keratitis, scleritis, corneal ulceration are other less common manifestations[83]. Glaucoma, posterior synechia, cystoid macular edema and cataract can occur due to chronic inflammation[84].

CARDIAC MANIFESTATIONS

Conduction disturbances occur in 5 -14% of patients with acute ReA.[85] It is related to HLA-B27 presence. Aortic valvular incompetence occurs in the chronic phase.[86]

Renal abnormalities include Haematuria, Pyuria and Proteinuria.

Genitourinary symptoms which occur commonly with Chlamydial infections include Prostatitis which occur in 80% of patients, cervicitis, haemorrhagic cystitis and urethritis.

LABORATORY INVESTIGATIONS

Diagnosis of Reactive arthritis is made mainly on the clinical symptoms since there is no definite diagnostic criteria. Reactive arthritis follows two different disease courses. The first one is with an acute course followed by resolution of symptoms gradually. During this phase patients can have elevated ESR and CRP. Other Inflammatory markers such as leukocytosis and thrombocytosis may also be found. Some patients may have a chronic course. They often have normal acute phase reactants. Aseptic pyuria may be seen in urinalysis. Rheumatoid factor and antinuclear antibodies are negative.[87]

SEROLOGY FOR CHLAMYDIA INFECTIONS

Chlamydia induced reactive arthritis is based on the evidence of preceding urethral or cervical infections[88].30-50% of cases of posturethritic ReA,69% of patients who had prior urogenital inflammation have evidence of chlamydial infections[89]. Microimmunofluoresence is the gold standard

serological test. Here the elementary bodies are fixed to glass slides to which specific immunoglobins are added,to detect IgG and IgA antibodies. EB bodies should be treated to remove lipopolysaccharides. It is costly and not suitable for testing large number of samples, but may be useful to discriminate between different serovars. Chlamydial culture is the gold standard test for diagnosis.[90]Its sensitivity is 70-80%. Antigen-detection tests such as direct fluorescent-antibody assay, enzyme Immunoassay, Immunoblotting, and Nonamplified nucleic acid hybridization are used in the diagnosis of chlamydial infection.Newer technologies such as Polymerase Chain Reaction, Ligase chain reaction, Hybrid capture system, Transcription-mediated amplification of RNA, Strand displacement assay may also help in diagnosis. They are of low expense, sensitive and timely available over culture[91,92]. Nucleic Acid amplification tests have a sensitivity and specificity of 82-100%.Immunofluoresence and Direct fluorescent antibody assay has sensitivity of 70-80% and specificity of 96-100%.Enzyme immunoassay based on peptides detecting IgG and IgA in serum samples of reactive arthritis have a sensitivity and specificity of 74% and 84% respectively.[93]Antibodies should combine tests for IgG, IgM and IgA antibodies. Antigens commonly used in the detection are MOMP and LPS.ELISA using these synthetic peptides are also useful with a sensitivity and specificity of 78% and 73% respectively. Determination of synovial fluid antiMOMP IgG and IgA are more specific with specificity around 80% and 90% respectively.[94] Differentiation between Chlamydia species is essential because of high prevalence of cross reactivity with Chlamydia pneumonia species.

DIAGNOSIS OF ENTERIC REACTIVE ARTHRITIS

For diagnosing enteric related reactive arthritis with preceding enteritis, stool culture appears to be useful. Yersinia and Salmonella are detected in stool culture only in 9% of patients who have preceding diarrhoea in 4 weeks. [95]

SEROLOGY FOR YESINIA INFECTION

In Yersinia induced reactive arthritis stool cultures are rarely positive, since the culture requires a special technique. Regarding the serological diagnosis both ELISA and EIA are used. Indirect Haemagglutination test was the first test used to detect Yersinial infections. Yersinia adhesion protein (YAD), YIL, and invasins are the adhesion molecules involved in the pathogenesis. Antibodies against these antigens increase in acute infections. YAD of enterocolitica and pseudotuberculosis are implicated in ReA. Most data are with EIA using either LPS or OMP as the antigens.[96] IgG and IgA isotopes are detected in patients with chonic reactive arthritis and IgM, IgG and IgA in patients with acute ReA. IgA antibodies persist for 14 to 16 months in patients with arthritis and in those without arthritis for about 5 months. IgG antibodies also persist longer but not as IgA[97].

SEROLOGY FOR SALMONELLA INFECTIONS

Salmonella antibodies can be demonstrated by both agglutination and ELISA. Initially used was the agglutination test where the sera of typhoid patients agglutinated with formalin fixed host bacterium. O antigens and flagella were used. These tests underwent modification and currently sera from typhoid patients are mixed with killed salmonella typhi. If antibodies are

present agglutination occurs. Anti IgO antibodies appear first, later by antiIgH in chronic phase. AntiIgV antibodies detect carrier status. Widal agglutination detects IgM antibodies and its sensitivity is low. ELISA is specific detecting different Immunoglobin classes and is preferable to agglutination. Sensitivity of ELISA is approximately 92% for detecting salmonella antibodies in both acute and late infections. These antibodies persist for 9- 14 months in patients with ReA than with enterocolitis which is about 4 months. In Salmonellosis response is seen in all classes of Immunoglobins compared to Yersiniae which has predominantly IgA class.

Shigella flexerni, Shigellla sonnei, Shigella dysentriae are the species identified in the etiology of reactive arthritis. It is diagnosed on the basis of stool culture. No specific serological test is available for diagnosis of Shigella. More advanced luminex technologies are used in the diagnosis of invasive plasmid antigens and the lipopolysaccharides of Shigella species[98].

Campylobacter jejuni infections can be detected by Immunofluorescence, Complement fixation and Agglutination techniques. Enzyme immunoassays used to detect antibodies to antigens such as LPS have sensitivity of 71%,60%,80% to IgG, IgA and IgM antibodies and specificity of 90%.Recently new antigens such as flagellin, Major Outer Membrane protein and periplasmic associated membrane protein can be detected by ELISA.

POLYMERASE CHAIN REACTION

Polymerase chain reaction is used in the detection of bacterial species DNA .However synovial membrane biopsy is more useful than PCR in the detection of bacterial DNA. Chlamydia is found to be positive in 65% of patients with reactive arthritis by PCR. Chlamydial DNA is also found to be positive in 21% of patients with RA, 35% of patients with OA and healthy subjects.[99]These results showing the presence of chlamydial DNA in patients other than ReA limits the usefulness of detecting organisms by PCR.There is no role of PCR in detecting Salmonella or Yersinia.

TREATMENT

There is no specific treatment for ReA. Management of ReA aims at the control of pain and prevention of joint destruction and preservation of joint function.

PHARMACOLOGIAL THERAPY

NSAIDS: NSAIDS both COX1 and COX2 Inhibitors play a key role in the management of ReA. They are helpful for articular symptoms. They are not useful in extraarticular symptoms.[100-102]NSAIDS may prevent radiological progression in other types of SPA but its role in chronic ReA arthritis is not known. No one NSAID is superior over another. NSAIDS are believed to potentiate the antiproteolytic potential of antibiotics and the facilitate entry of antibiotics to the site of inflammation.

STEROIDS

They are helpful for peripheral arthritis and not useful in axial arthritis. Intraarticular steroids may be helpful in monoarthritis. Topical steroids are

helpful in extra-articular manifestations such as iritis, balanitis and Keratoderma blenorrhagicum. Systemic steroids are indicated in severe polyathritis and atrio-ventriular conduction disturbances[103].

ANTIBIOTICS

Since reactive arthritis is triggered by bacteria the role of antibiotics in the treatment of ReA has been suggested. Eradication of pathogen may prevent the subsequent arthritis[104] and shorten its course[105].Antibiotics usage may be helpful in ReA due to urogenital infection than gastrointestinal infections[106].

ANTIBIOTICS IN UROGENITAL ARTHRITIS

Studies have shown that prompt treatment of urogenital infections reduces relapses of reactive arthritis. A study performed in Greenland which has a high frequency of HLA B27 and ReA showed that the incidence of postvenereal reactive arthritis significantly reduced from 37% in untreated patients to 10% after treatment with Erythromycin or Tetracycline[107].In Chlamydia induced ReA, treatment with Lymecycline for 3 months reduced the duration of arthritis in the treatment group to 15 weeks compared to placebo group which was around 39 weeks[108]. But long term treatment did not change the course [109,110].Clinical parameters also improved with the treatment of minocycline[111]. Sieper et al showed that Ciprofloxacin was superior to placebo in Chlamydia induced reactive arthritis. Chlamydia induced urethritis can be treated with either Doxycyline 100mg twice a day or Azithromycin 1 gm orally as a single dose or Ofloxacin 300mg twice daily. Sexual partner of the patient should also be treated .Acute ReA due to Chlamydia can be treated

with Tetracycline or Ciprofloxacin for 4 to 12 weeks. Studies have also shown beneficial effect of combination therapy with Azithromycin and Rifampicin[112].A study in 2004 showed that combination therapy with Rifampin and Doxycycline showed significant improvement than with single therapy of Doxycycline in Chlamydia induced reactive arthritis[113].

ANTIBIOTICS IN ENTEROARTHRITIS

Several reports have shown that antibiotics have no effect in the development of ReA due to gastrointestinal infections.[114] Antibiotic trials in Salmonella enteric serovars using Ciprofloxacin, Ofloxacin, Doxycycline and Cotrimoxazole showed no benefit[115,116]. In a non-blinded prospective study of patients with enteroarthritis secondary to agents such as Salmonella, Yersinia, Enterocolitica or Campylobacter conducted by Fryden et al showed that treatment with or without antibiotics showed no difference in duration of arthritis, involvement of the number of joints and the degree of inflammation.[117] Treatment with antibiotics either with Ciprofloxacin or Tetracycline for 3 months in patients with reactive arthritis secondary to enterobacterial infection did not show beneficial effects over placebo in long term controlled studies.[118-121]in the early stages of ReA. However a study shown by Yli-kerttula et al showed that in patients treated with ReA in the acute phase with Ciprofloxacin for 3 months when followed after 4 to 7 years had better outcome than the placebo group[122].

SECOND LINE THERAPIES

As discussed above NSAIDS have shown benefit only in few patients, hence the usage of DMARD therapy has been discussed.[123]

SULFASALAZINE

Sulfasalazine is the best studied DMARD.A prospective placebo controlled trial of 134 patients demonstrated improvement in 62% of participants compared with 47% of placebo controlled participants[124].Sulfasalazine exerts beneficial effect by reducing the mucosal permeability to antigens.[125] It also has antibacterial action[126].However there was no significant improvement in clinical parameters such as tender joint or swollen joint count. As 67% of patients with reactive arthritis have underlying inflammatory bowel disease, this might be a therapeutic option in patients with postenteric variety[127].

METHOTREXATE

Though Methotrexate has been used widely there are no controlled studies to show its beneficial effects.[128,129]

AZATHIOPRINE

Azathioprine has been found to be beneficial in peripheral arthritis at a dose of 1to 2 mg/kg in few placebo controlled studies [130,131].

Other DMARDS which have been tried are Cyclosporine, Leflunomide, Cyclophosphamide, 6 Mercaptopurine and Levamisole however there are no controlled studies[132].

TUMOR NECROSIS FACTOR ANTAGONIST

TNF-α antagonists have been shown to have great success in the treatment of spondyloarthropathy. Its role in reactive arthritis has many theoretical concerns. Reactive arthritis is TH_2 mediated disease and TNFα is

found to be low [133,134]. ReA is most commonly trigerred by Chlamydia[135,165] and persistent Ct and Cpn levels are inversely associated with TNF levels[137,138]..But inversely patient with reactive arthritis are found to have high TNF levels and hence TNF α antagonist are useful.[139].There are only case reports and open label studies which have analysed the role of TNF antagonists but no controlled studies are available[140.141].However treatment of reactive arthritis induced by Chlamydia had led to the increase in bacterial load when compared to pretreatment level. This has been demonstrated by synovial biopsy in an open label trial and hence it may not be useful in chronic Chlamydia induced arthritis. But it may be useful in postenteric variant of reactive arthritis since there is no persistence of viable microorganism. However the role of TNF antagonist usage in reactive arthritis is unanswered.

PROGNOSTIC FACTORS

Prognosis of ReA is affected by the nature of triggering infection, gender of the patient and presence of HLAB27 and the occurrence of recurrent symptoms.[142] Persistence of inflammatory foci in the gut and recurrent urogenital infection lead to the progression of chronic reactive arthritis to SPA.[143].HLAB27 is associated with severe disease, extra-articular manifestations and higher frequency of sacroilitis.[144].Male sex and family history of SPA are adverse factors.

COURSE

Reactive arthritis follows various courses .It can be self limiting and short, recurrent or continuous or unremitting .The duration of acute arthritis is 6

months. Arthritis persisting after 6 months is said to have a chronic course.[145].Duration of arthritis is about 3-5 months on an average in Finnish study. Enthesitis, balanitis, and skin lesions tend to persist even after the inflammation in joints have subsided .75% of patients go in for complete remission at the end of 2nd year when all symptoms are taken into account.15-30% of patients may have a chronic course[146].

PROGNOSIS

Prognosis of reactive arthritis is good and the disease duration generally varies from days to weeks. About 15-30% of patients develop chronic reactive arthritis either peripheral or axial arthritis. Reactive arthritis triggered by Shigella , Salmonella and Yersinia infections are best known. Recurrent attacks are frequent in these patients[147,148].16% patients developed reactive arthritis after a mean of 11years in a Finnish study[138].Similiarly in a study with Yersinia induced ReA about one third of the patients developed sacroilitis[149].In a 20 year follow up study in patients with Shigella induced arthritis 32/100 had Ankylosing spondylitis[150].HLAB27 patients developed recurrent or chronic symptoms. Prognosis in HLAB27 positive patients is less favourable[151].

MATERIALS AND METHODS

PLACE OF STUDY

This cross sectional study was conducted in the Department of Rheumatology, Madras Medical college and Rajiv Gandhi government General Hospital, Chennai.

STUDY PERIOD AND DESIGN

This study was done for a period of one year from January 2013 to January 2014.

ETHICAL CONSIDERATION

Approval was obtained from the institutional ethical committee before the commencement of the study. Informed consent was obtained from the study population. All patients satisfying the inclusion criteria were documented. Patients were interviewed by structured questionnaire.

STUDY POPULATION

Sample size

After analyzing 100 patients who attended the Rheumatology OPD with predominant lower limb arthritis,46 patients who satisfied the diagnostic criteria for Reactive arthritis were chosen for the study.

Inclusion criteria

- Patients satisfying the diagnostic criteria for Reactive arthritis

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Exclusion criteria

- ❖ JIA
- ❖ Septic arthritis
- ❖ Inflammatory polyarthritis of known connective tissue disorders such as Ankylosing spondylitis, Rheumatoid arthritis and Psoriatic arthritis.

STUDY

After thorough clinical examination all these patients underwent routine laboratory investigations such as Haemogram, Liver function tests and Renal function tests. Ultrasound was done in these patients to confirm the arthritis and enthesitis.CT pelvis was done at the onset and after 1 year to look for the radiological evidence of sacroilitis.

All patients underwent ECHO and Opthalmological examination. Dermatogical consultation was obtained whenever necessary.

Urine culture was done in patients with dysuric symptoms.

URINE CULTURE

Urine culture is done by inoculating a loopful of urine on blood agar and Macconkey agar. The inoculated plates are incubated aerobically at 35-37^{o}c overnight.

Colonies that are normally found on blood agar and MacConkey agar are

a. Escherichia coli
b. Proteus species
c. Pseudomonas aeruginosa

d. Klebsiella strains

e. Staphylococcus aureus

f. Enterococci

Additionally to detect S.typhi 7-10ml of urine is centrifuged in a test tube at high speed for 5-10minutes , the supernatant fluid is removed and the sediment transfered to selenite enrichment broth at 35-37ºC, then subcultured on the plate and incubated at 35-37ºC for 24 hours.

After 24 hours look for the colonies. Most urinary infections produce growth of single type of organism. Count the approximate no of colonies. Estimate the number of bacteria (colony forming unit /ml of urine)

A bacterial count of 100000/ml or more indicates a urinary infection.

Urine PCR was used to detect Chlamydia species in few patients due to cost constraints.

STOOL CULTURE

Stool culture was done in patients with history of diarrhoea. In our set up we have culture medium to identify only Salmonella and Shigella. Campylobacter and Yersinia species could not be identified.

A loopful of the emulsified faeces or fluid specimen transported in special medium such as Cary-blair medium, is inoculated on XLD agar and several loopful into selenite F enrichment broth. The XLD agar pate is incubated aerobically at 35-37ºC overnight.

XLD agar

This selective medium is recommended for the isolation of Salmonella and Shigella from the faecal specimens. It contains the indicator phenol red which is red at alkaline PH and yellow at an acid PH.

SELENITE F BROTH

This is an enrichment and selective broth for salmonella. It inhibits the growth of colifoms.

After overnight incubation in XLD aga,Shigella form red colonies because they do not ferment xylose, lactose or sucrose.

Salmonella form red colonies with black centre except S.Typhimurium.

Escherichia coli, Enterobacter species produce yellow colonies.

After identification of suspected Salmonella and Shigella species we have to perform lysine decarboxylase test and Triple sugar iron test

Shigella –LDC negative

Salmonella –LDC positive except S.Paratyphi.

Then confirm with serological identification by slide agglutination technique by adding appropriate antiserum.

Patients also underwent serological test for identification of Brucella (agglutination test) and salmonella typhi and Paratyphi. (widal agglutination test).

CRP METHODOLOGY

This test is based on the immunological reaction between CRP as an antigen and latex particles coated with monospecific anti-human CRP. It is a qualitative slide test. A drop of test serum is placed within the circle area on the special slide provided and a drop of the latex CRP reagent is added. It

then mixed well and rocked gently in a to and fro motion . After 2 minutes agglutination is looked for.

HLA B27 METHODOLOGY

HLA B27 was done for all the patients. In our lab the methodology used is complement dependent microlymphocytotoxicity assay.

PRINCIPAL OF THE ASSAY

The antibodies to HLA antigens used in this serological assay are known as allo-antisera, which are obtained from humans who had been sensitized to HLA molecules ,through previous pregnancy or previous transplantation or multiple transfusions of blood. Monoclonal antibodies produced through hybridoma techniques are also used. The cells used for the test are the peripheral blood mononuclear cells. Hence when specific antisera are added to lymphocytes, antigen-antibody reaction take place. Subsequently when complement is added, complement will be utilized wherever antigen antibody reaction has taken place, resulting in complement mediated death of the cells bearing specific antigen.

SAMPLE

Heparinised blood is collected .Approximately 10 ml o blood sample is collected in 100microliter of heparin. (10,000units/ml)

The blood and heparin are mixed thoroughly and gently.

The testing should be done on the same day of collection.

REQUIREMENTS

Terasaki plates (60 or 72 welled plate)

Ficoll–hypaque (lymphocyte separation medium) .Graduated 10 ml centrifuge tubes.

Pasteur pipettes,Phosphate buffered saline(PBS),Alloantisera of different specificity.Rabbit complement ,Eosin yellow 4% solution.

Light liquid paraffin,Hamilton syringes

Repeating dispenser with 50 divisions

PROCEDURE

STEP-1: Separation of peripheral blood mononuclear cells by differential centrifugation.

The heparinised blood is diluted 1:1 with PBS.2ml of lymphocyte separation medium is taken in a centrifuge tube and about 8 ml of diluted blood is layered over it by adding the blood along the sides of the tube.

The tube is then centrifuged for 30 minutes at 2000rpm.

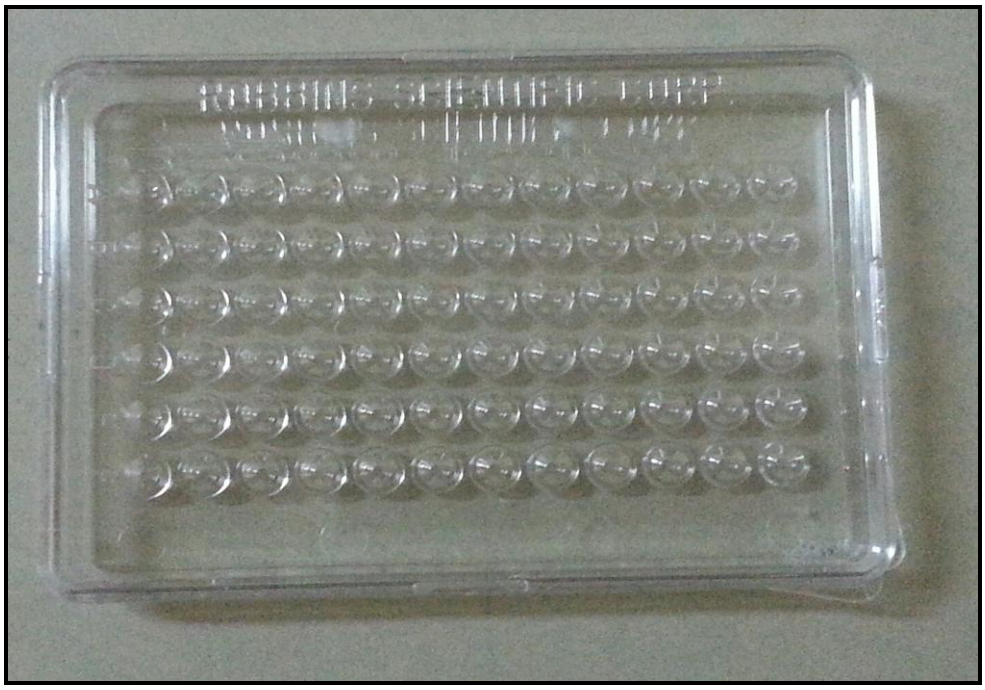
At the end of centrifugation, the RBCS get settled at the bottom of tube, while peripheral blood mononuclear cells are seen as a white band at the interface of lymphocyte separation medium and plasma.

The cells are carefully harvested with help of pasteur pipettes and transferred to test tubes.

The cells are then washed 2-3 times in PBS by centrifuging at 1000rpm to get rid of platelets.

The total number of cells are adjusted to 2 million cells per ml of cell suspension by counting the cells in the Neubaur chamber.

FIGURE-1 TERASAKI PLATE



PLATING

The Terasaki plates are coated with 1µl of different HLA allo-antisera. 1µl of cell suspension is added to antisera in the wells of Terasaki plates.The plate is incubated for 30 minutes at room temperature. One plate is utilized for each patient. 5µl of fresh complement is then added to all wells .The plate is incubated for 1 hour at room temperature.8µl of eosin yellow is added to all the wells and the reading is taken under inverted phase contrast microscope.

READING AND INTERPRETATION

The percentage of dead cells (cells which have taken up the dye and appear bigger, flatter and darker) are counted in each well.

In the well coated with positive control ,100% dead cells should be present. This assures the potency of complement

In negative control well no dead cells should appear. This assures non-toxicity of reagents and smooth handling of cells.

The percentage of dead cells found in the HLA B27 well are interpretated as follows

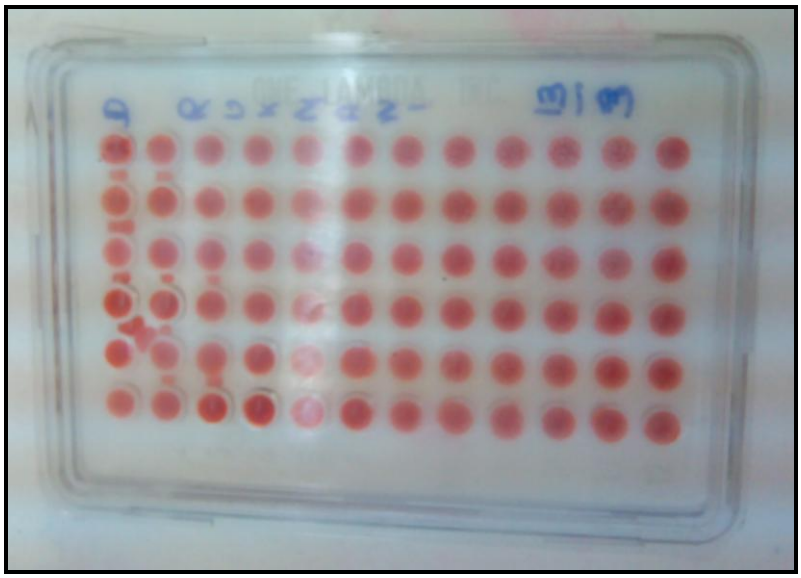
100% dead cells –strong positive

More than 50% dead cells –positive

20-50% dead cells –weak positive

Less than 20% dead cells –negative.

FIGURE-2 HLA B27 TYPING



IL 17 A METHODOLOGY

IL17A assay is done on these patients by ELISA

STEP 1- Addition

Preparation of Standard

Standard vials must be reconstituted with volume of standard diluent. This gives a stock solution of 100pg/ml of IL17A. Serial dilutions of the standard are made directly in the assay plate to provide the concentration range from 100 to 3.125pg/ml.A fresh standard curve should be produced for each new assay.

Immediately after reconstitution add 200 µl of reconstituted standard to wells A_1 to A_2 which provide the highest concentration standard at 100pg/ml.

Add 100µl of appropriate standard diluent to the remaining wells B_1 to B_2 .Continue this 1:1 dilution using 100µl from wells B_1 and B_2 through to wells F_1 to F_2 providing a serial diluted standard curve from 100pg/ml to 3.125pg/ml.Discard 100µl from the final well of the standard curve.

Step-2 Addition

Add 100µl of each, sample and zero in duplicate to appropriate number of wells.

Step-3: Incubation

Incubate at room temperature for 2 hours.

Step- 4: Incubation

Wash three times with the wash buffer.

Step-5: Addition

Add 50µl of diluted biotinylated anti-IL17A to all wells.

Step-6: Addition

Incubate at room temperature for 1hour.

Step-7: Wash

Repeat step 4

STEP-8: ADDITION

Add 100µl of streptavidine –HRP solution into all wells.

Step-9: Incubation

Incubate at room temperature for 30 minutes.

Step- 10: Wash

Repeat wash step 4

Step-11: Addition

Add 100µl of ready to use TMB substrate solution into all wells.

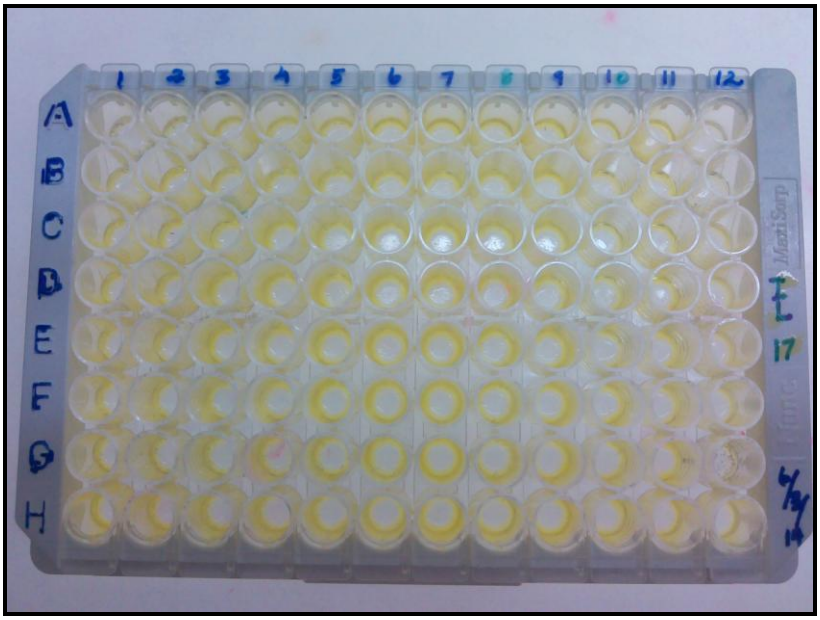
Step-12: Incubation

Incubate in the dark for 5-15 minutes at room temperature .Avoid direct exposure to sunlight.

Step-13: Addition

Add 100µl off H_2SO_4 stop reagent into all wells.Read the absorbance value of each well on spectrophotometer using 450 as primary wavelength and optionally 620nm as reference wavelength. Value above 3 is taken as positive.

Figure-3: IL 17A ELISA PLATES



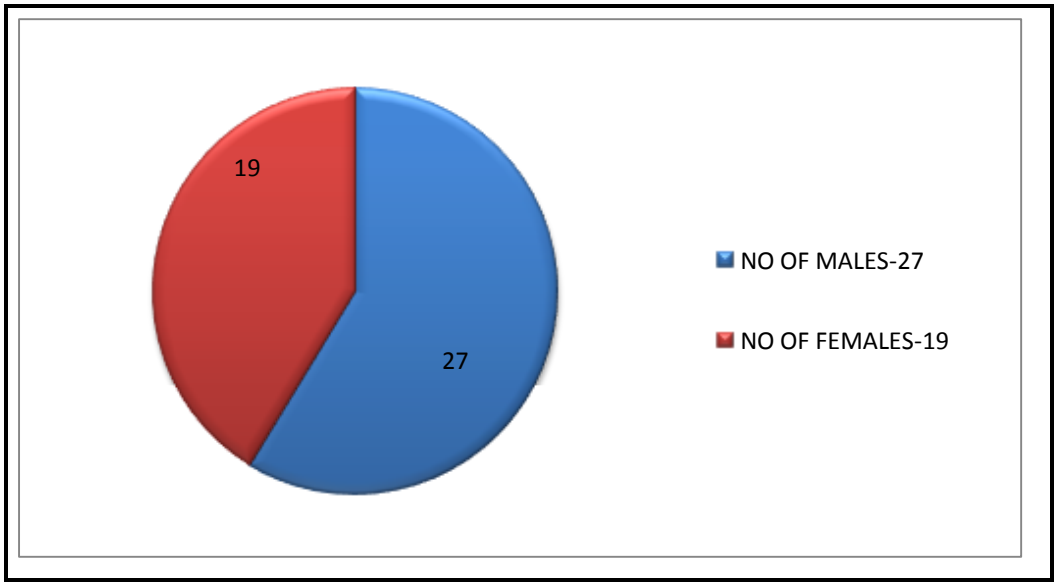
CALCULATION OF DAREA(Development of a disease activity index for the assesement of Reactive arthitis)

DAREA is computed by adding the Swollen joint count + Tender joint count + Global Health assessment + Patient's pain assessment + CRP(mg/dl).Patient's global assessment is taken on a 3 point scale 0=good, 1=fair, 2=poor.Pain assessment by 3 point visual analog scale 0=none, 1=moderate, 2=severe

Statistical Methods: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD and results on categorical measurements are presented in percentage. (%). Chi-square test has been used to find the significance of study parameters on categorical scale between two groups. Student 't' test has been used to determine the significance between two group means. All analyses were two tailed and $p < 0.05$ was considered significant. SPSS version 16.0 was used for data analysis.

RESULTS

Figure -4 Total no of Patients



Total no of patients studied were 46. Among them 58.7% were males and 41.3% were females.

Table -2: Sex and Outcome(SPA)

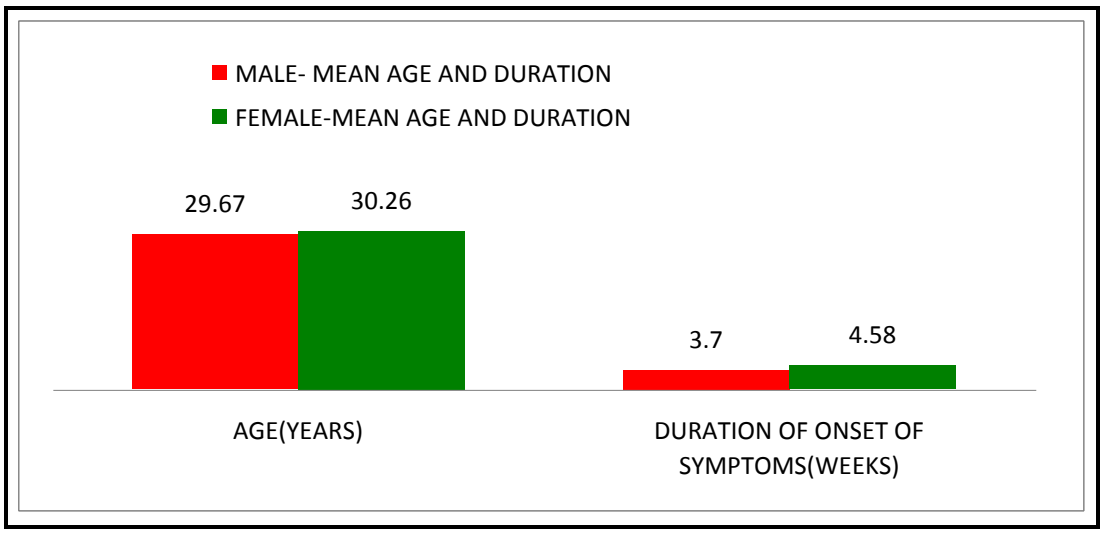
Sex		Outcome		Total
		SPA+	SPA-	
Male	Count	6	21	27
	% within sex	22.2%	77.8%	100.0%
Female	Count	5	14	19
	% within sex	26.3%	73.7%	100.0%
Total	Count	11	35	46
	% within sex	23.9%	76.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided) (P Value)	Exact Sig. (1-sided)
Pearson Chi-Square	.103a	1	.749		
Continuity Correction	.000	1	1.000		
Likelihood Ratio	.102	1	.749		
Fisher's Exact Test				**1.000**	.508
Linear-by-Linear Association	.100	1	.751		
No of Valid Cases	46				

Sex has no significant correlation with the outcome. P Value 1.0

Figure-5: Mean Age and Duration



Total mean age of the patients is 29.91 years and the mean duration is 4.07 weeks. Mean age among the males is 29.67years and their mean duration is 3.70 weeks. Mean age among the females is 30.26years and their mean duration is 4.58 weeks.

Figure -6: No of Patients with Gastrointestinal and Genitourinary Symptoms

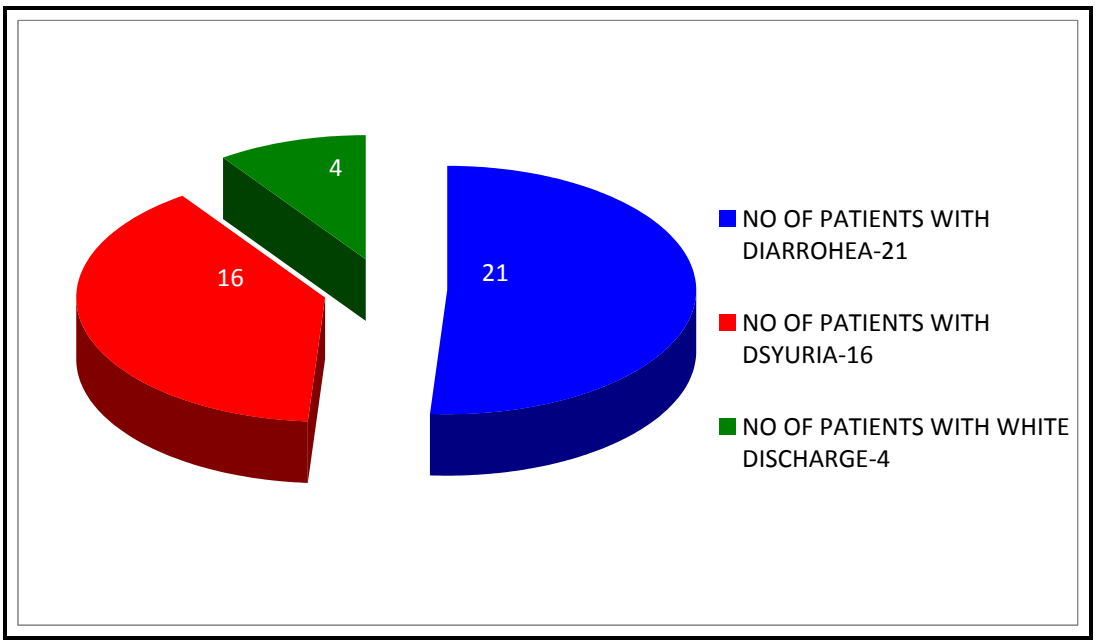


Table -3: GI Symptoms

Valid	Frequency	Percent	Valid Percent	Cumulative Percent
Diarrhoea	21	45.7	45.7	45.7
Nil	25	54.3	54.3	100.0
Total	46	100.0	100.0	

Table -4: Genitourinary Symptoms

Valid	Frequency	Percent	Valid Percent	Cumulative Percent
Dysuria/ White Discharge	20	43.5	43.5	43.5
Nil	26	56.5	56.5	100.0
Total	46	100.0	100.0	

Among the 46 patients 45.5% had diarrhea and 43.5% of patients had genitourinary symptoms such as dysuria and white discharge

Table -5: GI Symptoms and Outcome(SPA)

GI Symptoms		outcome		Total
		SPA+	SPA-	
Diarrhoea	Count	9	12	21
	% within GI SYMPTOMS	42.9%	57.1%	100.0%
Nil	Count	2	23	25
	% within GI SYMPTOMS	8.0%	92.0%	100.0%
Total	Count	11	35	46
	% within GI SYMPTOMS	23.9%	76.1%	100.0%

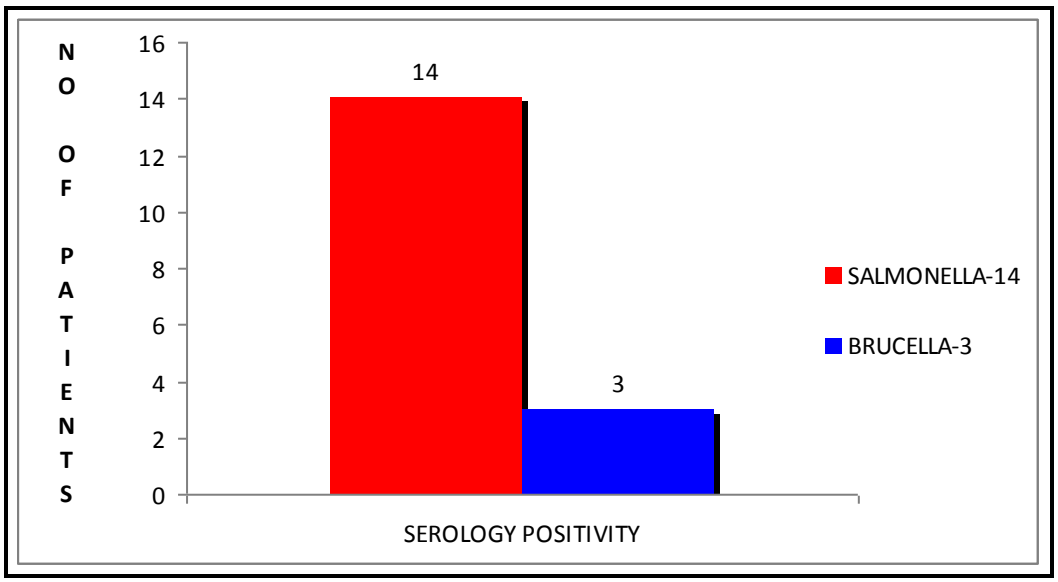
Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)(PValue)	Exact Sig. (1-sided)
Pearson Chi-Square	7.621a	1	.006		
Continuity Correction	5.826	1	.016		
Likelihood Ratio	7.986	1	.005		
Fisher's Exact Test				**.013**	.007
Linear-by-Linear Association	7.456	1	.006		
N of Valid Cases	46				

The proportion of SPA was significantly higher among the patients with Gastrointestinal symptoms. p value is.0.013.

Genitourinary symptoms had no statistical significance with the outcome (SPA).

Figure-7 No.of Patients with Serological Positivity



Total no of serology positive patients-37%.

Salmonella positivity was found in 30% of the patients.

Brucella positivity was found in 7% of the patients .

Table -6: Salmonella Positivity and SPA

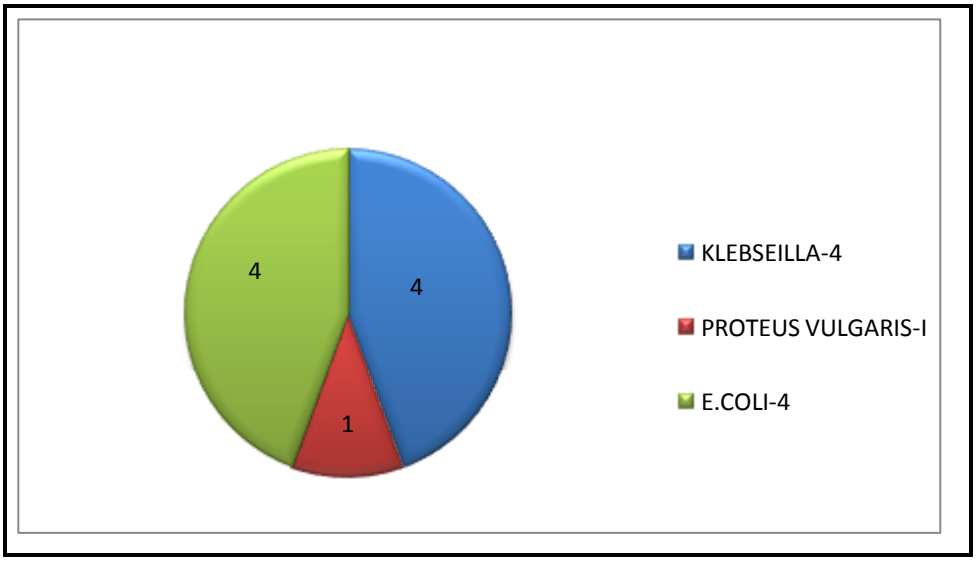
Salmonella		outcome		Total
		SPA+	SPA-	
Positive	Count	8	6	14
	% within salmonella	57.1%	42.9%	100.0%
Nil	Count	3	29	32
	% within salmonella	9.4%	90.6%	100.0%
Total	Count	11	35	46
	% within salmonella	23.9%	76.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)(p value)	Exact Sig. (1-sided)
Pearson Chi-Square	12.214a	1	.000		
Continuity Correction	9.729	1	.002		
Likelihood Ratio	11.573	1	.001		
Fisher's Exact Test				**.001**	.001
Linear-by-Linear Association	11.948	1	.001		
N of Valid Cases	46				

The proportion of SPA is significantly higher among the patients with salmonella positivity, P Value 0.001

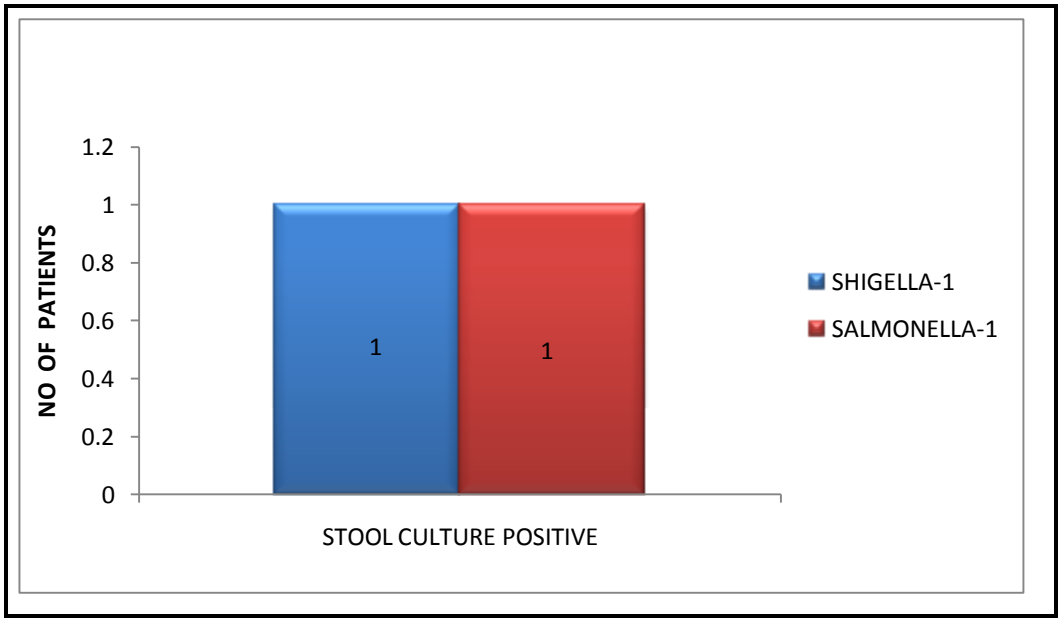
Figure-8: Urine Culture positivity



Urine culture was positive in 20% of the patients.

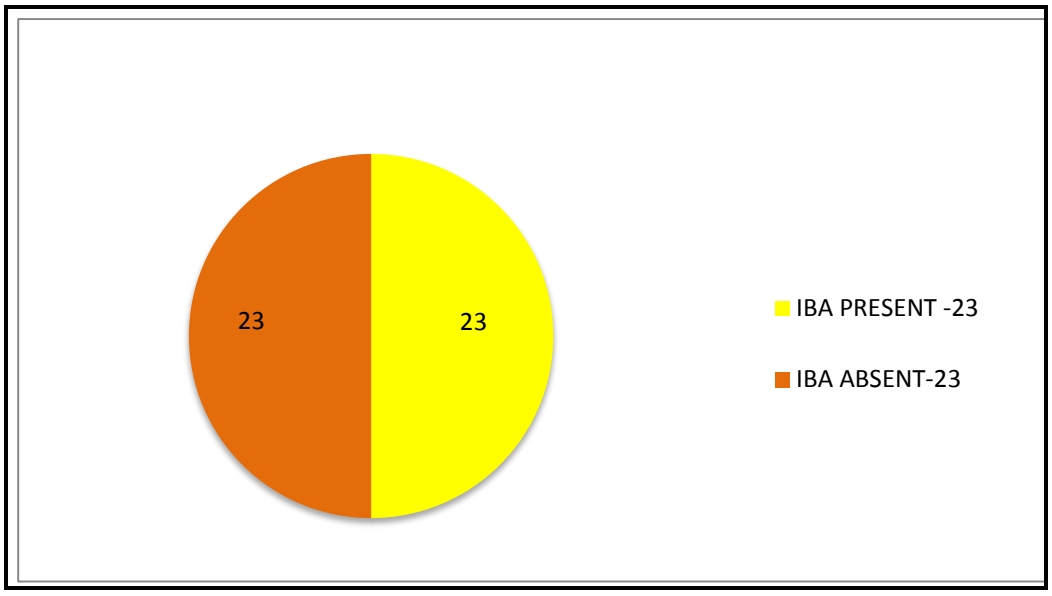
Chlamydia was identified by urine PCR in one person.

Figure-9 stool culture positivity



Stool culture was positive in 4% of the patients.

Figure -10 Inflammatory back pain



IBA was present in 50% of the patients

Table -7: IBA and SPA

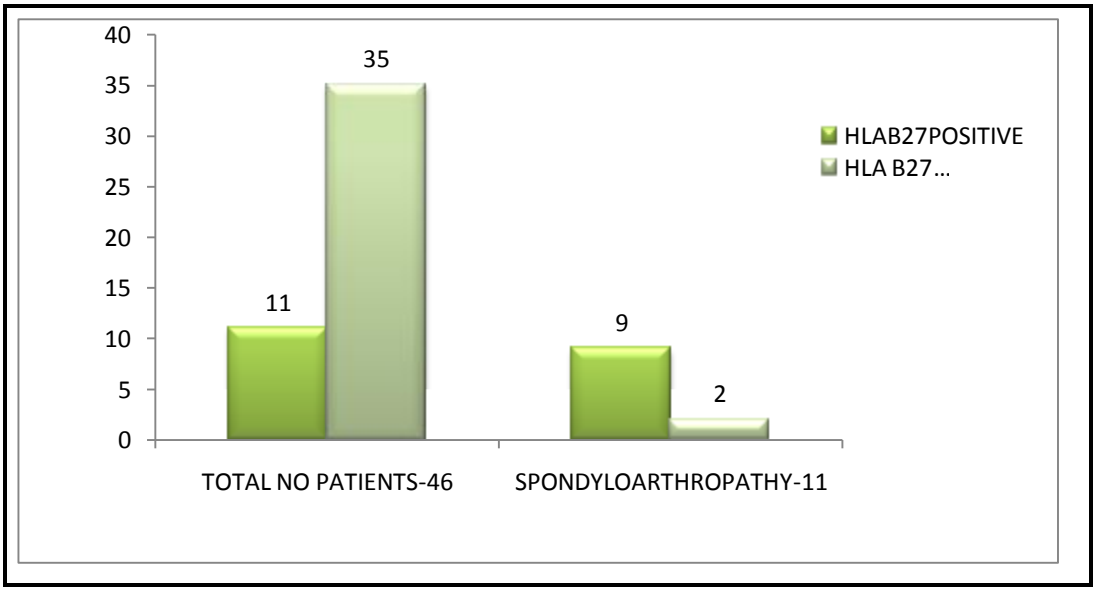
IBA		Outcome		Total
		SPA+	SPA-	
Present	Count	11	12	23
	% within IBA	47.8%	52.2%	100.0%
Absent	Count	0	23	23
	% within IBA	.0%	100.0%	100.0%
Total	Count	11	35	46
	% within IBA	23.9%	76.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided) P value	Exact Sig. (1-sided)
Pearson Chi-Square	14.457a	1	.000		
Continuity Correction	11.948	1	.001		
Likelihood Ratio	18.766	1	.000		
Fisher's Exact Test				**.000**	.000
Linear-by-Linear Association	14.143	1	.000		
N of Valid Cases	46				

IBA had significant correlation with the outcome(SPA). P value0.000

Figure -11 HLAB27 and Spondyloarthropathy



HLAB27 was negative in 76.1% of patients .

HLA B27 was positive in 23.9% of patients.

HLA B27 positivity was seen in 81.8% of SPA patients.

HLAB27 negativity was seen in 5.7% of SPA patients.

Table -8: HLAB27 Positivity and SPA

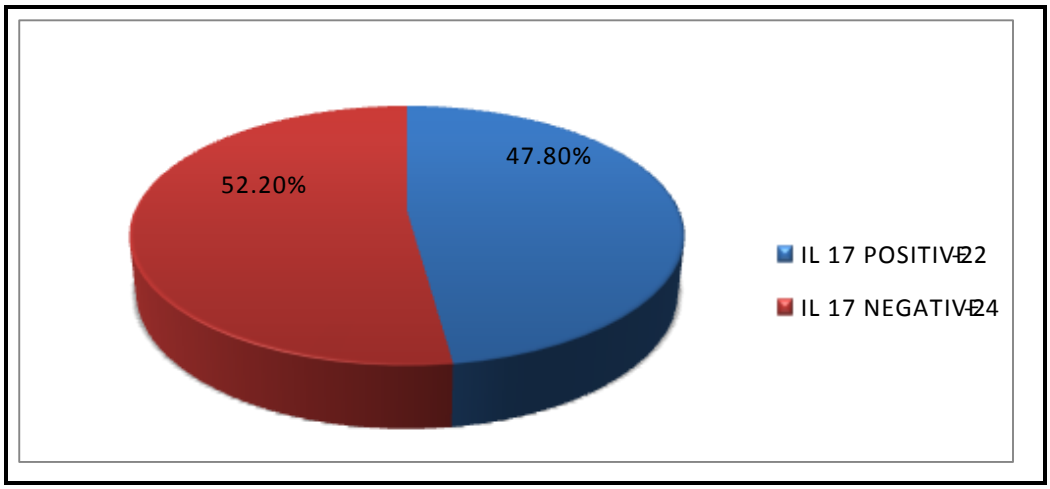
HLAB27		outcome		Total
		SPA+	SPA-	
Positive	Count	9	2	11
	% within HLAB27	81.8%	18.2%	100.0%
Negative	Count	2	33	35
	% within HLAB27	5.7%	94.3%	100.0%
Total	Count	11	35	46

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided) (pvalue)	Exact Sig. (1-sided)
Pearson Chi-Square	26.642a	1	.000		
Continuity Correction	22.624	1	.000		
Likelihood Ratio	24.844	1	.000		
Fisher's Exact Test				**.000**	.000
Linear-by-Linear Association	26.063	1	.000		
N of Valid Cases	46				

The proportion of SPA is significantly higher among the HLAB27 positive patients.P value is 0.000

Figure-12-IL17APOSITIVITY



Among the 46 patients, IL-17A was positive in 47.8% and negative in 52.2% of patients.

.FIGURE 13--IL17A AND SPA

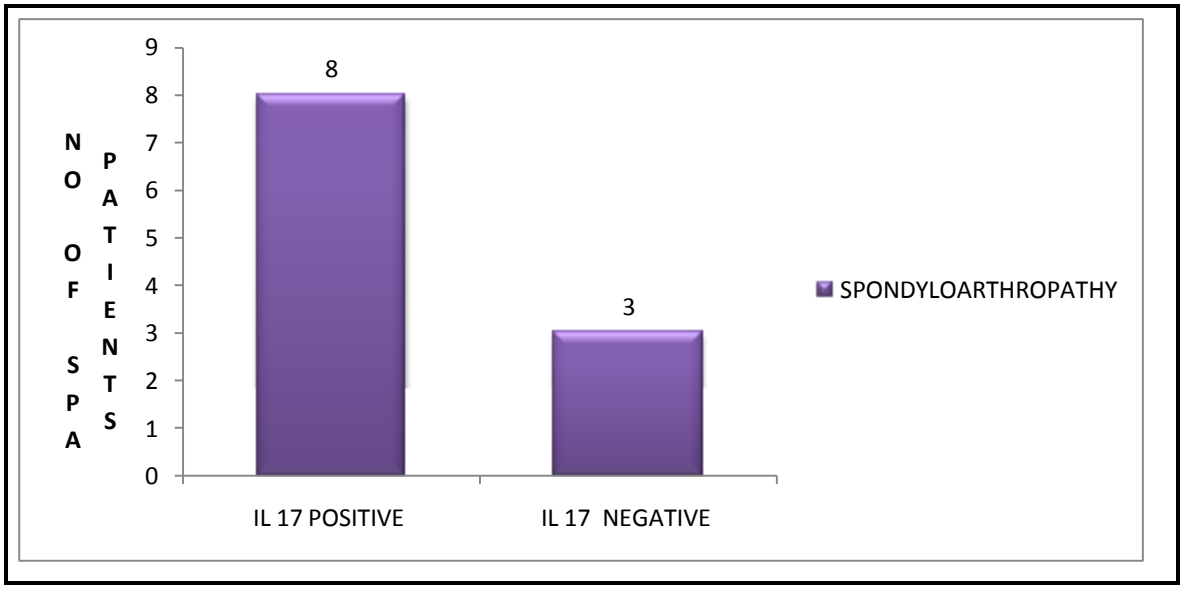


TABLE-9: IL17 A Level and SPA

IL17		Outcome		Total
		SPA+	SPA-	
Positive	Count	8	14	22
	% within IL17	36.4%	63.6%	100.0%
Negative	Count	3	21	24
	% within IL17	12.5%	87.5%	100.0%
Total	Count	11	35	46
	% within IL17	23.9%	76.1%	100.0%

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Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)(P Value)	Exact Sig. (1-sided)
Pearson Chi-Square	3.593a	1	.058		
Continuity Correction	2.401	1	.121		
Likelihood Ratio	3.681	1	.055		
Fisher's Exact Test				**.086**	.060
Linear-by-Linear Association	3.514	1	.061		
N of Valid Cases	46				

36.4% of the patients with IL17Apositivity had SPA. It was not statistically significant. P Value is 0.86.

Figure-14: DAREA SCORE -ONSET

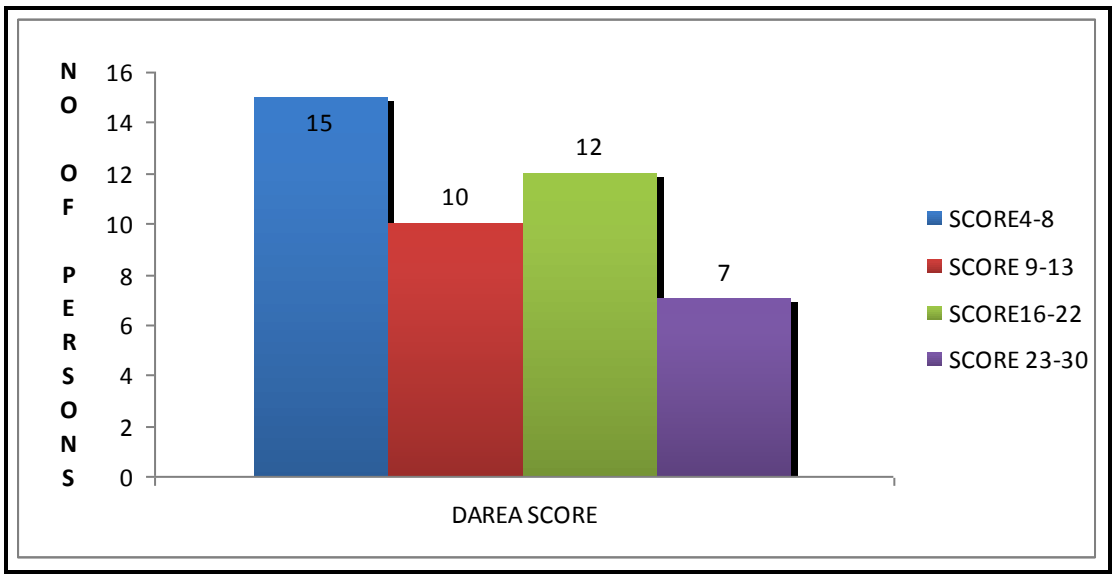


Figure15- DAREA SCORE-6MONTHS

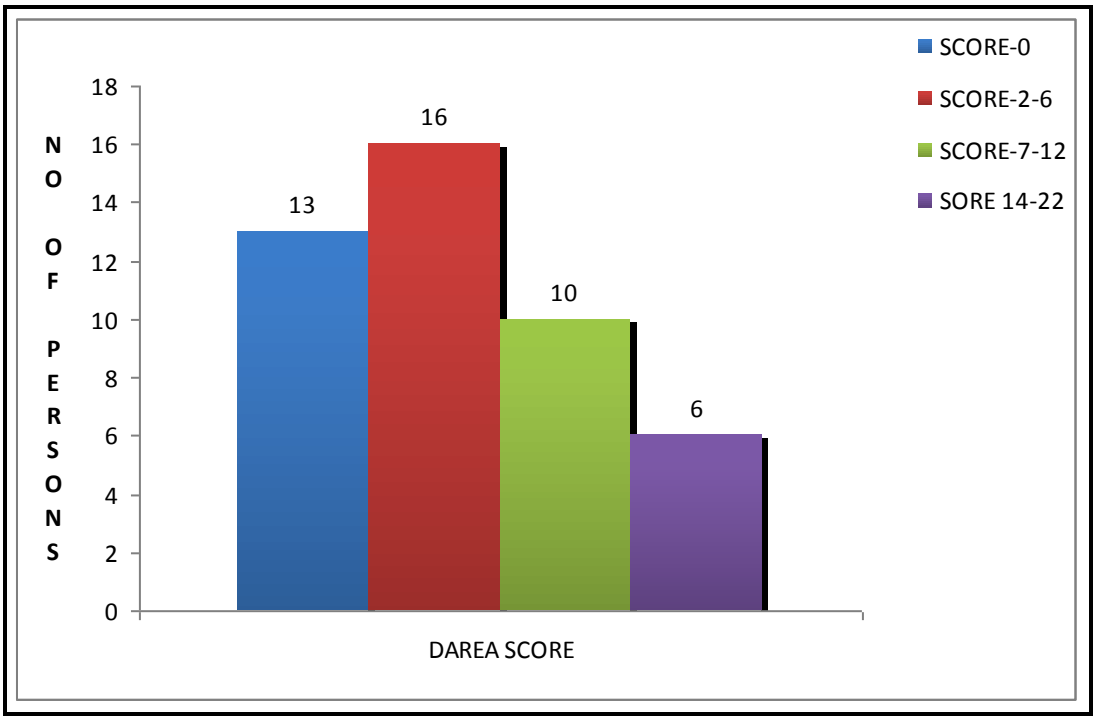


Figure -16 DAREA SCORE-1 YEAR

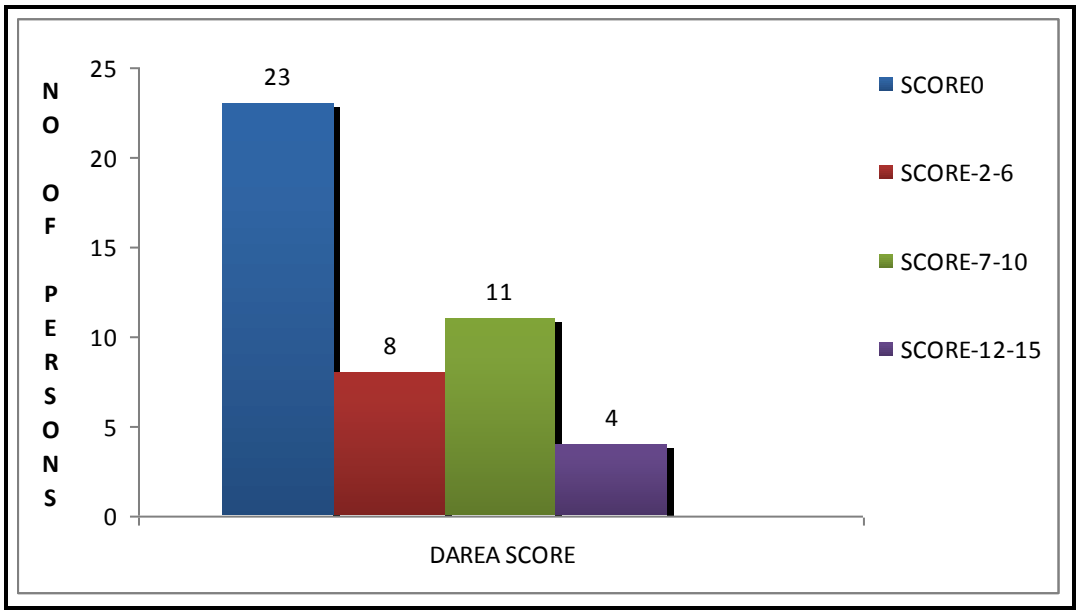


Table-10

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.621a	1	.006		
Continuity Correction	5.826	1	.016		
Likelihood Ratio	7.986	1	.005		
Fisher's Exact Test				**.013**	.007
Linear-by-Linear Association	7.456	1	.006		
N of Valid Cases	46				

.The proportion of SPA is significantly higher among the patients with high DAREA score.P value is 0.007.

FIGURE 17 DAREA SCORE AND IL17A ASSOCIATION

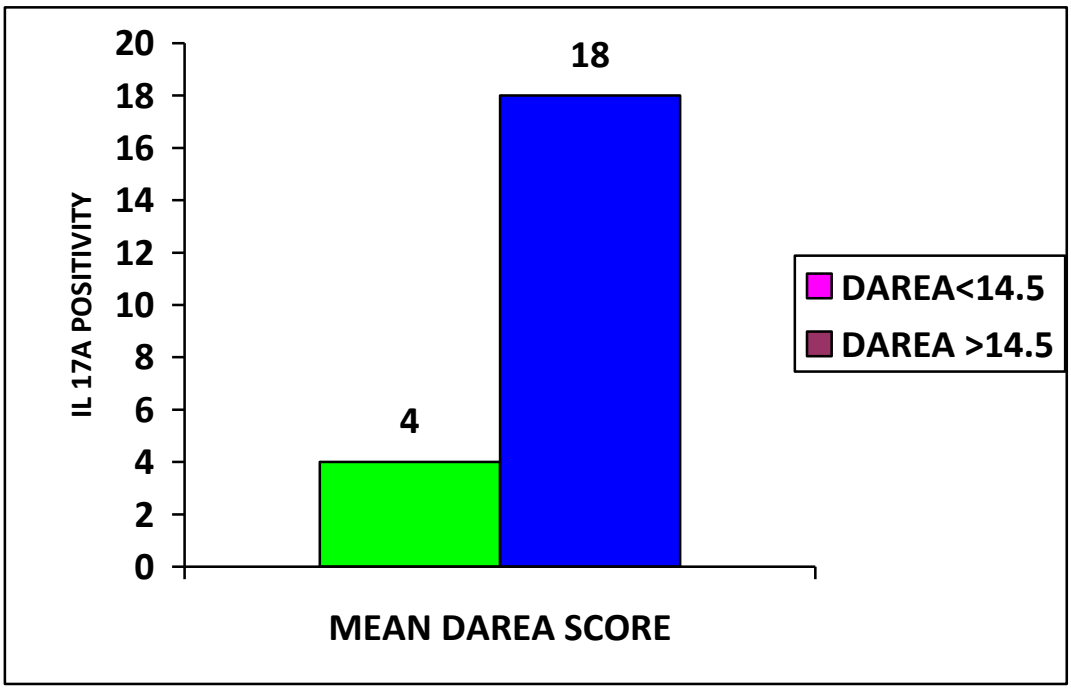


Table-11 DAREA AND IL-17A ASSOCIATION

DAREA		IL17A		Total
		Positive	Negative	
Mean score<14.5	Count	4	21	25
	% within DAREA	16.0%	84.0%	100.0%
Mean score>=14.5	Count	18	3	21
	% within DAREA	85.7%	14.3%	100.0%
Total	Count	22	24	46
	% within DAREA	47.8%	52.2%	100.0%

Mean DAREA Score >14.5 was found in 85.7% of IL 17A positive patients.

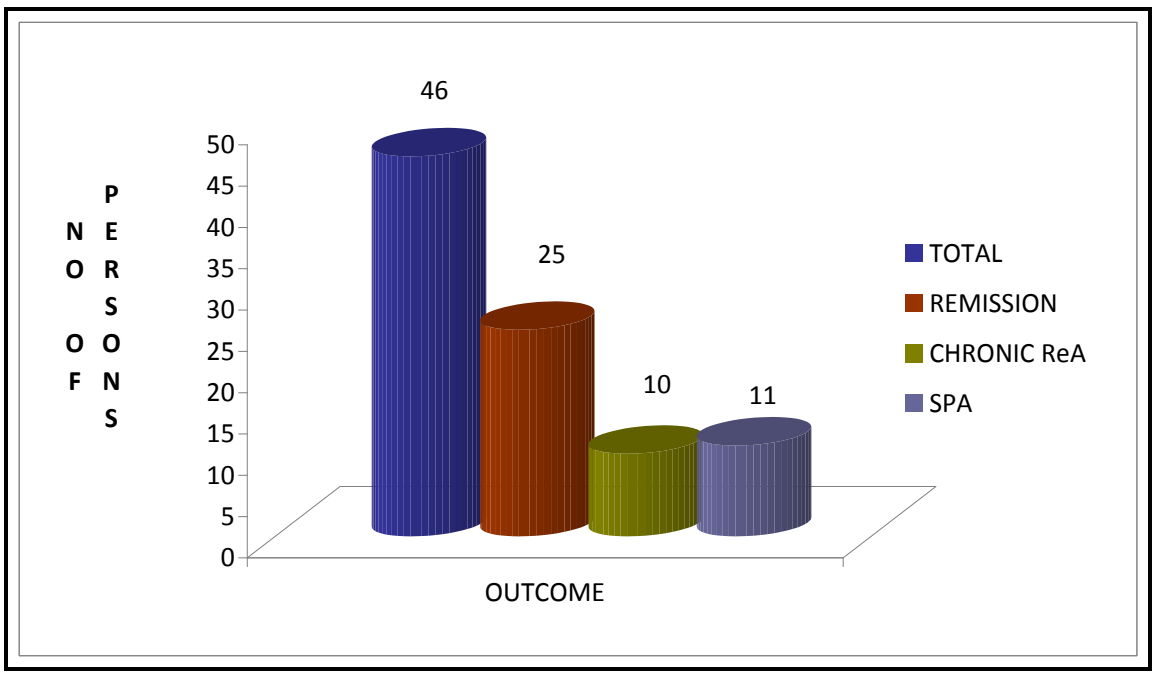
Mean DAREA score <14.5 was found in 16% of IL17A positive patients

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)(p value)	Exact Sig. (1-sided)
Pearson Chi-Square	22.229a	1	.000		
Continuity Correction	19.523	1	.000		
Likelihood Ratio	24.474	1	.000		
Fisher's Exact Test				**.000**	.000
Linear-by-Linear Association	21.746	1	.000		
N of Valid Cases	46				

IL 17A levels correlated significantly with high disease activity score. P value is 0.000

FIGURE 18 CLINICAL OUTCOME OF REACTIVE ARTHRITIS



At the end of 1year 50 % of patients achieved remission.26% of the patients progressed to chronic ReA and 24% of the patients had SPA.

FIGURE19- RADIOLOGICAL OUTCOME (SACROILITIS)

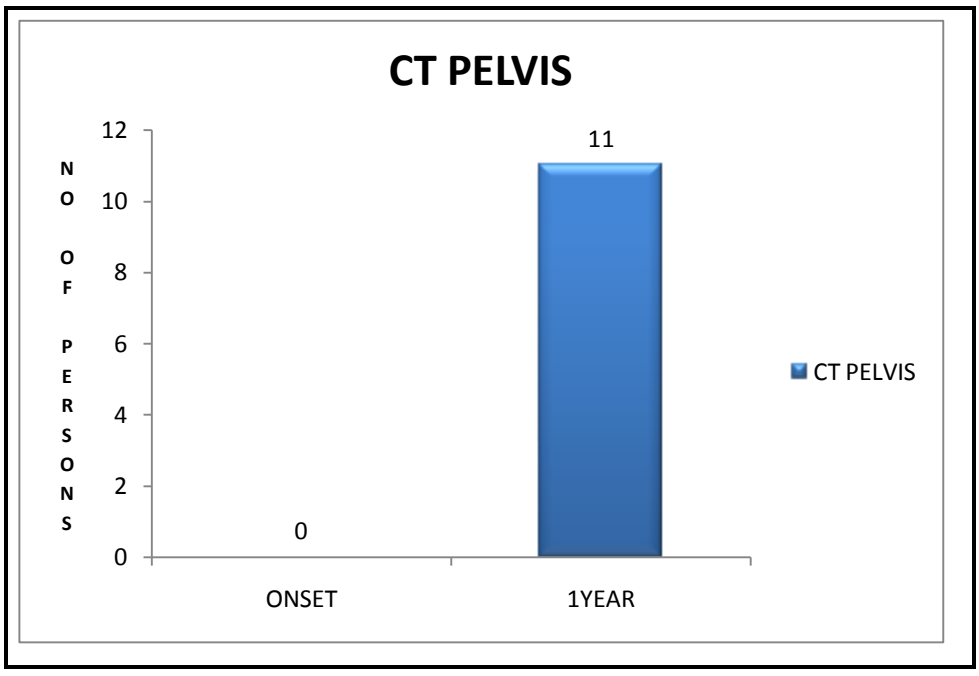
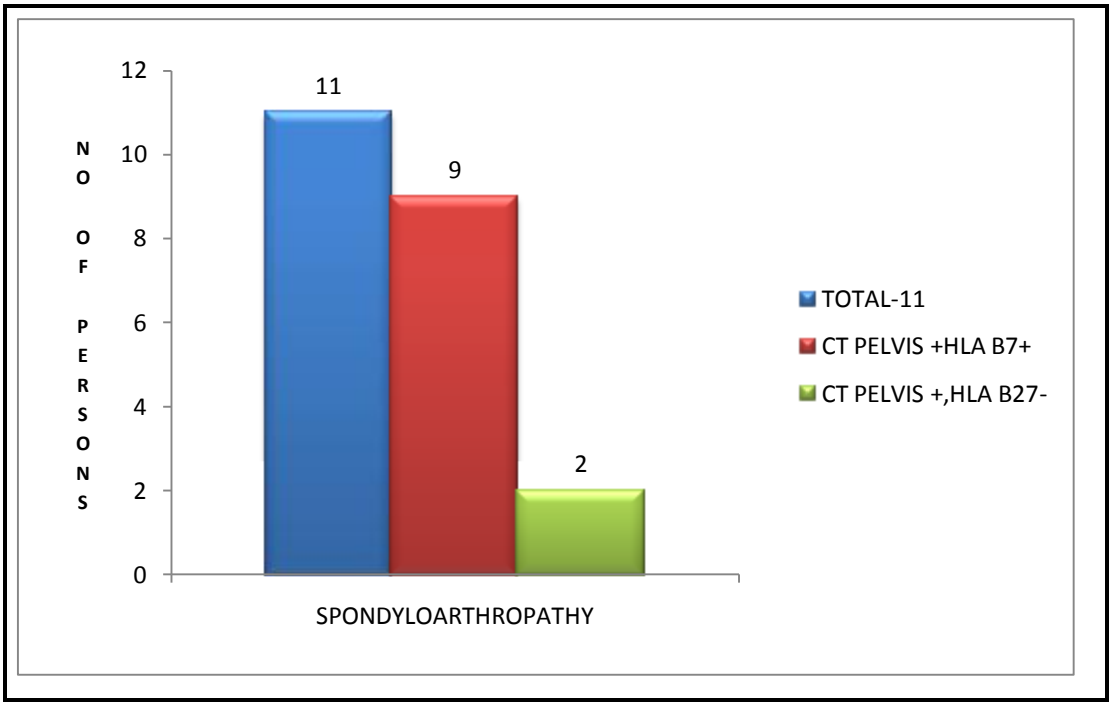


FIGURE-19- HLA B27 AND RADIOLOGICAL OUTCOME



Radiological positivity was found in 23.9% of the patients. 9 patients had association with HLA B27.

DISCUSSION

This is a cross sectional prospective study conducted in our institute to study the clinical features and outcome of reactive arthritis.When we analysed the history of Spondyloarthropathy patients attending our institute we found that many of them attribute an episode of infection when they first noticed their joint symptoms. Hence we have chosen this study about reactive arthritis and its outcome .

We have chosen the diagnostic criteria proposed by the third international workshop for categorizing the patients with reactive arthritis, since we find it applicable in our set up where we do not have certain essential diagnostic tests proposed in the latest preliminary criteria . More over the preliminary criteria has not been validated. We have also analysed the association of reactive arthritis with HLA B27.

Serum samples of these patients were collected and IL17A levels analysed.

Among the 46 patients studied, 58.7% of the patients were males and 41.3% of them were females. Mean duration from the onset of symptoms to the manifestation of the disease was 4.07 weeks According to Towen et al after an episode of infection arthritic symptoms may appear upto 4weeks[152].Males were more affected than females in our study. The average age in our study was 29.91 years. According to Wright V et al the average age group is 20-40years[153].Though males are more affected than females, outcome of the disease did not have statistical significance with sex. In our study at the

end of 1yea ,11 patients had SPA, out of which 6 were males and 5 were females.It did not have statistical significance.

The joints commonly affected in our study were the ankles and knees. Plantar fascia and Achilles tendon were the most commonly affected entheses. This is in concurrence with the study done by Carter et al.[38] Dactylitis was seen in 6 patients.4 patients had conjunctivitis and one had uveitis. Balanitis was seen in one patient.

IBA was present in about 50% of the patients. It had statistical significance with the outcome. All the patients who had spondyloarthropathy at the end of the study were found to have IBA.($p<.000$). Sigal et al studied the sensitivity and specificity of inflammatory back pain in ReA which was 71% and 77% respectively.[170]

At the end of 6 months,28% of the patients had complete resolution of the symptoms as evident by the DAREA score of 0 and at the end of 1year 54% of the patients showed complete resolution. Though 72% of the patients showed persistent disease activity at end of 6months, their score was low compared to the score at the onset.At the end of 1year 23.9% of the patients progressed to spondyloarthropathy and 21.7 % of the patients had chronic arthritis as evidenced by DAREA score>1.According toMichet CJ et al about 30-50% of the patients may progress to chronic ReA[171].

IL 17A levels were high in 22% of the patients. Proportion of patients with IL17A positivity correlated well with disease activity.

Analysing the symptoms associated with ReA in our study both gastrointestinal and genitourinary symptoms were associated with almost equal frequency. But gastrointestinal symptoms were 2.2% higher than genitourinary symptoms.

The organism commonly associated with reactive arthritis in our study was Salmonella. Salmonella paratyphi is the common subspecies identified by serological method.

Many outbreak studies have been published since 2000 on the outbreak of salmonella species and the reactive arthritis associated with it. In a study from USA by Dworkin et al in 2001 on 217 patients with salmonella enteritidis, 29% patients of developed reactive arthritis[154].But none of the patients were associated with HLAB27.

In a study from Germany on 286 children with salmonella enteritidis by Rudwaleit et al in 2001 none of the patients developed reactive arthritis[155].In a study from Denmark in 2002 by Locht et al on 94 patients with Salmonella enteritidis 19% of patients developed reactive arthritis.[156]

In a study by Hannu et al from Finland in 2002 on 78 patients with Salmonella typhimurium 8% of patients had reactive arthritis[157].2 persons had association with HLA B27.He also concluded that the frequency of reactive arthritis after various enteric infections was around 10%.A Canadian based study in 2005 by Lee et al on 261 patients with Salmonella typhimurium showed that 14.6% of patients developed reactive arthritis. HLA B27 was associated with 5/30 patients.[158]An Australian study in 2008 by Rohekar et al.

on 592 patients with Salmonella enteritidis revealed that 19.2% patients developed reactive arthritis.5/37 Patients had association with HLA B27[159].

In our study out of 21 patients who presented with GI symptoms 78.5% of patients developed reactive arthritis. The draw back in our study is, out of 46 patients only 2 patients had acute diarrhea. Other patients had history of diarrhea and presented to us with arthritis. Hence the stool culture did not give us a positive result.

Though we focused mainly on the outcome,the common organism identified in our study was Salmonella paratyphi.Serological positivity obtained in these patients was by Widal agglutination test. These patients had a higher O antigen titre. We were not able to conclude that it is the typhoidal species or the cross reaction with other enteritidis producing Salmonella species such as as S.typhimurium that produced the positivity.Organism isolation was the main drawback of our study.

There are only few studies analysing the outcome of reactive arthritis. In our study about 57.1% of patients with Salmonella positivity had SPA.In a study by M Leirisalo-Repo et al on the long term prognosis of Salmonella 36% of patients developed chronic arthritis[160]. In an American study by Thomson GT et al on the long the term sequelae of Salmonella arthritis,about half of the patients developed spondyloartropathy[161] .

In our study HLA B27 was present in 23.9% of patients and was present in 81.8% of the patients with spondyloarthropathy. It was statistically significant.(p=0.000). HLAB27 was found to be present in about 30-50% of

patients with reactive arthritis. Based on the epidemiological studies association with Salmonella, Campylobacter and Chlamydia induced ReA is 50%[162]. In Shigella induced ReA it is about 80%.[163]

In our study the association of Salmonella and HLA B27 was around 63.63%.In 1998 Mattilal et al has revealed that the association of HLAB27 with Salmonella Bovismorbificans was around 45%[165].Studies from England and Scandinavian countries showed 97% prevalence of HLAB27 in patients with reactive arthritis after Salmonella infections.[166] Leirisalo et al showed in his study that 2 out of 9 patients developed Spondyloarthropathy and they were associated HLA B27[167]. In a study by Seiper et al in 2002 the association of HLA B27 with enteric pathogens was about 50%.[168]

We have also analysed IL17A levels in these patients.To the best of our knowledge this is the first South Indian study where we have analysed IL17A levels in the serum of patients with reactive Arthritis. IL 17A levels were elevated in 47.8% of the patients. Patients with elevated IL 17A levels had a persistent high disease activity score and had progressed to SPA and chronic reactive arthritis.

DRAWBACKS OF OUR STUDY

We were not able to carry out tests for identification of Chlamydia in all patients with dysuria. We were not able to carry out test for Campylobacter and Yersinia which are also commonly implicated in reactive arthritis ,due to non availability of the antiserum.

CONCLUSION

- Knees and ankles were the commonly affected joints.
- Plantar fascia and Achilles tendon were the commonly affected entheses.
- Extraarticular manifestations were not commonly observed in our study.
- IBA has significant association with the outcome.
- Patients with high mean DAREA score at the onset progressed to chronic reactive arthritis and Spondyloarthropathy.
- Persistent disease activity was found in patients with elevated IL17A levels.
- HLAB27 was found to be associated with 11/46 patients. Among the HLA B27patients,9patients had spondyloarthropathy.
- 11/46 patients had CT evidence of sacroilitis at follow up.
- Salmonella is the most common organism associated with reactive arthritis in our study.

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PROFORMA

Name: Age: Sex: Date:

RCC No:

H/o. Present Illness:

Past History:

Personal History:

Treatment History:

Family History:

GENERAL EXAMINATION

Pallor: Icterus Cyanosis

Clubbing: Lymphadenopathy Pedal Edema

Skin Nails

Hair

Puse Rate Blood Pressure

SYSTEM EXAMINATION

Cardiovascular System Respiratory System

Abdomen Central Nervous System

Musculoskeletal System Examination

Dermatology

Ophthalmology

INVESTIGATION

Haemogram

Hb:	TC:	DC
Platelet:	ESR:	

Immunological

CRP	RF	ANA

Biochemical

Sugar:	Urea:	Creatinine:

Radiography

USG Abdomen & CT Pelvis

Cultures

Urine	Blood	Stool

Swab

Throat	Urethral	Cervical

ECHO

DAREA SCORE

HIV

SI NO	NAME	AGE	SEX	RCCNO	SYMPTOM DURATION	GI SYMPTOM	GENITIURINARY	SEROLOGY	URINE CULTURE	STOOL CULTURE	THROAT SWAB	IBA	ARTHRITIS
1	GOPAL	23	M	55174	2 MONTHS	DIARRHOEA	NIL	SALMONELLA TYPHI	NIL	NIL	NIL	NIL	BOTHKNEE,ANKLE
2	AKKEM	40	M	55178	1MONTH	DIARRHOEA	NIL	SALMONELLATYPHI	NIL	NIL	NIL	NIL	ANKLE ,KNEE,MIDTARSAL
3	ANBU	24	M	50912	1MONTH	NIL	NIL	NIL	NIL	NIL	NIL	PRESENT	BOTHKNEES
4	VIJAY	17	M	55399	2WEEKS	NIL	DYSURIA	NIL	ECOLI	NIL	NIL	PRESENT	BOTHKNEES,ANKLE,RT HIP
5	SUNDER	20	M	55412	1MONTH	DIARRHOEA	NIL	NIL	NIL	NIL	NIL	PRESENT	BOTH ANKLES,MIDTARSAL
6	BABU	20	M	55433	1MONTH	DIARRHOEA	NIL	BRUCELLA	NIL	NIL	NIL	PRESENT	BOT KNEES,HIP
7	SRINIVASAN	25	M	12670	1MONTH	DIARRHOEA	NIL	SALMONELLA TYPHI	NIL	NIL	NIL	PRESENT	BOTH KNEES,ANKLE,SOULDER
8	KAMUDAS	23	M	55573	2MONTHS	NIL	DYSURIA	NIL	NIL	NIL	NIL	NIL	ANKLE ,MIDTARSAL
9	DHARMARAJ	27	M	55663	10DAYS	NIL	NIL	NIL	NIL	NIL	KLEBSIELLA	PRESENT	KNEE,ANKLE,MIDTARSAL,SUBTALAR
10	KANNAN	46	M	55666	4WEEKS	DIARRHOEA	NIL	SALMONELLA P. TYPHI	NIL	NIL	NIL	PRESENT	BOTHKNEE,ANKLE,MIDTARSAL
11	GANESAN	23	M	54490	1MONTH	NIL	NIL	BRUCELLA	NIL	NIL	NIL	NIL	BOTH KNEES,ANKLES,MIDTASAL
12	VIJAYAN	52	M	55721	2WEEKS	NIL	DYSURIA	NIL	PROTEUSVULGARIS	NIL	NIL	NIL	BOTH ANKLE,MIDTARSAL,SUBTALAR
13	BASKARAN	19	M	55797	3WEEKS	DIARRHOEA	NIL	NIL	NIL	SHIGELLA	NIL	PRESENT	BOTH KNEES,ANKLE,
14	PETER	24	M	55821	4WEEKS	DIARRHOEA	NIL	NIL	NIL	SALMONELLA	NIL	NIL	BOTHANKLES,KNEES
15	SHANMUGAM	43	M	55918	2WEEKS	DIARRHOEA	NIL	SALMONELLAP.TYPHI	NIL	NIL	NIL	PRESENT	BOTHKNEES,ANKLE,SUBTALAR
16	NALLATHAMBI	44	M	55940	6WEEKS	DIARRHOEA	NIL	SALMONELLAP.TYPHI	NIL	NIL	NIL	PRESENT	BOTKNEES,ANKLES,
17	VINOTH	24	M	56303	2WEEKS	NIL	DYSURIA	NIL	NIL	NIL	NIL	ABSENT	BOTHKNEES,ANKLES
18	CHELLAPPAN	35	M	56591	4WEEKS	NIL	DYSURIA	NIL	NIL	NIL	NIL	PRESENT	BOTHKNEES,ANKLE
19	GANESH	25	M	56791	4WEEKS	NIL	DYSURIA	NIL	KLEBSEILLA	NIL	NIL	PRESENT	BOTHKNEES,ANKLES,MIDTARSAL
20	SETTU	24	M	56867	4WEEKS	NIL	DYSURIA	NIL	KLEBSEILLA	NIL	NIL	PRESENT	BOTHKNEE,ANKLE,MIDTARSAL
21	PARTHIBAN	24	M	56951	4WEEKS	DIARRHOEA	NIL	SALMONELLAP.TYPHI	NIL	NIL	NIL	PRESENT	BOTHKNEE,MIDTARSAL
22	SUBHASHINI	35	F	55704	6WEEKS	NIL	NIL	NIL	NIL	NIL	KLEBSIELLA	PRESENT	BOTHANKLE,KNEES,SHOULDER
23	MENAKA	35	F	55943	4WEEKS	DIARRHOEA	NIL	SALMONELLAP.TYPHI	NIL	NIL	NIL	ABSENT	BOTHANKLE,KNEES,
24	AMUTHA	33	F	55972	6WEEKS	DIARRHOEA	NIL	NIL	NIL	NIL	NIL	PRESENT	BOTHANKLES,KNEES
25	CHITRA	23	F	56084	6WEEKS	NIL	WHITEDISCHARGE	NIL	ECOLI	NIL	NIL	ABSENT	BOTHANKLES
26	SASIKALA	35	F	56147	6WEEKS	DIARRHOEA	NIL	SALMONELLAP.TYPHI	NIL	NIL	NIL	PRESENT	BOTHANKLES,ANKLES
27	SUGANYA	24	F	56340	4WEEKS	NIL	WHITEDISCHARGE	NIL	NIL	NIL	NIL	ABSENT	BOTHKNEES,ANKLES
28	GERISYAL	18	F	56637	6WEEKS	DIARRHOEA	NIL	SALMONELLAP.TYPHI	NIL	NIL	NIL	PRESENT	BOTHKNEES,ANKLES,MIDTARSAL
29	KOWSALYA	30	F	55557	6WEEKS	NIL	DYSURIA	NIL	NIL	NIL	NIL	ABSENT	BOTHANKLES
30	MANJULA	31	F	56129	6WEEKS	NIL	NIL	BRUCELLA	NIL	NIL	NIL	PRESENT	BOTHANKLES
31	SAMUNDEESWARI	26	F	56218	8WEEKS	DIARRHOEA	NIL	NIL	NIL	NIL	NIL	ABSENT	BOTHKNEES
32	KOMALA	31	F	56350	4WEEKS	NIL	WHITEDISCHARGE	NIL	NIL	NIL	NIL	ABSENT	BOTHKNEES,ANKLES,MIDTARSAL
33	MALLIGA	22	F	52316	6WEEKS	DIARRHOEA	NIL	SALMONELLAP.TYPHI	NIL	NIL	NIL	PRESENT	BOTHKNEE,ANKLES,HIP
34	SULTHAN	30	F	10134	2WEEKS	NIL	DYSURIA,WHITEDISCHARGE	NIL	NIL	NIL	NIL	NIL	BOTHKNEES,ANKLES
35	MERCY	50	F	10453	1WEEK	NIL	DYSURIA	NIL	KLEBSEILLA	NIL	NIL	NIL	BOTHKNEES
36	SARIKA	26	F	11263	2WEEKS	NIL	DYSURIA	NIL	CHLAMYDIA	NIL	NIL	PRESENT	RTKNEE,LFT ANKLE,
37	DEVI	35	F	10545	4WEEKS	DIARRHOEA	NIL	SALMONELLA TYPHI	NIL	NIL	NIL	ABSENT	BOTHKNEES
38	TAMILARASAN	40	M	11231	3WEEKS	NIL	DYSURIA	NIL	NIL	NIL	NIL	ABSENT	BOTHKNEES,ACHILLES
39	SUMATHY	30	F	12345	6WEEKS	NIL	WHITEDISCHARGE	NIL	NIL	NIL	NIL	NIL	BOTHKNEES,ANKLES
40	PARTHIBAN	24	M	10263	15DAYS	NIL	NIL	NIL	NIL	NIL	NIL	NIL	KNEE,ANKLE
41	PANCHANATHAN	45	M	35645	3WEEKS	NIL	DYSURIA	NIL	NIL	NIL	NIL	NIL	BOTHANKLES,ANKLES,MIDTARSAL
42	THILGAVATHY	35	F	406958	3WEEKS	NIL	DYSURIA	NIL	ECOLI	NIL	NIL	PRESENT	BOTHKNEES,ANKLES,MIDTARSAL
43	SUDHAKAR	31	M	11562	6WEEKS	NIL	DYSURIA,URETHRALDISCHARGE	NIL	ECOLI	NIL	NIL	ABSENT	BOTHKNEES
44	POORNIMA	26	F	55533	1WEEK	DIARRHOEA	NIL	SALMONELLATYPHI	NIL	NIL	NIL	ABSENT	BOTH KNEES,RTANKLE
45	VIJAYAN	35	M	55729	2WEEKS	NIL	DYSURIA	NIL	NIL	NIL	NIL	ABSENT	BOTHKNEES
46	IYYAPAN	24	M	54155	1WEEK	DIARRHOEA	NIL	NIL	NIL	NIL	NIL	PRESENT	BOTHKNEES,ANKLES,ELBOW

ENTHESITIS	SYSTEMICSYMPTOMS	SKIN	OPTHAL	ECHO	HLAB27	IL 17	CTPELVIS ONSET	DAREA ONSET	DAREA 6MON	DAREA1YR	CT PELVIS1YR	OUTCOME
ACHILLES,PLANTAR FASCIA	FEVER	NIL	NIL	NORMAL	NEGATIVE	POSITIVE5.4OD	NORMAL	17	8	5	NORMAL	C.ReA
TIBIAL TUBERCLE	FEVER	PLAQUES OVERPALM ,SOLES	NIL	LVH,TRIVIAL AR	NEGATIVE	NEGATIVE	NORMAL	10	0	0	NORMAL	NORMAL
PLANTARFASCIA	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	5	0	0	NORMAL	NORMAL
PLANTAFASCITIS	FEVER	NIL	NIL	MVPPS	NEGATIVE	NEGATIVE	NORMAL	11	3	0	NORMAL	NORMAL
FLEXOR TENOSYNOVITIS ANKLE,DACTYLITIS	FEVER	NIL	NIL	NORMAL	NEGATIVE	POSITIVE5.4OD	NORMAL	7	4	4	NORMAL	C.ReA
PLANTARFASCIA,	FEVER	NIL	NIL	NORMAL	POSITIVE	NEGATIVE	NORMAL	10	5	3	B/LSACROILITIS	SPA
ACHILLES,PLANTAR FASCIA,ASIS,TIBIAL	NIL	NIL	NIL	NORMAL	NEGATIVE	POSITIVE4.4OD	NORMAL	13	5	2	NORMAL	C.ReA
ACHILLES,PLANTAR FASCIA	STRICTRE URETHRA	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	7	4	0	NORMAL	NORMAL
ACHILLES,PLANTAR FASCIA,ASIS,TIBIAL	NIL	NIL	CONJUCTIVITIS	NORMAL	NEGATIVE	POSITIVE4.2OD	NORMAL	26	12	0	NORMAL	NORMAL
ACHILLES,ASIS	NIL	NIL	NIL	NORMAL	POSITIVE	POSITIVE20.2OD	NORMAL	22	6	4	B/LSACROILITIS	SPA
DACTYLITIS	NIL	PAPULARLESION OVER TRUNK,ABDOMEN	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	24	11	0	NORMAL	NORMAL
PLANTARFASCIATIS	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	20	6	0	NORMAL	NORMAL
PLANTARFASCIA,TIBIALTUBERCLE	NIL	NIL	NIL	NORMAL	POSITIVE	NEGATIVE	NORMAL	24	16	15	B/LSACROILITIS	SPA
ACHILLES,DACTYLITIS	FEVER	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	4	0	0	NORMAL	NORMAL
PLANTARFASCIA	NIL	NIL	CONJUCTIVITIS	NORMAL	NEGATIVE	POSITIVE5.25OD	NORMAL	20	6	5	B/LSACROILITIS	SPA
PLANTARFASCIATIS,TIBIAL TUBERCE	NIL	NIL	NIL	NORMAL	POSITIVE	NEGATIVE	NORMAL	10	8	8	B/LSACROILITIS	SPA
ACHILLESTENDITIS	FEVER	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	6	0	0	NORMAL	NORMAL
PLANTARFASCIA,ACHILLES,TIBIALTUBERCLE	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	6	0	0	NORMAL	NORMAL
PLANTARFASCIA,ACHILLES,ASIS	NIL	N	NIL	NORMAL	NEGATIVE	POSITIVE34OD	NORMAL	26	12	10	NORMAL	C.ReA
PLANTARFASCITIS,DACTYLITIS 2TOE	DM	TINEAVERSICOLOR	NIL	NORMAL	POSITIVE	POSITIVE5.6OD	NORMAL	16	12	8	B/LSACROILITIS	SPA
PLANTARFASCIA,TIBIALTUBERCLE	FEVER	NIL	NIL	NORMAL	POSITIVE	POSITIVE4.2OD	NORMAL	22	8	2	NORMAL	NORMAL
DACTYLITIS,ACHILLESTENDINITIS	FEVER	NIL	NIL	NORMAL	POSITIVE	POSITIVE5.6OD	NORMAL	34	14	4	B/LSACROILITIS	SPA
PLANTARFASCIA	FEVER	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	10	2	0	NORMAL	NORMAL
ACHILLES,PLANTARFASCIA	FEVER	SEBORRHIC DERMATITIS	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	8	5	0	NORMAL	NORMAL
PLANTARFASCITIS,	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	8	2	0	NORMAL	NORMAL
PLANTARFASCIA,ACHILLES,TIBIALTUBERCLE	FEVER	NIL	NIL	NORMAL	POSITIVE	POSITIVE5.6OD	NORMAL	18	8	6	B/LSACROILITIS	SPA
PLANTARFASCIA	NIL	NIL	NIL	NORMAL	NEGATIVE	POSITIVE280D	NORMAL	16	6	2	NORMAL	C.ReA
PLANTARFASCIA,ACHILLES,TIBIALTUBERCLE,ASIS	NIL	NIL	NIL	NORMAL	NEGATIVE	POSITIVE9.2OD	NORMAL	18	6	4	B/LSACROILITIS	SPA
ACHILLESTENDITIS	NIL	NIL	CONJUCTIVITIS	NORMAL	NEGATIVE	NEGATIVE	NORMAL	6	0	0	NORMAL	NORMAL
PLANTARFASCITIS	NIL	NIL	NIL	NIL	NEGATIVE	NEGATIVE	NORMAL	7	0	0	NORMAL	NORMAL
ACHILLES,PLANTARFASCIA,LATERALEPICONDYLITIS	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	6	0	0	NORMAL	NORMAL
ACHILLES,PLANTARFASCIA	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	12	0	0	NORMAL	NORMAL
ASIS,ACHILLES,PLANTARFASCIA,TIBIALTUBERCLE	NIL	NIL	NIL	NORMAL	POSITIVE	POSITIVE12.4OD	NORMAL	26	18	14	B/LSACROILITIS	SPA
PLANTARFASCIA,ACHILLESTENDON	NIL	NIL	NIL	NORMAL	NEGATIVE	POSITIVE52OD	NORMAL	18	5	5	NORMAL	C.ReA
PLANTARFASCIA	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	4	0	0	NORMAL	NORMAL
B/L PLANTAR FASCITIS	FEVER	NORMAL	NORMAL	NORMAL	POSITIVE	POSITIVE 5.6OD	NORMAL	16	7	3	B/LSACROILITIS	SPA
ACHILLESTENDITIS	FEVER	NORMAL	NORMAL	NORMAL	NEGATIVE	POSITIVE4.2OD	NORMAL	4	0	0	NORMAL	NORMAL
PLANTARFASCITIS,ASIS	FEVER	NORMAL	NORMAL	NORMAL	NEGATIVE	POSITIVE4.2OD	NORMAL	16	4	0	NORMAL	NORMAL
ACHILLESTENDITIS	NIL	NORMAL	NORMAL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	6	0	0	NORMAL	NORMAL
ACHILLES TENDINITIS	FEVER	NORMAL	UVEITIS	NOMAL	NEGATIVE	POSITIVE4.2OD	NORMAL	23	14	3	NORMAL	C.ReA
PLANTARFASCIATIS,ACHILESTENDINITIS	NIL	NORMAL	NORMAL	NORMAL	NEGATIVE	POSITIVE9.4OD	NORMAL	13	8	3	NORMAL	C.ReA
ACHILLESTENDITIS,TIBIALTUDERCLEENTHESITIS	NIL	NORMAL	NORMAL	NORMAL	NEGATIVE	POSITIVE40OD	NORMAL	30	18	12	NORMAL	C.ReA
LFTMIDDLEFINGERDACTYLITIS	NIL	BALANITIS	CONJUCTIVITIS	NORMAL	POSITIVE	POSITIVE29OD	NORMAL	31	22	6	NORMAL	C.ReA
PLANTARFASCITIS,ACHILLESTENDINITIS	NIL	NIL	NIL	NORMAL	NEGATIVE	NEGATIVE	NORMAL	9	6	0	NORMAL	NORMAL
PLANTARFASCITIS	NIL	NIL	NIL	NIL	NEGATIVE	NEGATIVE	NORMAL	8	0	0	NORMAL	NORMAL
DACYTILITIS	FEVER	NIL	NIL	AML,PMLRESTRITED	NEGATIVE	NEGATIVE	NORMAL	12	4	0	NORMAL	NORMAL

PATIENT CONSENT FORM

Study Details: **Clinical features and outcome of patients with Reactive Arthritis**

Study Centre: Department of Rheumatology,
Rajiv Gandhi Government General Hospital,
Madras Medical College, Chennai-600 003.

Patient may check (✓) these boxes

I confirm that I have read and understood the Information Sheet for the above study. I have- had the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I understand that the Clinical study personnel, the Ethics Committee and the Regulatory Authorities will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

I hereby consent to participate in this study. ☐

Signature of Investigator Thumb Impression of Patient

Patient Name/ Address

Name of the Investigator

Institution

INFORMATION SHEET

- We are conducting a study on **"Clinical features and outcome of patients with Reactive Arthritis"** at Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-600003.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the Participant **Signature of the Investigator**

Institution
Date :

<u>ஆராய்ச்சி ஒப்புதல் படிவம்</u>

ஆராய்ச்சி தலைப்பு

வினையாற்றும் கீழ்வாத நோய்

ஆராய்ச்சி நிலையம் : முடக்குவாதவியல் துறை,
சென்னை மருத்துவக் கல்லூரி மற்றும்
ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை.

பங்கு பெறுவரின் பெயர் :

பாலினம் :

பங்குபெறபவரின் எண் :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். எனது உடல் நலம்பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கதிற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்து அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு மருத்துவ பரிசோதனை, இரத்தப் பரிசோதனை செய்துகொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனை முடக்குவாதவியல் துறைக்கு வரும் நோயாளிகளிடம் வினையாற்றும் கீழ்வாத நோய் பற்றிய ஆராய்ச்சி.

நீங்களும் ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ, சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

_____ _____

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

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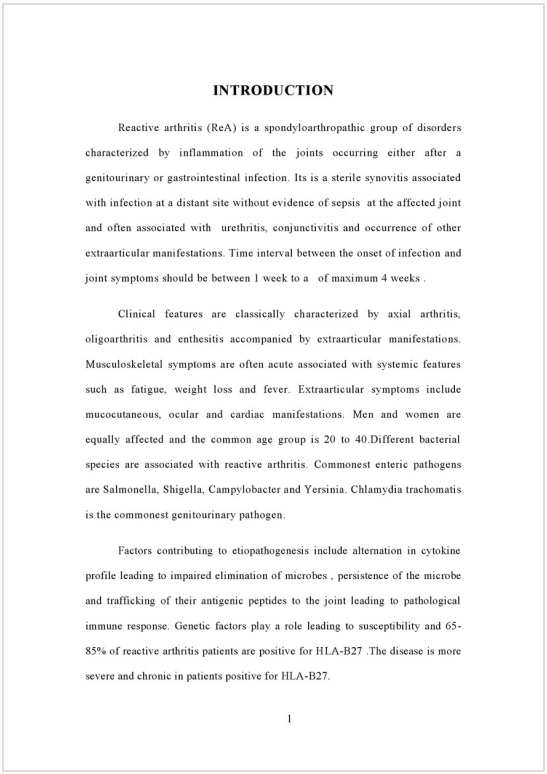

INTRODUCTION

Reactive arthritis (ReA) is a spondyloarthropathic group of disorders characterized by inflammation of the joints occurring either after a genitourinary or gastrointestinal infection. Its is a sterile synovitis associated with infection at a distant site without evidence of sepsis at the affected joint and often associated with urethritis, conjunctivitis and occurrence of other extraarticular manifestations. Time interval between the onset of infection and joint symptoms should be between 1 week to a of maximum 4 weeks .

Clinical features are classically characterized by axial arthritis, oligoarthritis and enthesitis accompanied by extraarticular manifestations. Musculoskeletal symptoms are often acute associated with systemic features such as fatigue, weight loss and fever. Extraarticular symptoms include mucocutaneous, ocular and cardiac manifestations. Men and women are equally affected and the common age group is 20 to 40.Different bacterial species are associated with reactive arthritis. Commonest enteric pathogens are Salmonella, Shigella, Campylobacter and Yersinia. Chlamydia trachomatis is the commonest genitourinary pathogen.

Factors contributing to etiopathogenesis include alternation in cytokine profile leading to impaired elimination of microbes , persistence of the microbe and trafficking of their antigenic peptides to the joint leading to pathological immune response. Genetic factors play a role leading to susceptibility and 65-85% of reactive arthritis patients are positive for HLA-B27 .The disease is more severe and chronic in patients positive for HLA-B27.

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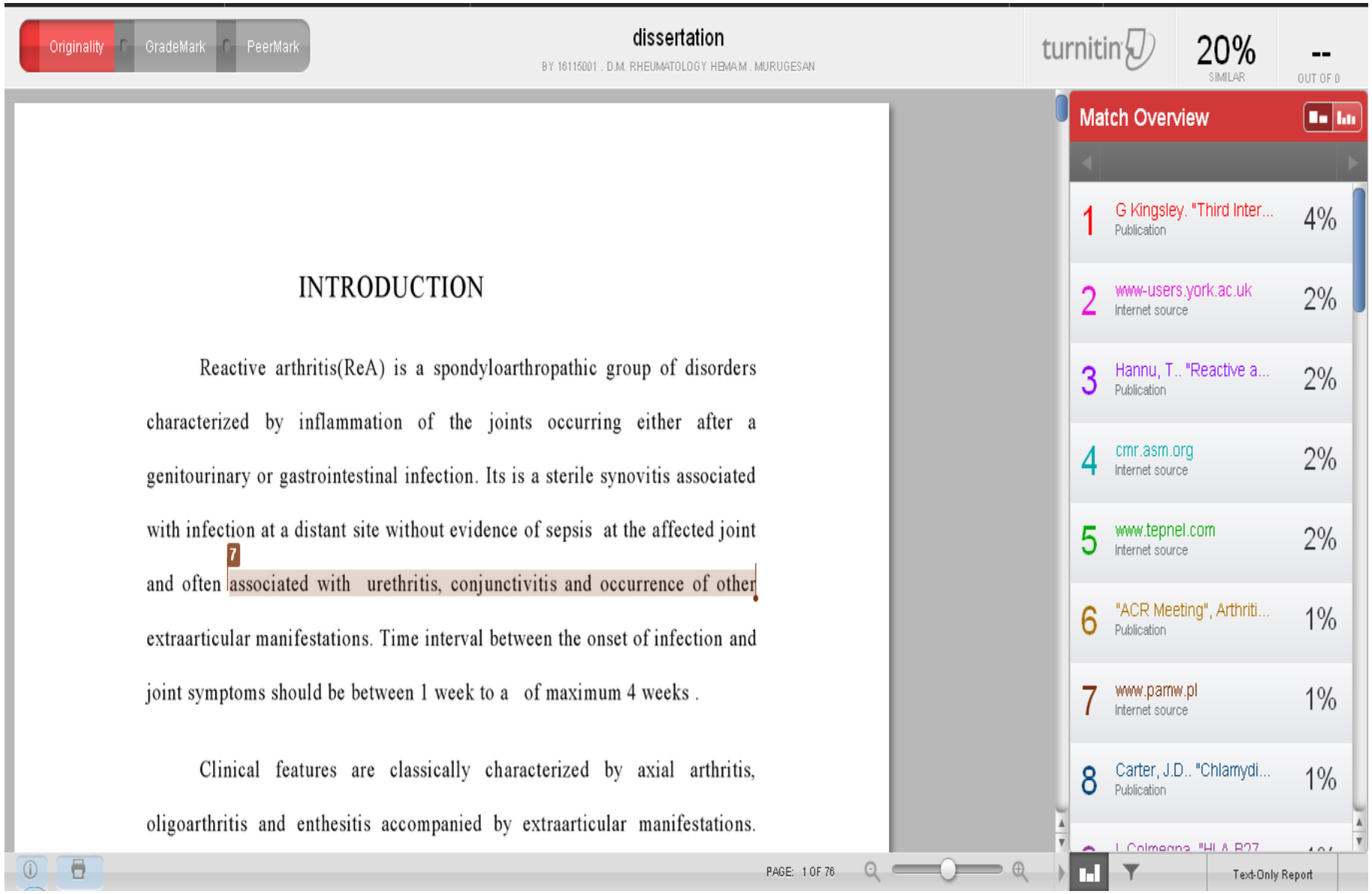
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