

Reactive arthritis

Seronegative spondyloarthropathies

A spectrum of diseases that share the following features:

- ▶ Axial inflammation
- ▶ Asymmetric arthritis
- ▶ Enthesitis
- ▶ Skin and genital lesions
- ▶ Eye and bowel inflammation
- ▶ Association with infection
- ▶ Common extra-articular involvement
- ▶ Association with HLA B27

Diseases belonging to the spondyloarthropathies

By Dougados M, Hochberg MC, 2002

- ▶ Ankylosing spondylitis
- ▶ Reactive arthritis
- ▶ Enteropathic (IBD) arthropathy
(Crohn's disease, ulcerative colitis)
- ▶ Psoriatic arthritis
- ▶ Undifferentiated spondyloarthropathies
- ▶ Juvenile chronic arthritis: juvenile onset of ankylosing spondylitis

To this classification will be added the degree of disease activity and the index of functional alteration, calculated by validated instruments.

Reactive arthritis

- ▶ The very definition of reactive arthritis (ReA) - *a sterile synovitis following an extra-articular infection.*
- ▶ ReA occupies **the conceptual ground** somewhere **between septic arthritis** and **the classic autoimmune rheumatic diseases**, such as rheumatoid arthritis.

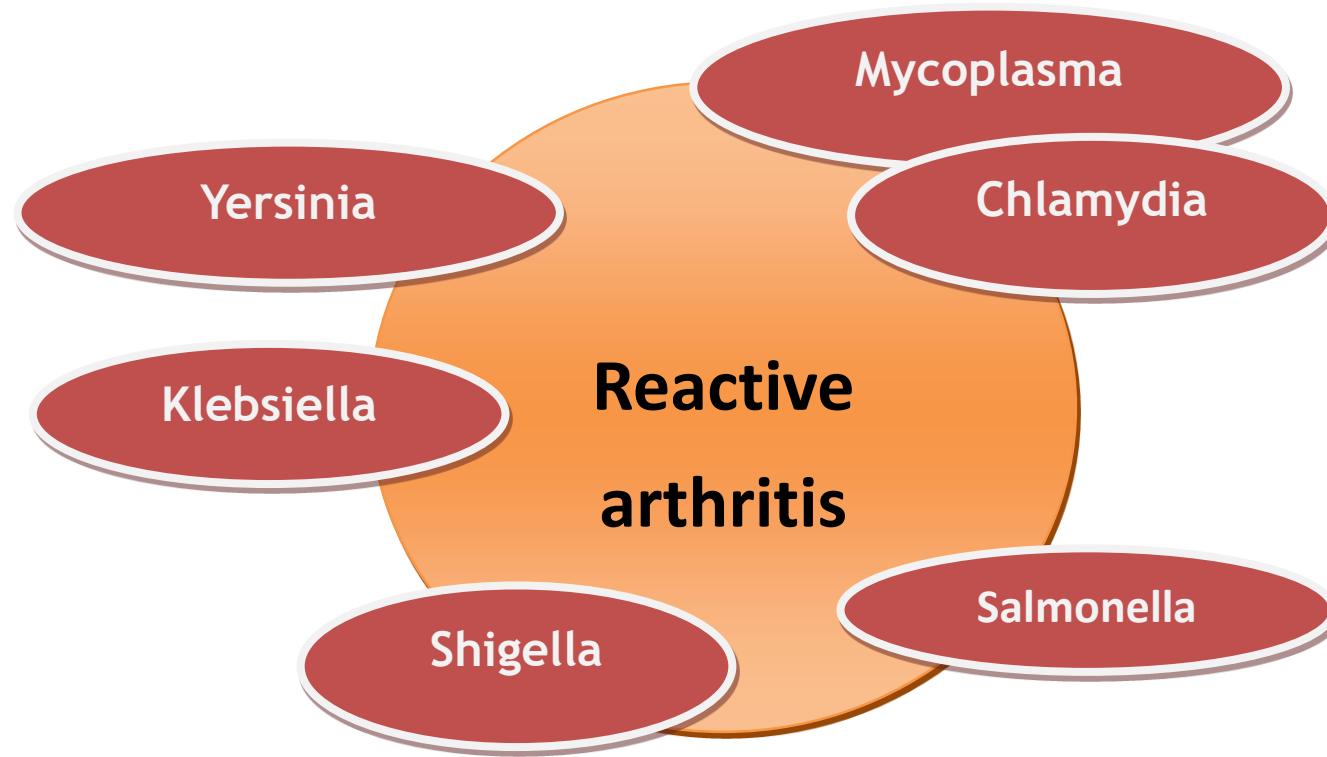
Epidemiology

- ▶ The annual incidence of ReA, found to be 28/100,000 individuals, it may exceed that of rheumatoid arthritis.
- ▶ Other authors report annual incidence of ReA 30-40 cases per 100,000 adults
- ▶ Prevalence is about 0.5-2 % in Caucasians
- ▶ Prevalence varies, depending upon ethnicity and different geographic locations

Epidemiology

- ▶ HLA-B27 and reactive arthritis are more common in white people than in black people.
- ▶ Reactive arthritis following foodborne **enteric infections is equally common in males and females.**
- ▶ The male-to-female ratio of disease associated with **venereally acquired infections is 9:1.**
- ▶ Most patients with reactive arthritis are aged 20-40 years.

- ▶ Reactive arthritis has been associated with gastrointestinal infections with *Shigella*, *Salmonella*, and *Campylobacter* species and other microorganisms, as well as with genitourinary infections (especially with *Chlamydia trachomatis*).



Chlamydia trachomatis, *Mycoplasma hominis*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*,
Salmonella enteritidis, *Salmonella typhimurium*, *Shigella flexneri*, *Shigella dysenteriae*,
Campylobacter jejuni, *Yersinia enterocolitica*, *Clostridia difficile*

PATHOGENESIS

- ▶ Reactive arthritis usually develops **2-6 weeks after** a genitourinary or gastrointestinal **infection**.
- ▶ Recent evidence indicates that a preceding *Chlamydia* **respiratory** infection may also trigger reactive arthritis.
- ▶ About **10%** of patients **do not have** a preceding symptomatic infection.
- ▶ The frequency of **reactive arthritis after enteric infection averages 1%-4%** but varies greatly, even among outbreaks of the same organism.

PATHOGENESIS

- ▶ Genetics and environmental factors play an important role in the pathogenesis of SpA .
- ▶ Strong linkage between HLA B27 and SpA.
- ▶ Twin studies in Ankylosing Spondylitis (AS)
 - ▶ Concordance of 63% and 13% in monozygotic and dizygotic twins, respectively
 - ▶ Approximately 90% of the risk for AS is related to genetic makeup.

PATHOGENESIS

- ▶ HLA B27 is present in at least 95% of AS patients in the US, Europe and China

- ▶ The prevalence of HLA B27 in the general population is up to 9%

(Feltkamp et al, Curr Opin Rheumatol 2001; 13: 285)

- ▶ The prevalence of AS parallels that of HLA B27

(Gonzales-Roces et al, Tissue Antigens 1997: 49: 116)

PATHOGENESIS

HLA B27 was found in :

- 90% of patients with Ankylosing spondylitis;
- 60-80% of patients with Reactive arthritis;
- 50% of patients with Enteropathic arthritis;
- 50% of patients with Psoriatic arthritis.

**Not every person HLA-B27 possessor develops
Seronegative spondyloarthropathy!!!**

HLA B27 contributes 16-50% of the total genetic risk for AS.
Other genetic and environmental factors may play a role.

PATHOGENESIS

HLA B27 – Structure and pathogenicity

- ▶ Belongs to the MHC class I molecules
- ▶ HYPOTHESIS – disease associated HLA B27 (HLA B2705 and HLA B2704) molecules induce arthritis by presenting to CD8+ T cells receptors certain “arthritogenic” peptides.
- ▶ Composed of 45kDa polymorphic heavy chain complexed with a 12kDa monomorphic unit - β 2 microglobulin

PATHOGENESIS

HLA B27 specific CD8+ T lymphocytes in SpA HYPOTHESIS

- ▶ There are certain immunodominant arthritis-causing HLA B27-specific antigenic peptides which are shared by the arthritis causing pathogens.
- ▶ These peptides also cross-react with autoantigens.
- ▶ When HLA B27 individual is infected with an arthritis-causing pathogen, an HLA B27 specific, CD8+ T lymphocytes mediated autoimmune response would be initiated in the joints.

PATHOGENESIS

HLA B27 specific CD8+ T lymphocytes (CTL) in SpA

- ▶ There are CD8+ lymphocytes in the joints that recognize bacterial and self-antigens.
- ▶ These CTL recognize HLA B27 in the context of bacteria-infected target cells or bacterial derived peptides, or simply HLA B27 positive target cells with only endogenous peptides.

PATHOGENESIS

HLA B27 specific CD8+ T lymphocytes (CTL) in SpA

- ▶ The T-lymphocyte response in the joints is oligoclonal, indicating that there is a limited number of responsible antigens.

PATHOGENESIS

Animal Models

- ▶ Introduction of the HLA B27 gene + the human β 2 microglobulin gene into rats results in a clinical syndrome that resembles ReA.
- ▶ Requirement for pathogen: Transgenic rats do not develop disease if raised in a germ-free environment.

PATHOGENESIS

Animal Models

- ▶ Mice that express human HLA B27 heavy chain transgene, but with deletion of the β 2 microglobulin gene, also develop arthritis.

(Khare et al, Rheum Dis Clin North Am 1998; 24: 883)

- ▶ Thus, HLA B27 may cause arthritis via a mechanism distinct from the classical model of peptide antigen presentation to CD8+ T cells.
- ▶ HLA B27 heavy chains can form stable dimers with no β 2 microglobulin.
- ▶ Those dimers can present antigens to T lymphocytes.

PATHOGENESIS

HLA B27 Unfolding Theory

- ▶ HLA B27 molecules differ from other MHC class I molecules by a significantly slower rate of folding in the endoplasmic reticulum (ER).
- ▶ Unfolded protein accumulates in the ER.
- ▶ This causes an overloading response.
- ▶ Activation of NF- κ B leads to proinflammatory cytokine production

PATHOGENESIS

Genes other than HLA B27

- ▶ HLA B60, alone or in tight linkage to another gene increases the susceptibility to AS, independently of HLA B27.

PATHOGENESIS

Infection in ReA

- ▶ Studies utilizing electron microscopy and PCR have documented the presence of fragments of mucosal bacteria in joints of ReA patients.

(Granfors et al, Arthritis Rheum 1998; 41: 855

Taylor-Robinson et al, Lancet 1992; 340: 81)

- ▶ Attempts to culture viable bacteria from joints of ReA patients have failed.
- ▶ The presence of Chlamydia Trachomatis DNA in the joints **is not** specific for ReA.

(Wilkinson et al, Arthritis Rheum 1998; 41: 485)

PATHOGENESIS

Interaction between infection and HLA B27 in ReA

- ▶ The bacteria associated with ReA have 2 features in common:
 - Invasive
 - Facultative intracellular
- ▶ Cell lines transfected with HLA B27 are more resistant to bacterial invasion.
- ▶ Invading bacteria to HLA B27 transfected cell lines survive longer
- ▶ HLA B27 can modify cellular activities that can be important in the pathogenesis of infection

Clinical features

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CLINICAL FEATURES

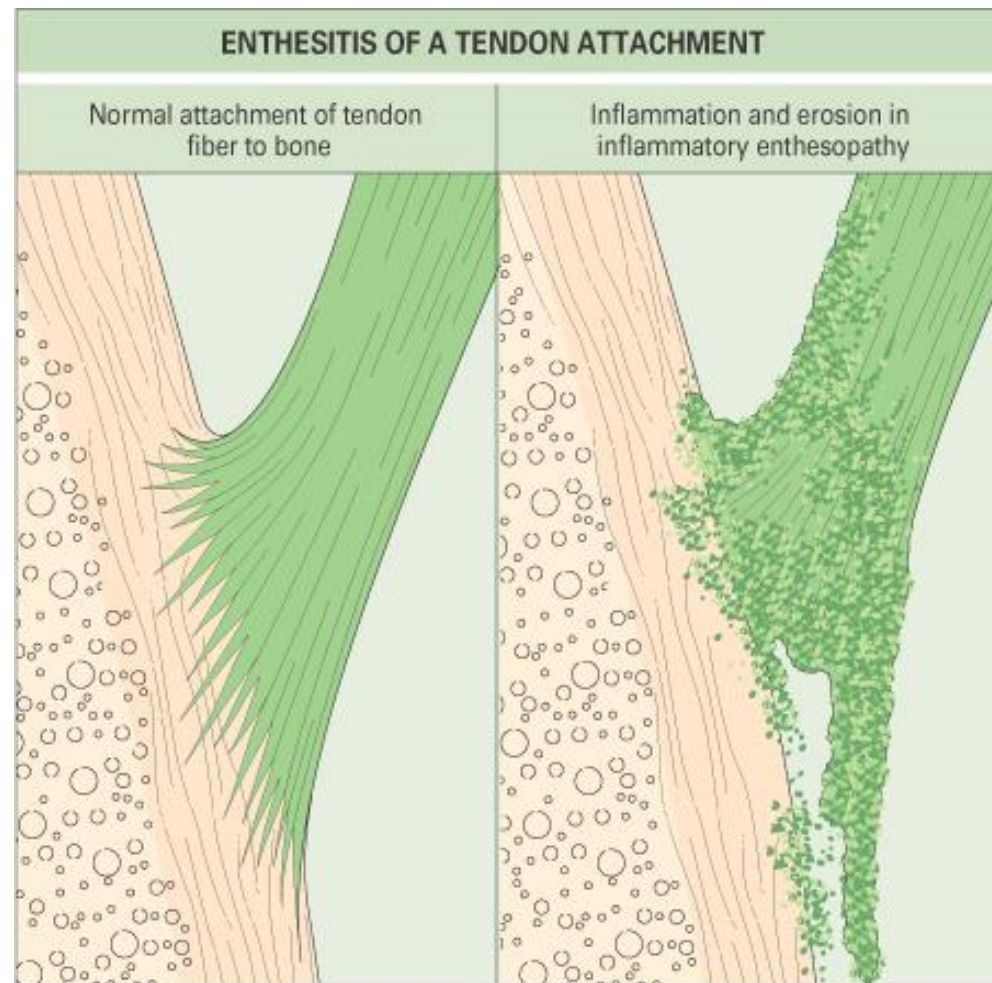
PERIPHERAL ARTHRITIS

- ▶ Acute onset
- ▶ Involves predominantly lower extremities
- ▶ Asymmetrical
- ▶ Oligoarticular (1-3 joints)

CLINICAL FEATURES

Enthesopathy

- ▶ Inflammation around the site of insertion of ligaments, tendons, capsules and fascia.
- ▶ Accompanied with new bone formation.
- ▶ Common sites – insertion of the Achilles tendon or the plantar fascia



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Enthesitis of a tendon attachment. The invagination of the tendon fiber into bone in a normal patient contrasts with the inflammation and erosion noted in enthesitis.



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Enthesitis involving the insertion of the right tendo Achilles.

TABLE 114.2 FREQUENCY OF ENTHESITIS IN THE DIFFERENT SPONDYLOARTHROPATHIES

Spondyloarthropathy	Frequency of enthesitis (%)
Ankylosing spondylitis	25–28
Reactive arthritis	13–58
Psoriatic arthritis	20
Spondarthritis associated with IBD	7–33
Undifferentiated spondarthritis	27

IBD, irritable bowel disease

CLINICAL FEATURES

Dactylitis (Sausage Finger)

- ▶ Swelling of the entire digit
- ▶ Enthesopathy along the entire digit
- ▶ Mild tenderness
- ▶ Occurs only in reactive arthritis and psoriatic arthritis



Sausage toe in Reiter's syndrome Sausage toe (with diffuse swelling) of the second digit and mild keratoderma blenorrhagica on the dorsum of the foot in a man with Reiter's syndrome. Courtesy of Craig Wiesenhuber, MD and David Yu, MD.



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Dactylitis of the second toe.

Dactylitis



CLINICAL FEATURES

Inflammatory Back Pain

- ▶ Begins before the age of 40
- ▶ Insidious in onset
- ▶ At least three months' duration
- ▶ Associates with morning stiffness
- ▶ Improved by exercise

CLINICAL FEATURES

Genital Lesions – Circinate Balanitis

- ▶ An important feature of ReA
- ▶ Occur even if disease is precipitated by GI infection
- ▶ Shallow ulcers on the glans penis or at the urethral meatus
- ▶ Usually painless

CLINICAL FEATURES

Skin Lesions – Keratoderma Blennorrhagica

- ▶ Involves soles and palms
- ▶ Identical to pustular psoriasis
- ▶ Nail involvement





Keratoderma blennorrhagica in Reiter's syndrome Keratoderma blennorrhagica on the soles of a patient with Reiter's syndrome. These lesions, which are indistinguishable from pustular psoriasis, begin as clear vesicles on erythematous bases and progress to macules, papules, and nodules. Courtesy of Professor Victor Newcomer, UCLA.



Keratoderma blenorrhagica Keratoderma blenorrhagica involving the toes of a patient with Reiter's syndrome. The lesions are composed of macules, papules, and nodules, and the nails are thickened and ridged. Courtesy of Professor Victor Newcomer, UCLA.

- Unghiile pot deveni opace, friabile, de culoare gălbue, oniholizis.



CLINICAL FEATURES

Nonspecific Urethritis

- ▶ Negative bacterial cultures
- ▶ Negative tests for Chlamydia infection
- ▶ May be associated with prostatitis

Oral Ulcers

- ▶ Early in the course
- ▶ Superficial
- ▶ painless



© ACR

CLINICAL FEATURES

Inflammatory eye disease

- ▶ **Conjunctivitis** – common in ReA
- ▶ **Iritis** –acute, unilateral,
lasts several months
not parallel to joint activity

Conjunctivitis in ReA



CLINICAL FEATURES

Inflammation of bowel mucosa

- ▶ Prevalence – up to 67% of patients with SpA
- ▶ Asymptomatic
- ▶ Acute or chronic
- ▶ Correlates with peripheral joint activity

CLINICAL FEATURES

Cardiovascular System Involvement

- ▶ In long standing and severe disease
- ▶ Aortic valve regurgitation
- ▶ Conduction abnormalities (AV node)
- ▶ Myocarditis

CLINICAL FEATURES

Kidney involvement

- Mild proteinuria and microhematuria.
- In some cases IgA deposition nephropathy with glomerulopathy was registered.
- Kidney amyloidosis - with A type amyloid can be registered in up to 9% of ReA patients.

Laboratory tests and imaging

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LABORATORY INVESTIGATION

- ▶ No specific laboratory tests
- ▶ Acute phase reaction: elevates ESR and CRP, mild anemia, leukocytosis

LABORATORY INVESTIGATION

Evidence of preceding infection

- ▶ Chlamidia trachomatis infection
 - ▶ May be clinically silent (particularly in women)
 - ▶ Diagnosed by serologic tests or by detection of chlamydial DNA in urine using ligase chain reaction (LCR) or PCR
- ▶ Stool cultures for arthritis-causing organisms
- ▶ Throat or urogenital tract cultures can be performed.

LABORATORY INVESTIGATION

Testing for HLA B27

- ▶ HLA B27 positive individuals have 20-fold increased risk of developing SpA
- ▶ Family history of SpA increases risk conferred to the presence of HLA B27 alone

LABORATORY INVESTIGATION

Testing for HLA B27

- ▶ When three or more features of SpA are present, the results of HLA B27 testing will not affect the diagnosis.
- ▶ Useful in patients with only one or two features of SpA.

(Rudawaleit et al. Ann Rheum Dis 2004; 63:535)

LABORATORY INVESTIGATION

Testing for HIV infection

- ▶ SpA are common in areas with high prevalence of HIV infection, regardless of the frequency of HLA B27.
- ▶ 272 out of 595 new consecutive patients attending an arthritis clinic in Zambia, were diagnosed with SpA. 87% of ReA and 98% of undifferentiated SpA were HIV seropositive

(Njobvu P et al, J Rheumatol 1998; 25:1553)

IMAGING

Peripheral joints

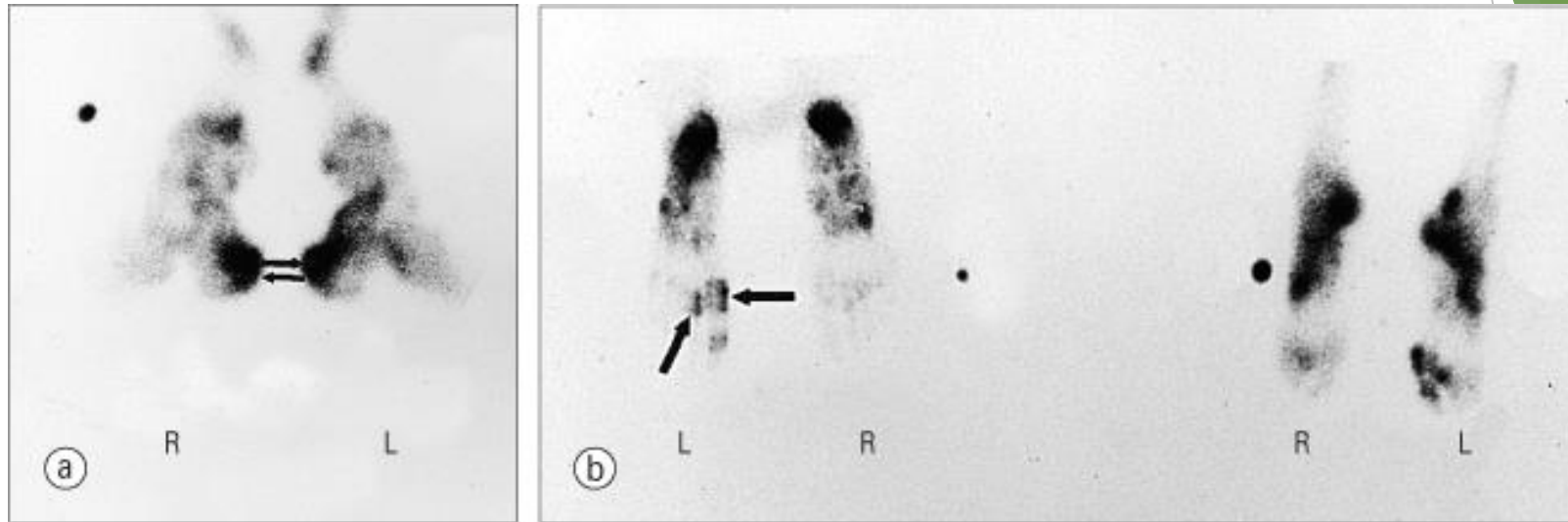
- ▶ Fluffy erosions at the enthesitis of the hindfoot – typical
- ▶ Periosteal spurs
- ▶ Destructive erosions at joint margins – not prominent



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Radiograph of enthesitis at the attachment of the plantar aponeurosis (arrow). (Courtesy of Dr Freyschmidt, Bremen, Germany).

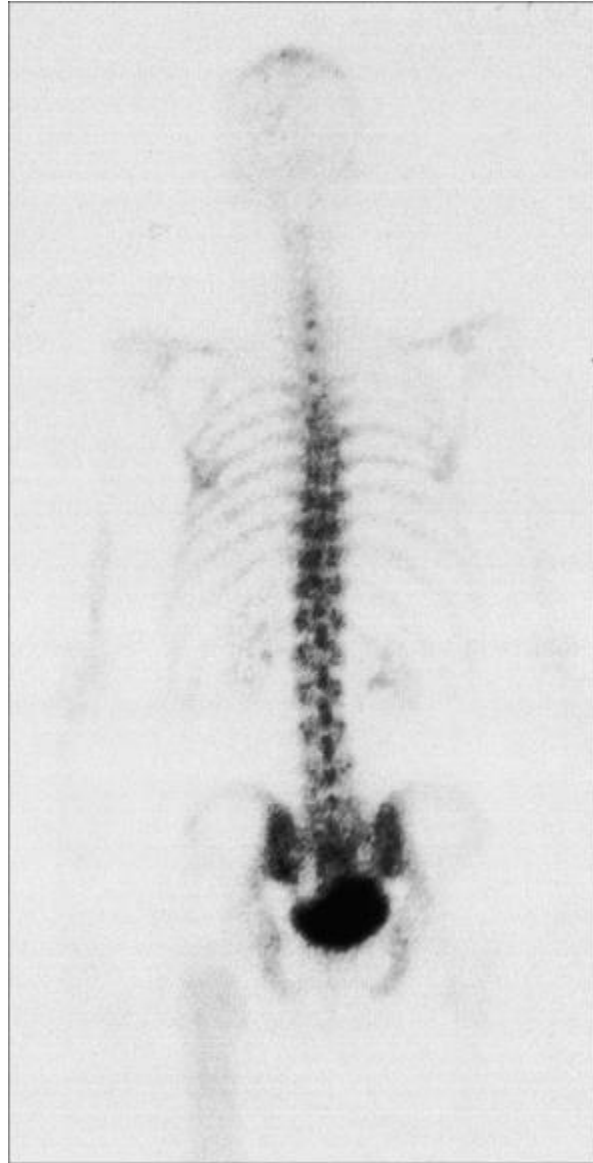




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Technetium-99m scan of the feet of a patient with reactive arthritis.

Although conventional radiographs were normal, this scan demonstrates the distribution of uptake in a patient with reactive arthritis. (a) There is uptake at the inferior aspect of the calcanei, at the attachment of the plantar aponeuroses (arrows). (b) There is also uptake along the outside of the proximal phalanges in the periosteal area of the first and second digit of the left foot (arrows).



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Scintigraphy of enthesitis of the processi spinosorum. An increased enhancement at the attachment of the processi spinosorum and of the iliac joint was detected by scintigraphy. (Courtesy of Drs Boerner and Gratz, Department of Nuclear Medicine, Medical School, Hannover, Germany.)

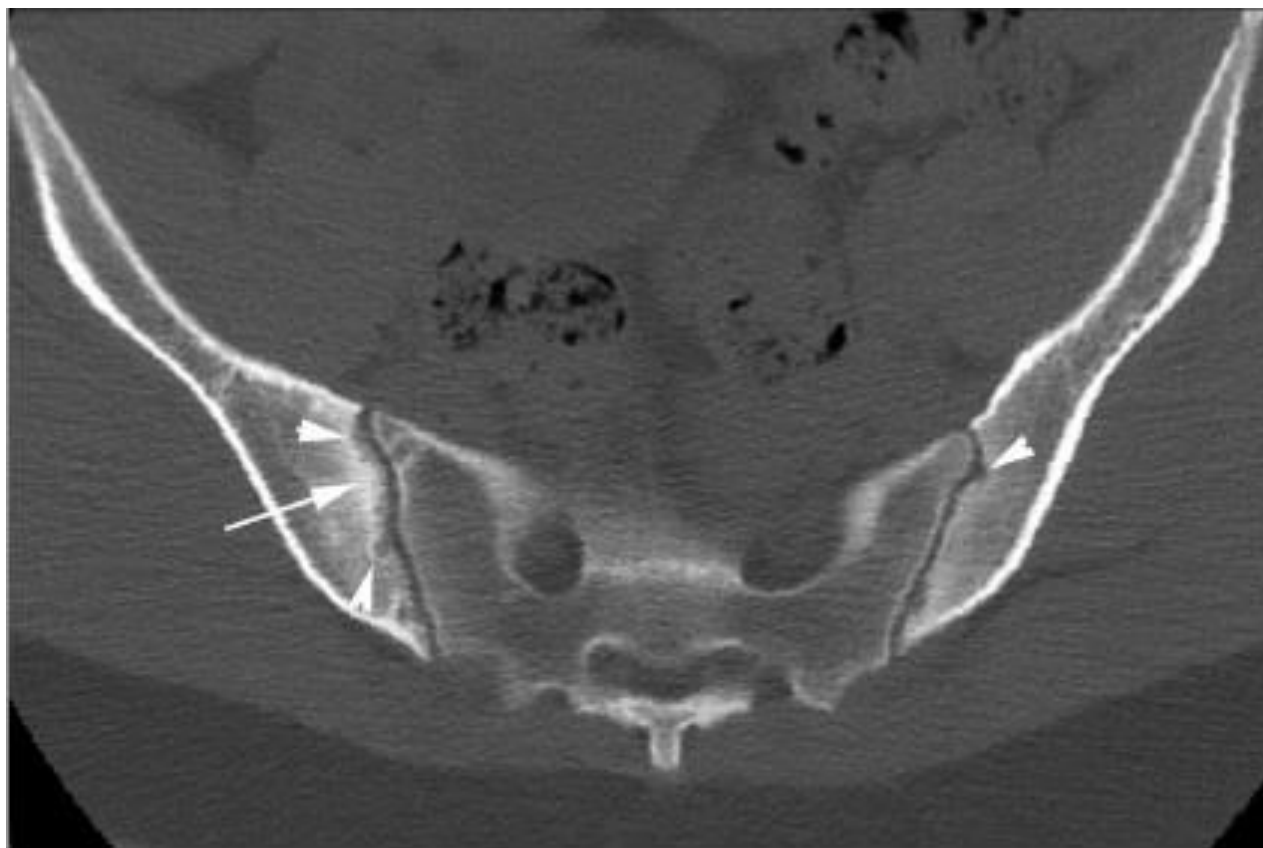
IMAGING

Sacroiliac joints

- ▶ 5-10% of patients with early SpA
- ▶ 14-49% of patients with chronic disease
- ▶ Often unilateral

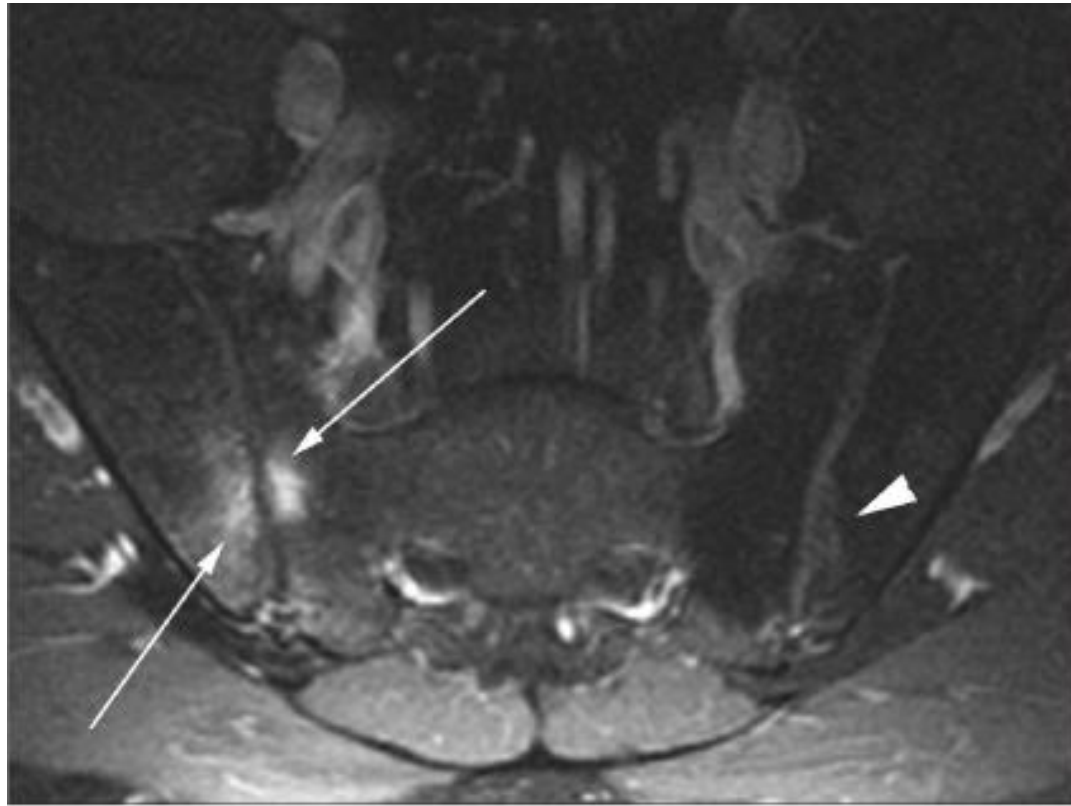


AP view of sacroiliac joint.
The white cortical line is intact
on the sacral side. It is ill-
defined on the iliac side
(arrows).



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Axial CT image of the sacroiliac joints in a patient with psoriatic arthritis. There is bilateral, asymmetric joint involvement. Erosions are noted bilaterally (arrow-heads) and there is eburnation (arrow).



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MR image of the sacroiliac joints in a patient with undifferentiated spondyloarthropathy. Axial T1-weighted image with fat suppression following intravenous administration of Gd-DTPA demonstrates increased signal intensity in the subchondral bone marrow within the iliac and sacral sides of the right joint (arrows) and early erosions of the left joint (arrowhead).

IMAGING

Syndesmophytes of the spine

- ▶ Bony overgrowths that result from enthesopathy
- ▶ Asymmetric in undifferentiated SpA and in PsA
- ▶ Comma-shaped
- ▶ Common in the lower thoracic and upper 3 lumbar vertebrae



Syndesmophyte in Reiter's syndrome An anterior syndesmophyte of the spine (arrow) in a patient with Reiter's syndrome. Syndesmophytes are bony outgrowths that are induced by an enthesopathy of the spine. The syndesmophytes in Reiter's syndrome and psoriasis are asymmetric, in contrast to their symmetric occurrence in ankylosing spondylitis. Courtesy of Craig Wiesenhutter, MD and David Yu, MD.

Classification criteria

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CLASSIFICATION AND DIAGNOSIS (ESSG)

TABLE 101.4 EUROPEAN SPONDYLOARTHROPATHY STUDY GROUP CLASSIFICATION CRITERIA

Inflammatory spinal pain

or

Synovitis (asymmetric, predominantly in lower limbs)

and any one of the following:

- Positive family history
- Psoriasis
- Inflammatory bowel disease
- Alternate buttock pain
- Enthesopathy

Sensitivity, 77%; specificity, 89%

Adding:

- Sacroiliitis

Sensitivity, 87%; specificity, 87%

(From Dougados *et al.*⁵)

Dougados *et al*, Arthritis Rheum 1991; 34:1218

UNDIFFERENTIATED SPONDYLOARTHROPATHY

Patients who

- ▶ fulfill the ESSG criteria for SpA
- ▶ Do not belong to any of the following categories:

Ankylosing Spondylitis

ReA

Psoriatic Arthritis

Arthropathy associated with IBD

Juvenile Chronic Arthritis – Juvenile
onset AS

CLASSIFICATION

- ▶ After onset of illness:
 - ▶ Acute <6 months;
 - ▶ Trenchant (dragged on) 6-12 months,
 - ▶ Chronic > 12 months;

COURSE AND PROGNOSIS

- ▶ Self-limiting, monophasic, resolves within 6 months – 35%
- ▶ Recurrent – 35%
- ▶ Chronic – 25%
- ▶ Severe destructive course – 5%

COURSE AND PROGNOSIS

Risk factors for chronic arthritis

- ▶ HLA B27
- ▶ Male gender
- ▶ Extra-articular lesions
- ▶ Post-venereal ReA:
 - ▶ 68% of post-Chlamydia ReA develop chronic disease (Keat A et al, N Engl J Med 1983;309:1606)
 - ▶ 5 % of post – Yersinia ReA have recurrent arthritis and 2.4% have chronic course (Leirisalo-Repo et al, Arthritis Rheum 1988; 31: 533)
 - ▶ 23% of post-Salmonella have recurrent arthritis (Leirisalo-Repo et al, Arthritis Rheum 1994; 37: 23)

TREATMENT

Nonsteroidal Anti-Inflammatory Drugs (NSAID)

- ▶ Pain caused by arthritis and enthesopathy usually responds to NSAID promptly.
- ▶ Low dose Prednisone – usually not effective
- ▶ There is no controlled study to indicate if a particular NSAID is superior to others.
- ▶ COX-2 inhibitors may have a role.
- ▶ It is unlikely that continuous use after resolution of symptoms will prevent recurrence.

TREATMENT

Antibiotics

- ▶ Should be considered when infection is present.
- ▶ Enteric infections by Salmonella, Shigella and Campylobacter are usually self-limited, and do not require antimicrobial therapy
- ▶ Quinolone therapy should be considered in cases of protracted enteric infection.

TREATMENT

Antibiotics

▶ Tetracycline group

- ▶ Doxycycline - 200 mg / day
- ▶ Lymecycline - 200 mg/day

▶ Macrolide group:

- ▶ Clarithromycin - 1 g / day
- ▶ Azithromycin - 500 mg - first day, after THEN 250 mg / day - 6 days
- ▶ Roxithromycin - 300 mg / day

▶ Quinolones:

- ▶ Ciprofloxacin - 1 g/ day
- ▶ Ofloxacin - 400 mg/ day
- ▶ Lomefloxacin - 400 mg/ day
- ▶ Perfloxacin - 800 mg/ day

TREATMENT

Antibiotics

- ▶ Ciprofloxacin for 3 months for enteric infection associated ReA significantly reduced the proportion of patients who developed chronic in long term follow-up, as compared to placebo (41% vs. 8%, respectively).

(Yli-Kerrotu et al, Ann Rheum Dis 2003; 62: 880)

- ▶ Until more data from controlled studies become available, the general consensus is that prolonged antimicrobial therapy does not change the course of the disease.

(Leirisalo-Repo et al, Rheum Dis Clin North Am 1998; 24: 737)

TREATMENT

Antibiotics

- ▶ Active urinary tract infection (UTI) with *Chlamydia trachomatis* – two week antimicrobial course for patient and sexual partner.

- ▶ Lymecycline (200mg/day) for 3 months decreases the duration of acute post-*Chlamydia* ReA in a double blind placebo-controlled trial

(Lauhio et al, *Arthritis Rheum* 1991; 34:6)

TREATMENT

Antibiotics

- ▶ The effect of antimicrobial therapy on patients with chronic or recurrent ReA is not clear.
- ▶ If antibiotics are given, doxycycline (100 mg/d), lymecycline (300 mg bid) and tetracycline (500 mg tid) seem to be equally effective)
- ▶ In a retrospective analysis of 109 patients with ReA, the incidence of recurrent arthritis was lower in patients treated with tetracycline or erythromycin for recurrent episodes of non-gonococcal urethritis, than in those treated with penicillin.

TREATMENT

Sulfasalazine

- ▶ 5-aminosalicylic acid (5-ASA) conjugated with sulfapyridine.
- ▶ Sulfapyridine – active in RA
- ▶ 5-ASA – active in IBD
- ▶ It is unclear which part is active in SpA.
- ▶ 5-ASA alone may have some efficacy in SpA

(Thomson et al, J Rheumatol 2000; 27: 714,

Dekker-Saeys et al, J Rheumatol 2000; 27:723)

TREATMENT

Sulfasalazine

- ▶ Dose: 2000-3000 mg/day
- ▶ Response expected within 4 months.
- ▶ Can be discontinued if a complete remission of several months duration is achieved.

TREATMENT

METHOTREXATE (MTX)

- ▶ Initial dose - 7.5 mg/week, orally
- ▶ Maximal dose – 25 mg/week
- ▶ Concurrent administration of Folic acid 1 mg/d reduces side effects.

TREATMENT

MTX

- ▶ Data from prospective placebo-controlled trials of MTX in SpA are not available.
- ▶ May be used in patients who failed 3-6 months course of salazopyrine and are not candidates for anti-TNF blockade

TREATMENT

Tumor necrosis factor α antagonists

- ▶ Infliximab (Remicade)- chimeric monoclonal anti-TNF α antibody
- ▶ Etanercept (Enbrel)- TNF α receptor linked to Fc portion of human IgG1
- ▶ Adalimumab (Humira) – recombinant monoclonal anti-TNF α antibody

SPONDYLOARTHROPATHY- TREATMENT

Tumor necrosis factor α antagonists

- ▶ Infliximab improved symptoms of peripheral and axial disease in patients with Crohn's disease and SpA.

(Van den Bosch et al, Lancet 2000; 356: 1821)

- ▶ In an open study. Infliximab (5 mg/kg at weeks 0, 2 and 6) improved symptoms in all subsets of patients with SpA (2/21 with undifferentiated SpA)

(Van den Bosch et al, Ann Rheum Dis 2000; 59:428)

- ▶ Maintenance therapy (5 mg/kg every 14 weeks) for one year in 19 of the above, was safe and controlled disease manifestations.

(Kruithof et al, Ann Rheum 2002; 61:207)

