RHEUMATOLOGIC DISORDERS ASSESSING THE MORTALITY RISK

Bruce Margolis, DO, MBA, FACOI, FCCP, DBIM
bruce.margolis@mutualofomaha.com

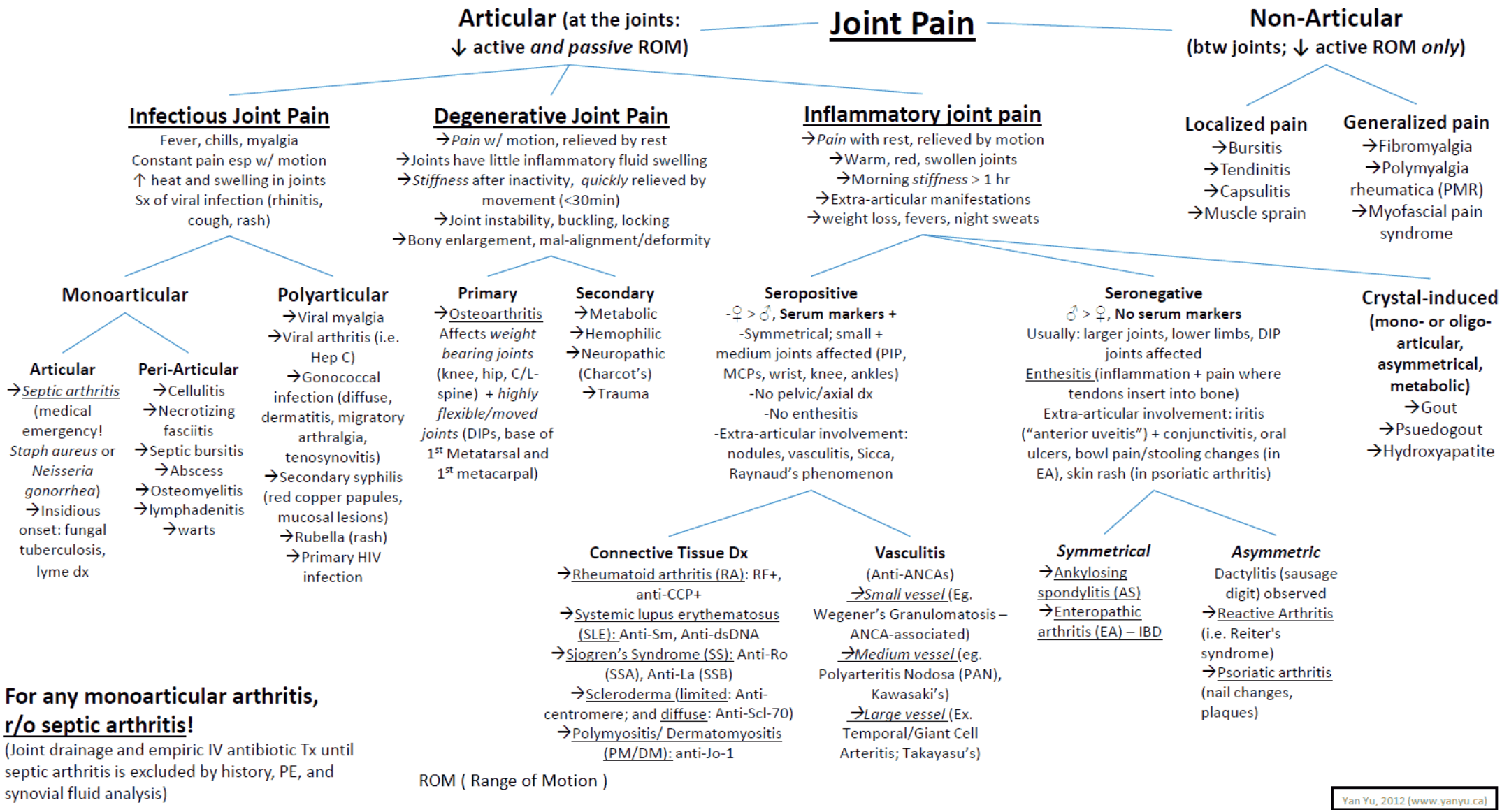
Classification of Rheumatologic Disorders

- Inflammatory Arthritis
  - Rheumatoid arthritis (RA)
  - Seronegative spondyloarthropathies
    - Ankylosing spondylitis
    - Psoriatic arthritis
    - Reactive arthritis
    - Enteropathic arthritis
- Connective Tissue Disorders (CTD)
  - Systemic lupus erythematosus (SLE)
  - Sjogren's syndrome
  - Systemic sclerosis (scleroderma)
  - Mixed connective tissue disease (MCTD)
  - Dermatomyositis/Polymyositis
- Vasculitides
  - Large-vessel: Giant cell arteritis, Takayasu arteritis
  - Medium-vessel: Polyarteritis nodosa, Kawasaki disease
  - Small-vessel: ANCA-associated vasculitis, IgA vasculitis
- Crystal arthropathies
  - Gout
  - Calcium pyrophosphate deposition disease (CRRD, pseudogout)
- Degenerative & Mechanical Disorders
  - Osteoarthritis
  - Soft tissue syndromes (bursitis, tendinopathies)
  - Fibromyalgia
- Pediatric Rheumatologic Disorders
  - Juvenile idiopathic arthritis (JIA)
  - Kawasaki disease
  - Pediatric lupus

Prevalence of Rheumatologic Disorders

- Osteoarthritis – 10-15% of adults (more common after age 60)
- Rheumatoid arthritis – 0.5-1% of adults
- Psoriatic arthritis – 0.1-0.3% of population
- Ankylosing spondylitis – 0.1-0.2% of population
- Gout – 3-5% of adults (higher in men, older adults)
- Systemic lupus erythematosus – 0.05-0.1% (40-100/100,000)
- Sjogren's syndrome – 0.1-0.6% of population
- Systemic sclerosis – 0.02-0.05%
- Juvenile idiopathic arthritis – 1/1,000 children

Evaluation of Patient with Joint Pain



For any monoarticular arthritis, r/o septic arthritis!
(Joint drainage and empiric IV antibiotic Tx until septic arthritis is excluded by history, PE, and synovial fluid analysis)

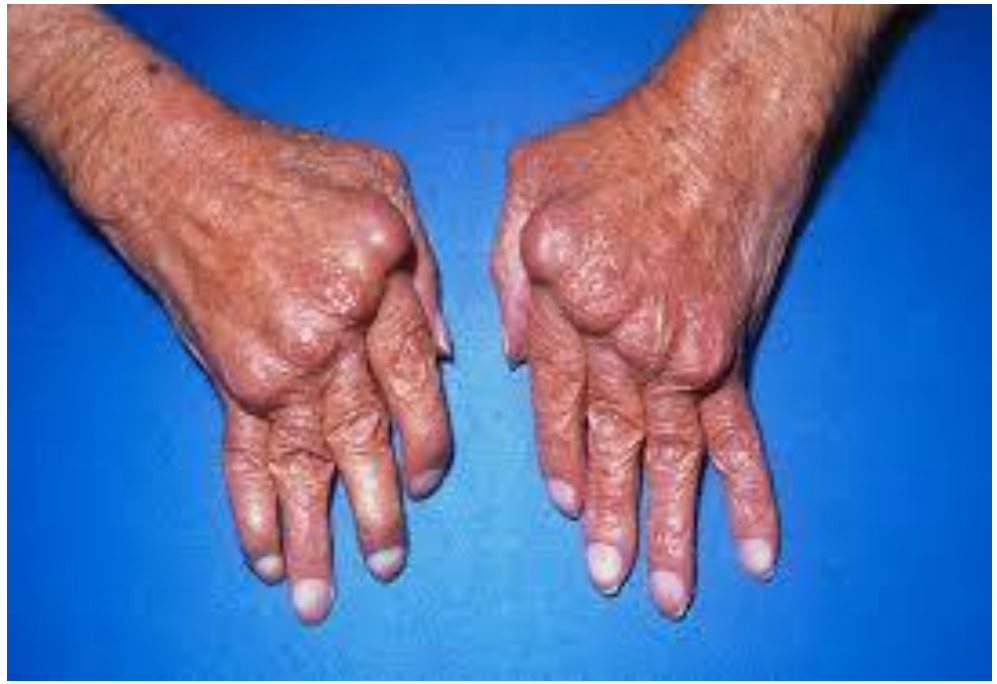
ROM (Range of Motion)

Case #1

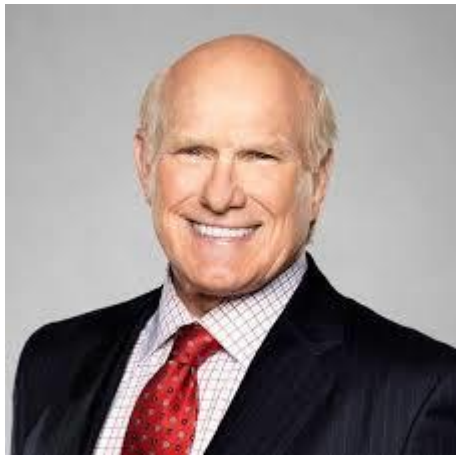
- 61 yo M NS trial for $20M UL
- Carries diagnosis of seronegative rheumatoid arthritis for at least 6 years
- Build, BP, basic chemistries, CBC in APS wnl
- Old rheumatology letter notes failed methotrexate, hydroxychloroquine, sulfasalazine. On Enbrel X 3 years.
- ANA history
  - 5/21 – screen (+)
  - 4/22 – ANA (+) 1:80 – nucleolar pattern
  - 11/22 – ANA (+) 1:160 – homogeneous pattern
- RF and CCP repeatedly (-)
- Anti-dsDNA, Scl, SS-A, SS-B all (-)
- Sed rate, CRP (-) (on meds)
- X-rays feet and ankles w/o erosions
- Providers notes handwritten
  - No deformities or limitations noted
  - 5/22 – 90% reduction tender and swollen joint counts
- Questions:
  - Is the diagnosis correct?
  - What is the severity of the disease?
  - What is the mortality risk?

Rheumatoid Arthritis (RA) - Defined

- Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune inflammatory disorder that primarily targets synovial joints, leading to symmetric, progressive, and potentially erosive arthritis. Key features:
  - Persistent synovitis and joint inflammation
  - Autoantibody production: Rheumatoid Factor (RF), Anti-CCP antibodies
  - Elevated acute phase reactants: ESR, CRP
  - Systemic manifestations: fatigue, low-grade fever, weight loss, extra-articular involvement (lungs, eyes, skin, heart)
  - Pathogenesis: genetic predisposition (HLA-DRB1), environmental triggers (e.g., smoking)
  - Potential for joint destruction, deformity, and disability if untreated



Rheumatoid Arthritis – Famous People With RA

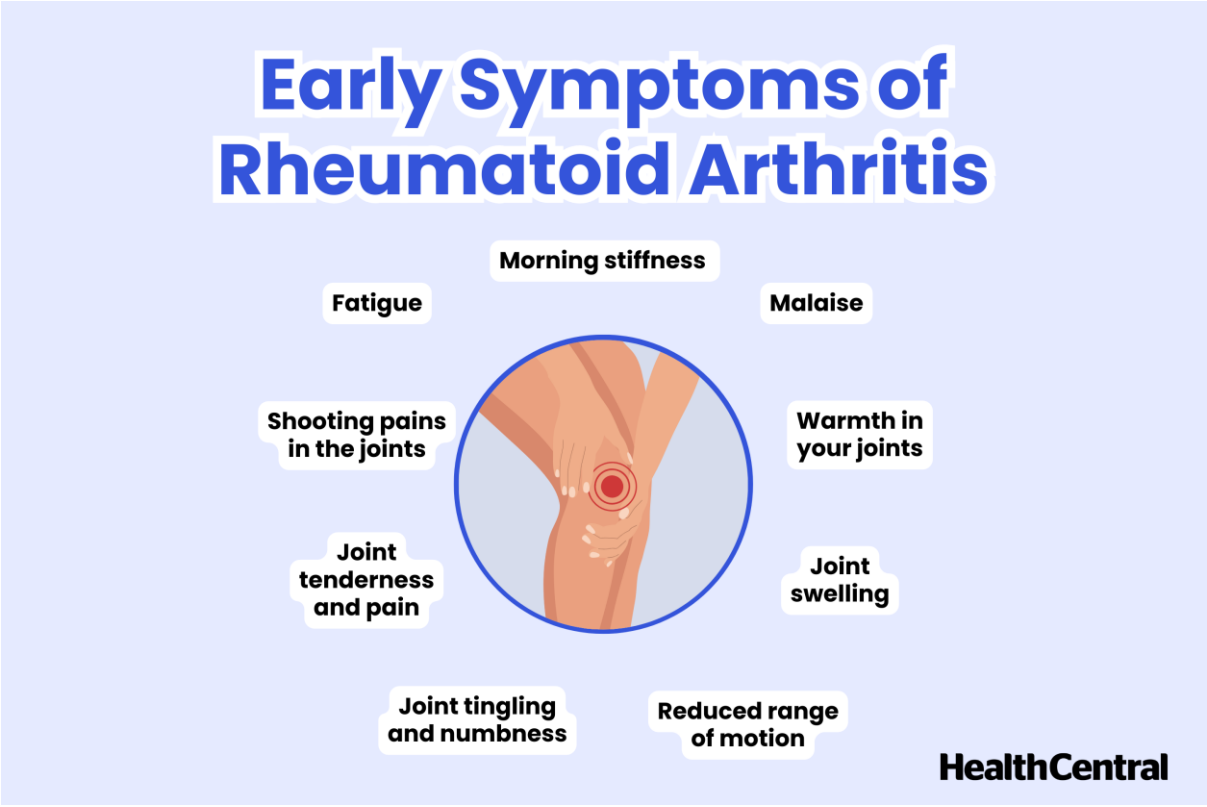


Rheumatoid Arthritis - Epidemiology

- Global prevalence and incidence
  - Prevalence: 0.5-1%
  - Incidence: 20-50 cases/100,000/year
  - Higher in industrialized nations
  - Varies by ethnicity – lower in some Asian and African groups
- Age and sex distribution
  - Can occur any age; most common ages 30-60 years
  - Female:Male ratio 2-3:1
- Geographic and ethnic variations
  - Higher rates: Northern Europe and North America
- Risk factors
  - Genetics: 50-60% of risk (HLA-DRB1 alleles) – “shared epitope” on chromosome 6
  - Smoking
  - Hormonal: postpartum, menopause
  - ?role of gut microbiome
- Mortality and Morbidity
  - 2-3 X higher risk of premature death (cardiovascular disease, infections)
  - Mortality declining with modern therapy
  - Reduced quality of life and major cause of disability

Rheumatoid Arthritis - Presentation

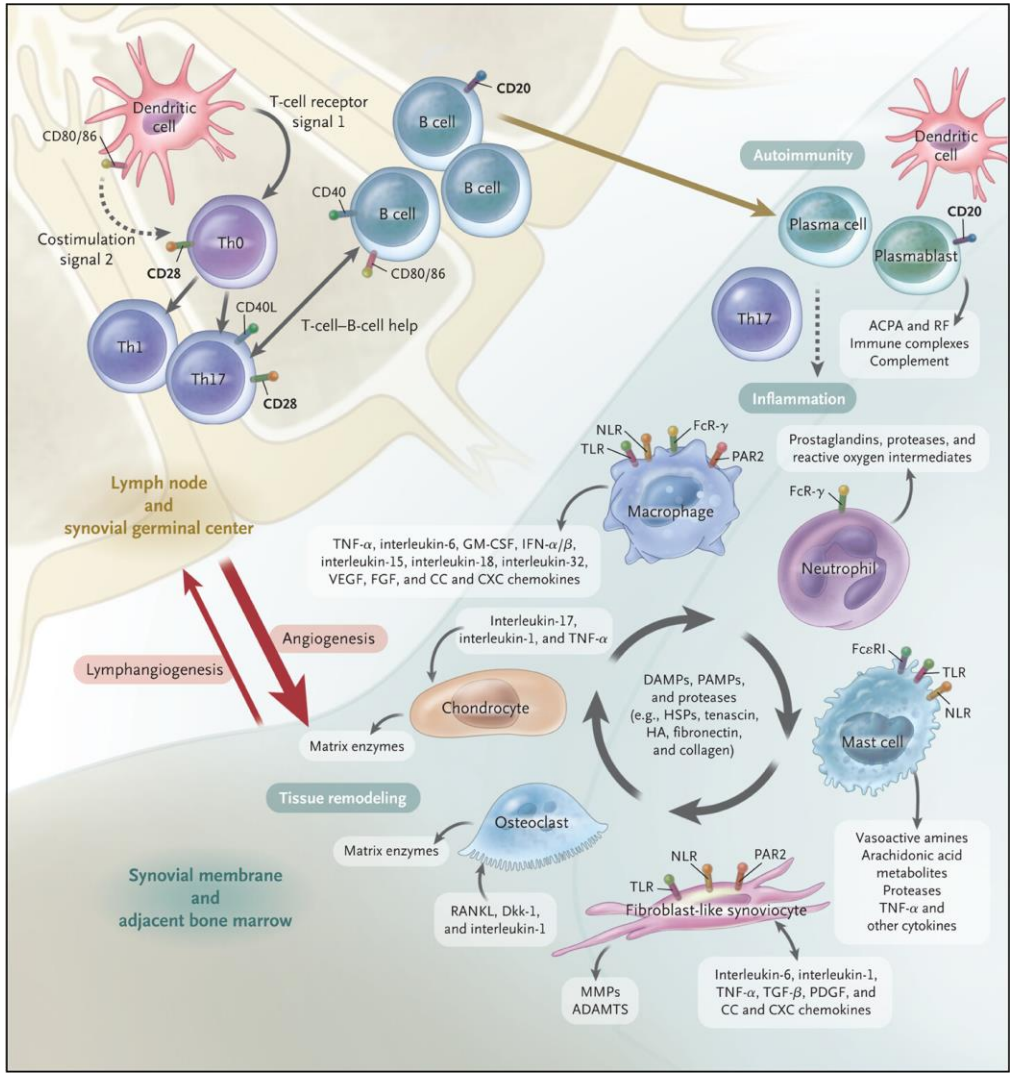
- Constitutional symptoms- weight loss, fatigue, myalgias, low grade fever
- Morning stiffness – lasting >1 hr suggests inflammatory joint disease
- Joint manifestations – joint pain and swelling of small joints hands and feet, particularly MCP, MTP and PIP joints
- Lab testing:
  - Elevated ESR and/or CRP
  - Abnormal rheumatoid factor (RF) - not specific for RA. Overall Sn/Sp: 69%/85%. Depends on pre-test probability.
  - Anti-cyclic citrullinated peptide (CCP) antibodies
  - Genetic testing – HLA-DRB1
- X-rays: periarticular osteopenia, joint space narrowing, bone erosions
- Ultrasound: to assess synovitis
- MRI: to assess synovitis
- Extraarticular abnormalities: e.g., rheumatoid nodule, scleritis, interstitial lung disease



Inflammatory Arthritis – Differential Diagnosis

Condition	Key Characteristics
Rheumatoid Arthritis (RA)	Symmetric polyarthritis; small joints; morning stiffness >1 hr; positive RF/anti-CCP
Psoriatic Arthritis (PsA)	Asymmetric oligoarthritis; dactylitis; nail pitting; skin psoriasis
Ankylosing Spondylitis (AS)	Axial involvement; sacroiliitis; young men; HLA-B27 positive
Reactive Arthritis	Post-infectious; asymmetric lower limb arthritis; enthesitis; conjunctivitis
Gout	Monoarthritis (often 1st MTP); urate crystals; tophi
CPPD (Pseudogout)	Knees, wrists; chondrocalcinosis; calcium pyrophosphate crystals
Systemic Lupus Erythematosus (SLE)	Non-erosive arthritis; systemic features; ANA, dsDNA positive
Sarcoidosis-associated Arthritis	Löfgren syndrome; erythema nodosum; bilateral hilar lymphadenopathy
Viral Arthritis	Acute, self-limiting; symmetric; parvovirus, hepatitis, HIV
Septic Arthritis	Acute monoarthritis; fever; high WBC; positive joint fluid culture

Rheumatoid Arthritis – Pathogenesis



McInnes IB, Schett G. *NEJM* 2011:365:2205

Rheumatoid Arthritis – Diagnostic Criteria

2020 ACR-EULAR Classification- Rheumatoid Arthritis

Joint Involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints, +/- large joints	3
>10 joints (at least 1 small joint)	5
Serology (need at least 1)	
Negative RF, negative anti CCP Ab	0
Low positive RF *or* low positive anti CCP Ab	2
High positive RF *or* high positive anti CCP Ab	3
Acute Phase reactants (need at least 1)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

For patients with at least 1 joint with definite clinical synovitis, not better explained by another disease

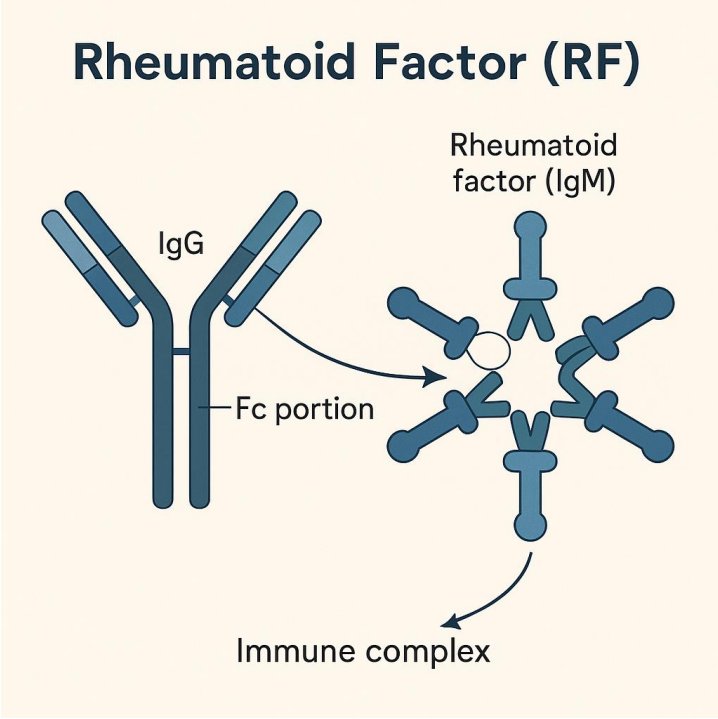
Rule out:
- Psoriatic arthritis
- Viral polyarthritis
- Gout
- CPPD
- SLE

≥ 6/10 definite RA

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

Rheumatoid Arthritis – Serology

- Discovered 1940 – one of oldest known autoantibodies
- IgM directed against Fc portion IgG
- Present 70-80% those with RA
- Not specific for RA
- High titers tend to correlate with more aggressive disease and extra-articular manifestations



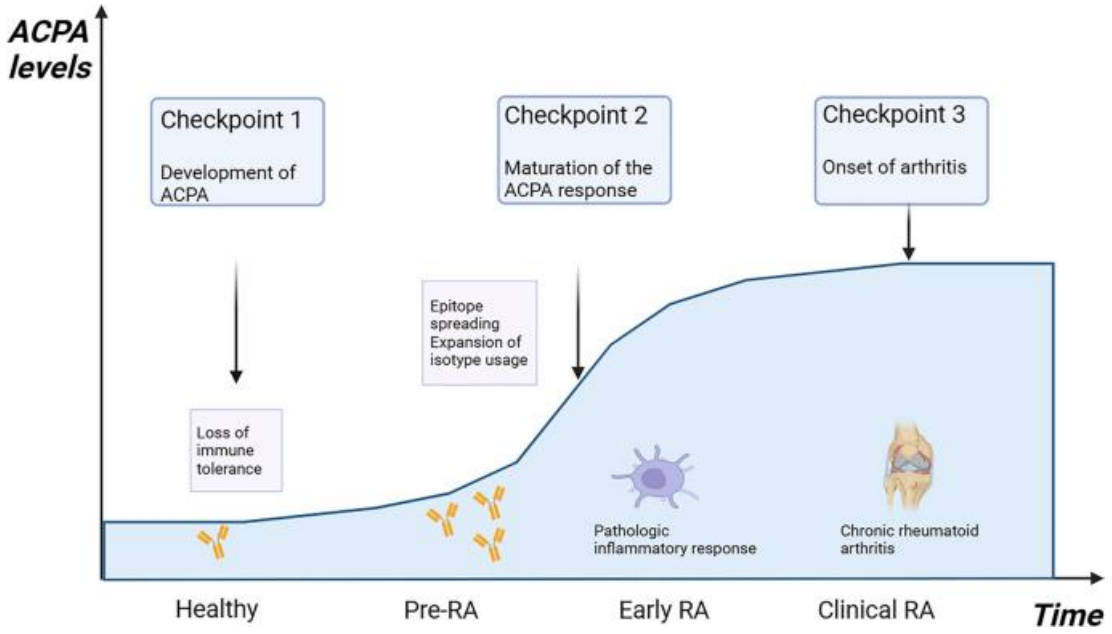
The major nonrheumatic diseases associated with rheumatoid factor (RF)-positivity

Condition	Frequency of RF, percent
Aging (>age 60)	5 to 25
Infection	
Bacterial endocarditis*	25 to 50
Hepatitis B or hepatitis C*	20 to 75
Tuberculosis	8
Syphilis*	Up to 13
Parasitic diseases	20 to 90
Leprosy*	5 to 58
Other viral infection*	15 to 65
Pulmonary disease	
Sarcoidosis*	3 to 33
Interstitial pulmonary fibrosis	10 to 50
Silicosis	30 to 50
Asbestosis	30
Miscellaneous diseases	
Primary biliary cholangitis*	45 to 70
Malignancy*	5 to 25
After multiple immunizations	10 to 15

* Refers to disorders that may cause symptoms suggestive of rheumatoid arthritis. The best-documented examples of viral infection (in addition to hepatitis B and C) are rubella, mumps, influenza, and HIV. Chagas' disease, Leishmaniasis, onchocerciasis, and schistosomiasis are major parasitic diseases. B cell neoplasms are the most common malignancies.

Rheumatoid Arthritis – Citrullinated Proteins

- Citrullination – post-translational modification converting arginine to citrulline
- Occurs in inflammatory environments (e.g., synovitis)
- Key enzymes – Activation of peptidylarginine deiminases (PADs)
- Anti-citrullinated protein antibodies (ACPAs) are highly specific for RA
- Overall Sn/Sp 67%/96% respectively
- ACPA positive individuals with early RA are at increased risk of progressive joint damage
- ACPAs present years before clinical onset, associated with severe disease course



Hang M, et al. *Clin and Exp Med* 2024;24:153

Rheumatoid Arthritis – X-Ray

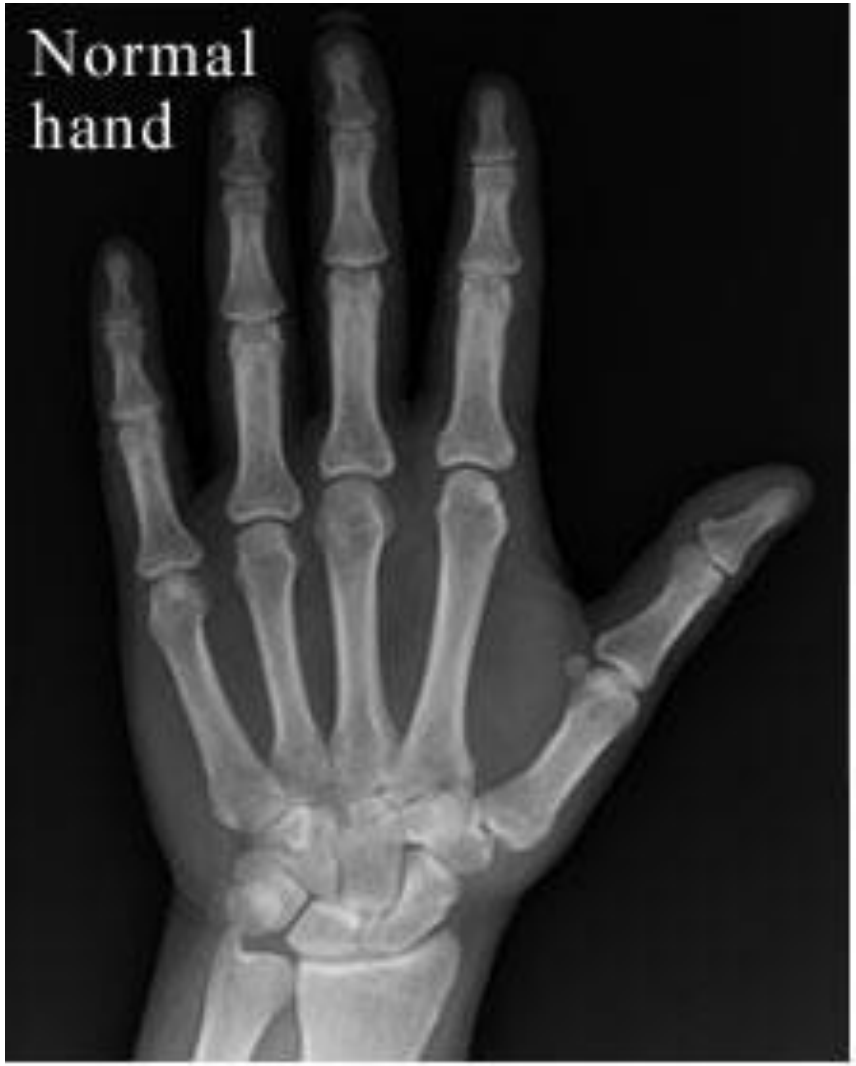


Figure 1

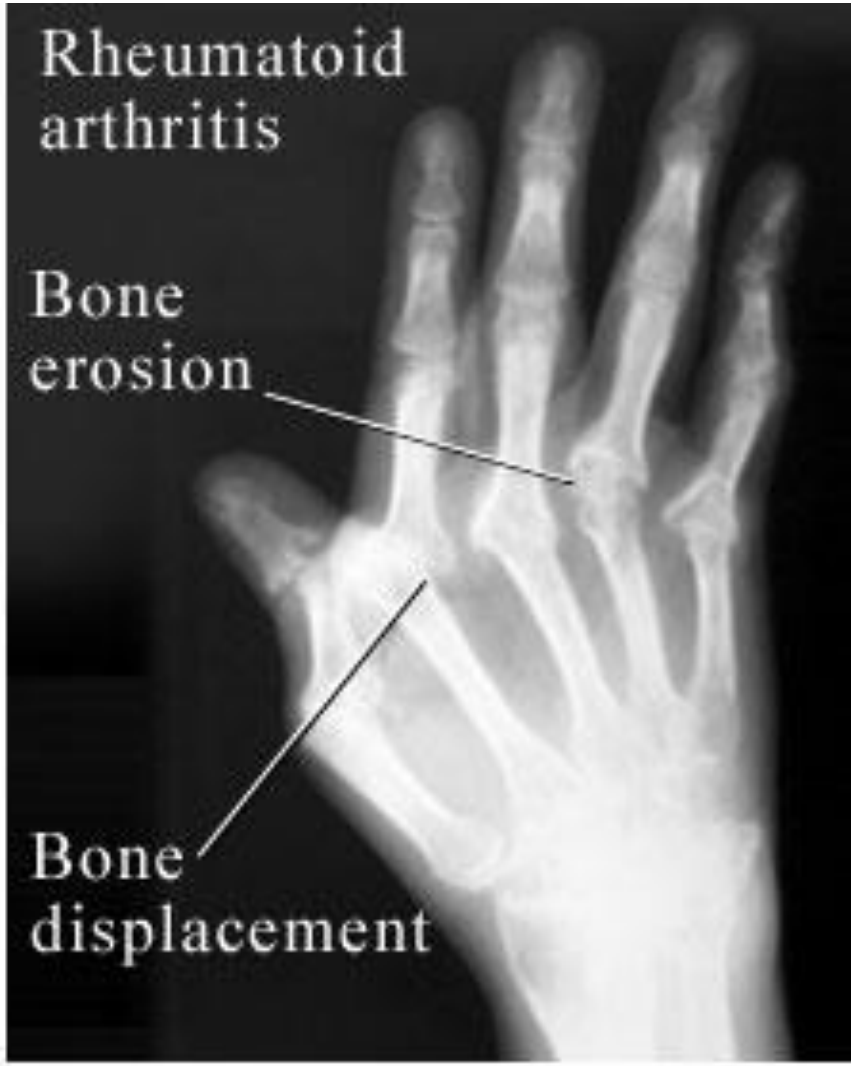


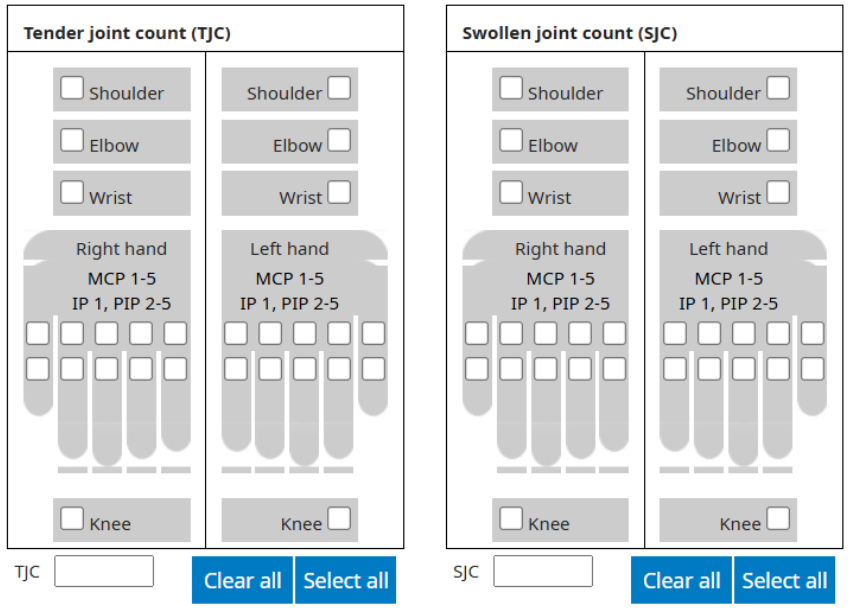
Figure 2

Rheumatoid Arthritis – Assessment of Disease Activity

RA Clinical Disease Activity Index (CDAI)

PGA [ ] [#]

EGA [ ] [#]



CDAI [ ] [score]

Decimal precision [1]

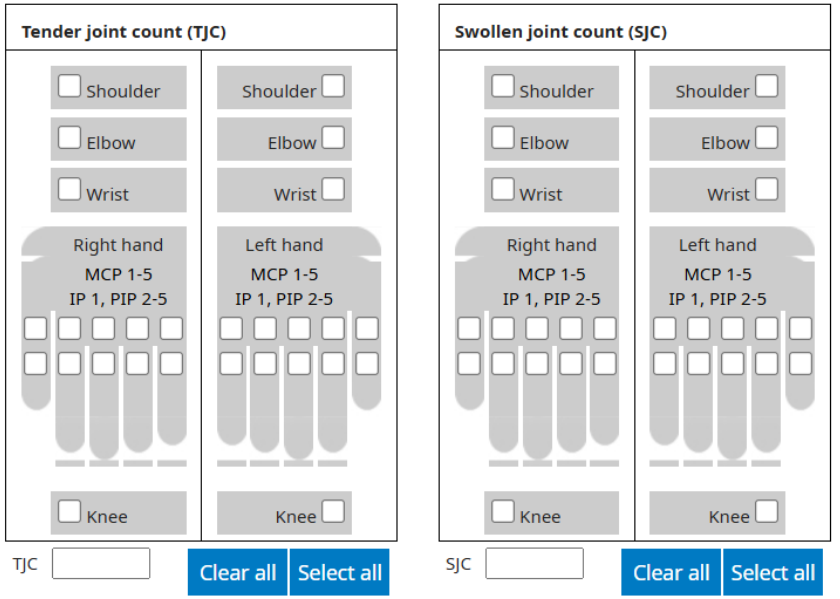
CDAI ≤2.8:	Remission
CDAI >2.8 and ≤10:	Low disease activity
CDAI >10 and ≤22:	Moderate disease activity
CDAI >22:	High disease activity

RA Simplified Disease Activity Index (SDAI)

CRP [ ] [mg/dL]

PGA [ ] [#]

EGA [ ] [#]

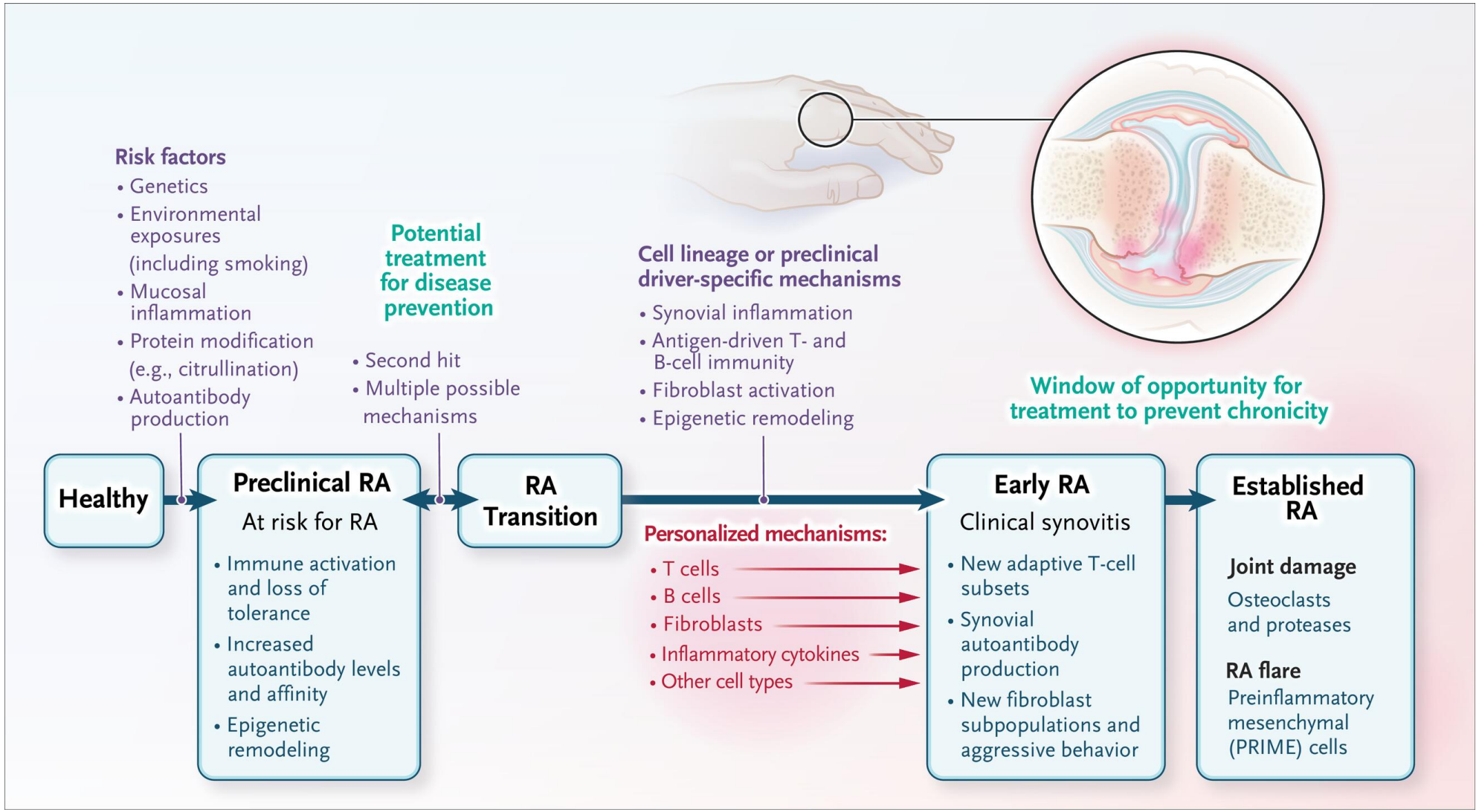


SDAI [ ] [score]

Decimal precision [1]

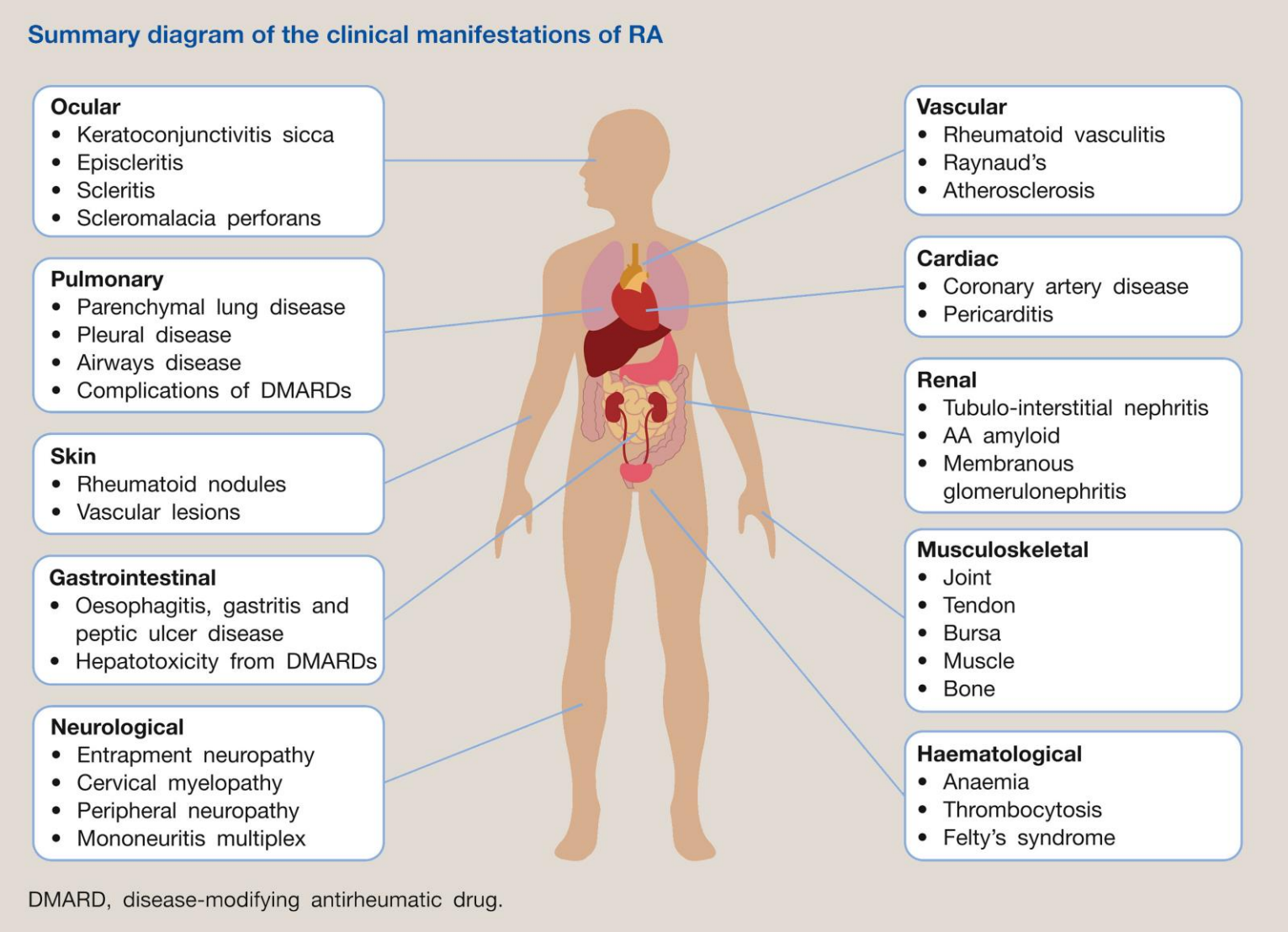
SDAI ≤3.3:	Remission
SDAI >3.3 and ≤11:	Low disease activity
SDAI >11 and ≤26:	Moderate disease activity
SDAI >26:	High disease activity

Rheumatoid Arthritis – Course of Disease



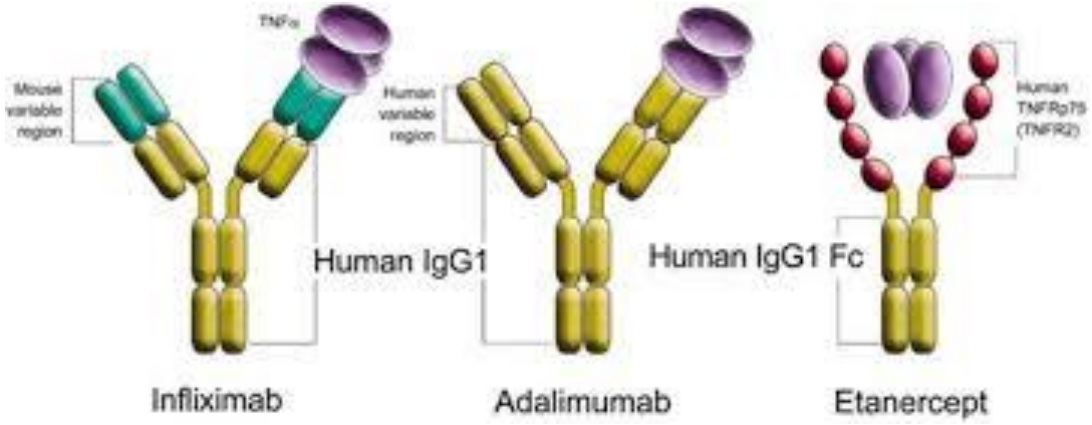
Gravallese EM, Firestein GS. *NEJM* 2003;388:529

Rheumatoid Arthritis – Complications

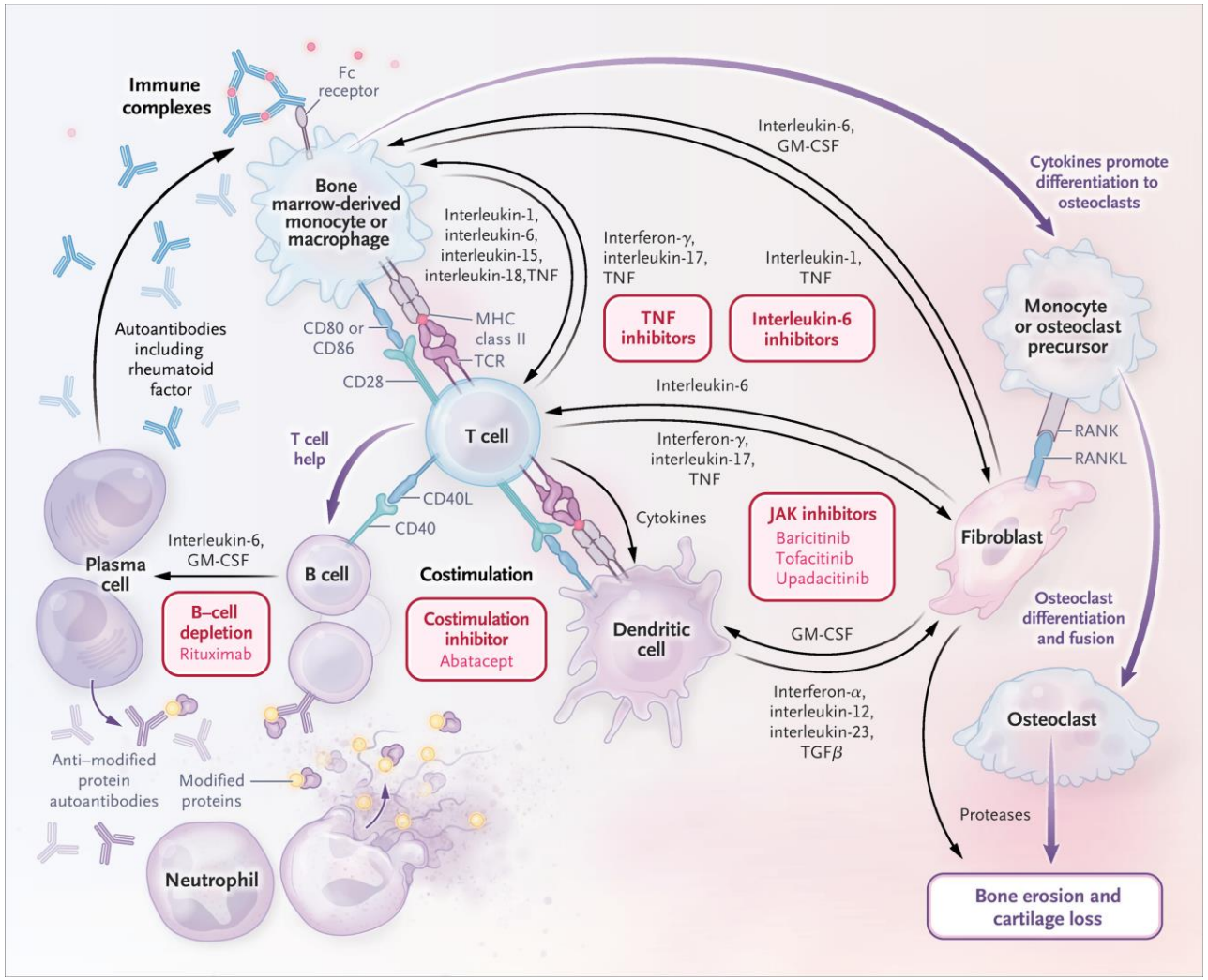


Rheumatoid Arthritis – Treatment

- Nonbiologic Disease-modifying antirheumatic drugs (DMARDs)
  - Methotrexate
  - Hydroxychloroquine
  - Sulfasalazine
  - Leflunomide
- Biologic DMARDs
  - TNF inhibitors – etanercept, infliximab, adalimumab, golimumab, certolizumab pegol
  - Interleukin 6 (IL-6) receptor antagonists – tocilizumab, sarilumab
  - T-cell costimulation blocker (CTLA4-Ig) - abatacept
  - Anti-CD20 B-cell depleting monoclonal antibody - rituximab
- Targeted synthetic DMARDs
  - Janus kinase (JAK) inhibitors – tofacitinib, baricitinib, upadacitinib

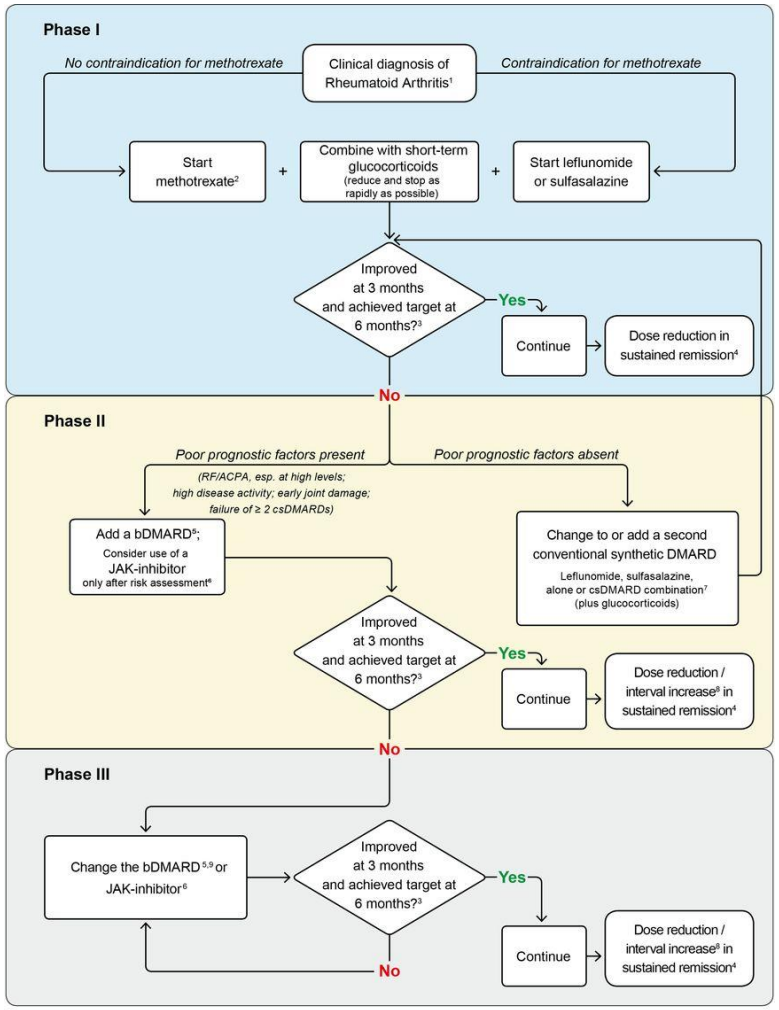


Rheumatoid Arthritis – Treatment



Gravallese EM, Firestein GS. *NEJM* 2003;388:529

Rheumatoid Arthritis – Treatment



1. 2010 ACR-EULAR classification criteria can support early diagnosis.
2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.
3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.
4. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.
5. Consider contraindications and risks. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication IL6-inhibitors and tsDMARDs have some advantages.
6. The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC), risk factors for thromboembolic events (history of MI or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile)
7. The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.
8. Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD, but before all this glucocorticoids must have been discontinued.
9. From a different or the same class.

Smolen JS, et al. *Ann Rheum Dis* 2023;82:3

Rheumatoid Arthritis – Mortality

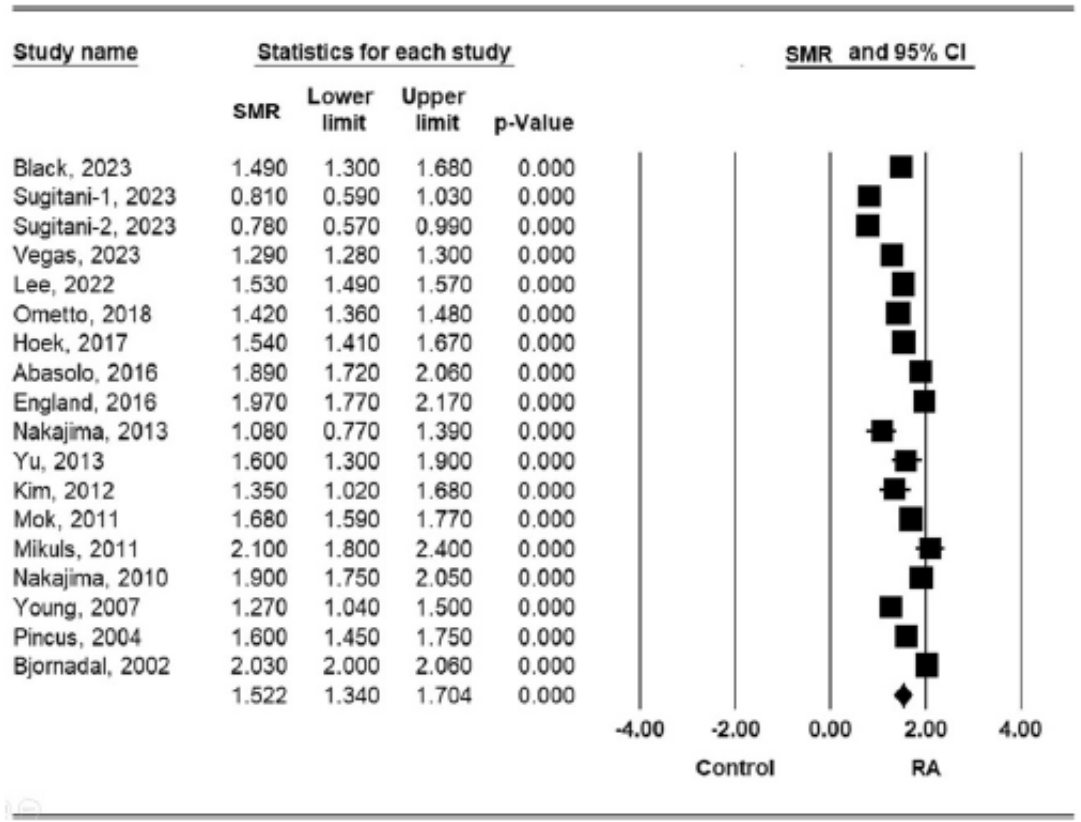


Fig. 2 ▲ Meta-analysis results illustrating the standardized mortality ratio (*SMR*) for all-cause mortality in individuals with rheumatoid arthritis (*RA*). *CI* confidence interval

Lee YH, Song GG. *Z Rheumatol* 2024:83(S); S314

- Meta analysis
- 560 papers/17 selected
- 486,098 patients with RA
- 63,988 observed deaths
- Overall, 1.5X increase in all-cause mortality in those with RA

Table 2 Meta-analysis of all-cause and cause-specific standardized mortality ratio in rheumatoid arthritis

Mortality	Population	No. of studies	Test of association			Test of heterogeneity			Publication bias *p*-value
			SMR	95% CI	*p*-value	Model	*p*-value	I^2	
All-cause	Overall	18	1.522	1.340–1.704	<0.001	R	<0.001	99.3	0.198
	Caucasian	6	1.575	1.207–1.943	<0.001	R	<0.001	99.7	0.395
	Asian	8	1.355	1.140–1.569	<0.001	R	<0.001	94.7	0.348
	American	3	1.873	0.561–2.184	<0.001	R	0.001	85.0	0.293
	Oceanian	1	1.490	1.300–1.680	<0.001	NA	NA	NA	NA
	Male	7	1.602	1.462–1.742	<0.001	R	0.003	70.0	0.603
	Female	6	1.644	1.467–1.820	<0.001	R	<0.001	87.2	0.380
Cause-specific	CVD	10	1.399	0.972–1.706	<0.001	R	<0.001	99.9	0.915
	Respiratory	10	2.459	1.936–2.982	<0.001	R	<0.001	97.9	0.448
	Infection	10	2.459	1.936–2.982	<0.001	R	<0.001	97.9	0.448
	Malignancy	9	0.984	0.873–1.096	<0.001	R	<0.001	88.7	0.797
	CVA	6	1.156	0.890–1.422	<0.001	R	<0.001	83.8	0.023

SMR standardized mortality ratio, *CI* confidence interval, *CVD* cardiovascular disease, *CVA* cerebrovascular attack, *R* random effects model, *NA* not available

Case #1

- 61 yo M NS trial for $20M UL
- Carries diagnosis of seronegative rheumatoid arthritis for at least 6 years
- Build, BP, basic chemistries, CBC in APS wnl
- Old rheumatology letter notes failed methotrexate, hydroxychloroquine, sulfasalazine. On Enbrel X 3 years.
- ANA history
  - 5/21 – screen (+)
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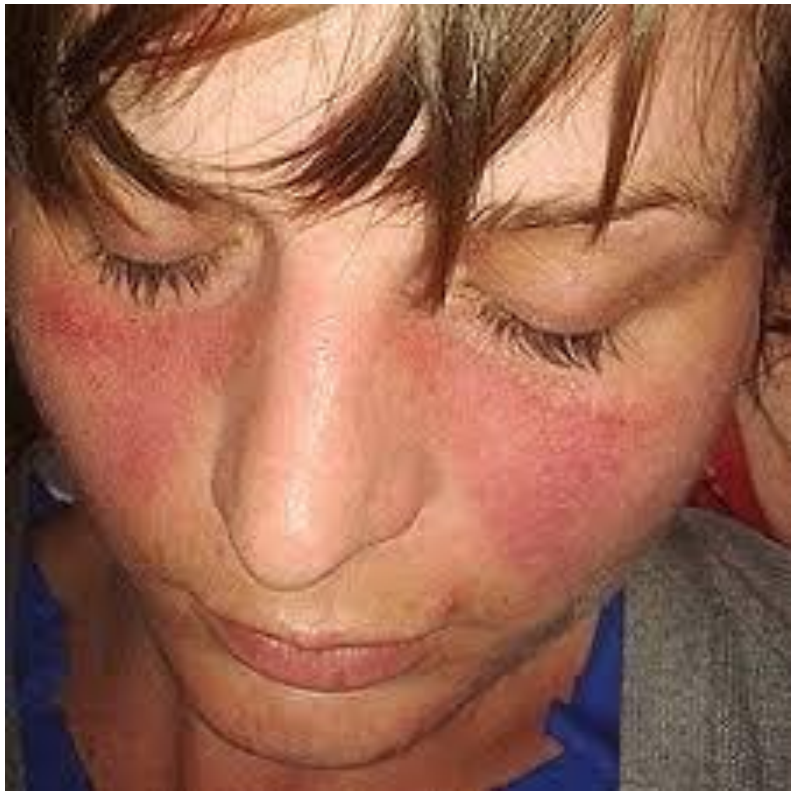
- Sed rate, CRP (-) (on meds)
- X-rays feet and ankles w/o erosions
- Providers notes handwritten
  - No deformities or limitations noted
  - 5/22 – 90% reduction tender and swollen joint counts
- Questions:
  - Is the diagnosis correct?
  - What is the severity of the disease?
  - What is the mortality risk?

Case #2

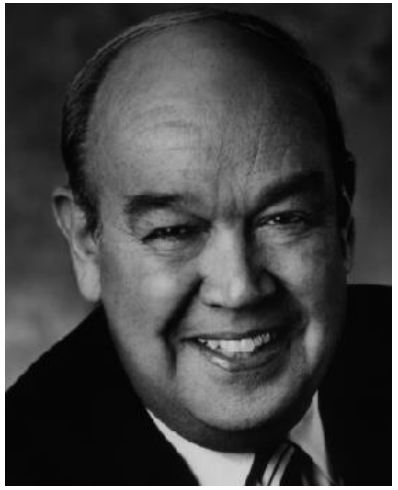
- 41 yo F NS for $500K UL
- Part 2 notes no PCP but sees rheumatologist for lupus diagnosed 6 years prior to application. Taking hydroxychloroquine.
- MIB – multiple application queries; connective tissue disorder, kidney disorder, albuminuria
- APS – 2017 developed joint pain/stiffness, hand swelling, ankle swelling. Serum Cr 3.1 with ANA 1:5120. Renal biopsy done which showed membranous lupus nephritis (LN) Class V with immunoglobulin and complement deposits. Treated with prednisone, mycophenolate (MMF), and cyclophosphamide. Weaned off steroids one year later with normalization of Cr. By 2020 was weaned off MMF; maintained on hydroxychloroquine. Occasional joint stiffness and hand joint swelling.
- At 12/2023 visit, PI clinically stable with benign exam. CBC wnl, serum Cr 0.97; ESR 15 mm/hr; CRP 2.4 mg/dl; dsDNA wnl; C3/C4 wnl; p/c 77 mg/g.
- Historic serologies – RF; CCP, RNP, Smith, Ro/LA antibodies all negative. Antiphospholipid panel negative.
- Questions:
  - What is the overall prognosis?
  - How does the prognosis of membranous LN compare to other forms of LN?
  - What is the mortality risk?
  - How does the history of lupus nephritis impact the mortality risk?

Systemic Lupus Erythematosus (SLE) - Defined

- Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disorder characterized by the production of autoantibodies leading to widespread inflammation and potential damage to virtually any organ system. The disease is highly variable in presentation and clinical course. Key features:
  - Fatigue, joint pain, photosensitivity, malar rash
  - Positive antinuclear (ANA), anti-double- stranded DNA (ant-dsDNA), anti-Smith (anti-Sm) antibodies
  - Low complement levels – C3, C4 during active disease
  - Elevated acute phase reactants: ESR, CRP
  - Relapsing-remitting course with variable clinical presentation
  - Pathogenesis involves a complex interplay of genetic predisposition, environmental triggers, and immune system deregulation
  - Can affect joints, heart, kidney, CNS



Systemic Lupus Erythematosus – Famous People With SLE

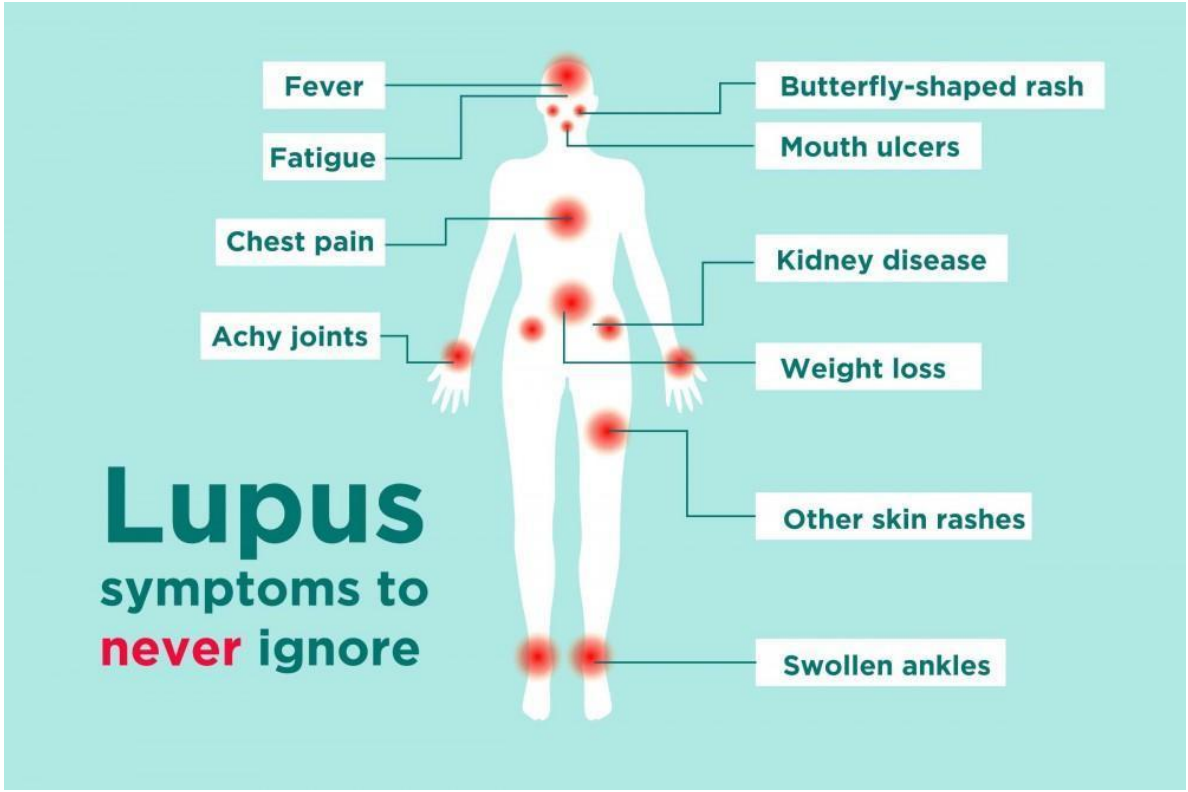


Systemic Lupus Erythematosus (SLE) - Epidemiology

- Approximately 204,000 in the US have SLE
- Incidence is ~5.1 cases/100,000 person-years; higher in African American, Hispanic, Asian and Native American populations
- Incidence higher in China – 14.1 cases/100,000 person-years
- Female:Male ratio 9:1
- African American women 2-3 times more likely to develop SLE than white women
- SLE most often diagnosed between ages 15 and 44
- Overall mortality rates have decline
- African Americans with SLE have higher death rates than White individuals

Systemic Lupus Erythematosus (SLE) - Presentation

- Constitutional symptoms – fatigue (80+%), fever (50%), malaise, anorexia, weight loss
- Musculoskeletal symptoms – arthritis (up to 90%) with morning stiffness; myalgias
- Skin/Hair – malar rash, red/scaly patches on sun-exposed areas, photosensitivity, mouth ulcers, hair loss
- Other – chest pain, pericarditis, endocarditis (Libman-Sacks), pleuritis, signs of nephritis (swelling, HTN, foamy/dark urine), vasculitis, Raynaud's, cephalgia, confusion, seizures, anemia
- Lab Testing: ANA, anti-Smith (Sm) (30%), anti-double stranded DNA (dsDNA) (70%), anti-Ro/SSA, and anti-La/SSB (more common Sjogren's), anti-U1 ribonucleoprotein (RNP) (more common MCTD), anti-ribosomal P (high Sp/low Sn), antiphospholipid antibody



Systemic Lupus Erythematosus (SLE) – Differential Diagnosis

- Rheumatoid arthritis
- Rhupus (features SLE and RA)
- Mixed connective tissue disorder (MCTD) – overlap features SLE, systemic sclerosis, polymyositis. High titers anti-RNP
- Undifferentiated connective tissue disorder (UCTD) – evidence of a systemic autoimmune disorder, but not satisfy classification criteria
- Systemic sclerosis
- Sjogren's disease
- Vasculitis
- Behcet syndrome
- Dermatomyositis/polymyositis
- Fibromyalgia
- Multiple sclerosis – optic neuritis

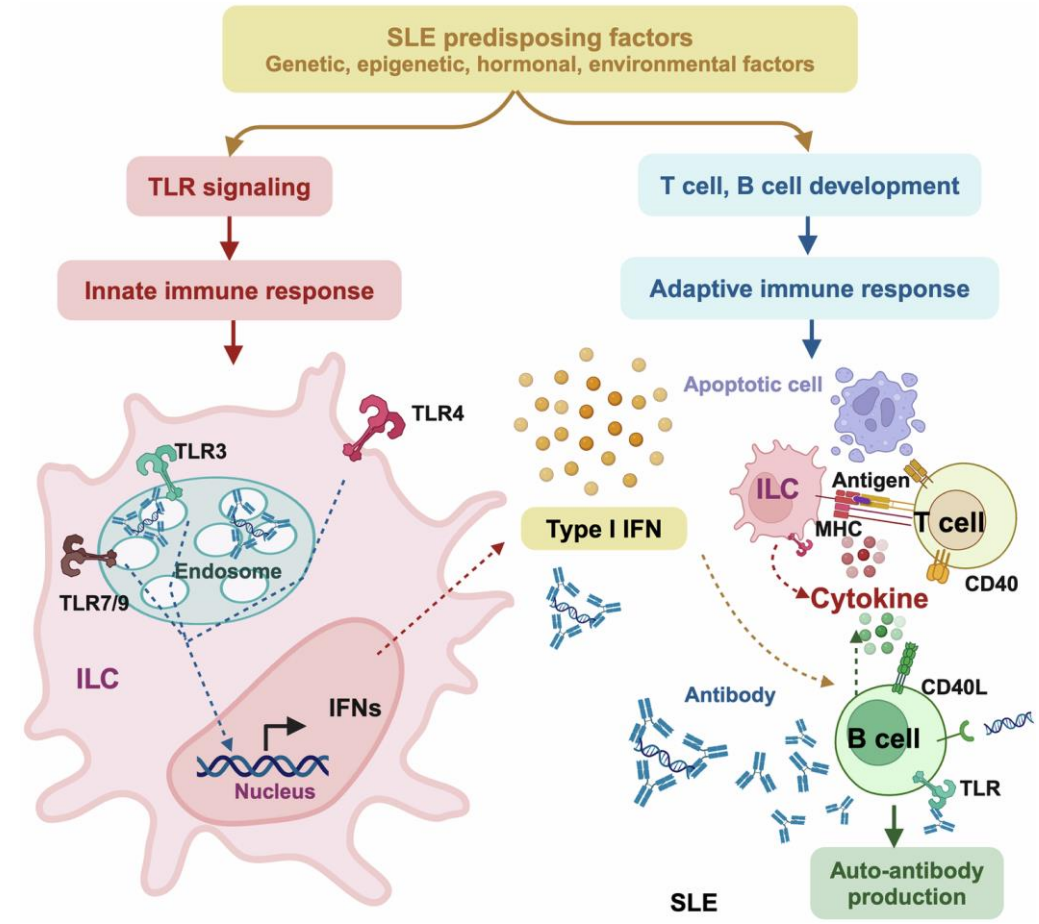
Systemic Lupus Erythematosus (SLE) vs. Rheumatoid Arthritis (RA)

Comparison of features of musculoskeletal disease in systemic lupus erythematosus or rheumatoid arthritis

Feature	Systemic lupus erythematosus	Rheumatoid arthritis
Arthralgia	Common	Common
Arthritis	Common	Deforming
Symmetry	Yes	Yes
Joints involved	PIP>MCP>wrist>knee	PIP+MCP>wrist>knee
Synovial hypertrophy	Rare	Common
Synovial membrane abnormality	Minimal	Proliferative
Synovial fluid	Transudate	Exudate
Subcutaneous nodules	Rare	35%
Erosions	Very rare	Common
Morning stiffness	Minutes	Hours
Myalgia	Common	Common
Myositis	Rare	Uncommon
Osteoporosis	Variable	Common
Avascular necrosis	5 to 50%	Uncommon
Deforming arthritis	Uncommon	Common
Swan neck	10%, reducible	Common, not reducible
Ulnar deviation	5%, reducible	Common, not reducible

PIP: proximal interphalangeal; MCP: metacarpophalangeal.

Systemic Lupus Erythematosus (SLE) - Pathogenesis



Mechanisms-of-action driving SLE pathogenesis via over-activating immune response. SLE predisposing factors including genetic, epigenetic, hormonal and environmental factors can function as or induce the production of immunoreactants to trigger Toll-like receptor (TLR) signaling in the innate immune system for enhanced generation of type I interferon (IFN), or modulate the development and maturation of T and B cells in the adaptive immune system for over-production of auto-antibodies. Type I IFN functions as the hub bridging the innate and adaptive immune systems. Specifically, type I IFN is produced from innate lymphoid cells (ILC), and directly triggers B cell activation to overtly produce auto-antibodies that ultimately contribute to SLE pathogenesis. Besides producing type I IFNs, ILCs can also present antigens to T cells via major histocompatibility complex (MHC) to activate T cells that express CD40L that interacts with B cells via the CD40L-CD40 bridge for enhanced auto-antibody production

Dai X, Fan Y, Zhao X. *Nature* 2025;
doi.org/10.1038/s41392-025-02168-0

Systemic Lupus Erythematosus (SLE) – Diagnostic Criteria

Classification criteria for systemic lupus erythematosus

ACR criteria[1,2] (4 of 11 criteria)*		SLICC criteria[3] (4 of 17 criteria, including at least 1 clinical criterion and 1 immunologic criterion;¶ **OR** biopsy-proven lupus nephritis△)	
Criterion	**Definition**	**Criterion**	**Definition**
		Clinical criteria	
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds	Acute cutaneous lupus	Lupus malar rash (do not count if malar discoid); bullous lupus; toxic epidermal necrolysis variant of SLE; maculopapular lupus rash; photosensitive lupus rash (in the absence of dermatomyositis); **OR** subacute cutaneous lupus (nonindurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or clinician observation		
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions	Chronic cutaneous lupus	Classic discoid rash; localized (above the neck); generalized (above and below the neck); hypertrophic (verrucous) lupus; lupus panniculitis (profundus); mucosal lupus; lupus erythematosus tumidus; chilblains lupus; **OR** discoid lupus/lichen planus overlap
		Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes, such as alopecia areata, drugs, iron deficiency, and androgenic alopecia)
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a clinician	Oral or nasal ulcers	Palate, buccal, tongue, **OR** nasal ulcers (in the absence of other causes, such as vasculitis, Behçet syndrome, infection [herpesvirus], inflammatory bowel disease, reactive arthritis, and acidic foods)
Arthritis	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion	Joint disease	Synovitis involving 2 or more joints, characterized by swelling or effusion **OR**
			Tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Serositis	Pleuritis – Convincing history of pleuritic pain or rubbing heard by a clinician or evidence of pleural effusion **OR**	Serositis	Typical pleurisy for more than 1 day, pleural effusions, or pleural rub, **OR**
	Pericarditis – Documented by ECG, rub, or evidence of pericardial effusion		Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day, pericardial effusion, pericardial rub, or pericarditis by electrocardiography in the absence of other causes, such as infection, uremia, and Dressler syndrome
Kidney disorder	Persistent proteinuria greater than 500 mg/24 hours or greater than 3+ if quantitation not performed **OR**	Renal	Urine protein-to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours, **OR**
	Cellular casts – May be red cell, hemoglobin, granular, tubular, or mixed		Red blood cell casts
Neurologic disorder	Seizures **OR** psychosis – In the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance)	Neurologic	Seizures; psychosis; mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis); myelitis; peripheral or cranial neuropathy (in the absence of other known causes, such as primary vasculitis, infection, and diabetes mellitus); **OR** acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)
Hematologic disorder	Hemolytic anemia – With reticulocytosis **OR**	Hemolytic anemia	Hemolytic anemia
	Leukopenia – Less than 4000/mm^3 total on 2 or more occasions **OR**	Leukopenia or lymphopenia	Leukopenia (<4000/mm^3 at least once) (in the absence of other known causes, such as Felty syndrome, drugs, and portal hypertension), **OR**
	Lymphopenia – Less than 1500/mm^3 on 2 or more occasions **OR**		Lymphopenia (<1000/mm^3 at least once) (in the absence of other known causes, such as glucocorticoids, drugs, and infection)
	Thrombocytopenia – Less than 100,000/mm^3 (in the absence of offending drugs)	Thrombocytopenia	Thrombocytopenia (<100,000/mm^3) at least once in the absence of other known causes, such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura

Systemic Lupus Erythematosus (SLE) – Diagnostic Criteria

		Immunologic criteria	
ANA	An abnormal titer of ANA 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	ANA	ANA level above laboratory reference range
Immunologic disorders	Anti-DNA – Antibody to native DNA in abnormal titer **OR** Anti-Sm – Presence of antibody to Sm nuclear antigen **OR** Positive antiphospholipid antibody on: 1. An abnormal serum level of IgG or IgM anticardiolipin antibodies **OR** 2. A positive test result for lupus anticoagulant using a standard method **OR** 3. A 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	Anti-dsDNA	Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
		Anti-Sm	Presence of antibody to Sm nuclear antigen
		Antiphospholipid	Antiphospholipid antibody positivity as determined by any of the following: Positive test result for lupus anticoagulant; false-positive test result for rapid plasma reagin; medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM); or positive test result for anti-beta 2-glycoprotein I (IgA, IgG, or IgM)
		Low complement	Low C3; low C4; **OR** low CH50
		Direct Coombs test	Direct Coombs test in the absence of hemolytic anemia

ACR: American College of Rheumatology; SLICC: Systemic Lupus International Collaborating Clinics; SLE: systemic lupus erythematosus; ECG: electrocardiogram; ANA: antinuclear antibodies; Anti-Sm: anti-Smith antibody; IgG: immunoglobulin G; IgM: immunoglobulin M; Anti-dsDNA: anti-double-stranded DNA; ELISA: enzyme-linked immunosorbent assay; IgA: immunoglobulin A.

* For the ACR criteria, no distinction is made between clinical and immunologic criteria in determining whether the required number has been met. The classification is based upon 11 criteria. For the purpose of identifying patients in clinical studies, a person is said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

¶ For the SLICC criteria, criteria are cumulative and need not be presently concurrently. A patient is classified as having SLE if he or she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion.

Δ Alternatively, according to the SLICC criteria, a patient is classified as having SLE if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.

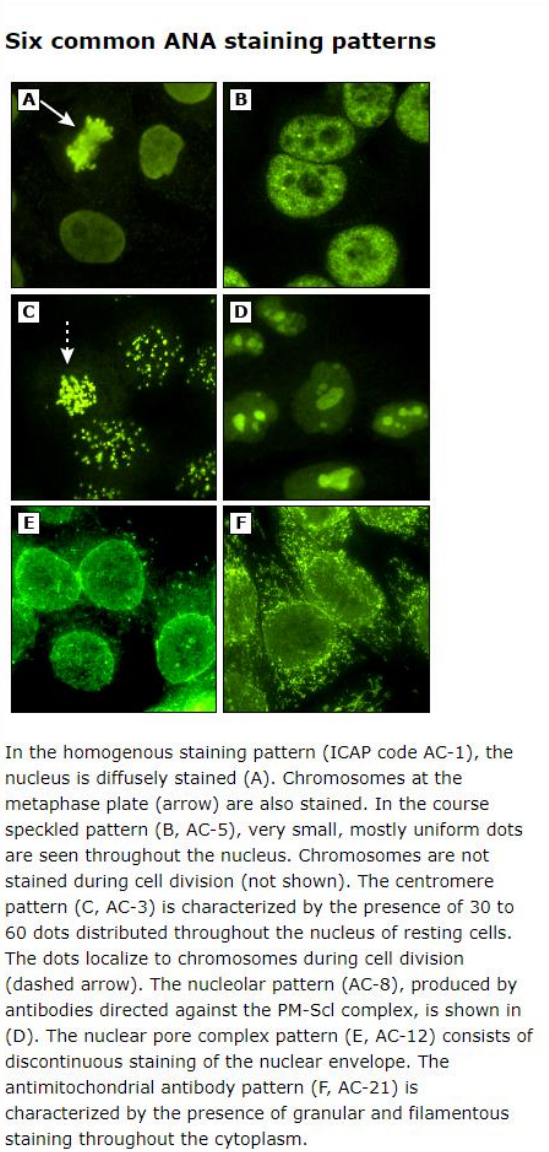
References:

1. *Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271.*
2. *Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus (letter). Arthritis Rheum 1997; 40:1725.*
3. *Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64:2677.*

Systemic Lupus Erythematosus (SLE) – Serology – Antinuclear Antibodies (ANA)

ANA Staining Patterns

- Homogeneous – DNA, histones (most common pattern – 36%)
  - SLE, drug-induced lupus, Sjogren's (SjD), Systemic Sclerosis (SS), RA, Hashimoto's, primary biliary cirrhosis (PBC), autoimmune hepatitis
- Nuclear speckled – Ro/SS-A, La/SS-B, RNP, Sm, Scl-70
  - Fine (20%) – SLE, SjD, SS, dermatomyositis (DM), polymyositis (PM), RA
  - Coarse (1.5%) – SLE, mixed connective tissue disease (MCTD)
  - Dense fine (wide range) – seen in healthy people, uncommon SLE
- Nucleolar (1.4%-17%)
  - SLE, RA, SjD, PM, DM, MCTD, Raynaud's
- Centromere (3%)
  - Limited SS (CREST), PBC, SjD, SLE, Raynaud's



In the homogenous staining pattern (ICAP code AC-1), the nucleus is diffusely stained (A). Chromosomes at the metaphase plate (arrow) are also stained. In the course speckled pattern (B, AC-5), very small, mostly uniform dots are seen throughout the nucleus. Chromosomes are not stained during cell division (not shown). The centromere pattern (C, AC-3) is characterized by the presence of 30 to 60 dots distributed throughout the nucleus of resting cells. The dots localize to chromosomes during cell division (dashed arrow). The nucleolar pattern (AC-8), produced by antibodies directed against the PM-Scl complex, is shown in (D). The nuclear pore complex pattern (E, AC-12) consists of discontinuous staining of the nuclear envelope. The antimitochondrial antibody pattern (F, AC-21) is characterized by the presence of granular and filamentous staining throughout the cytoplasm.

Systemic Lupus Erythematosus (SLE) – Serology – Antinuclear Antibodies (ANA)

Diseases associated with a positive ANA

	% with positive ANA
Systemic autoimmune diseases	
Mixed connective tissue disease	100%
SLE:	
▪ Active	98 to 100%
▪ Remission	90%
Scleroderma	95%
Drug-induced LE	80 to 95%
Sjögren's disease	60%
Rheumatoid arthritis	45%
Raynaud phenomenon	40%
Polymyositis/dermatomyositis	35%
Juvenile idiopathic arthritis	15 to 40%
Organ-specific autoimmune diseases	
Autoimmune hepatitis	70%
Primary biliary cholangitis	50 to 70%
Hashimoto's thyroiditis	50%
Graves' disease	50%
Viral infections*	
EBV	
HIV	
HCV	
Parvovirus 19	
Malignancies*	

Antinuclear antibodies and Systemic lupus

Antibody	ANA (ICAP*) pattern	Frequency	Comments
Anti-dsDNA	Nuclear homogeneous	**60-80%**	Association with disease activity (when with Farr assay) and lupus nephritis. Can also be measured using ELISA-based or IF on *Crithidia Luciliae*
Anti-nucleosome	Nuclear homogeneous	**60-70%**	Highly specific for SLE. Often searched for when ANA+ without anti-dsDNA
Anti-histone	Nuclear homogeneous	**60-70%**	Association with both SLE (60-70%) & drug-induced lupus (90%)
Anti-SSA	Nuclear fine speckled	**30-40%**	Target: SS-A/Ro (60kD). Associated with SCLE, neonatal lupus and Sjogren
Anti-SSB	Nuclear fine speckled	**5-10%**	Associated with Sjogren and neonatal lupus
Anti-(U1)RNP	Nuclear large/coarse speckled	**15-30%**	Associated with MCTD, Raynaud's phenomenon and
Anti-Sm	Nuclear large/coarse speckled	**10-30%**	Highly specific. Higher prevalence in non-white (30%-40%) than white (5-10%)
Anti-Ribo-P	Cytoplasmic dense fine speckled	**5-15%**	If SLE is clinically suspected, tests to ribosomal P phosphoproteins (P0, P1, P2, C22 RibP peptide) are recommended*. Controversial association with NPSLE.
Anti-Ku	Nuclear fine speckled	**5-10%**	Associated with SLE-SSc-AIM overlap syndromes*
Anti-PCNA	Pleomorphic speckled nucleoplasmic	**1-5%**	Considered higly specific for SLE (debated)
Anti-DFS70	Nuclear dense fine speckled	**0-3%**	Rarely confirmed in patients with typical SLE. Negative association with auto-immune diseases only if Ag target is LEDGF/p75 and there is no common ENA*

*International Consensus on ANA pattern (anapatterns.org)

@Lupusreference

Systemic Lupus Erythematosus (SLE) – Assessment of Disease Activity

SLEDAI-2K[1]

The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was developed and validated as a clinical index for the measurement of disease activity in SLE (systemic lupus erythematosus).

Patient name: _____ **Date:** _____

Check the score column of each descriptor that is present at the time of the visit or in the preceding 10 days.

8	☐	**Seizure** - Recent onset, exclude metabolic, infectious or drug causes.
8	☐	**Psychosis** - Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	☐	**Organic brain syndrome** - Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia, or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	☐	**Visual disturbance** - Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate, or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	☐	**Cranial nerve disorder** - New onset of sensory or motor neuropathy involving cranial nerves.
8	☐	**Lupus headache** - Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	☐	**CVA** - New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	☐	**Vasculitis** - Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	**Arthritis** - >2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4	☐	**Myositis** - Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	**Urinary casts** - Heme-granular or red blood cell casts.
4	☐	**Hematuria** - >5 red blood cells/high power field. Exclude stone, infection, or other cause.
4	☐	**Proteinuria** - >0.5 gram/24 hours.
4	☐	**Pyuria** - >5 white blood cells/high power field. Exclude infection.
2	☐	**Rash** - Inflammatory type rash.
2	☐	**Alopecia** - Abnormal, patchy, or diffuse loss of hair.
2	☐	**Mucosal ulcers** - Oral or nasal ulcerations.
2	☐	**Pleurisy** - Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	☐	**Pericarditis** - Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	☐	**Low complement** - Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	☐	**Increased DNA binding** - Increased DNA binding by Farr assay above normal range for testing laboratory.
1	☐	**Fever** - >38°C. Exclude infectious cause.
1	☐	**Thrombocytopenia** - <100,000 platelets / x10^9/L, exclude drug causes.
1	☐	**Leukopenia** - <3,000 white blood cells / x10^9/L, exclude drug cause.

Add all the checked scores above to calculate the total score.

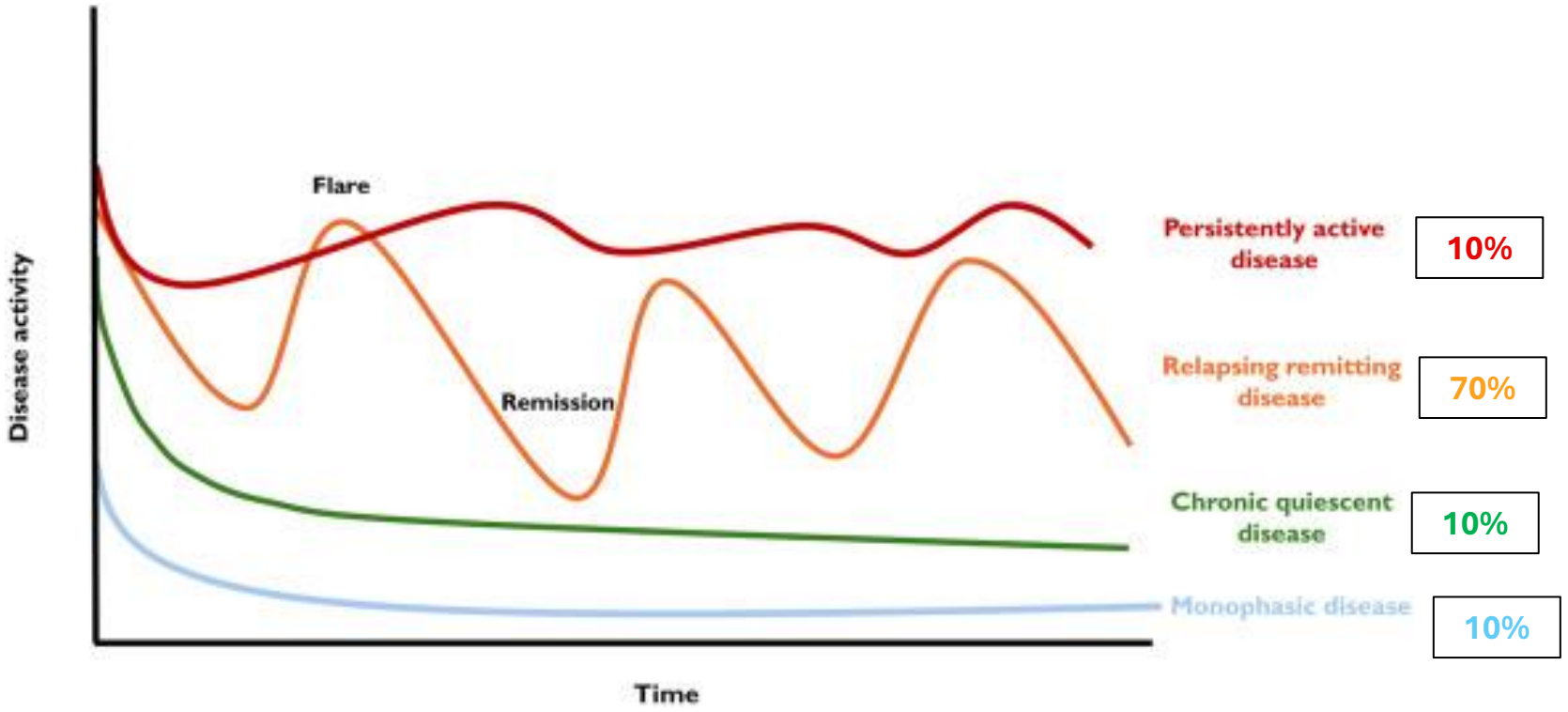
Total SLEDAI-2K Score: _____

Reference: 1. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. Journal of Rheumatology 2002, 29(2):288-91. CA-8366E

SLEDAI SCORE

0: No disease activity (remission)
1-5: Mild disease activity
6-10: Moderate disease activity
11-19: High disease activity
≥20: very high disease activity

Systemic Lupus Erythematosus (SLE) – Clinical Course



Systemic Lupus Erythematosus (SLE) – Complications

- **Renal**
  - Lupus nephritis → proteinuria, hematuria, renal failure
  - Hypertension, ESRD
- **Cardiovascular**
  - Premature ASCVD, CAD
  - Endocarditis (Libman-Sacks)
  - Pericarditis, myocarditis, heart failure
- **Pulmonary**
  - Pleuritis, pleural effusion
  - Interstitial lung disease, pulmonary hypertension
  - Diffuse alveolar hemorrhage (rare, severe)
- **Neurologic**
  - Seizures, psychosis, cognitive dysfunction
  - Peripheral neuropathy, transverse myelitis
- **Hematologic**
  - Autoimmune hemolytic anemia
  - Thrombocytopenia, leukopenia
  - Antiphospholipid antibody syndrome → thrombosis, pregnancy loss
- **Infectious**
  - Immunosuppression (disease + therapy) → increase bacterial, viral, opportunistic infections
- **Other**
  - Osteoporosis (steroid use)
  - Malignancy (esp. lymphoma)
  - Chronic fatigue, reduced quality of life

Systemic Lupus Erythematosus (SLE) – Lupus Nephritis (LN)

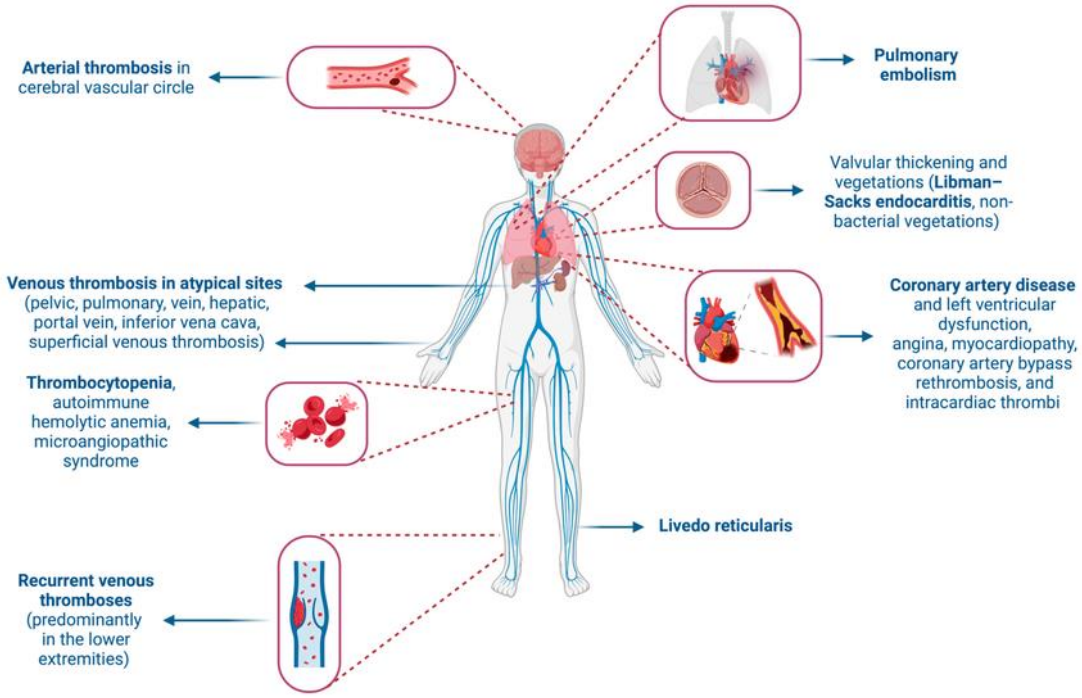
- Most individuals with SLE will have some clinical evidence of renal disease at some time during the course of their disease.
- LN typically develops early in their disease
- 50% will develop significant renal disease and 10% will develop ESRD
- Greater risk in African Americans, Hispanic population, male sex
- The presence of LN increases the mortality risk
- Is an immune complex glomerulonephritis
- Pathogenesis related to neutrophil activation, increased interferon expression, and upregulation of myeloid cell transcriptomes (RNA transcripts)
- Clinical signs and symptoms include: proteinuria, hematuria, hypertension, edema

Systemic Lupus Erythematosus (SLE) – Lupus Nephritis (LN) - Classification

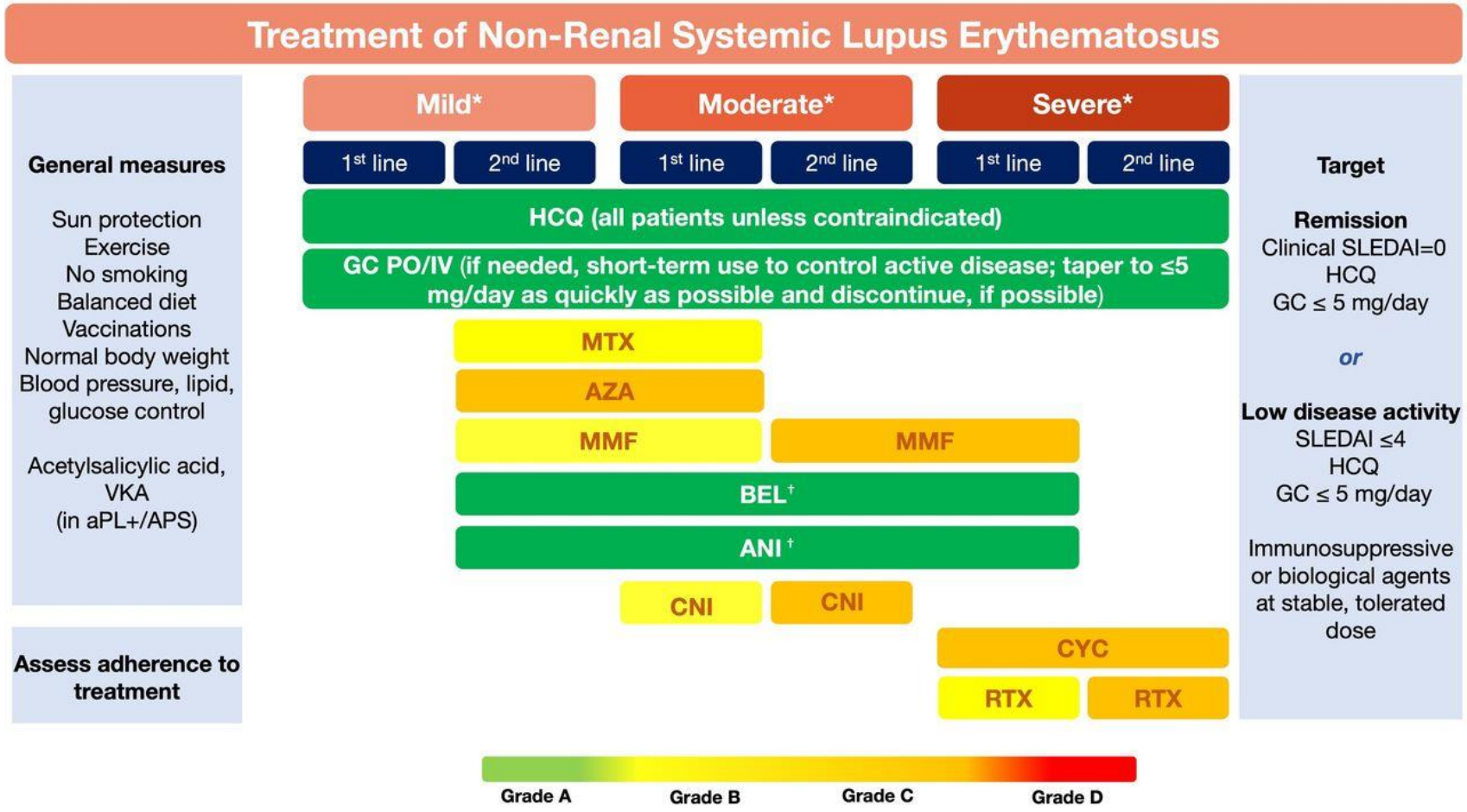
Class	Pathology	Clinical Features	Prognosis
I – Minimal Mesangial	Normal glomeruli on LM; mesangial deposits on IF	Usually asymptomatic	Excellent
II – Mesangial Proliferative	Mesangial hypercellularity & deposits	Mild proteinuria, hematuria	Excellent to Good
III – Focal	<50% glomeruli affected; segmental/global proliferation	Hematuria, proteinuria, mild renal impairment	Variable – treat early
IV – Diffuse	≥50% glomeruli; endocapillary proliferation, wire-loop lesions	Nephritic syndrome, nephrotic proteinuria, ↓ renal function	Guarded to Poor – aggressive treatment needed
V – Membranous	Thickened capillary walls; subepithelial deposits	Nephrotic syndrome, mild renal impairment	Variable – better if isolated, worse if combined with III/IV
VI – Advanced Sclerosing	≥90% globally sclerotic glomeruli	Chronic kidney disease	Poor – often irreversible

Antiphospholipid Syndrome (APS) and Systemic Lupus Erythematosus

- An autoimmune syndrome characterized by evidence of antiphospholipid antibodies (aPL) and clinical manifestations of venous thrombosis, arterial thrombosis, adverse pregnancy outcomes
- APS may occur as a primary condition or in setting of underlying autoimmune disease such as SLE
- aPL heterogeneous group of IgG directed against phospholipids and phospholipid binding proteins
- aPL can be transient (e.g., infection), or persistent
- Typical aPL assay includes:
  - Anticardiolipin Ab (aCL) – IgG or IgM
  - Anti-beta2 glycoprotein I Ab
  - Lupus anticoagulant (LA) – assayed in a clotting test
- Risk stratification
  - High – LA+ w/wo aCL/anti-beta2GPI. Highest risk if all three positive
  - Moderate – aCL+ and/or anti-beta2GPI+ with LA-
  - Low – low titer aCL+ and/or anti-beta2GPI+ with LA-



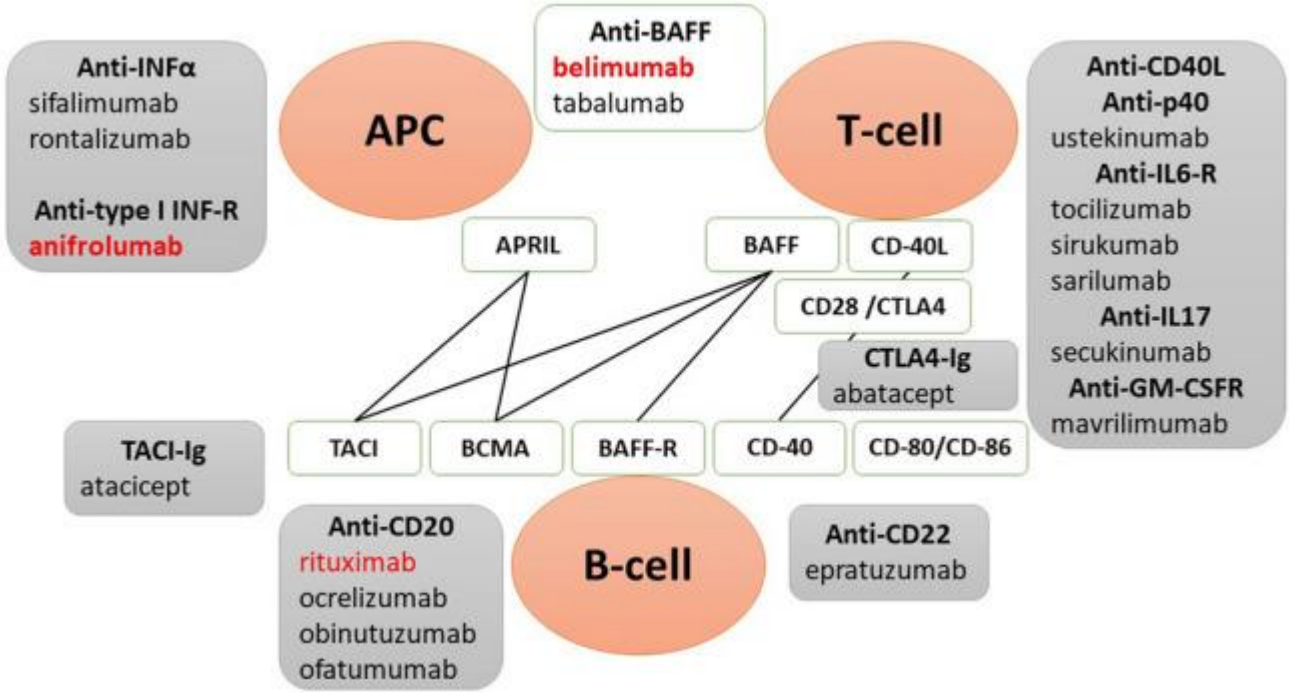
Systemic Lupus Erythematosus (SLE) – Treatment



HCQ = hydroxychloroquine
GC = glucocorticoids
MTX = methotrexate
AZA = azathioprine
MMF = mycophenolate mofetil
BEL = belimumab
ANI = anifrolumab
CNI = calcineurin inhibitor
CYC = cyclophosphamide
RTX = rituximab

Antonis Fanouriakis et al. *Ann Rheum Dis* 2024;83:15-29

Systemic Lupus Erythematosus (SLE) – Treatment – Mechanism of Action



APC – antigen-presenting cell
BAFF – B lymphocyte stimulator (BLyS)
APRIL – A proliferation inducing ligand
TACI – transmembrane activator/cyclophilin ligand-interactor
BCMA- B cell maturation antigen
CTLA – cytotoxic T-lymphocyte antigen
GM-CSFR – granulocyte colony-stimulating factor receptor

Katarzyna P, et al. *Rheum Intl* 2023:43;1395

Systemic Lupus Erythematosus (SLE) – Mortality

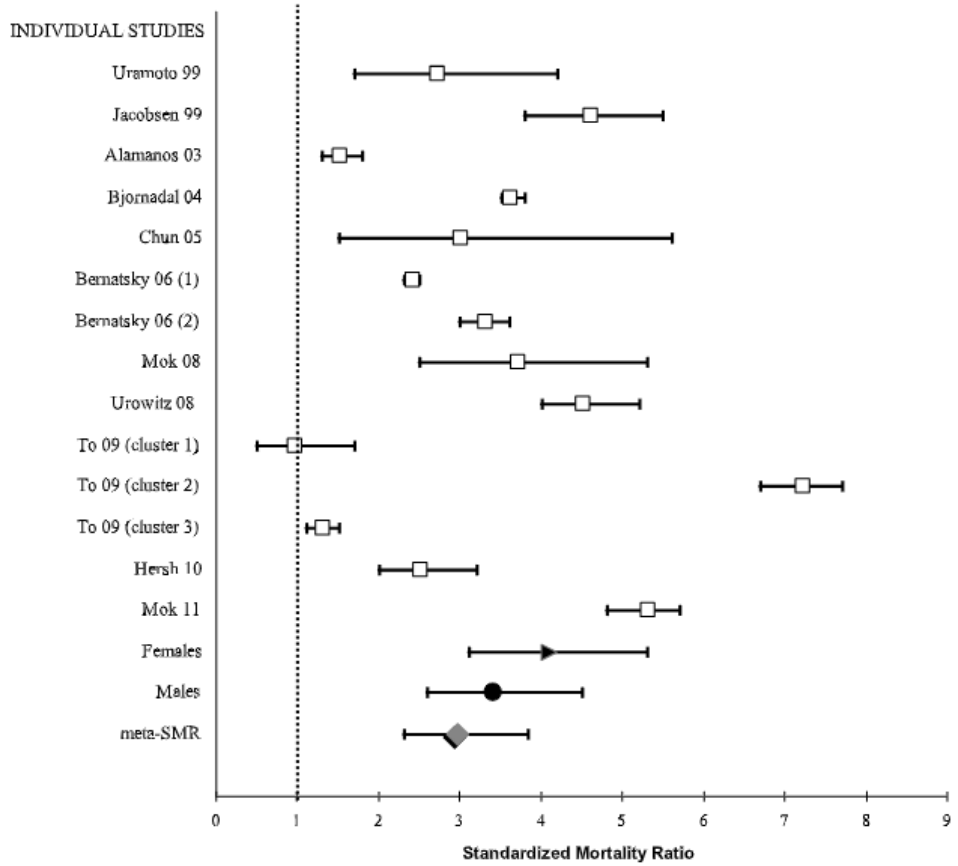
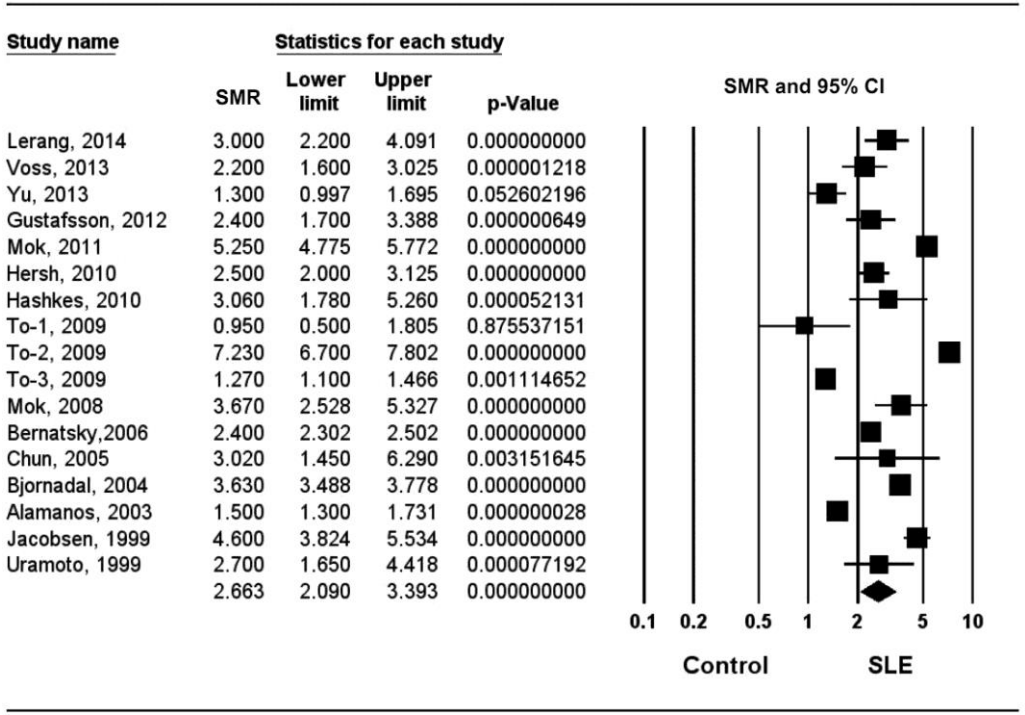


Figure 3. Meta-analysis of 12 studies on all-cause mortality in patients with systemic lupus erythematosus. meta-SMR = weighted–pooled summary estimates of standardized response means.

- Meta analysis
- 566 papers/12 selected
- 27,210 patients with lupus
- 4,989 observed deaths
- Median age 33.4 years
- 89.6% females
- Overall 3X increase in all-cause mortality in those with SLE

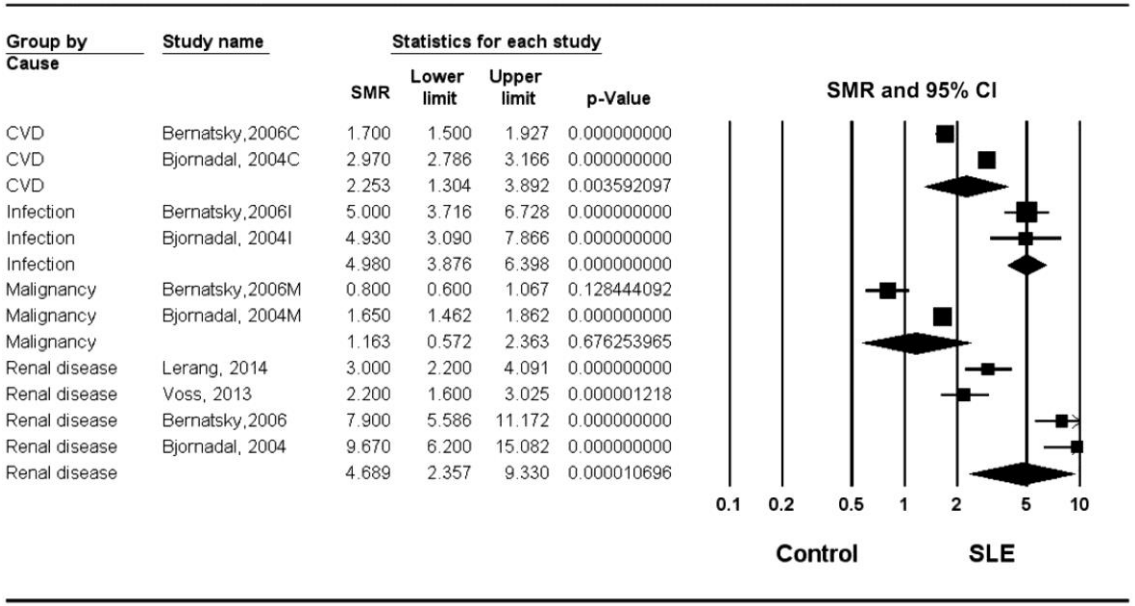
Yurkovich M, et al. *Arth Care & Res* 2014; 66:608

Systemic Lupus Erythematosus (SLE) – Mortality



Study name	SMR	Lower limit	Upper limit	p-Value
Lerang, 2014	3.000	2.200	4.091	0.000000000
Voss, 2013	2.200	1.600	3.025	0.000001218
Yu, 2013	1.300	0.997	1.695	0.052602196
Gustafsson, 2012	2.400	1.700	3.388	0.000000649
Mok, 2011	5.250	4.775	5.772	0.000000000
Hersh, 2010	2.500	2.000	3.125	0.000000000
Hashkes, 2010	3.060	1.780	5.260	0.000052131
To-1, 2009	0.950	0.500	1.805	0.875537151
To-2, 2009	7.230	6.700	7.802	0.000000000
To-3, 2009	1.270	1.100	1.466	0.001114652
Mok, 2008	3.670	2.528	5.327	0.000000000
Bernatsky,2006	2.400	2.302	2.502	0.000000000
Chun, 2005	3.020	1.450	6.290	0.003151645
Bjornadal, 2004	3.630	3.488	3.778	0.000000000
Alamanos, 2003	1.500	1.300	1.731	0.000000028
Jacobsen, 1999	4.600	3.824	5.534	0.000000000
Uramoto, 1999	2.700	1.650	4.418	0.000077192
	2.663	2.090	3.393	0.000000000

- Meta analysis
- 58 papers/15 selected
- 26,101 patients with lupus
- 4,640 observed deaths
- Overall, 2.6X increase in all-cause mortality in those with SLE



Group by Cause	Study name	SMR	Lower limit	Upper limit	p-Value
CVD	Bernatsky,2006C	1.700	1.500	1.927	0.000000000
CVD	Bjornadal, 2004C	2.970	2.786	3.166	0.000000000
CVD		2.253	1.304	3.892	0.003592097
Infection	Bernatsky,2006I	5.000	3.716	6.728	0.000000000
Infection	Bjornadal, 2004I	4.930	3.090	7.866	0.000000000
Infection		4.980	3.876	6.398	0.000000000
Malignancy	Bernatsky,2006M	0.800	0.600	1.067	0.128444092
Malignancy	Bjornadal, 2004M	1.650	1.462	1.862	0.000000000
Malignancy		1.163	0.572	2.363	0.676253965
Renal disease	Lerang, 2014	3.000	2.200	4.091	0.000000000
Renal disease	Voss, 2013	2.200	1.600	3.025	0.000001218
Renal disease	Bernatsky,2006	7.900	5.586	11.172	0.000000000
Renal disease	Bjornadal, 2004	9.670	6.200	15.082	0.000000000
Renal disease		4.689	2.357	9.330	0.000010696

Lee YH, et al. *Lupus* 2016;25:727

Case #2

- 41 yo F NS for $500K UL
- Part 2 notes no PCP but sees rheumatologist for lupus diagnosed 6 years prior to application. Taking hydroxychloroquine.
- MIB – multiple application queries; connective tissue disorder, kidney disorder, albuminuria
- APS – 2017 developed joint pain/stiffness, hand swelling, ankle swelling. Serum Cr 3.1 with ANA 1:5120. Renal biopsy done which showed membranous lupus nephritis (LN) Class V with immunoglobulin and complement deposits. Treated with prednisone, mycophenolate (MMF), and cyclophosphamide. Weaned off steroids one year later with normalization of Cr. By 2020 was weaned off MMF; maintained on hydroxychloroquine. Occasional joint stiffness and hand joint swelling.
- At 12/2023 visit, PI clinically stable with benign exam. CBC wnl, serum Cr 0.97; ESR 15 mm/hr; CRP 2.4 mg/dl; dsDNA wnl; C3/C4 wnl; p/c 77 mg/g.
- Historic serologies – RF; CCP, RNP, Smith, Ro/LA antibodies all negative. Antiphospholipid panel negative.
- Questions:
  - What is the overall prognosis?
  - How does the prognosis of membranous LN compare to other forms of LN?
  - What is the mortality risk?
  - How does the history of lupus nephritis impact the mortality risk?

Summary

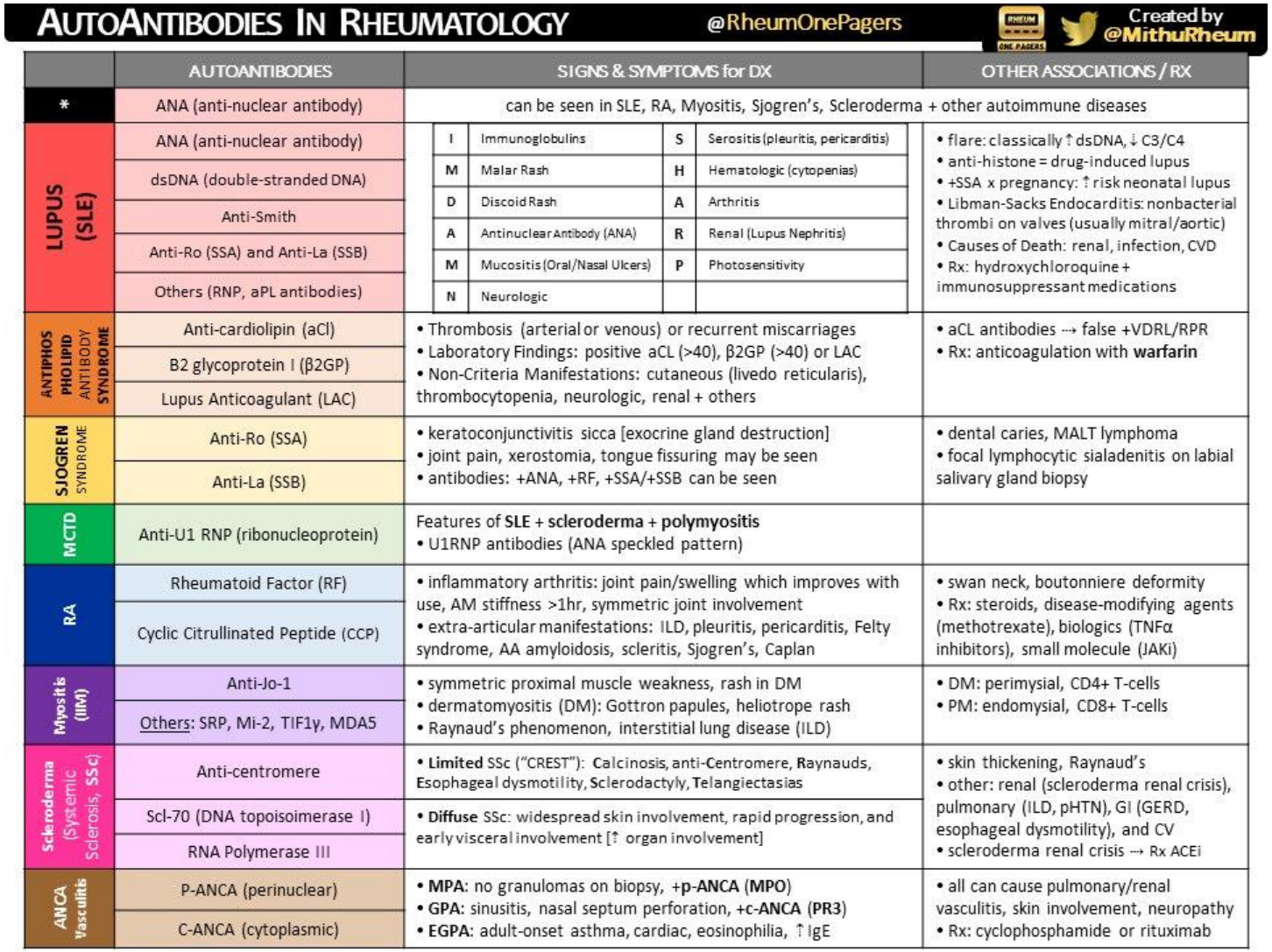
- Rheumatologic disorders encompass a wide array of disorders from mechanical disorders to inflammatory, autoimmune, connective tissue disorders and vasculitis.

- Osteoarthritis and osteoporosis are common disorders with more morbidity than mortality impact.

- Rheumatoid arthritis is an autoimmune inflammatory disorder that targets synovial joints causing joint destruction and potential deformity. RA can have systemic manifestations as well. Rheumatoid factor and anti-citrullinated protein antibodies are key lab findings. RA is associated with increased risk of cardiovascular disease and all-cause mortality. Meta analysis studies suggest an overall 1.5X increase in all-cause mortality risk.

- Systemic lupus erythematosus is a systemic autoimmune disorder that can result in end-stage renal disease. Anti-nuclear antibodies and antibodies to double stranded DNA are key lab findings. SLE often has a variable course with remissions and exacerbations. Meta analysis studies suggest an overall 2.6X increase in all-cause mortality risk.

Autoantibodies and Rheumatologic Disease



AUTOANTIBODIES IN RHEUMATOLOGY

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Created by @MithuRheum

	AUTOANTIBODIES	SIGNS & SYMPTOMS for DX	OTHER ASSOCIATIONS / RX
*	ANA (anti-nuclear antibody)	can be seen in SLE, RA, Myositis, Sjogren's, Scleroderma + other autoimmune diseases	
LUPUS (SLE)	ANA (anti-nuclear antibody) dsDNA (double-stranded DNA) Anti-Smith Anti-Ro (SSA) and Anti-La (SSB) Others (RNP, aPL antibodies)	I Immunoglobulins; S Serositis (pleuritis, pericarditis) M Malar Rash; H Hematologic (cytopenias) D Discoid Rash; A Arthritis A Antinuclear Antibody (ANA); R Renal (Lupus Nephritis) M Mucositis (Oral/Nasal Ulcers); P Photosensitivity N Neurologic	• flare: classically ↑ dsDNA, ↓ C3/C4 • anti-histone = drug-induced lupus • +SSA x pregnancy: ↑ risk neonatal lupus • Libman-Sacks Endocarditis: nonbacterial thrombi on valves (usually mitral/aortic) • Causes of Death: renal, infection, CVD • Rx: hydroxychloroquine + immunosuppressant medications
ANTIPHOSPHOLIPID ANTIBODY SYNDROME	Anti-cardiolipin (aCl) B2 glycoprotein I (β2GP) Lupus Anticoagulant (LAC)	• Thrombosis (arterial or venous) or recurrent miscarriages • Laboratory Findings: positive aCL (>40), β2GP (>40) or LAC • Non-Criteria Manifestations: cutaneous (livedo reticularis), thrombocytopenia, neurologic, renal + others	• aCL antibodies ⇢ false +VDRL/RPR • Rx: anticoagulation with **warfarin**
SJOGREN SYNDROME	Anti-Ro (SSA) Anti-La (SSB)	• keratoconjunctivitis sicca [exocrine gland destruction] • joint pain, xerostomia, tongue fissuring may be seen • antibodies: +ANA, +RF, +SSA/+SSB can be seen	• dental caries, MALT lymphoma • focal lymphocytic sialadenitis on labial salivary gland biopsy
MCTD	Anti-U1 RNP (ribonucleoprotein)	Features of **SLE** + **scleroderma** + **polymyositis** • U1RNP antibodies (ANA speckled pattern)	
RA	Rheumatoid Factor (RF) Cyclic Citrullinated Peptide (CCP)	• inflammatory arthritis: joint pain/swelling which improves with use, AM stiffness >1hr, symmetric joint involvement • extra-articular manifestations: ILD, pleuritis, pericarditis, Felty syndrome, AA amyloidosis, scleritis, Sjogren's, Caplan	• swan neck, boutonniere deformity • Rx: steroids, disease-modifying agents (methotrexate), biologics (TNFα inhibitors), small molecule (JAKi)
Myositis (IIM)	Anti-Jo-1 Others: SRP, Mi-2, TIF1γ, MDA5	• symmetric proximal muscle weakness, rash in DM • dermatomyositis (DM): Gottron papules, heliotrope rash • Raynaud's phenomenon, interstitial lung disease (ILD)	• DM: perimysial, CD4+ T-cells • PM: endomysial, CD8+ T-cells
Scleroderma (Systemic Sclerosis, SSc)	Anti-centromere Scl-70 (DNA topoisomerase I) RNA Polymerase III	• **Limited** SSc ("CREST"): Calcinosis, anti-Centromere, Raynauds, Esophageal dysmotility, Sclerodactyly, Telangiectasias • **Diffuse** SSc: widespread skin involvement, rapid progression, and early visceral involvement [↑ organ involvement]	• skin thickening, Raynaud's • other: renal (scleroderma renal crisis), pulmonary (ILD, pHTN), GI (GERD, esophageal dysmotility), and CV • scleroderma renal crisis ⇢ Rx ACEi
ANCA Vasculitis	P-ANCA (perinuclear) C-ANCA (cytoplasmic)	• **MPA**: no granulomas on biopsy, +**p-ANCA** (**MPO**) • **GPA**: sinusitis, nasal septum perforation, +**c-ANCA** (**PR3**) • **EGPA**: adult-onset asthma, cardiac, eosinophilia, ↑ IgE	• all can cause pulmonary/renal vasculitis, skin involvement, neuropathy • Rx: cyclophosphamide or rituximab

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MPA – microscopic polyangiitis
GPA – granulomatosis with polyangiitis (Wegener's granulomatosis)
EGPA – eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

QUESTIONS?