Rheumatology Updates

Choosing Wisely
American College of Rheumatology
Jefferson Roberts, MD

Number 1

- Do not test ANA sub-serology without positive ANA and clinical suspicion of immune-mediated disease

Negative ANA

Do Not Test

- Double stranded DNA
- Smith
- RNP
- Scl-70
- Centromere

Consider Testing

- Jo-1
- SSA/Ro
- SSB/La

Disease	Frequency of Positive ANA Result, %
Diseases for which an ANA test is very useful for diagnosis	
SLE	95–100
Systemic sclerosis (scleroderma)	60–80
Diseases for which an ANA test is somewhat useful for diagnosis	
Sjögren syndrome	40–70
Idiopathic inflammatory myositis (dermatomyositis or polymyositis)	30–80
Diseases for which an ANA test is useful for monitoring or prognosis	
Juvenile chronic oligoarticular arthritis with uveitis	20–50
Raynaud phenomenon	20–60
Conditions in which a positive ANA test result is an intrinsic part of the diagnostic criteria	
Drug-induced SLE	~100
Autoimmune hepatic disease	~100
MCTD	~100
Diseases for which an ANA test is not useful in diagnosis	
Rheumatoid arthritis	30–50
Multiple sclerosis	25
Idiopathic thrombocytopenic purpura	10–30
Thyroid disease	30–50
Discoid lupus	5–25
Infectious diseases	Varies widely
Malignancies	Varies widely
Patients with silicone breast implants	15–25
Fibromyalgia	15–25
Relatives of patients with autoimmune diseases (SLE or scleroderma)	5–25
Normal persons†	
≥1:40	20–30
≥1:80	10–12
≥1:160	5
≥1:320	3

Arch Pathol Lab Med. 2000 Jan;124(1):71-81.

Criterion		Definition
1. Malar rash		Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash		Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity		Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers		Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis		Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a)	Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *OR*
	b)	Pericarditis—documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a)	Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed *OR*
	b)	Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed
8.Neurologic disorder	a)	Seizures—in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance *OR*
	b)	Psychosis—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a)	Hemolytic anemia—with reticulocytosis *OR*
	b)	Leukopenia—less than 4,000/mm³ total on 2 or more occasions *OR*
	c)	Lymphopenia—less than 1,500/mm³ on 2 or more occasions *OR*
	d)	Thrombocytopenia—less than 100,000/mm³ in the absence of offending drugs
10. Immunologic disorder	a)	Positive LE cell preparation *OR*
	b)	Anti-DNA: antibody to native DNA in abnormal titer *OR*
	c)	Anti-Sm: presence of antibody to Sm nuclear antigen *OR*
	d)	False positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody		An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

Arthritis Rheum. 1982 Nov;25(11):1272-1277.

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Arthritis & Rheum. 2019 Sep;71(9):1400-12.

Arch Pathol Lab Med. 2000 Jan;124(1):71-81.

ANA Testing

1. Only if autoimmune rheumatic disease symptoms
   - May be present in non-rheumatic diseases
   - Seen in "healthy" control subjects
2. Consider ANA 1:80 as decision-making levels
   - Negative <1:80
   - Positive ≥1:80
3. Do not use titers to gauge disease activity

Arthritis & Rheum. 2019 Sep;71(9):1400-12.
Am J Clin Pathol. 2002 Feb;117(2):316-24.

*Number 2

- Do not gout out on gout: 2020 ACR guideline for management of gout

Indications for urate-lowering therapy (ULT)

- Tophi, erosions, flares ≥2 annually
- Avoid in asymptomatic hyperuricemia
- Avoid in 1st flare except CKD stage ≥3, SU >9 mg/dl, urolithiasis

Recommendation	PICO question	Certainty of evidence
For patients with 1 or more subcutaneous tophi, we strongly recommend initiating ULT over no ULT.	1	High
For patients with radiographic damage (any modality) attributable to gout, we strongly recommend initiating ULT over no ULT.	2	Moderate
For patients with frequent gout flares (≥2/year), we strongly recommend initiating ULT over no ULT.	3	High
For patients who have previously experienced >1 flare but have infrequent flares (<2/year), we conditionally recommend initiating ULT over no ULT.	4	Moderate
For patients experiencing their first flare, we conditionally recommend *against* initiating ULT over no ULT, with the following exceptions:	5	Moderate
For patients experiencing their first flare and CKD stage ≥3, SU >9 mg/dl, or urolithiasis, we conditionally recommend initiating ULT.	5	Very low
For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl) with no prior gout flares or subcutaneous tophi, we conditionally recommend *against* initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid) over initiation of pharmacologic ULT.	57	High†

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CKD = chronic kidney disease; SU = serum urate.
† There is randomized clinical trial data to support the benefit that ULT lowers the proportion of patients who develop incident gout. However, based on the attributable risk, 24 patients would need to be treated for 3 years to prevent a single (incident) gout flare leading to the recommendation against initiating ULT in this patient group.

Arthritis Care & Research. 2020;72(6):744-760.

Recommendations for choice of initial ULT

- Allopurinol is 1st line especially in CKD stage ≥3
- Avoid Probenecid in CKD stage ≥3
- Start low dose ULT + concomitant anti-inflammatory prophylaxis (3-6 months)

Recommendation	PICO question	Certainty of evidence
For patients starting any ULT, we strongly recommend allopurinol over all other ULT as the preferred first-line agent for all patients, including in those with CKD stage ≥3.	10	Moderate
We strongly recommend a xanthine oxidase inhibitor over probenecid for those with CKD stage ≥3.		
For allopurinol and febuxostat, we strongly recommend starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., ≤100 mg/day [and lower in patients with CKD] for allopurinol or ≤40 mg/day for febuxostat).	7	Moderate
For probenecid, we conditionally recommend starting at a low dose (500 mg once or twice daily) with dose titration over starting at a higher dose.		
We strongly recommend initiating concomitant antiinflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) over no antiinflammatory prophylaxis. The choice of specific antiinflammatory prophylaxis should be based upon patient factors.	9	Moderate
We strongly recommend continuing prophylaxis for 3–6 months rather than <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience flares.	9	Moderate
When the decision is made that ULT is indicated while the patient is experiencing a gout flare, we conditionally recommend starting ULT during the gout flare over starting ULT after the gout flare has resolved.	6	Moderate
We strongly recommend *against* pegloticase as first-line therapy.	10	Moderate†

Arthritis Care & Research. 2020;72(6):744-760.

Recommendations for all ULT patients

Recommendation	PICO question	Certainty of evidence
For all patients taking ULT, we strongly recommend a "treat-to-target strategy" ULT dose management that includes dose titration and subsequent dosing guided by serial SU values to achieve an SU target over a fixed, standard-dose ULT strategy.	13	Moderate
For all patients taking ULT, we strongly recommend continuing ULT to achieve and maintain an SU target of <6 mg/dl over no targets.	14	High
For all patients taking ULT, we conditionally recommend delivery of an augmented protocol of ULT dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol.	8	Moderate
We conditionally recommend continuing ULT indefinitely over stopping ULT.	19	Very low

Recommendations for specific ULT

Allopurinol		
We conditionally recommend testing HLA-B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American patients, who have a higher prevalence of HLA-B*5801.	12	Very low
We conditionally recommend *against* HLA-B*5801 testing in all others.		
For patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT, we conditionally recommend using allopurinol desensitization.	23	Very low
Febuxostat		
For patients with gout taking febuxostat with a history of CVD or a new CV event, we conditionally recommend switching to an alternative ULT agent if available and consistent with other recommendations in this guideline.	22	Moderate
Uricosurics		
For patients considered for, or taking uricosuric treatment, prior to starting any uricosuric treatment, we conditionally recommend *against* checking urinary uric acid over checking urinary uric acid.	28	Very low
For patients taking uricosuric treatment, we conditionally recommend *against* alkalinizing urine.	29	Very low

Arthritis Care & Research. 2020;72(6):744-760.

When to consider switching to a new ULT strategy

Recommendation	PICO question	Certainty of evidence
For patients with gout taking their first XOI monotherapy at maximum-tolerated or FDA-indicated dose who are not at SU target and/or have continued frequent gout flares or nonresolving subcutaneous tophi, we conditionally recommend switching the first XOI to an alternate XOI agent over adding a uricosuric agent.	24	Very low
For patients with gout where XOI, uricosurics, and other interventions have failed to achieve SU target and who have frequent gout flares or nonresolving subcutaneous tophi, we strongly recommend switching to pegloticase over continuing current ULT.	27	Moderate
For patients with gout for whom XOI, uricosurics, and other interventions have failed to achieve serum urate target and who have infrequent gout flares (≤2 flares/year) and no tophi, we strongly recommend *against* switching to pegloticase over continuing current ULT.‡	27	Moderate

Gout flare management

For patients experiencing a gout flare, we strongly recommend using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences). When colchicine is the chosen agent, we strongly recommend low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects.	32	High†
For patients experiencing a gout flare for whom other antiinflammatory therapies are poorly tolerated or contraindicated, we conditionally recommend using IL-1 inhibition over no therapy (beyond supportive/ analgesic treatment).	33	Moderate
For patients who may receive NPO, we strongly recommend glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH.	32	High†
For patients experiencing a gout flare, we conditionally recommend using topical ice as an adjuvant treatment over no adjuvant treatment.	31	Low

Arthritis Care & Research. 2020;72(6):744-760.

Management of lifestyle factors

Recommendation	PICO question	Certainty of evidence
For patients with gout, regardless of disease activity, we conditionally recommend limiting alcohol intake.	41	Low
For patients with gout, regardless of disease activity, we conditionally recommend limiting purine intake.	42	Low
For patients with gout, regardless of disease activity, we conditionally recommend limiting high-fructose corn syrup.	43	Very low
For overweight/obese patients with gout, regardless of disease activity, we conditionally recommend weight loss.	46	Very low
For patients with gout, regardless of disease activity, we conditionally recommend *against* adding vitamin C supplementation.	48	Low

Management of concurrent medications

For patients with gout, regardless of disease activity, we conditionally recommend switching hydrochlorothiazide to an alternate antihypertensive when feasible.	47	Very low
We conditionally recommend choosing losartan preferentially as an antihypertensive when feasible.	47	Very low
We conditionally recommend *against* stopping low-dose aspirin (in those who are taking this medication for appropriate indications).	47	Very low
We conditionally recommend *against* adding or switching to fenofibrate.	47	Very low

Arthritis Care & Research. 2020;72(6):744-760.

Management

- Indication to start ULT:
  - Tophi, erosions, flares ≥2 annually
- Avoid ULT in asymptomatic hyperuricemia
- Avoid ULT in first gout flare except:
  - CKD stage ≥3, SU >9 mg/dl, urolithiasis
- Allopurinol is 1st line especially in CKD stage ≥3
- Target serum uric acid <6 mg/dl
- Concomitant anti-inflammatory prophylaxis + continue 3–6 months after achieving target
- Screen HLA-B*5801 before starting Allopurinol in Southeast Asian + African Americans
- Losartan is preferred antihypertensive agent

Clin Infect Dis. (2006) 43 (9): 1089-1134.

Number 3

- Do not perform MRI of the peripheral joints to routinely monitor inflammatory arthritis

Rheumatoid Arthritis

MRI Not Indicated

- Diagnosis
- Prognosis

MRI Indicated

- May predict progression in certain RA populations

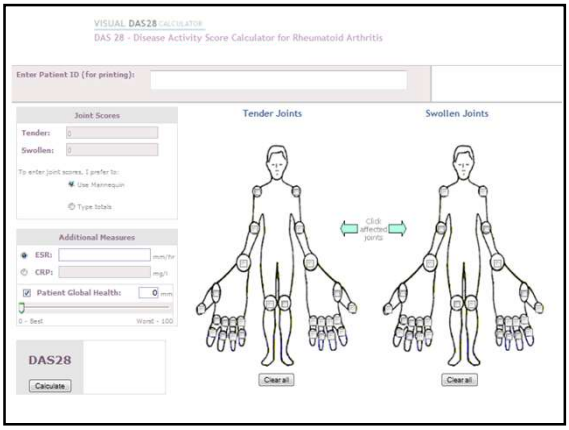
- **The 2008 American College of Rheumatology recommendations for the use of non-biologic and biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis: Where the rubber meets the road**
- **2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying anti-rheumatic drugs and biologic agents in the treatment of rheumatoid arthritis.**

2010 ACR/EULAR Diagnostic criteria for RA

Categories	Score
Patients who need to be investigated: (1) At least one joint involved with definite clinical synovitis (2) Patients presenting with synovitis not explained by any other disease	
Classification criteria for RA (add scores of categories A-D; definite RA = a score of ≥6/10)	
A) Joint involvement	
• 1 large joint	0
• 2-10 large joints	1
• 1-3 small joints (with or without large joint involvement)	2
• 4-10 small joints (with or without large joint involvement)	3
• >10 joints (with at least 1 small joint involved)	5
B) Serology (at least 1 test result is needed for classification)	
• Negative RF and negative ACPA	0
• Low positive RF or low positive ACPA	2
• High positive RF or high positive ACPA	3
C) Acute-phase reactant (at least 1 test result is needed for classification)	
• Normal CRP and normal ESR	0
• Abnormal CRP or abnormal ESR	1
D) Duration of symptoms	
• <6 weeks	0
• ≥6 weeks	1
Abbreviations: **ACPA:** Anti-citrullinated protein antibody; **CRP:** C reactive protein; **ESR:** Erythrocyte sedimentation rate; **RA:** Rheumatoid arteritis; **RF:** Rheumatoid factor	

For further details regarding the above criteria refer to reference:

Ref: Aletaha D, Neogi T, Silman A J, et al. 2010 Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis & Rheumatism September 2010; (62), pp 2569–2581



Recommendation

- Clinical examination is gold standard for detecting arthritis
- Ultrasound and MRI may help in detecting synovitis in difficult cases
  - Greater sensitivity for synovial thickening
  - Ultrasonography is more sensitive for synovitis in knees
  - Limited evidence for detecting early arthritis
  - MRI more sensitive than exam and radiograph for detecting early arthritis
  - Synovitis, bone edema, erosions may predict radiographic progression
  - Level of evidence is low
  - Changes resembling synovitis or small erosions can be seen in healthy subjects
- Altogether, the expert committee thought that MRI and ultrasonography are **promising** techniques that may become valuable in the diagnosis, prognosis, and therapeutic monitoring of early arthritis. However, their use is still experimental and sometimes controversial, and their merits in routine clinical practice have yet to be defined.

Ann Rheum Dis2007;66:34-45.

Recommendation

- Monitor disease using tender and swollen joint count, global assessments and inflammatory markers
- Arthritis activity assessed at 1-3 months intervals
- Structural damage assessed by *x* rays every 6-12 months during 1st few years
- Functional assessment used to complement the disease activity and structural damage monitoring
- Target DAS <2.4
- Intensive care based on regular monitoring of DAS associated with better outcomes

Ann Rheum Dis2007;66:34-45.

Number 4

- Do not prescribe biologics for rheumatoid arthritis before a trial of methotrexate (or other conventional non-biologic DMARDs)

DMARDs

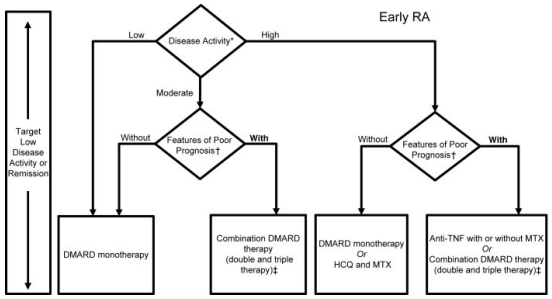
Non-Biologics (3 months trial)

- Methotrexate (MTX)
- Sulfasalazine (SSZ)
- Plaquenil (HCQ)
- Leflunomide
- Minocycline

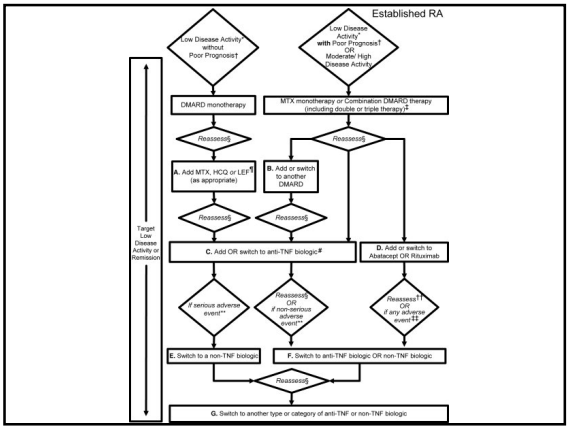
Biologics

- High disease activity
- Poor prognostic features
  - Functional limitations
  - Extra-articular disease
  - Seropositive (RF and/or CCP)
  - Bony damage/erosions

2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis



Arthritis Care & Research
Volume 64, Issue S, pages 625-639, 2 APR 2012 DOI: 10.1002/acr.21641
http://onlinelibrary.wiley.com/doi/10.1002/acr.21641/full#fig1



Recommendation

- MTX is the anchor drug and has lower discontinue rates
- MTX has better toxicity profile than other DMARDs
- MTX is one of the first conventional DMARDs
- MTX has proven efficacy on radiographic progression
- MTX almost as effective as TNF blocker monotherapy in early severe arthritis
- MTX + TNF blockers has greater efficacy than monotherapy
- MTX + SSZ has not been shown to be superior to single drug treatment
- Leflunomide and SSZ have similar clinical efficacy to MTX
- Leflunomide is as effective as MTX in slowing radiographic damage
- SSZ may be inferior to Leflunomide and MTX

Although formal **evidence** that prioritizes methotrexate as the first DMARD in early arthritis or early rheumatoid arthritis is **lacking**, the **expert committee recommends that treatment should be started with methotrexate (unless contraindicated)** in patients at risk of persistent or erosive disease. This recommendation is based on its clinical and radiological efficacy in combination with the relatively beneficial safety profile, and on its beneficial properties in treatment combinations. **Leflunomide, and to a lesser extent, sulfasalazine are considered the best alternatives.**

Ann Rheum Dis2007;66:34-45.

Jefferson's *Number 5

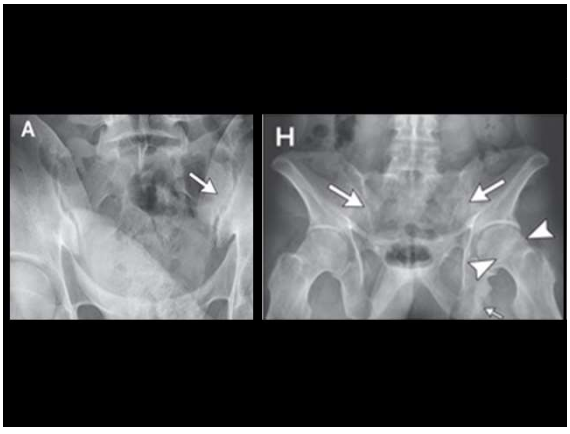
- Do not avoid HLA B27 testing in the appropriate clinical scenario

Table 2. Characteristics of Inflammatory Back Pain.*

Characteristic
Age at onset, <45 yr
Duration, >3 mo
Insidious onset
Morning stiffness >30 min
Improvement with exercise
No improvement with rest
Awaking from pain, especially during second half of night, with improvement on arising
Alternating buttock pain

* The presence of two or more of these features should arouse suspicion for inflammatory back pain, and the presence of four or more features can be considered diagnostic. The sensitivity of inflammatory back pain for the diagnosis of axial spondyloarthritis is 70 to 80%. The specificity varies, depending on the population being studied.[8,9]

N Engl J Med 2016; 374:2563-2574



Features

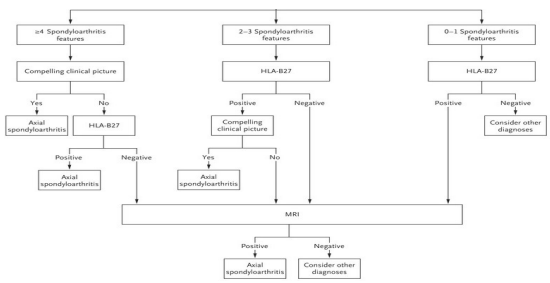
- Enthesitis
- Dactylitis
- Uveitis
- Psoriasis
- Nail pitting
- Inflammatory bowel
- Sterile pyuria
- NSAID responsive
- Peripheral arthritis
- Family history
- Elevated ESR
- C-reactive protein

Relevance of several findings for the diagnosis of axial spondyloarthritis

	LR+ according to [9, 10]	Score if test result is positive
Inflammatory type of back pain [12, 13]	3.1	11
Heel pain (enthesitis)	3.4	12
Peripheral arthritis	4.0	14
Dactylitis	4.5	15
Iritis or anterior uveitis	7.3	20
Psoriasis	2.5	9
IBD (Crohn's disease or ulcerative colitis)	4.0	14
Positive family history of axial SpA, reactive arthritis, psoriasis, IBD or anterior uveitis	6.4	19
Good response to NSAIDs	5.1	16
Raised acute-phase reactants (CRP/ESR)	2.5	9
HLA-B27	9.0	22
Sacroiliitis shown by MRI	9.0	22

Definite axial SpA if sum of scores >51 (probability > 90%).
Probable axial SpA if score sum >43 (probability > 80%)
Axial SpA improbable if score sum <13 (probability < 15%).

Rheumatology 2013;52:1648



N Engl J Med 2016; 374:2563-2574
van den Berg R, et al. Ann Rheum Dis 2013;72:1646–1653

5 Things Physicians and Patients Should Question

1. Don't test ANA sub-serologies without ANA and clinical suspicion of immune-mediated disease
2. Don't gout out on gout: 2020 ACR guidelines of gout management
3. Don't perform MRI of the peripheral joints to routinely monitor inflammatory arthritis
4. Don't prescribe biologics for rheumatoid arthritis before a trial of methotrexate (or other conventional non-biologic DMARDs)
5. Don't avoid HLA B27 testing in the appropriate clinical scenario