

Recommendation 9: Predictors of Persistent Inflammatory Arthritis in Patients with UPIA

Recommendation 9

Learning Objectives



At the end of this section participants should be able to:

- **Describe and give examples of the predictors of persistent inflammatory arthritis in patients with UPIA**

Learning Objectives

At the end of this section participants should be able to:

- Describe and give examples of the predictors of persistent inflammatory arthritis in patients with UPIA

Recommendation 9

Predictors of persistent inflammatory arthritis should be documented and include:

- Disease duration of ≥ 6 weeks [1b, A]
- Morning stiffness >30 min [4, C]
- Functional impairment [4, C]
- Involvement of small joints [4, C] and/or knee [4, C]
- ≥ 3 joints [1b, B], ACPA [4, C] and/or RF positivity [4, C]
- Presence of radiographic erosion [1b, B]

Recommendation 9

Predictors of persistent inflammatory arthritis should be documented and include disease duration of ≥ 6 weeks [1b, A], morning stiffness >30 min [4, C], functional impairment [4, C], involvement of small joints [4, C] and/or knee [4, C], ≥ 3 joints [1b, B], ACPA [4, C] and/or RF positivity [4, C] and presence of radiographic erosion [1b, B].

This recommendation had an agreement of 8.6/10.

67% of rheumatologists felt that this recommendation was already implemented in their practice and 25% felt it would change their practice.

Undifferentiated Arthritis



Undifferentiated Arthritis

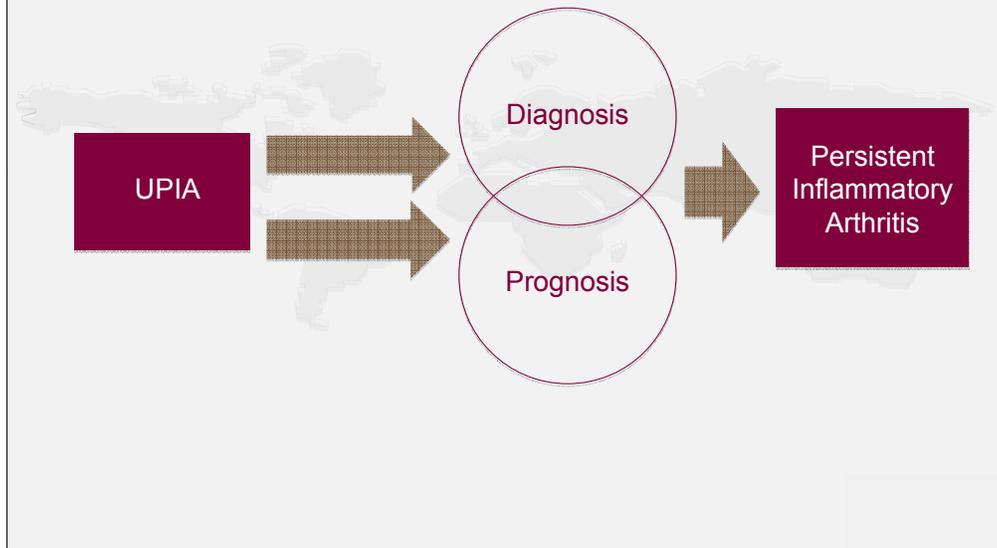
- Early stage of classifiable disease
- Part of an overlap of disease
- Partial form of a defined disease
- Disease of unknown origin

UA envelops a heterogeneous group of recent onset arthritides that are not classifiable within established criteria sets such as those of the American College of Rheumatology (ACR) and The European League Against Rheumatism (EULAR).

UA may represent an early stage of a classified form of arthritis that will eventually be definable; an overlap of more than one disease; a partial form of a defined disease; or a disease of unknown origin. UA overall has a better prognosis than RA as it encompasses a spectrum of self-limited disorders. As compared to RA, a patient with UA usually presents with fewer affected joints, less radiographic erosions, better functional ability, and a greater likelihood of being seronegative. Patients with UA are also less likely than patients with RA to require treatment that involves the use of corticosteroids (such as Prednisone) or DMARDs and a substantial proportion of UA patients remit spontaneously.

Hitchon CA, Peschken CA, Shaikh S, El-Gabalawy HS. Early undifferentiated arthritis. *Rheum Dis Clin N Am*. 2005;31:605-626.

Factors which predict diagnosis & prognosis also predict persistence



With a diagnosis of UPIA, it is important to identify factors which will help predict a certain diagnosis and/or prognosis.

A key question is which patients will develop a persistent inflammatory arthritis. This can be thought of as a prognostic question, however, once persistent inflammatory arthritis is diagnosed, treatment is usually initiated. Thus, persistent inflammatory arthritis is in a sense a specific diagnosis. There is therefore overlap when considering the diagnostic and prognostic predictors of UPIA.

Summary Predictors of Persistent Disease



	UA	Mixed population
History	Disease duration	Disease duration ≥ 4 mo
		Symptom duration > 6 wk
	Morning stiffness	Morning stiffness
	Change of HAQ at 3 mo	HAQ at baseline
Physical exam	Synovitis at 2 wk	Arthritis ≥ 3 joints
		Swollen PIP joint, Small joint arthritis
	Knee involvement	MTP squeeze test +
Lab	Rheumatoid factor	IgM- Rheumatoid factor
	Anti-CCP	Anti-CCP (presence and level)
Imaging		Erosion (hand or feet)

Summary

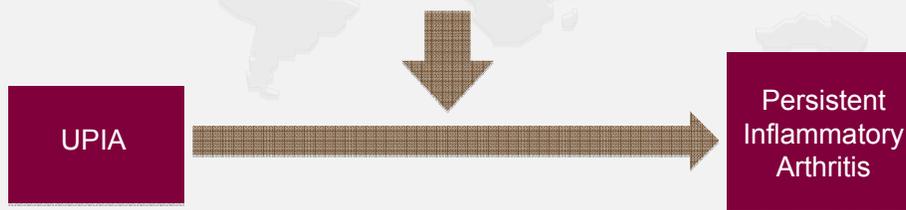
Predictors of persistent disease

- All variables listed in this table were independent predictors of persistent arthritis in UA and mixed population.
- There is no data regarding predictive value of genetic and soluble markers, ultrasound, and MRI for persistent arthritis.
- According to the "Oxford level of evidence scale", the level of evidence of each predictor is 1b, individual cohort study with $\geq 80\%$ follow-up

Factors which are independently associated with persistence of inflammatory arthritis



- Disease duration of ≥ 6 weeks [1b, A]
- Morning stiffness > 30 min [4, C]
- Functional impairment [4, C]
- Involvement of small joints [4, C] and/or knee [4, C]
- ≥ 3 joints [1b, B], ACPA [4, C] and/or RF positivity [4, C]
- Presence of radiographic erosion [1b, B]



Factors which are independently associated with persistence of inflammatory arthritis

The magnitude of the association in the same predictor was diverse among the studies depending on the patient characteristics (namely if the population was purely UPIA or not), the study design, and the variables used to adjust for in the models.

Disease Persistence



Features that predict persistent disease include:

- **History: disease duration, AM stiffness, change in HAQ**
- **Physical exam: presence of synovitis over time, knee involvement**
- **Laboratory findings: +RF, +ACPA**
- **Imaging findings: erosions of the hands or feet**

Summary

There are many important features on history, physical exam and investigations which are helpful in determining a patient's risk of developing a persistent arthritis

This recommendation incorporates many of the other recommendations

Summary



- **These features on history, physical exam and investigations are helpful in determining a patient's risk of developing a persistent arthritis**
- **This recommendation incorporates many of the other recommendations**

Summary

There are many important features on history, physical exam and investigations which are helpful in determining a patient's risk of developing a persistent arthritis

This recommendation incorporates many of the other recommendations

References (cont.)



-
- van der Helm-van Mil AH, Verpoort KN, Breedveld FC, Huizinga TW, Toes RE, de Vries RR. The HLA-DRB1 shared epitope alleles are primarily a risk factor for anti-cyclic citrullinated peptide antibodies and are not an independent risk factor for development of rheumatoid arthritis. *Arthritis Rheum.* 2006 Apr; 54(4):1117-1121.
 - van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum.* 2007 Feb; 56(2):433-440.
 - van Dongen H, van Aken J, Lard LR, Visser K, Roday HK, Hulsmans HM, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2007 May; 56(5):1424-1432.
 - van Gaalen FA, Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum.* 2004 Mar; 50(3):709-715.
 - Emad Y, Ragab Y, Shaarawy A, Raafat H, El-Kiki HA, Rasker JJ. Enhanced MRI in early undifferentiated oligoarthritis of the knee joints: improvements already visible after 2 months of DMARDs treatment. *Clin Rheumatol.* 2008 Sep; 27(9):1177-1182.

References



- Berthelot JM, Maugars Y, Castagne A, Audrain M, Prost A. Antiperinuclear factors are present in polyarthritis before ACR criteria for rheumatoid arthritis are fulfilled. *Ann Rheum Dis.* 1997 Feb; 56(2):123-125.
- Blaauw I, Dijkmans B, Bouma P, van der Linden S. Rational diagnosis and treatment in unclassified arthritis: how clinical data may guide requests for Lyme serology and antibiotic treatment. *Ann Rheum Dis.* 1993 Mar; 52(3):206-210.
- Feitsma AL, Toes RE, Begovich AB, Chokkalingam AP, de Vries RR, Huizinga TW, et al. Risk of progression from undifferentiated arthritis to rheumatoid arthritis: the effect of the PTPN22 1858T-allele in anti-citrullinated peptide antibody positive patients. *Rheumatology (Oxford).* 2007 Jul; 46(7):1092-1095.
- Inaoui R, Bertin P, Preux PM, Treves R. Outcome of patients with undifferentiated chronic monoarthritis: retrospective study of 46 cases. *Joint Bone Spine.* 2004 May; 71(3):209-213.
- Kaarela K, Tiitinen S, Luukkainen R. Long-term prognosis of monoarthritis. A follow-up study. *Scand J Rheumatol.* 1983; 12(4):374-376.

References (cont.)



-
- Kudo-Tanaka E, Ohshima S, Ishii M, Mima T, Matsushita M, Azuma N, et al. Autoantibodies to cyclic citrullinated peptide 2 (CCP2) are superior to other potential diagnostic biomarkers for predicting rheumatoid arthritis in early undifferentiated arthritis. *Clin Rheumatol.* 2007 Oct; 26(10):1627-1633.
 - Kvien TK, Glennas A, Melby K. Prediction of diagnosis in acute and subacute oligoarthritis of unknown origin. *Br J Rheumatol.* 1996 Apr; 35(4):359-363.
 - Saleem B, Mackie S, Quinn M, Nizam S, Hensor E, Jarrett S, et al. Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis? *Ann Rheum Dis.* 2008 Aug; 67(8):1178-1180.
 - Tamai M, Kawakami A, Uetani M, Takao S, Arima K, Fujikawa K, et al. Anti-cyclic citrullinated peptide antibody and magnetic resonance imaging-detection of bone marrow oedema are most important predictors in classification as well as prognostic evaluation of undifferentiated arthritis. *Ann Rheum Dis.* 2007; 66(Suppl II):338.
 - van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. *Ann Rheum Dis.* 2006 Jan; 65(1):20-25.

References (cont.)



-
- Duer A, Ostergaard M, Horslev-Petersen K, Vallo J. Magnetic resonance imaging and bone scintigraphy in the differential diagnosis of unclassified arthritis. *Ann Rheum Dis*. 2008 Jan; 67(1):48-51.
 - Kraan MC, Haringman JJ, Post WJ, Versendaal J, Breedveld FC, Tak PP. Immunohistological analysis of synovial tissue for differential diagnosis in early arthritis. *Rheumatology (Oxford)*. 1999 Nov; 38(11):1074-1080.
 - Morel J, Legouffe MC, Bozonat MC, Sany J, Eliaou JF, Daures JP, et al. Outcomes in patients with incipient undifferentiated arthritis. *Joint Bone Spine*. 2000 Jan; 67(1):49-53.
 - Appel H, Mertz A, Distler A, Sieper J, Braun J. The 19 kDa protein of *Yersinia enterocolitica* O:3 is recognized on the cellular and humoral level by patients with *Yersinia* induced reactive arthritis. *J Rheumatol*. 1999 Sep; 26(9):1964-1971.
 - Baeten D, Kruithof E, De Rycke L, Vandooren B, Wyns B, Boullart L, et al. Diagnostic classification of spondylarthropathy and rheumatoid arthritis by synovial histopathology: a prospective study in 154 consecutive patients. *Arthritis Rheum*. 2004 Sep; 50(9):2931-2941.

References (cont.)



-
- Braun J, Laitko S, Treharne J, Eggens U, Wu P, Distler A, et al. *Chlamydia pneumoniae*--a new causative agent of reactive arthritis and undifferentiated oligoarthritis. *Ann Rheum Dis.* 1994 Feb; 53(2):100-105.
 - Braun J, Tuszewski M, Ehlers S, Haberle J, Bollow M, Eggens U, et al. Nested polymerase chain reaction strategy simultaneously targeting DNA sequences of multiple bacterial species in inflammatory joint diseases. II. Examination of sacroiliac and knee joint biopsies of patients with spondyloarthropathies and other arthritides. *J Rheumatol.* 1997 Jun; 24(6):1101-1105.
 - Canete JD, Rodriguez JR, Salvador G, Gomez-Centeno A, Munoz-Gomez J, Sanmarti R. Diagnostic usefulness of synovial vascular morphology in chronic arthritis. A systematic survey of 100 cases. *Semin Arthritis Rheum.* 2003 Jun; 32(6):378-387.
 - Dryll A, Lansaman J, Cazalis P, Peltier AP, De Seze S. Light and electron microscopy study of capillaries in normal and inflammatory human synovial membrane. *J Clin Pathol.* 1977 Jun; 30(6):556-562.
 - El-Gabalawy HS, Goldbach-Mansky R, Smith D, 2nd, Arayssi T, Bale S, Gulko P, et al. Association of HLA alleles and clinical features in patients with synovitis of recent onset. *Arthritis Rheum.* 1999 Aug; 42(8):1696-1705.

References (cont.)

- Fendler C, Laitko S, Sorensen H, Gripenberg-Lerche C, Groh A, Uksila J, et al. Frequency of triggering bacteria in patients with reactive arthritis and undifferentiated oligoarthritis and the relative importance of the tests used for diagnosis. *Ann Rheum Dis*. 2001 Apr; 60(4):337-343.
- Hernandez-Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, et al. Exogenous sex hormones and the risk of rheumatoid arthritis. *Arthritis Rheum*. 1990 Jul; 33(7):947-953.
- Higami K, Hakoda M, Matsuda Y, Ueda H, Kashiwazaki S. Lack of association of HLA-DRB1 genotype with radiologic progression in Japanese patients with early rheumatoid arthritis. *Arthritis Rheum*. 1997 Dec; 40(12):2241-2247.
- Hitchon CA, Alex P, Erdile LB, Frank MB, Dozmorov I, Tang Y, et al. A distinct multicytokine profile is associated with anti-cyclical citrullinated peptide antibodies in patients with early untreated inflammatory arthritis. *J Rheumatol*. 2004 Dec; 31(12):2336-2346.
- Jansen LM, van Schaardenburg D, van der Horst-Bruinsma IE, Dijkmans BA. One year outcome of undifferentiated polyarthritis. *Ann Rheum Dis*. 2002 Aug; 61(8):700-703.

References (cont.)



- Jendro MC, Raum E, Schnarr S, Kohler L, Zeidler H, Kuipers JG, et al. Cytokine profile in serum and synovial fluid of arthritis patients with Chlamydia trachomatis infection. *Rheumatol Int.* 2005 Jan; 25(1):37-41.
- Jones VE, Jacoby RK, Cowley PJ, Warren C. Immune complexes in early arthritis. II. Immune complex constituents are synthesized in the synovium before rheumatoid factors. *Clin Exp Immunol.* 1982 Jul; 49(1):31-40.
- Jones V, Taylor PC, Jacoby RK, Wallington TB. Synovial synthesis of rheumatoid factors and immune complex constituents in early arthritis. *Ann Rheum Dis.* 1984 Apr; 43(2):235-239.
- Machold KP, Stamm TA, Eberl GJ, Nell VK, Dunky A, Uffmann M, et al. Very recent onset arthritis--clinical, laboratory, and radiological findings during the first year of disease. *J Rheumatol.* 2002 Nov; 29(11):2278-2287.
- Matsumoto I, Lee DM, Goldbach-Mansky R, Sumida T, Hitchon CA, Schur PH, et al. Low prevalence of antibodies to glucose-6-phosphate isomerase in patients with rheumatoid arthritis and a spectrum of other chronic autoimmune disorders. *Arthritis Rheum.* 2003 Apr; 48(4):944-954.
- Nissila M, Isomaki H, Kaarela K, Kiviniemi P, Martio J, Sarna S. Prognosis of inflammatory joint diseases. A three-year follow-up study. *Scand J Rheumatol.* 1983; 12(1):33-38.

References (cont.)



-
- Parker JD, Capell HA. An acute arthritis clinic--one year's experience. *Br J Rheumatol.* 1986 Aug; 25(3):293-295.
 - Pazdur J, Ploski R, Bogunia-Kubik K, Polak M, Jastrzebska E, Lange A, et al. Can HLA-DRB1 typing have prognostic value in patients with undifferentiated chronic arthritis? *Tissue Antigens.* 1998 Jun; 51(6):678-680.
 - Rooney T, Murphy E, Benito M, Roux-Lombard P, FitzGerald O, Dayer JM, et al. Synovial tissue interleukin-18 expression and the response to treatment in patients with inflammatory arthritis. *Ann Rheum Dis.* 2004 Nov; 63(11):1393-1398.
 - Savolainen E, Kautiainen H, Koivula MK, Luosujarvi R, Risteli J, Kaipainen-Seppanen O. Change of diagnoses and outcome of patients with early inflammatory joint diseases during a mean 13-month follow-up. *Scand J Rheumatol.* 2007 May-Jun; 36(3):194-197.
 - Shine B, Bourne JT, Begum Baig F, Dacre J, Doyle DV. C reactive protein and immunoglobulin G in synovial fluid and serum in joint disease. *Ann Rheum Dis.* 1991 Jan; 50(1):32-35.
 - Siala M, Jaulhac B, Gdoura R, Sibilia J, Fourati H, Younes M, et al. Analysis of bacterial DNA in synovial tissue of Tunisian patients with reactive and undifferentiated arthritis by broad-range PCR, cloning and sequencing. *Arthritis Res Ther.* 2008; 10(2):R40.

References (cont.)



-
- Stahl HD, Seidl B, Hubner B, Altrichter S, Pfeiffer R, Pustowoit B, et al. High incidence of parvovirus B19 DNA in synovial tissue of patients with undifferentiated mono- and oligoarthritis. *Clin Rheumatol.* 2000; 19(4):281-286.
 - van der Helm-van Mil AH, Verpoort KN, le Cessie S, Huizinga TW, de Vries RR, Toes RE. The HLA-DRB1 shared epitope alleles differ in the interaction with smoking and predisposition to antibodies to cyclic citrullinated peptide. *Arthritis Rheum.* 2007 Feb; 56(2):425-432.
 - Verpoort KN, van Gaalen FA, van der Helm-van Mil AH, Schreuder GM, Breedveld FC, Huizinga TW, et al. Association of HLA-DR3 with anti-cyclic citrullinated peptide antibody-negative rheumatoid arthritis. *Arthritis Rheum.* 2005 Oct; 52(10):3058-3062.
 - Verpoort KN, Jol-van der Zijde CM, Papendrecht-van der Voort EA, Ioan-Facsinay A, Drijfhout JW, van Tol MJ, et al. Isotype distribution of anti-cyclic citrullinated peptide antibodies in undifferentiated arthritis and rheumatoid arthritis reflects an ongoing immune response. *Arthritis Rheum.* 2006 Dec; 54(12):3799-3808.

References (cont.)



-
- Visser K, Verpoort KN, van Dongen H, van der Kooij SM, Allaart CF, Toes RE, et al. Pretreatment serum levels of anti-cyclic citrullinated peptide antibodies are associated with the response to methotrexate in recent-onset arthritis. *Ann Rheum Dis.* 2008 Aug; 67(8):1194-1195.
 - Wesoly J, Hu X, Thabet MM, Chang M, Uh H, Allaart CF, et al. The 620W allele is the PTPN22 genetic variant conferring susceptibility to RA in a Dutch population. *Rheumatology (Oxford).* 2007 Apr; 46(4):617-621.
 - Wilbrink B, van der Heijden IM, Schouls LM, van Embden JD, Hazes JM, Breedveld FC, et al. Detection of bacterial DNA in joint samples from patients with undifferentiated arthritis and reactive arthritis, using polymerase chain reaction with universal 16S ribosomal RNA primers. *Arthritis Rheum.* 1998 Mar; 41(3):535-543.
 - Wilkinson NZ, Kingsley GH, Sieper J, Braun J, Ward ME. Lack of correlation between the detection of *Chlamydia trachomatis* DNA in synovial fluid from patients with a range of rheumatic diseases and the presence of an antichlamydial immune response. *Arthritis Rheum.* 1998 May; 41(5):845-854.

References (cont.)

- Zavala-Cerna MG, Nava A, Garcia-Castaneda E, Duran-Gonzalez J, Arias-Merino MJ, Salazar-Paramo M. Serum IgG activity against cyclic citrullinated peptide in patients evaluated for rheumatoid factor correlates with the IgM isotype. *Rheumatol Int.* 2008 Jul; 28(9):851-857.
- Zeidler H, Werdier D, Klauder A, Brinkmann S, Viswat M, Mones ML, et al. Undifferentiated arthritis and spondylarthropathy as a challenge for prospective follow-up. *Clin Rheumatol.* 1987 Sep; 6 Suppl 2:112-120.
- O'Hara R, Murphy EP, Whitehead AS, FitzGerald O, Bresnihan B. Local expression of the serum amyloid A and formyl peptide receptor-like 1 genes in synovial tissue is associated with matrix metalloproteinase production in patients with inflammatory arthritis. *Arthritis Rheum.* 2004 Jun; 50(6):1788-1799.