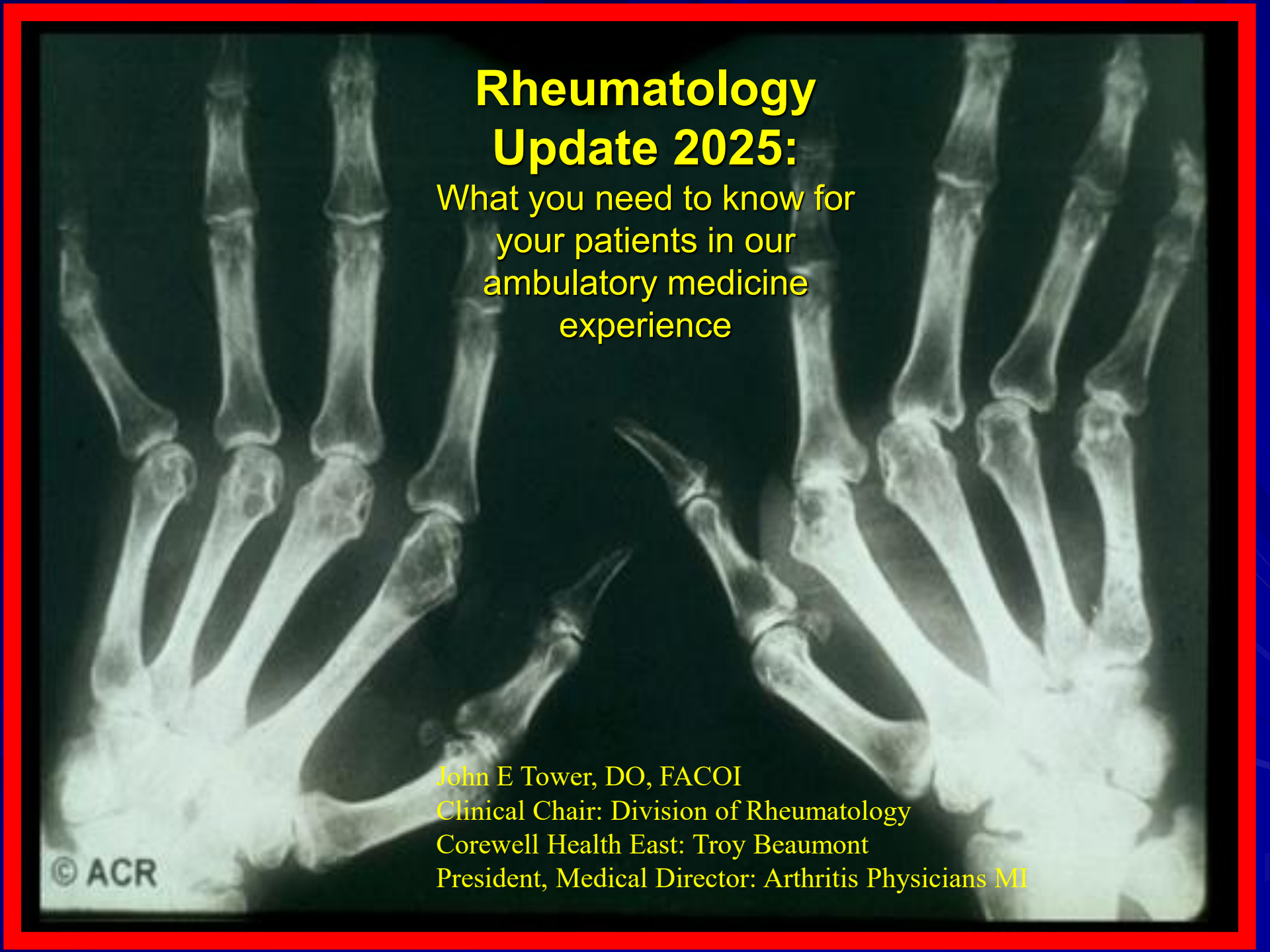


Rheumatology Update 2025:

What you need to know for your patients in our ambulatory medicine experience

John E Tower, DO, FACOI
Clinical Chair: Division of Rheumatology
Corewell Health East: Troy Beaumont
President, Medical Director: Arthritis Physicians MI

Objectives

1. Review the current projections of patient with rheumatic disease and manpower/workforce shortages.

2. Share the American College of rheumatology guidelines for referral to rheumatology(in the slides provided)

3. Share clinical scenarios/findings where patient should be considered for referral to rheumatologist

4. Discuss some of the common categories of rheumatic disease and some traditional and newer treatment options that may prompt such referrals

Arthritis Basics

For Everyone
MARCH 22, 2024

Arthritis is more common in women (23.5%) compared with men (18.1%), more common among adults with fair/poor health (40.5%) compared with those who have excellent/very good health (15.4%), and less common among adults who meet physical activity recommendations (18.1%) compared with adults who are insufficiently active or inactive (23.1% and 23.6%, respectively). Arthritis prevalence increases with age.[1]

KEY POINTS

- Arthritis affects about 1 in 5 U.S. adults.
- It affects the joints, tissues around the joint, and other connective tissues.
- Arthritis is a leading cause of work disability among adults.
- People with other chronic conditions—such as obesity, diabetes, and heart disease—often have arthritis.

Overview

Arthritis is a general term for conditions that affect the joints, tissues around joints, and other connective tissues. There are more than 100 types of arthritis.

The causes of some forms of arthritis are unknown.

Did you know?

About 54 million U.S. adults have arthritis.[1] The number of people with arthritis is expected to increase as the population grows and ages.[2]

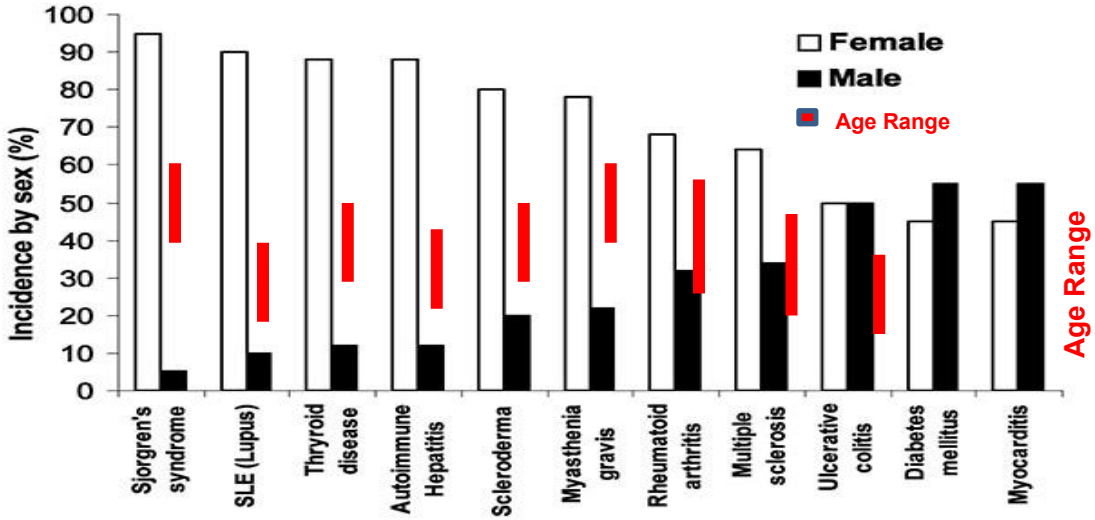
ON THIS PAGE

Autoimmune Disease in the USA

Graves disease
Thyroiditis
Systemic sclerosis
Myositis
SLE (lupus)
Sjögren's syndrome
Rheumatoid arthritis
Psoriasis
Psoriatic arthritis
Ankylosing spond
Spondyloarthritis
Reactive arthritis
Crohns disease
Ulcerative colitis
Juvenile arthrtitis
Juvenile diabetes
Autoimmune hepatitis
Hemolytic anemia/ITP
Multiple sclerosis
Myasthenia gravis
Uveitis
Vasculitis

- USA: 8% (78%♀) have Autoimmune diseases (AID)
- 1997: 8,511,845 (1/31) have AID
- 2005: 23.5 million (1/12♀ and 1/20♂ have AID)

Autoimmune Dz by Age & Sex



J Autoimmun. 2009 Nov–Dec; 33(3-4): 197–207 Emerg Infect Dis 2004.

The Autoimmunity Market

- >80 “autoimmune” diseases – incidence rising!
- 24 to 50 million Americans have autoimmune disease
- 14-22 million according to NIH report
- Leading cause of morbidity/mortality in young and middle age women

American Autoimmune Related Diseases Association, Inc.

we are 50 million

NIH

24 million

8.4%F 5.4%M

MAYO CLINIC

Crowson C, et al. Arthritis Rheum. 2011 March; 63(3): 633–639.

Economic Impact of Autoimmune Disease

- 2011 American Autoimmune Related Diseases Association (AARDA)
- Patient out-of-pocket costs, patient job earnings and productivity losses and the impact on Social Security Disability and Medicare.

- >$100 billion in direct and indirect costs to individual patients, insurance companies and the federal government.
- Likely and underestimate

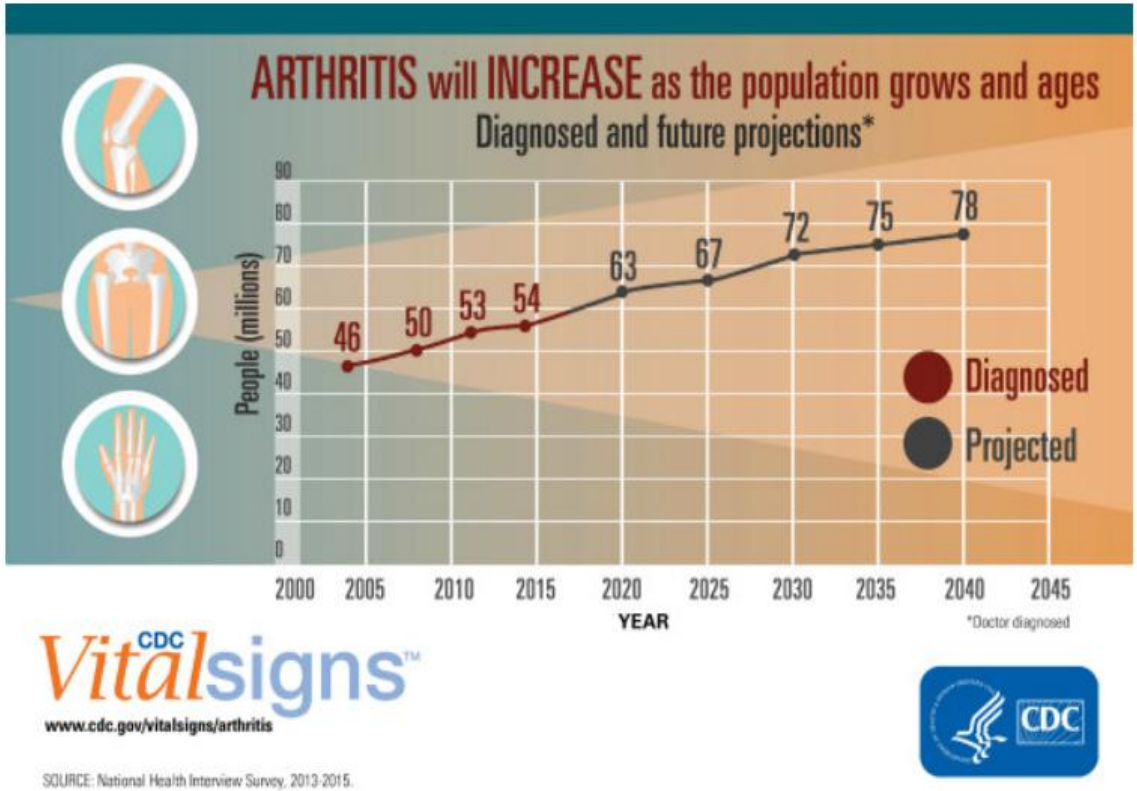
- For only 7/100+ AD (CD, UC, SLE, MS, RA, Psoriasis, Scleroderma) $51.8-$70.6 billion annually."

- Annual costs for type 1 diabetes $4.6-9.2 billion; for multiple sclerosis ~ $2.5 billion, RA ~ $19.3 billion

Future Arthritis Burden

The prevalence of doctor-diagnosed arthritis is expected to increase in the coming decades. By the year 2040, an estimated 78.4 million adults aged 18 years and older (25.9% of the projected total adult population) will have doctor-diagnosed arthritis,[2] compared with the 58.5 million adults in 2013–2015. Two-thirds of those with arthritis are expected to be women. Also by 2040, an estimated 34.6 million adults (43.2% of adults with arthritis or 11.4% of all US adults) will report arthritis-attributable activity limitations.[2]

National Arthritis Prevalence Projections



Volume 21, Issue 5

Perspective: Where Have All the Rheumatologists Gone?

More HCP training is not the only answer to filling the rheumatology gap – we need multifaceted solutions that improve reimbursement rates, increase access to care, and adequately manage chronic pain.

Rheumatology Shortage: The Data Reveal Gaps in Access to Care

The current rheumatology workforce of 5,500 full time equivalent (FTE) healthcare providers (HCPs) has also not kept up with demand.[3] This gap can be traced to a flat, fixed number of rheumatologists entering the field while there has been an increase in physician retirements – myself included. As the general population lives longer, there has been a significant increase in arthritis diagnoses, with an expected 30% to 50% increase in rheumatic disease diagnoses in the next 15 years.[3] Estimates are that this increase will result in a 25% to 50% loss of US rheumatology FTE by the year 2030, with a potential shortage of 2,000 to 4,000 FTE providers.[3]

Semin Arthritis Rheum. 2020 May 25;50(4):791–796. doi: 10.1016/j.semarthrit.2020.05.009

Addressing the rheumatology workforce shortage: A multifaceted approach

Eli M Miloslavsky [1,*], Marcy B Bolster [1]

Author information · Article notes · Copyright and License information

PMCID: PMC7255118 PMID: 32540672

Abstract

A significant challenge facing the field of rheumatology is the projected gap between the growing demand for rheumatologists and the available workforce. In order to improve access to care, augmenting the rheumatology workforce is required. Herein we discuss potential solutions to the anticipated workforce shortage, including 1) expanding the training of rheumatology physicians; 2) increasing nurse practitioner, physician assistant and pharmacist utilization in rheumatology practice; 3) growing the use of telemedicine; and 4) reducing burnout in order to retain practicing rheumatologists. Building on the existing literature in these areas, we propose a multifaceted approach to addressing the rheumatology workforce shortage.

Key Areas of conditions being referred: Basic Testing and Rx trials

- Inflammatory Arthritis
  -RA, spondyloarthropathies(Inflammatory low back pain)
  - Labs: Inflammatory Markers(ESR, CRP, RF, CCP, & HLA B27)
  - Basic Imaging(Hands, Wrists, Feet, Ankles, SI joint)
  - Response to inflammatory meds, NSAID's, steroids, sulfasalazine

Key Areas of conditions being referred.

- Non inflammatory back pain
  - Appropriate imaging
  - HLA B27 for 40 and under, ESR, CRP
  - Response to NSAID’s, steroids and PT

Key Areas of conditions being referred.

- Systemic Lupus or Lupus like conditions:
  - ANA(+/- reflex)
  - Serum complements
  - Inflammatory markers
  - Immunoglobulins
  - Symptomatic imaging: msk xrays, CXR, ECG, +/- ECHO & Full PFT's
  - Response to NSAID's, steroids, simple analgesics

Key Areas of conditions being referred.

- Crystal induced arthritis
  - Renal function, Urate, ESR, CRP,
  - Symptomatic imaging
  - Response to treatment, NSAID’s, steroid and colchicine

Key Areas of conditions being referred.

- Vasculitis:
  - ESR, CRP, Ig's, ANCA, PR3, MPO, skin biopsy
  - Symptomatic imaging
  - Response to treatments

Mechanical vs. Inflammatory Arthritis

TABLE 1-1. NONINFLAMMATORY VS INFLAMMATORY DISORDERS

	Noninflammatory disorders (e.g., OA)	Inflammatory disorders (e.g., RA, lupus)
Symptoms		
Morning stiffness	Focal, brief	Significant, prolonged, >1 hr
Constitutional symptoms	Absent	Present
Peak period of discomfort	After prolonged use	After prolonged inactivity
Locking or instability	Implies loose body, internal derangement, or weakness	Uncommon
Symmetry (bilateral)	Occasional	Common
Signs		
Tenderness	Unusual	Over entire exposed joint area
Inflammation (fluid, tenderness, warmth, erythema, synovitis)	Unusual	Common
Multisystem disease	No	Often
Lab abnormalities	No	Often

Adapted from American College of Rheumatology ad hoc Committee on Clinical Guidelines. Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. *Arthritis Rheum* 1996;39:1.

Latinis, K., et al *The Washington Manual Rheumatology Subspecialty Consult.*, LWW, 2003.

Inflammatory Arthritis

- Rheumatoid arthritis
- Spondyloarthropathies
  -Undifferentiated
  -Ankylosing spondylitis
  -Psoriatic arthritis
  -Reactive arthritis (formerly Reiter's syndrome)
  -Enteropathic arthritis
- SLE, Sjogrens, Scleroderma, Polymyalgia rheumatica, Vasculitis, Infectious (bacterial, viral, other), Undifferentiated connective tissue disease

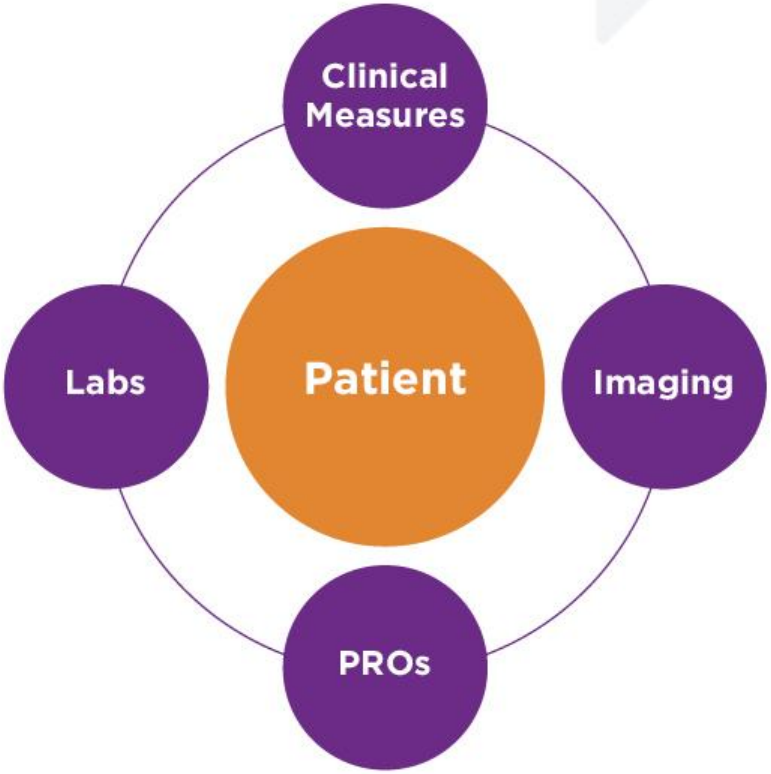
Morbidity & Mortality of Rheumatoid Arthritis

- Average life expectancy shortened by 5-15 years.
- Twice as likely to have MI or CVA
  - Twice as likely to develop a myocardial infarction (MI)
  - 70% more likely to suffer a stroke
- Increased risk of infection
  - 70% more likely to develop an infection
- Risk of lymphoma 2-3 times greater than general population

Brown SL, et al. *Arthritis Rheum*. 2002;46:3151–3158; Bjornadal L, et al. *J Rheumatol*. 2002;29:906–912; Wolfe F, et al. *J Rheumatol*. 2003;30:36–40; Doran MF, et al. *Arthritis Rheum*. 2002;46:2287–2293; Asten P, et al. *J Rheumatol*. 1999;26:1705–1714; Jones M, et al. *Br J Rheumatol*. 1996;35:738–745; Baecklund E, et al. *BMJ*. 1998;317:180–181; Isomaki HA, et al. *J Chronic Dis*. 1978;31:691–696; Solomon DH, et al. *Circulation*. 2003;107:1303–1307.

Rheumatoid Arthritis

The Complexity of Rheumatoid Arthritis Assessment



Measurements may be discordant

Rheumatoid Arthritis

Controlling Destructive Disease with a Multi Assessment Approach to Improve Patient Functionality

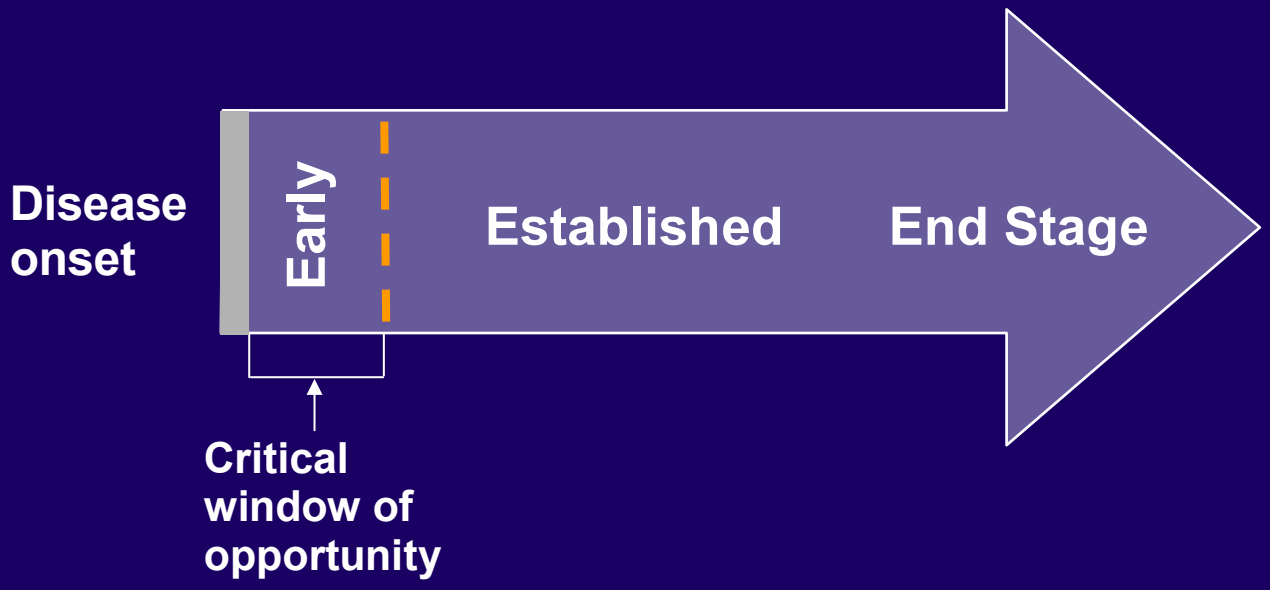
- **Early detection, disease activity monitoring, and treatment have improved outcomes**, reduced disease severity, co-morbidity, disability, mortality and made remission possible

- **Historically, 36-84% of RA patients had reduced work capacity** and eventually stopped working after their diagnosis[1]
  - Average lifetime earnings loss = 50%
  - RA patients will be unable to work within 8-10 years of disease onset

1.Journal of Vocational Rehabilitation 30 DOI 10-3233/JVR-2009-0458

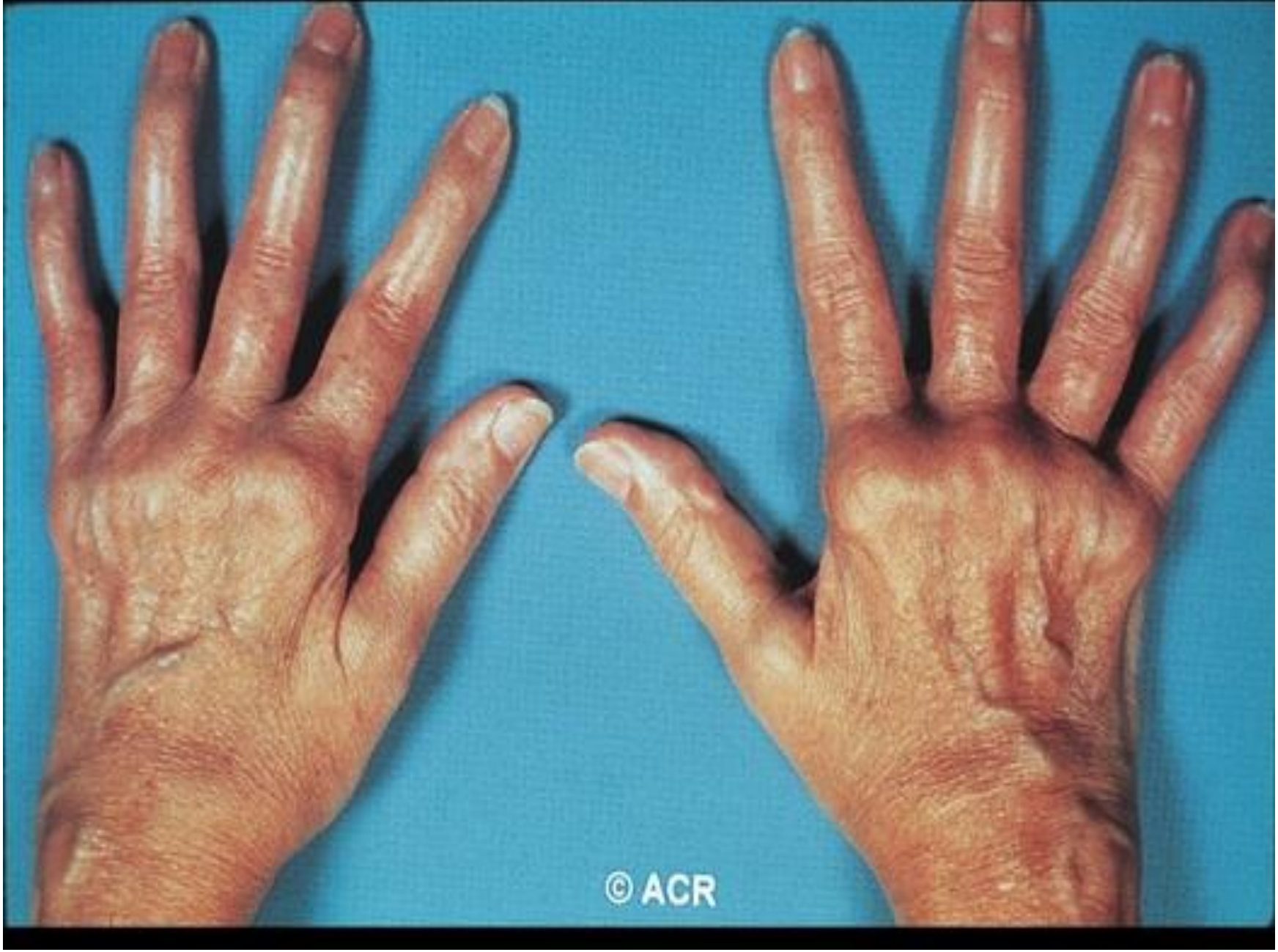
Early, Aggressive Therapy Can Be Important

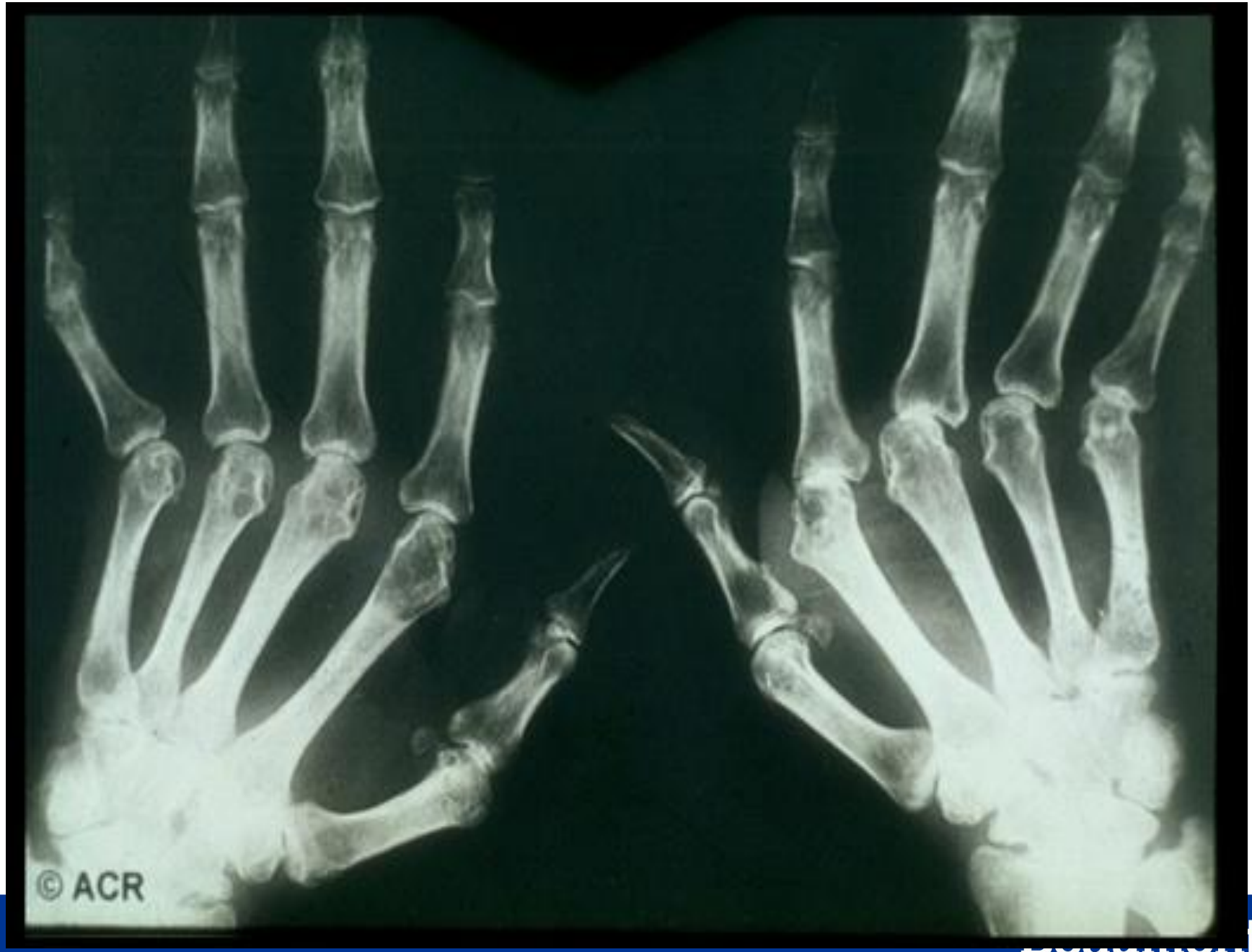
- Radiographic progression occurs early and continues over the lifetime of a patient
- 70% of patients have radiographic damage within the first 3 years



- Severe functional decline
- Radiographic damage
- Work disability
- Premature death

O'Dell JR. *Arthritis Rheum.* 2002;46:283-285. Editorial.
Landewe RBM, et al. *Arthritis Rheum.* 2002;46:347-356.


© ACR


© ACR

Rheumatoid Arthritis-Distribution

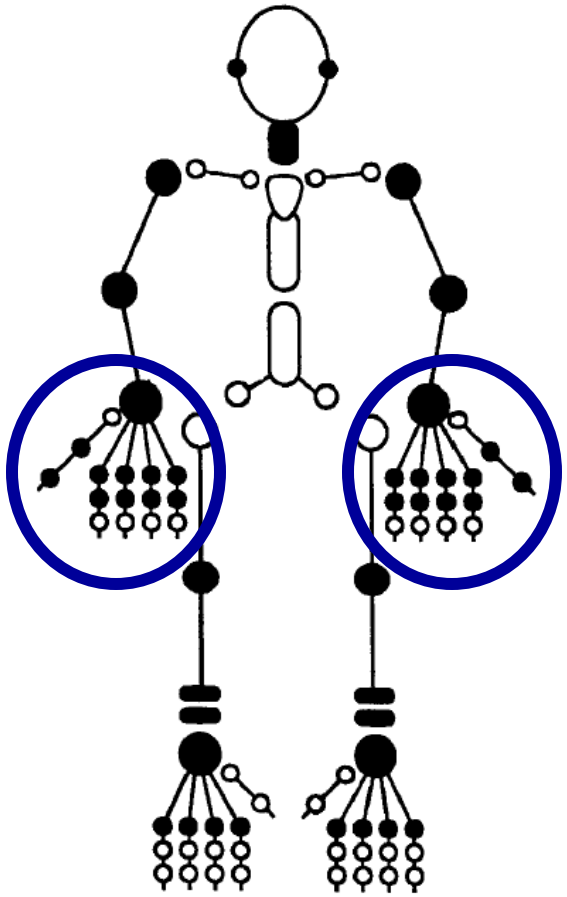


FIG. 10-1. Joint involvement in rheumatoid arthritis.

Latinis, K., et al
The Washington Manual Rheumatology Subspecialty Consult., LWW, 2003.

Rheumatoid Arthritis

Improving Disease Control with Treat-to-Target Strategies

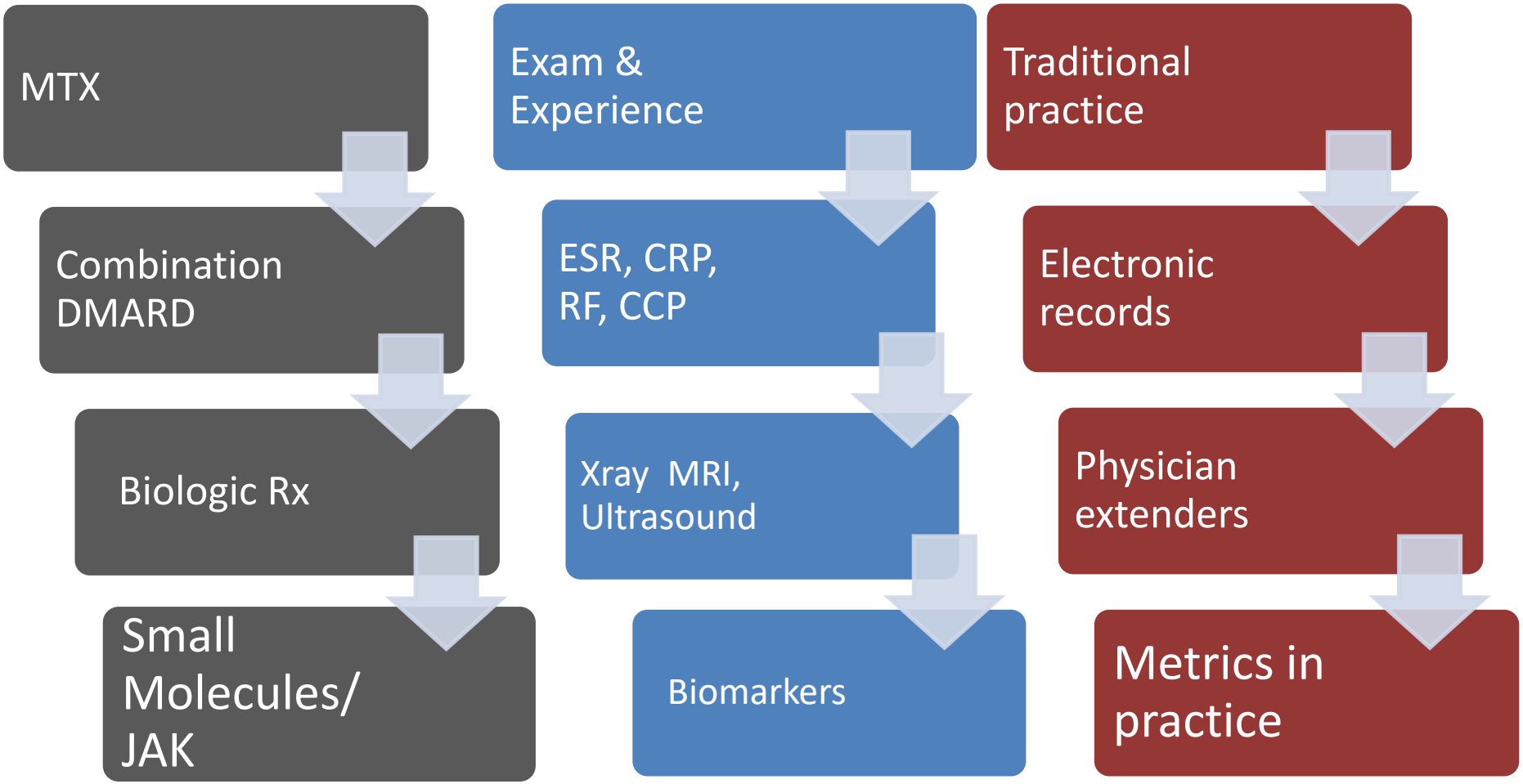
The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target[1]

Achieving a state of disease remission in rheumatoid arthritis (RA) is considered a primary treatment goal[1]

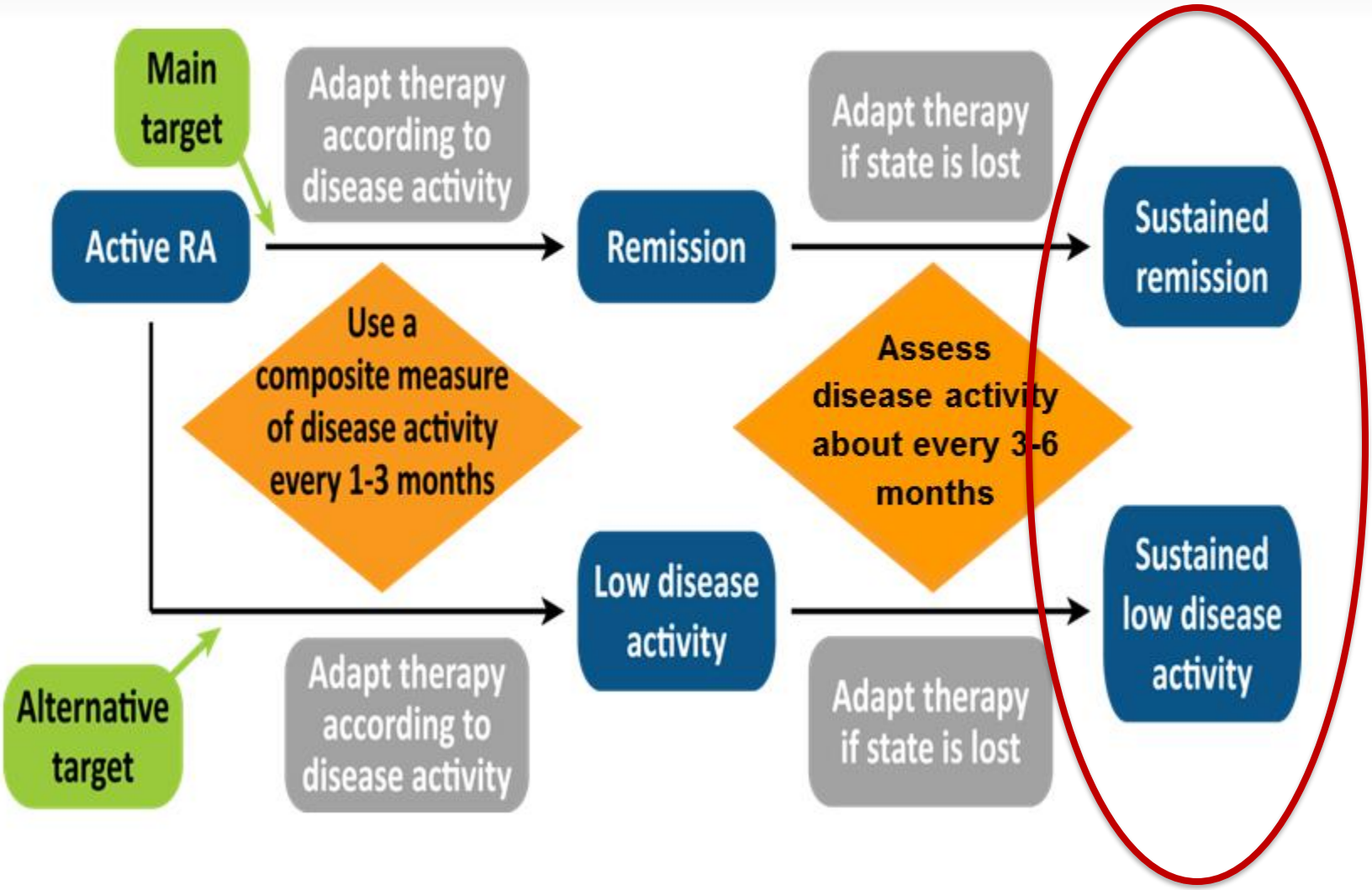
Until the desired treatment target is reached, drug therapy should be adjusted at least every three to six months. The desired treatment target should be maintained throughout the remaining course of the disease[1]

1. Smolen JS, et al., Ann Rheum Dis 2016;75:3-15.

Changes in RA Care

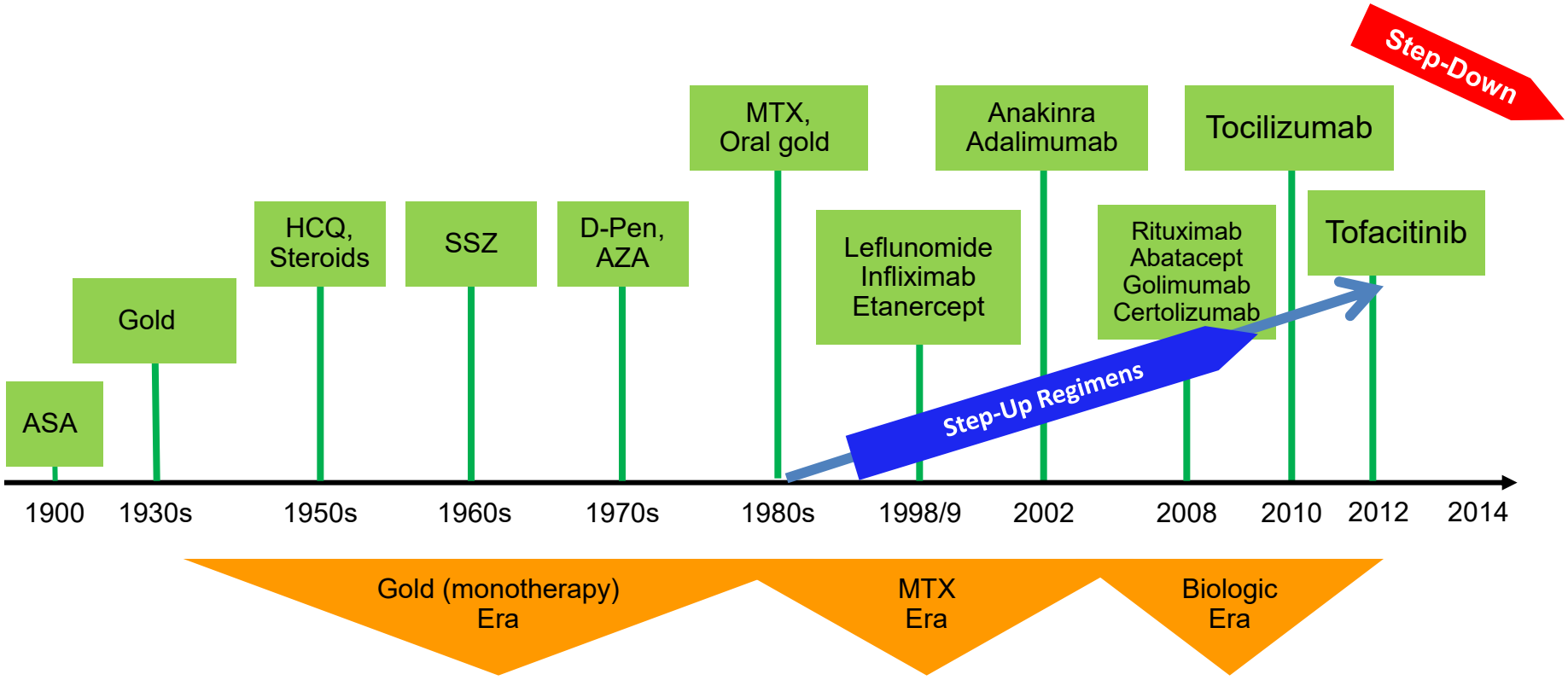


Treating to Target



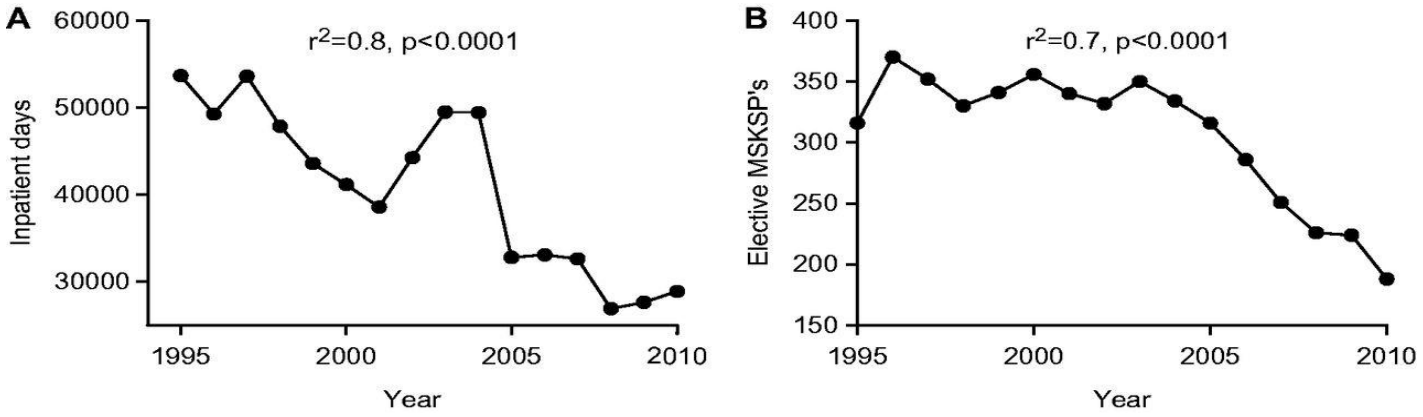
Reproduced from Smolen JS, et al. *Ann Rheum Dis*. 2010;69:631-637.

Evolution of RA Treatment



RA and Decade of Change 2000 – 2010 (Ireland)

- RA in-patient days from 53,671 (1995) to 29,000 (2010)
- MSK surgeries from 370 (1996) to 188 (2010)
- MTX treated patients: 3300 (2001) to 9600 (2010)
- TNFi treated patients: 2389 (2000) to 116,747 (2010)
- # Rheumatologists increased several fold



Less hospitalizations/surgeries, but more DMARDs and Biologics

Important Principles

- Joint damage may occur at a more rapid rate in early RA, compared to late disease
- Short term studies have shown that traditional DMARDS can improve outcome (HAQ, X-ray), but the magnitude of the improvement is substantially greater in early RA
- Disability (RA disease impact) is more associated with disease activity in early RA, but highly correlated with radiographic scores in late disease
- Combination therapy improves outcomes

RA Therapeutic Classes

- NSAIDs (Traditional and COXII Selective)
- Corticosteroids(Bridge)
- Traditional(Non-Biologic) DMARDs
  - Antimalarials, Sulfasalazine, Methotrexate, Azothioprine, Leflunomide
- Biologic Agents
  - Tumor necrosis factor (TNF) inhibitors,
    - Remicaide, Enbrel, Humira, Orencia, Golimumab
    - Interleukin 1 Receptor Antagonist (IL1RA)
- Newer biologics for Disease resistant to TNF inhibition
  - Abatacept, Rutiximab.
- Small Molecules/JAK inhibitors
  - tofacitinib

2020 ACR Treatment Guidelines for RA

2021 ACR Guideline for the Treatment of Rheumatoid Arthritis

Major Topic	Subtopic	Recommendations
DMARD-naive with Mod-High Disease Activity	DMARD Monotherapy	– MTX strongly recommended over HCQ or SSZ – MTX conditionally recommended over LEF – MTX strongly recommended over biologic or tsDMARD monoRx
	DMARD Mono vs Combination Rx	– Strongly recommended MTX monoRx over HCQ or SSZ – Conditionally recommended MTX monoRx over csDMARD dual or triple Rx – Conditionally recommended MTX monoRx over MTX + TNFi – Strongly recommended MTX monoRx over MTX + non TNFi-biologic or tsDMARD
	Glucocorticoids	– DMARDs without short-term (<3ms) GCs conditionally recommended over DMARD + short-term GCs – DMARDs without longer-term (≥3ms) GCs strongly recommended over DMARD + longer-term GCs
DMARD-naive with Low Disease Activity	DMARDS	– HCQ conditionally recommended over other csDMARDs – SSZ conditionally recommended over MTX – MTX conditionally recommended over LEF
Administration of MTX	Administration of MTX	– When starting, oral conditionally recommended over SC – If not tolerating oral, split dose or SC or increase folic acid, conditionally recommended over switch to new DMARD – If not a target on oral, switch to SC MTX conditionally recommended over add/switch to new DMARD
For Patients Not at Target	Treat to Target (TTT)	– TTT strongly recommended over usual care if biologic and tsDMARD naive – TTT conditionally recommended over usual care if IR to ≥1 biologic or tsDMARD – Minimal initial treatment goal of low disease activity conditionally recommended over remission
	Use of GCs	– On GCs to remain at target: add/switch DMARDs conditionally recommended over continuing GCs – On DMARDs and not at target: add/switch DMARDs, +/- intraarticular (IA) GCs, conditionally recommended over IA GCs alone
	Modification of DMARDs	– On maximally tolerated doses of MTX: add biologic or tsDMARD conditionally recommended over add HCQ + SSZ (triple Rx) – On biologic or tsDMARD: switch to biologic or tsDMARD in different class conditionally recommended over same class

MTX👍

Combo👍

Pred👎

T2T👍

Switch👍

Methotrexate Overview

- Methotrexate is a 1st line, cornerstone drug
- Rheums Love MTX, but…..
  - High noncompliance - 20-60%
  - MTX discontinuations: 6.7-15.5%
  - AEs: 23% -80%
    - N/V/D
    - Mucositis
    - Leukopenia
    - CNS AE's: "blahs", HA, nausea/quesy, etc

WARNING: SEVERE TOXIC REACTIONS, INCLUDING EMBRYO-FETAL TOXICITY

Methotrexate can cause the following severe or fatal adverse reactions.
Monitor closely and modify dose or discontinue methotrexate as appropriate.

- Bone marrow suppression (5.1)
- Serious infections (5.2)
- Renal toxicity and increased toxicity with renal impairment (5.3)
- Gastrointestinal toxicity (5.4)
- Hepatic toxicity (5.5)
- Pulmonary toxicity (5.6)
- Hypersensitivity and dermatologic reactions (5.7)
- Methotrexate can cause embryo-fetal toxicity, including fetal death. Use in pJIA is contraindicated in pregnancy. Consider the benefits and risks of XATMEP and risks to the fetus when prescribing XATMEP to a pregnant patient with a neoplastic disease. Advise females and males of reproductive potential to use effective contraception during and after treatment with XATMEP (4, 5.9, 8.1, and 8.3).

See Full Prescribing Information for complete boxed warning.

Starting Methotrexate

- Obtain PPD, Chest X-ray, renal and hepatic tests, and exclude HCV before starting
- Good long-term efficacy and tolerability
- Slows radiographic measured erosions
- Hi-risk in elderly and renal impaired patients
- Chemical monitoring indicated
- Hepatic biopsy rarely indicated
- Be aware of pulmonary toxicity in first 4 months of therapy

TNF Inhibitors

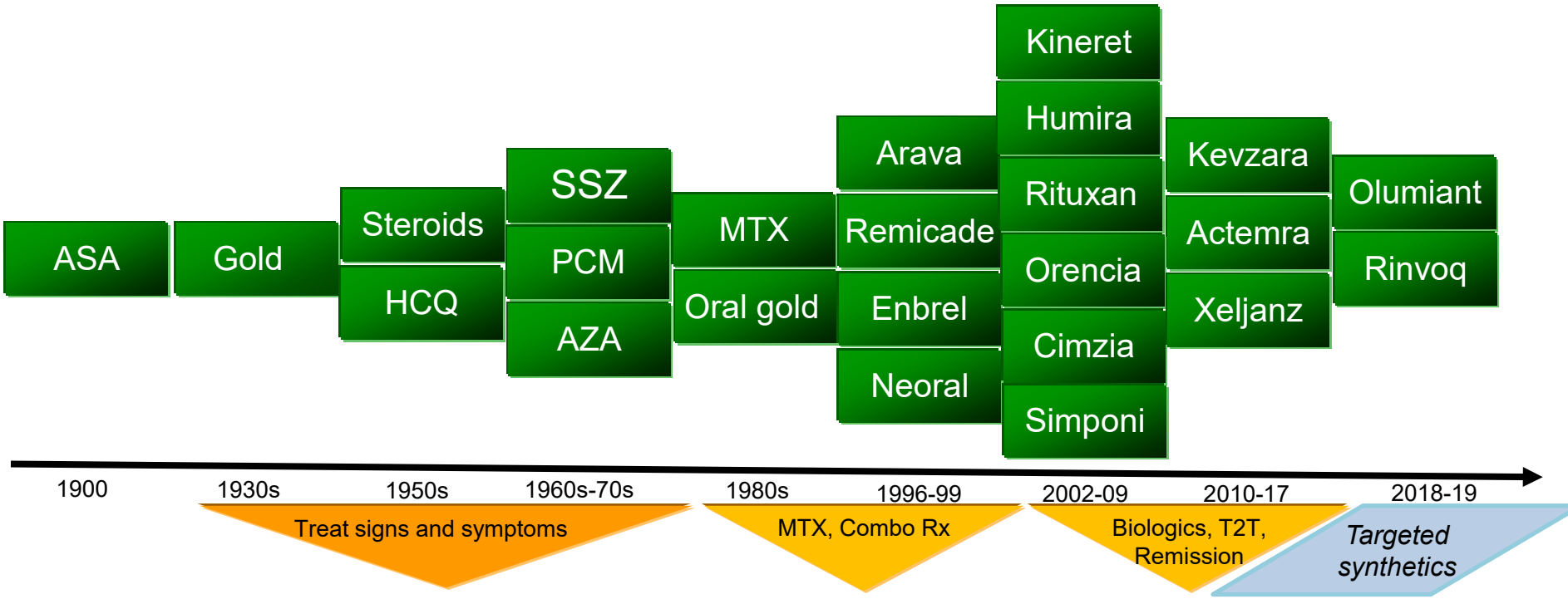
Generic (Brand)	Class	Route	Dose	Frequency
Etanercept (Enbrel)	Soluble TNFR	SQ	50 mg	Q week
Infliximab (Remicade)	Chimeric mAb	IV	3-10 mg/kg	At 0, 2, 6 weeks, then q 8 weeks
Adalimumab (Humira)	Humanized mAb	SQ	40 mg	Q 2 weeks
Golimumab (Simponi)	Human mAb	SQ	50mg	Q month
Certolizumab pegol (Cimzia)	PEGylated fragment of humanized mAb	SQ	400 mg	At wks 0, 2, 4, then 200 mg q 2 wk or 400 q 4 wk

13 New Agents* in Rheumatoid Arthritis

Agent	Biologic Target	Construct
Infliximab/Remicade	TNF α	Chimeric MAb
Etanercept/Enbrel	TNF αβ	IgG-p75 receptor
Adalimumab/Humira	TNF α	Human MAb
Golimumab*/Simponi	TNFα	Human MAb
Certolizumab*/Cimzia	TNFα	Peg-Fab'
Abatacept/ Orencia	T-cell costim	IgG-CTLA4 fusion
Rituximab/Rituxan	B-cells	Chimeric MAb
Anakinra/Kineret	IL-1	Receptor antagonist
Tocilizumab/Actemra	IL-6	Receptor Mab
Sarilumab/Kevzara	IL-6	Receptor Mab
Tofacitinib/Xeljanz	JAK	Oral smDMARD
Baricitinib/Olumiant	JAK	Oral tsDMARD
Upadacitinib/Rinvoq	JAK	Oral tsDMARD

* 11 biosimilars: INFdyyb,INFabda,INF-qbtx,ETNszzs,ADAatto,ADA-abdm,ADA-adaz,ADA-dwwb, ETN-ykro

Rheumatoid Arthritis Therapy Options



JAK Inhibitors – Head 2 Head Results

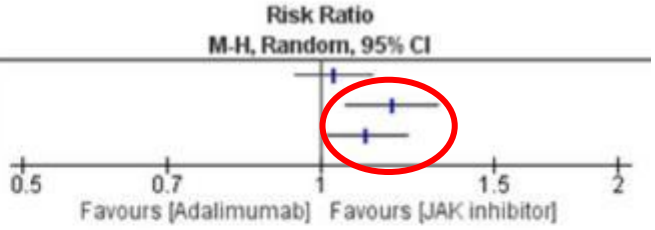
Taking the Lead?

Tofacitinib/Xeljanz	**JAK > MTX**
Baricitinib/Olumiant	**JAK > ADA**
Upadacitinib/Rinvoq	**JAK > ABA**

JAK vs ADA

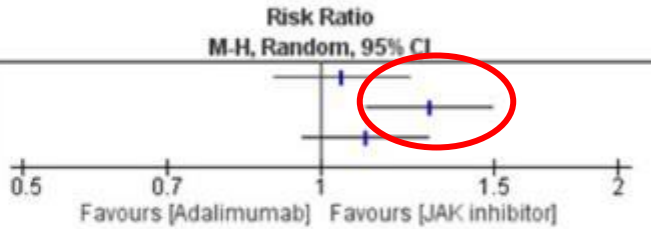
ACR20 Response

Study or Subgroup	JAK inhibitor Events	Total	Adalimumab Events	Total	Risk Ratio M-H, Random, 95% CI
Fleischmann (ORAL-Strategy)[1]	275	376	274	386	1.03 [0.94, 1.13]
Fleischmann (SELECT-COMPARE)[2]	439	651	187	327	1.18 [1.06, 1.31]
Taylor (RA-BEAM)[3]	360	487	219	330	1.11 [1.01, 1.22]



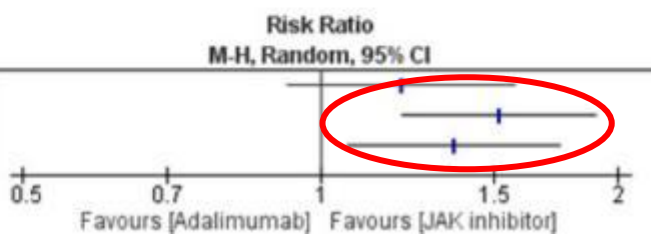
ACR50 Response

Study or Subgroup	JAK inhibitor Events	Total	Adalimumab Events	Total	Risk Ratio M-H, Random, 95% CI
Fleischmann (ORAL-Strategy)[1]	173	376	169	386	1.05 [0.90, 1.23]
Fleischmann (SELECT-COMPARE)[2]	351	651	137	327	1.29 [1.11, 1.49]
Taylor (RA-BEAM)[3]	246	487	150	330	1.11 [0.96, 1.29]



ACR70 Response

Study or Subgroup	JAK inhibitor Events	Total	Adalimumab Events	Total	Risk Ratio M-H, Random, 95% CI
Fleischmann (ORAL-Strategy)[1]	94	376	80	386	1.21 [0.93, 1.57]
Fleischmann (SELECT-COMPARE)[2]	226	651	75	327	1.51 [1.21, 1.90]
Taylor (RA-BEAM)[3]	145	487	72	330	1.36 [1.07, 1.74]



FDA Warnings on JAK Inhibitors

- Sept 1, 2021
- Warnings: TOFA, BARI, UPA about CV & Cancer concerns
- Based on Pfizer/Xeljanz Oral Surveillance Study in RA
  - Drug side effects from high risk RA patients >50 yrs (>65 yrs)
- Drug Safety Communication concludes "there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with the arthritis and ulcerative colitis medicines Xeljanz and Xeljanz XR (tofacitinib)". Extended to other JAKs also treating chronic inflammatory Dz.
- Risks of VTE seen with both doses of Tofa (5 or 10 mg bid)
- Higher rate of lymphomas; ⇧risk of lung cancers in smokers
- Inform Patients
- Reserve JAK inhibitors for (those failing) TNF blockers

1133 ORAL Surveillance Study

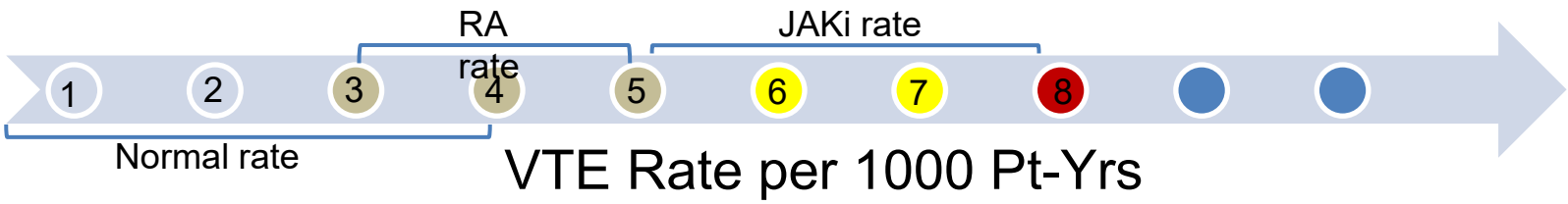
Post-marketing Safety study

- 5000+ RA >50 yrs, with ≥1 CV risk factor
- Randomized: TNFi or TOFA (5,10 mg)
- More VTE CV and CA with TOFA
- TOFA was not noninferior
- Rec? Don't Stop Effective JAKi Rx

JAKi NNH (literature)

- Adverse Event – 27 (GI); 15 (skin)
- AE D/C – 63 (GI); 56-133 (RA)
- Zoster – 22; 36; 62-66
- LDL – 5, 6, 50
- MACE – 793

VTE Risk and JAK inhibition



- VTE risk ⇧ with age, obesity, Cancer, RA, inflammatory diseases & prior VTE; JAKs – pose an added, possible risk
- VTE risk linked to inflammation and disease activity in RA
- Never use the higher (unapproved) dose of TOFA, BARI or UPA (higher VTE risk)
- Don't START JAK inhibitors in pts with a well documented hx of VTE (PE, DVTs)
- Controlled RA on JAKi (hx reveals past VTE)? □ discuss, but don't Stop
- Active RA with new VTE or VTE risk factors □ consider other Rx options

2020 TNF Inhibitor Biosimilars

Biosimilar	Reference	Pharma	Generic-suffix	**Approved**
Inflectra	Remicade	Celltrion	infliximab-dyyb	April 2016
Erelzi	Enbrel	Sandoz	etanercept-szzs	August 2016
Amjevita	Humira	Amgen	adalimumab-atto	September 2016
Renflexis	Remicade	Samsung	infliximab-abda	May 2017
Cyltezo	Humira	Boehringer	adalimumab-adbm	August 2017
Ixifi	Remicade	Pfizer	infliximab-abda	December 2017
Hyrimoz	Humira	Sandoz	adalimumab-adaz	October 2018
Eticovo	Enbrel	Samsung	etanercept-szzs	April 2019
Hadlima	Humira	Samsung	adalimumab-bwwd	July 2019
Abrilada	Humira	Pfizer	adalimumab-afzb	November 2019
Avsola	Remicade	Amgen	infliximab-axxq	December 2019

All FDA approved for commercial use in USA

Biosimilars: Few RCTs, Many Indications

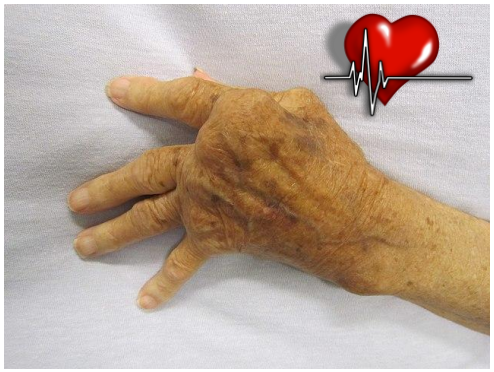
Generic	Infliximab	Adalimumab*	Etanercept	Rituximab
Available Biosimilars (approval date)	Inflectra (4/16) Renflexis (5/17) Ixifi (12/17) Avsola (12/19)	Amjevita (9/16) Cyltezo (8/17) Hyrimoz (10/19) Hadlima (7/19) Abrilada (11/19)	Erelzi (8/16) Eticovo(4/19)	Ruxience# (7/19)
Indications	RA JIA Pso PsA AS CD UC	RA JIA Pso PsA AS CD UC	RA pJIA PsO PsA AS	GPA

Rituximab biosimilars – Truxima (RTX-abss) is approved for NHL, CLL only but Rituximab-pvvr (Ruxience) is also approved for GPA)

Caution with Biologic Anti-Rheumatic agents!

- Active infection - TB, HCV, HCB should be excluded.
- Biologic agents should not be given with any active infection.
- If PPD +, must receive prophylactic therapy
- Patients should receive non-live vaccines
- Vaccinate for pneumococcus and influenza.
- Infections should be promptly treated and agent withheld at least temporarily
- Herpes Zoster (shingles) should be recognized and treated promptly.
- Be aware of increased incidence of lymphoma.

CV Risk in RA: The Stats



- 40% of RA deaths are due to CV disease
- RA confers 50% inc. risk of CVD related mortality (SMR 1.5)
- 1 unit increase in DAS28 increases CV risk by 33%
- Every 6 weeks of disease flares is assoc with 7% increase CV risk
- Elevated CRP/ESR are assoc with higher risk for CVD
- Patients in remission have 53% less risk for CV event

BMJ 2018;361:k1036
Clin Exp Rheumatol 2008;26(Suppl51):S35-61
Ann Rheum Dis 2012;71:1524-9
Ann Rheum Dis 2015;74:998- 1003
Ann Rheum Dis 2016;75:560-5. 10.1136
Arthritis Rheum 2008;59:1690-7

ACR/AAHKS* Guidelines for Perioperative Management

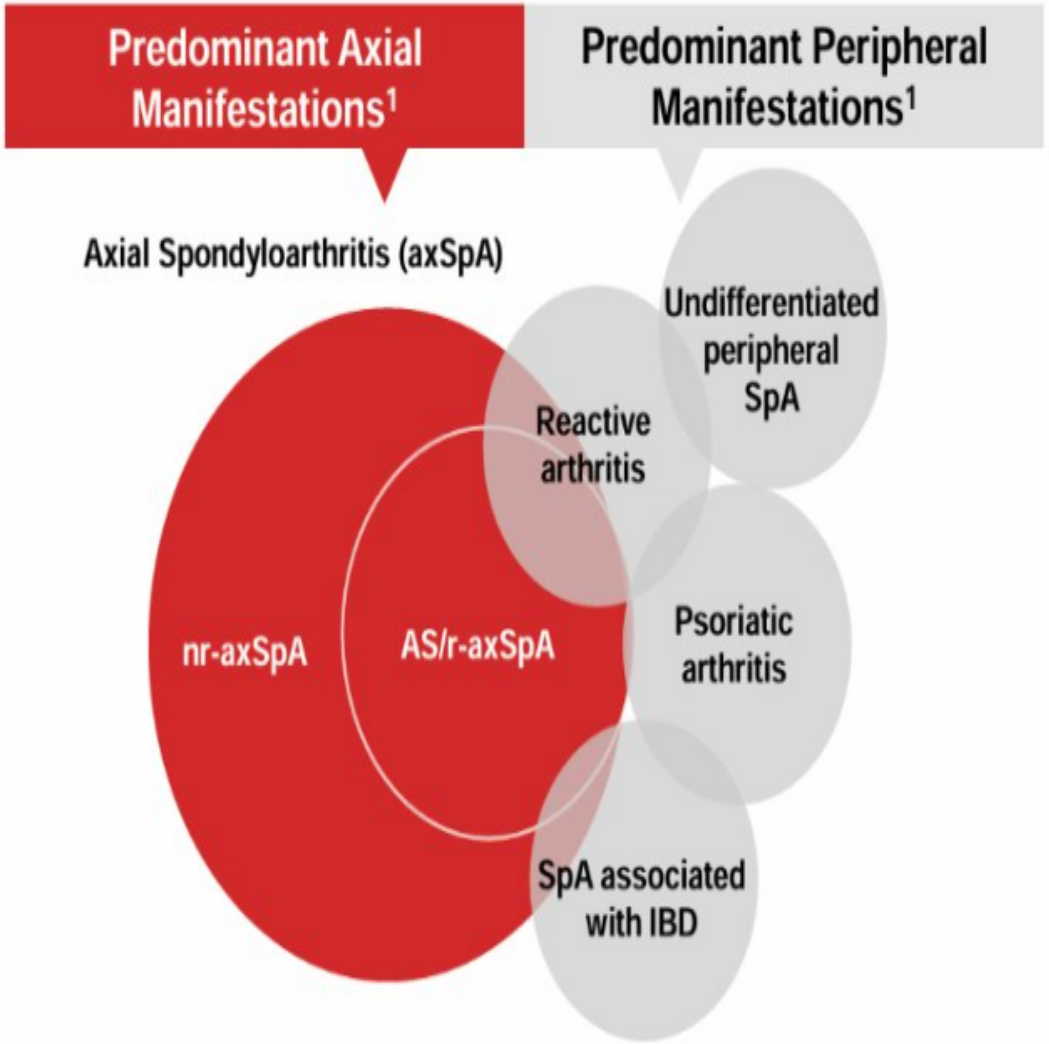
- Patients are more likely to fear perioperative infection than disease flare
- 7 low evidence recommendations for arthroplasty in RA, JIA, PsA, SpA and SLE:

1. Continue synthetic DMARDs thru THA or TKA surgery
2. Hold Biologics for surgery – hold for one dosing cycle before surgery
3. Hold tofacitinib(Xeljanz) for 7 days before & surgery
4. Severe SLE: Continue immunosuppressives thru surgery
5. Non-Severe SLE: Hold immunosuppressives for 7 days before surgery
6. Restart biologics with start of wound healing, sutures out, no infection (~14days)
7. Continue daily steroids (rather than stress dosing)

Spondyloarthritis (SpA)

- Ankylosing Spondylitis (AS)
- Non-radiographic axial spondyloarthritis (nr-SpA)
- Psoriatic arthritis
- Arthritis associated with inflammatory bowel disease (IBD-SpA)
  - Ulcerative colitis and Crohn's disease
- Reactive arthritis (ReA)
  - chlamydia, campylobacter, salmonella, shigella
- Undifferentiated Spondyloarthropathy (uSpA)

axSpA Belongs to the Spectrum of Spondyloarthropathies



The spectrum of SpA and overlap (cross-sectional and longitudinal) between different SpA forms.[1,2]

Note: A larger circle does not imply a greater prevalence.

AS=Ankylosing Spondylitis; IBD=Inflammatory Bowel Disease; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; SpA=Spondyloarthritis.

Differentiating IBP from Mechanical Back Pain

13%
of adults in the US have chronic back pain.[1]

5%
of patients with chronic back pain are estimated to have axSpA.[2]

5%-15% and **28%-35%**
of patients with acute and chronic back pain, respectively, are reported to have IBP.[2]

14%-16% of patients with IBP are estimated to have axSpA.[2]

IBP Symptoms[2]

- Insidious onset of back pain.
- Morning stiffness in the lower back.
- Improvement of back pain with exercise but not with rest.
- Awakening at night or early morning because of back pain.
- Alternating buttock pain.

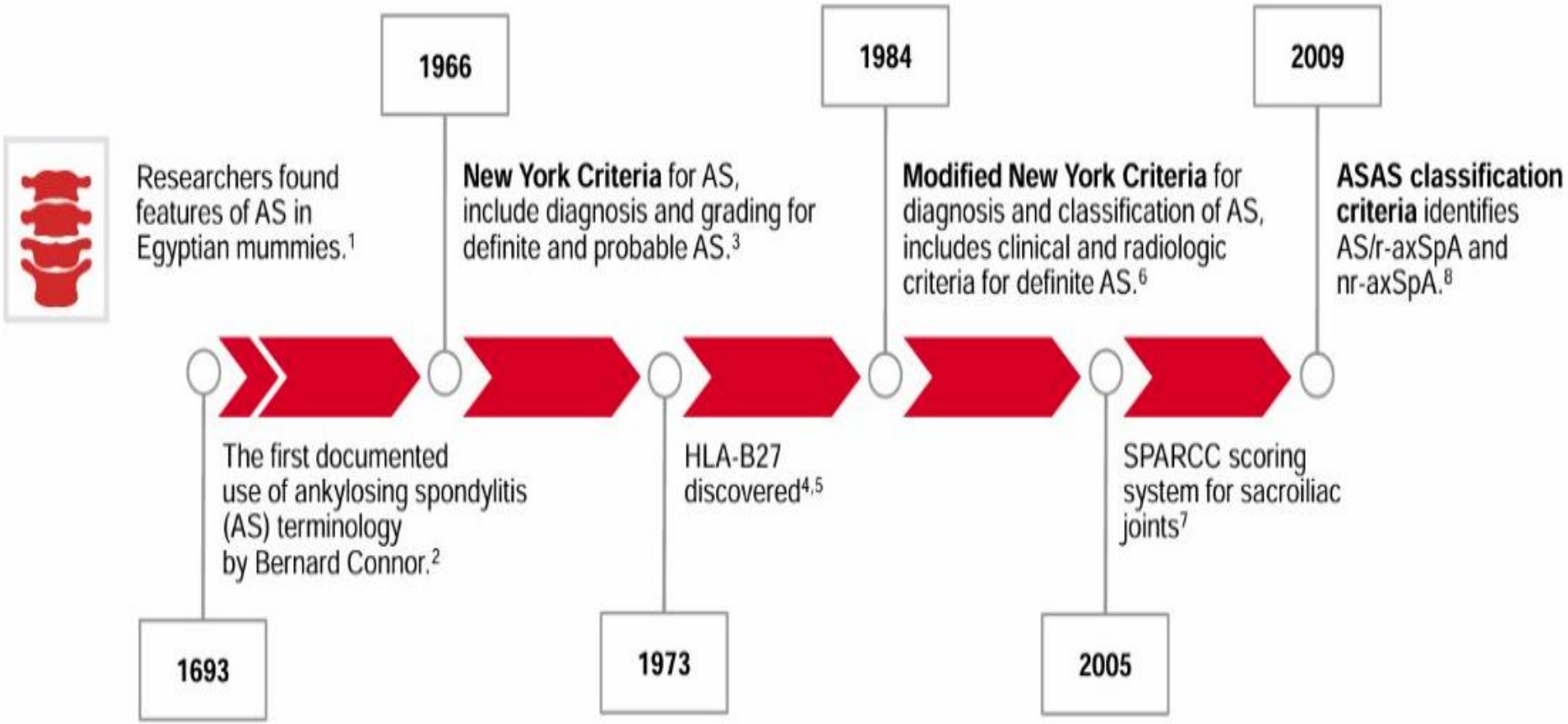
Why do we care?

- Higher incidence and prevalence than we realize

- Early identification has consequences
  - Early treatment makes a difference

- As primary care providers, you will be the ones before surgeons, pain physicians, and physiatrists that will likely be the first ones to encounter these patients
  - Back pain is most common presenting complaints

axSpA Terminology and Classification

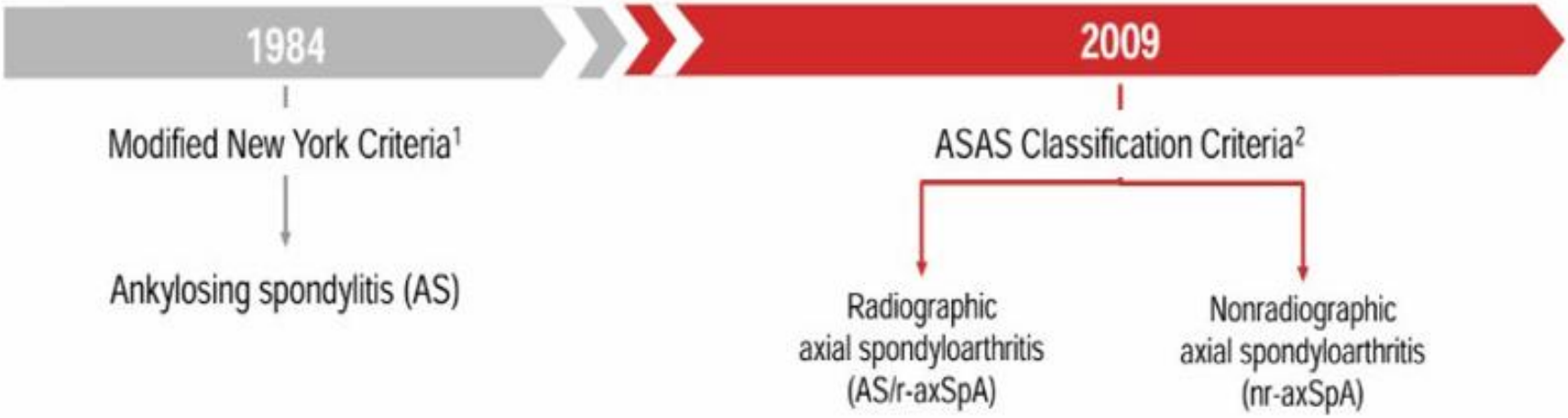


AS=Ankylosing Spondylitis; ASAS=Assessment of SpondyloArthritis International Society; HLA=Human Leukocyte Antigen; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; SPARCC=Spondyloarthritis Research Consortium of Canada.

1. Saleem SN, et al. *Arthritis Rheumatol.* 2014;66(12):3311-3316. 2. Keitel W. *Z Rheumatol.* 2012;71(4):330-339. 3. Moll JM, Wright V. *Ann Rheum Dis.* 1973;32(4):354-363. 4. Reveille JD, Weisman MH. *Am J Med Sci.* 2013;345(6):431-436. 5. Schlosstein L, et al. *N Engl J Med.* 1973;288(14):704-706. 6. van der Linden S, et al. *Arthritis Rheum.* 1984;27(4):361-368. 7. Landewé RB, et al. *J Rheumatol.* 2005;32(10):2050-2055. 8. Rudwaleit M, et al. *Ann Rheum Dis.* 2009;68(6):777-783.

AS/r-axSpA and nr-axSpA Classification

- Diagnosis and classification of AS has been based on the modified New York (mNY) criteria, which require the presence of radiographic sacroiliitis.[1]
- The ASAS criteria allow for the classification of patients without radiographic changes as nr-axSpA.[2]
  - Positive MRI may be used to identify this subtype.
  - The criteria also contains a clinical arm, which enhances the capability to identify patients without MRI findings as it requires the presence of positive HLA-B27 and two SpA features.
- The imaging arm of the ASAS classification criteria includes sacroiliitis on X-rays (as per mNY criteria) as one of its criterion and therefore, identifies patients with AS/r-axSpA.[2]



AS=Ankylosing Spondylitis; ASAS=Assessment of SpondyloArthritis International Society; axSpA=Axial Spondyloarthritis; HLA=Human Leukocyte Antigen; mNY=modifed New York; MRI=Magnetic Resonance Imaging; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis; SpA=Spondyloarthritis.

1. van der Linden S, et al. *Arthritis Rheum* 1984;27(4):361-368. 2. Rudwaleit M, et al. *Ann Rheum Dis* 2009;68(6):777-783.

ASAS Classification Criteria

SpA features:[1]

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Ulcerative colitis/Crohn's disease
- Good response to NSAIDs
- Family history of SpA
- HLA-B27 positive
- Elevated CRP

ASAS Classification Criteria[1]

In patients with ≥3 months chronic back pain and age at onset <45 years:

IMAGING ARM		CLINICAL ARM
Sacroiliitis on imaging: Acute inflammation on MRI highly suggestive of sacroiliitis **OR** Definite sacroiliitis according to modified New York criteria[2]	OR	HLA-B27 positive
+ ≥1 SpA feature		+ ≥2 other SpA features

nr-axSpA classification is based on a positive MRI (imaging arm) OR on clinical arm.[1,2]

ASAS=Assessment of Spondyloarthritis International Society; CRP=C-Reactive Protein; HLA-B27=Human Leukocyte Antigen B27; MRI=Magnetic Resonance Imaging; nr-axSpA=Nonradiographic Axial Spondyloarthritis; NSAID=Nonsteroidal Anti-Inflammatory Drug; SpA=Spondyloarthritis.

1. Rudwaleit M, et al. *Ann Rheum Dis*. 2009;68:777-783. 2. van der Linden S, et al. *Arthritis Rheum*.1984;27:361-368.

Prevalence of HLA-B27

<10%

Prevalence of HLA-B27 in the general population[1-3]

70-90%

Prevalence of HLA-B27 in White patients with axSpA[1,3,4]

Frequency of HLA-B27 in General Worldwide Populations[5]

The absolute risk of axSpA in persons with HLA-B27 positivity, without a first-degree relative affected by the disease, is estimated to be **2-10%**.[4]

Note: The 40-50% frequency in Siberia and Alaska refer to the frequency in native Siberians and Alaskans, and not the White settlers. The <1% frequency in Australia refers to that in Australian Aborigines, and not in the White settlers. The <1% frequency in Japan, Africa, and the 2% frequency in Brazil refer to the general population frequencies of HLA-B27 in those regions.

axSpA=Axial Spondyloarthritis; B=Black; H=Hispanic; HLA-B27=Human Leukocyte Antigen B27; W=White.

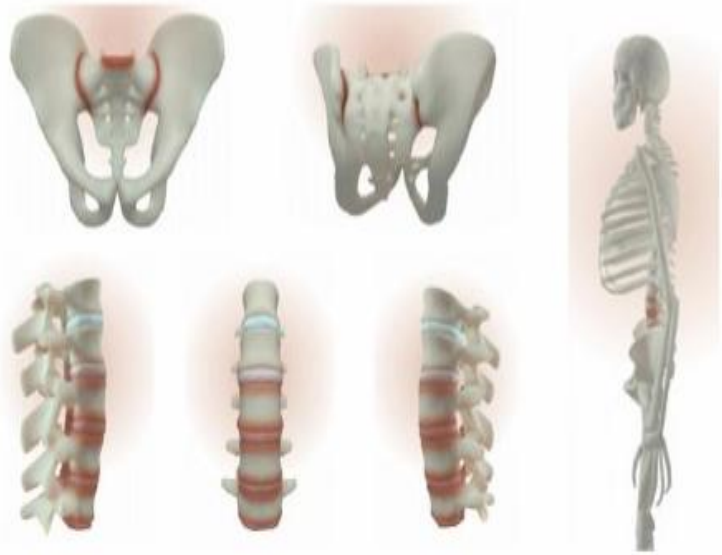
1. Walsh JA, Magrey M. *J Clin Rheumatol*. 2021;27(8):e547-e560. 2. Reveille JD, et al. *Arthritis Rheumatol*. 2012;64(5):1407-1411. 3. Sieper J, et al. *Nat Rev Dis Primers*. 2015;1:15013.
4. Taurog JD, et al. *N Engl J Med*. 2016;374(26):2563-2574. 5. https://spondylitis.org/wp-content/uploads/2020/11/DiseaseSeverity_JohnReveille.pdf (Accessed May 2023).

Axial Spondyloarthritis (axSpA)

axSpA is a chronic inflammatory disease of the sacroiliac (SI) joint and axial skeleton that can progress to spinal fusion.[1]

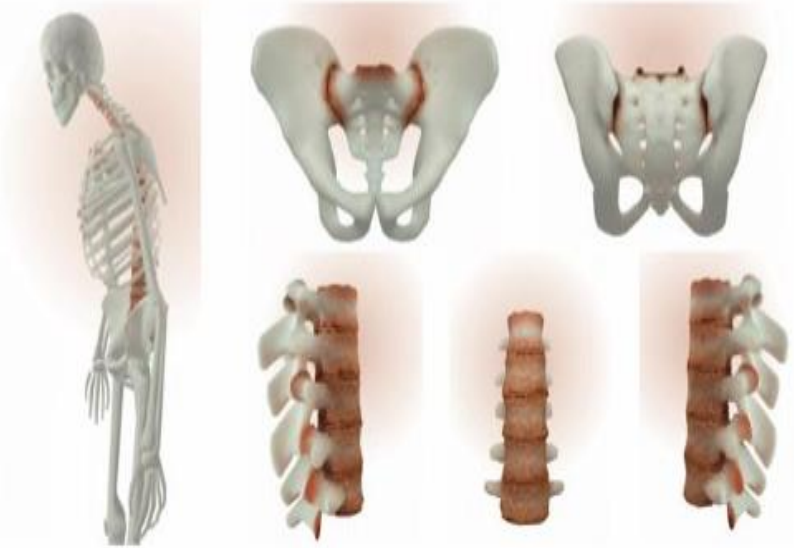
- It may also involve peripheral joints (hips, shoulders), entheses and digits, and extra-articular organs (intestines, skin, eyes, lung, and heart).[1]

Early SIJ/Spine Abnormalities



- Abnormalities include inflammation, such as bone marrow edema, and small localized areas of erosion in the SIJs.[2,3]
- Inflammatory changes may not be obvious via x-ray. MRI is better suited to detect abnormalities.[2,3]

Late SIJ/Spine Abnormalities



- Spine abnormalities include bridging syndesmophytes and fused facet joints, as well as partial or complete bone fusion of the SIJ (ankylosis).[2,3]
- Structural changes can be seen via x-ray.[2,3]

axSpA=Axial Spondyloarthritis; MRI=Magnetic Resonance Imaging; SIJ=Sacroiliac Joint.

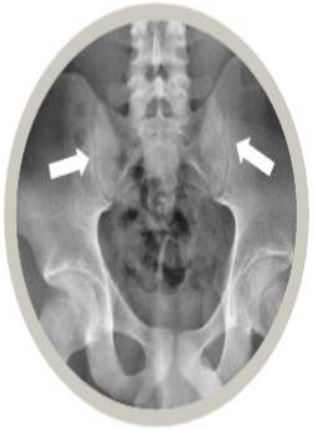
1. van der Heijde D. In: *Primer on the Rheumatic Diseases*. 2008:193-199. 2. Van Mechelen M, et al. *Calcif Tissue Int*. 2018;102(5):547-558. 3. Østergaard M, et al. *Ther Adv Musculoskel Dis*. 2012;4(4):301-311.

axSpA: One Disease, Two Subtypes

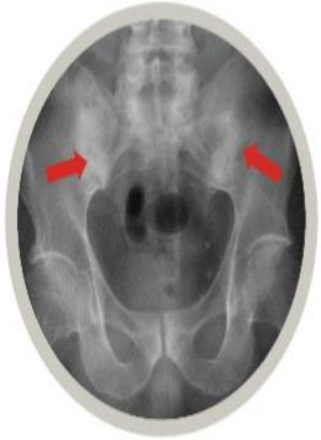
axSpA encompasses 2 subtypes of the same disease[1-3]

nr-axSpA[4]
No definite sacroiliitis according to mNY criteria

AS/r-axSpA[4]
Definite sacroiliitis according to mNY criteria



Grade 2 or less unilaterally
sacroiliitis according to mNY criteria[4]



Definite
radiographic sacroiliitis[4]

AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; mNY=Modified New York; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

1. Ward MM, et al. *Arthritis Rheumtol*. 2016;68(2):282-298. 2. Taurog JD, et al. *N Engl J Med*. 2016;374(26):2563-2574. 3. van der Linden S, et al. *Arthritis Rheum*.1984;27(4):361-368. 4. Sieper J, et al. *Ann Rheum Dis*. 2009;68(Suppl 2):ii1-44.

Diagnosis of axSpA in Clinical Practice

In clinical practice, diagnosis can be based on a range of different assessments and information:

Personal and family history, and physical examination.

Symptoms, such as chronic inflammatory back pain, fatigue, stiffness.

Evaluation of other causes of back pain, and differentiation between inflammatory and mechanical back pain.

Imaging including radiograph of the sacroiliac joint, in some cases also of the spine, and possibly MRIs.

Laboratory tests (e.g., HLA-B27, CRP).

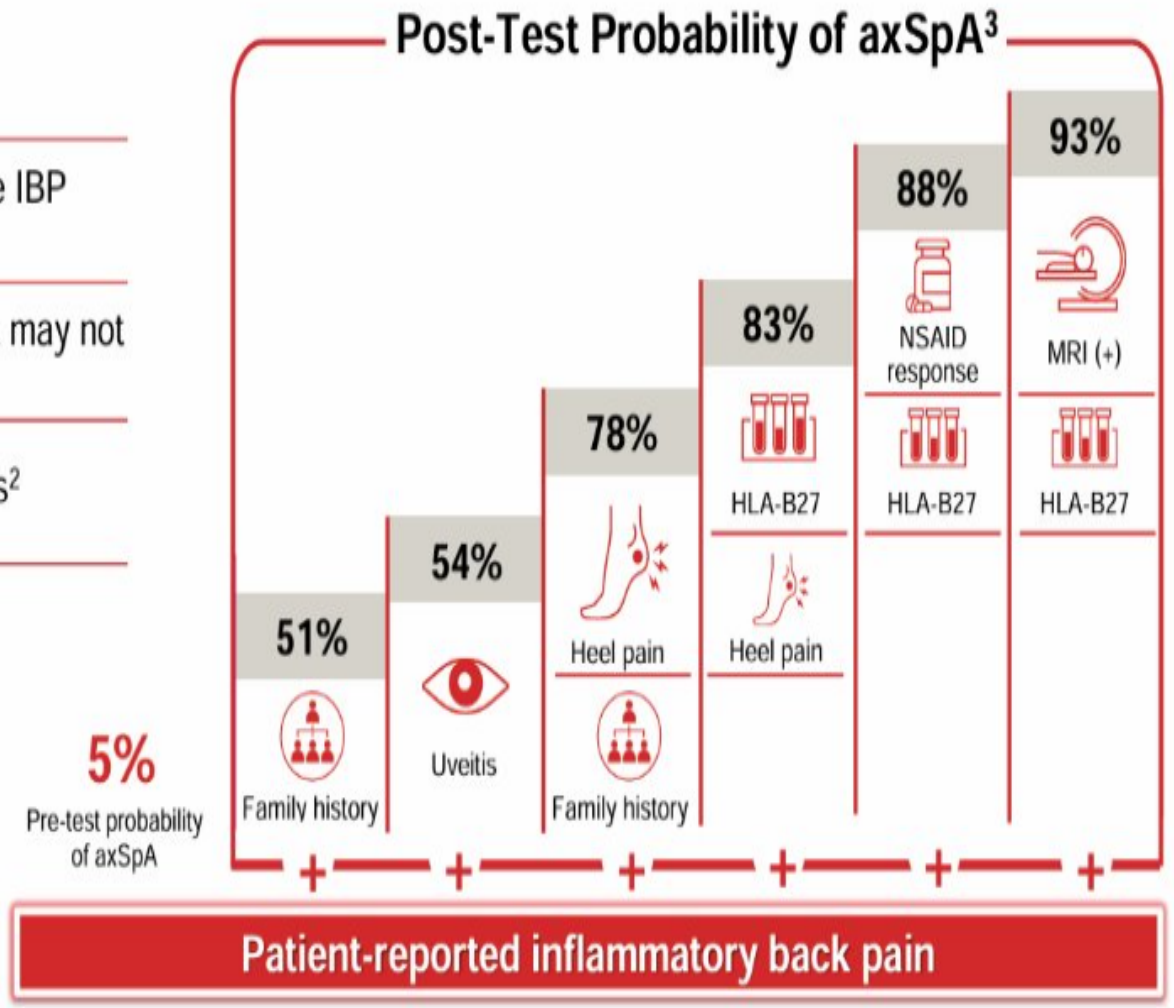
Other causes of back pain confound diagnosis.

axSpA=Axial Spondyloarthritis; CRP=C-Reactive Protein; HLA=Human Leukocyte Antigen; MRI=Magnetic Resonance Imaging.

Walsh JA, Magrey M. *J Clin Rheumatol.* 2021;27(8):e547-e560.

Diagnosing axSpA – Recognizing the Compelling Clinical Picture

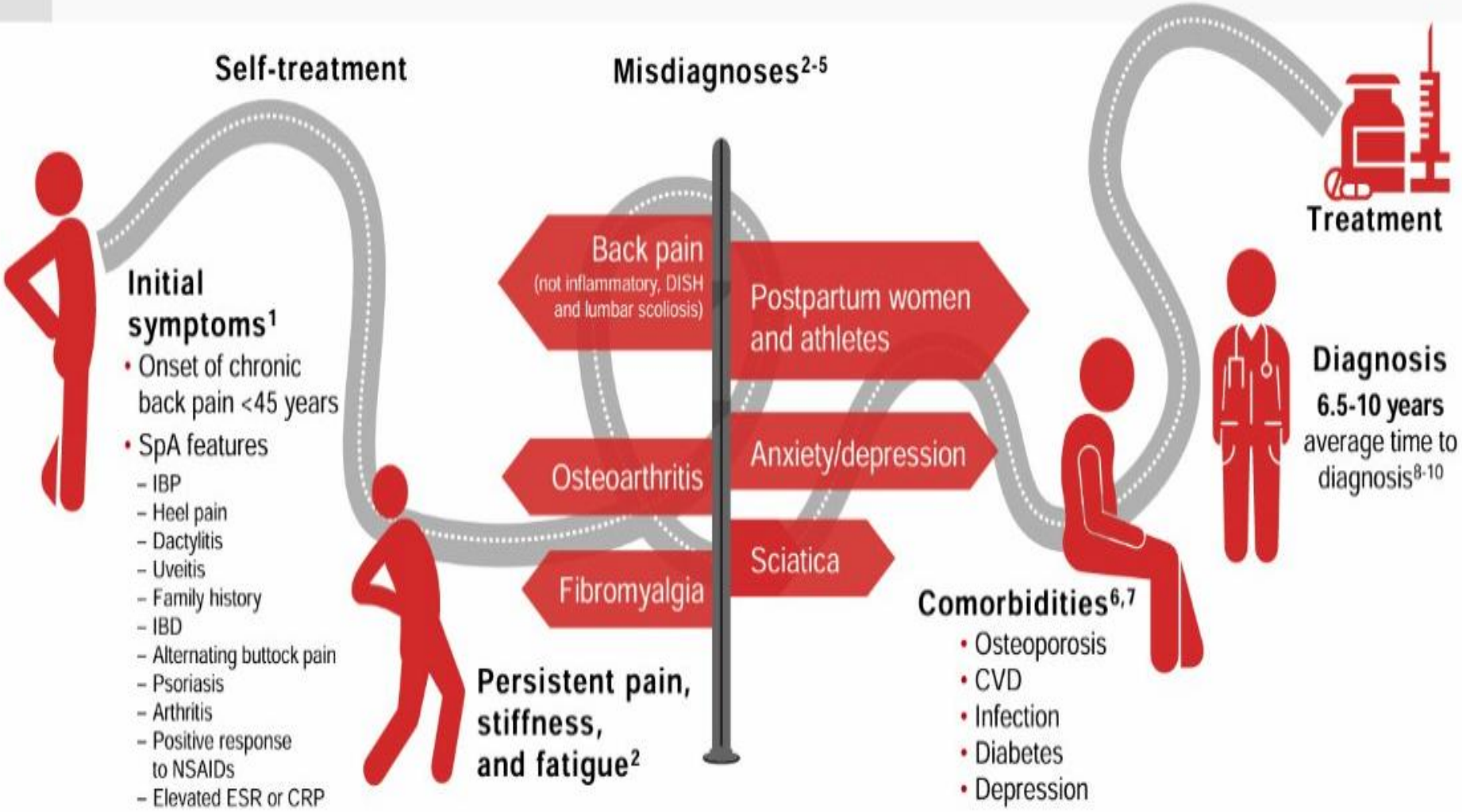
- Ask questions to help differentiate IBP from mechanical back pain[1]
- Recognize that features of axSpA may not be objective[2]
- Use SpA features as clinical clues[2]



axSpA=Axial Spondyloarthritis; HLA-B27=Human Leukocyte Antigen B27; IBP=Inflammatory Back Pain; MRI=Magnetic Resonance Imaging; NSAID=Nonsteroidal Anti-Inflammatory Drug.

1. NASS. Differentiating Inflammatory and Mechanical Back Pain. April 2018. Available from: https://nass.co.uk/wp-content/uploads/2020/03/Physiotherapy-modules-1.pdf. (Accessed March 2023).
2. Deodhar AA. *Am J Managed Care*. 2019;25 (17, suppl):S319-S330. 3. Rudwaleit M, et al. *Ann Rheum Dis*. 2004;63(5):535-543.

The Journey to an axSpA Diagnosis



axSpA=Axial Spondyloarthritis; CRP=C-Reactive Protein; CVD=Cardiovascular Disease; DISH=Diffuse Idiopathic Skeletal Hyperostosis; ESR=Erythrocyte Sedimentation Rate; IBD=Inflammatory Bowel Disease; IBP=Inflammatory Back Pain; NSAID=Nonsteroidal Anti-inflammatory Drug; SpA=Spondyloarthritis.

1. Rudwaleit M, et al. *Ann Rheum Dis*. 2009;68:777-783. 2. Ogdie A, et al. *Rheumatol Ther*. 2019;6:255-267. 3. Danve A, et al. *Clin Rheumatol*. 2019;38:625-634. 4. Walsh JA, Magrey M. *J Clin Rheumatol*. 2021;27(8):e547-e560. 5. Voirin-Hertz M, et al. *Semin Arthritis Rheum*. 2020;50(1):48-53. 6. Moltó A, et al. *Best Pract Res Clin Rheumatol*. 2018;32(3):390-400. 7. Strand VC, et al. *J Clin Rheumatol*. 2017;23(7):383-391. 8. Lapane KL, et al. *BMC Fam Pract*. 2021;22(1):251. 9. Zhao SS, et al. *Rheumatology (Oxford)*. 2021;60(4):1620-1628. 10. Carvalho PD and Machado PM. *Best Pract Res Clin Rheumatol*. 2019;33(4):101427.

Challenges in Diagnosing axSpA

Differentiating IBP from mechanical back pain[1]

5% of patients with chronic **lower back pain** are estimated to have **axSpA.**[1,2]

Lack of reliable biomarkers[3-5]

HLA-B27 (varies by ethnicity and sex), **CRP** and **ESR** (low sensitivity and specificity).[3-5]

Lack of awareness of axSpA among HCPs[6,7]

Brief duration of clinical visits and **limited referral** to rheumatologists.[6]

Need for accurate interpretation of MRIs[8]

The need to **standardize** the use of MRI and the **interpretation** of lesions in relation to axSpA.[8]

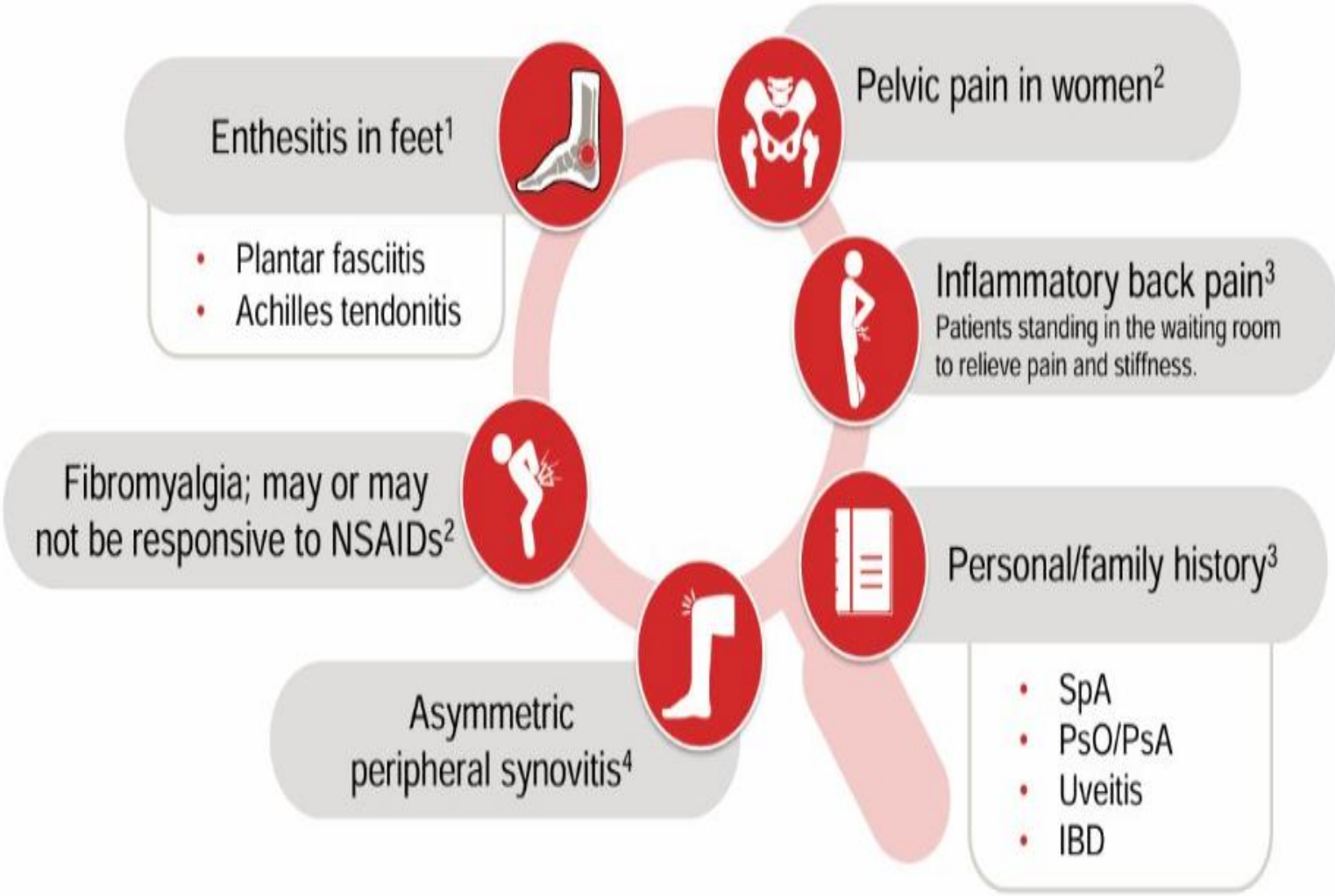
Absence of diagnostic crtieria[1]

Classification criteria developed for **clinical research** purposes.[9]

axSpA=Axial Spondyloarthritis; CRP=C-reactive Protein; ESR=Erythrocyte Sedimentation Rate; HCP=Healthcare Professional; HLA-B27=Human Leukocyte Antigen B27; IBP=Inflammatory Back Pain; MRI=Magnetic Resonance Imaging; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

1. Danve A, Deodhar A. *Clin Rheumatol.* 2019;38:625-634. 2. Poddubnyy D, et al. *RMD Open.* 2018;4:e000825. 3. Reveille JD. *Clin Rheumatol.* 2015;34(6):1009-1018. 4. Danve A, O'Dell J. *Int J Rheum Dis.* 2015;18(8):826-834. 5. Rusman T, et al. *Rheumatology (Oxford).* 2020;59(Suppl. 4):iv38-iv46. 6. Lapane KL, et al. *BMC Fam Pract.* 2021;22(1):251. 7. Sieper J, et al. *Ann Rheum Dis.* 2002;61 Suppl 3(Suppl 3):iii8-iii18.
8. Deodhar A, et al. *Arthritis Rheumatol.* 2016;68(7):1699-1676. 9. Aggarwal R, et al. *Arthritis Care Res (Hoboken).* 2015;67(7):891-897.

Common Clues in axSpA Diagnosis – What to Look for?



axSpA=Axial Spondyloarthritis; IBD=Inflammatory Bowel Disease; NSAID=Non-steroidal Anti-inflammatory Drug; PsA=Psoriatic Arthritis; PsO=Psoriasis; SpA=Spondyloarthritis.

Summary

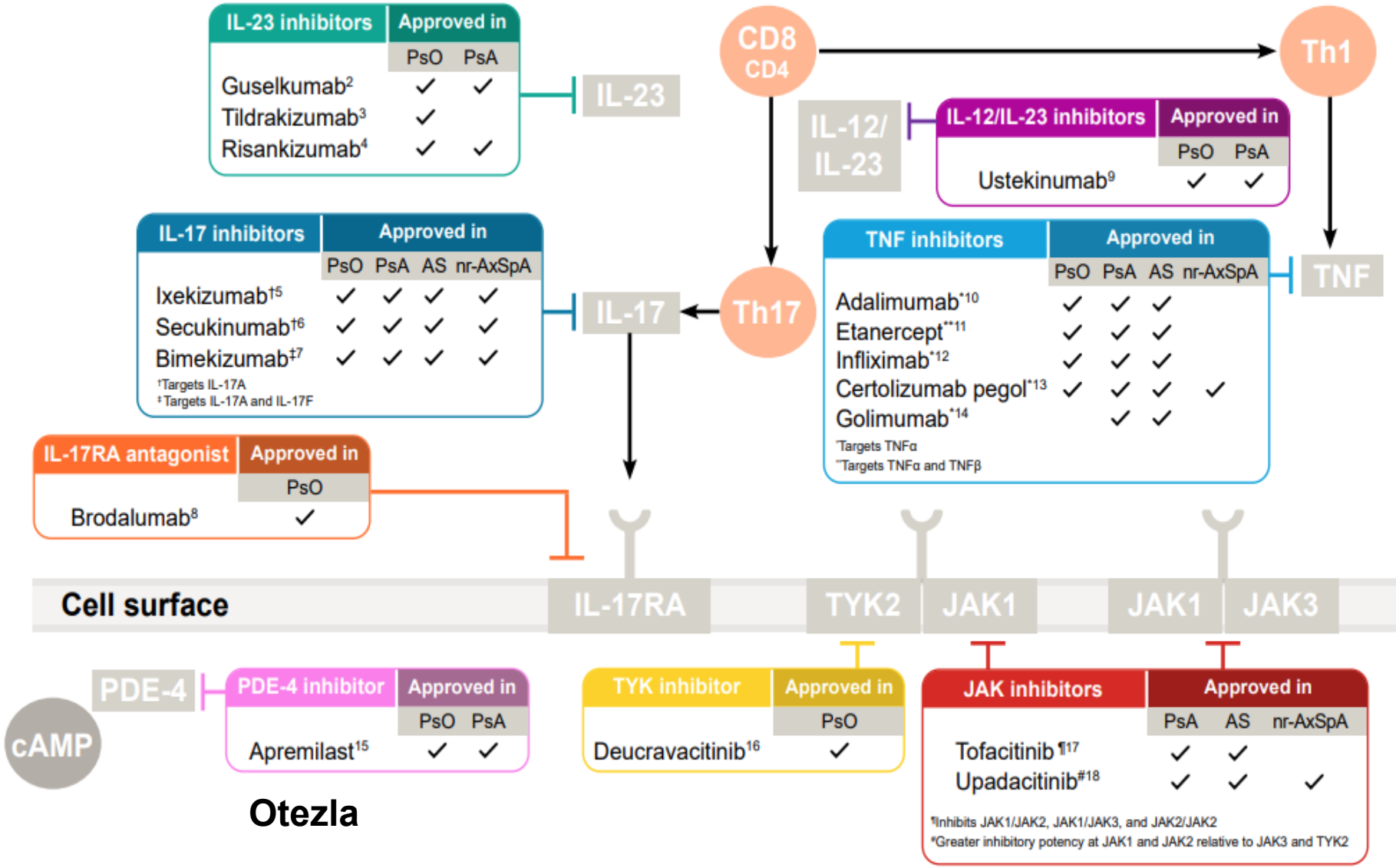
- axSpA refers to the **inflammation of the axial skeleton** and encompasses **two subtypes**: AS/r-axSpA and nr-axSpA.[1-4]
  - nr-axSpA is defined as patients without changes consistent with sacroiliitis that meets mNY criteria.[4]
  - r-axSpA is defined as definite sacroiliitis according to mNY criteria, plus at least one SpA feature if we are going to use ASAS criteria.[4]
- **Diagnosis can be challenging** with multiple factors contributing to delays, particularly in patients presenting with less definitive clinical features.[5-13]
- **Classification criteria** are used to identify eligible patients for clinical trial enrollment and are **not intended to be used to diagnose patients.**[5,13]

AS=Ankylosing Spondylitis; axSpA=Axial Spondyloarthritis; mNY=modified New York; nr-axSpA=Nonradiographic Axial Spondyloarthritis; r-axSpA=Radiographic Axial Spondyloarthritis.

1. Ward MM, et al. *Arthritis Rheumatol.* 2016;68(2):282-298. 2. Taurog JD, et al. *N Engl J Med.* 2016;374(26):2563-2574. 3. van der Linden S, et al. *Arthritis Rheum.*1984;27(4):361-368. 4. Sieper J, et al. *Ann Rheum Dis.* 2009;68(Suppl 2):ii1-44. 5. Danve A, Deodhar A. *Clin Rheumatol.* 2019;38:625-634. 6. Poddubnyy D, et al. *RMD Open.* 2018;4:e000825. 7. Reveille JD. *Clin Rheumatol.* 2015;34(6):1009-1018. 8. Danve A, O'Dell J. *Int J Rheum Dis.* 2015;18(8):826-834. 9. Rusman T, et al. *Rheumatology (Oxford).* 2020;59(Suppl. 4):iv38-iv46. 10. Lapane KL, et al. *BMC Fam Pract.* 2021;22(1):251. 11. Sieper J, et al. *Ann Rheum Dis.* 2002;61 Suppl 3(Suppl 3):iii8-iii18. 12. Deodhar A, et al. *Arthritis Rheumatol.* 2016;68(7):1699-1676. 13. Aggarwal R, et al. *Arthritis Care Res (Hoboken).* 2015;67(7):891-897.

Mechanism of Action of Systemic Treatment Options for Psoriasis, Psoriatic Arthritis, and Axial Spondyloarthritis

Approved systemic treatment options for PsO, PsA, and AxSpA (AS and nr-AxSpA) target several signaling pathways[1]

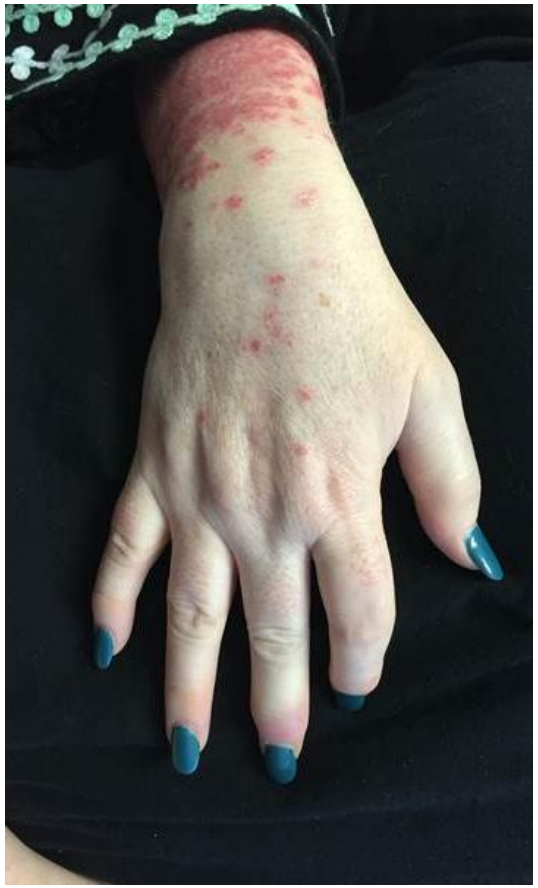


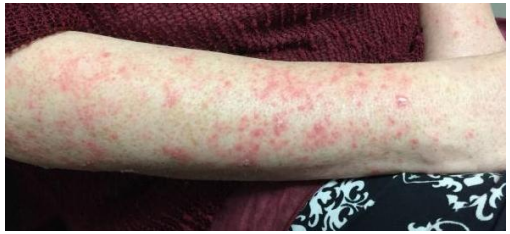
Otezla

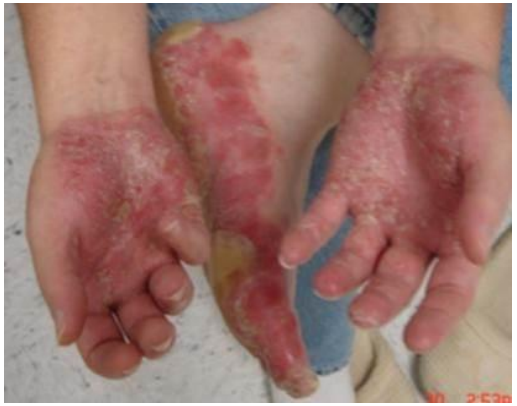
AS=ankylosing spondyloarthritis; AxSpA=axial spondyloarthritis; cAMP=cyclic adenosine monophosphate; IL=Interleukin; JAK=Janus Kinase; nr-AxSpA=non-radiographic axial spondyloarthritis; PDE-4=phosphodiesterase 4; PsA=psoriatic arthritis; PsO=plaque psoriasis; TNF=Tumor Necrosis Factor; TYK=Tyrosine Kinase.

1. Adapted from Azuaga AB, Ramírez J, Cañete JD. Psoriatic Arthritis: Pathogenesis and Targeted Therapies. Int J Mol Sci. 2023 Mar 3;24(5):4901. 2. Tremfya [US PI]. Horsham, PA, USA: Janssen Biotech, Inc. 09-2024.
3. Ilumya [US PI]. Sharjah, UAE: Sun Pharma Global FZE, Inc., 09-2024. 4. SKYRIZI™ [US PI] North Chicago, IL, USA: AbbVie Inc., 06-2024. 5. Taltz® [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 08-2024.

Psoriatic Arthritis







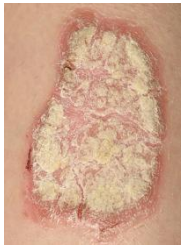
Moll & Wright - Classification of Psoriatic Arthritis

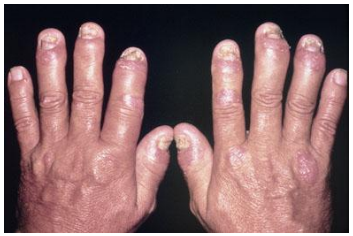
Type	Key Clinical Features	Incidence
Asymmetric polyarthritis or oligoarthritis	Morning stiffness, DIP and PIP involvement, nail disease, ≤ 4 joints involved	40%
Symmetric polyarthritis	Symmetric polyarthritis, RA-like distribution, but RF negative	25%
Ankylosing spondylitis	Inflammatory low back pain, sacroilitis, axial involvement, 50% HLA-B27+	20%
Distal interphalangeal joint disease	Nail changes, often bilateral joint involvement	15%
Arthritis mutilans	Destructive form of arthritis, telescoping digits, joint lysis, typically in phalanges and metacarpals	<5%

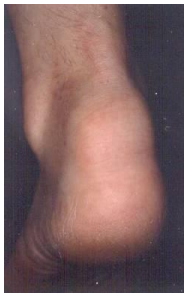
Moll JM, Wright V. *Semin Arthritis Rheum* 1973; **3**: 55-78.

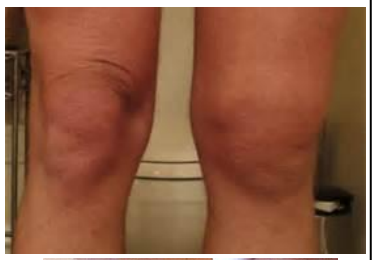
Psoriatic Arthritis: Multifaceted disease

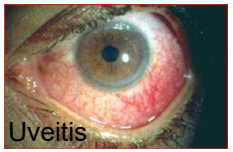
Joint & Skin & other features

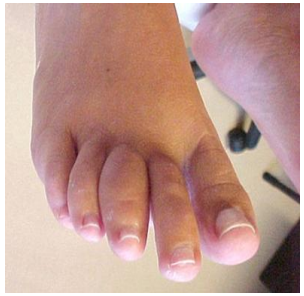




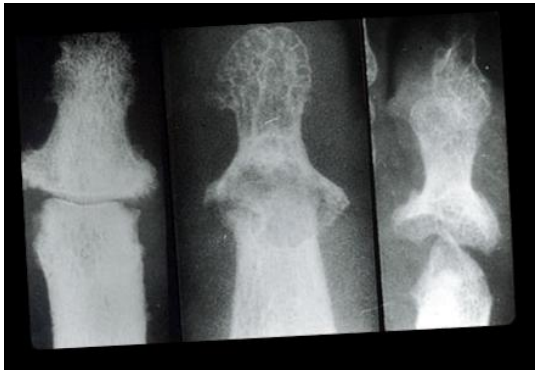




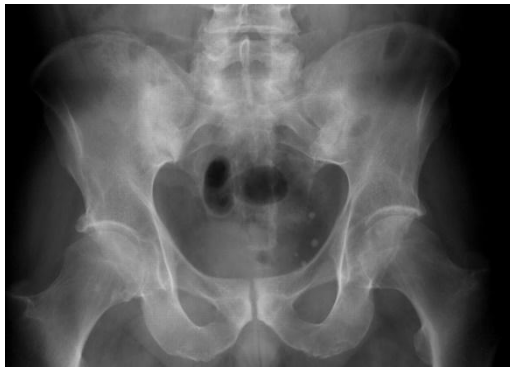




Imaging



Pencil in cup deformity



Sacrolilitis – X-ray

Seronegative

Psoriatic Arthritis (PsA)

- A chronic inflammatory arthropathy in patients with psoriasis
- Prevalence of Psoriasis
    - ~ 2% to 3% of population
  - Psoriatic arthritis
    - Occurs in 30% (5-39%) of patients with psoriasis
- Skin precedes joint involvement (65%; joints 1st 20%)
- 39% of patients hospitalized with severe psoriasis
- PsA makes up 15% of cases in early synovitis clinic
- Recent NPF survey suggested 1 million PsA patients in USA
- Equal incidence in males and females
- Peak onset in late 20s to 30s

Farber EM, et al. *Dermatol Clin*. 1994;12:805-816.
Gladman DD. *Rheum Dis Clin North Am*. 1998;24:829-844.

PsA – Who is at risk?

- Risk factors for PsA:
  - obesity
  - nail dystrophy
  - smoking
  - severe psoriasis
  - trauma
  - Family Hx
  - Rubella vaccination
- Is there Pre-clinical PsA? (PsO + Time + above factors)

PsA Epidemiology

- Incidence of PsA varies from 3.4 to 8 per 100,000 population
- PsO precedes PsA in 70 - 80% of patients
- < 10% have joint Sx prior to skin Sx (psoriatic arthritis sine psoriasis)
- PsA develops in up to 10%-30% of patients with psoriasis
- Occurs equally in men and women
- Mean Sx onset: between ages 30 and 50 yrs.
- USA Numbers - SpA (1.4mill) more prevalent RA
  - 1.3 million RA pts
  - 800K PsA
  - 600k AS

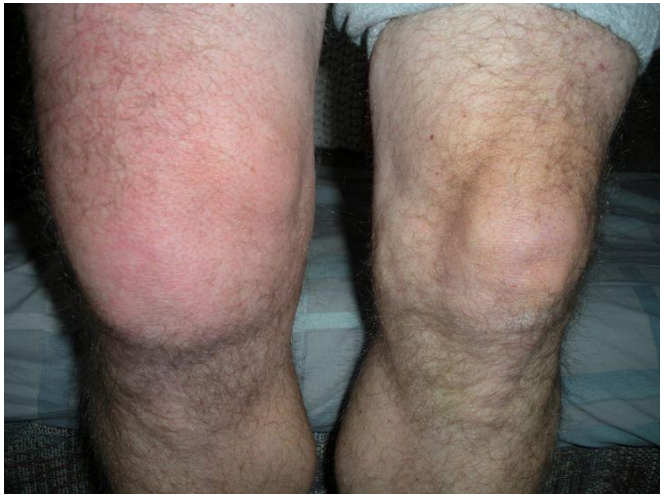
1. Bax M, et al. *Immunogenetics.* 2011;63(8):459-466. 2. McInnes IB, Schett G. *N Engl J Med.* 2011;365(23):2205-2219. 3. Myasoedova E, et al. *Arthritis Rheum.* 2010;62(6):1576-1582. 4. Scott DL, Kingsley GH. *N Engl J Med.* 2006;355(7):704-712. 5.Gladman DD. *Rheum Dis Clin North Am.* 1998;24:829

Risk Factors for Psoriatic Arthritis in Patients With Psoriasis: A Prospective Cohort Study

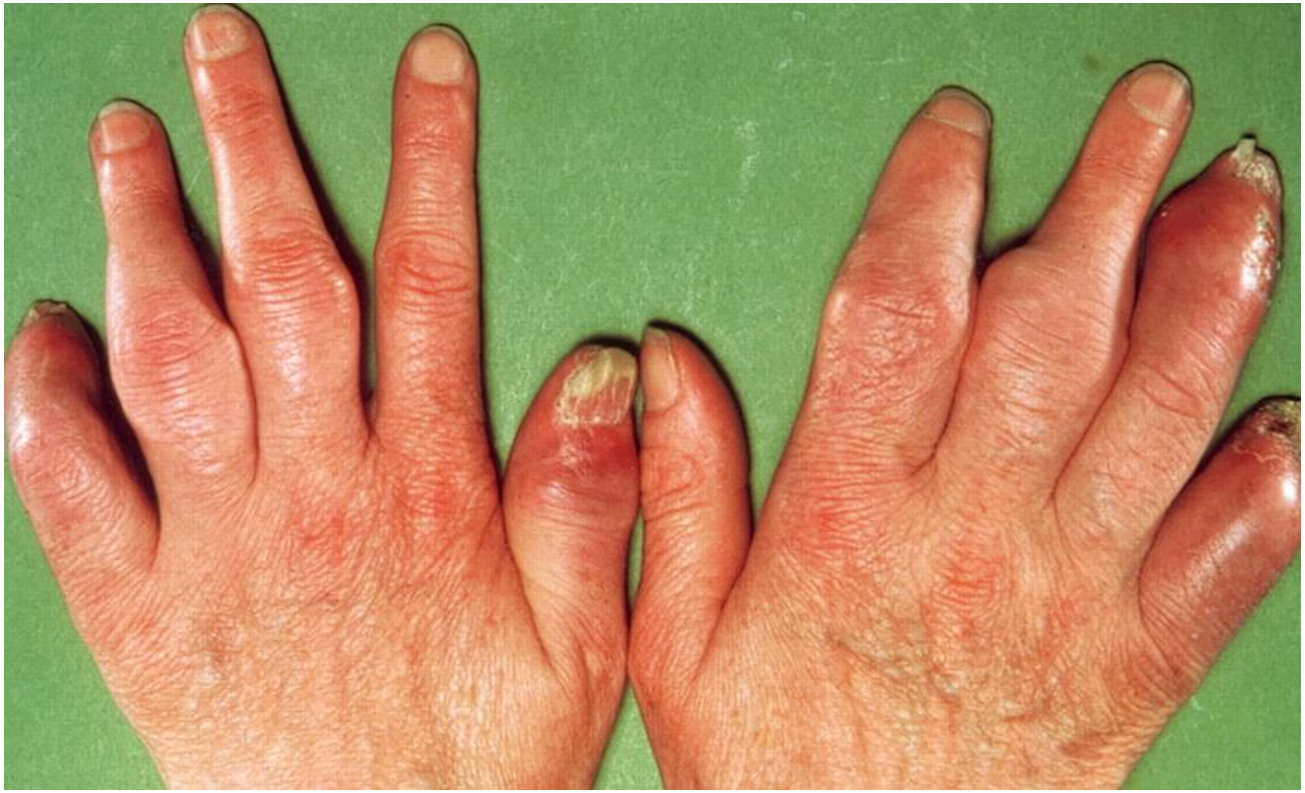
- 464 Psoriasis patients followed up for 8 years
- 51 patients developed PsA
  - annual incidence rate was 2.7 cases per 100 PsO
- Risk Factors
  - severe psoriasis (RR 5.4, $P = 0.006$),
  - low level of education
  - retinoid medications (RR 3.4, $P = 0.02$).
  - psoriatic nail pitting (RR 2.5, $P = 0.002$)
  - Uveitis (RR 31.5, $P = 0.0002$)

Peripheral Arthritis

- Acute Onset
- Predominately effects the lower extremities
- Associated with swelling
- Usually asymmetric
- Effects 1 to 3 joints
  - Oligoarthritis

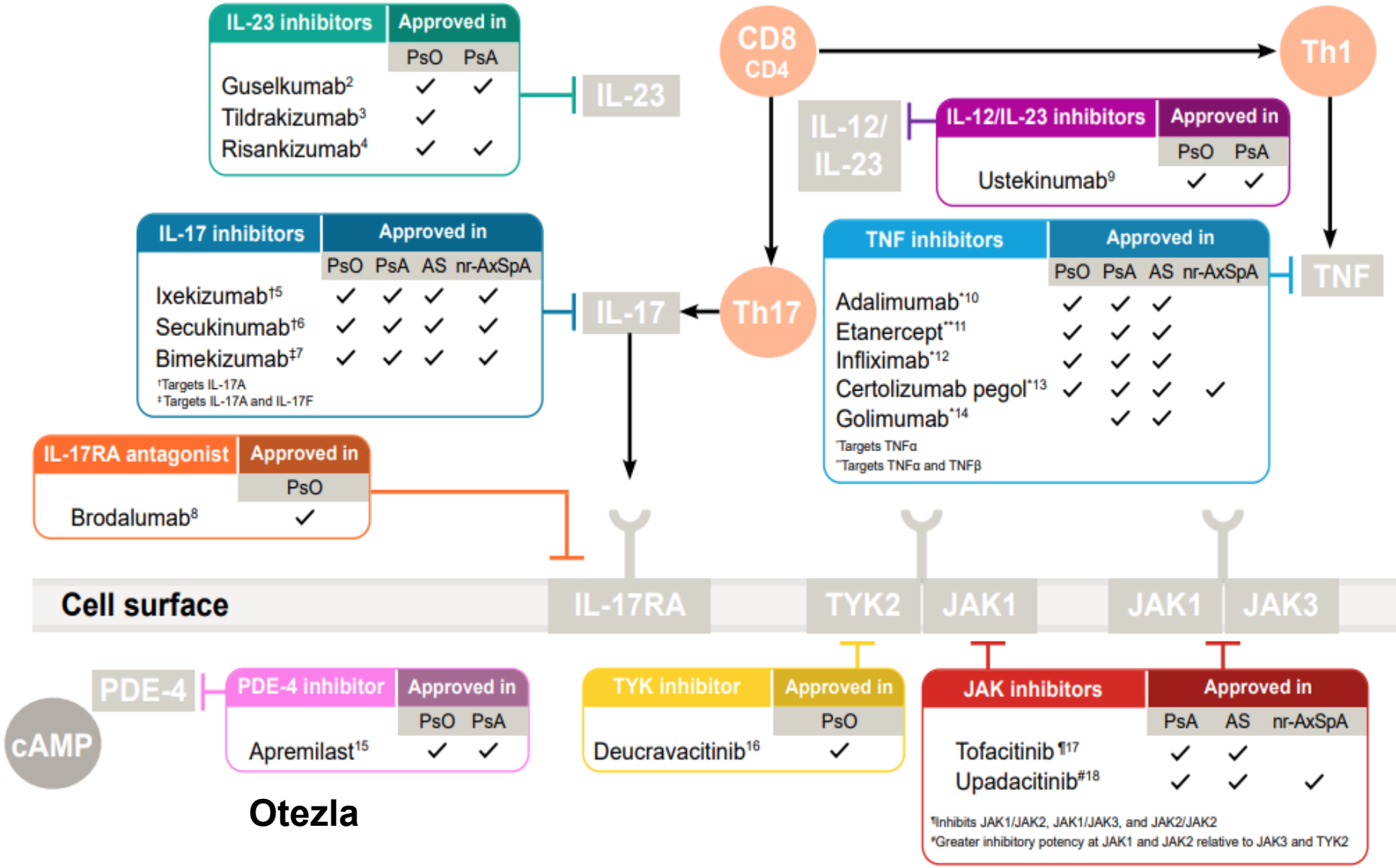


Dactylitis



Mechanism of Action of Systemic Treatment Options for Psoriasis, Psoriatic Arthritis, and Axial Spondyloarthritis

Approved systemic treatment options for PsO, PsA, and AxSpA (AS and nr-AxSpA) target several signaling pathways[1]



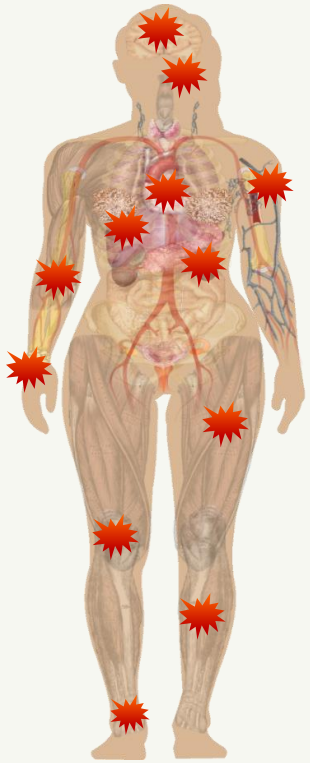
Otezla

AS=ankylosing spondyloarthritis; AxSpA=axial spondyloarthritis; cAMP=cyclic adenosine monophosphate; IL=Interleukin; JAK=Janus Kinase; nr-AxSpA=non-radiographic axial spondyloarthritis; PDE-4=phosphodiesterase 4; PsA=psoriatic arthritis; PsO=plaque psoriasis; TNF=Tumor Necrosis Factor; TYK=Tyrosine Kinase.

1. Adapted from Azuaga AB, Ramírez J, Cañete JD. Psoriatic Arthritis: Pathogenesis and Targeted Therapies. Int J Mol Sci. 2023 Mar 3;24(5):4901. 2. Tremfya [US PI]. Horsham, PA, USA: Janssen Biotech, Inc. 09-2024.
3. Ilumya [US PI]. Sharjah, UAE: Sun Pharma Global FZE, Inc., 09-2024. 4. SKYRIZI™ [US PI] North Chicago, IL, USA: AbbVie Inc., 06-2024. 5. Taltz® [US PI]. Indianapolis, IN, USA: Eli Lilly and Company, 08-2024.

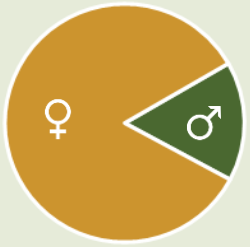
What Is Systemic Lupus Erythematosus?

- Systemic lupus erythematosus (SLE) is a progressive chronic autoimmune disease that results in inflammation and tissue damage. Systemic/multi-organ inflammation, multiple autoantibodies and deposition of immune complexes
- Characterized by flares, spontaneous remission, and relapses
- Highly heterogeneous….Can affect any part of the body
- Demographics: peak onset between 15 - 40 yrs. Female: Male ratio 10:1. This female predominance decreases among older patients. There is a racial disparity -African descent has both a greater incidence & more severe disease.
  - More severe in Asians, Latinos, Children, Males
  - Milder: Caucasians, Elderly, Drug induced disease

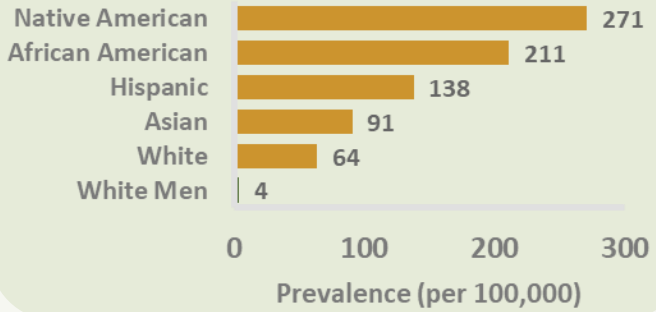


What Are Some Characteristics of Patients with SLE

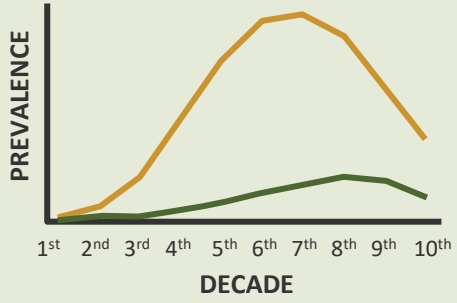
85% are women



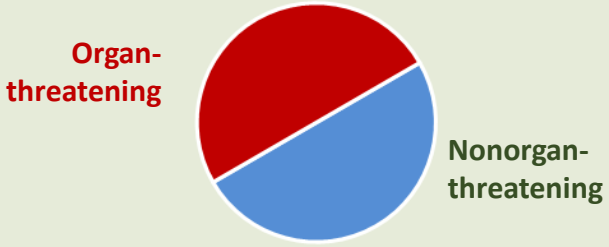
Sex, Race, and Ethnicity



Ratio peaks in reproductive years



Half develop organ-threatening disease



Petri M. *Best Pract Res Clin Rheumatol*. 2002;16:847-858. Petri M. *Systemic Lupus Erythematosus*. In: Imboden JB, et al, eds. *Current Rheumatology Diagnosis and Treatment*. 2007. Uramoto KM, et al. *Arthritis Rheum*. 1999;42(1):46-50. Rees F, et al. *Ann Rheum Dis*. 2017;69:2006-2017. Izmirly PM, et al. *Arthritis Rheum*. 2017;69:2006-2017.

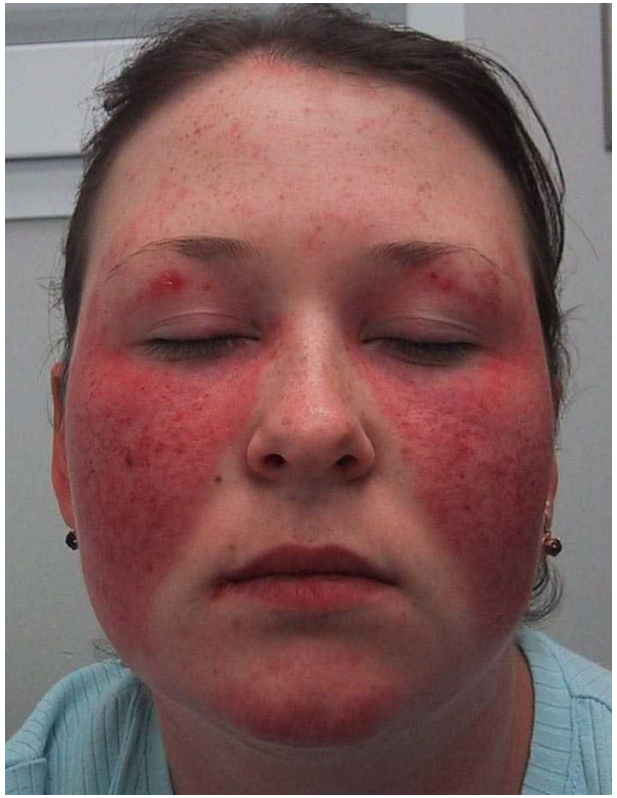
Systemic lupus erythematosus classification criteria
(SOAP BRAIN MD)

1. ***S***erositis:
   (a) pleuritis, or
   (b) pericarditis
2. ***O***ral ulcers
3. ***A***rthritis
4. ***P***hotosensitivity

10. ***M***alar rash
11. ***D***iscoid rash

". ..A person shall be said to have SLE if four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation."

5. ***B***lood/Hematologic disorder:
   (a) hemolytic anemia or
   (b) leukopenia of < 4.0 x 10^9
   (c) lymphopenia of < 1.5 x 10^9
   (d) thrombocytopenia < 100 X 10^9
6. ***R***enal disorder:
   (a) proteinuria > 0.5 gm/24 h or 3+ dipstick or
   (b) cellular casts
7. ***A***ntinuclear antibody (positive ANA)
8. ***I***mmunologic disorders:
   (a) raised anti-native DNA antibody binding or
   (b) anti-Sm antibody or
   (c) positive anti-phospholipid antibody work-up
9. ***N***eurological disorder:
   (a) seizures or
   (b) psychosis



23 yoF, Cerebritis, arthritis, malar, alopecia, photosensitivity, +ANA, +dsDNA, low C3 & C4

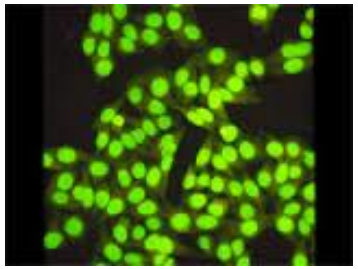
Antinuclear Antibodies

- 99.99% of SLE patients are ANA positive

- Significance rests w/ ***Clinical Hx***, titer, pattern
- Higher the titer, the greater the suspicion of SLE
- ANA should be used to confirm clinical suspicion based on history and PE

Antinuclear Antibodies

- ANA+ not synonymous with a Dx of SLE
  - Highly sensitive, but poorly specific
- May be present in other conditions:
  - Drug-induced
  - Age (3X increase > 65 yrs.)
  - Autoimmune disease
  - Chronic Renal or Hepatic disease
  - Neoplasia
  - Pregnancy 9-18%
- Ineffective “screen” for arthritis or lupus
- USA: 20 million ANA+
  - but only 1-2% risk of SLE



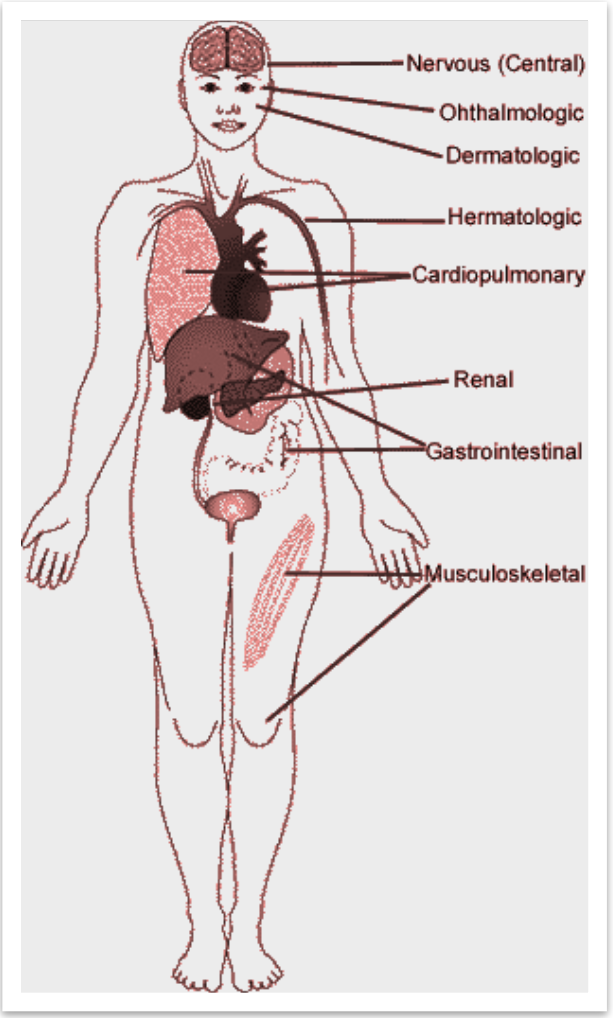
Systemic Lupus Erythematosus

COMMON FEATURES

- Constitutional – fever, fatigue
- Skin – malar rash
- Joint pains
- Hematologic

WORRISOME FEATURES

- Renal
- Lung
- Brain
- Heart



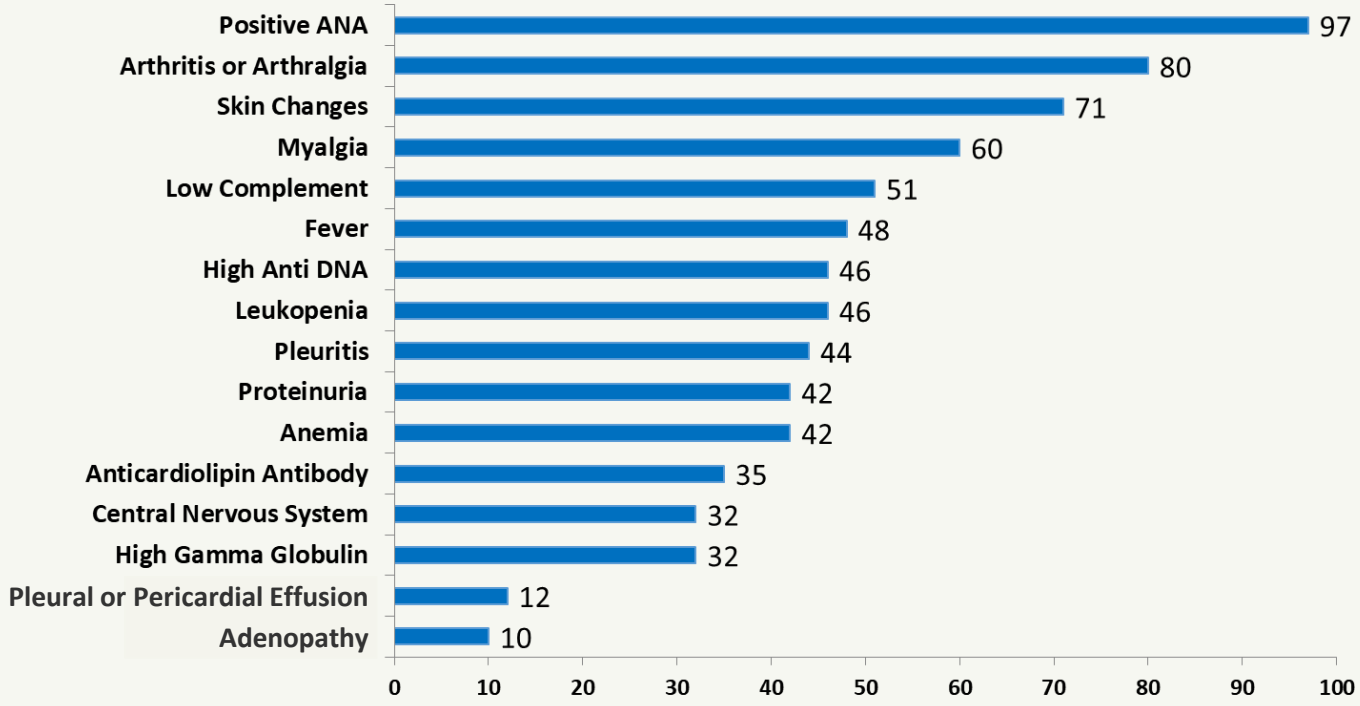
“Newer” Criteria

2019 ACR/EULAR Criteria

1. +ANA >1:80 (entry criteria)
2. Fever > 38.3°C
3. Leukopenia
4. Thrombocytopenia
5. Autoimmune hemolysis
6. Delirium
7. Psychosis
8. Seizures
9. Non-scarring alopecia
10. Oral ulcers
11. SCLE or Discoid lupus
12. ACLE
13. Pericardial or pleural effusion*
14. Acute pericarditis (not pleuritis!)
15. Joint pain
16. Proteinuria > 0.5 g/24 hours
17. Lupus nephritis on biopsy
18. + Antiphospholipid antibodies
19. Low C3/C4
20. +dsDNA, +Smith antibodies

The 2019 EULAR/ACR classification criteria for SLE include positive ANA at least once as obligatory entry criterion; followed by additive weighted criteria grouped in 7 clinical (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunological (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains, and weighted from 2 to 10. Patients accumulating ≥10 points are classified. In the validation cohort, the new criteria had a sensitivity of 96.1% and specificity of 93.4%,

Incidence of Clinical and Laboratory Manifestations of SLE



Summary of Useful Tests in SLE

LEVEL

1. Routine screening for all patients
2. Readily available and inexpensive testing for select patients
3. Reflex panel testing to characterize nature of lupus involvement
4. Specialized testing limited to selected clinical circumstances

Summary of Useful Tests in SLE

1. **Routine screening for all patients**
2. **Readily available and inexpensive testing for select patients**
3. **Reflex panel testing to characterize nature of lupus involvement**
4. **Specialized testing limited to selected clinical circumstances**

Total cost under $500

- CBC
- Comprehensive metabolic profile
- Urinalysis
- Muscle enzymes
- Acute phase reactants (eg, CRP, ESR)
- Chest X-ray
- EKG
- ANA
- C3 or C4 complement
- Anti-dsDNA

Summary of Useful Tests in SLE

1. Routine screening for all patients
2. Readily available and inexpensive testing for select patients
3. Reflex panel testing to characterize nature of lupus involvement
4. Specialized testing limited to selected clinical circumstances

Relatively inexpensive

- Clotting tests (eg, PTT)
- 2D echo
- Musculoskeletal X-rays/ultrasound
- Rheumatoid factor
- Anti-CCP
- Bone densitometry

Summary of Useful Tests in SLE

1. Routine screening for all patients
2. Readily available and inexpensive testing for select patients
3. Reflex panel testing to characterize nature of lupus involvement
4. Specialized testing limited to selected clinical circumstances

Extractable nuclear antigens

- Anti-Sm
- Anti RNP
- Anti SSA (Ro) and SSB (La)

Antiphospholipid panel

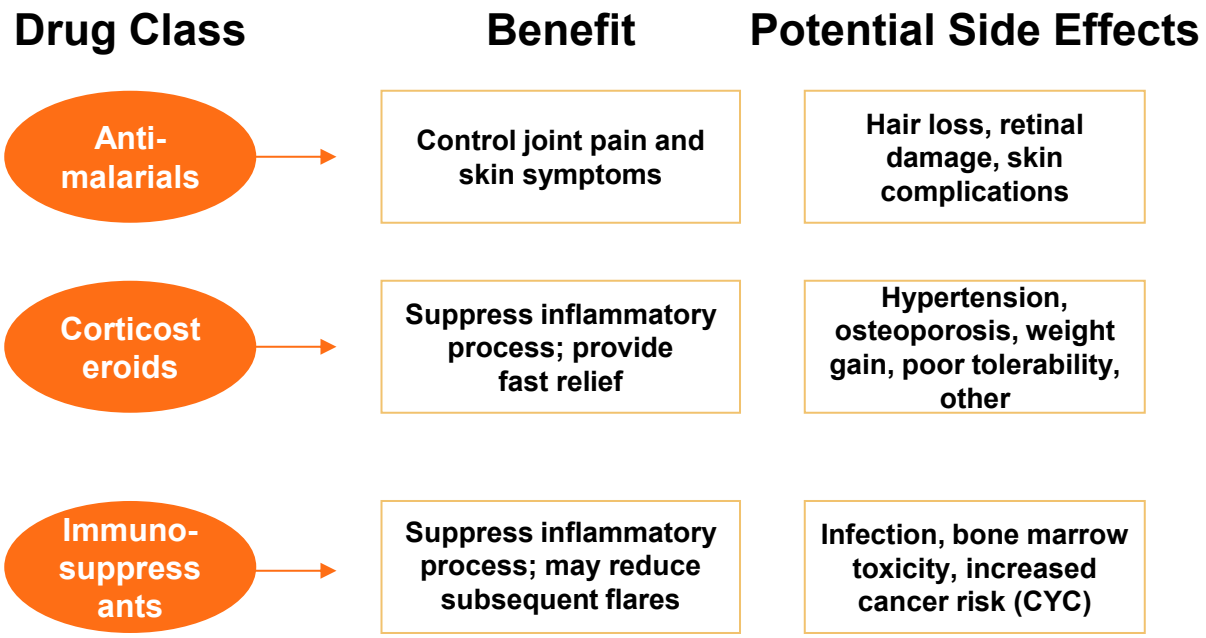
- RPR (false positive syphilis serology)
- Lupus anticoagulant
- Anticardiolipin
- Other antiphospholipid antibodies

Summary of Useful Tests in SLE

1. Routine screening for all patients
2. Readily available and inexpensive testing for select patients
3. Reflex panel testing to characterize nature of lupus involvement
4. Specialized testing limited to selected clinical circumstances

- CT or MR imaging
- Electrical studies (eg, EEG, EMG)
- Bone scan
- Niche serologies (eg, Coombs, anti-histone, myositis panel)

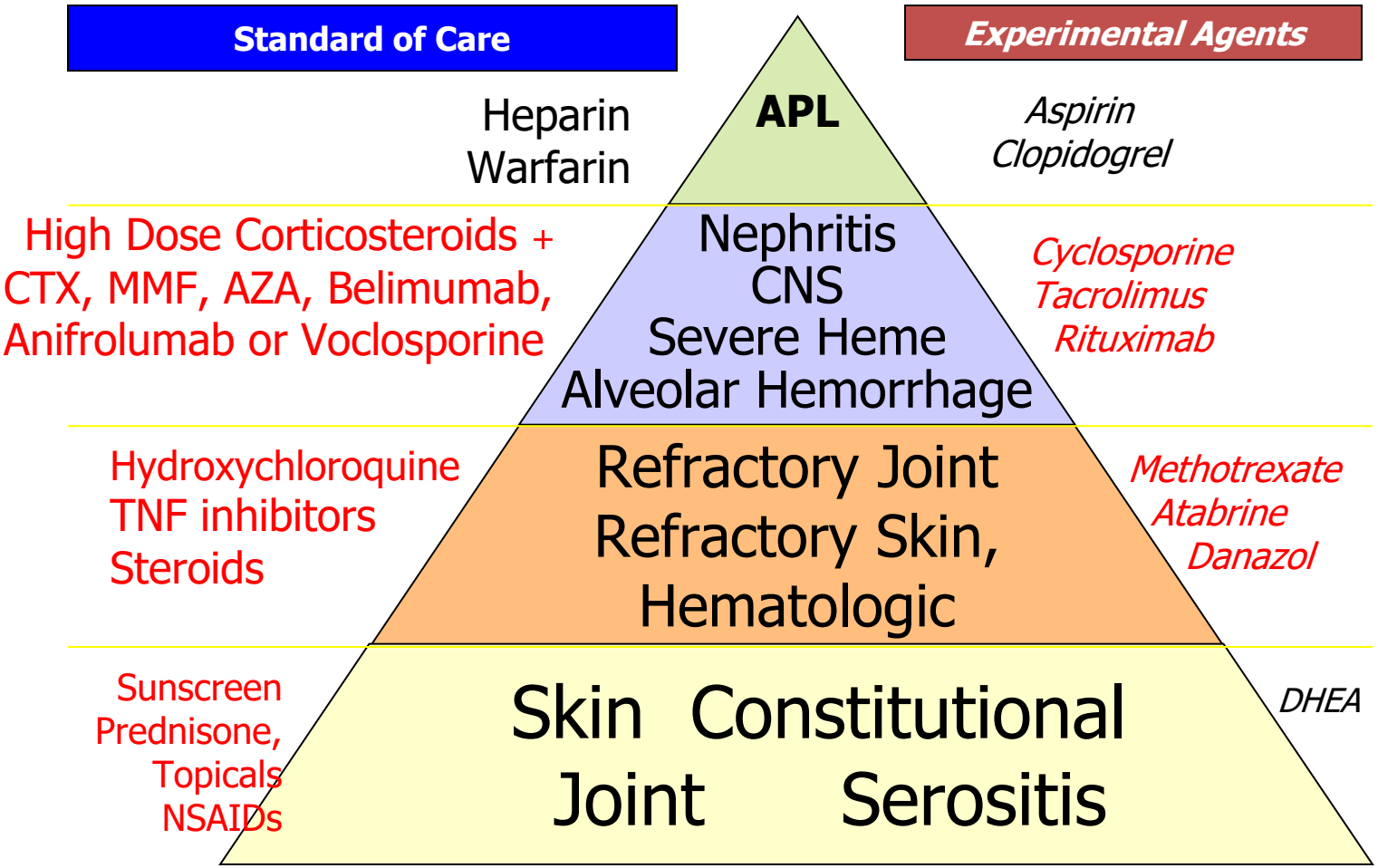
Current Treatment Options for SLE



Used to treat moderate–severe disease and flares

Adapted from Datamonitor, 2003.

Management of Lupus



New Treatment Options in Lupus Nephritis

Pauline M Montigny [1] [2], Frédéric A Houssiau [3] [4]

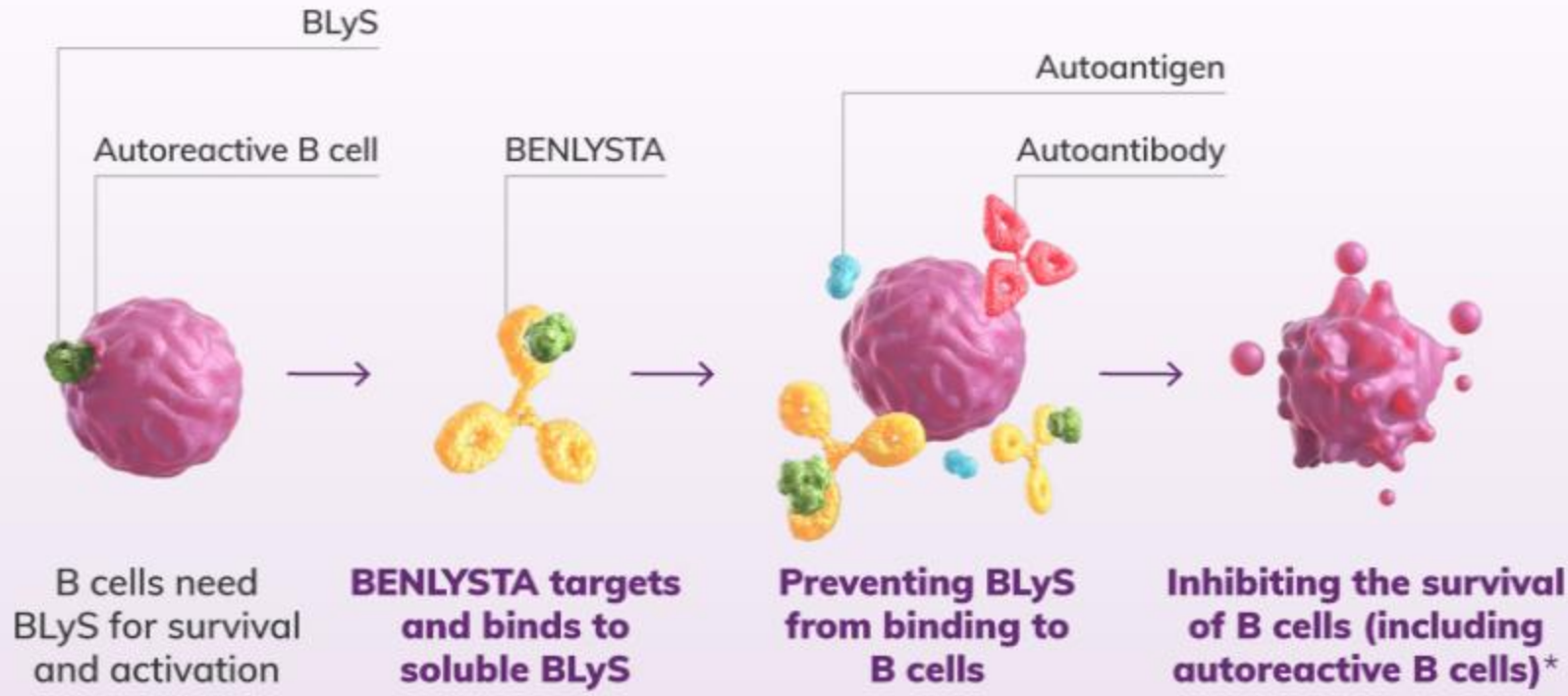
Affiliations + expand

PMID: 35298708 DOI: 10.1007/s00005-022-00647-8

Abstract

The aim of this study is to report major recent progresses in the treatment of lupus nephritis (LN). Results of controlled randomized trials are discussed in view of the unmet needs in the field. Current treatments of LN are not satisfactory, with a disappointing proportion of 20-30% of patients achieving complete renal response within 6-12 months, and 5-20% developing end-stage kidney disease within ten years. Two drugs (belimumab and voclosporin) have been officially registered by the medical agencies as add on treatment of LN, a first-in-history success after decades of use of non-registered drugs and trial failures. Other targeted therapies (obinutuzumab and anifrolumab) are currently tested in Phase III trials, after interesting results in Phase II studies. Unanswered questions related to the use of these new drugs are discussed. Recent trials have opened new avenues for the treatment of LN which will hopefully reduce the rate of chronic kidney disease.

Belimumab/Benlysta



Old and New Calcineurin Inhibitors in Lupus Nephritis

Claudio Ponticelli [1], Francesco Reggiani [2], Gabriella Moroni [2]

Affiliations + expand

PMID: 34768354 PMCID: PMC8584552 DOI: 10.3390/jcm10214832

Free PMC article

Abstract

Calcineurin inhibitors (CNIs) are drugs that inhibit calcineurin, a key phosphatase that dephosphorylates a transcription factor called the nuclear factor of activated T cells (NFAT), allowing its translocation into the nucleus of quiescent T cells. In the nucleus, NFAT activates interleukin 2, which stimulates the proliferation and differentiation of T-cells. CNIs can also stabilize the actin cytoskeleton of podocytes reducing proteinuria. Thanks to these characteristics, CNIs have been often used in the treatment of autoimmune diseases. However, the therapeutic index of CNIs is narrow, and their interactions with other drugs can increase toxicity or reduce efficacy. In lupus nephritis, cyclosporine and tacrolimus have been used both in induction and maintenance therapies. Observational studies and randomized controlled trials showed that both cyclosporine and tacrolimus can increase efficacy. Tolerance is satisfactory if low doses are used and the patient is carefully monitored. More recently, a new CNI, called voclosporin (VCS), has been approved by the Food and Drug Administration for use in lupus nephritis. VCS offers potential advantages over other CNIs. In

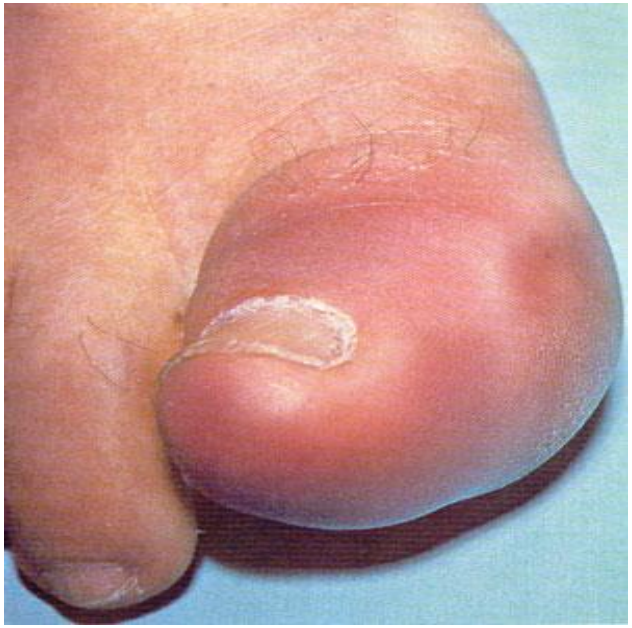
“Rhupus”

- <10% SLE pts may develop “Rhupus”
- 6-9% SLE pts are ACPA+ or CarP+
- 40% of RA pts are ANA+
  - Risk of Drug induced lupus from TNFi is 0.2-0.4%
- Rhupus arthritis follows RA pattern & may progress to inflammatory erosions, deformations and disability.
- Lack of consensus on the definition of Rhupus (dual seropositivity needed)
- Treatment: HCQ, MTX, TNF inhibitors, CNI, Belimumab

Comparison	Rhupus	Rheumatoid
Serologies	10-20% Lupus are RF+	40% of RA are ANA+
Lupus activity	Low	Nil
RA activity	Erosive, polyarthritis, Jaccouds	RA, nodules, Xtraarticular Dz
DMARDs used	HCQ, MTX, AZA, MMF?	MTX, HCQ, LEF, SSZ, AZA
Biologics to use	Belimumab, RTX, ABA ??*	>20 Biologics

Acute gout

- Treat early
- Continue established urate lowering treatment
- NSAID
- Colchicine
- Severe attacks
  - combination therapy



Chronic gout

- General health, diet and lifestyle measures
- Avoid
  - Offal/Organ meats
  - Soft and energy drinks
  - Alcohol overuse
- Limit
  - Purine rich meat and seafood
  - alcohol
- Encourage
  - Vegetables
  - Low fat dairy products

Arthritis Care & Research
Vol. 0, No. 0, June 2020, pp 1–17
DOI 10.1002/acr.24180

American College of Rheumatology
Empowering Rheumatology Professionals

ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

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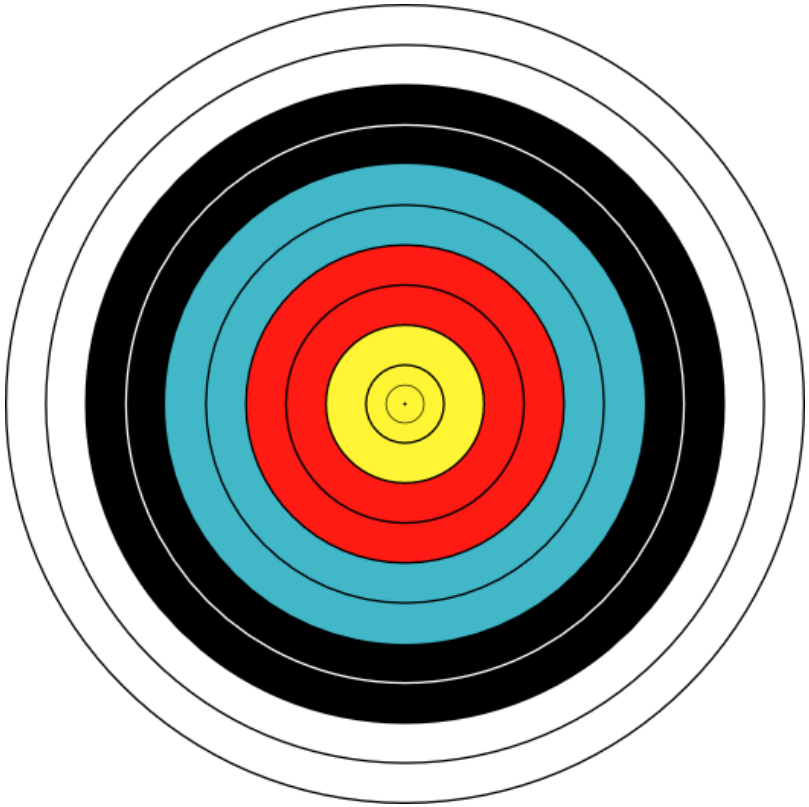
Objective. To provide guidance for the management of gout, including indications for and optimal use of urate-lowering therapy (ULT), treatment of gout flares, and lifestyle and other medication recommendations.

Methods. Fifty-seven population, intervention, comparator, and outcomes questions were developed, followed by a systematic literature review, including network meta-analyses with ratings of the available evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, and patient input. A group consensus process was used to compose the final recommendations and grade their strength as strong or conditional.

Results. Forty-two recommendations (including 16 strong recommendations) were generated. Strong recommendations included initiation of ULT for all patients with tophaceous gout, radiographic damage due to gout, or frequent gout flares; allopurinol as the preferred first-line ULT, including for those with moderate-to-severe chronic kidney disease (CKD; stage ≥3); using a low starting dose of allopurinol (≤100 mg/day, and lower in CKD) or febuxostat (≤40 mg/day); and a treat-to-target management strategy with ULT dose titration guided by serial serum urate (SU)

Treat to target- a potential for cure

- Uric acid level << 6.0
- Dissolves crystals
- No new crystals



Urate lowering therapy- 1st line

- Allopurinol
- Starting dose 100mg/day
- Up to 800mg/day
- Acute gout prophylaxsis

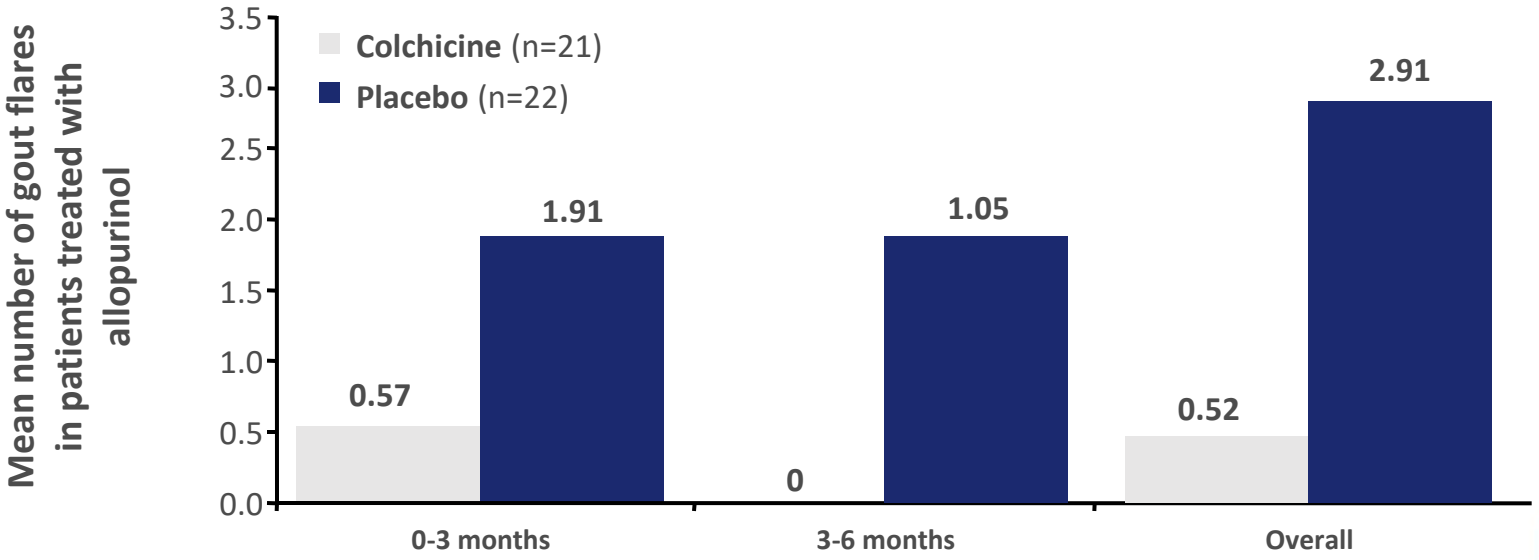
IL-1 inhibition

- Canakinumab
  - Monoclonal antibody blocks IL-1β signalling
  - 150 mg s/c v 40mg triamcinolone acetonide
  - 2 randomized trials 456 patients.
  - Canakinumab resulted in a significantly greater reduction in a mean 72-hour pain score using a 100 mm visual analog scale (decrease of 35.7 versus 25 mm).
  - Four patients receiving canakinumab, required hospitalization for treatment of infections (one abscess of the jaw, one abscess of the forearm, pneumonia, and gastroenteritis)

  - *Schlesinger N, Ann Rheum Dis.2012;71(11):1839.*

Reduction in flares when using colchicine for prophylaxis

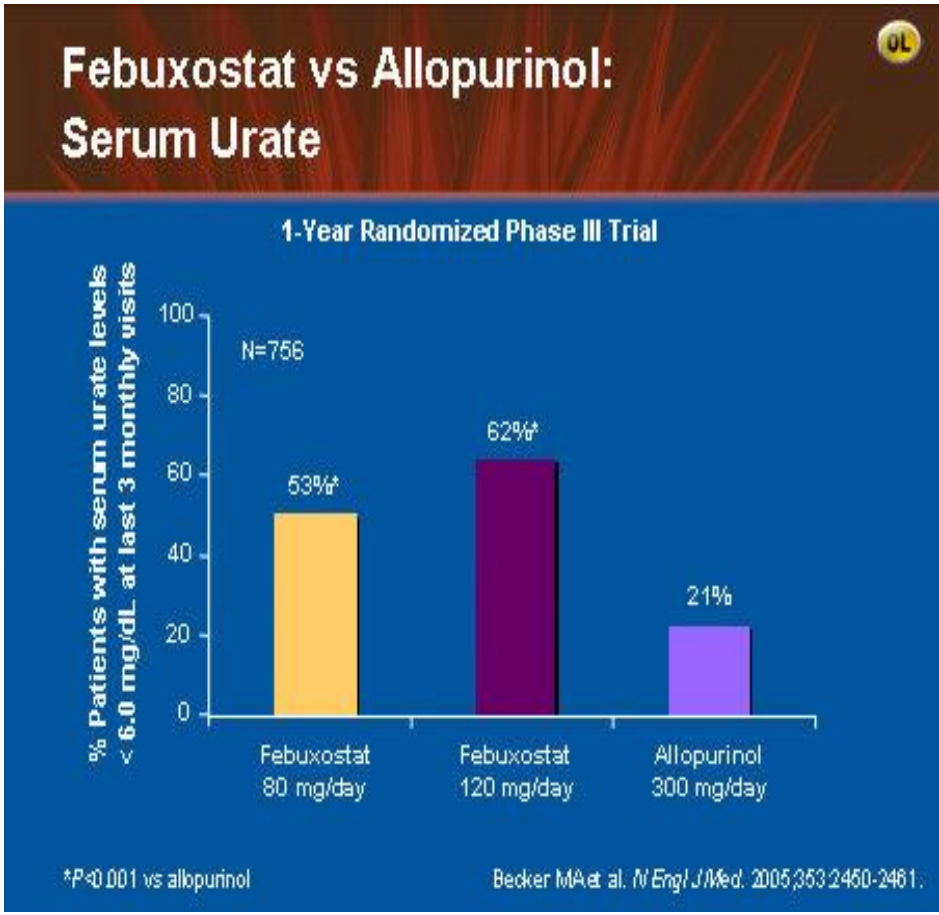
- **Colchicine prophylaxis during initiation of ULT for chronic hyperuricaemia with urate deposits:**
  - Reduces the frequency and severity of acute flares
  - Reduces the likelihood of recurrent flares
  - Evidence supports the use of low dose colchicine for up to 6 months following initiation of urate-lowering therapy



Borstad GC, *et al.* J Rheumatol 2004; **31**(12): 2429-32.

Febuxostat

- Oral 40mg, 80mg or 120 mg
- inhibits xanthine oxidase



Febuxostat

- NICE approved in patients
  - can't take allopurinol for medical reasons or
  - the side effects of allopurinol are so bad that the person either has to stop taking it or can't be given the most effective dose.
- Not recommended for people with IHD or CCF

Clinical Trial with Urate Lowering Therapy

- Clinical trials with febuxostat (vs placebo or allopurinol) showed a non-dose-related numerical (not statistical) increase in cardiac events (~1 per 1000 patient-years)
- US and European regulatory bodies required collection of post-approval safety data for febuxostat
  - CARES trial (US)
  - FAST trial (UK and Denmark)
- CARES trial:
  - Enrolled only those with significant history of CV disease
  - Results:
    - Significant increase in cardiac and all-cause mortality
    - No increase in the primary composite CV endpoint or its other specific components
  - BUT:
    - 57% participants discontinued trial early; 45% lost to follow-up
    - Post hoc ascertainment of "lost" patients showed more deaths in patients treated with allopurinol → statistical significance lost
    - Majority of events occurred after participants had STOPPED the drugs
    - Imbalance in ASA and NSAID use and effect

Clinical Trial with Urate Lowering Therapy

- CARES trial results led to a black box warning in the PI for febuxostat
  - In patients with gout and established CV disease, treatment with febuxostat results in a higher rate of CV death compared to allopurinol
- 2019 ACR gout guideline
  - Lists allopurinol as the first-line xanthine oxidase inhibitor
  - Suggests consideration to change from febuxostat to an alternative in patients with known or new CV disease

Pegloticase: Krystexis

Dosage Forms & Strengths

injectable solution

- 8mg/mL

Gout

Indicated for treatment of chronic gout in adults refractory to conventional treatment

8 mg IV infusion q2wk coadministered with methotrexate 15 mg PO qWeek

If coadministering with methotrexate, initiate weekly methotrexate and folic acid or folinic acid supplementation at least 4 weeks before to initiating, and throughout pegloticase treatment

Pegloticase alone may be used in patients for whom methotrexate is contraindicated or not clinically appropriate

Dosage Modifications

Renal impairment

- No dosage adjustment required

Pegloticase/Krystexis: Faculty Commentary and Analysis

- Real-world use of pegloticase has changed in ways other than immunosuppressive co-therapy that may influence the development of neutralizing antibodies.

- My own experience with pegloticase, without use of immunosuppressive co-therapy, has been far superior to the 50% success rate reported in the initial RCT.

- The low percentage of patients who maintained an appropriate target SUA after completing or discontinuing early pegloticase likely reflects the challenges in treating patients with severe gout and who have only a few therapeutic options.

RheumNow

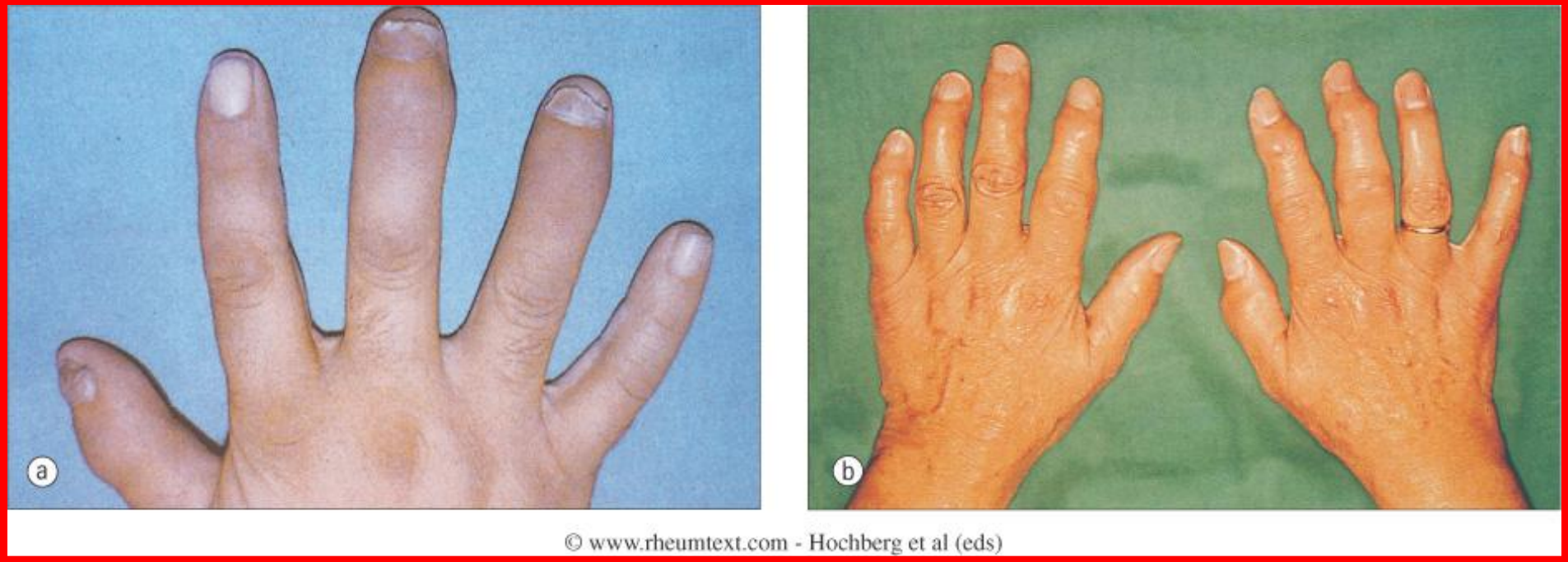
http://rheumnow.com/homepage

UpToDate®

https://www.uptodate.com/login

Bonus Slides

Clinical Pearl:
Arthritis of the DIP joint



Psoriatic Arthritis (inflammatory)

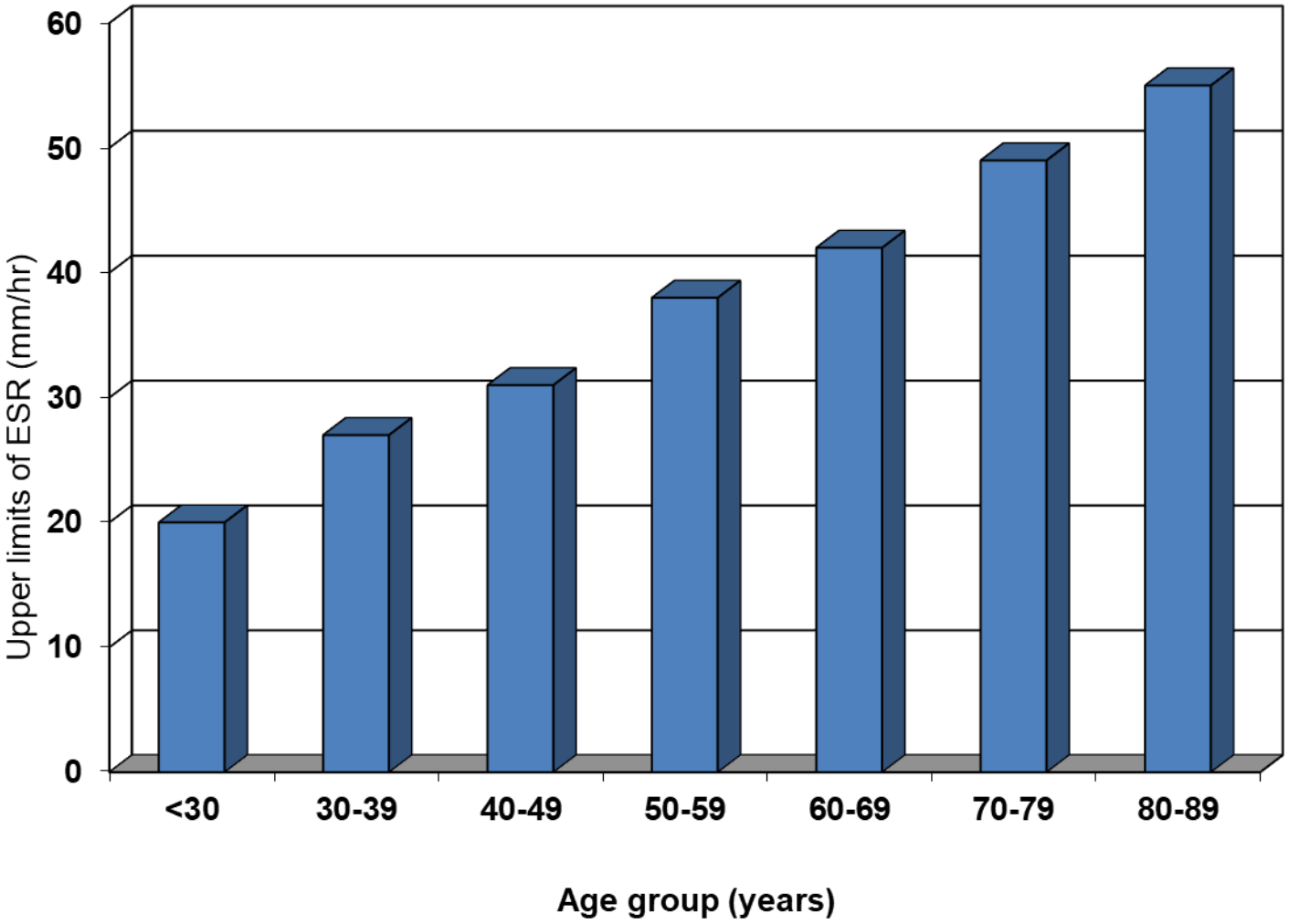
OA (non-inflammatory)

Utility of Common Rheumatic Tests

Test	Sensitivity	Specificity	in Dx-ing
RF	70%	85	RA
ACPA(CCP)	65%	98%	RA
ANA	98%	57%	SLE
dsDNA	57%	97%	SLE
Smith	30%	97%	SLE
Uric Acid	63%	96%	Gout
HLA-B27	80-95%	94%	AS/SpA
ESR/CRP	50-60%	<40%	RA

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/rheumatology/laboratory-evaluation-rheumatic-diseases/

ESR & Age



ESR Calculation
Men=Age/2
Women= Age+10/2

High In:
Age
CKD
Anemia
Pregnancy
Liver Dz
Cancer
Infection
Drug induced

Miller A, et al. Br Med J (Clin Res Ed). 1983;286:266
http://www.rheumaknowledgy.com/acute-phase-reactants/

Arthritis Myths

1. Snap, crackle, pop/popping (crepitus) = arthritis
2. Cracking your knuckles causes arthritis
3. Arthritis is hereditary
4. Diet will cause or cure arthritis
5. Gout is from over-production of uric acid
6. Arthritis can only be diagnosed by a blood test
7. Prednisone is a safe option
8. Arthritis drugs are contraindicated in pregnancy

Does Cracking Your Knuckles Cause Arthritis?

- Multiple studies have indicated that ***there is no evidence to suggest cracking knuckles causes or worsens arthritis***. However, chronic knuckle cracking may lead to reduced grip strength, and there have been occasional reports of tendon injuries and dislocations.4

- Although patients who crack their knuckles are not at greater risk for osteoarthritis, it's important that they pay attention to pain in their joints. If knuckle cracking proves painful, there could be an abnormality in the structure of the joint.

New Study Suggests Cannabis May Be Effective For Rheumatoid Arthritis, And Why It May Not Matter

- "Joints for Joints – cannabinoids in the treatment of rheumatoid arthritis," cautiously concludes that "cannabinoids could be a suitable treatment for RA."

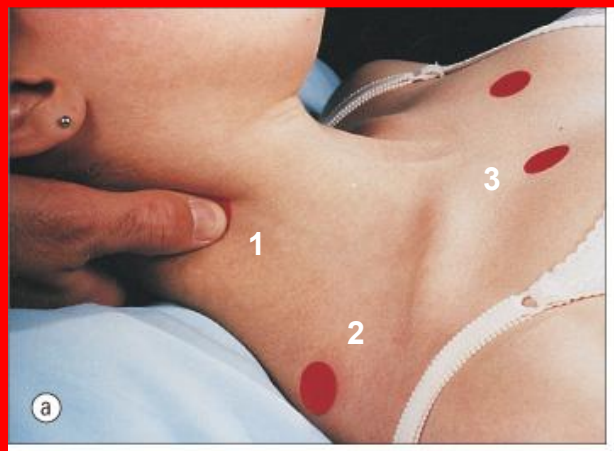
- We don't quite understand all the details of how it works, but we do know that cannabis is a powerful anti-inflammatory agent, and that it operates in a different way than other anti-inflammatory drugs such as ibuprofen, steroids, or even the biological options available for treating RA and other autoimmune diseases.

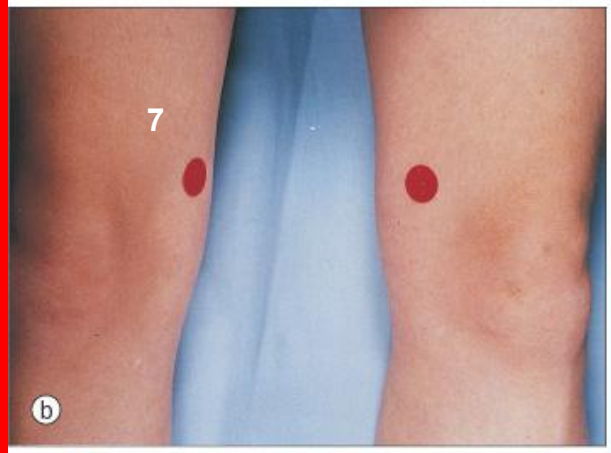
Fibromyalgia-Background

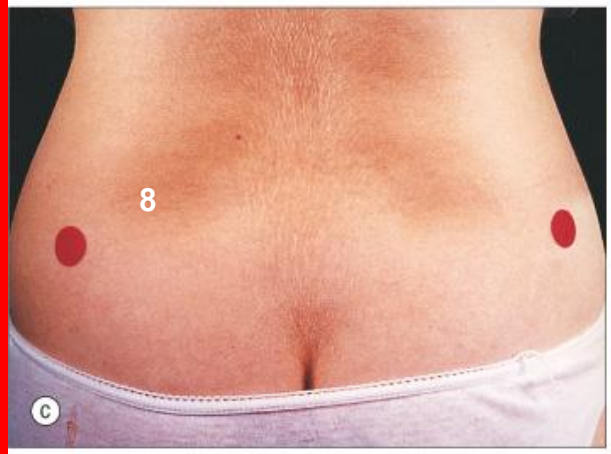
- Chronic musculoskeletal pain syndrome of unknown etiology
- Characterized by diffuse pain, tender points, fatigue, and sleep disturbances
- Prevalence is 2-5% with a female to male predominance of 8:1
- Mean age is 30-60

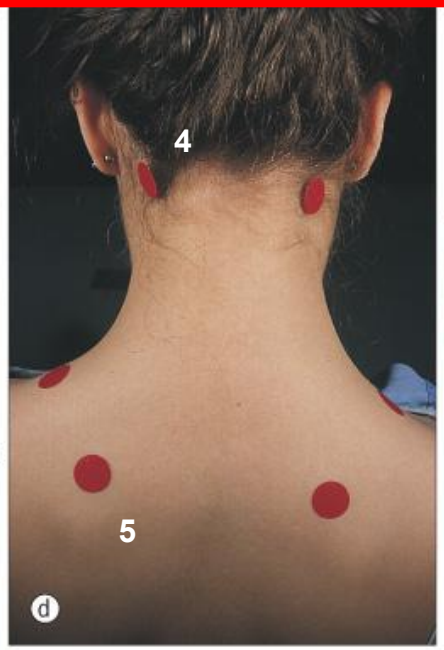
Fibromyalgia-Diagnosis

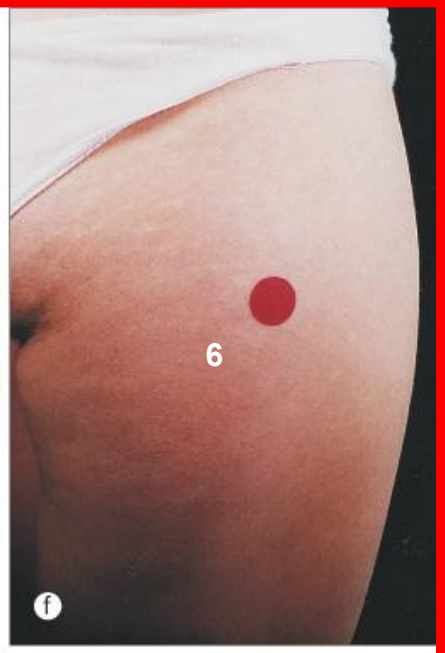
TABLE 62.1 DIAGNOSTIC FEATURES OF FIBROMYALGIA
Cardinal features*
Chronic, widespread pain Tender points on examination
Characteristic features
Fatigue Sleep disturbances Stiffness Paresthesias Headaches Irritable bowel syndrome Raynaud's-like symptoms Depression Anxiety
*For classification criteria, patients must have pain for at least 3 months involving the upper and lower body, right and left sides, as well as axial skeleton, and pain in at least 11 of 18 tender points on digital examination.

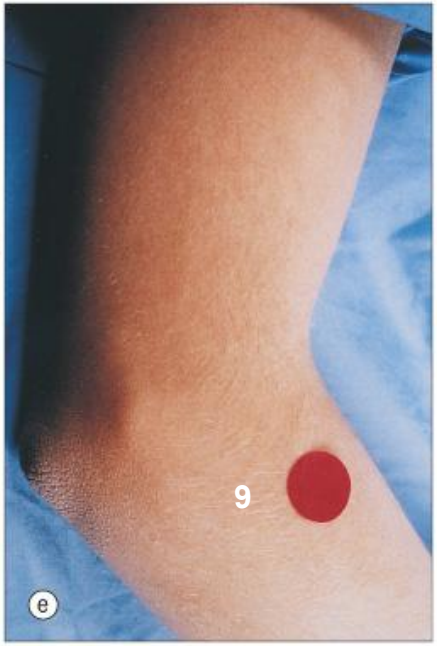












TENDER POINTS IN FIBROMYALGIA

Pain on digital palpation must be present in at least 11 of the following 18 tender point sites:

Occiput: bilateral, at the suboccipital muscle insertions (d)

Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7 (a)

Trapezius: bilateral, at the midpoint of the upper border (d)

Supraspinatus: bilateral, at origins, above the scapula spine near the medial border (d)

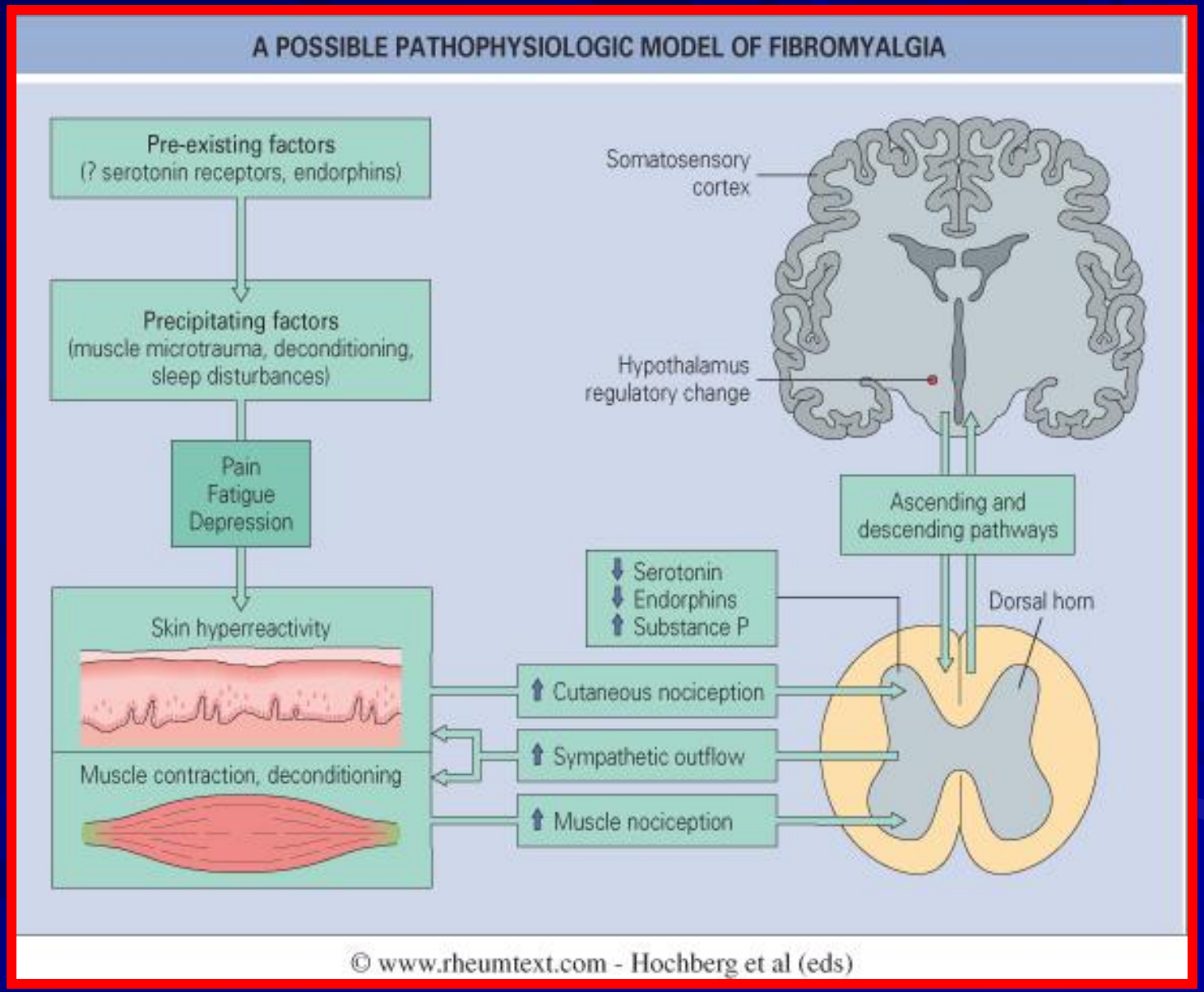
Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces (a)

Lateral epicondyle: bilateral, 2cm distal to the epicondyles (e)

Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle (c)

Greater trochanter: bilateral, posterior to the trochanteric prominence (f)

Knee: bilateral, at the medial fat pad proximal to the joint line (b)


A POSSIBLE PATHOPHYSIOLOGIC MODEL OF FIBROMYALGIA
Pre-existing factors
(? serotonin receptors, endorphins)
Precipitating factors
(muscle microtrauma, deconditioning, sleep disturbances)
Pain
Fatigue
Depression
Skin hyperreactivity
Muscle contraction, deconditioning
Somatosensory cortex
Hypothalamus regulatory change
Ascending and descending pathways
Serotonin
Endorphins
Substance P
Dorsal horn
Cutaneous nociception
Sympathetic outflow
Muscle nociception
© www.rheumtext.com - Hochberg et al (eds)

Fibromyalgia-Treatment

TABLE 62.7 STEPWISE APPROACH TO FIBROMYALGIA TREATMENT

First-line treatment

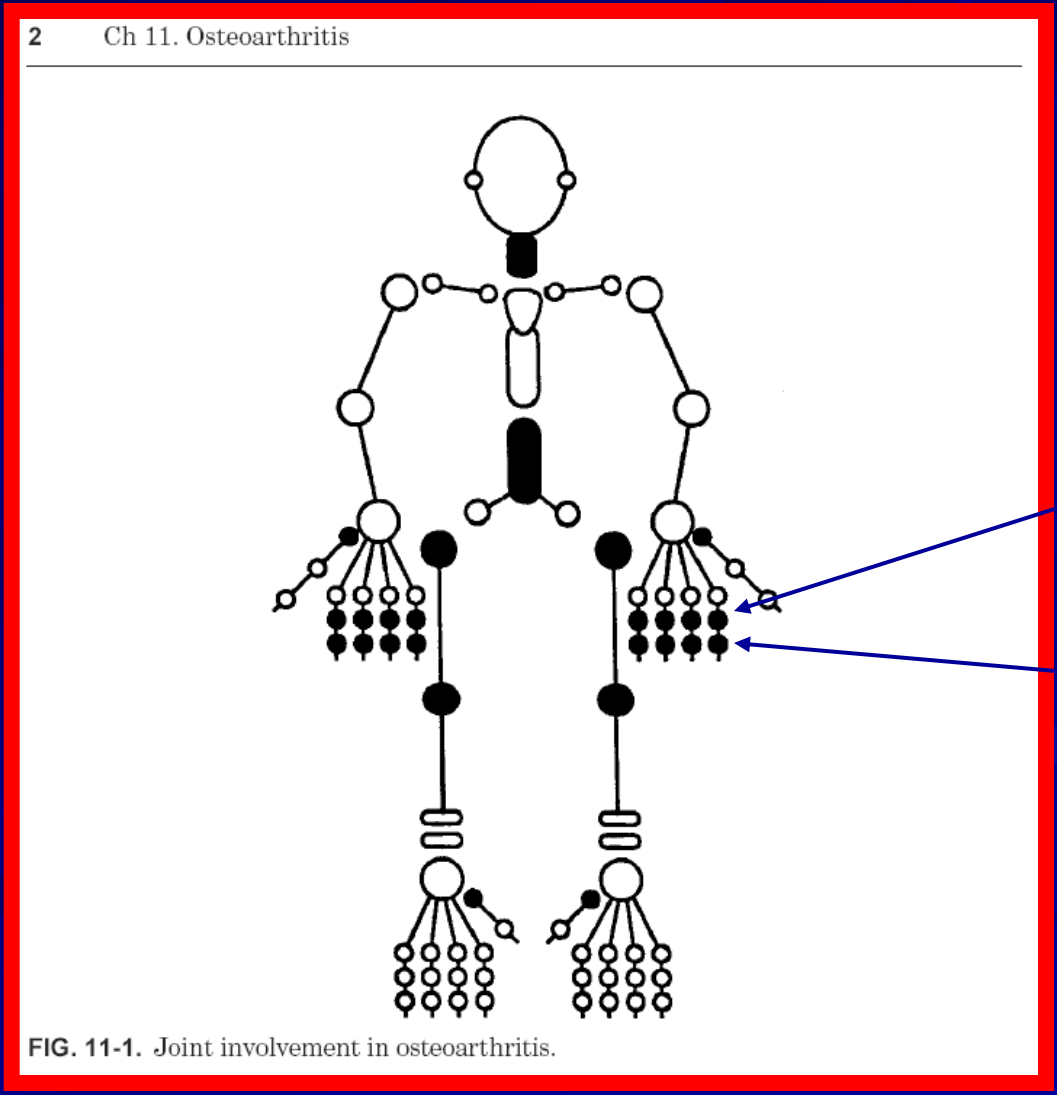
Medications: simple analgesics, NSAIDs, low-dose tricyclic antidepressants* or serotonin receptor inhibitors **Neuroblockage agents, Cymbalta**
Education*
Exercise*: low impact, such as walking, water exercises
If mood disturbances, treat with appropriate medications

Second-line treatment

Medications: tramadol*, combinations of antidepressants* or other analgesics
Cognitive behavioral program*, stress management therapy*
Structured exercise program*
Physical medicine and rehabilitation program
Trigger point injections, acupuncture
Pain management program

* Evidence of efficacy in controlled clinical trials.
NSAIDs, non-steroidal anti-inflammatory drugs.

Osteoarthritis-Distribution



Latinis, K., Dao, K, Shepherd, R, Gutierrez, E, Velazquez, C. *The Washington Manual Rheumatology Subspecialty Consult.*, LWW, 2003.

Osteoarthritis-Diagnosis

- Clinical
- Supported by X-rays
- Non-inflammatory lab data, if any

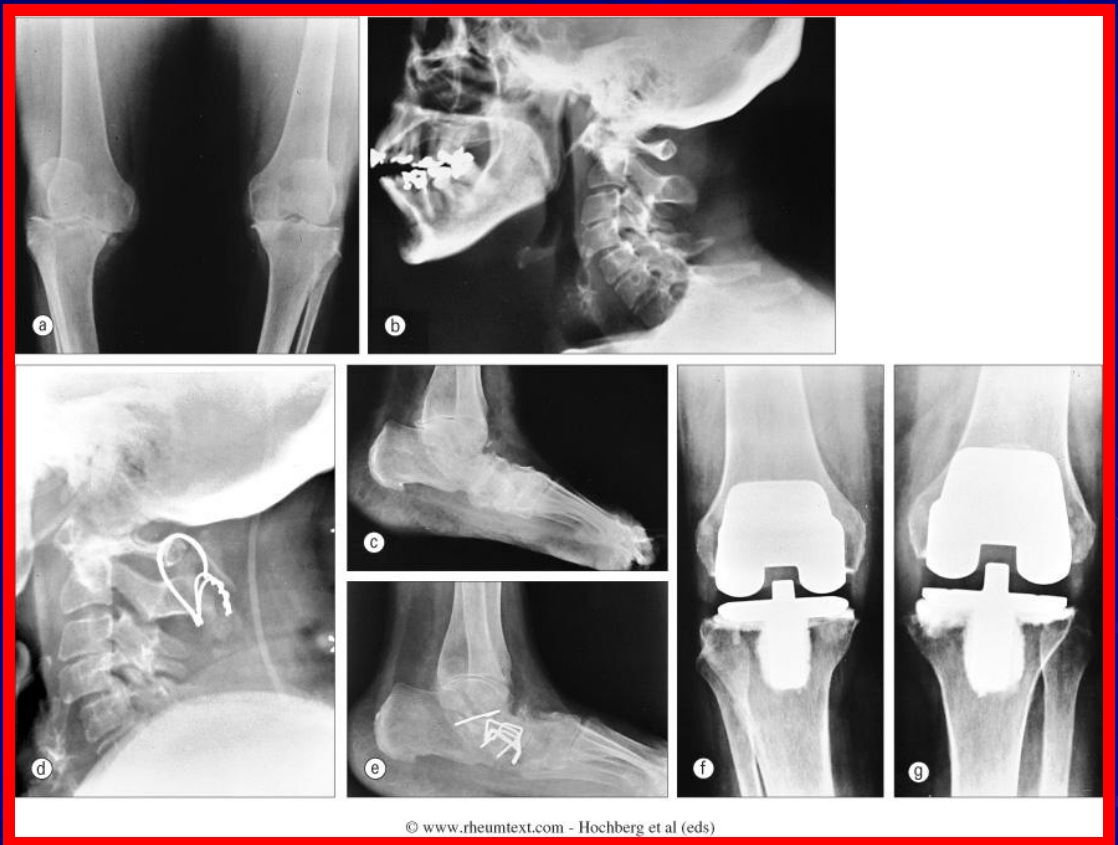
Osteoarthritis-Treatment

- Pain relief
  -Analgesics and NSAIDs/Cox-2 Inhibitors
- -Glucosamine Sulfate
  -Complementary,
- -Topicals
- - Viscosupplementation: Knees
- Non-pharmacologic approaches
  -Reduce stress/load on joint
  -Strengthen surrounding muscles-PT/OT
  -Weight reduction
  -Patient education
- Limit disability and improve quality of life
- Arthroplasty

Osteoarthritis-Treatment

- Joint Replacement Surgery
  -Primarily of knee and hip, shoulders,& emerging ankles and elbows

- Indications:
- 1. Failure of conservative measures, meds, PT/OT
- 2. Rest pain
- 3. Sleep disruption
- 4. Instability/Fall risk



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