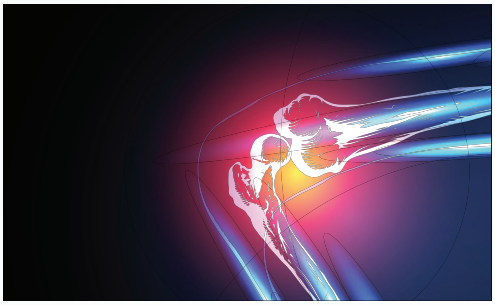
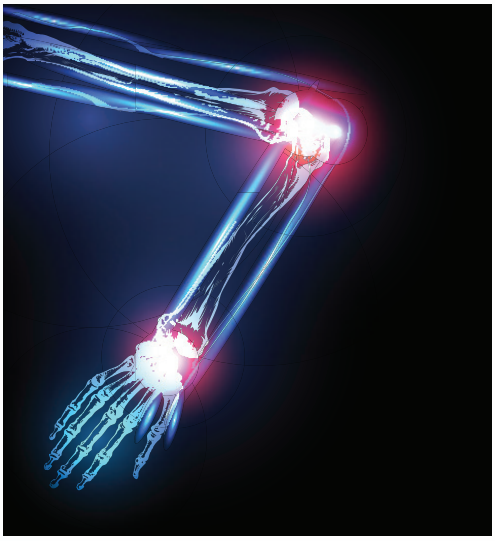
2019 RHEUMATOLOGY UPDATE
FOR PRIMARY CARE AND HOSPITAL MEDICINE





A CME Update for Health Care Professionals

Friday, August 23 &
Saturday, August 24, 2019

The Redmont Hotel,
Curio Collection by Hilton
Birmingham, AL

uab.edu/RheumatologyUpdate

UAB SCHOOL OF MEDICINE

Division of Clinical Immunology and Rheumatology

Clinical Approach to Rheumatic Disease

Maggie Guthrie, MD
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UAB Division of Clinical Immunology and Rheumatology

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Objectives

- An overview of approaching a patient with musculoskeletal complaints
- To understand the utility and limitation of initial laboratory tests in rheumatic complaints
- To recognize the key radiographic findings in patients with suspected rheumatic disease.

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Disclosure

- None to be disclosed

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Approach to Joint Pain

- Q1. Articular Vs. Peri-articular Vs. Non-articular?

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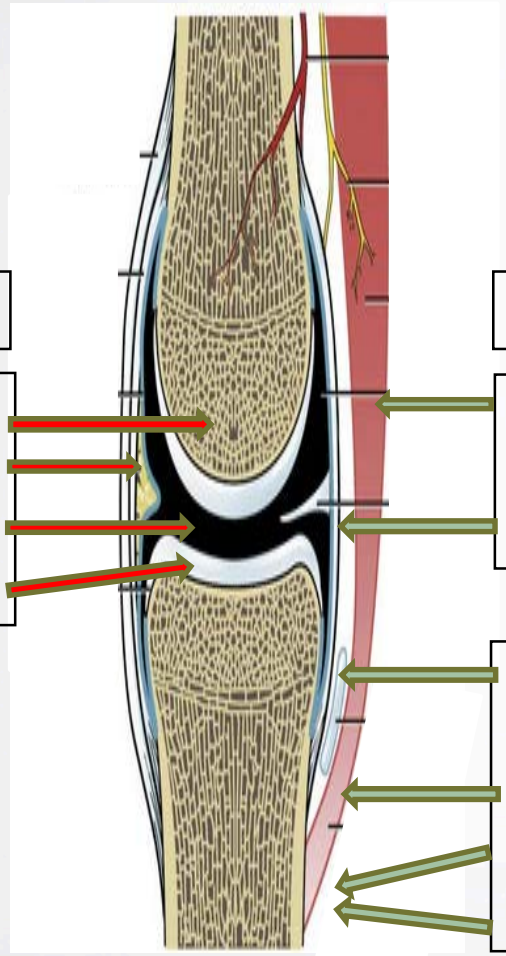

Articular

Subchondral bone
Synovium
Synovial fluid
Cartilage

Periarticular

Muscle

Ligament

Bursa

Tendon
Tenosynovium
Enthesis

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Periarticular Pain

- Pain/Tenderness and swelling near/over part of joint; may extend away from joint
- Limited/painful ROM in some directions
- Pain with active ROM > passive ROM

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Peri-articular

- Trauma
- Fracture
- Fibromyalgia
- Polymyalgia rheumatic
- Bursitis
- Tendinitis

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Articular (arthritis) Pain

- Pain/Swelling and tenderness of entire joint line
- Limited/painful ROM in all directions
- Pain with active ROM = passive ROM

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Approach to Joint Pain

- Q1. Articular Vs. Peri-articular Vs. Non-articular?
  - A: Articular.

- Q2. Duration? 6 weeks?

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Acute (< 6 weeks)

- Septic
- Infectious related (bacterial, Viral)
- Reactive (Rheumatic fever, Reactive arthritis)
- Crystalline (Gout, Pseudogout)
- Intra-articular structural injury

- Initial presentation of chronic arthritis

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Role of thumb

- Arthrocentesis should be performed on all cases as a rule of thumb

- Synovial fluid analysis – gross examination, cell count with diff, gram stain, culture, crystal analysis

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Approach to Joint Pain

- Q1. Articular Vs. Peri-articular Vs. Non-articular?
  - A: Articular.
- Q2. Duration? 6 weeks?
  - A: Chronic.
- Q3. Inflammatory Vs. Non-inflammatory?

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Chronic Non-inflammatory

- Mechanical pain: ↑ use, ↓ rest/night
- Slow steady progression
- Short time of morning stiffness/Intermittent gelling
- Bony enlargement
- Crepitus/grating
- No erythematous or warm joints
- No systemic symptoms

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Chronic Non-inflammatory

- Osteoarthritis
- Osteonecrosis
- Charcot arthritis

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Chronic Inflammatory

- Inflammatory pain: ↑ rest, ↓ activity
- Long time of morning stiffness/Intermittent gelling
- Erythematous and/or warm joints
- Synovitis (firm sponge)
- Systemic symptoms: fever, rash ..etc
- Elevated inflammatory markers

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Approach to Joint Pain

- Q1. Articular Vs. Peri-articular Vs. Non-articular?
  - A: Articular.
- Q2. Duration? 6 weeks?
  - A: Chronic.
- Q3. Inflammatory Vs. Non-inflammatory?
  - A: Inflammatory
- Q4. Oligo Vs. Poly? (<4 Vs. >4)

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Chronic Inflammatory Mono/Oligoarthritis

- Indolent infection
- Psoriatic arthritis
- Reactive arthritis
- Pauciarticular JIA

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Approach to Joint Pain

- Q1. Articular Vs. Peri-articular Vs. Non-articular?
  - A: Articular.
- Q2. Duration? 6 weeks?
  - A: Chronic.
- Q3. Inflammatory Vs. Non-inflammatory?
  - A: Inflammatory

- Q4. Oligo Vs. Poly?
  - A: Polyarticular

- Q5. Asymmetric Vs. Symmetric?

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Asymmetric Polyarticular Inflammatory

- Psoriatic arthritis
- Reactive arthritis

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Approach to Joint Pain

- Q1. Articular Vs. Peri-articular Vs. Non-articular?
  - A: Articular.
- Q2. Duration? 6 weeks?
  - A: Chronic.
- Q3. Inflammatory Vs. Non-inflammatory?
  - A: Inflammatory
- Q4. Oligo Vs. Poly?
  - A: Polyarticular
- Q5. Asymmetric Vs. Symmetric?
  - A: Symmetric
- Q.6 Distribution?

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- PIPs, MCPs and/or MTPs → RA, Psoriasis
- Other → SLE, Systemic Sclerosis, Polymyositis

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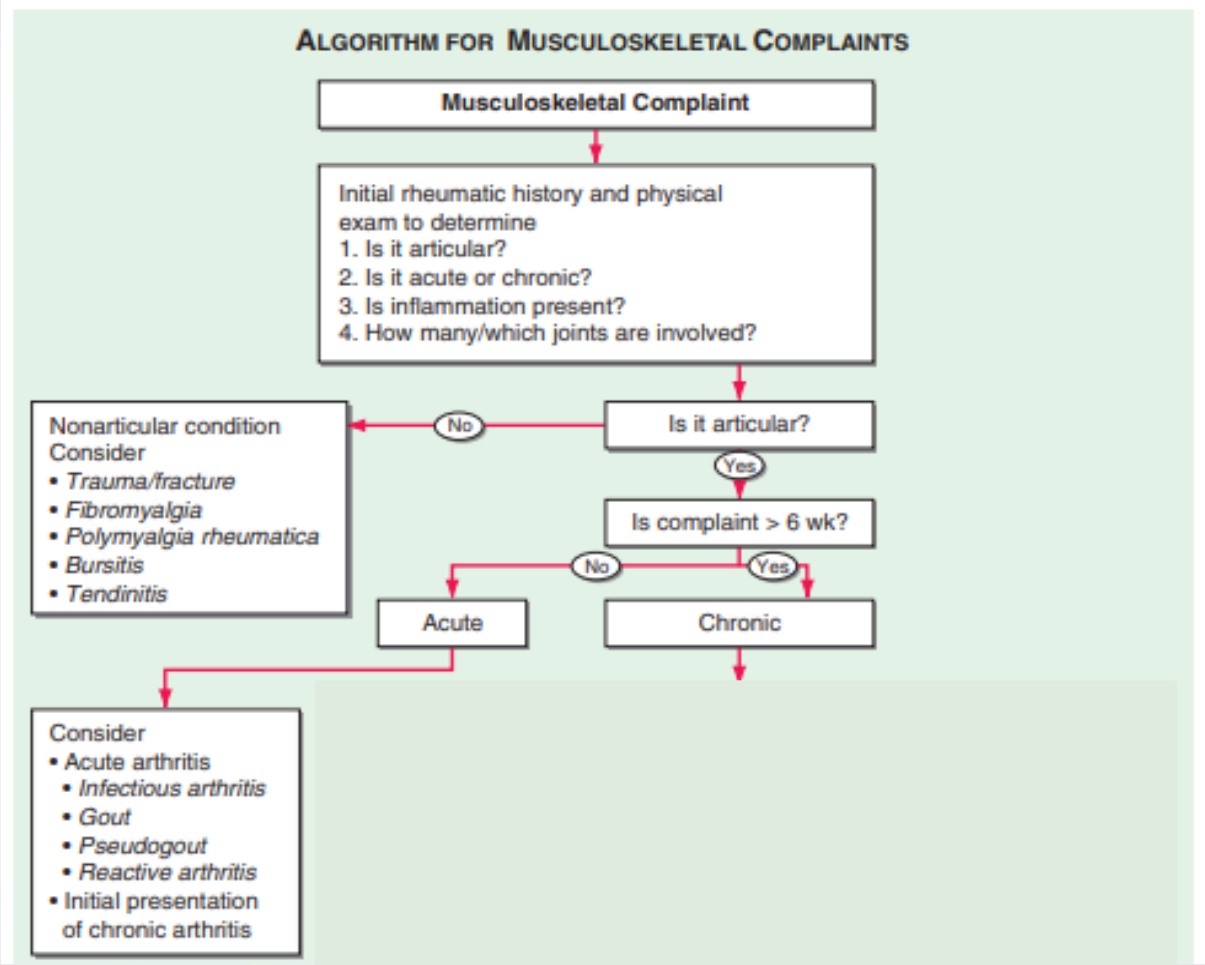

Fauci, Anthony, and Carol Langford. *Harrison's Rheumatology, 4E*. McGraw-Hill Education, 2014.

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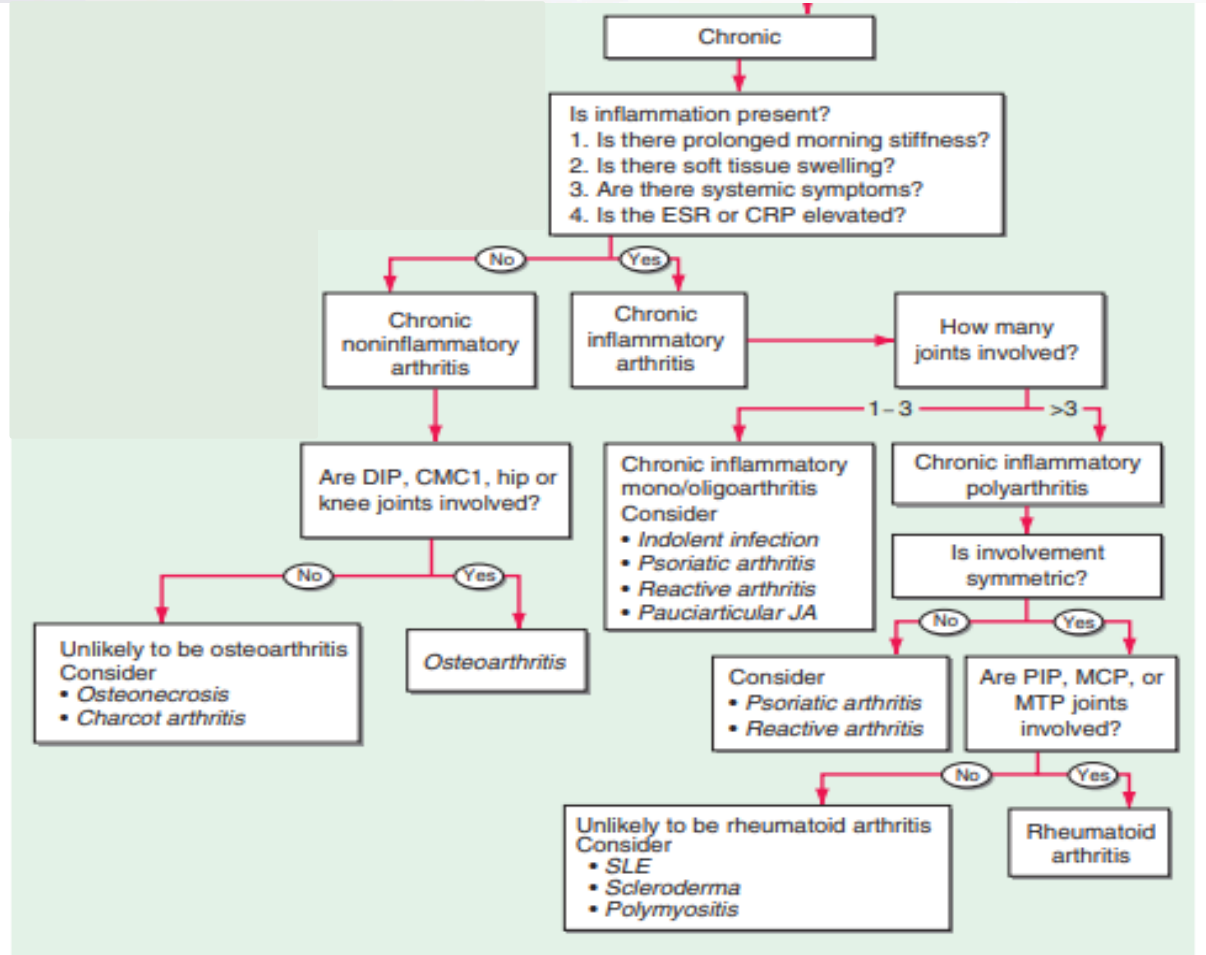

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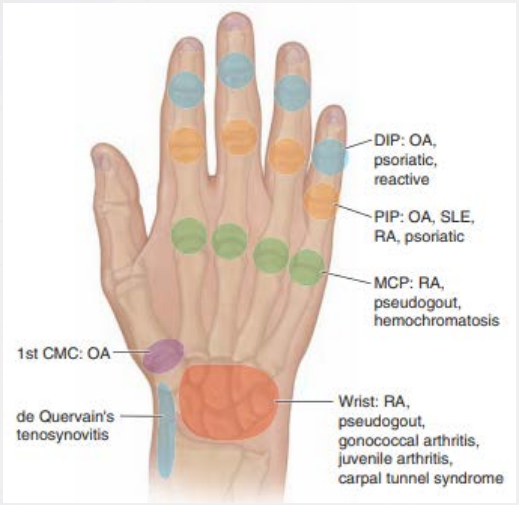

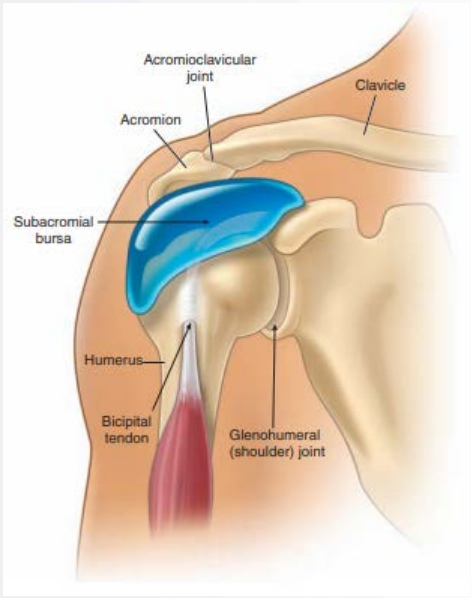

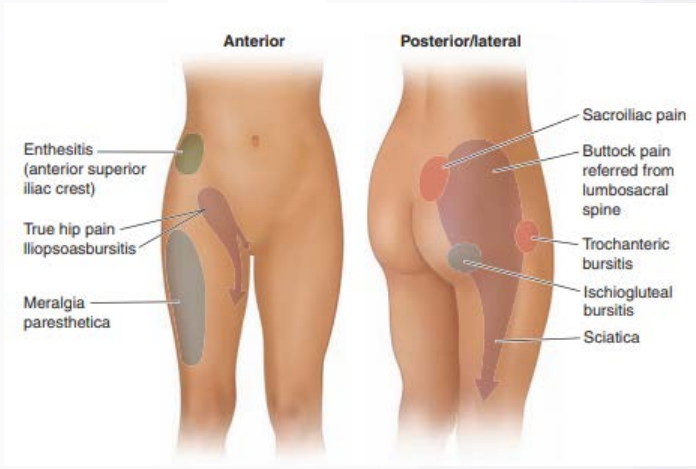

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What else can we learn from history?

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Demographics

- SLE
  - Most commonly affects women of child-bearing age
  - 9:1 female:male
  - More prevalent and more severe disease in AA and Hispanic patients

- Giant Cell Arteritis/PMR
  - Exceedingly rare before the age of 50
  - Much more common in Caucasians/northern Europe

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Demographics

- Gout
  - Exceedingly rare in pre-menopausal women
  - Renal insufficiency and obesity are predisposing co-morbidities
- Ankylosing Spondylitis/Reactive Arthritis
  - Most commonly affects Young (<40) Caucasian men
- Behcet's
  - Exceedingly rare in patients not of Middle Eastern or Japanese descent

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Exercise

- Depends on the type and severity of exercise
- Elevated CK
- Tendonitis/bursitis
- Glenohumeral OA (e.g. swimming, baseball)

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Travel

- Predisposition to infectious arthritis
  - Lyme (New England, Europe)
  - Dengue (Caribbean)
  - Chikungunya (SE Asia)

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Family history

- Many rheumatic diseases have a genetic component

- RA, OA, SLE, and spondyloarthritis all have increased incidence among first degree relatives

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Substance Abuse

- Alcohol abuse
  - Gout
  - Elevated CK
- Cocaine
  - Elevated CK
  - Vasculitis
  - Raynaud's
- Tobacco
  - RA
  - Burger's disease

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Drug-Induced MSK/Rheumatic Conditions

- Arthralgias
  - Vaccines, Beta blockers, cimetidine, quinidine, chronic acyclovir, quinolones, interferon, nicardipine, rifabutin, aromatase inhibitors, protease inhibitors
- Myalgia/Myopathy
  - Statins, fibrates, glucocorticoids, colchicine, quinolones, hydroxychloroquine, cocaine, alcohol, amiodarone, cyclosporine, paclitaxel, imatinib
- Drug-induced lupus
  - Hydralazine, procainamide, phenytoin, carbemazepine, methylopa, isoniazide, minocycline, lithium, TNF blockers, ACEI, chlorpromazine, lithium, quinidine, ticlodipine, HCTZ, PPI, diltiazem, terbinafine

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Drug-Induced MSK/Rheumatic Conditions

- Vasculitis
  - Allopurinol, cocaine (levimasole), amphetamines, HCTZ, PTU, penicillamine, montelukast, TNF blockers, micocycline, hydralazine, hepatitis B vaccine, trimethoprim/sulfamethoxazole
- Tendon rupture
  - Quinolones, Steroids, isotretinoin, statins, collagen injections
- Gout:
  - Diuretics, ASA, cyclosporine, alcohol, moonshine, ethambutol, fructose-containing soft drinks, cytotoxics
- Osteonecrosis
  - Steroids, alcohol, radiation, bisphosphonates

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Drug-Induced MSK/Rheumatic Conditions

- Osteopenia
  - Steroids, chronic heparin, phenytoin
- Systemic sclerosis
  - Vinyl chloride, bleomycine, barcitinib, pentazocine, organic solvents, carbidopa, tryptophan, rapeseed oil

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Laboratory and Radiological Analysis in Rheumatic Disease

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- I have nothing to disclose

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Acute Phase Reactants

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Acute Phase Reactants

- Defined as one whose plasma concentration increases or decreases by at least 25% during an inflammatory process
- Conditions that lead to changes in acute phase reactants:
  - Infection
  - Trauma/surgery
  - Infarction
  - Malignancy
  - Rheumatic disease

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Acute Phase Proteins

Plasma concentration increase

- C-reactive protein
- Fibrinogen
- Complement
- Ceruloplasmin
- Haptoglobin
- Serum amyloid A
- Ferritin

Plasma concentration decrease

- Albumin
- LDL
- HDL

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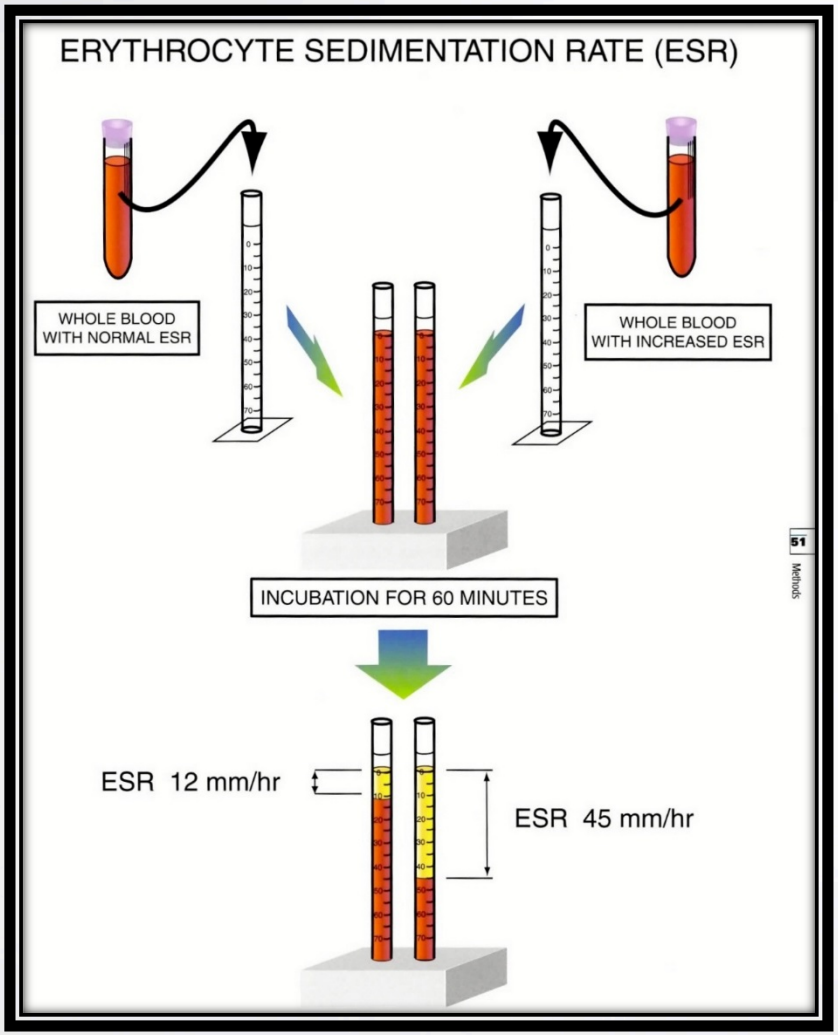

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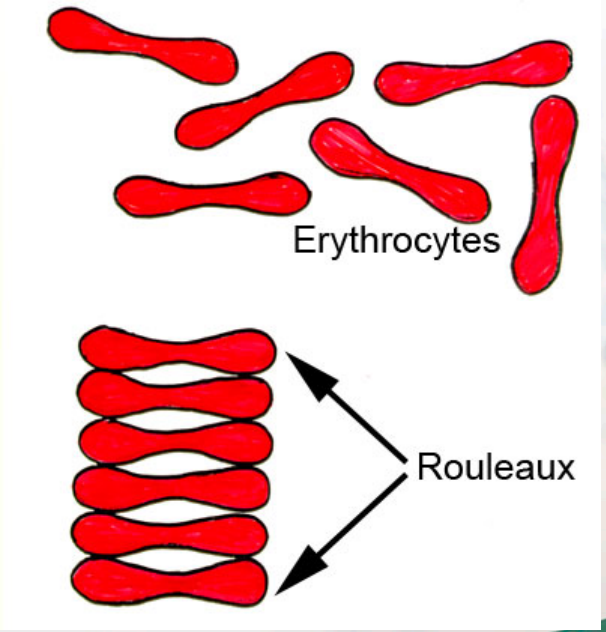
Erythrocyte Sedimentation Rate

- Red Blood Cells have a negative Charge
- It can be affected by numerous things. Essentially anything that alters the charge of plasma and promotes blood cells to stick together.

- Formation of the Rouleaux



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Factors That Can Affect the ESR

Increase

- Aging
- Female Sex
- Obesity
- Pregnancy
- Infection (bacterial)
- Connective tissue disease
- Malignancy (Lymphoma, MM)

ESR >100

Decrease

- Polycythemia (Hct>65%)
- Agammaglobulinemia
- Dysfibrinoginemia
- Increased viscosity syndromes such as CLL with extremely high white count
- Things that alter RBC morphology such as hereditary spherocytosis.

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C-Reactive Protein (CRP)

- Protein synthesized in the liver in response to IL-6
- Highly conserved over hundreds of millions of years of evoloution
- Biologic functions of CRP:
  - Recognition and clearance of damaged nuclear material
  - Activation of classical complement pathway
  - Interaction with Fc receptors of immunoglobulins

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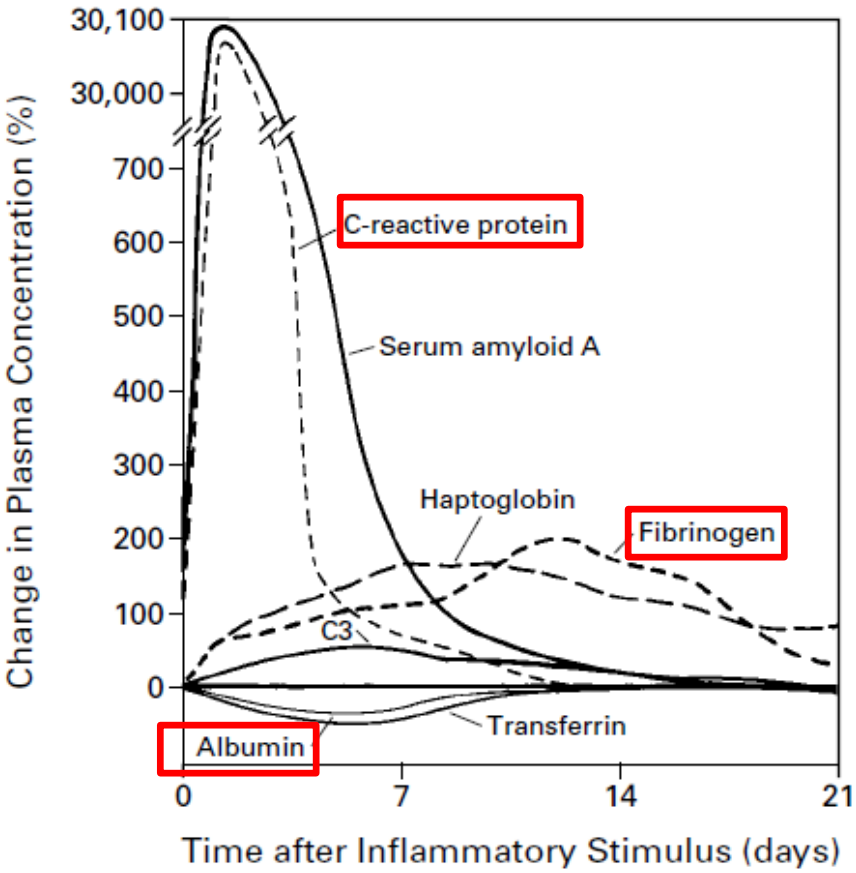

Figure 1. Characteristic Patterns of Change in Plasma Concentrations of Some Acute-Phase Proteins after a Moderate Inflammatory Stimulus.

Gabay and Kushner, N Engl J Med 1999; 340:448-454.

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C-Reactive Protein (CRP)

- Levels >8-10 mg/dL (>80-100mg/L)
  - Bacterial infection
  - Systemic vasculitis
  - Acute polyarticular crystal disease
  - Widely metastatic cancer

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Clinical Pearl

- Lupus patients have low levels of CRP

at baseline.

- Elevations of CRP out of proportion to ESR in a SLE patient suggest infection rather than SLE flare

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Age Calibration of ESR and CRP

- ESR Upper Limit of Normal

  Men= Age/2

  Women= (Age+10)/2

- CRP Upper Limit of Normal

  Men=Age/5(mg/L)

  Women=(Age+30)/5

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Tests Utilized for Rheumatoid Arthritis

Laboratory and Radiological Analysis in Rheumatic Disease

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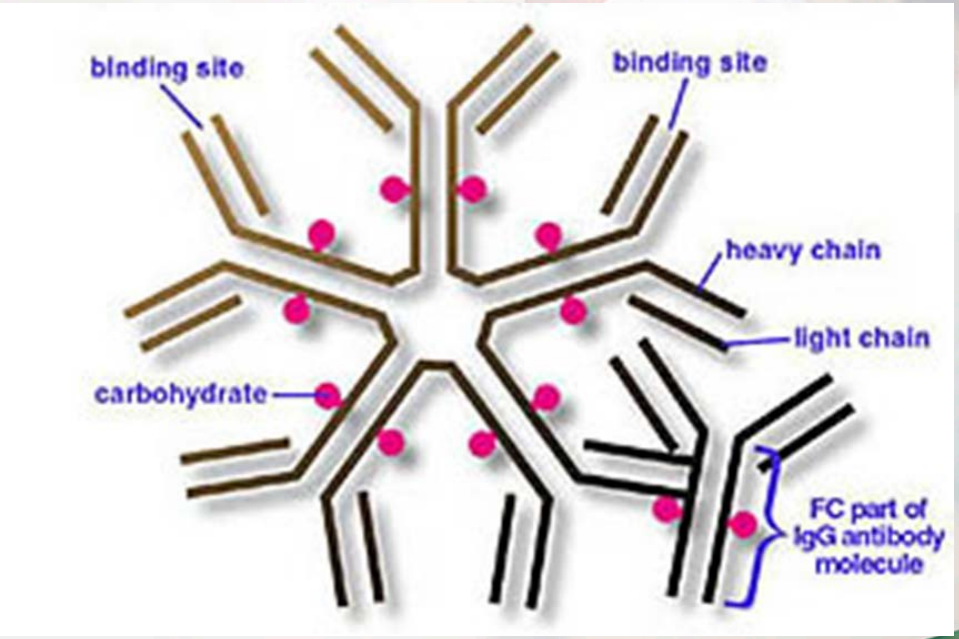
The Rheumatoid Factor

- Rheumatoid factor (RF)
  - autoantibodies directed against the Fc chains of IgG molecules.
- In clinical practice, laboratories tend to test only for IgM RF
- RF occurs with chronic immune stimulation



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What does a positive RF mean?

- Ch – Chronic disease
  - chronic bronchitis, fibrosing alveolitis, Silicosis, primary biliary cirrhosis, chronic autoimmune hepatitis
- R – RA
- O – Other Rheumatic disease
  - Sjögren's syndrome, MCTD, SLE, polyarticular-onset form of juvenile inflammatory arthritis (JIA)
- N – Neoplasms
- I – Infection
  - Bacterial endocarditis, HIV, hepatitis B and C, Tuberculosis, Syphilis
- C – Cryoglobulinemia
- 5% to 6% among the elderly in the normal population.

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Anti-CCP/Anti Citrullinated Protein Antibodies(ACPA)

- Anti-CCP has similar sensitivity to RF (67%), but increased specificity (95%)
- Prognostic indicator for erosive, severe RA
- RF and CCP can occur years before the onset of clinical disease

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Deconstructing the ANA

Laboratory and Radiological Analysis in Rheumatic Disease

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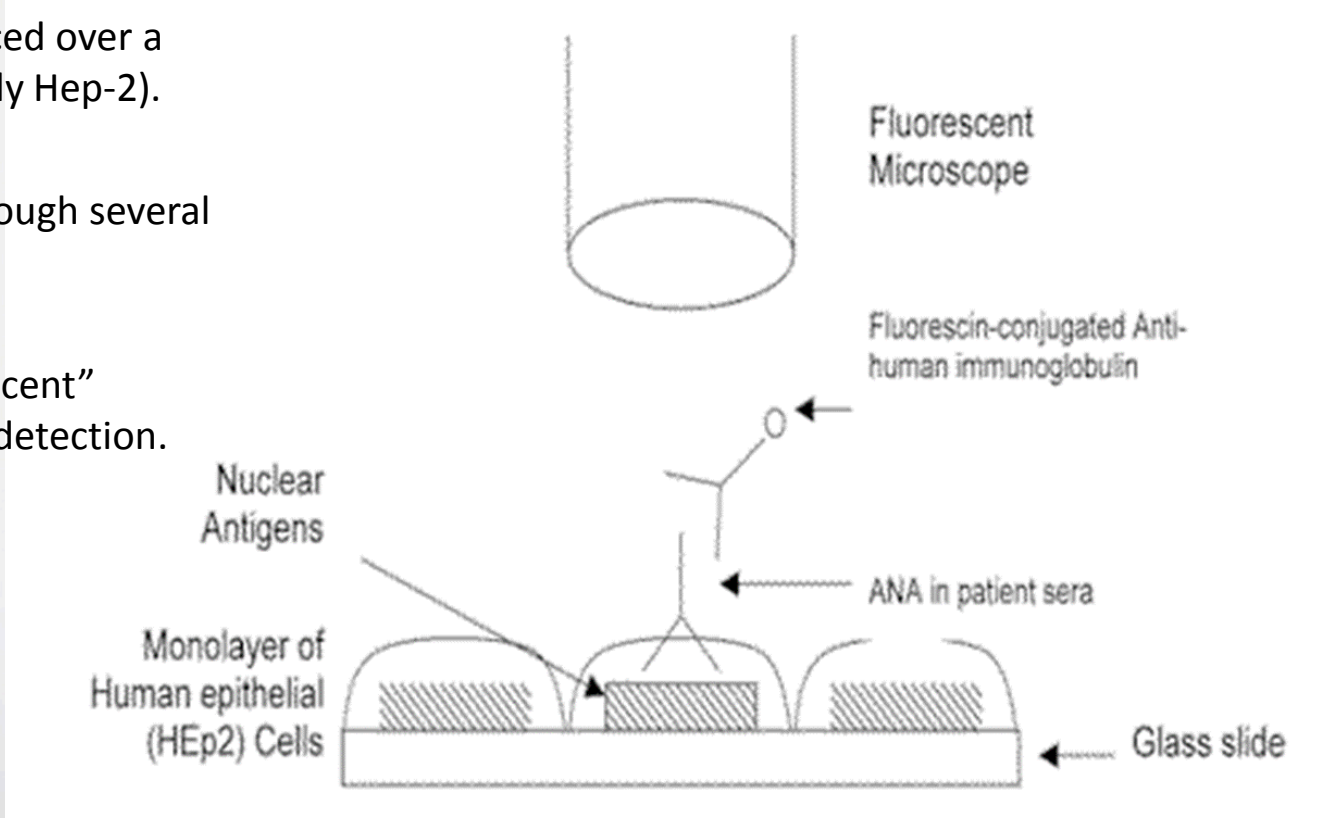
ANA Indirect-Immunofluorescence

Patient Serum is placed over a plate of Cells(Typically Hep-2).

The **serum** is put through several dilutions.

A secondary “fluorescent” antibody is used for detection.



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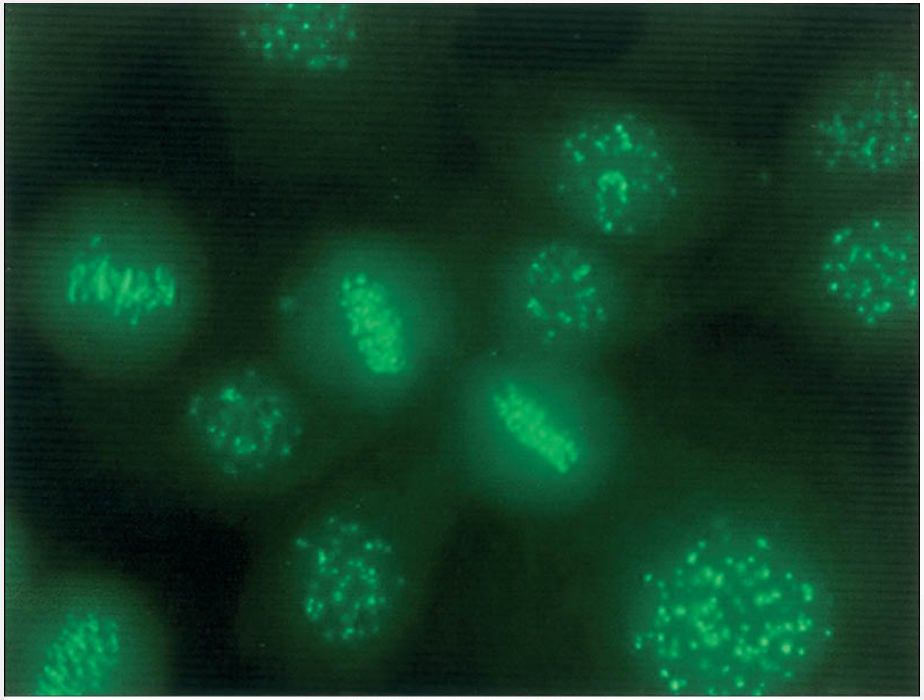
The ANA



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ANA Indirect-Immunofluorescence

- Results expressed as a titer
  - Low titer 1:40 - Occurs in 20-30% of healthy individuals
  - Low titer 1:80 – Occurs in 10-15% of healthy individuals
  - Clinically significant titer ≥ 1: 160 – Occurs in 5% of healthy individuals
- There is no evidence that variations in ANA titer correlate with disease activity
- Results expressed as a pattern by a microscopist

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ANA Patterns

PATTERN	NUCLEAR ANTIGEN	DISEASE
Homogeneous	Histone/DNA	SLE, Drug induced SLE
Speckled	Saline-ENA's	MCTD, SLE, Sjogrens syndrome, poly/dermatomyositis, infection and neoplasia
Nucleolar	RNA associated antigens	Scleroderma
Peripheral	DNA	SLE
Centromere	Centromere	Limited Scleroderma

Nuclear dense fine speckled pattern almost exclusively found in normal patients

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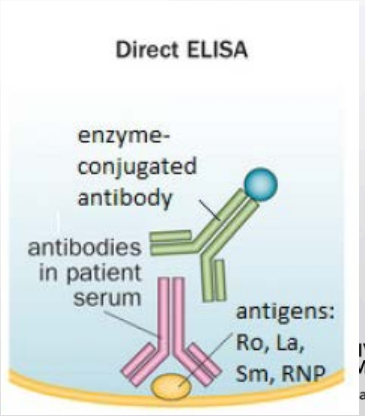
The Small Lab(DIRECT) approach

- The first screening step is a minimally diluted IFA. If positive then an ELISA.
- ELISA's are generally limited to 8 to 10 autoantigens which are then processed on the tested serum.
  - i.e. U1 RNP, Sm, dsDNA, SSa(ro), SSb(la), Scl-70, Centromere, Histone, Jo-1, etc



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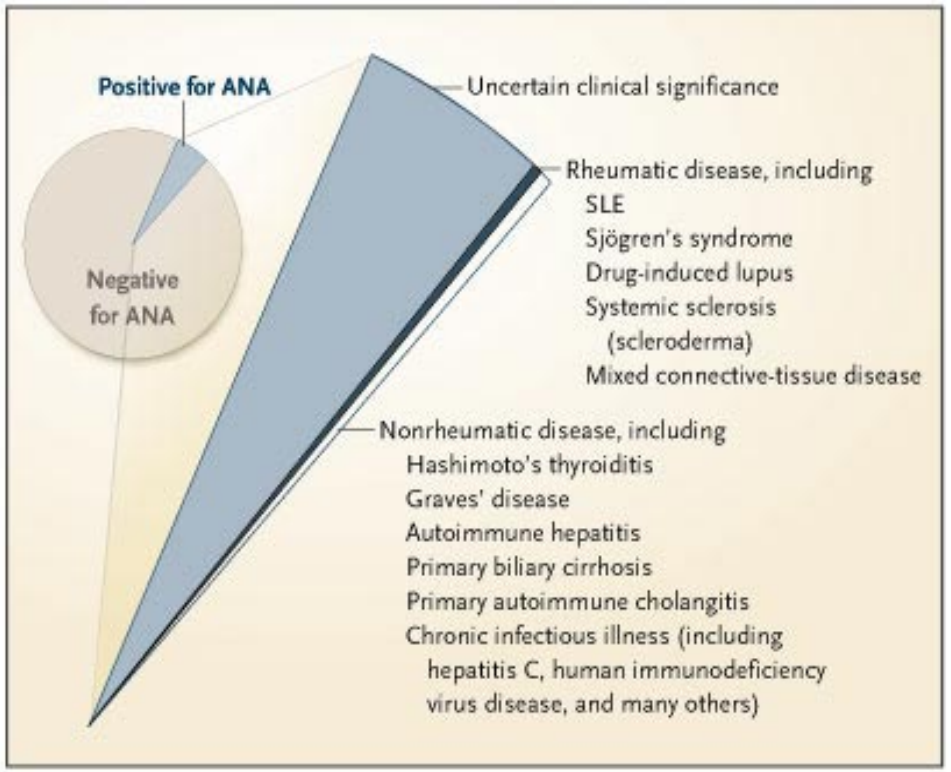
Differential Diagnosis of Positive ANA



Shmerling, R. H. N Engl J Med 2003;349:1499-1500

The NEW ENGLAND JOURNAL of MEDICINE

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Extracted Nuclear Antigens

- Anti-Ro/SSa – Found in both SLE and Sjogren Syndrome
- Anti-La/SSb – Found in both SLE and Sjogren Syndrome
- Anti-Smith – Very Specific for SLE
- Anti RNP – Found in SLE but can be the defining molecule of MCTD
- dsDNA – Highly specific for Systemic Lupus.
- Anti-Histone – Drug induced Lupus

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ANA

- The clinical value of an ANA is tremendously enhanced by ordering it when there is a reasonable pretest probability of CTD.
- Negative ANA indicates SLE is highly unlikely
  - Negative predictive value >99%

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These labs only have meaning in the proper context.

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Radiographs

Laboratory and Radiological Analysis in Rheumatic Disease

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Questions we ask when utilizing our radiology colleagues

- Is there damage present in a joint?
  - Consistent with Inflammation
  - Consistent with Mechanical wear and tear
  - Trauma?
- Are there signs of chronic inflammation?
- What is the pattern of joints that are involved?

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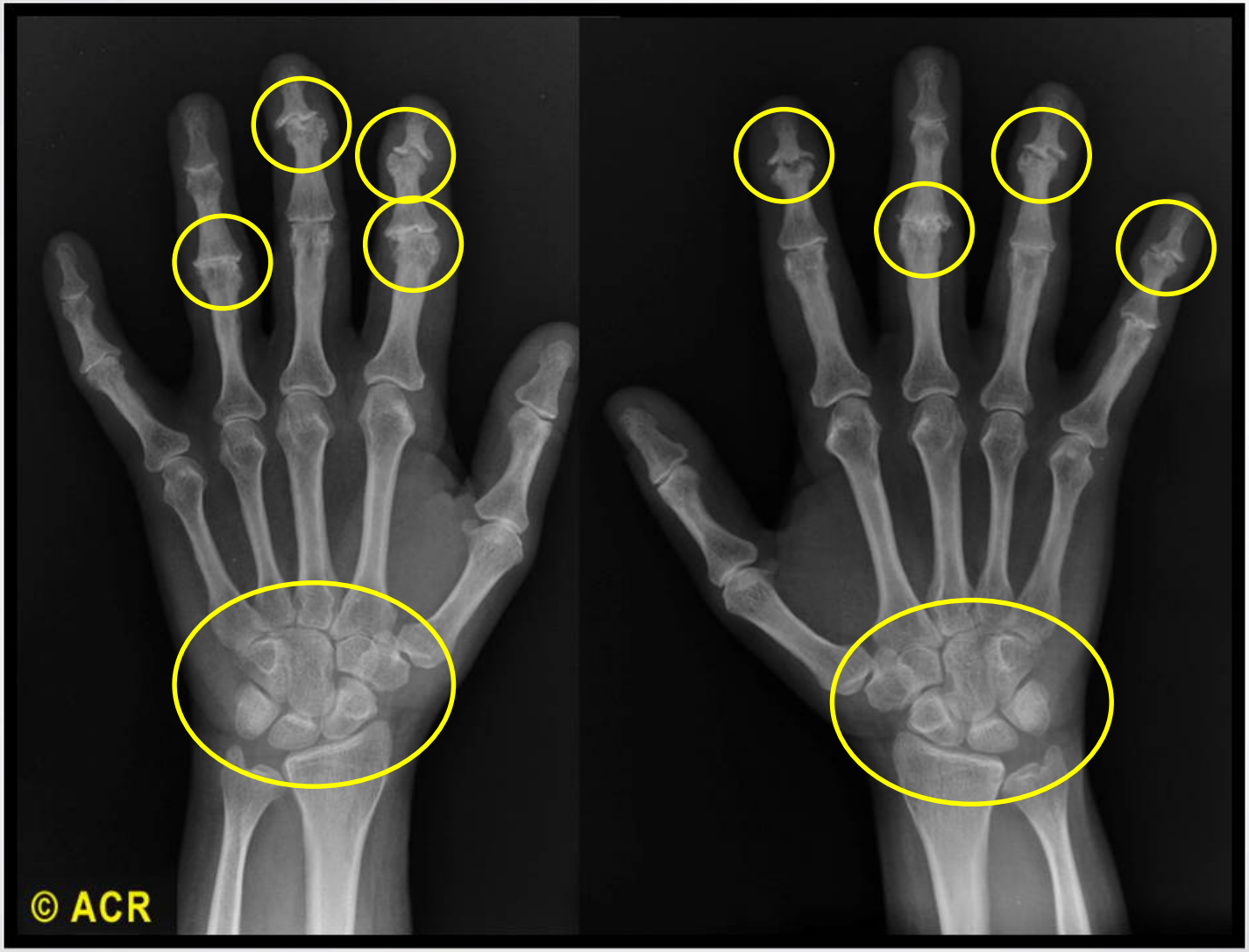

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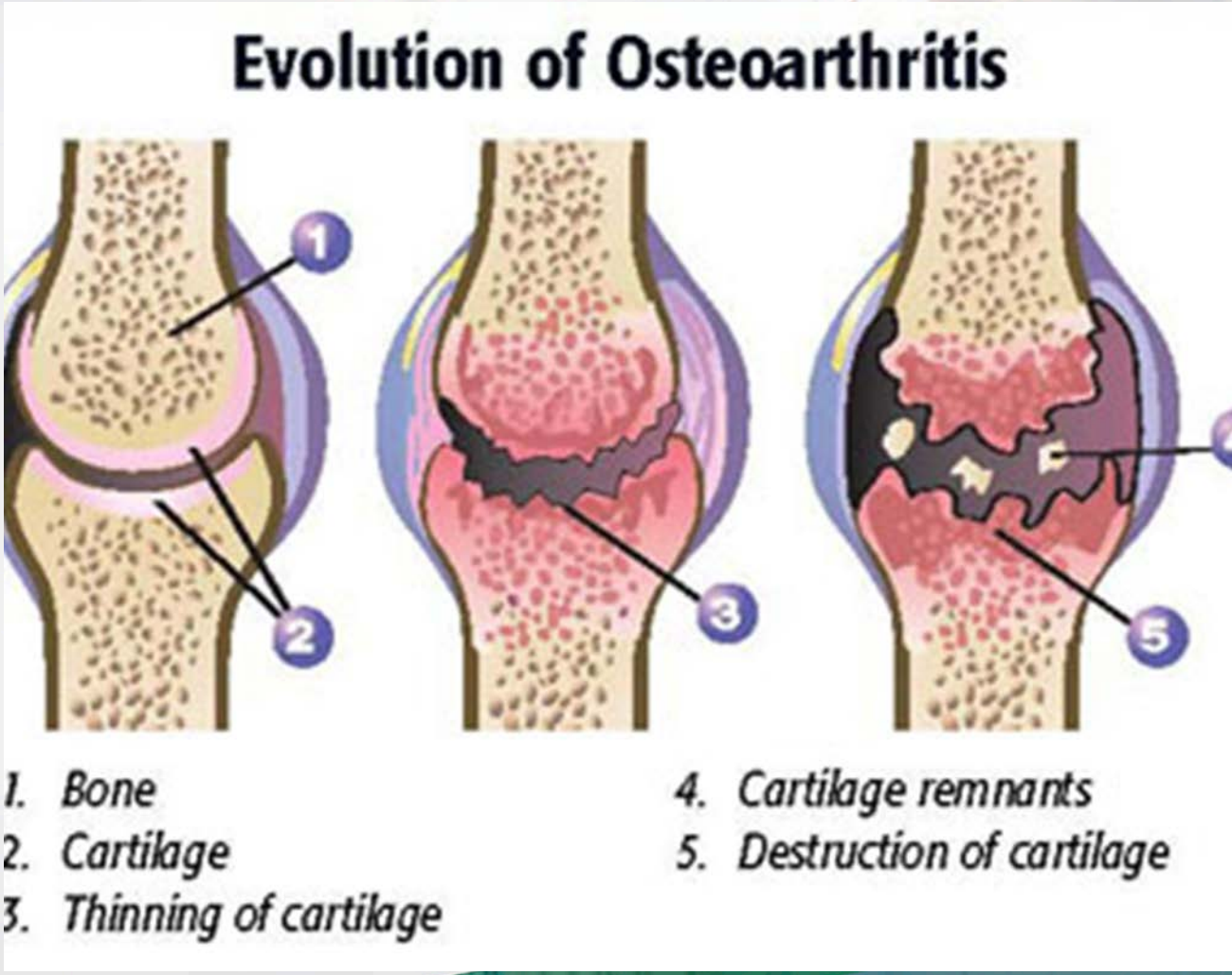
Erosive Osteoarthritis



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Rheumatoid Arthritis

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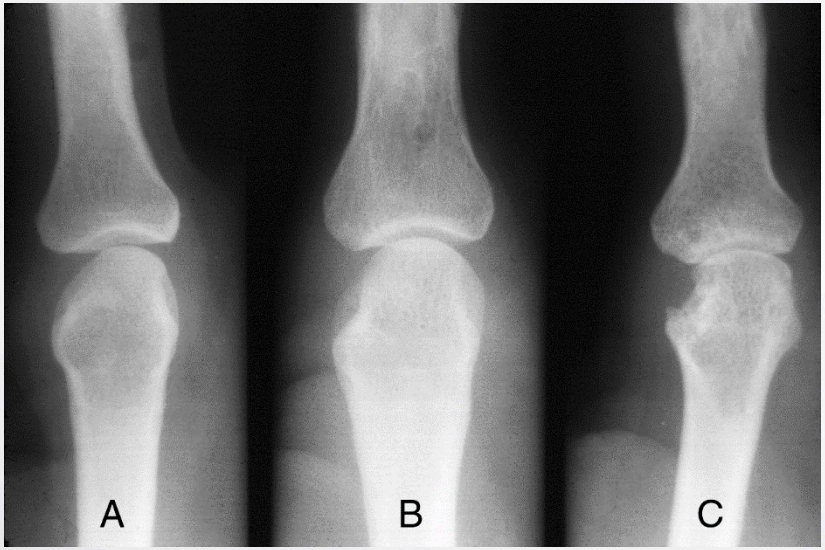
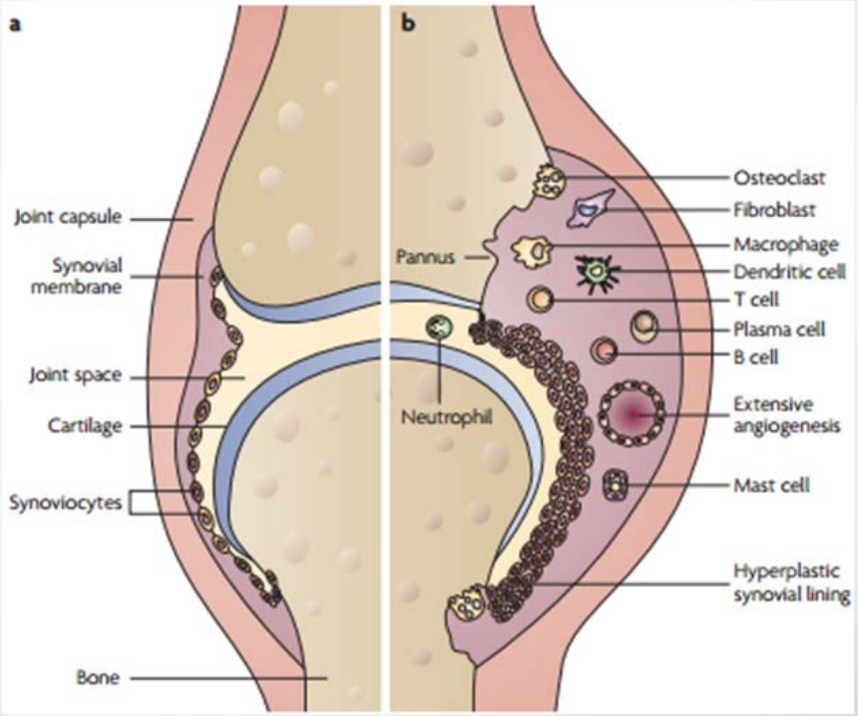
The Marginal Erosion: Found in Inflammatory Disorders





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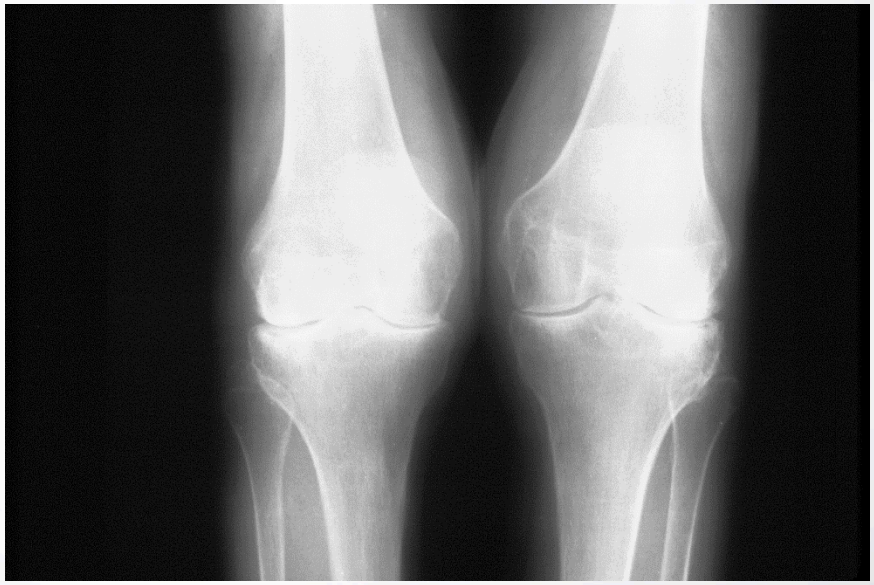
Osteoarthritis vs. Rheumatoid Arthritis in The Knee



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The Destructive Potential of Gout

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Objectives

- An overview of approaching a patient with musculoskeletal complaints
- To understand the utility and limitation of initial laboratory tests in rheumatic complaints
- To recognize the key radiographic findings in patients with suspected rheumatic disease.

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Thank You

- Questions?

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Antibody Tables for Reference

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The Scleroderma Antibodies

Antibody	Skin Distribution	PAH	Pulmonary Fibrosis	Other	5 Year Survival
Anti-Centromere Antibody	Limited Skin	Yes	No	Digital Ulcers	86% 5yr Survival
Th/To	Limited Skin	Yes	Yes		65% 5yr Survival
Scl-70	Diffuse Skin	No	Yes	Cardiac/Digital Ulcers	80% 5 yr Survival
RNA Polymerase III	Diffuse Skin(bad)	No	No	Renal Crisis	90% 5 yr Survival
Pm/Scl	Diffuse Skin	Yes	No	Muscle	92% 5yr Survival
U1RNP	Limited Skin	Yes	No	Muscles/Joints	95% 5y Survival
U3RNP	Diffuse Skin	Yes	Yes	Heart/Kidney	77% 5yr Survival

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The Myositis Antiodies

Antibody	Specificity	Frequency	Clinical
Jo-1	Histidyl tRNA	15-30%	PM/DM, ILD, RP, Mechanic
PL-7	Theonyl tRNA	5-10%	
PL-EJ	Glycyl tRNA	5-10%	
PL-12, OJ, KS, YRS, MJ, PMS1		<1-5%	
SRP	Signal Rec Particle	5-10%	Necrotizing Myopathy
Mi-2	218/240kDA	5-10%	Dermatomyositis
P155(p140)	Transcription intermediary factor	20%	Dermatomyositis especially cancer associated
U1RNP	U1 small nuclear RNP	10%	Overlap
Ku	DNA-PK	20-30%	Pm-SSc in japanese
PM-Scl	Nucleolar proteins	8-10%	Pm-SSc caucasians

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Nuclear

Chromatin-Associated Antigens

	dsDNA	Rim, homogeneous	RIA, ELISA, CIF, Farr	SLE
DNA	ssDNA, dsDNA	Rim, homogeneous	RIA, ELISA, CIF	SLE
	ssDNA	Undetectable	ELISA	SLE, DIL, RA
	(Nucleosome structure)		IB, RIA, ELISA	
Histone	H1, H2A/B, H3, H4	Homogeneous, rim	SLE, DIL, RA, PBC, SSc	
	H3	Large speckles		SLE, UCTD
Kinetochore (centromere)	CENP-A, -B, -C, and/or -D (mitotic spindle apparatus)	Speckles*	IF, ELISA	SSc, SLE, SS
Ku	Regulatory subunit (Ku70/80) of DNA-dependent protein kinase (DNA break repair)	Diffuse-speckled nuclear or nucleolar*	ID, IPP, IB	SLE, PM/SSc overlap
PCNA/Ga/LE-4	PCNA (DNA scaffold)	Nuclear/nucleolar speckles*	ELISA, ID, IB, IPP	SLE

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Spliceosome Components	(Splicing of pre-mRNA)	Speckled	ID, ELISA, IB, IPP	
<u>Sm</u>	Sm core B′/B, D, E, F, and G			SLE
	U1 snRNP 70K, A, and C			SLE, MCTD
	U2 snRNP			SLE, MCTD, overlap
<u>RNP, nRNP</u>	U4/U6 snRNP			SS, SSc
	U5 snRNP			SLE, MCTD
	U7 snRNP			SLE
	U11/U12 snRNP			SSc
	SR		ELISA, IB, IPP	SLE

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Other Ribonucleoproteins

Ro/SS-A	Ro (ribosomal RNA processing)	Speckled or negative†	ID, ELISA, IB, IPP	SS, SCLE, NLE, SLE, PBC, SSc
La/SS-B/Ha	La (ribosomal RNA processing)	Speckled	ID, ELISA, IB, IPP	SS, SCLE, NLE, SLE
RNA helicase A	RNA helicase A	?	IP	SLE
TIA-1, TIAR	TIA-1, TIAR	?	IB, IPP	SLE, SSc
Mi-2	NuRD complex (transcription regulation)	Homogeneous	ID, IPP	DM
p80-coilin	Coiled bodies	Speckled		SS
MA-I	Mitotic apparatus	Speckled*		SS, SSc

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Nucleolar

	(RNA transcription)	Punctate	IPP, IB	
RNA polymerases (RNAP)	RNAP I	Nucleolar		SSc
	RNAP II	Nuclear/nucleolar[‡]		SSc, SLE, overlap
	RNAP III	Nuclear/nucleolar[‡]		SSc
Ribosomal RNP	Ribosomal RNPs (protein translation)	Nucleolar, cytoplasmic	ID, IB, IPP, ELISA	SLE
Topoisomerase I (Scl-70)	Topoisomerase I (DNA gyrase)	Diffuse, grainy, nuclear or nucleolar	ID, IB, ELISA	SSc
Topoisomerase II	Topoisomerase II (DNA gyrase)	?	ELISA	SSc
U3 snoRNP (fibrillarin)	U3 snoRNP (ribosomal RNA processing)	Clumpy	IB, IPP	SSc
Th snoRNP (RNase MRP)	RNase MRP (mitochondrial RNA processing)	Diffuse with sparse nuclear	IPP	SSc
NOR 90 (hUBF)	hUBF (ribosomal RNA transcription)	10-20 discrete spots or nuclear*	IB, IPP	SSc
PM-Scl (PM-1)	Exosome (RNA processing/degradation)	Homogeneous nuclear or nucleolar	ID, IPP, IB	PM, DM, SSc, overlap
Nucleobindin-2 (Wa)	Nucleobindin-2	?	ELISA	SSc, SLE, PM/DM

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Cytoplasmic				
tRNA Synthetases	(Translational machinery)			
Jo-1	$tRNA^{His}$	Diffuse	ID, IPP, IB, ELISA, AAI	PM, DM
PL-7	$tRNA^{Thr}$	Diffuse	ID, IPP, IB, ELISA, AAI	PM, DM
PL-12	$tRNA^{Ala}$	Diffuse	ID, IPP, IB, ELISA, AAI	PM, DM
EJ	$tRNA^{Gly}$	Diffuse	ID, IPP, IB, ELISA, AAI	PM, DM
OJ	$tRNA^{Ile}$	Diffuse	ID, IPP, IB, ELISA, AAI	PM, DM
KS	$tRNA^{Asn}$	Diffuse	ID, IPP, IB, ELISA, AAI	UCTD, ?
Mas	$tRNA^{[Ser]Sec}$	?	IPP	Myositis
Fodrin	α- and/or β-Fodrin (cytoskeletal component)	Diffuse subplasmalemmal	ELISA	SS
Signal recognition particle	Signal recognition particle (transmembrane protein handling)	?	IPP, IB	PM
KJ	Translational apparatus	?	ID, IB	Myositis
		?	IPP	Myositis
Elongation factor 1α (Fer)	Elongation factor 1α (protein translation)			
CADM-140	140 kD	?	IPP, IB	Amyopathic DM
p140	Nuclear matrix protein NXP-2	?	IPP	Juvenile DM
		?	IPP	DM
SUMO-1	Small ubiquitin-like modifier 1 activating enzyme α- and β-subunits			
p155	?	?	IPP	DM and cancer-associated DM

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Osteoarthritis:
Causes, Symptoms, and Medical Treatment

Laura B. Hughes MD, MSPH
Professor of Medicine
Division of Clinical Immunology and Rheumatology

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- Disclosure
  - none

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Learning Objectives:

- Understand the epidemiology of osteoarthritis (OA)
- Understand the complexity in the pathogenesis of OA
- Recognize the clinical and radiographic features and joint distribution in patients with OA
- Implement a treatment plan for patients with OA

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OA – Background

- Most common form of arthritis
  - *Radiographic* OA in 70% of adults ≥65 years of age
  - 1/3-2/3 of those suffer with *symptomatic* OA
- Prevalence of OA is expected to increase
  - ageing of the population
  - increased prevalence of obesity - especially at a younger age (Flugsrud et al, Arthritis Rheum, 2006)
- Bulk of OA disability due to hip or knee disease
  - *leading cause of disability in the US (22.7 million people with arthritis related activity limitations)*

(Cisternas, Arthritis Care Res, 2016)

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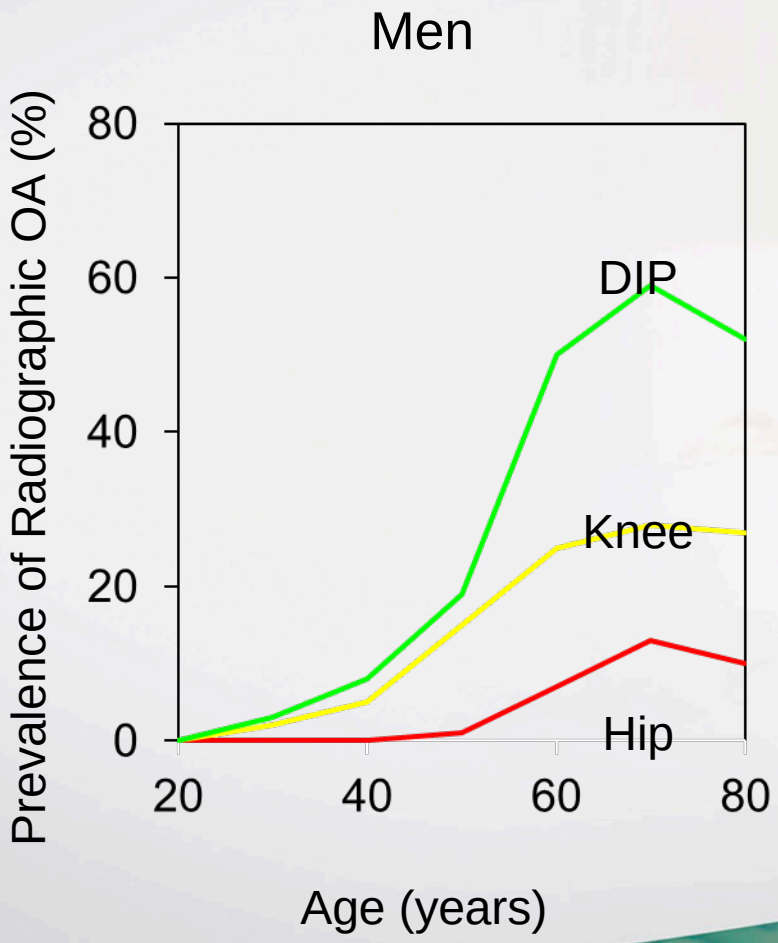
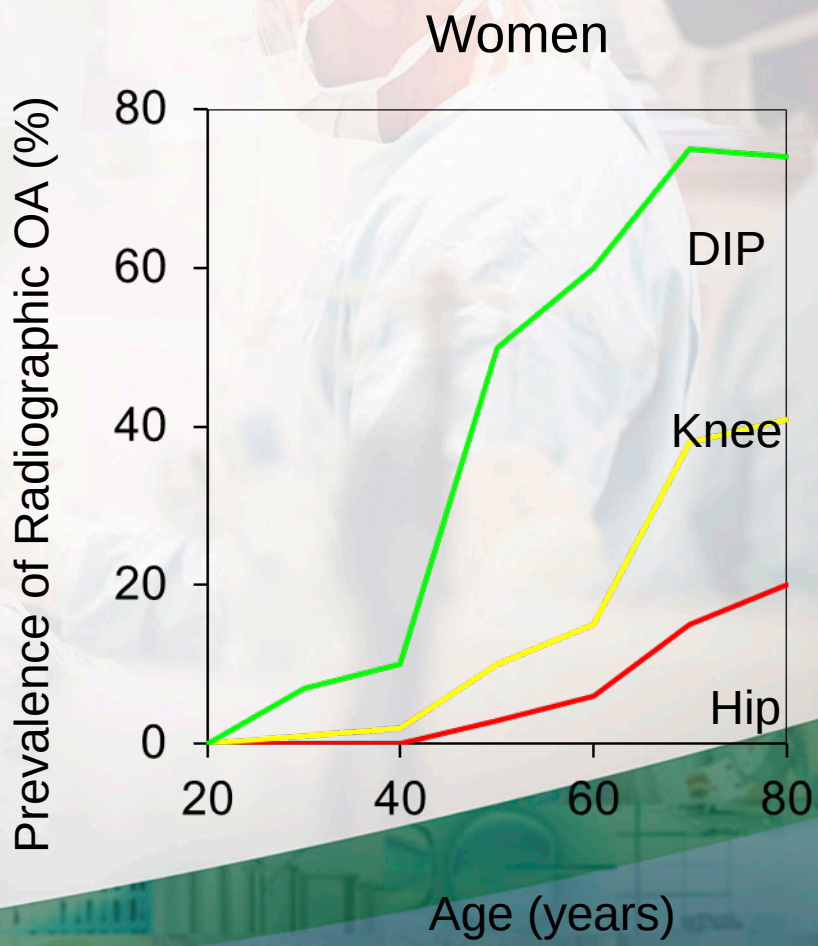
OA
Age-Related Prevalence





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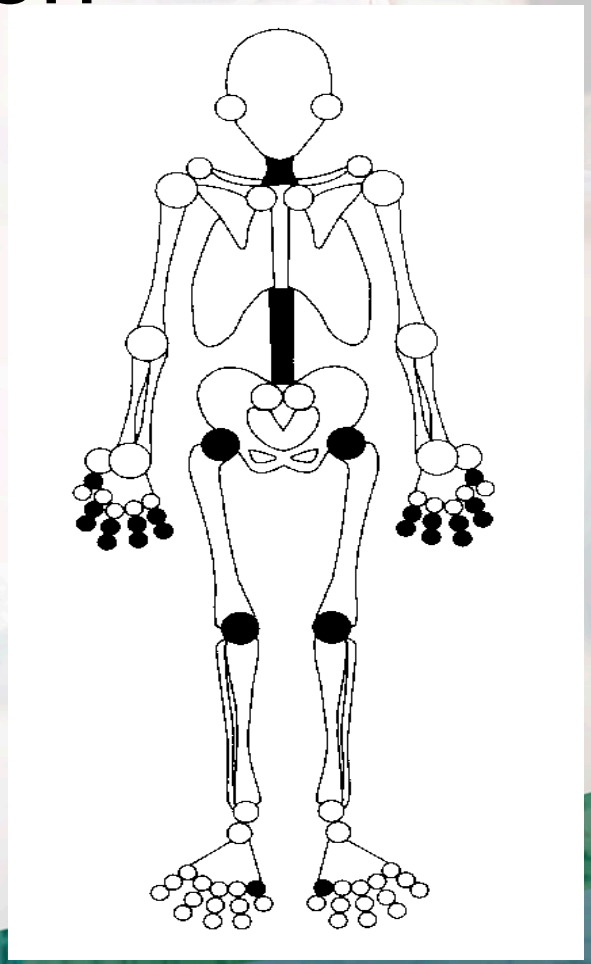
OA Distribution

- Primary OA - variable number of joints in characteristic locations
  - Knee, hip, thumb, fingers, great toe, cervical and lumbar spine
- Seconday OA - previous joint trauma or damage increases risk for OA



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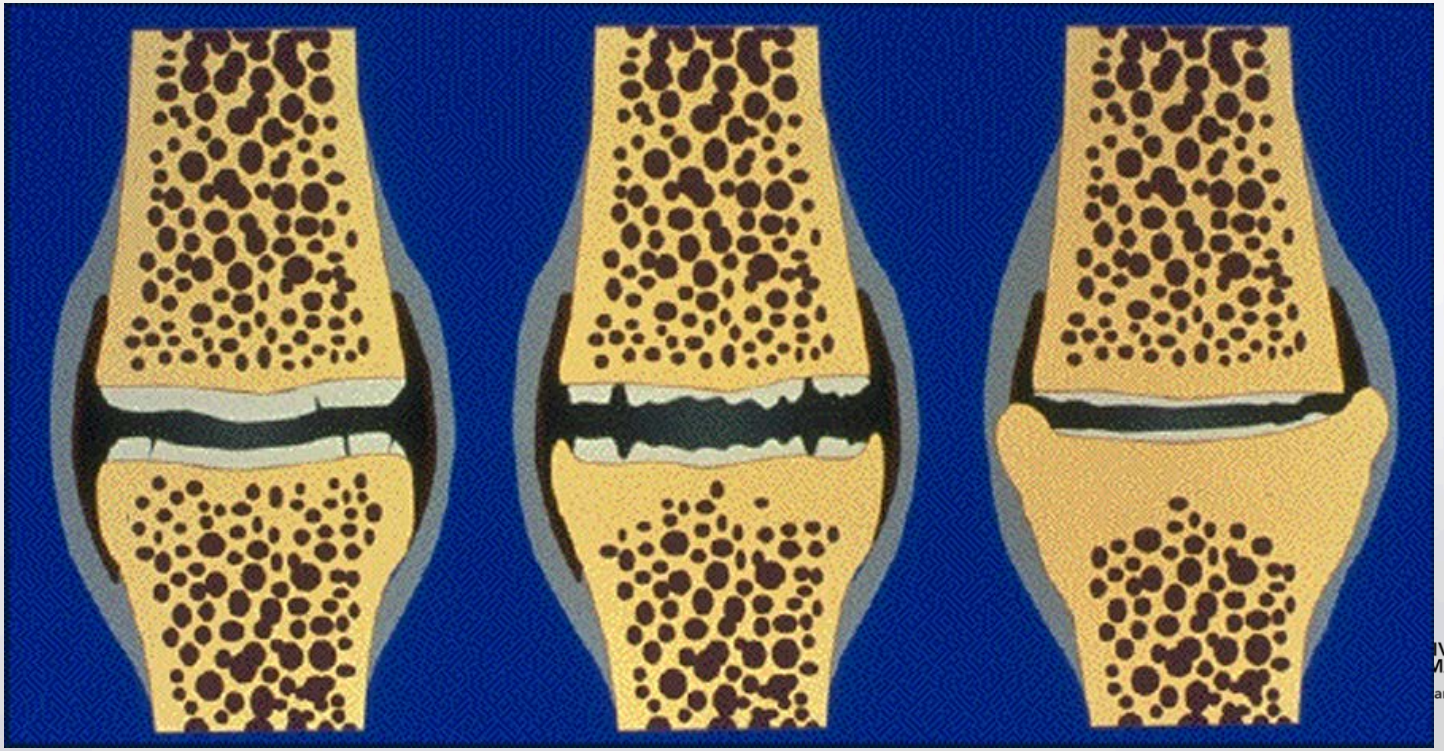
OA-Pathogenesis

Old Paradigm

- Slow cartilage loss, bone thickening
- Non-inflammatory
- Progressive



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OA-Pathogenesis
New Paradigm

- OA is joint failure (akin to heart, kidney failure) which can involve all joint structures
  - Cartilage
  - Bone
  - Menisci
  - Synovium
  - Ligaments
  - Muscles

Felson et al, N Engl J Med 2006
Hunter et al, BMJ, 2006

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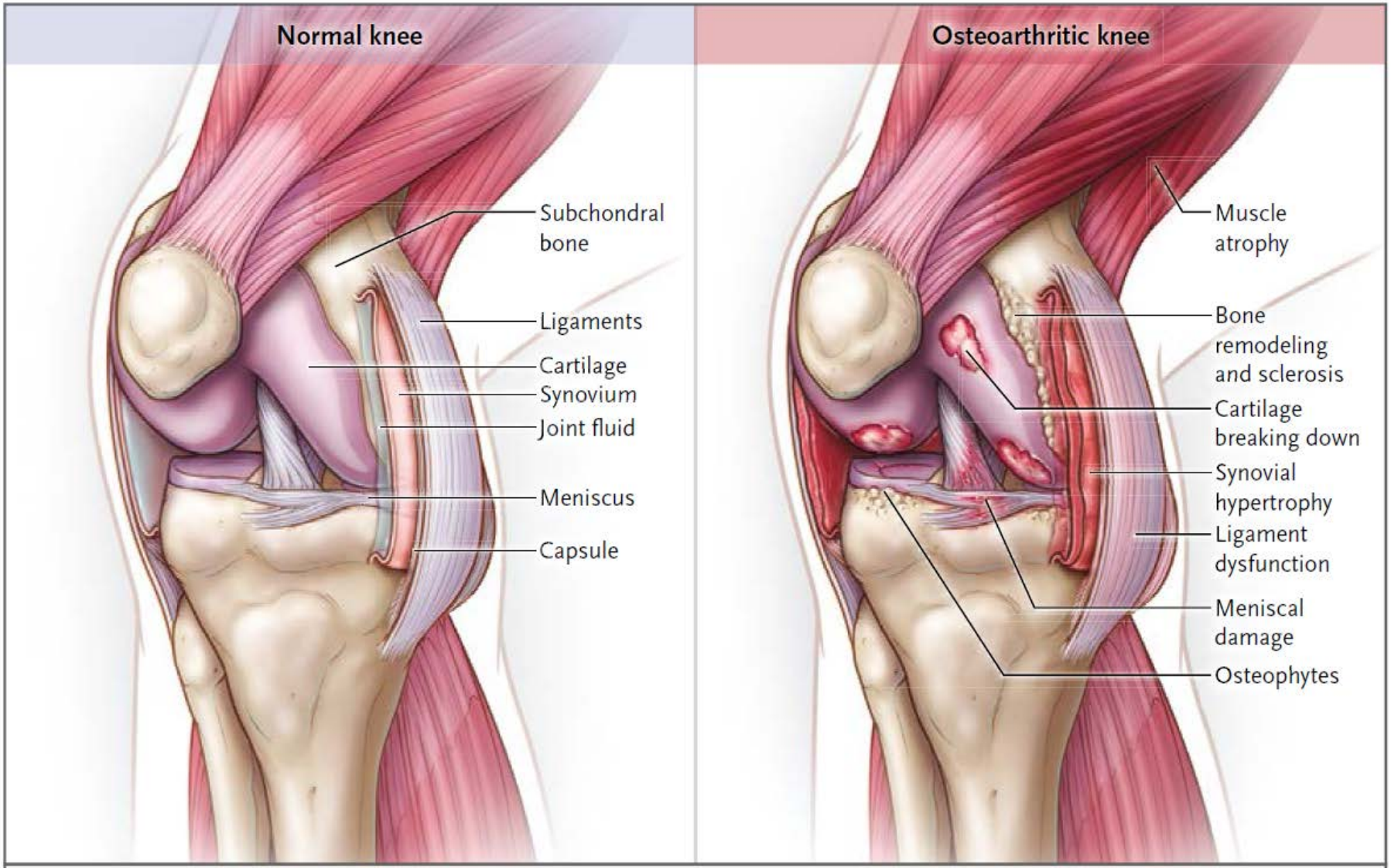

Figure 1. Schematic of the Knee Joint, Showing the Synovial Joint Tissues Affected in Osteoarthritis.

This schematic shows the way in which each structural part of the knee is affected by osteoarthritis, an observation that is consistent with the theory that osteoarthritis is a disease of the entire synovial joint.

Hunter, NEJM, 2015

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OA Pathogenesis-Cartilage

- Old paradigm - cartilage degenerates and is unable to repair extracellular matrix
- Recent studies -
  - Chondocytes in OA cartilage synthesize high levels of extracellular matrix.
- New Paradigm – OA is characterized by a process where chondrocytes are stimulated to remove and repair damaged matrix, catabolic events > anabolic events.

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OA Pathogenesis
Bone

- Old paradigm – Osteophytes form as a response to cartilage loss.
- Recent studies –
  - Subchondral bone remodeling and attrition occur in early in OA and are associated with progression of OA
  - New understanding of master regulatory pathways in bone and joint metabolism
  - MRI findings of bone marrow edema associated with pain and progression in OA

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OA Pathogenesis
Meniscal Lesions

- Meniscal lesions and meniscectomy are risk factors or knee OA
- Meniscal and ligament lesions are a common component of primary knee OA (Hunter, Arthritis Rheum 2004)
- Meniscal lesions often seen in early-stages of knee OA (Hunter, J Rheumatol, 2007)

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OA Pathogenesis-Synovium

- **Old paradigm** – OA is non-inflammatory lesion
- **New studies** –
  - Synovitis - 40%-50% of subjects with knee and hip OA, even in early disease (Haywood, Arthritis Rheum 2003, Pearle, Osteoarthritis Cartilage, 2006)
  - **Synovitis is associated with symptomatic knee OA** (Torres, Osteoarthritis Cartilage, 2006).

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OA Pathogenesis - Muscle and Ligament

- Quadriceps muscle weakness has been associated with knee OA, esp in woman (Baker, Arthritis Rheum, 2004)
- Muscle weakness - predates OA. Weakness in knee extensors increased risk of developing symptomatic knee OA (OR 1.65) (Oiestad, Arthritis Care Res, 2015)
- Strength training can improve pain, physical function, and quality of life (Baker J Rheumatol, 2001, Amin S Arthritis Rheum, 2009)

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OA - Progression

- Old paradigm – OA is slowly progressive
  - Inter and intra-individual heterogeneity of OA course
  - *Many subjects with OA don't progress*
    - Group mean rate of OA progression is affected by a few "fast progresors" (Dieppe, Osteoarthritis Cartilage 2000)
    - Small proportion OA patients ultimately require joint replacement

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OA - Summary

- Multi-factorial process with a common endpoint - joint failure
  - diverse triggers and outcomes
  - various systemic and local factors
  - site of insult may be any tissue of the joint
  - periods of equilibrium and successful compensation (joint remodeling keeps pace with tissue loss)
  - periods of decompensation (severity/chronicity outweighs repair response)

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OA: Risk Factors

- Systemic
  - **Increased age**
  - **Female sex** - estrogen loss assoc. with increased prevalence of OA *(Richette, Joint Bone Spine 2003)*
  - **Genetics** –30%-70% disease risk:
    - Depending on site of OA
    - No single gene is responsible for OA but many genes have shown small effects
  - Obesity – obese fatty tissue produces inflammatory proteins (adipokines)
  - Smoking – decreases risk for knee OA (Kong, Osteoarthr Cartil, 2017)
  - Increased BMD – associated with OA of hip, knee, hand and spine

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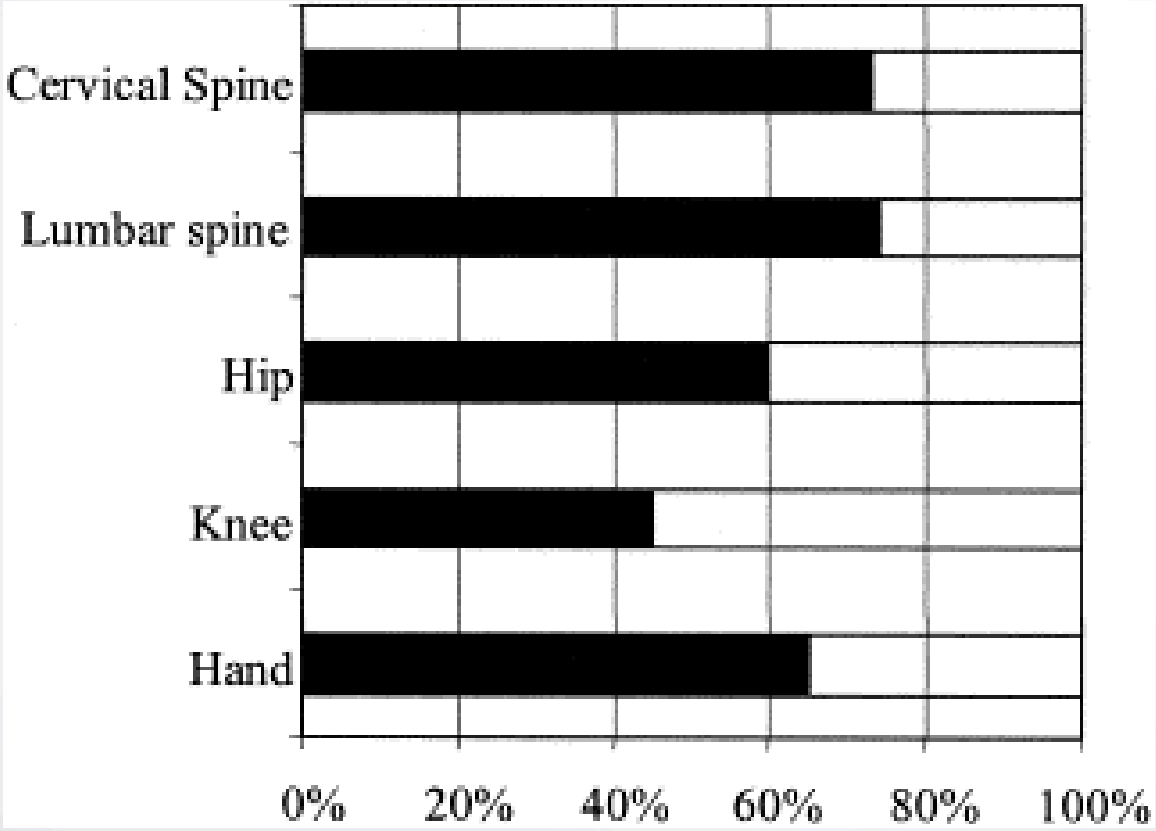
OA – Genetic Risk by Site



Spector,T Osteoarthritis Cartilage, Suppl A12, 2004

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OA-Risk Factors

- Local (mechanical) factors
  - Increased BMI – increases risk for knee > hip > hand OA (knee: OR 1.98 if overweight, OR 2.66 if obese) (Silverwood, Osteoarthr Carti, 2015)
  - Malalignment –risk factor for knee and hip OA
  - Selected Activities – soccer players, weight lifters (knee OA), miners, carpenters (knee OA), assembly workers (hand OA)
  - Trauma/damage
  - Muscle weakness/ligament laxity

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Knee OA - Alignment

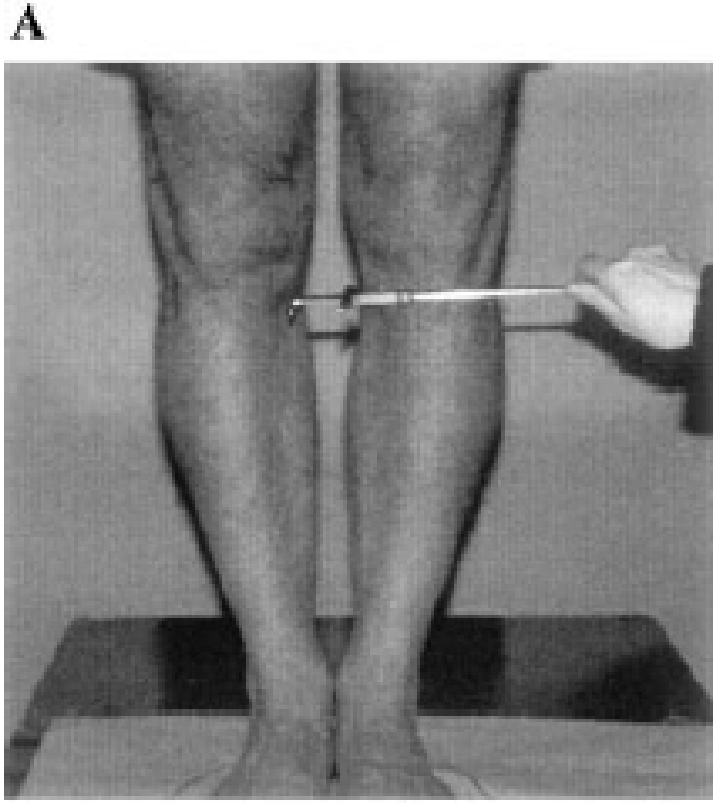
- Varus malalignment (bow legs) - 4-fold increased risk of medial compartment OA

- Valgus malalignment (knock knees) – 4-fold increased risk of lateral compartment OA

Hinman,Arthrits & Rheum, 2006

- *Leg length discrepancy > 1cm – 2 fold increase risk of knee OA in shorter leg*

Harvey, Ann Intern Med, 2010



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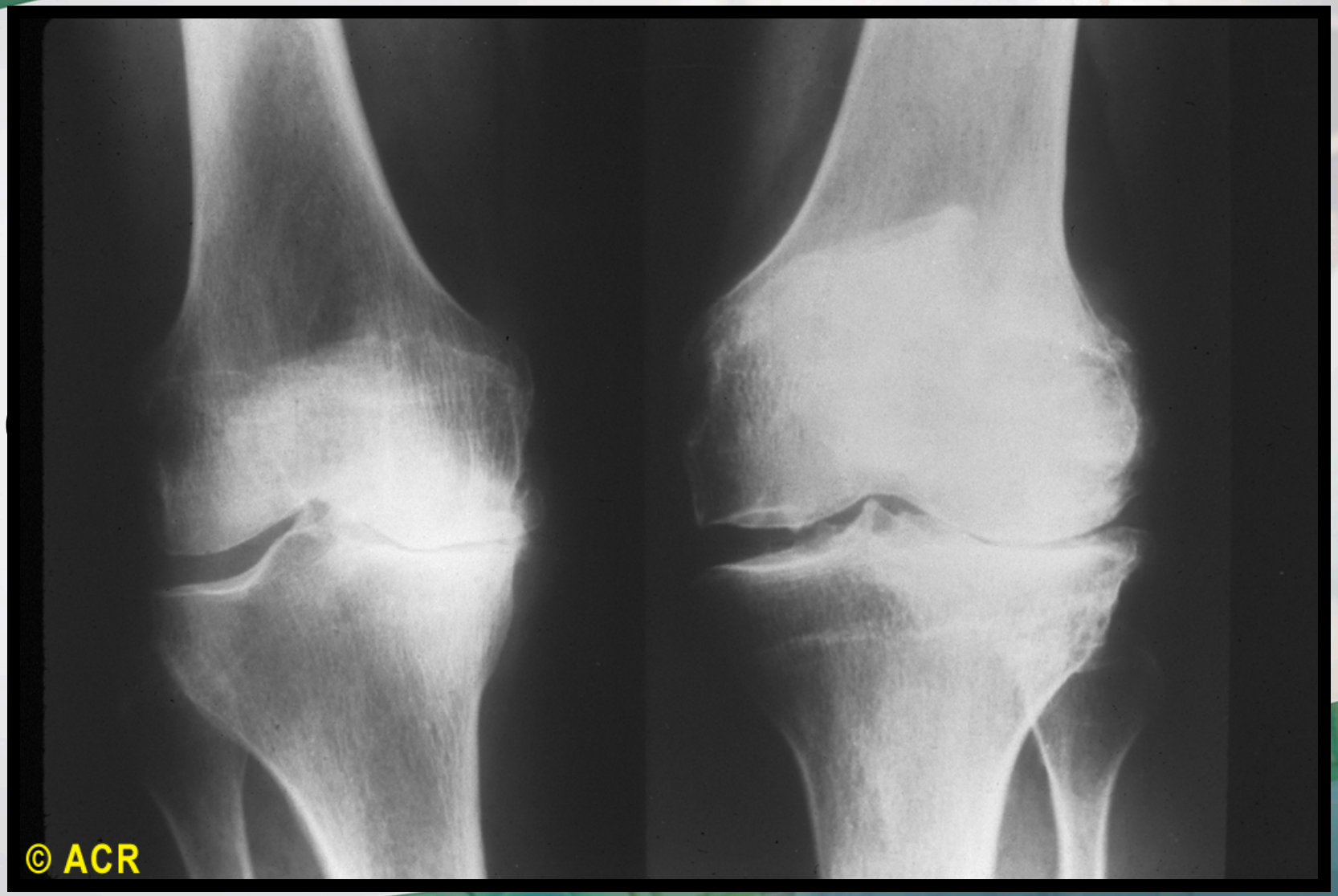

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Joint Damage / Joint Pain Yin and Yang

•Correlation between radiographic OA and symptomatic disease is weak

•Joint pain is not always OA - referred pain, tendonitis, bursitis, nerve damage

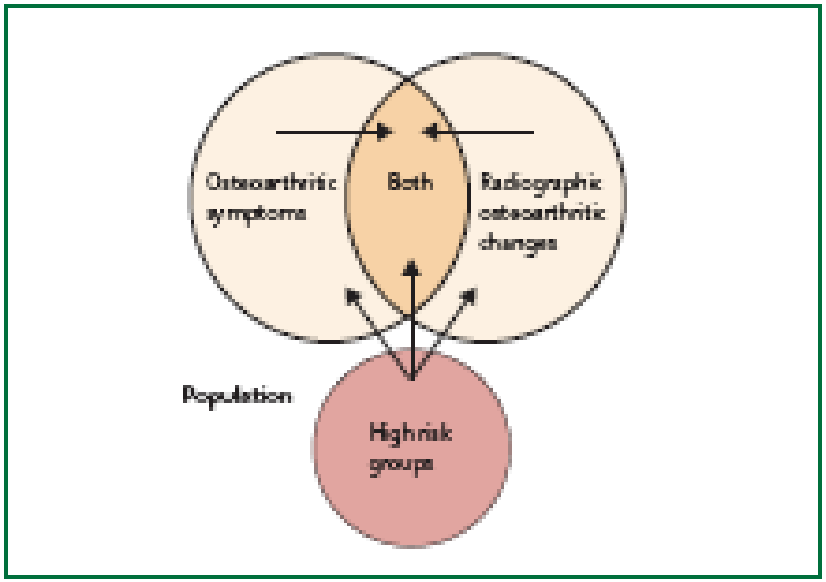

Figure 3: Schematic relations between different groups in the community. Some people have risk factors for osteoarthritis, but no disease; some have radiographic changes but no symptoms; and some have symptoms and signs associated with osteoarthritis, and hence so-called classical osteoarthritis. Our understanding of drivers of conversion from one of these states to another is incomplete.

Dieppe, Lancet 2005

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OA – New Insights
MRI Imaging

- Poor correlation between radiographic severity and joint pain
  - Joint pain: associated with bone marrow lesions, bone attrition, synovitis/effusions, meniscal tears (Torres, Osteoarthritis Cartilage 2006. Felson, Ann Intern Med 2001. Zhai, Arthritis Rheum 2006)
- Poor understanding of who will progress
  - OA progression: bone marrow lesions, severe meniscal extrusion, severe medial meniscal tear (Boegard, Osteoarthritis Cartilage 2001. Felson, Ann Intern Med 2003. Pessis Osteoarthritis Cartilage 2003. Raynauld, Arthritis Res Ther 2006)

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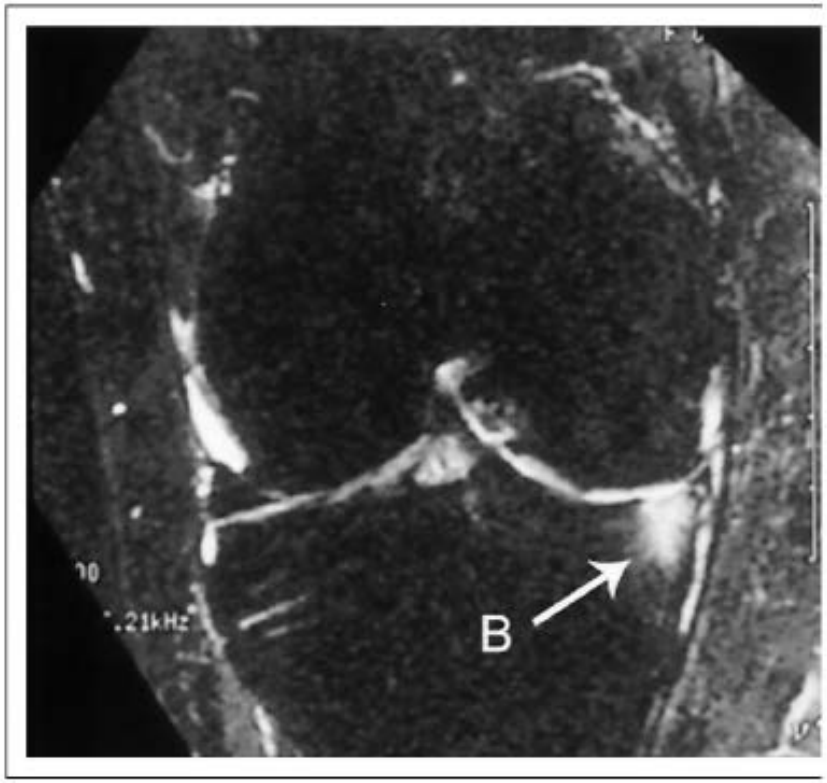
Bone Marrow Edema on MRI

Figure 1. Bone marrow edema lesion (*B*) on magnetic resonance imaging.



This lesion was scored as grade 2 in size on a scale of 0 to 3.

Ann Intern Med. 2003;139:330-336.

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OA: Diagnosis
Clinical Findings

- Pain is related to activity
- Minimal morning stiffness (<30 min)
- Range of motion decreases
- Bony enlargement
- Crepitus (crunching)
- Variable swelling and/or instability

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Hand OA

Distal and Proximal Interphalangeal Joints

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Hand OA
1st Carpometacarpal Joint

- Very common
- Causes thumb or wrist pain
- May cause significant loss of function

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Hip OA

- Second most common large joint affected - prevalence 3%-11%
- Symptoms-
  - deep groin pain that radiates into the thigh (knee)
  - Pain with hip rotation
- Not to be confused with Greater Trochanteric bursitis:
  - lateral hip pain over gr. trochanter, common in women, “can’t sleep on side of bursitis”

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Hip OA

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Osteoarthritis: Axial joint involvement

Cervical Spine:

- **Disc degeneration with marginal osteophytes at vertebral body margins C5/C6, C6/C7 levels**

- **Osteophytes at neural foramen [C6, C7]**

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OA Management 2019

- Educate Patients
- Control Pain
- Maintain or Improve Function
- Limit Disability
- Avoid Drug Toxicity

OA management 2019-Beyond

- Alter Disease Process – Disease Modifying Drugs for OA (DMOADs)
- Predict those at highest risk for disability

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Treatment guidelines for OA

- OARSI (2019), ACR (2012), EULAR, NICE, AAOS
- Common themes –

  -Use non-pharmacologic therapies first and, if needed, pharmacologic treatment

  -Identify and modify patient risk factors

  -Treat according to severity of symptoms

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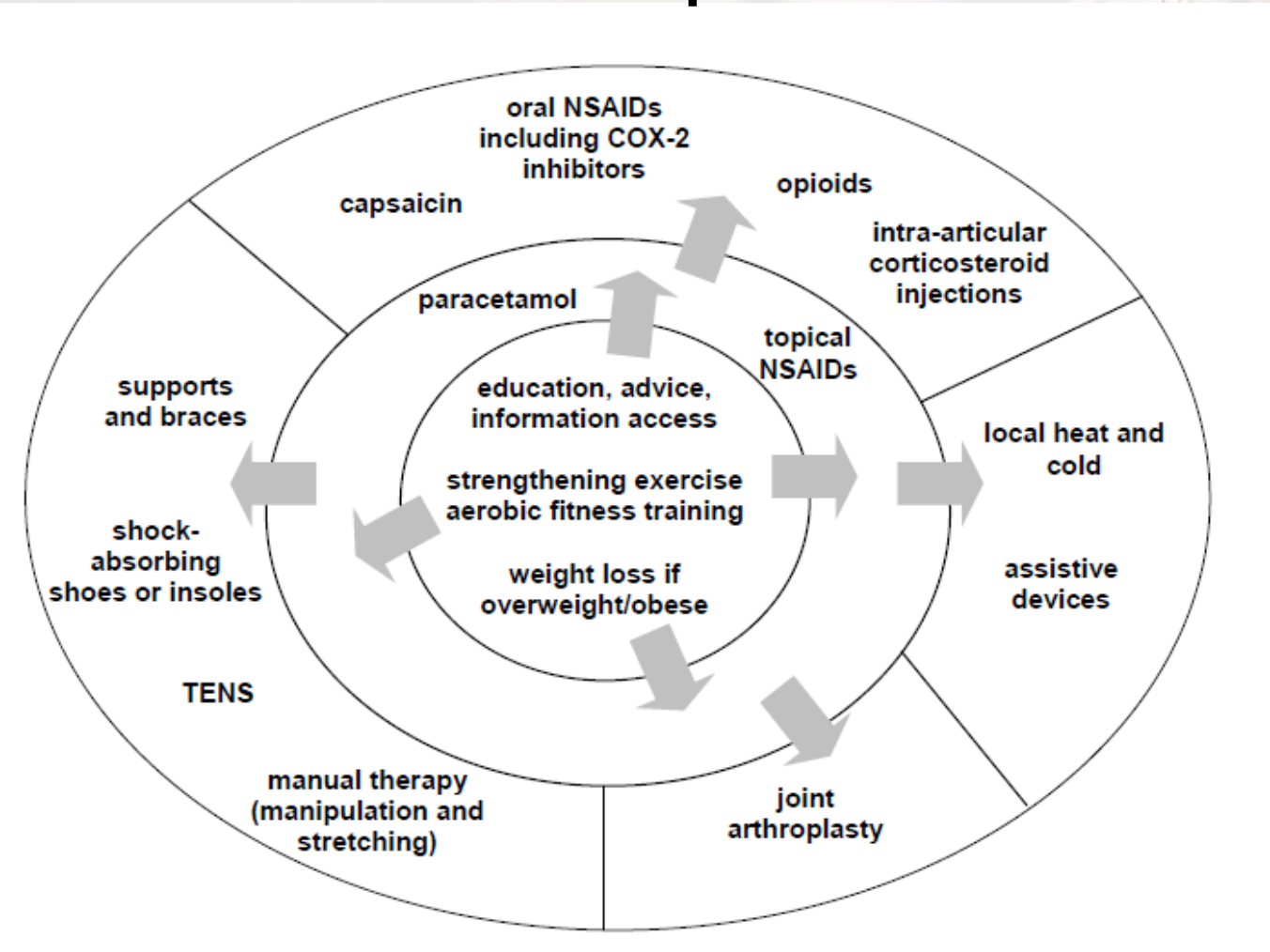
National Institute for Health and Clinical Excellence (NICE) Guidelines for Hip and Knee OA



http://guidance.nice.org.uk/CG59

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Knee OA Treatment

Tailored according to:

–Knee risk factors (obesity, malalignment, physical activity, trauma)

–General risk factors (age, comorbidity, polypharmacy)

–Level of pain intensity and disability

–Sign of inflammation (effusion)

–Location and degree of structural damage

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Non-Pharmacologic Management

- Exercise
  - Appropriately dosed (frequency, intensity) and progressed to improve pt outcome.

- Patient education
  - Self-management programs (i.e.Arthritis Foundation, NIA) and social support network results in fewer visits to PCP (*Mazzuca et al, Arthritis Rheum, 1997)*
- Weight loss –
  - *Every 1 lb lost decreases load knee 4 lbs*

    (Messier et al, Arthritis Rheum, 2005)

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Treatment for Knee OA

Table II

Recommended treatments, by level, for knee osteoarthritis

Recommendation level	Strength	Treatment type	No comorbidities	Gastrointestinal	Cardiovascular	Frailty
CORE	Strong	Arthritis Education; Structured Land-Based Exercise Programs (Type 1- strengthening and/or cardio and/or balance training/neuromuscular exercise OR Type 2- Mind-body Exercise including Tai Chi or Yoga) with or without Dietary Weight Management				
Level 1A **High Consensus** ≥75% "*in favor*"	Strong	Pharmacologic Non-Pharmacologic	Topical NSAIDs *refer to Level 1B*	Topical NSAIDs *refer to Level 1B*		Topical NSAIDs *refer to Level 1B*
Level 1B **High Consensus** ≥75% "*in favor*" & >50% "*conditional*" *Recommendation*	Conditional	Pharmacologic Non-Pharmacologic	• Non-selective NSAIDs • Non-selective NSAID + PPI • COX-2 Inhibitors IACS Aquatic Exercise, Gait Aids, Self-Management Programs	COX-2 Inhibitors IACS, IAHA Aquatic Exercise, Gait Aids, Self-Management Programs	IACS, IAHA	IACS, IAHA Aquatic Exercise, Gait Aids, Self-Management Programs
Level 2 **Low Consensus** 60%-74% "*in favor*"	Conditional	Pharmacologic Non-Pharmacologic	IAHA Cognitive Behavioral Therapy with Exercise	Non-selective NSAID + PPI Cognitive Behavioral Therapy with Exercise	*see below*	*see below* Cognitive Behavioral Therapy with Exercise
Good Clinical Practice Statements	Conditional	Various	*Intra-articular (IA) treatment*	*IA treatment, NSAID risk mitigation*		*IA treatment, NSAID risk mitigation*

Bannuru, Osteoarthr Cartil, 2019

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ACR recommendations for Hand OA

Table 1. Nonpharmacologic recommendations for the management of hand OA*

We conditionally recommend that health professionals should do the following:

- Evaluate the ability to perform activities of daily living (ADLs)
- Instruct in joint protection techniques
- Provide assistive devices, as needed, to help patients perform ADLs
- Instruct in use of thermal modalities
- Provide splints for patients with trapeziometacarpal joint OA

* No strong recommendations were made for the nonpharmacologic management of hand osteoarthritis (OA). The evidence supporting these interventions demonstrated only a small to moderate effect size (see supplementary bibliography for hand OA in Supplementary Appendix B, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Arthritis Care Res 64, 2012

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Thumb Spica splint – CMC OA

- Moderate to large effect on pain
- Small to moderate effect on function (after 3-12 months)

(Buhler, Osteoarthr Cartil, 2019)

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ACR recommendations for Hand OA

Table 2. Pharmacologic recommendations for the initial management of hand OA*

We conditionally recommend that health professionals should use one or more of the following:

- Topical capsaicin
- Topical NSAIDs, including trolamine salicylate
- Oral NSAIDs, including COX-2 selective inhibitors
- Tramadol

We conditionally recommend that health professionals should not use the following:

- Intraarticular therapies
- Opioid analgesics

We conditionally recommend that persons age ≥75 years should use topical rather than oral NSAIDs. In persons age <75 years, the TEP expressed no preference for using topical rather than oral NSAIDs.

* No strong recommendations were made for the pharmacologic management of hand osteoarthritis (OA). For patients who have an inadequate response to initial pharmacologic management, please see the Results for alternative strategies. NSAIDs = nonsteroidal antiinflammatory drugs; COX-2 = cyclooxygenase 2; TEP = Technical Expert Panel.

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Arthritis Care Res 64, 2012

Pharmacologic Management of OA - 2019

- NSAIDs – topical vs. systemic, non-selective vs. selective COX-2 inhibition.
- Topical agents – NSAIDs, capsaicin, lidocaine patch, compounding gels
- Intra-articular agents - corticosteroids, hyaluronate, *stem cell, platelet rich plasma*
- Duloxetine (Cymbalta) (SNRI) - treats central sensitization to chronic pain
- Neutraceuticals – glucosamine, chondroitin, turmeric,

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NSAIDs

- Appropriate for patients at low risk for GI complications, normal renal function, and no CV comorbidities
- *Lower dose NSAIDs are less effective but better tolerated than high dose*
- Gastroprotection with PPI to reduce risk of ulcers
  - *patients with GI risk, > 75 yo, aspirin, prednisone*

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NSAIDs – CV risk

- All NSAIDs (except naproxen) have been associated with increased CV risk
- Pts with CV disease and on low dose ASA

  Topical NSAID

  NSAID + PPI

  Avoid ibuprofen (may render ASA less effective)
- COX-2 inhibitors - should not be used

Arthritis Care & Research Vol. 64, No. 4, April 2012

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Topical Agents

- Topical NSAIDs (diclofenac)
  - Improves pain in knee and hand OA
  - Safe (<6% absorbed)
    - Main Side effect – skin reaction (7%)
- Topical capsaicin
  - Modest effect in knee OA
- Lidocaine patch
  - Effective in knee OA
  - Use 3-4 patches for 12 hrs every 24 hrs

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Opioid Analgesics for OA in 2019

- OK for severe disease? Maybe not.
- Veterans Administration pts with OA – flexible treatment with opioids vs non-opioids. No difference among the groups and more adverse events in the opioid group (Krebs, JAMA, 2018)
- Similar results with Osteoarthritis Initiative (OAI) patients – increased adverse events with opioid use (falls – 22%) (Lo-Ciganic, Osteoarthr Cartil, 2017)
- Pts. using opioids for severe knee OA prior to TKA had more pain 6 months after surgery than those who did not use opioids (Smith, JBJS, 2017)

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OA: Intra-articular Therapy

- Intra-articular steroids
  - Good pain relief 1-4 weeks average
  - Recommend 3-4 months between injections
  - With frequent injections- systemic effects.
  - *Knee injections with triamcinolone Q3 months for 2 years showed no improvement compared to placebo, slight decrease in cartilage thickness on MRI*

(McAlindon, JAMA, 2017)

- Hyaluronate
  - Modest effect to no effect
  - Greatest effects seen 5-12 weeks after injection
  - Expensive
  - Safe and well tolerated
- PRP, Stem Cells
  - "best quality reviews suggest we don't have strong enough data to recommend these"

(Mandl, Osteoarthr Cart, 2019)

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Future Analgesics

- Anti-Nerve Growth Factor Antibodies
  - NGF elevated in painful inflammatory states (arthritis, pancreatitis, prostatitis)
  - Tanezumab – subQ 2.5 mg, 5mg, 10 mg doses every 8 weeks
  - Study in JAMA, July 2019 pts with hip or knee OA received 2 doses of tanezumab with co-primary outcomes of pain and function at week 16.
  - Tanezumab showed improvement in pain and function vs placebo
  - Rapidly progressive OA occurred in 6 pts in tanezumab groups and more joint replacements

Schnitzer JAMA, 2019

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When to Refer for Joint Replacement- 2019

- Total joint replacement is highly effective in patients with advanced knee and hip OA
  - Severe pain
  - Conservative therapies have failed
  - Age > 55 yo
  - Non-obese
  - DM, chronic diffuse pain, depression/anxiety - poorer outcomes
  - No intra-articular steroids for 3-6 months prior to surgery (date suggests increases risk for infection)

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Summary

- OA is the endpoint of a process affecting the joint with variable course
- Major advances are being made regarding the pathogenesis of joint pain in OA
- Use of both non-pharmacological and pharmacological treatment is most effective for treating OA

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Patient Resources

- **Arthritis Foundation** –
  - National: arthritis.org
  - Local-www.arthritis.org/alabama - online communities, publications, camps, natl conferences, etc.
  - *Practice Resources* – handouts, Partners 4 Patients with Arthritis practice.
- ***Go4Life -*** https://go4life.nia.nih.gov/. Exercise and physical activity campaign from the National Institute on Aging/NIH, designed to help pts fit exercise and physical activity into their daily life.

Useful References:

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Common Joint Injections

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Disclosures

- None

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Objectives

- Review Indications for Injections
- Review common injection medications
- Review pertinent anatomy for safe injection technique
- Be confident in how to safely perform knee, subacromial bursa, and trochanteric bursa injections
- Recognize potential complications of joint and bursal injections

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Arthrocentesis Indications - *Diagnostic*

- Evaluate synovial fluid for:
  - Infection
  - Inflammatory arthropathy (crystals, RA, SNSA)
  - Trauma (hemarthrosis)

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Arthrocentesis Indications - *Therapeutic*

- Relief of pain/inflammation caused by:
  - Large effusion
  - OA, RA, Gout, CPPD
  - Bursitis
  - Selected tendinopathies

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Contraindications:

- Local cellulitis/psoriasis
- Prosthetic joint (can aspirate but not inject)
- Septicemia
- Acute fracture
- Allergy to injection medications
- Unstable coagulopathy

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Types of Injections

- Intra-articular
- Peri-articular
- Intra-bursal
- Intra-muscular
- Soft tissue

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Types of Medications for Injections

- Corticosteroids
- Anesthestic (1% sterile lidocaine)
- Hyaluronic acid supplements
- Platelet Rich Plasma Preparations (PRP)
- Stem cells, amniotic fluid, others

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Steroid types

- Short-acting
  - hydrocortisone
- Intermediate-acting (most commonly used)
  - *triamcinolone acetonide (Kenalog)*
  - *Methylprednisolone (Depo-medrol)*
- Long-acting
  - dexamethasone

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Table 2 – Injectable corticosteroids

Solubility/ Generic name	Effect onset	Large-joint dose (mg)	Small-joint dose (mg)
Somewhat insoluble			
Triamcinolone acetonide	Variable	5 - 40	2.5 - 5
Triamcinolone hexacetonide	Variable	10 - 40	2 - 6
Slightly soluble			
Methylprednisolone acetate	Very slow	20 - 80	4 - 10
Triamcinolone diacetate	Variable	20 - 40	2 - 5
Soluble (not preferred for joints)			
Dexamethasone sodium phosphate	Rapid	2 - 4	0.8 - 1
Combination			
Betamethasone sodium phosphate and betamethasone acetate	Rapid	6 - 12	1.5 - 3

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Local anesthetics

- Lidocaine (xylocaine) – rapid acting, last approximately 30 minutes, *most widely used*
- Bupivacaine (Marcaine) – slower onset (30 min), lasts 8 hours
- Most injections are a combination of steroids and anesthetic
- Local anesthetics – reversibly block conduction along nerve fibers
  - Analgesic – temporary effect, makes procedure less unpleasant, break pain cycle
  - Dilution – increased volume helps to spread it around, less likely damage or cause atrophy to soft tissues.

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Dose of Medications

Body Area	Specific Location	Corticosteroid Dosing (methylprednisolone /triamcinolone)	1% Sterile lidocaine dosing
Shoulder	Subacromial Bursa	40 mg	2-4 cc
Knee	Intra-articular	40-80 mg	4 cc
Hip	Greater troch. Bursa area	40 mg	4 cc

General rule for max methylprednisolone dose:

120 mg in 1 day

160 mg in 1 month

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Other injection products

- Viscosupplements – hyaluronic acid
  - less medication induced SE
  - Thicker products (improve joint lubrication, increase synovial fluid viscosity)
  - Longer acting (8 weeks post injection)

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Aseptic Technique

- Sterile, disposable needles
  - 20g-21g 1.5” (intra-articular, aspiration of fluid, 18g if suspect infection)
  - 22g-25g 1.5”- bursal injections
- Single dose ampules when possible
- Change needles after drawing up solutions
- Gloves (sterile vs. non sterile)
- Skin prep (betadine/alcohol vs. chloroprep)
- Aspirate joint as advancing needle
- Aspirate a joint effusion first, before injecting

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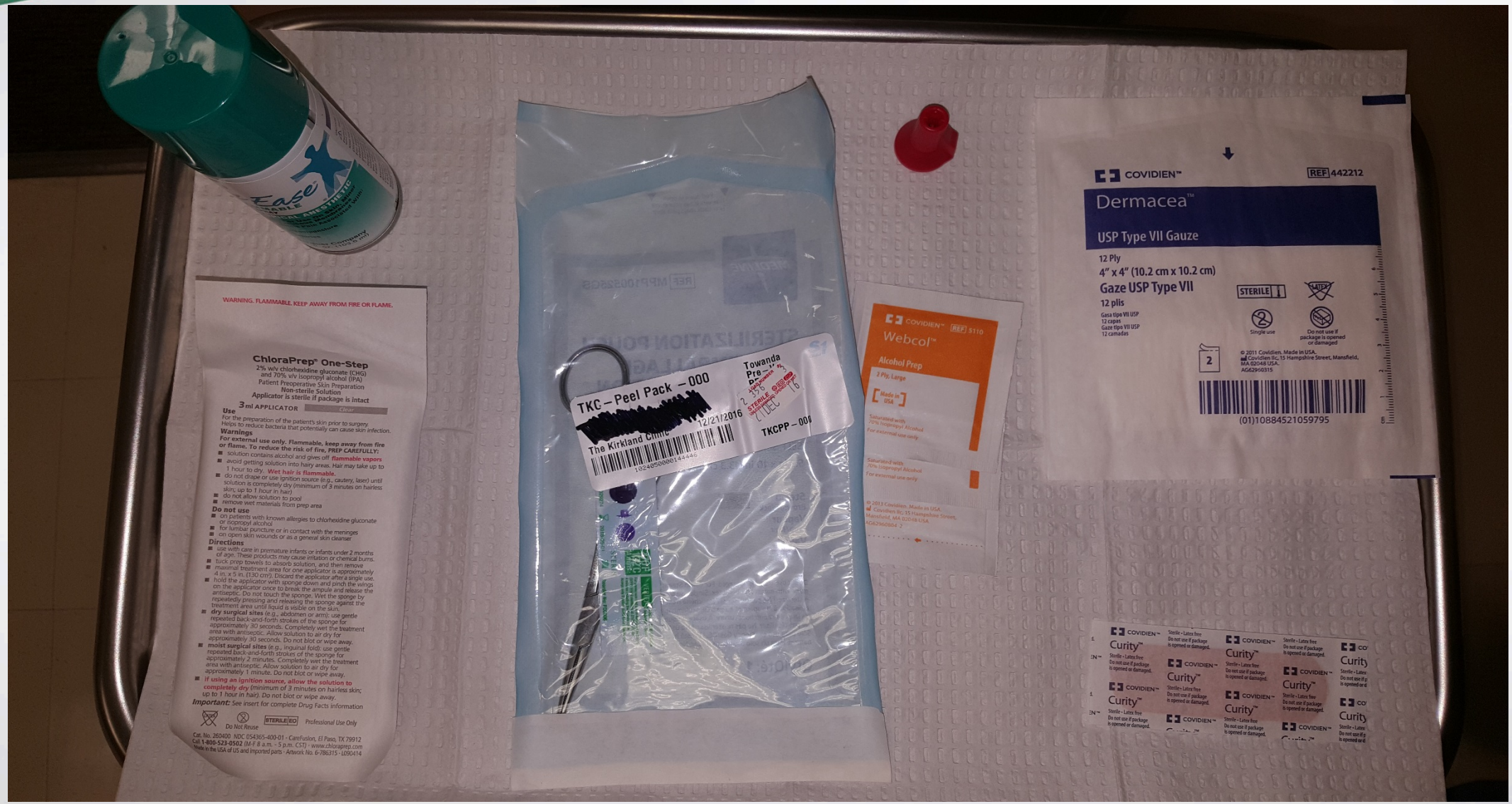

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Arthrocentesis supplies (cont)

- Synovial fluid supplies –
  - Culture bottles (Aer/Anaer)
  - Purple top (CBC w diff)
  - Black top (crystals, gram stain)

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Joint Injection Procedure

- Prepare Patient
  - Treatment options, procedures, SE
  - *Informed consent, time out*
  - *Positioning*
- Prepare Equipment
  - Meds, gauze, skin prep, ect.
  - Prepare site
  - Mark structures, landmarks, etc.

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Adverse Reactions/Complications

- 2%-10% Post injection (steroid) flare
- Iatrogenic infection (1:15,000-75,000)
- Bleeding/bruising
- Skin atrophy and depigmentation (1%)
- Facial flushing (1-5%)
- Elevated serum glucose in pts with DM2
- Vagal reaction
- Anaphylaxis

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Frequency

- Large joints
  - Consensus opinion is q 3-4 months
  - Weigh risks/benefits for your patient
  - Older patient with multiple medical problems unable to undergo surgery but needing relief, maybe more often
  - If able, treat underlying cause of issue
    - Overuse
    - Poor biomechanics

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Shoulder : subacromial (SA) bursitis

- SA bursitis/rotator cuff tendonitis – most common cause of shoulder pain in adults.
- Repetitive activity, above shoulder work
- Pain with: above shoulder movement, lying on affected side
- Test for impingement

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Subacromial Impingement Testing

- Hawkin's Test
  - Passive
  - 90˚ abduction, 90˚ elbow flexion
  - Scapular plane
  - Maximal internal rotation

- Neer's Test
  - Passive
  - Elbow extended
  - Pronation
  - Sagittal plane
  - "Near to the ear"

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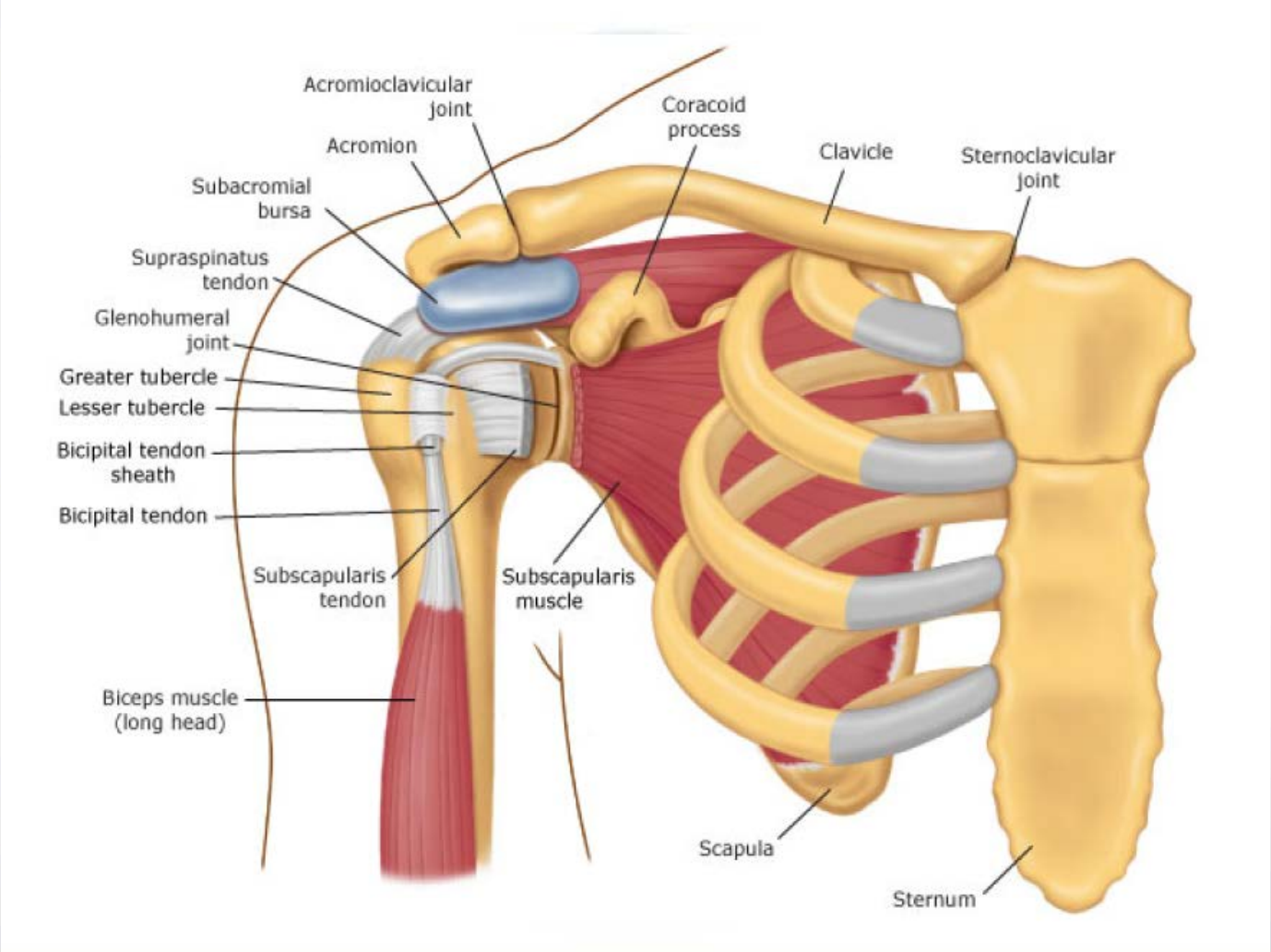
Subacromial bursa space



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Subacromial Bursal Injection

- Given lateral or posterior
- Direct needle under acromion

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Greater trochanteric Pain Syndrome (GTPS)

- Lateral hip pain
- Tenderness to palpation
  over greater trochanter
- Pain when lying on affected side

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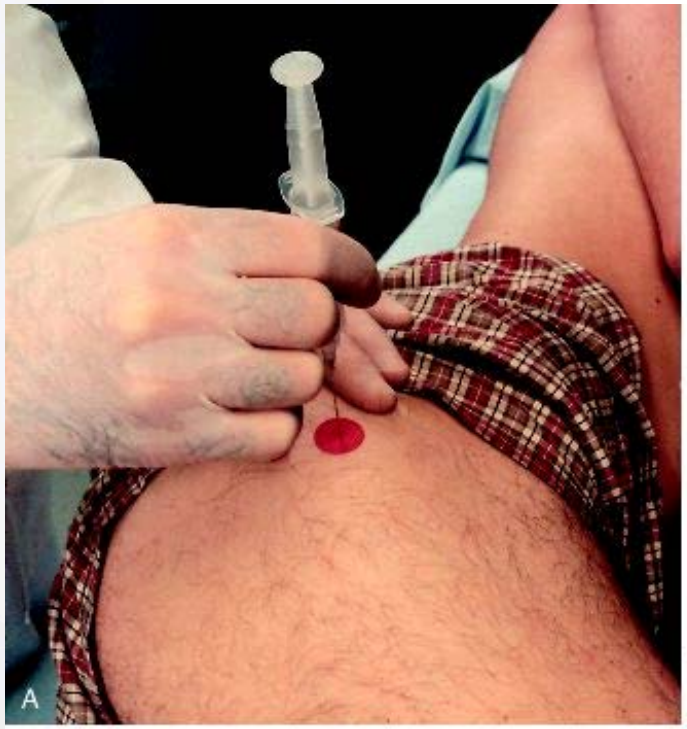
GTPS Injection -

- Pt lying on unaffected side
- Palpate area of GT tenderness
- Guide needle to GT and inject
- Use spinal needle for obese pts
- Fan injection or place in single area



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Knee Arthrocentesis

- Indications
  - Osteoarthritis
  - Large Effusion
  - Inflammatory arthritis
  - Trauma (hemarthrosis)
  - Suspected infection
  - Suspected crystal disease

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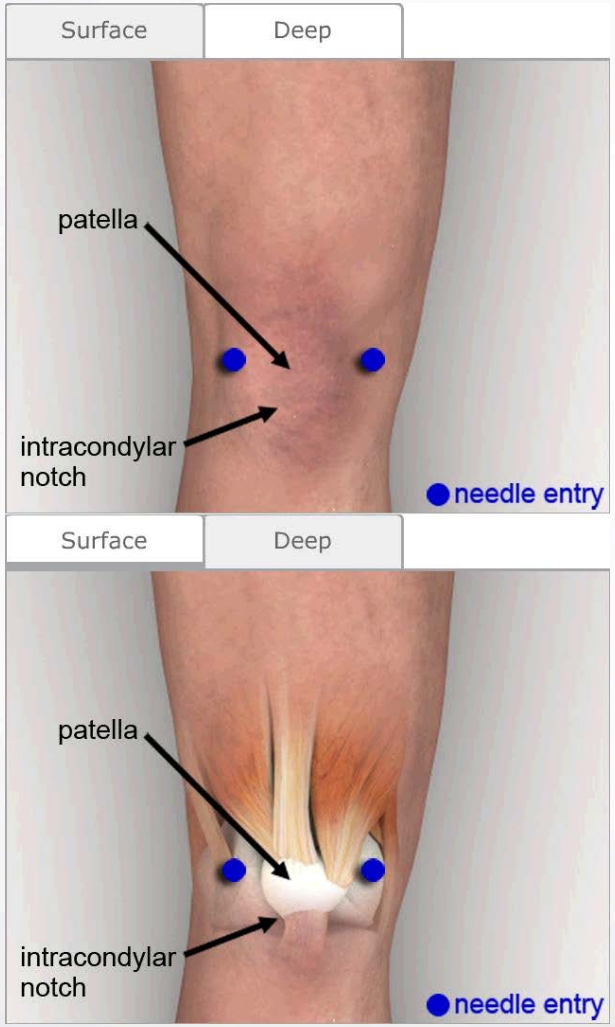
Technique

- Extend knee
- Identify superior and inferior margins of patella
- Assess for effusion
- Mark site for procedure - upper 1/3 patella medial or lateral
- Assistant - press fluid from suprapatellar pouch area



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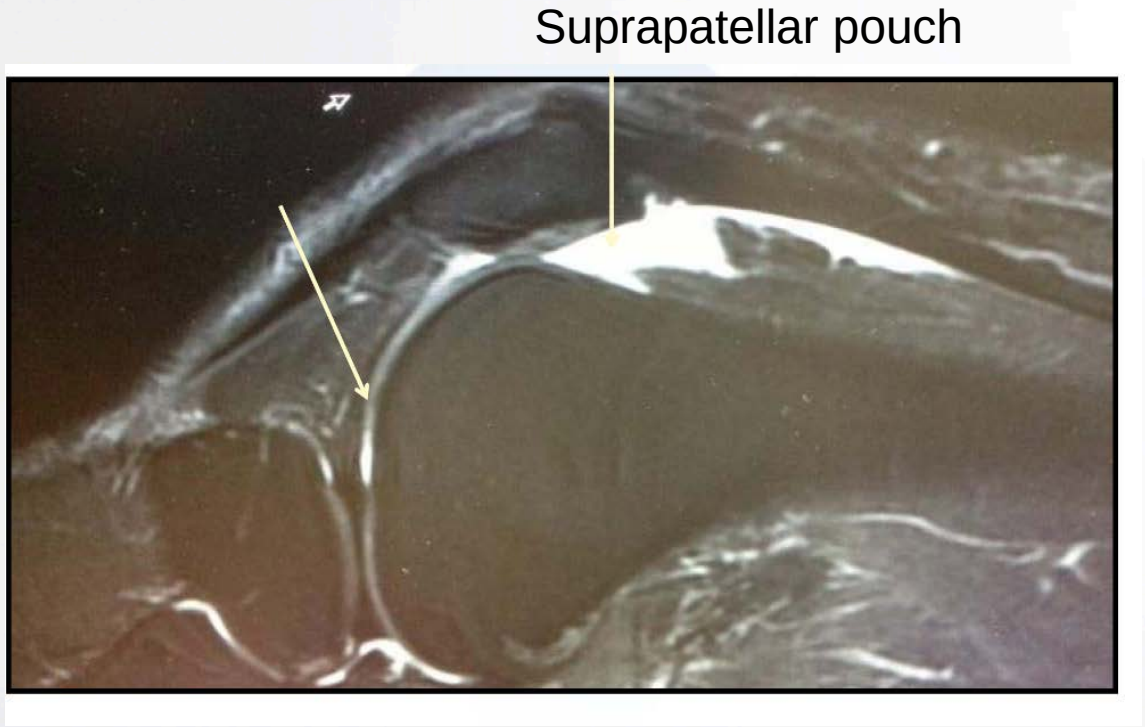
MRI – Sagittal Knee



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MRI – Axial Knee

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Technique

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Knee Injection

- Knee extended
- Junction upper third and lower two thirds of the patella
- Insert needle under patella and aim slightly superiorly

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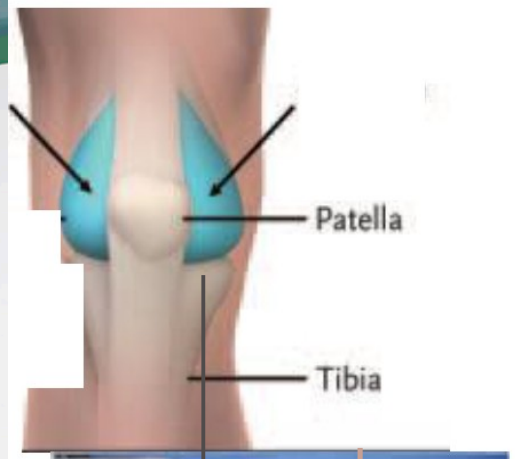

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After care

- Relative rest (48 hours)
- Ice
- Often accompanied by PT (subacromial bursa injections)
- Steroid side effects – 24-48 hours to 1 week
- Lasts 3 weeks to 3 months

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Questions??

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Patient #1 – “Rand”

62yo M with a past medical history of HTN and HLD who presents to clinic with chronic right knee pain. He presents to clinic with desire to return to work but “he needs some help.”

- 2008 - motorcycle accident; required surgical fixation
- 2009 – TKA - due to continued pain after hardware fixation
- 2009 – 2016 -, 4 revision arthroplasties and multiple irrigation and debridement
- 1/11/16 - last surgery

Ideas?

Patient #2 – “Nance”

65yo F with a past medical history of HTN, HLD, and anxiety who presents to clinic with chronic lumbar pain. Patient states that her pain began in 2006. She has most recently been taking hydrocodone – APAP 10/325mg PO QID. She notes poor pain control but does not want to escalate opiates.

allergies - relafen and mobic (mouth ulcers), morphine and oxycodone (skin stinging and breaking out), neurontin and lyrica (breathing, blurred vision, and itching)

- 2006 - spinal fusion 2006 L4-S1
- 5/2007 - L5/S1 microdiscectomy
- 11/2007 - fusion hardware removal
- 2014 - L3/4 lumbar fusion
- She has been off and on opiates since 2006.

Ideas?

Effective Pain Management Strategies

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205-332-3155

Financial Disclosures

None

Objectives

- Approach to Pain
  - ETIMS or “Smite pain”
- OPIATES
  - Opioid Statistics
  - How Opioids work
  - Opioid Recommendations
  - Opioid Follow Through, Dosing, When to Refer
- Questions

S-M-I-T-E

- Education
- Therapies
- Injections
- Medications
- Surgery

Education

- Safest and least invasive means of treating pain
- Very hard
- American Academy of Pain Medicine (painmed.org) offers patient education and resources

Patient #1 – “Rand”
62yo M with chronic right post surgical knee pain

- Education
  - Why does his knee continue to hurt?
  - What can he do for himself to improve his functional and pain level?
  - What is his long term plan and is it realistic?
- Education
  - Multiple surgeries
  - Lifestyle – diet and exercise
  - Make it to retirement – works 12 hour shifts at a lime factory

Patient #2 – “Nance”
65yo F with chronic lumbar pain and radicular leg pain s/p four surgeries

- Education
  - Why does her back continue to hurt?
  - What types of pain does she have and are they treated the same?
  - Is she an addict?

- Education
  - New pathology - Recurrent disc herniation
  - Nociceptive and neuropathic – hard no
  - Is she?

Therapy

Cognitive	• Address distressing negative cognitions and beliefs • Catastrophizing - pain coping characterized by excessively negative thoughts and statements about the future	
Behavioral Approaches	• Mindfulness • Meditation • Yoga	• Relaxation • Biofeedback
Physical	• Activity coaching • Graded exercise	
Spiritual	• Identify existential distress • Seek meaning and purpose in life	
Education (Patient And Caregivers)	• Promote patient efforts aimed at increased functional capabilities	

Patient #1 – “Rand”
62yo M with chronic right post surgical knee pain

- Therapy
  - Has he previously attempted therapies?
  - What kind of therapy is warranted?
  - Do he understand the importance of continued therapy?

- Therapy
  - Yes multiple sessions
  - Physical
  - Yes, he admits to benefit

Patient #2
65yo F with chronic lumbar pain and radicular leg pain s/p four surgeries

- Therapy
  - Has she previously attempted therapies?
  - What kind of therapy is warranted?
  - With her poor pain control, is therapy even a consideration?
  - Do I really need cognitive behavioral therapy?

- Therapy
  - Yes multiple sessions – “makes my pain worse”
  - Aquatic therapy with transition to physical
  - Yes – always a consideration
  - Yes – total treatment plan

Injections

- Spinal injections (ESI, TFESI, SNRB, caudal)
- Joint injections (C or L facets, hips, knees, etc)
- Sympathetic blocks (Stellate, LSB)
- Spinal Cord Stimulation
  - Post laminectomy cases
- Regenerative (PRP, BMA, stem cells)

Patient #1 – "Rand"
62yo M with chronic right post surgical knee pain

- Injections
  - With his history of knee replacement, does he have options?
  - If so, what kind?

- Injections
  - Yes
  - Geniculate nerve blocks and genicular radiofrequency lesioning

Patient #2 – "Nance"
65yo F with chronic lumbar pain and radicular leg pain s/p four surgeries

- Injections
  - "I've had so many nothing works"
  - In a post-surgical candidate, what considerations?
  - What is spinal cord stimulation?

- Injections
  - "I've had so many nothing works"
  - 3 ways ESI – interlaminar, transforaminal, and caudal
  - Electrical interference of chronic neuropathic and nociceptive pain through dorsal column stimulation

Medications - Non-opioid analgesics

- **NSAIDs**:
  - Nociceptive pain - MSK pain syndromes (traumatic, infectious, or degenerative)
  - Ex: meloxicam, celecoxib, ibuprofen
  - Limitations – renal disease, CAD/MI, gastric bypass

- **Anticonvulsant drugs**:
  - Neuropathic pain – nerve related pain (radiculitis, shingles, neuropathy)
  - Ex: gabapentin, lyrica, topiramate
  - Limitations – sedation, nausea,

Medications - Non-opioid analgesics

- **Antidepressants (TCAs/SNRIs):**
  - Neuropathic pain – nerve related pain (radiculitis, shingles, neuropathy)
  - Ex: amitriptyline/nortriptyline, duloxetine, venlafaxine
  - Limitations - long time to affect neuropathic pain; watch for potential cognitive impairment or sedation with anticonvulsants and TCAs

- **Muscle relaxants and anti-spasticity drugs**:
  - Muscle pain – spasms, cramps, spasticity
  - Ex: baclofen, tizanidine, cyclobenzaprine, methocarbamol (avoid carisoprodol)
  - Limitations - Muscle relaxants have limited evidence for effectiveness for chronic pain and are predominantly sedative.

Patient #1- “Rand”
62yo M with chronic right post surgical knee pain

- Medications
  - Does he need anything?
  - Where do you start? What has he tried?

- Medications
  - Yes – he wants to return to work
  - He has tried OTC NSAIDS – ibuprofen and naproxen with ok benefit and methocarbamol
  - He denies a trial of prescription NSAIDS – diclofenac, meloxicam, and celecoxib or neuropathic agents

Patient #2 – “Nance”
65yo F with chronic lumbar pain and radicular leg pain s/p four surgeries

- Medications
  - With her pain pattern, what kind of medications may potentially be beneficial for her pain?
  - What he she tried?

- Medications
  - Nociceptive and Neuropathic agents
  - Relafen and Mobic (mouth ulcers), Neurontin and Lyrica (breathing, blurred vision, and itching)
  - Benefit with methocarbamol, clonazepam

Poppy Plant (Papaver somniferum)

History of Opiates

- 5000 BC
- Sumeria (3400 BC, joy plant), Greece, Egypt, Roman Empire
- Theriac, Paregoric (camphorated tincture), Laudanum (tincture of opium)
  - Diarrhea, Cough, Pain, Menstrual Cramps
- Morphine – 1805 – Wilhelm Serturner
  - Morpheus (Greek God of Sleep)
- Opium Wars
  - First (1839-1842)
  - Second (1856-1860)

History of Opiates

- Codeine – 1832 – Pierre Jean Robiquet
  - 2% of opium
- Heroin – 1874 – CR Alder Wright, 1897 – Felix Hoffmann - first semi-synthetic opiate
  - Bayer pharmaceuticals - 1902 - 5% of company's profit
- Oxycodone – 1916 – Freund and Speyer
  - Thebaine – in response to Bayer stopping Heroin production
- Hydrocodone – 1920 – Carl Mannich and Helene Lowenheim
- Methadone - 1937 – IG Farben
  - Synthetic opiate – Germany - WWII
- Meperidine – 1939 – Otto Eisleb – IG Farben
  - Norpethidine – myoclonus, convulsions, hyponatremia
- Fentanyl – 1959 – Paul Janssen
  - Mid 1990s – duragesic patch

History of Opiates in the US

- Per Smithsonian Magazine article
  - In 1895, 1/200 Americans; Opiates made up 15% of all scripts in Boston in 1888
- 1920s - Heroin made an illegal drug – Anti-Heroin Act of 1924
- 1950s – Heroin use rising
- 1960s – Marijuana and psychedelics
- 1970s – Vietnam War – returning soldiers increase use
  - Controlled Substances Act – Heroin Schedule 1, Morphine, Fentanyl, Oxycodone, Methadone Schedule 2
  - 1971 Congressional Report – 10-15% of US servicemen in Vietnam were addicted to Heroin
  - Vicodin and Percocet
- 1980s medical literature recommended avoidance of opiates due to addictive nature
- 1980s "War on Drugs" due to widespread cocaine and crack use
- January 1980 – NEJM - "Addiction Rare in Patient Treated with Narcotics"
  - NEJM rebuttal published in June 2017 – hospitalized patients

History of Opiates in the US- 1990s/2000s

- Late 90s – 100 million pain sufferers (1/3 US population)
  - Opiates most prescribed class of drug
  - FDA and drug companies to expand use
- 1990 – Dr. Mitchell Max – President American Pain Society
  - 1991 – APS released quality assurance standards
    - Chart and display pain and relief; floor dependent scale; each clinic determine treatment
  - 1997 – JCAHO – pain fifth vital sign
  - 2001 – JCAHO – Examples of Implementation - pain is considered the fifth vital sign
  - 2002- JCAHO – pain used to be considered the fifth vital sign
  - 2004 – JCAHO – no longer appeared in Accreditation Standards Manual
- 1996 Purdue Pharmaceuticals released OxyContin
  - FDA – abuse resistant
  - 1995 – 68% extracted when crushed
- From 1991 – 2012, painkillers script 76 million to 255 million per year

Most Recent Opiate Statistics

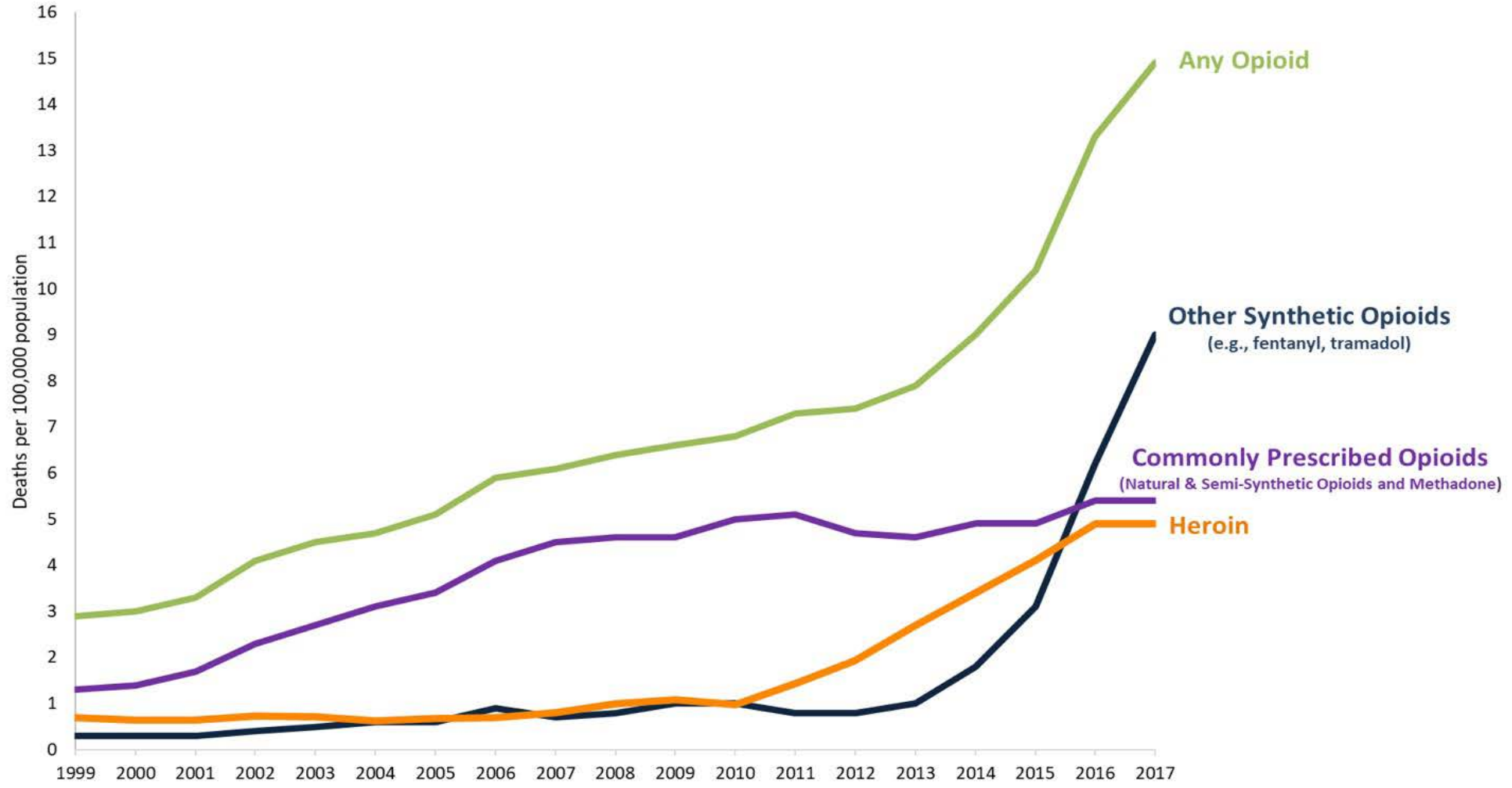
- From drugabuse.gov - revised January 2019
  - Every day, 130 (115) people die from opiate overdose in the US
  - Economic burden $78.5 billion per year
  - Per the CDC, 47,600 deaths in 2017 due to opioid overdose (42K in 2016)
  - Opiate scripts
    - 1992 – 112 million
    - 2012 – 255 million (81.3/100)
    - 2017 – 191 million (58.7/100)
  - In 2016, 6.2 billion hydrocodone and 5 billion oxycodone pills were distributed in US
    - Intl Narc Control Board reported that Americans used 99.7% of world's hydrocodone

Risk of overdose events

- **There is no completely safe opioid dose.**

- > 100 mg/day MED - up to 9 times the risk; compared to those on 20 mg/day MED
  - Every 7 overdoses, 1 was fatal.
- At high doses, patients are at higher risk for:
  - Poor functional status
  - Increased pain sensitivity (hyperalgesia and allodynia)
  - Continuation of chronic opioids for a prolonged period
- Drugabuse.gov
  - 2017 – Alabama – 18 opioid related overdose deaths per 100,000
  - 2017 – Alabama – 107.2 scripts/100 persons (1/51); US Avg 57.8/100
    - Walker County – 216/100 persons
    - Jefferson County – 104/100 persons

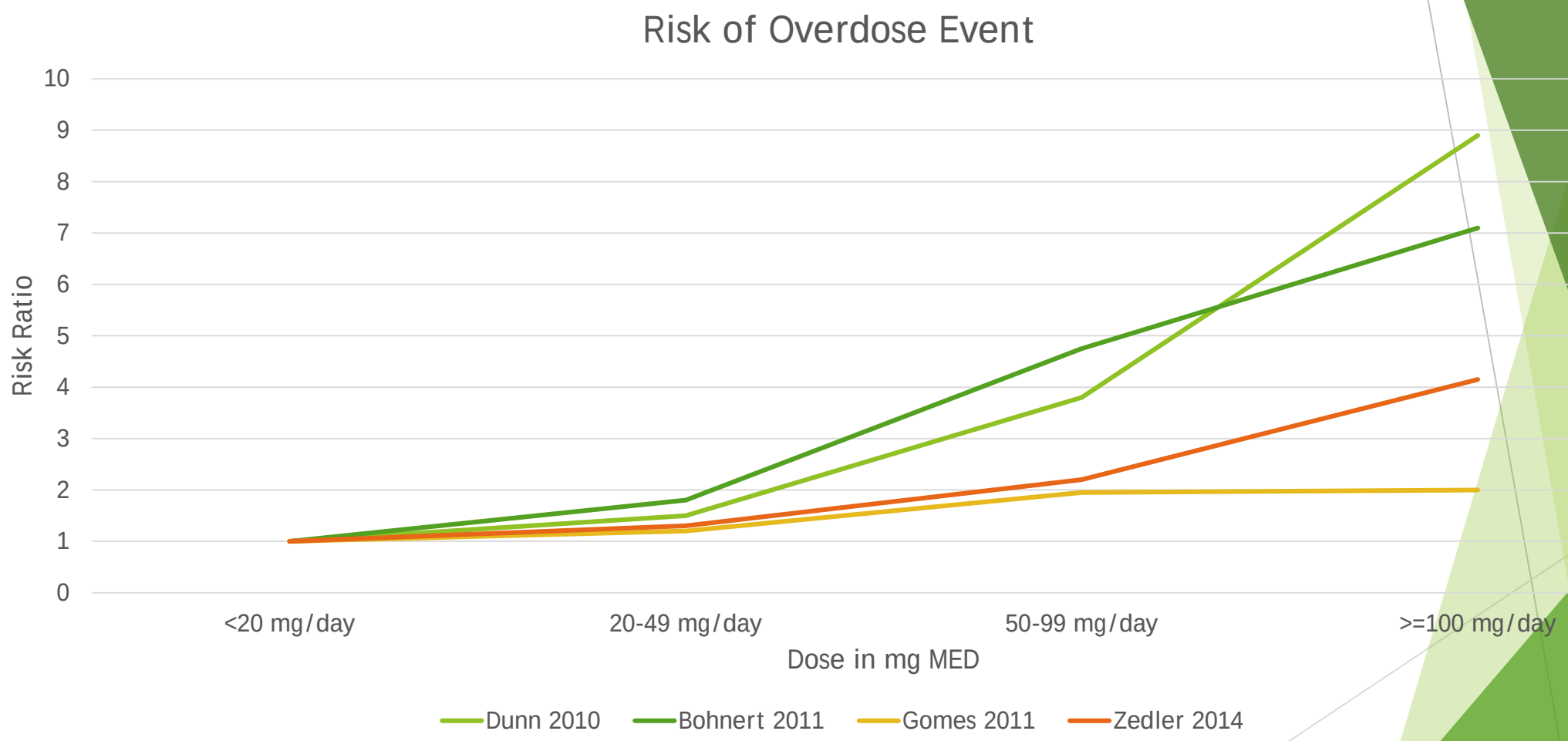
Overdose Death Rates Involving Opioids, by Type, United States, 2000-2017



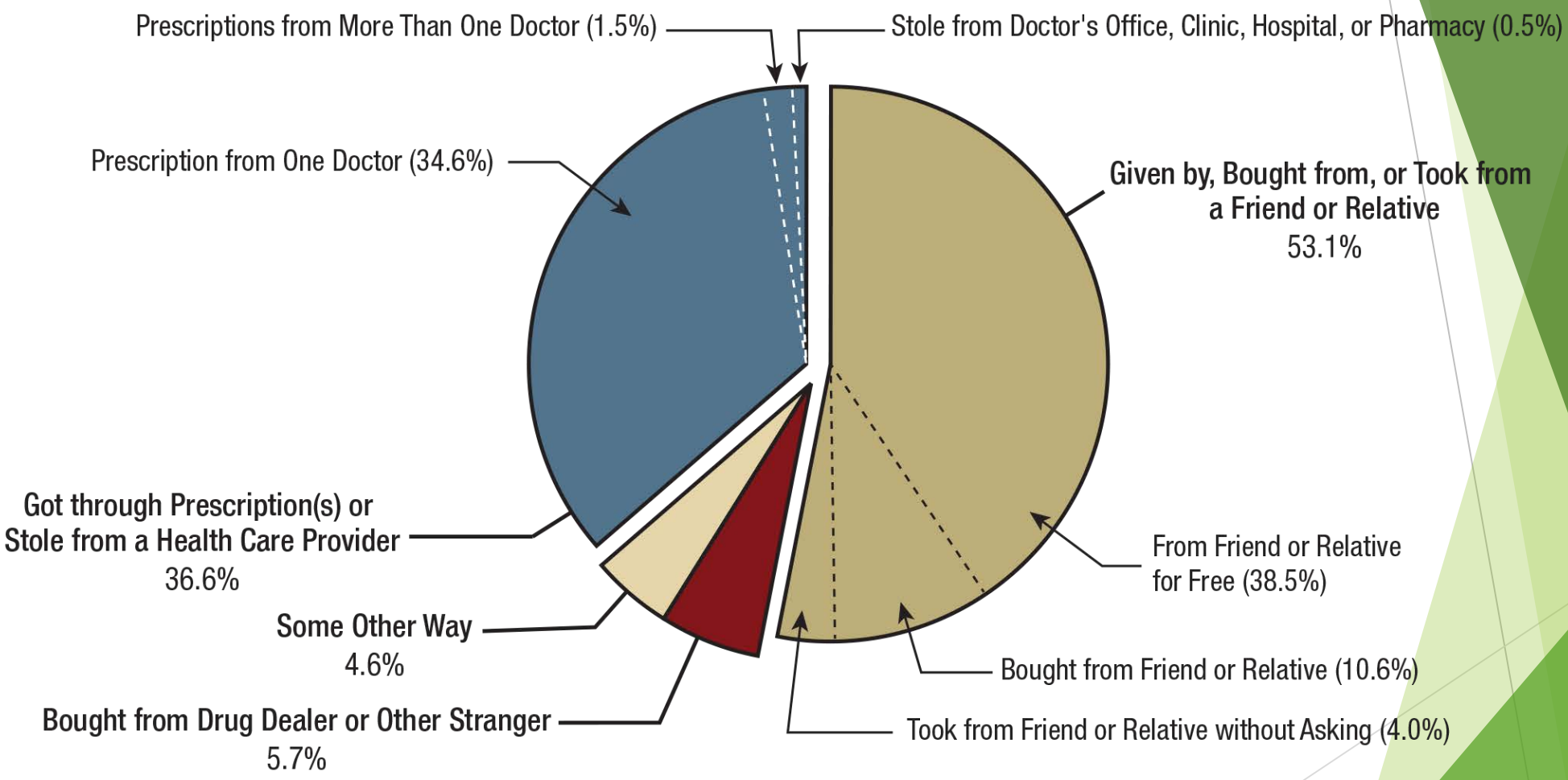
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://wonder.cdc.gov/.

www.cdc.gov
Your Source for Credible Health Information

Risk of overdose events in 4 populations



Opioid diversion



2017, Substance Abuse and Mental Health Services Administration

How Opiates Work

- Mu, Delta, Kappa Receptors
  - Mu and Delta - analgesic and rewarding; Kappa - dysphoric
  - Mu - respiration, cardiovascular functions, intestinal transit, feeding, learning and memory, locomotor activity, thermoregulation, hormone secretion, and immune functions
    - All, except hormone secretion, are depressed by receptor stimulation
    - Respiratory depressant effects of MOP agonists result from a decrease in sensitivity to hypercapnia
  - Delta - analgesia, motor integration, gastrointestinal motility, respiration, olfaction, cognitive function, and mood driven behavior
  - Kappa - nociception, diuresis, feeding and neuroendocrine secretions, control of immune function, thermoregulation, and modulation of cardiorespiratory function

Center for Disease Control Recommendations

Major Recommendations

Determining When to Initiate or Continue Opioids for Chronic Pain

1.Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy, as appropriate (**recommendation category: A, evidence type: 3**).

2.Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (**recommendation category: A, evidence type: 4**).

3.Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (**recommendation category: A, evidence type: 3**).

Opioid Selection, Dosage, Duration, Follow-up, and Discontinuation

4.When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids (**recommendation category: A, evidence type: 4**).

5.When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day (**recommendation category: A, evidence type: 3**).

6.Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (**recommendation category: A, evidence type: 4**).

7.Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (**recommendation category: A, evidence type: 4**).

Assessing Risk and Addressing Harms of Opioid Use

8.Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present (**recommendation category: A, evidence type: 4**).

9.Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (**recommendation category: A, evidence type: 4**).

10.When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (**recommendation category: B, evidence type: 4**).

11.Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (**recommendation category: A, evidence type: 3**).

12.Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (**recommendation category: A, evidence type: 2**).

CDC Recommendations - Summary

1. Opioids are not first line
2. Establish Goals for Pain and Function
3. Discuss Risks and Benefits
4. Use immediate-release opioids when starting
5. Use the lowest effective dose
6. Prescribe short durations for acute pain
7. Evaluate benefits and harms frequently
8. Use strategies to mitigate risk
9. Review PDMP data
10. Use urine drug test
11. Avoid concurrent opioid and benzodiazepine prescribing
12. Offer treatment for opioid use disorder

Opioids in the acute phase

- Acute phase: 0-6 weeks post episode of pain or surgery
- Lowest necessary dose and for the shortest duration (usually less than 14 days)
- Receiving a one week supply or ≥2 opioid prescriptions after an acute back sprain is associated with doubling of the patient's risk for long-term disability

Opioids in the acute phase

- Clinical recommendations
  1. Expect patients to improve in function and pain and resume their normal activities in a matter of days to weeks after an acute pain episode.
     - Strongly consider re-evaluation for those who do not follow the normal course of recovery.
  2. Assess function and pain at baseline and with each follow-up visit when opioids are prescribed. Document clinically meaningful improvement in function and pain using validated tools.
  3. Taper opioids by 6 weeks if clinically meaningful improvement in function and pain has not occurred.
  4. Prescribe opioids for dental pain only after complex dental procedures and at the lowest dose and duration.

Critical recommendations

- Overtreatment, excess attention, or labeling a patient during the acute pain phase can precipitate or increase “sickness behavior,” and avoidance of activity

- **Importance of activity:** Unless contraindicated, advise to remain active and engaged in usual activity seems to be the most effective intervention early in the course of a pain episode.
  - A well-studied example is low back pain with or without sciatica. For this condition, advice to remain active has been repeatedly shown to predict better pain and functional outcomes than advice to take bed rest, and is as effective as specific exercises.

- **Psychosocial factors:** These factors, such as normal activity (fear avoidance), catastrophizing, and low expectations of healing are strong predictors of the development of persistent pain in patient populations. Practitioners’ beliefs and attitudes can impact clinical decision-making and subsequent treatment outcomes.
  - The treatment of depression was shown to have significant benefits in terms of pain reduction, improved functional status, and quality of life in a group of older individuals with depression and arthritis.

Clinically Meaningful Improvement in Function

- Clinically meaningful improvement is defined as an improvement in pain AND function of at least 30% as compared to the start of treatment or in response to a dose change.

- A decrease in pain intensity in the absence of improved function is not considered meaningful improvement except in very limited circumstances such as catastrophic injuries (e.g. multiple trauma, spinal cord injury, etc.)

Opioids in the sub-acute phase

- Sub-acute phase: 6-12 weeks post episode of pain or surgery
- Patients with substance use and/or psychiatric disorders are more likely to have complications from opioid use, such as misuse, abuse or overdose
- Unfortunately, patients who receive high-risk chronic opiate analgesic therapy (COAT) are also more likely to have
  - High-risk characteristics
    - Younger age
    - History of substance use disorder
    - Mental disorders
    - Presence of opioid misuse

Opioids in the sub-acute phase

- Clinical recommendations:
  1. Do not continue to prescribe opioids if use during the subacute phase does not lead to clinically meaningful improvement in function.
  2. Have a plan for how and when to discontinue opioids if treatment has not resulted in clinically meaningful improvement in function and pain.
  3. Screen for depression (PHQ-9) and anxiety (GAD-7) or other validated tools.

     ** If comorbid mental health conditions exist in the presence of pain, they need to be treated or the patient's pain will not improve regardless of opioid therapy.
  4. Do not prescribe opioids if results of a baseline UDT reveal "red flags" such as the confirmed presence of cocaine, amphetamines, non-prescribed benzodiazepines, alcohol, or any other drugs you did have knowledge of or did not prescribe.

     ** It would be prudent to have a policy regarding the concomitant use of cannabis and opioids.

Opioids in the sub-acute phase

- Evidence
  - Systematic reviews of efficacy of opioids for low back pain demonstrate modest improvement in pain but little improvement in function and no clear evidence that pain relief will be sustained.
  - For headaches and fibromyalgia, there is a paucity of evidence on effectiveness.
    - European Federation of Neurological Societies and the American Academy of Neurology recommend against the use of opioids for headache

Opioids and chronic disability

- Chronic opiate analgesic therapy (COAT) that focuses only on pain intensity can lead to rapidly escalating dosage with deterioration in function and quality of life.
- There is evidence in the worker's compensation population that early opioid use increases the risk of disability and it is difficult to discontinue COAT once initiated, as over 60% of patients taking opioids for at least 3 months are still on opioids 5 years later.
- More effective early intervention strategies for acute low back pain, such as physical activity and emphasizing options for staying at or returning to work, are recommended to avoid transitioning to chronic low back pain.
- By 2011, nearly 25% of disabled Medicare beneficiaries under 65 were on opioids chronically. Preventing a transition from acute and subacute pain to chronic pain and disability could have a significant impact on saving productive lives.

Prescribing opioids for chronic non-cancer pain

- Opioids in the chronic phase
  - >12 weeks after an episode of pain or surgery
- The key to effective COAT is sustained improvement in physical function and pain with frequent monitoring to adjust therapies as necessary.
- Assess and document function
- Discuss the potential benefits and risks associated with COAT including addiction and overdose. Have a signed opioid treatment agreement to document this discussion and set behavioral expectations including the use of a single prescriber or pharmacy.

Prescribing opioids for chronic non-cancer pain

- Use extreme caution and consider consultation before prescribing COAT in patients with:
  - comorbid health disorders (especially PTSD and major depressive disorder)
  - family or personal history of substance use disorder
  - concurrent use of benzodiazepines or sedative-hypnotics
  - medical conditions that could increase sensitivity to opioid-related side effects (e.g. COPD, CHF, sleep apnea, advanced age, or renal or hepatic dysfunction).
- Reassess the need for COAT in transferred patients who are already using opioids
  - If current treatment is not benefiting the patient, a dose reduction or discontinuation is warranted.
  - Consider non-opioid options for pain treatment.
- Consult with a pain management specialist before exceeding 30 mg/day MED.

Prescribing opioids for chronic non-cancer pain

- Check the state's PDMP
- Prescribe opioids in multiples of a 7-day supply to reduce the incidence of the supply ending on a weekend.
- Repeat random UDTs at the frequency determined by the patient's risk category to identify aberrant behavior, undisclosed drug use and/or abuse and verify compliance with treatment
- Initiate a bowel regimen to prevent opioid-induced constipation, especially in older adults.
- Monitor for opioid-related adverse outcomes such as central sleep apnea, endocrine dysfunction, opioid-induced hyperalgesia, opioid use disorder, or signs of acute toxicity.
- Monitor for medication misuse, aberrant drug-related behaviors and diversion

Prescribing opioids for chronic non-cancer pain

- Do not combine opioids with benzodiazepines, sedative-hypnotics, or barbiturates.
- Increase the frequency of monitoring for high-risk patients on opioids. Monthly visits are often needed.
- 1 in 5 patients on chronic opioid analgesic therapy will develop opioid use disorder as defined by DSM 5.
  - If tolerance and withdrawal are considered, the prevalence rises to nearly 1 in 3.
- Discontinue opioids during this phase based on the criteria on the next slide.

When to Reduce, Taper, or Discontinue COAT

- Patient requests opioid taper
- Patient is maintained on opioids for at least 3 months, and there is no sustained clinically meaningful improvement in function (CMIF).
- Patient's risk from continued treatment outweighs the benefit (decreased function and increased risk for opioid-related toxicity from concurrent drug therapy or comorbid medical conditions)
- Patient has experienced a severe adverse outcome or overdose event
- Patient has a substance use disorder (not tobacco)
- Patient exhibits aberrant behaviors (see table of aberrant behaviors)

Aberrant Behaviors

LESS SUGGESTIVE FOR ADDICTION BUT ARE INCREASED IN DEPRESSED PATIENTS	MORE SUGGESTIVE OF ADDICTION AND ARE MORE PREVALENT IN PATIENTS WITH SUBSTANCE USE DISORDER
• Frequent requests for early refills; claiming lost or stolen Rx • Opioids used more frequently, or at higher doses than prescribed • Using opioids to treat non-pain symptoms • Borrowing or hoarding opioids • Using alcohol or tobacco to relieve pain • Requesting more or specific opioids • Recurring ER visits for pain • Concerns expressed by family • Unexpected drug test results • Inconsistencies in the patient's history	• Buying opioids on the street; stealing or selling drugs • Multiple prescribers ("Doctor Shopping") • Trading sex for opioids • Using illicit drugs, +UDT for illicit • Forging prescriptions • Aggressive demand for opioids • Injecting oral/topical opioids • Signs of intoxication (EtOH odor, sedation, slurred speech, motor instability, etc)

Patient #1- “Rand”
62yo M with chronic right post surgical knee pain

- Opiates
  - Does he need anything?
  - What he has previously tried?
  - What dose?

- Opiates
  - Yes – he wants to return to work but NSAIDs alone have not been enough
  - He has tried hydrocodone (IR and ER), oxycodone, and tramadol. He received benefit with hydrocodone IR but no benefit with hysingla, Percocet, or tramadol
  - Lowest dose as possible

Patient #2 – "Nance"
65yo F with chronic lumbar pain and radicular leg pain s/p four surgeries

- Opiates
  - Does she need anything?
  - What is her opiate history? Maximum dosage?
  - What dose do you continue?

- Medications
  - Yes – she wants to continue opiate management as she feels that it is the only thing that has helped.
  - She has tried hydrocodone, tapentadol, methadone, oxycodone, and morphine. At her maximum intake, she was taking methadone 10mg PO TID and hydrocodone 10mg PO QID. 130 OME. At this dose, she was not pleased with her functional level.
  - Lowest dose as possible

MED for selected opioids

Opioid	Approximate Equi-analgesic Dose
Morphine (Reference)	30 mg
Codeine	200 mg
Fentanyl transdermal	12.5 mcg/hr
Hydrocodone	30 mg
Hydromorphone	7.5 mg
Oxycodone	20 mg
Oxymorphone	10 mg
Tapentadol	75 mg
Tramadol	300 mg
Methadone	10 mg (*)

Med calculation

For patients taking more than one opioid, the MED of the different opioids must be added together to determine the cumulative dose. For example, if a patient takes six Hydrocodone 5 mg/Acetaminophen 325 mg and two 20 mg Oxycodone extended release tablets per day, the cumulative dose may be calculated as follows:

1. Hydrocodone 5 mg x 6 tablets per day = 30 mg per day
2. Using the Equinalgesic Dose table, 30 mg Hydrocodone = 30 mg Morphine equivalents
3. Oxycodone 20 mg x 2 tablets per day = 40 mg per day
4. Per Equinalgesic Dose table, 20 mg Oxycodone = 30 mg Morphine so 40 mg Oxycodone = 60 mg Morphine equivalents
5. Cumulative dose is 30 mg + 60 mg = 90 mg Morphine equivalents per day

Dosing threshold for selected opioids

Opioid	Recommended dose threshold for pain consult	Recommended starting dose	Considerations
Hydrocodone	30mg per 24 hours	Immediate release 5-10 mg q 12 hours	Avoid concurrent use of any OTC products containing same ingredient.
Oxycodone	30mg per 24 hours	Immediate release 5 mg q 12 hours	Avoid concurrent use of any OTC acetaminophen products.

Dosing threshold for opioids

Opioid	Recommended dose threshold for pain consult	Recommended starting dose	Considerations
Morphine	30mg per 24 hours	Immediate release 10 mg q 12 hours Sustained release 15 mg q 12 hours	Metabolites may accumulate in patients with impaired renal or hepatic function resulting in prolonged effects and toxicity.

Dosing thresholds for opioids

Opioid	Recommended dose threshold for pain consult	Recommended starting dose	Considerations
Tramadol	200mg per 24 hours	Immediate release 50 mg q 8 hours	Dual mechanism of action- binds to mu-opioid receptors and inhibits reuptake of norepinephrine. Use caution when combining with other medications that affect serotonin as it may increase risk of seizures and serotonin syndrome. Do not exceed 400 mg/day for IR
Tapentadol	200mg per 24 hours	Sustained release 50 mg q 12 hours	Do not exceed 600 mg/day for IR and 500 mg/day for SR.

Dosing threshold for selected opioids

Opioid	Recommended dose threshold for pain consult	Recommended starting dose	Considerations
Buprenorphine Transdermal	10 mcg	5 mcg/hr q 7 days	Maximum dose: 20 mcg/hr due to risk of QTc prolongation
Fentanyl Transdermal	Before initiation	12.5 mcg/hour q 72 hours	Use only in opioid-tolerant patients who have been taking ≥60 mg MED daily for a week or longer.

Naloxone

- CDC #8 - Mitigate risks
  - Consider naloxone therapy:
    - History of overdose
    - History of substance abuse
    - Concurrent benzodiazepine use
    - High dose opiates greater than 50 OME
    - Other medical comorbidities (COPD, OSA, etc)

Monitoring Opioid therapy

- UDT
  - Assessing Risk (Opioid risk tool (ORT), SOAPP-r, PMQ)
  - How frequently and when to confirm
- Aberrant Drug Behaviors
- Diversion
- Addiction or Opioid Use Disorder

“Red Flags” indicating need for further patient evaluation

- Presence of neurological deficits
- History of malignancy
- New signs and symptoms of underlying disease
- Sudden increase in severity or nature of previous pain complaint
- Unexpected results from urine drug tests (ex: positive for cocaine, amphetamines, alcohol, etc.)
- Wounds that do not heal within normal time expectations
- Evidence of adverse side effects from current treatment regimen

Symptoms and Treatment of Opioid Abstinence Syndrome (aka Withdrawal)

Restlessness, Sweating, or Tremors	CLONIDINE 0.1-0.2mg orally every 6HRS or Transdermal patch 0.1-0.2mg weekly (if using the patch, oral meds may be needed for the first 72 hours) during taper. Monitor for significant hypotension and anticholinergic side effects
Nausea	Anti-emetics such as ondansetron or prochlorperazine
Diarrhea	Loperamide or Dicyclomine
Muscle pain, Neuropathic pain, or Myoclonus	NSAIDs, gabapentin, muscle relaxants
Insomnia	Sedating antidepressants (ex: Nortriptyline 25mg at bedtime or Mirtazapine 15mg at bedtime or Trazadone 50mg at bedtime). Avoid benzodiazepines or sedative-hypnotics

Patient #1 – “Rand”
62yo M with chronic right post surgical knee pain

- Update
  - Rand continues to work full time in the lime factory
  - He boxes three times a week
  - He currently is taking hydrocodone/APAP 7.5/325mg PO QID (30 mme) daily and OTC ibuprofen
    - He did suffer a rotator cuff tear and underwent surgery. Increased hydrocodone/APA to 10/325mg PO QID for one month before returning to pre-surgical dosing

Patient #2 – "Nance"
65yo F with chronic lumbar pain and radicular leg pain s/p four surgeries

- Update
  - Nance underwent SCS permanent implantation on 4/28/18.
  - Since her implant, she has drastically increased her function
    - She walks on bikes five times a week
    - She has returned to gardening
  - She currently is taking hydrocodone/APAP 7.5/325mg PO BID-TID (75pills/month) (15-22.5 mme), methocarbamol 750mg PO TID prn spasm, and topiramate 100mg PO BID
    - She underwent TKA March 2019 and was rotated to Percocet in the post operative period for 2 weeks before resuming pre-surgical hydrocodone.

Keys to success

- SMITE
- Non pharmacologic therapy
- Multidisciplinary care
- Proper Evaluation
  - When Do I Refer
- Identify comorbidities impacting the pain condition
  - Depression, Anxiety, PTSD, or other psychological comorbidity
  - Sleep disturbance, Sleep Apnea, obesity etc
  - Secondary gain, perceived disability

Thank You

Questions?

Rheumatoid Arthritis

2019 Rheumatology Update for Primary Care and Hospital Medicine
August 24, 2019

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Rheumatoid Arthritis

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Relevant Disclosures: None

Rheumatoid Arthritis - Outline

- Definition
- Epidemiology
- Pathogenesis
- Clinical Manifestations
- Diagnosis
- General Principles of Treatment (more to come in Dr. Danila's talk)

Rheumatoid Arthritis

A chronic arthritis characterized by:

- symmetrical inflammation (synovitis) involving both small and large joints that leads to
- progressive joint destruction and loss of function
- the presence of serum autoantibodies.

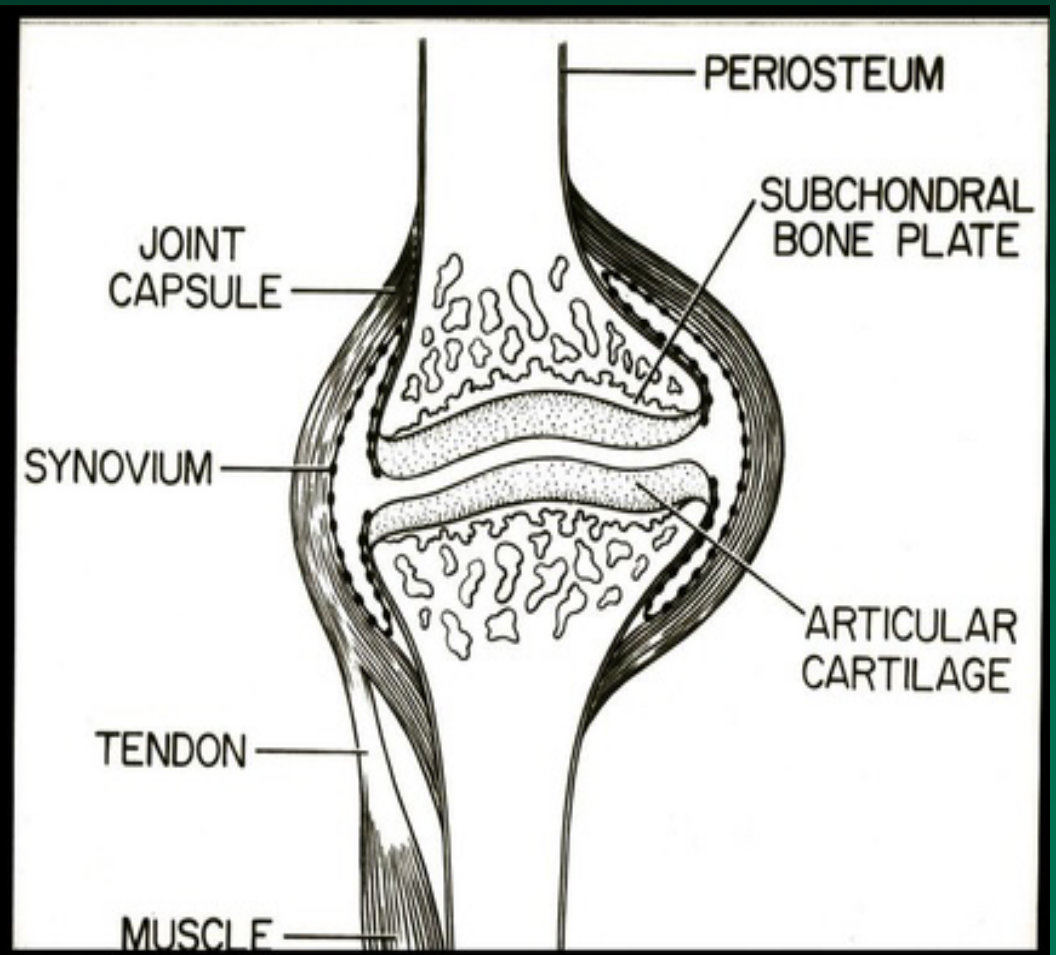
Epidemiology

- Incidence: 0.2 - 0.4 new cases/1000 persons/year
- Peak incidence - women age 30-50
- Prevalence: 0.8 – 1.3% of populations worldwide. Less is known about prevalence in Africans and African-Americans, but is perhaps lower than in Caucasians
- About 2/3 of patients are women, with highest prevalence in older women

Risk Factors

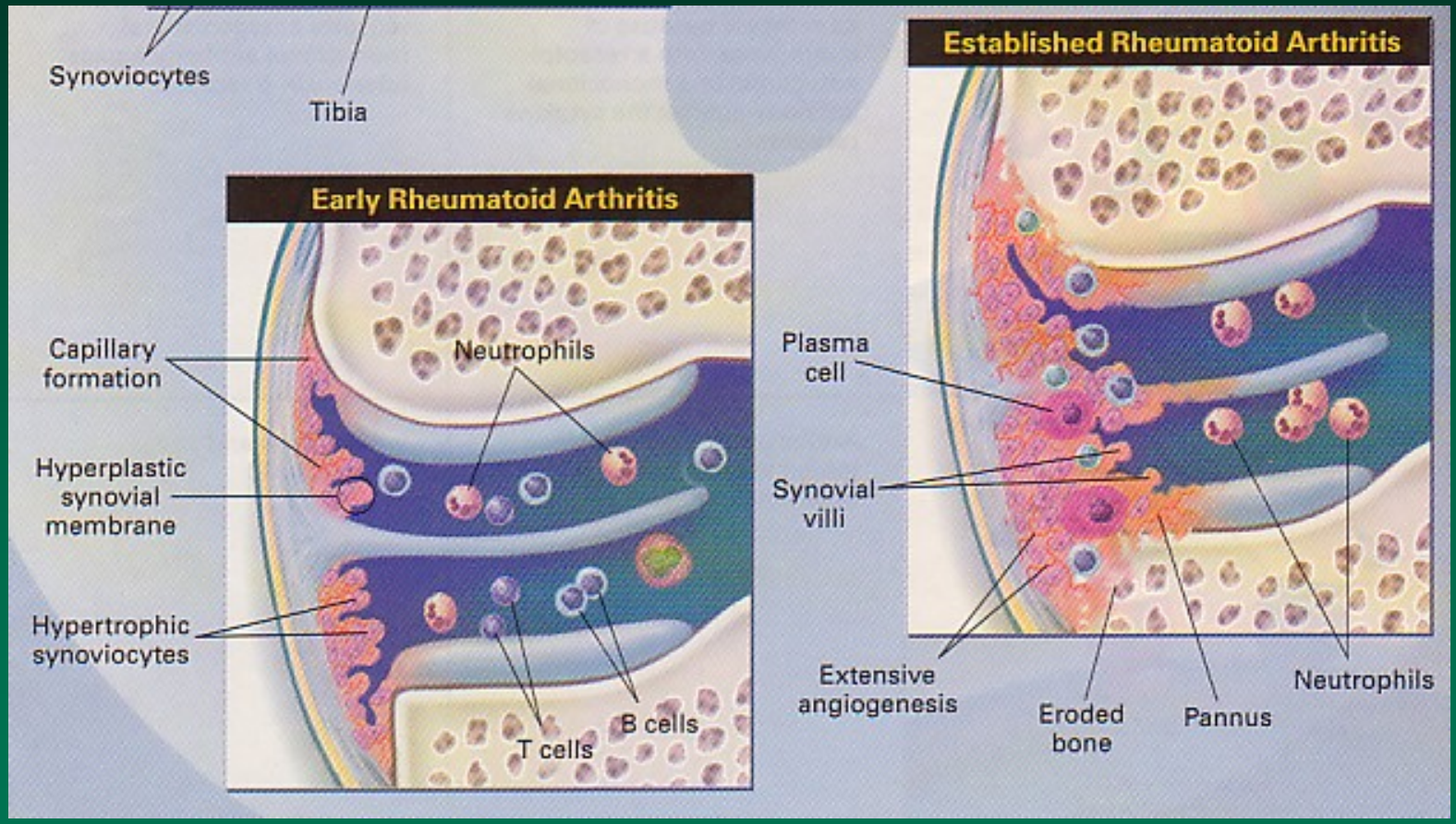
- Genetic
  - Monozygotic twins
    - 15-30% concordance
  - HLA-DRB1 is the most strongly associated locus.
    - There are about 110 other risk loci with small contributions
    - Some genetic loci vary by race/ethnicity
- Demographic
  - Gender (women)
  - Role of Female Sex Hormones, Pregnancy have been investigated with conflicting results
- Environmental Exposures
  - Infections
  - Proteus, Mycoplasma
  - EBV, Parvovirus
  - Cigarette smoking

Anatomy of a Normal Joint



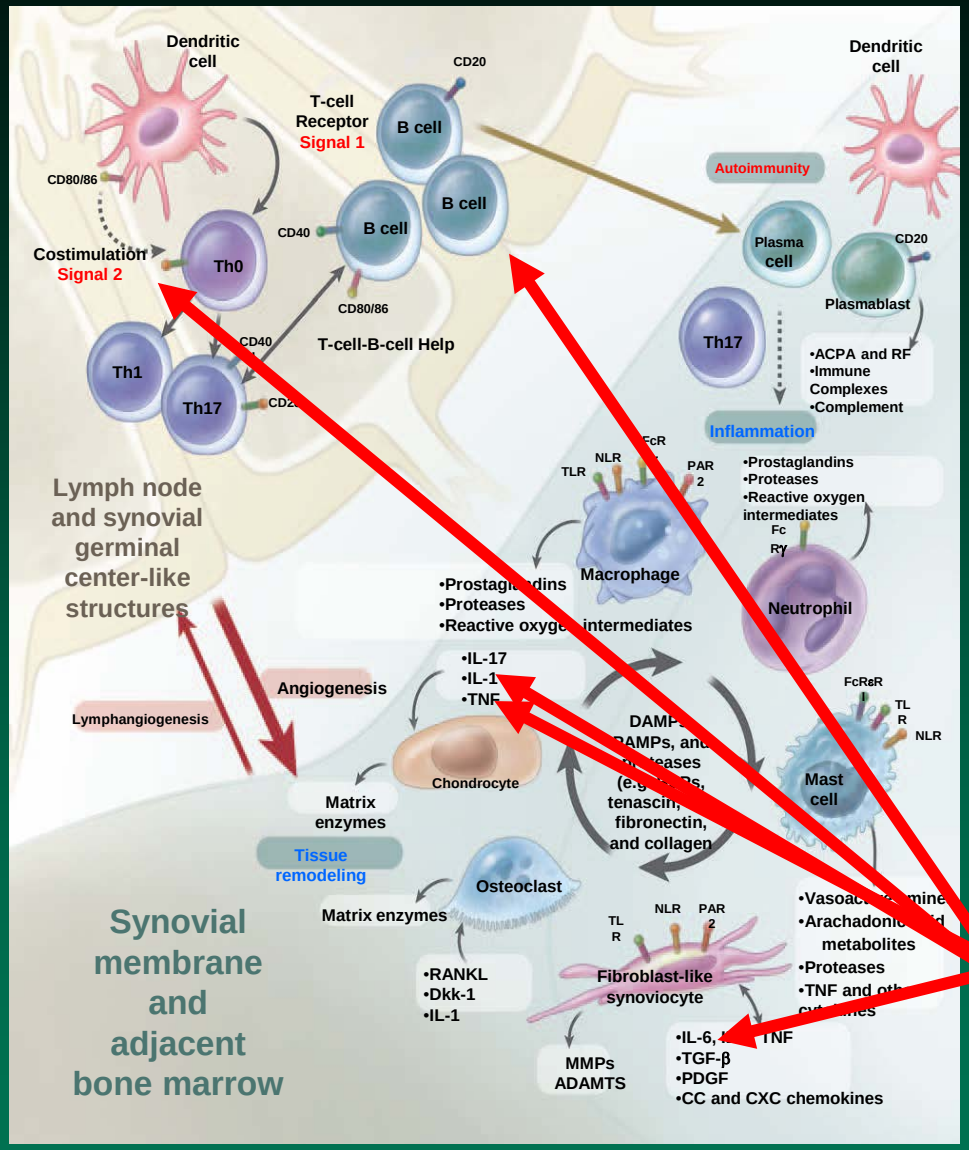
Pathogenesis of Rheumatoid Arthritis

- Influx of monocytes/lymphocytes into synovium
- Influx of neutrophils into synovial fluid
- Maturation of monocytes into macrophages/osteoclasts
- Synovial fibroblast proliferation



From: Choy and Panayi New Engl J Med. 344: 907-16, 2001.

Adaptive and Innate Immune Processes within the RA Joint



Targets of FDA-approved biologic medications

Rheumatoid Arthritis: Clinical Manifestations

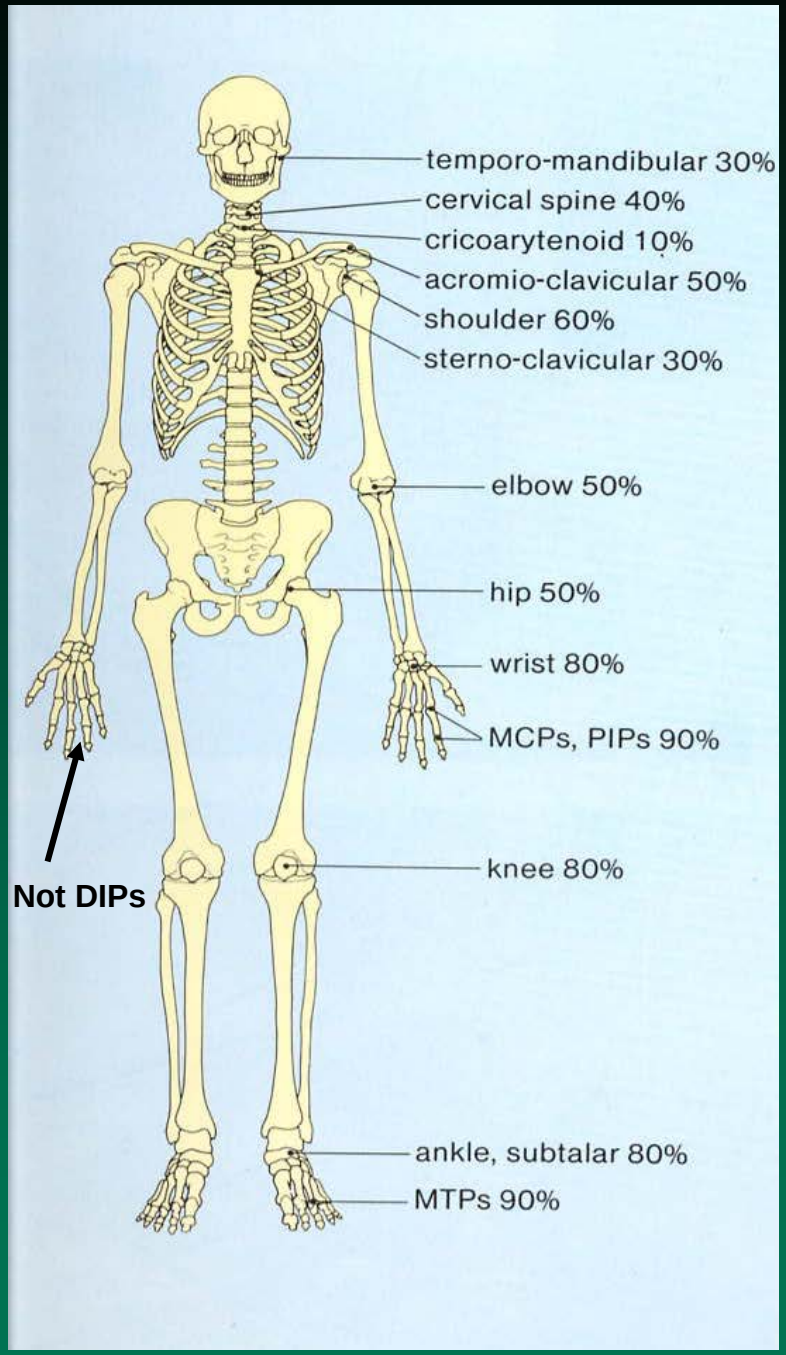
- Symptoms > 6 weeks' duration
  - Often lasts the remainder of the patient's life
- Inflammatory synovitis
  - Palpable synovial swelling
  - Morning stiffness >1 hour, fatigue

Rheumatoid Arthritis: PIP Swelling

- Swelling is in the area of the joint capsule
- Synovial thickening feels like a firm sponge

RA: Joint Distribution

- Symmetrical and polyarticular (>3 joints)
- Typically involves wrists and finger joints
- Typically spares certain joints:
  - Thoracolumbar spine
  - Distal Inter-Phalangeal (DIP) joints of the fingers and Inter-Phalangeal (IP) joints of the toes



Chronic RA Hand Deformities

These may evolve over time, particularly in the absence of appropriate treatment

- Ulnar deviation at MCP's
- Radial deviation at wrists
- Swan-neck deformities
- Boutonniere deformities
- Tendon nodules
- Tendon rupture
  - 3rd, 4th, and 5th extensor tendons
- Carpal tunnel syndrome
- Ulnar neuropathy

Rheumatoid Arthritis: Ulnar Deviation and MCP Swelling

- Prominent ulnar deviation in the right hand
- MCP and PIP swelling in both hands
- Synovitis of left wrist

Rheumatoid Arthritis: Swan Neck and Boutonnière Deformities

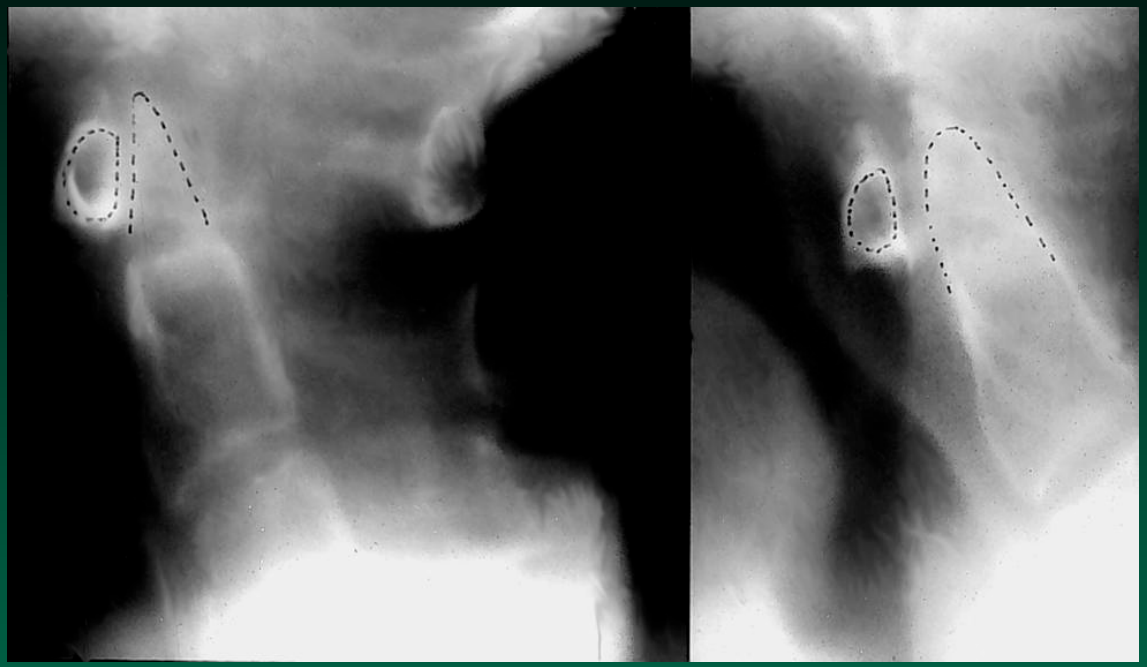
- Late-stage findings indicating serious changes in the joints
- Swan neck (digits 2 to 4) is caused when the flexor tendons slip dorsally and act as extensors of the PIP joint
- Boutonnière (digit 5) is the reverse; extensors act as PIP flexors

RA – foot and ankle complications

- MTP synovitis
  - Direct palpation
  - Global lateral/medial squeezing
- MTP subluxation
  - Cock-up deformities of toes
  - Callus formation on soles
  - Overlapping toes
- Ankles - synovitis/effusions
  - Tarsal tunnel syndrome -- medial foot and sole paresthesias

RA Feet – Cock-up Deformity

RA Cervical Spine Involvement



- RA can cause asymptomatic instability of the neck due to destruction of stabilizing ligaments
- Predominantly occurs at C1/C2 and C3/C4
  - lateral extention view on left, flexion view on right—note widening of space between dens of C2 and anterior transverse process of C1
- Minor trauma can cause spinal cord injury

RA—Systemic Disease with Extra-articular Features

- Constitutional sx's
  - Fever/fatigue/wt loss
- Eye
- Lung
  - Interstitial disease
  - Pleuritis
- Cardiac
  - Pericarditis
- Sjögren's syndrome
  - Dry eyes/mouth
- Vascular
  - Rheumatoid vasculitis
- Neurologic
  - Foot Drop (vasculitis)
  - Carpal Tunnel Syndrome
    - (compression of median nerve by wrist synovitis)
- Hematologic
  - Anemia of Chronic Disease
  - Felty's Syndrome
    - Leucopenia, splenomegaly

Extraarticular Features

- Rheumatoid nodules (15%)
  - Central necrosis surrounded by palisading fibroblasts and lymphocytes
  - Subcutaneous, bursal, tendon sheaths
  - Extensor surfaces / Pressure points
    - Forearms
    - Achilles
    - Ischial area
    - MTP's
    - Flexor surface of fingers

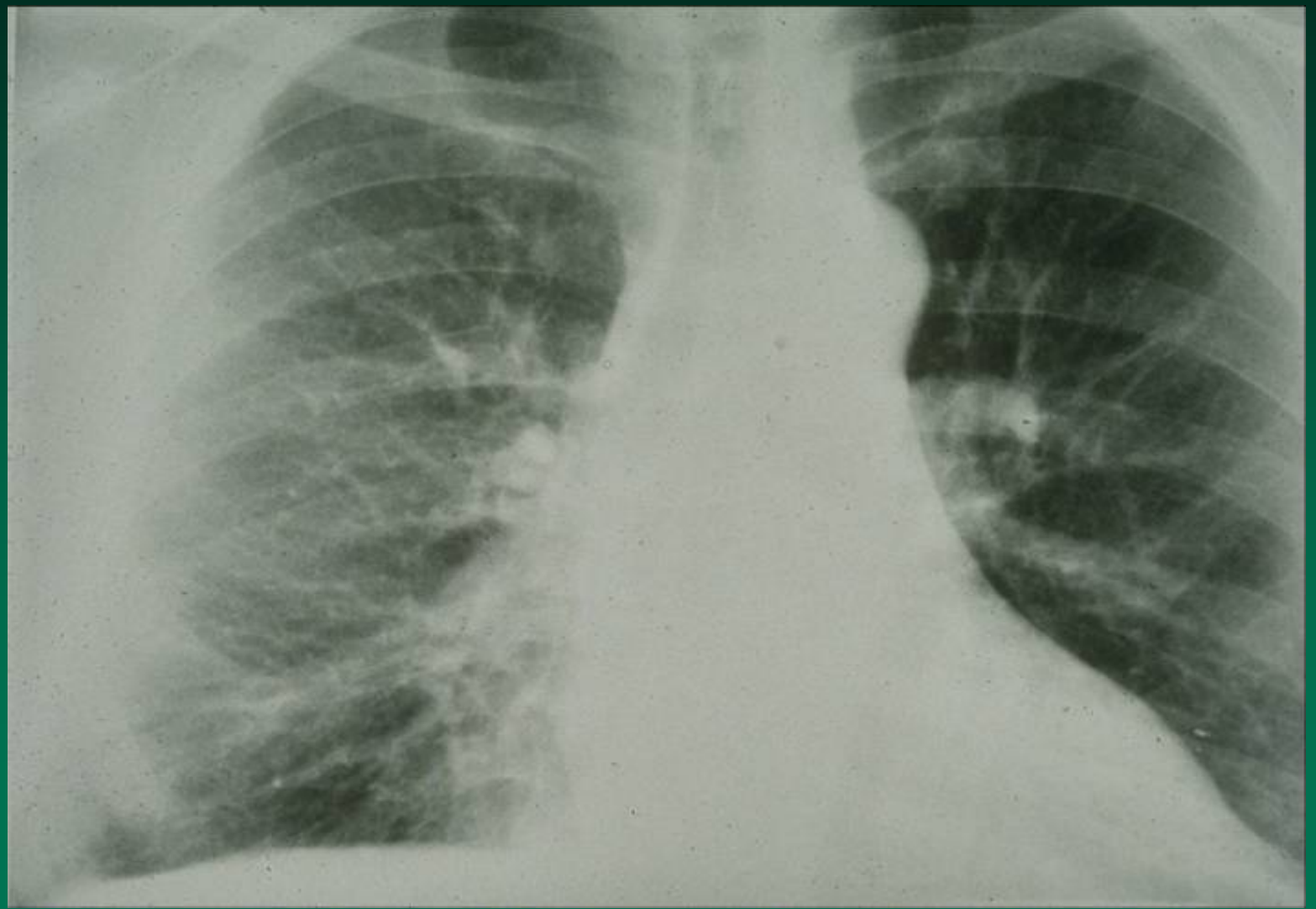
Rheumatoid Nodules

- Subcutaneous or periosteal at pressure points
- More common in patients with serum rheumatoid factor

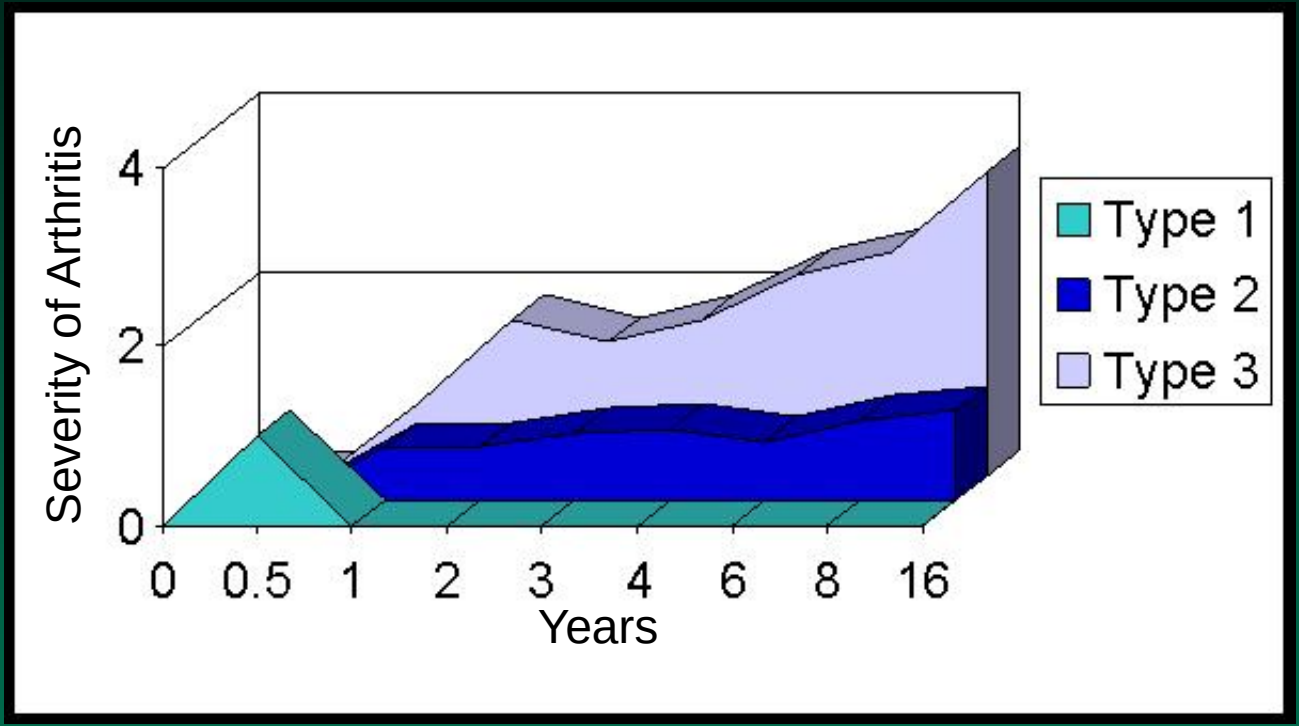
RA: Extra-articular features: Lung Disease

- Pleurisy with/without effusion
- Nodular Disease
  - Necrobiotic nodules
  - Caplan's Syndrome
- Interstitial Lung Disease
- "Airway Disease"/Bronchiolitis Obliterans
- Pulmonary arteritis/Pulmonary hypertension
- Pneumonitis

RA: Extra-articular features
Interstitial lung disease



Clinical Course of RA



Type 1 = Self-limited—5% to 20%
Type 2 = Minimally progressive—5% to 20%
Type 3 = Progressive—60% to 90%

Pincus. *Rheum Dis Clin North Am*. 1995;21:619.

Classification Criteria

- Employed to define subjects for entry into studies
- Meeting criteria enhances likelihood a patient has the disorder being studied
- Not necessary to commit to memory, but note the features that render the highest point value

ACR/EULAR 2010 RA Classification Criteria: A Focus on Early Diagnosis

Mandatory Requirements for Testing

- Swelling in at least 1 joint
- Synovitis is not better explained by an alternative diagnosis

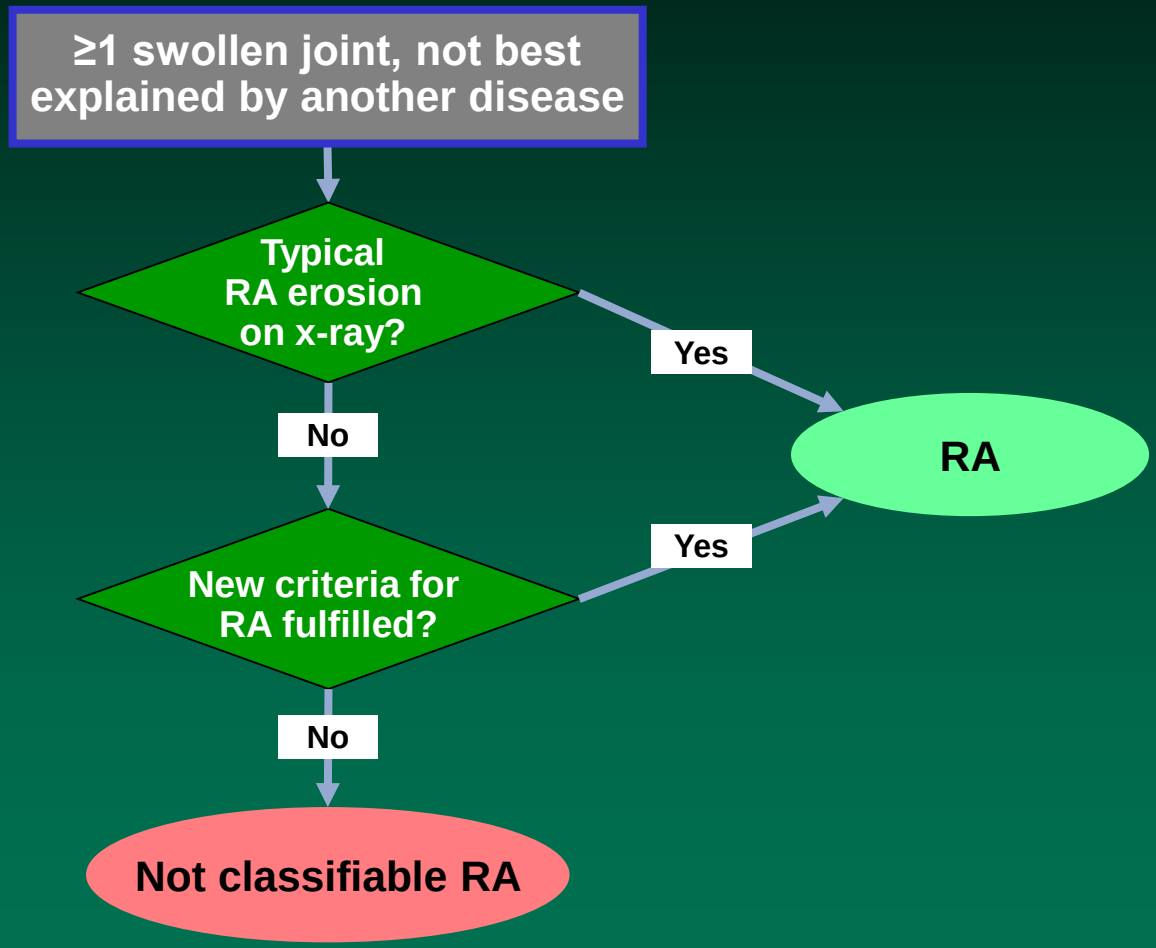
Cutpoint for RA ≥6

In addition to criteria above, the following patients are classified as having RA:
Erosive disease; with a history compatible with prior fulfillment of criteria above
Long standing disease; including inactive disease who have previously fulfilled criteria above

	Score (0-10)
JOINTS	
=1	0
>1 large	1
1-3 small	2
4-10 small	3
>10 small or large	5
SEROLOGY	
Negative	0
Low positive	2
High positive	3
DURATION	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE	
Normal	0
Abnormal	1

Aletaha D, et al. *Arthritis Rheum*. 2010;62:2569-2581.

ACR/EULAR 2010 RA Classification Criteria: Who Should Be Tested?



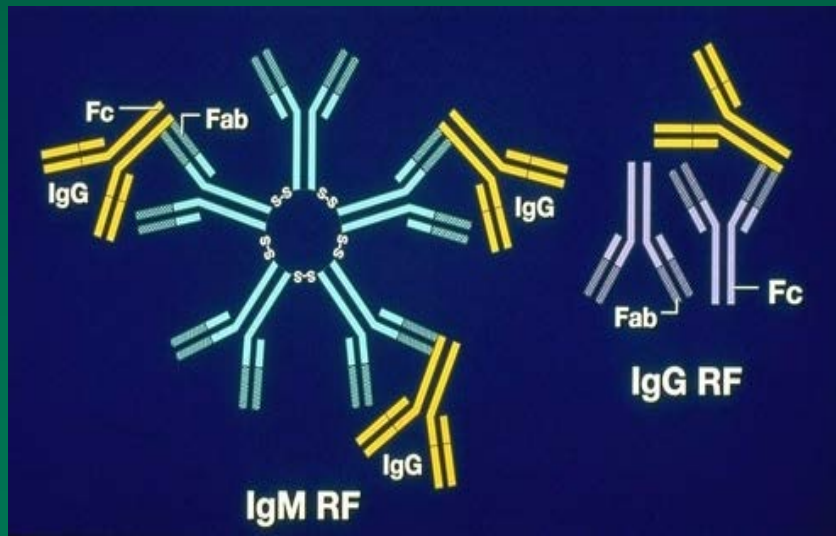
Aletaha D, et al. *Arthritis Rheum*. 2010;62:2569-2581.

Autoantibodies in RA

- Rheumatoid factor
- Anti-CCP antibodies

Rheumatoid Factor in RA

- Autoantibody against Fc fragment of normal immunoglobulin (Ig)
- Present in serum of 70-80% of RA patients
- Can predate diagnosis of RA
- Present in immune complexes in synovial tissue
- Associated with:
  - More severe synovitis
  - Radiographic severity
  - Rheumatoid nodules, extra-articular features
  - Higher mortality



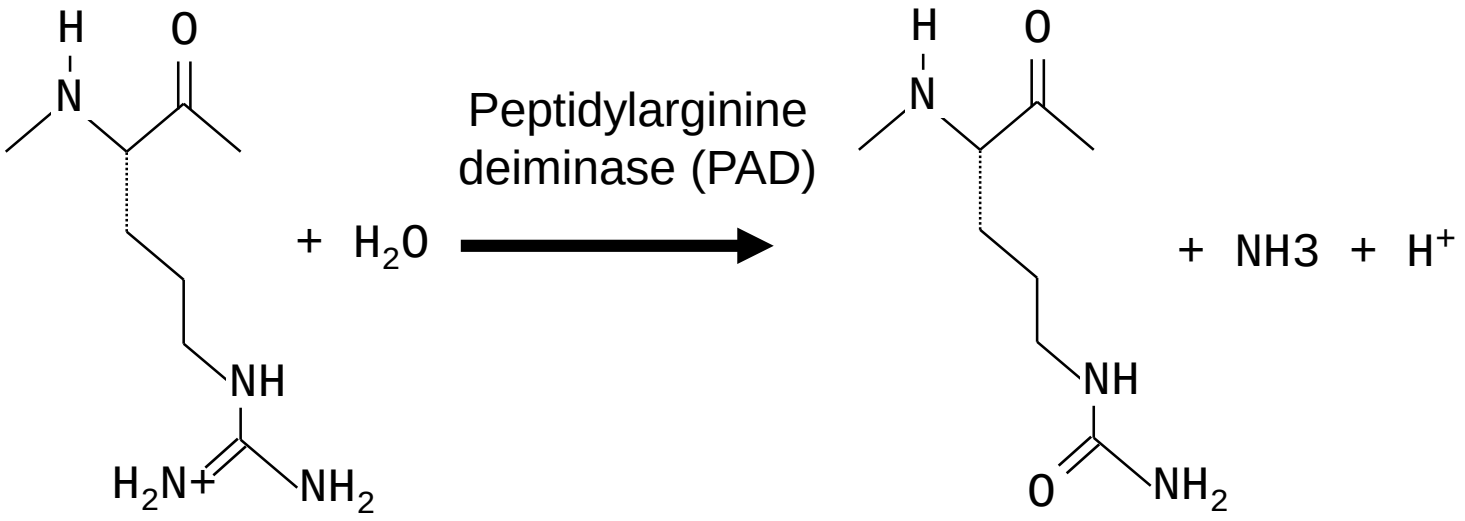
RF is not specific for RA
It can be present in other conditions

- Other autoimmune diseases
  - Primary Sjögren's Syndrome, SLE
- Chronic infections
  - Hepatitis B and C, SBE, Viral, Parasites, TB
- Pulmonary inflammation
  - Sarcoidosis, IPF, Silicosis, Asbestosis
- Malignancy
- Healthy
  - 4% young
  - 5-25% > age 60

Anti-Cyclic Citrullinated Peptide (CCP) Antibody

- Present in serum of 50-70% of RA patients.
- Relatively specific for RA (~90%).
- Associated with:
- More severe synovitis
- Radiographic severity
- Can be present in the preclinical phase.
  - Initial citrullination of peptides with attendant autoantibody production may occur in the lung

Citrullination (deimination) of peptidylarginine by peptidylarginine deiminase



Peptidylarginine
(+ charged)

Peptidylcitrulline
(neutral)

The guanidino group of arginine is hydrolyzed, yielding a ureido group and ammonia and changing a charged amino acid residue to a neutral one.

Adapted from Vossenaar et al. Bioessays 25 (11):1106-1118, 2003.

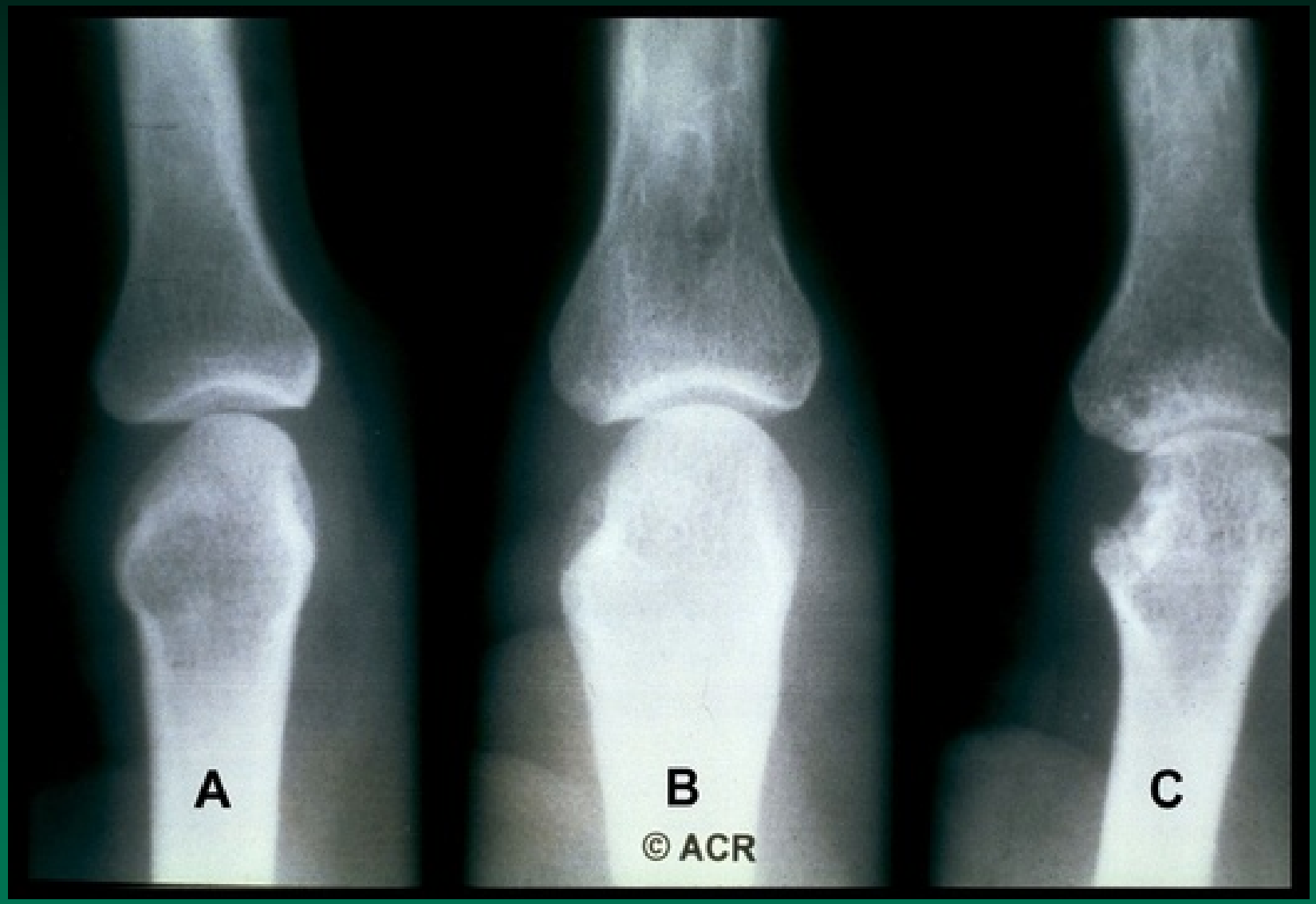
Other Clinical Laboratory findings – Evidence of Inflammation

- Synovial Fluid – WBC > 2,000/mm^3
  - Predominance of neutrophils
- Serum – Acute phase proteins
  - CRP
  - Ferritin
- Erythrocyte sedimentation rate

Radiography

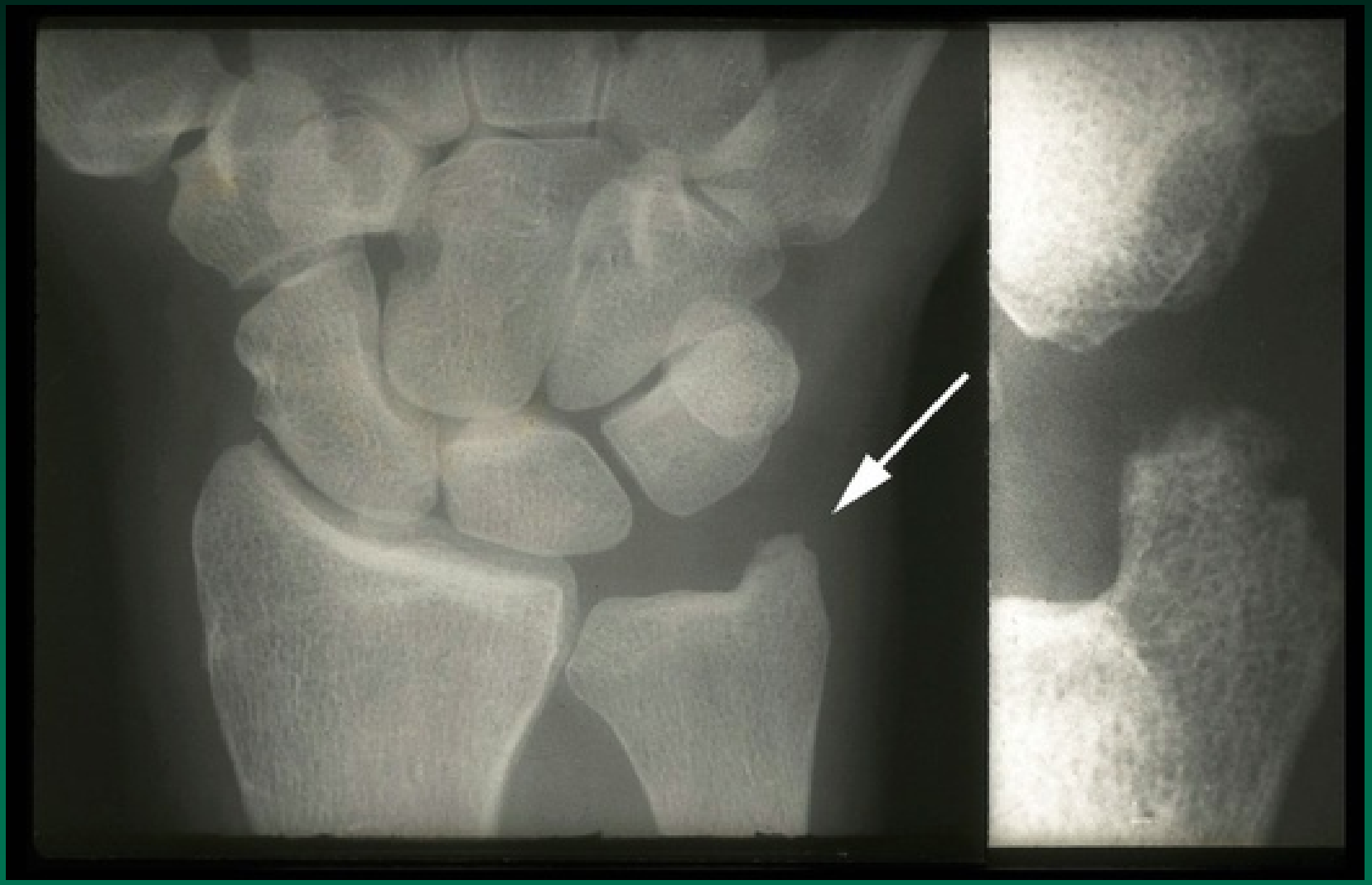
- Periarticular osteopenia
- Symmetric joint space loss
- Erosions at joint margins
  - (where synovium attaches to bone)
- Absence of productive changes (osteophytes)
- Best films for diagnosis:
  - Bilateral Hand Series
  - Bilateral Foot Series
- Larger joints may not show erosions early due to thicker cartilage.

RA – Progression of a Marginal Erosion



RA Wrist X-ray: Early Disease

Marginal erosions developing on the ulnar styloid



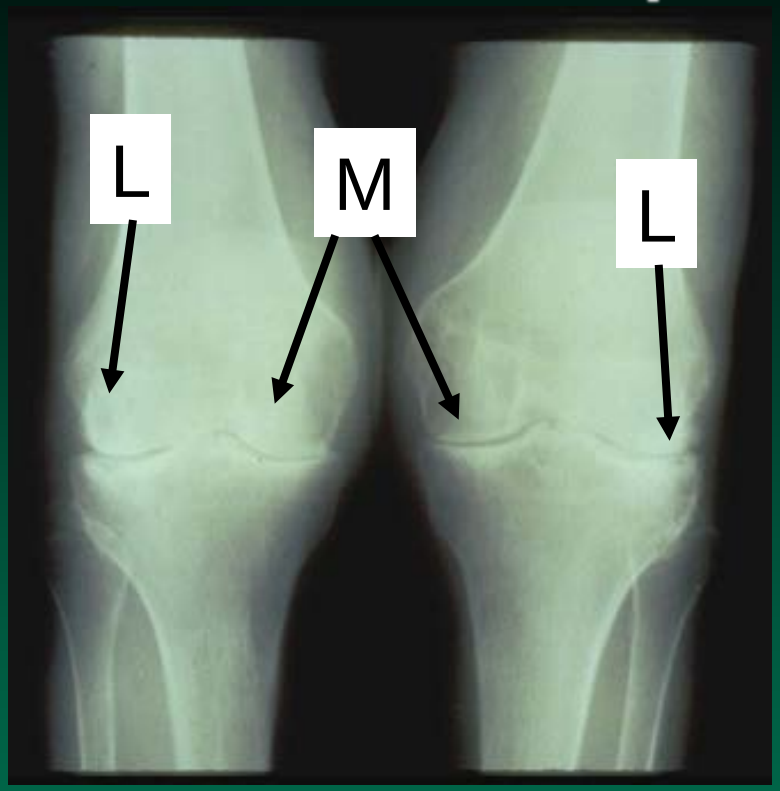
Rheumatoid Arthritis: radiographic findings

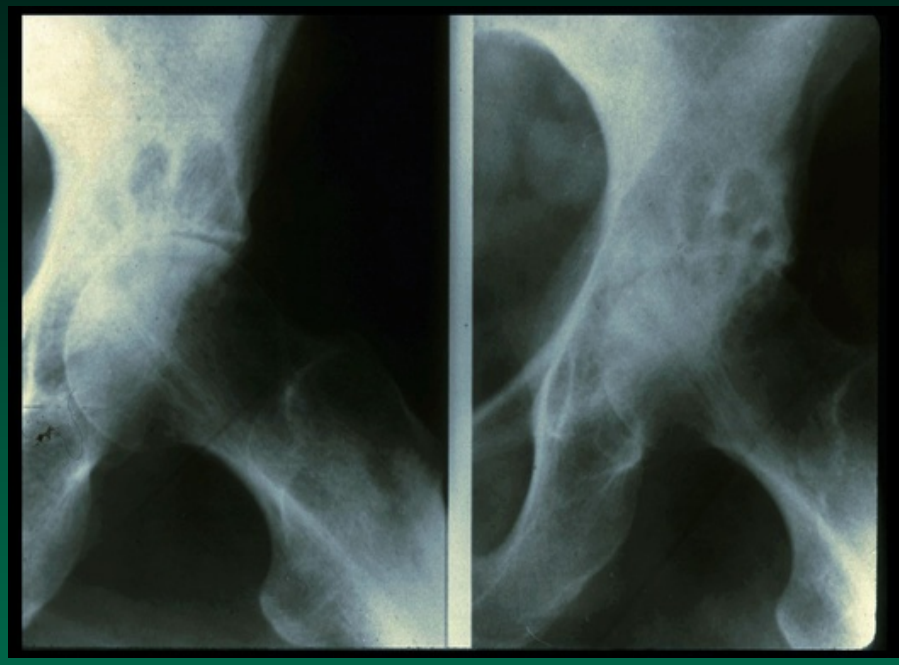
Marginal erosions (white arrows) and joint space narrowing (red arrows)

RA Hand X-ray: Advanced Disease

note erosions, joint space narrowing, MCP subluxations

RA Knee and Hip Radiographs





Knees: characteristic tricompartmental cartilage loss affecting medial (M), lateral (L), and patellofemoral (not shown) compartments

Hips: characteristic medial cartilage loss

Rheumatoid Arthritis: Treatment Principles

- Confirm the diagnosis with early referral to rheumatology
- Determine disease activity
- Start effective treatment early
- Use the safest treatment that matches the disease severity
- Monitor treatment for adverse effects
- Monitor disease activity
- Aim for Remission or Low Disease Activity
- Adapt treatment as needed
- Encourage adherence to treatment

How do we objectively measure functional status and disease activity in RA?

Tools for assessing disease activity and patient's functional status are typically composite.

These usually incorporate data from three sources:

- Patient
- Provider
- Laboratory

Measures of RA Disease Activity and Functional Status

- Modified Health Assessment Questionnaire Disability Index (HAQ-DI)
- Disease Activity Score in 28 Joints (DAS-28)
- Clinical Disease Activity Index (CDAI)

Modified Health Assessment Questionnaire – Disability Index

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Dress yourself, including tying shoelaces and doing buttons?	○	○	○	○
Get in and out of bed?	○	○	○	○
Lift a full cup or glass to your mouth?	○	○	○	○
Walk outdoors on flat ground?	○	○	○	○
Wash and dry your entire body?	○	○	○	○
Bend down to pick up clothing from the floor?	○	○	○	○
Turn regular faucets on and off?	○	○	○	○
Get in and out of a bus, car, train, or airplane?	○	○	○	○

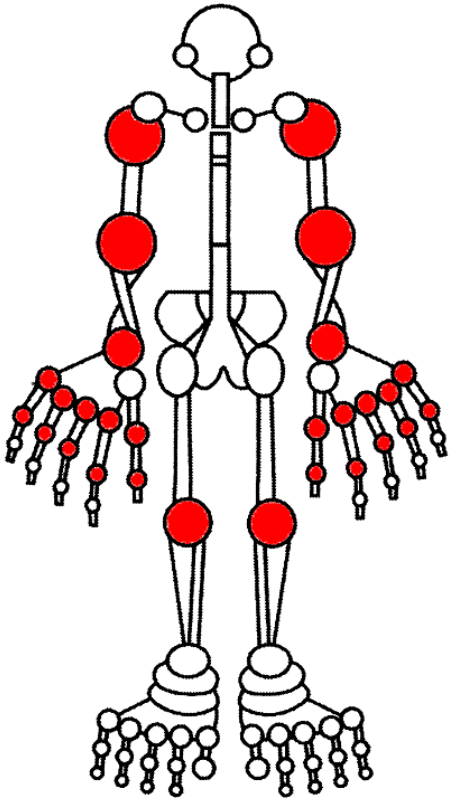
Scoring: 0, 1, 2, 3 for each response

Total sum

MHAQ score = Total/8

MHAQ score < 0.3 is considered “normal”

Components of Disease Activity Score on 28 Joints (DAS28)



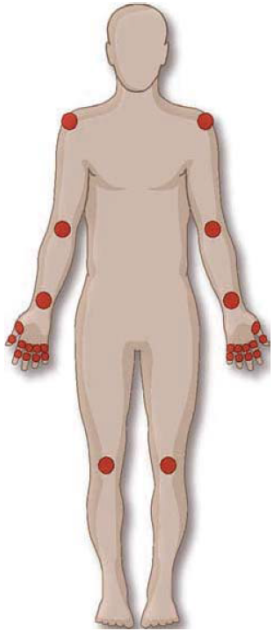
- Swollen Joint Count (SJC)
  Number of Swollen Joints out of 28 joints: Bilateral shoulders, elbows, wrists, metacarpal phalangeal (MCP) joints, proximal interphalangeal (PIP) joints, and knees
- Tender Joint Count (TJC)
  Number of Tender Joints out of 28 joints

DAS28 Instruction Video
http://www.das28.nl/das28/en/difference-between-the-das-and-das28/how-to-measure-the-das28/instruction-videos.html

van Riel PLCM, van Gestel AM, Scott DL. EULAR Handbook of Clinical Assessments in Rheumatoid Arthritis. Alphen aan den Rijn, The Netherlands: Van Zuiden Communications; 2004.

Clinical Disease Activity Index (CDAI)

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
Knee				
Total	Tender:		Swollen:	



How to Score the CDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
Add the above values to calculate the CDAI score	**(0-76)**	

CDAI Score Interpretation	
0.0 – 2.8	Remission
2.9 – 10.0	Low Activity
10.1 – 22.0	Moderate Activity
22.1 – 76.0	High Activity

Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very Well ○ 0 ○ 0.5 ○ 1.0 ○ 1.5 ○ 2.0 ○ 2.5 ○ 3.0 ○ 3.5 ○ 4.0 ○ 4.5 ○ 5.0 ○ 5.5 ○ 6.0 ○ 6.5 ○ 7.0 ○ 7.5 ○ 8.0 ○ 8.5 ○ 9.0 ○ 9.5 ○ 10 Very Poor

Your Name_____ **Date of Birth** _____ **Today's Date** _____

Provider Global Assessment of Disease Activity

Very Well ○ 0 ○ 0.5 ○ 1.0 ○ 1.5 ○ 2.0 ○ 2.5 ○ 3.0 ○ 3.5 ○ 4.0 ○ 4.5 ○ 5.0 ○ 5.5 ○ 6.0 ○ 6.5 ○ 7.0 ○ 7.5 ○ 8.0 ○ 8.5 ○ 9.0 ○ 9.5 ○ 10 Very Poor

Smolen JS, et al. *Rheumatology.* 2003;42:244-257.

Instruments Used to Measure RA Disease Activity

	Threshold of Disease Activity			
	Remission	Low	Moderate	High
DAS28-ESR	<2.6	≤3.2	>3.2 and ≤5.1	>5.1
SDAI	≤3.3	≤11	>11 and ≤26	>26
CDAI	≤2.8	≤10	>10 and ≤22	>22

Saag K, et al. *Arthritis Rheum*. 2008;59(6):762-784.
Pincus T, et al. *Arthritis Care Res* (*Hoboken*). 2011;63(8):1142-1149.
Iking-Konert C, et al. *Ann Rheum Dis*. 2011;70(11):1986-1990.

Pearls for Hospitalists

- Don’t assume that a swollen joint in a hospitalized patient with RA is due to RA (arthrocentesis – cell count, gram stain, culture of fluid are needed).
- Methotrexate lung toxicity (MTX pneumonitis) is uncommon, but may present with a variety of radiographic patterns on HRCT, including:
  - Patchy or diffuse ground glass attenuation
  - Ill-defined centrilobular nodules
  - Bilateral, reticular opacities associated with traction bronchiectasis and architectural distortion.
- Consider avoiding concomitant use of MTX and sulfonamides (eg, trimethoprim/sulfamethoxazole) due to possibility of enhanced toxicity of MTX.

Seronegative Arthritis

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UAB MEDICINE
CLINICAL IMMUNOLOGY & RHEUMATOLOGY

Disclosures

Honoraria: M3 Global Research

Learning Objectives

- Understand the distinguishing features of seronegative arthritis
- Recognize extra-articular features in seronegative arthritis
- Review classification criteria and diagnostic features of the different spondyloarthritis subtypes
- Understand initial management of seronegative arthritis

Seronegative Spondyloarthritis (SpA)

An inflammatory arthropathy characterized by the following features:

- Absence of rheumatoid factor (seronegative)
- Presence of sacroiliitis and/or spondylitis
- Enthesitis
- Dactylitis
- Uveitis
- Peripheral arthritis (typically asymmetric)
- Association with HLA B27 allele
- Associated with IBD and Psoriasis

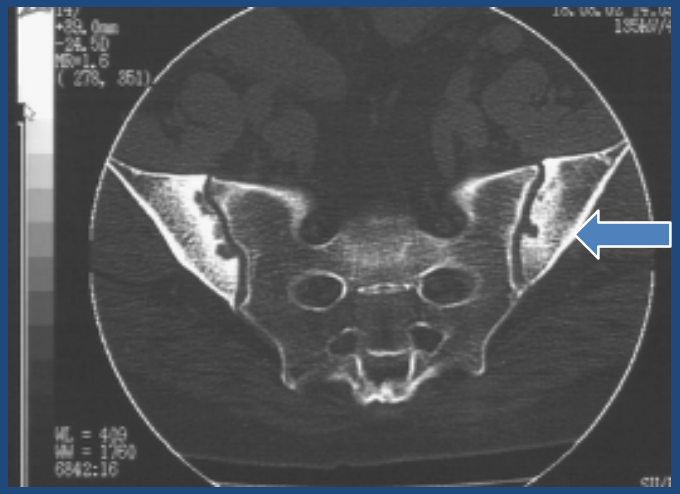
	RA	SpA
Presence of autoantibodies	**YES**	**NO**
Symmetric Joint disease	**YES**	**Less common**
Sacroiliitis	**NO**	**YES**
Axial involvement	**RARE (exception is advanced RA with cervical spine involvement)**	**YES**
Extra-articular Features	**YES**	**YES**

Spondyloarthritis Subtypes

- Axial Spondyloarthritis:
  - Ankylosing spondylitis (AS)
- Peripheral Spondyloarthritis:
  - Reactive arthritis (ReA)
  - Psoriatic arthritis (PsA)
  - Inflammatory bowel disease (IBD) associated arthritis

Inflammatory back pain

- History:
  - Onset < age 40
  - Prolonged morning stiffness
  - Improvement with exercise
  - Good response to NSAIDs
- Exam:
  - Sacroiliac tenderness
  - Positive FABER test
- Radiographic evidence of sacroiliitis



Overlapping features in SpA

- **HLA-B27**
  - Presence varies among the different SpA subtypes with strongest association with Ankylosing Spondylitis
  - present in 8-10% of Caucasians
  - 90% of Caucasian patients diagnosed with AS* are HLA-B27+

- **Uveitis**
  - Inflammation of uveal tract within the eye
  - Typically Anterior and unilateral
  - Symptoms of redness, pain and photophobia
  - Diagnosis confirmed by slit lamp exam

Overlapping features in SpA

- Enthesitis: Inflammation at the entheses- site where tendons, ligaments attach to bone
  - Common sites:
    Achilles tendon
    Lateral epicondyle

  - Dactylitis: “sausage digit”

    Mechanisms responsible:

    Tenosynovitis

    Synovitis

Ankylosing Spondylitis (AS)

AS: Background

- Incidence of 7.2 per 100,000 in U.S.
- 80-95% of patients are HLA-B27 positive
- More common among males (2-3:1)

AS: Clinical Features

- Articular features
  - Inflammatory back pain
  - Sacroiliitis
  - Enthesitis
  - Synovitis
- Non-articular features
  - Uveitis (25-40% of patients)
  - Cardiac manifestations (conduction abnormalities, valvular disease, aortitis, CAD)
  - Pulmonary disease (Apical fibrosis)

Differentiating Low Back Pain

	Inflammatory LBP	Mechanical LBP
Age of onset	< 40 years of age	Any age
Type of onset	Insidious	Acute
Symptom duration	> 3 months	< 4 weeks
Morning stiffness	> 60 minutes	< 30 minutes
Nocturnal pain	Frequent	Uncommon
Effect of exercise	Improvement	Exacerbation
Sacroiliac tenderness	Frequent	Absent
Chest expansion	Often decreased	Normal
Neurologic deficits	Unusual	Possible

AS: Longstanding Disease

Over time, inflamed ligaments in spine calcify, leading to impaired axial motion

- Stooped posture
- Flexion contractures at cervical spine
- Loss of lumbar lordosis

AS: Radiographic features

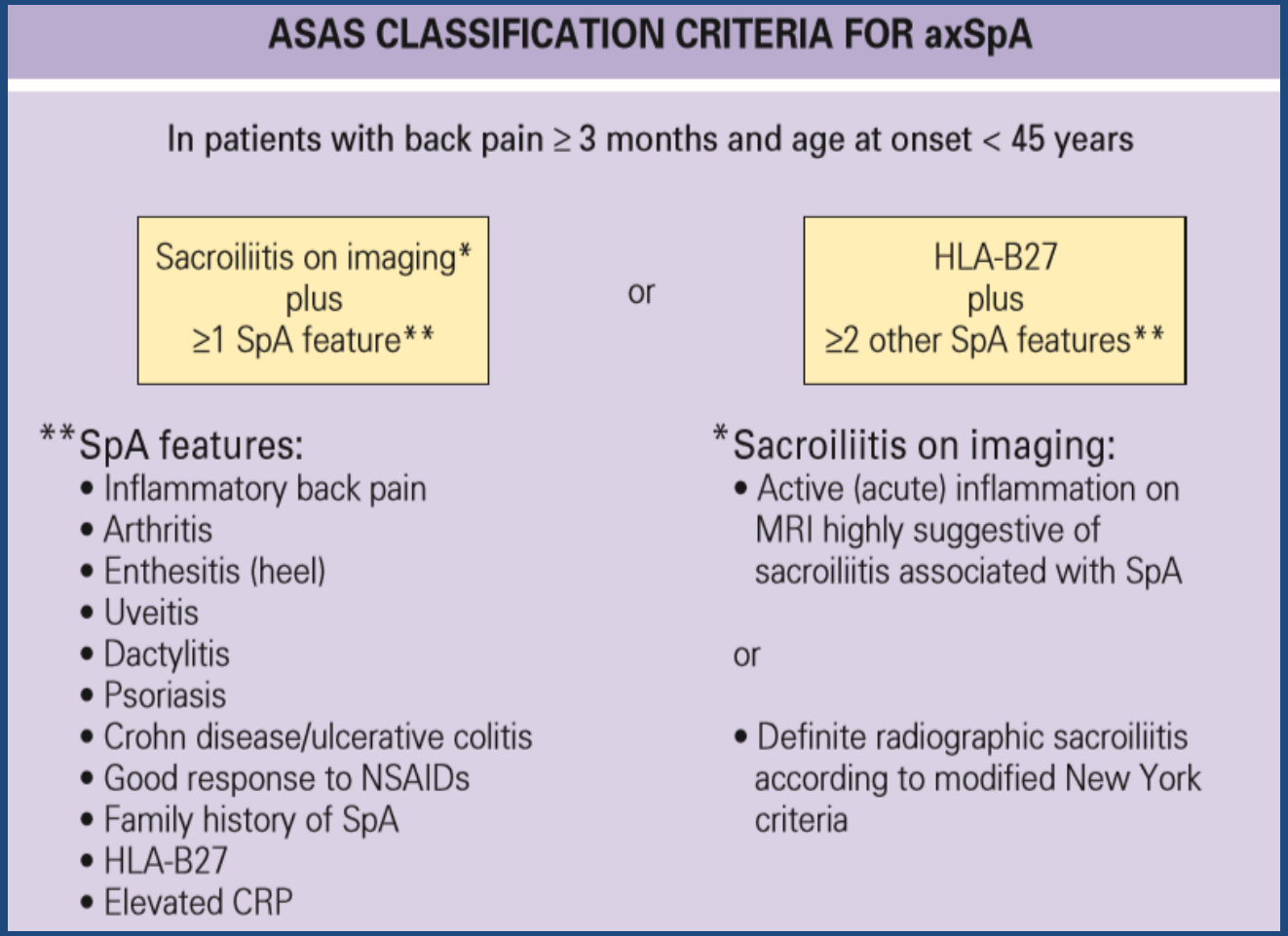
- Bilateral sacroiliitis

- Syndesmophytes

AS: Diagnostic Evaluation

- Patients with early disease may not have evidence of radiographic changes
- HLA-B27 positivity increases the probability of AS, but is not diagnostic by itself
- MRI of SI joints can be helpful in patients with early disease and negative x-rays

AS: Diagnostic Evaluation



AS: Treatment Strategies

- Pharmacologic:
  - NSAIDs (multiple drugs proven to be effective)
  - Glucocorticoids (intra-articular)
  - DMARDs
    - Sulfasalazine (peripheral joint disease)
    - Methotrexate and leflunomide not effective
  - Biologic therapies
    - TNF- inhibitors
    - IL-17 inhibition
- Non-Pharmacologic
  - Individualized Physical Therapy program

Reactive Arthritis (ReA)

ReA: Background

- Definition: **a sterile synovitis following an extra-articular infection**
- Formerly known as Reiter's syndrome
- About 50% of cases of ReA can be attributed to a specific organism
- B27 prevalence: highly variable (30-50% based on some studies)
- Incidence in the US: 0.6 to 3 cases per 100,000
- Causative organisms:
  - *Chlamydia trachomatis*
  - *Yersinia, Salmonella, Shigella, Campylobacter*
  - *Escherichia coli* and *Clostridioides difficile*
  - *Chlamydia pneumoniae*

ReA: Clinical Features

- Clinical triad of “can’t see, can’t pee, can’t climb a tree”
- Features that characterize reactive arthritis:
  - An interval ranging from several days to weeks between the antecedent infection and arthritis
  - Mono- or oligoarticular pattern of arthritis
  - Dactylitis
  - Enthesitis (Achilles tendon commonly)
  - Inflammatory lower back pain

ReA: Clinical Features

ReA: Clinical Features

- **Extra-articular features:**
  - Circinate balanitis
  - Uveitis (only ~5%)
  - Keratoderma blenorrhagicum
  - Mucositis
    - urogenital, ocular, intestinal

ReA: Diagnostic Evaluation

- Lab evaluation:
  - Elevated acute phase reactants
  - HLA-B27
  - Negative CCP, RF
  - STD screening if preceding GU infection
- Arthrocentesis
  - Gram stain/culture, cell count, crystals
  - Usually inflammatory with WBCs over 2000/mm3
- Radiography usually not specific

ReA: Treatment Strategies

- Azithromycin or doxycycline if chlamydia detected
- NSAIDs
- Glucocorticoids (Intra-articular)
- DMARD therapies in refractory cases:
  - Sulfasalazine
  - Methotrexate
  - TNF-inhibitors

Psoriatic Arthritis (PsA)

PsA: Background

- PsA is an inflammatory arthritis associated with psoriasis
- Prevalence estimated between 0.3-1.0% of U.S. population and between 18-42% of patients with psoriasis
- Gender frequency is nearly equal
- Arthritis develops after onset of psoriasis in ~85%, but can precede skin disease in 5-10% of patients

PsA: Clinical Features

PsA: Diagnostic Evaluation

- Remains largely a clinical diagnosis
- Laboratory evaluation:
  - Elevated acute phase reactants
  - Obtain RF and CCP levels (to exclude RA)
- Arthrocentesis (aspiration of joint fluid)
  - Usually inflammatory with WBCs > 2000 and <50,000
  - Exclude crystal disease or infectious process
- Radiography:
  - Periostitis
  - New bone formation
  - Erosive changes

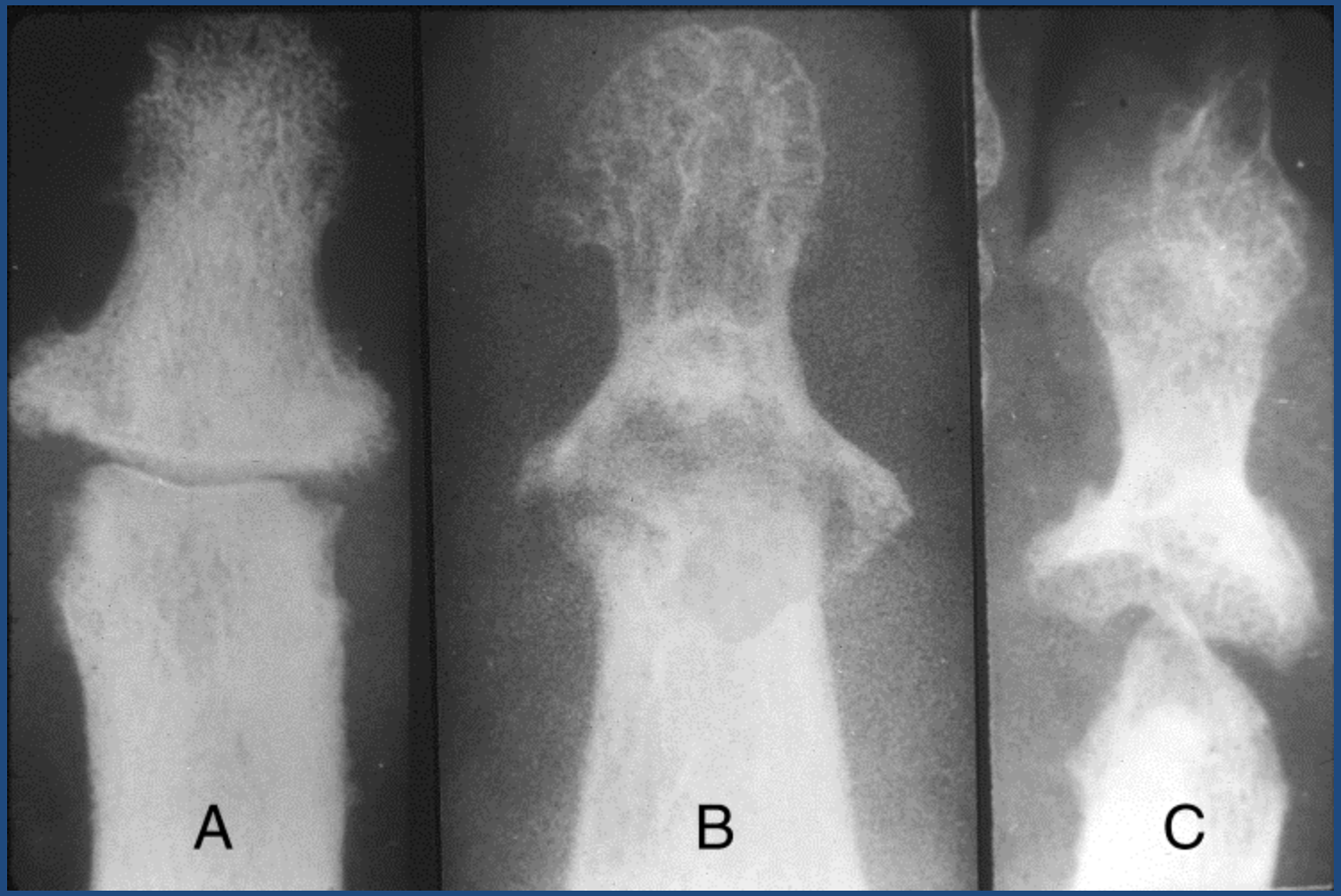
CASPAR classification criteria

- Current Psoriasis (2 points)
- Personal or family history of psoriasis (1 point)
- Psoriatic nail dystrophy on exam (1 point)
- Negative RF (1 point)
- Dactylitis (1 point)
- Juxtarticular new bone formation on radiographs (1 point)
- PsA diagnosed when inflammatory arthritis present and 3 or more points are assigned

PsA: Patterns of Joint Involvement

- **Five articular patterns:**
  1. Polyarticular/symmetric (resembles RA)
  2. Oligoarticular/asymmetric
  3. Distal (restricted to DIP joints)
  4. Spondyloarthritis
  5. Arthritis Mutilans

PsA: Radiography



PsA: Treatment Strategies

- NSAIDs
- Conventional DMARDs
  - Leflunomide
  - SSZ
  - Methotrexate
- Biologic DMARDs
  - TNF-alpha inhibition
  - IL-17 inhibition
  - IL-12, IL-23 inhibition
- Small molecular inhibitors
  - Apremilast
  - tofacitinib

Inpatient Pearls

- Systemic steroids do not play a large role in the treatment of SpA
- In patients with psoriasis steroid withdrawal can worsen psoriasis and even lead to erythrodermic disease
- Always ask about recent infections in patients with new monoarticular arthritis

Questions??

Treatment of Rheumatoid and Seronegative Arthritis

Maria I. Danila, MD, MSc, MSPH

2019 UAB Rheumatology Update
August 24, 2019

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Disclosures

- Research grants from NIAMS, Pfizer
- Honoraria Regeneron-Sanofi, Novartis

Objectives

- Recognize the importance of early treatment
- Recognize available biologic therapies and newer therapies for inflammatory
- Recognize the need for preventive services in patients with rheumatoid arthritis on biologic and newer therapies.

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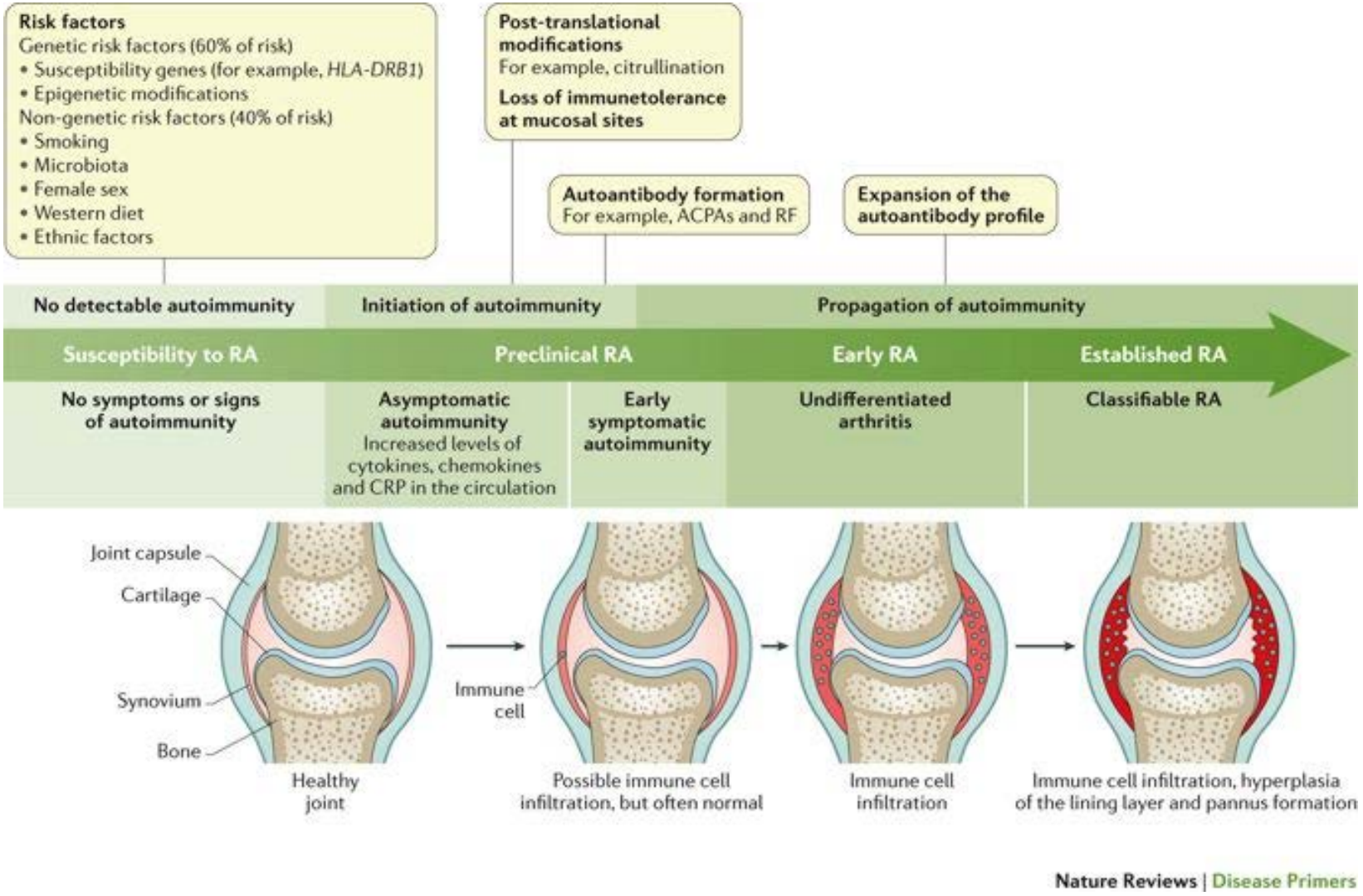
Development and Progression of Rheumatoid Arthritis



Smolen et al. *Nature Reviews Disease Primers.* 2018

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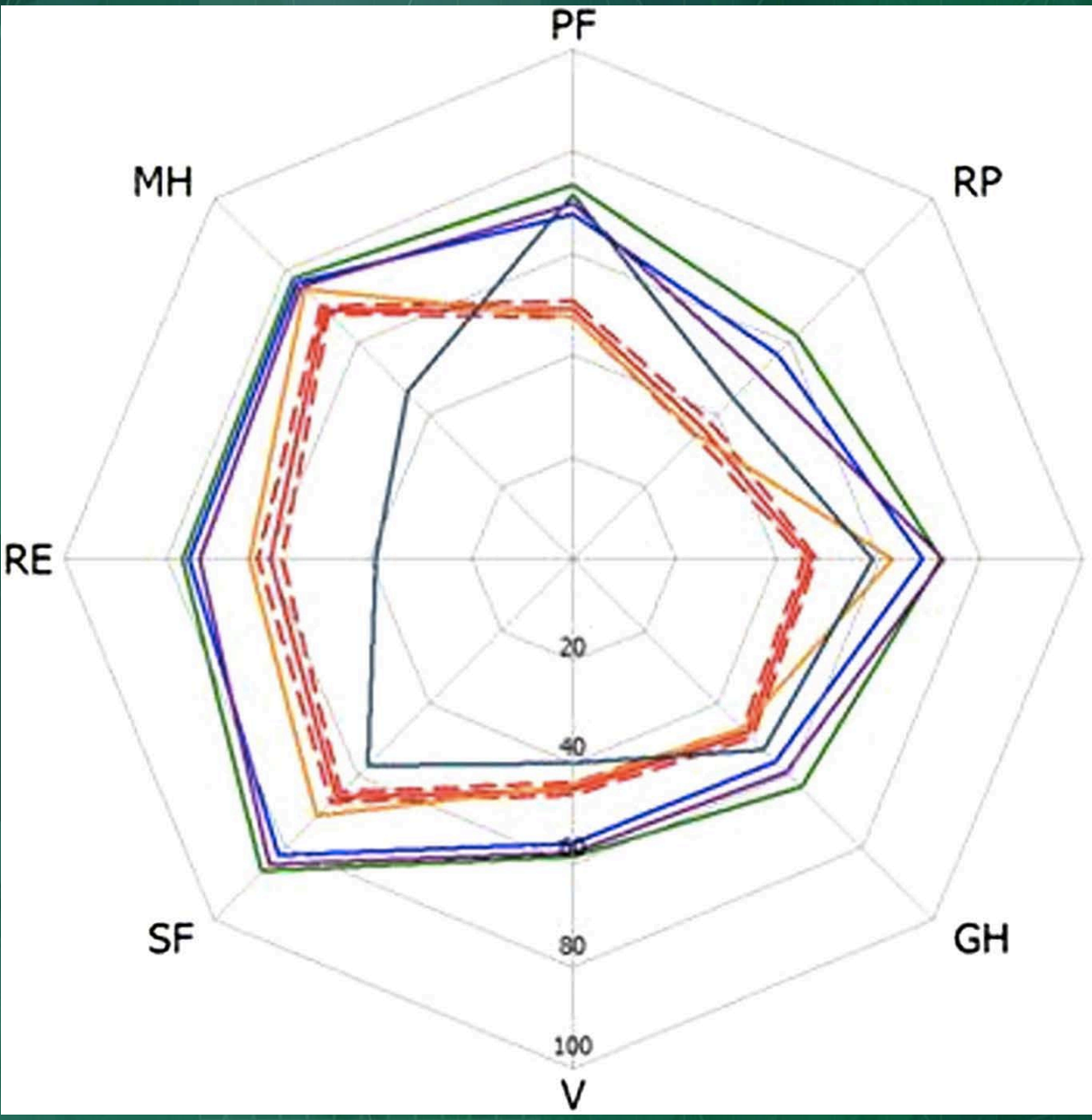
Quality of Life in RA vs Other Diseases



Short Form 36
PF = Physical Function
RP = Role Physical
BP = Bodily Pain
GH = General Health Profile
V = Vitality
SF = Social Functional
RE = Role Emotional
MH = Mental Health

- Rheumatoid Arthritis
- 95% Confidence Interval
- Type 2 Diabetes
- Hypertension
- Chronic Heart Failure
- Myocardial Infarction
- Clinical Depression

Matcham F. Sem Arthritis and Rheum. 2014, 44:123-130

Goals of Treatment in Inflammatory Arthritis

- Control disease activity
- Reduce pain
- Maintain joint function for essential daily activities
- Slow progression/rate of joint damage
- Maximize quality of life
- Minimize impact on work and social participation

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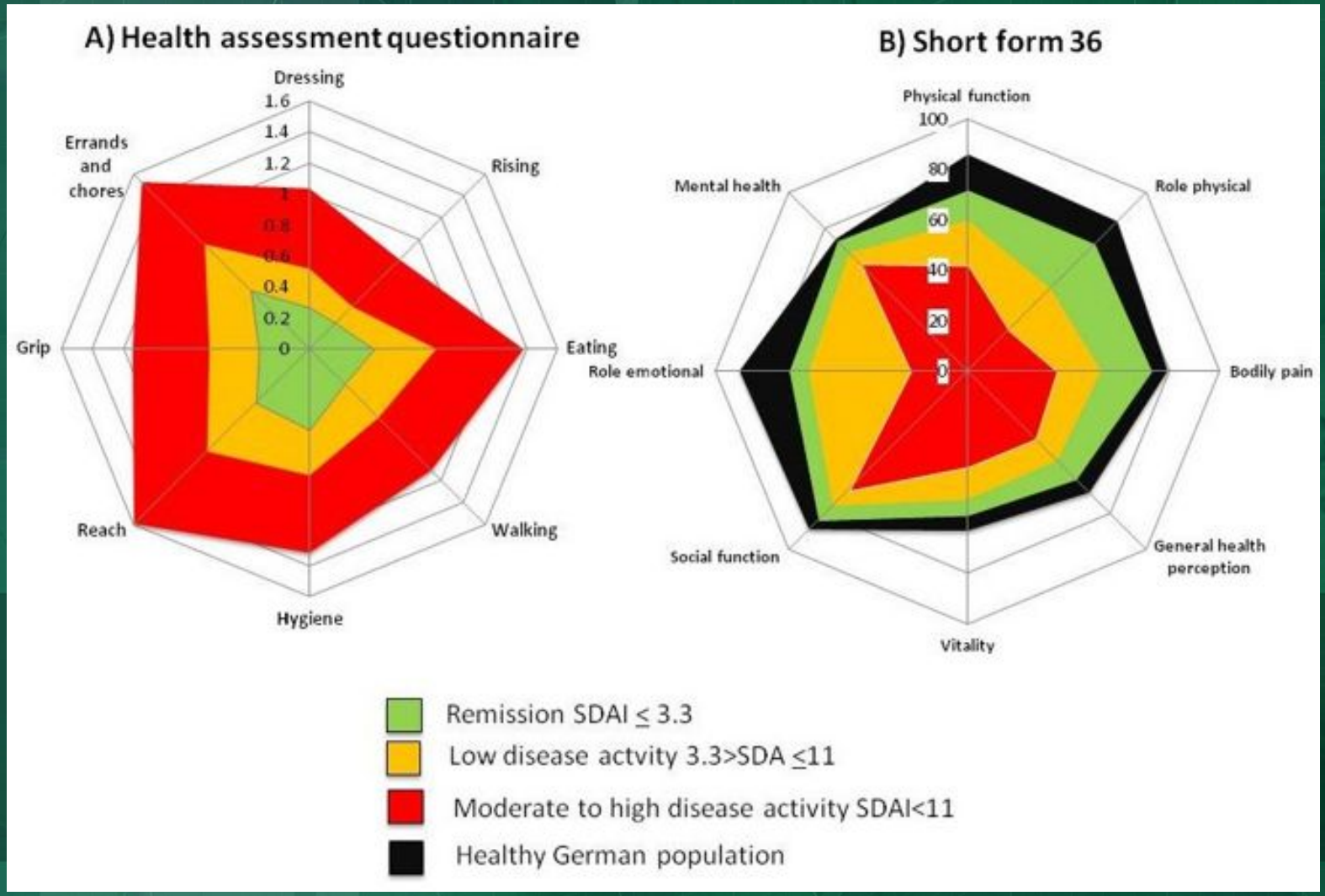
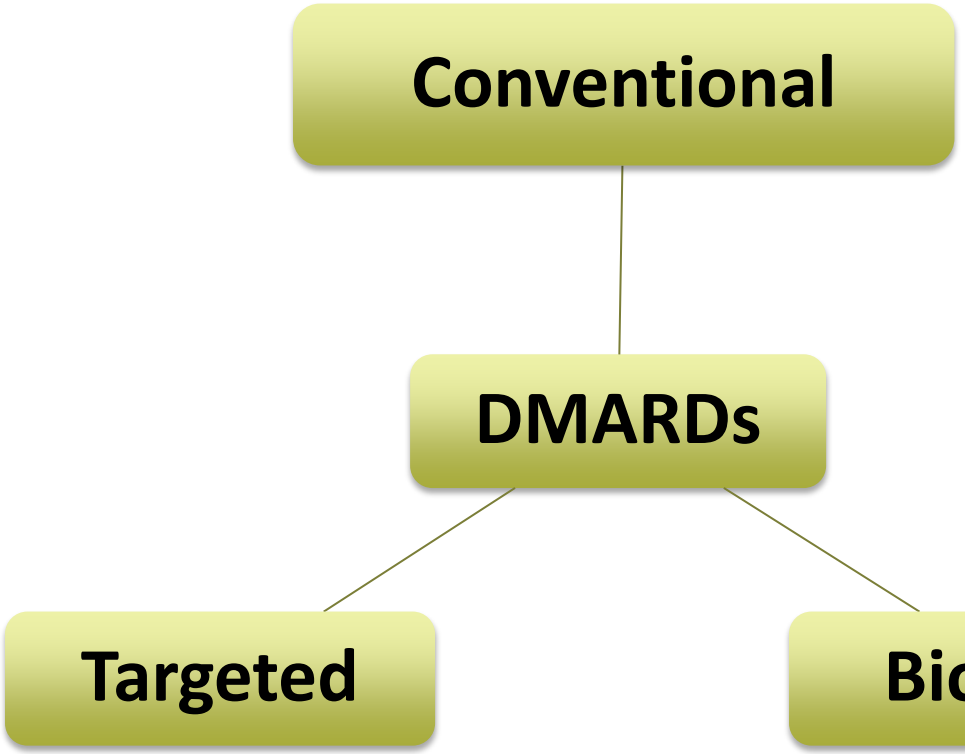


Differences in domains of Health Assessment Questionnaire (A) and Short Form 36 (B) by levels of disease activity (SDAI).

Radner H. et al . *Arthritis Research & Therapy*, 2014

Disease Modifying Anti-Rheumatic Drugs (DMARDs)

- **Seminal development**
- **Better outcomes**



- Methotrexate
- Leflunomide
- Hydroxychloroquine
- Sulfazalazine

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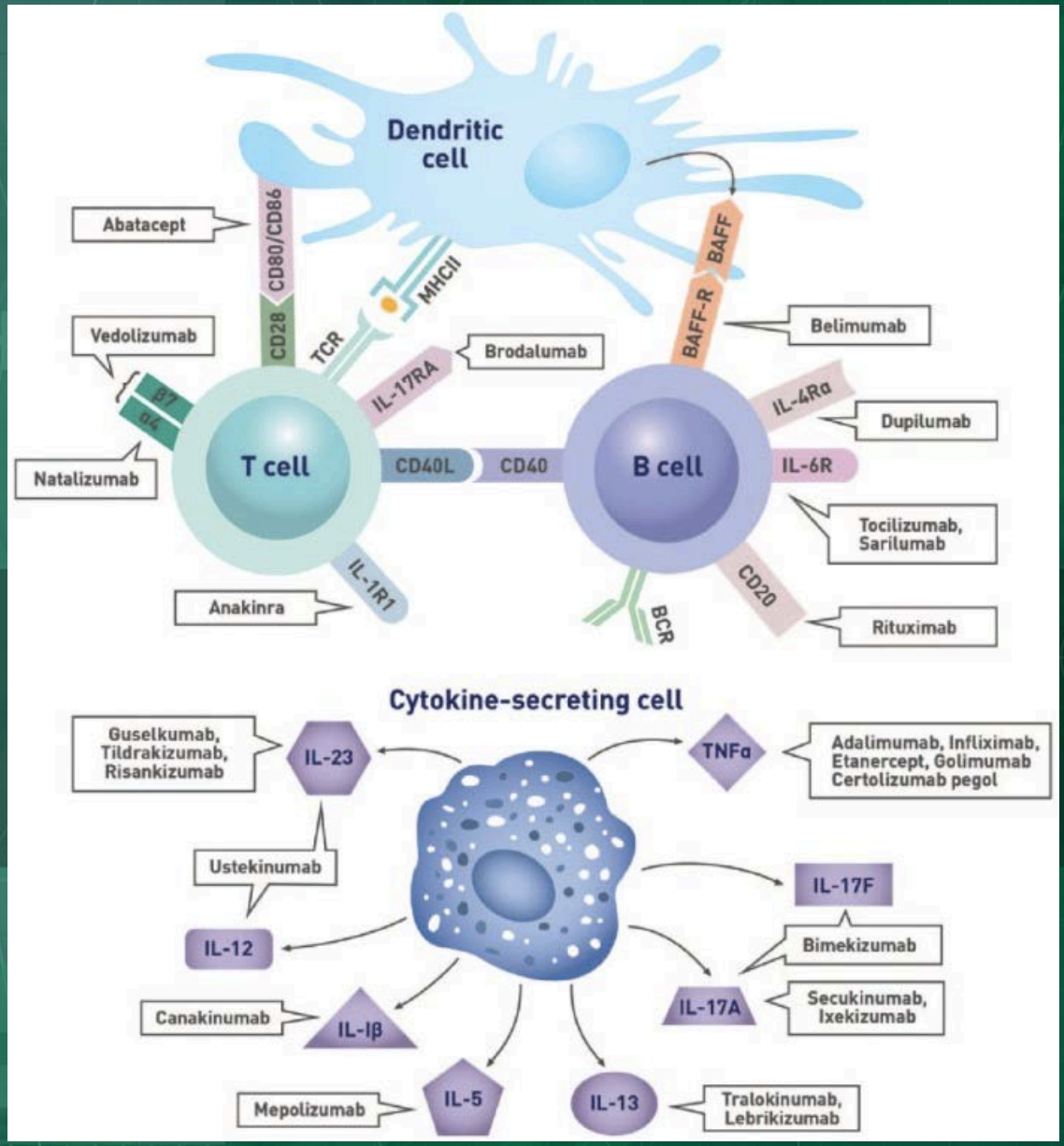
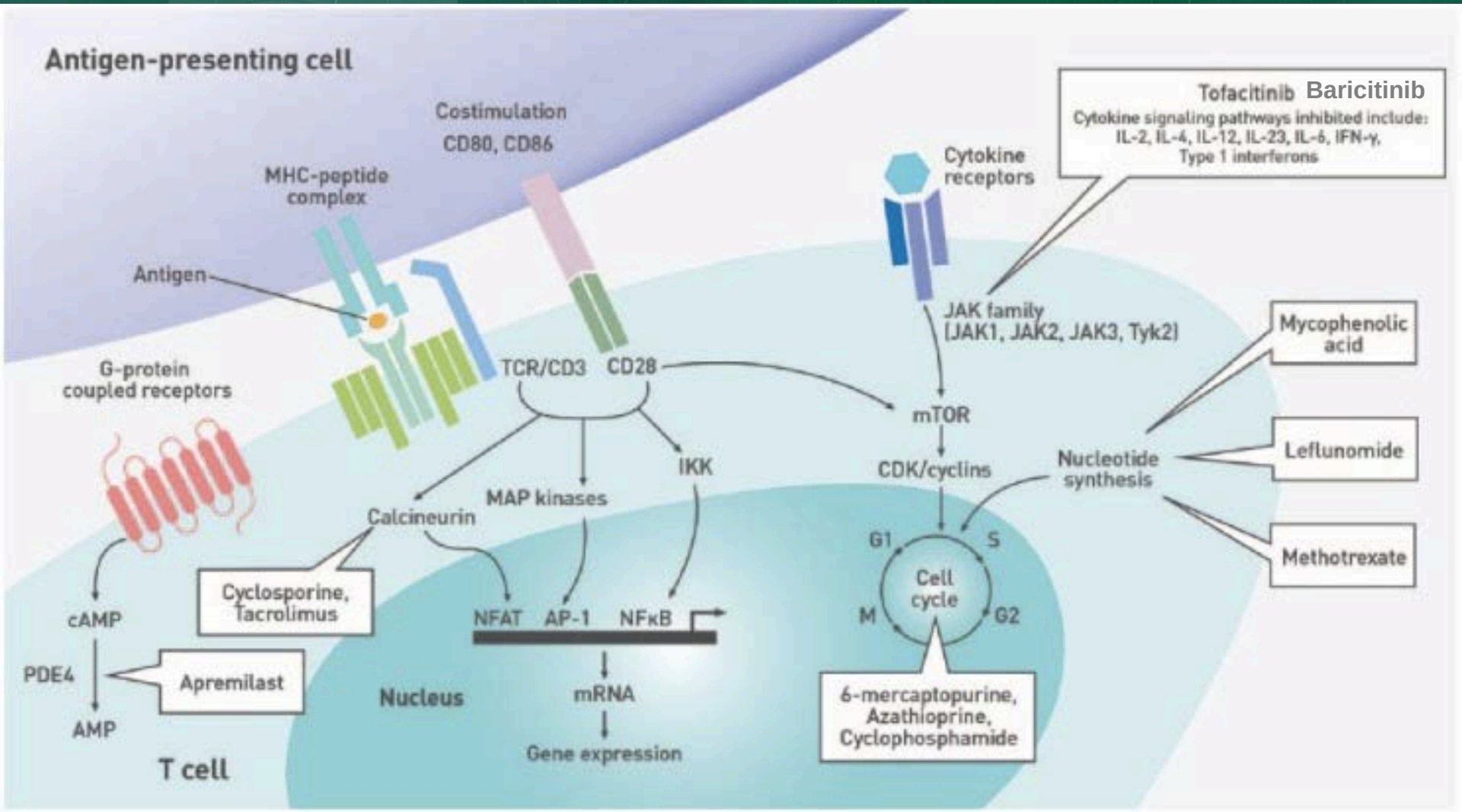
Targets for Biologic DMARDs



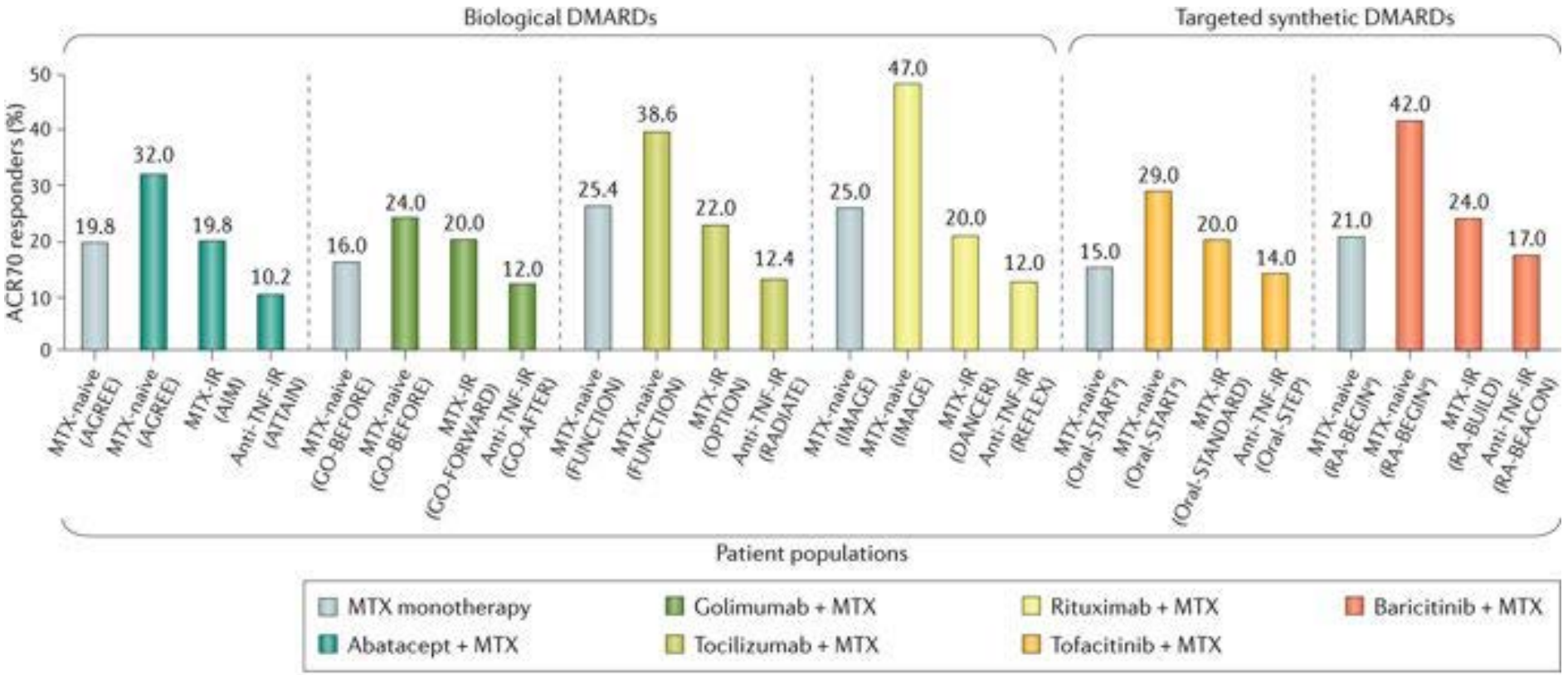
Papp A. et al. J Cutan Med Surg. 2019 Jan; 23(1): 50–74

Targets for Conventional and Targeted DMARDs



Papp A. et al. J Cutan Med Surg. 2019 Jan; 23(1): 50–74

Treatment Response to DMARDs in RA



ACR 70 = 70% improvement in 3 out of 5 criteria:

- patient global assessment
- physician global assessment
- functional ability measure [Health Assessment Questionnaire (HAQ)]
- visual analog pain scale
- ESR or CRP

Nature Reviews | Disease Primers

Smolen et al. *Nature Reviews Disease Primers* **volume4**, (2018)

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Biologic DMARDs: The Potential Bad

WARNINGS:
SERIOUS INFECTIONS AND MALIGNANCIES
See full prescribing information for complete boxed warning.

SERIOUS INFECTIONS

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.
- Enbrel should be discontinued if patient develops a serious infection or sepsis during
- Perform test for latent TB infection prior to starting Enbrel.
- Monitor all patients for active TB during treatment, even if initial latent TB test is negative.

MALIGNANCIES

- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients receiving TNF blocking agents, including Enbrel. (5.3)

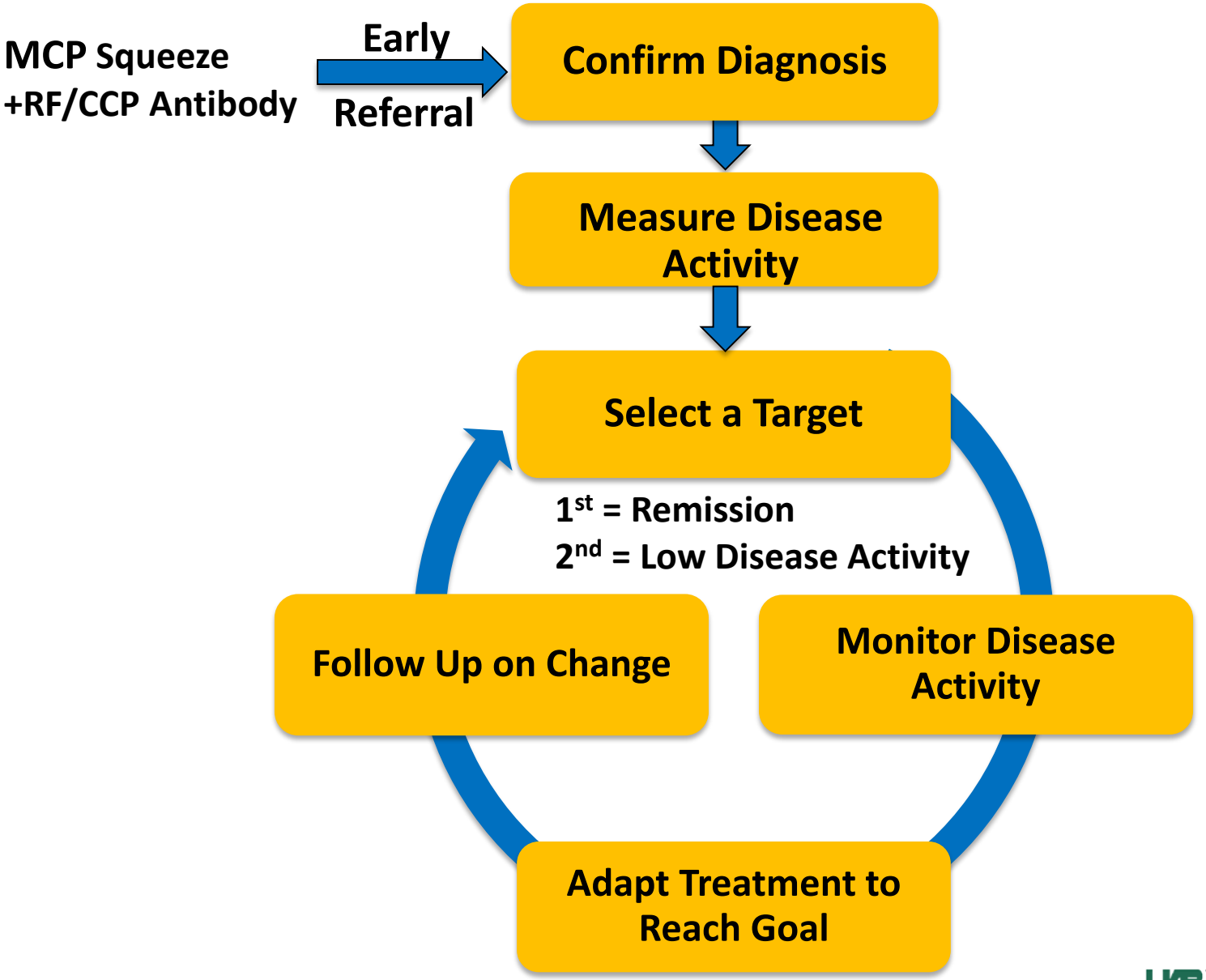
WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
See full prescribing information for complete boxed warning.

- Fatal infusion reactions within 24 hours of Rituxan infusion occur; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).
- Tumor lysis syndrome (5.2).
- Severe mucocutaneous reactions, some with fatal outcomes (5.3).
- PML resulting in death (5.4).

Biologics & Targeted DMARDs in Inflammatory Arthritis

- Pros
  - Improved disease related outcomes
  - Improved function
  - Reduced joint damage (imaging)
  - Improved quality of life
  - Improved work and home productivity
  - Many choices
- Cons
  - Side effects
  - Expensive (e.g. ~$40,000/year)

Treat to Target Strategy in RA



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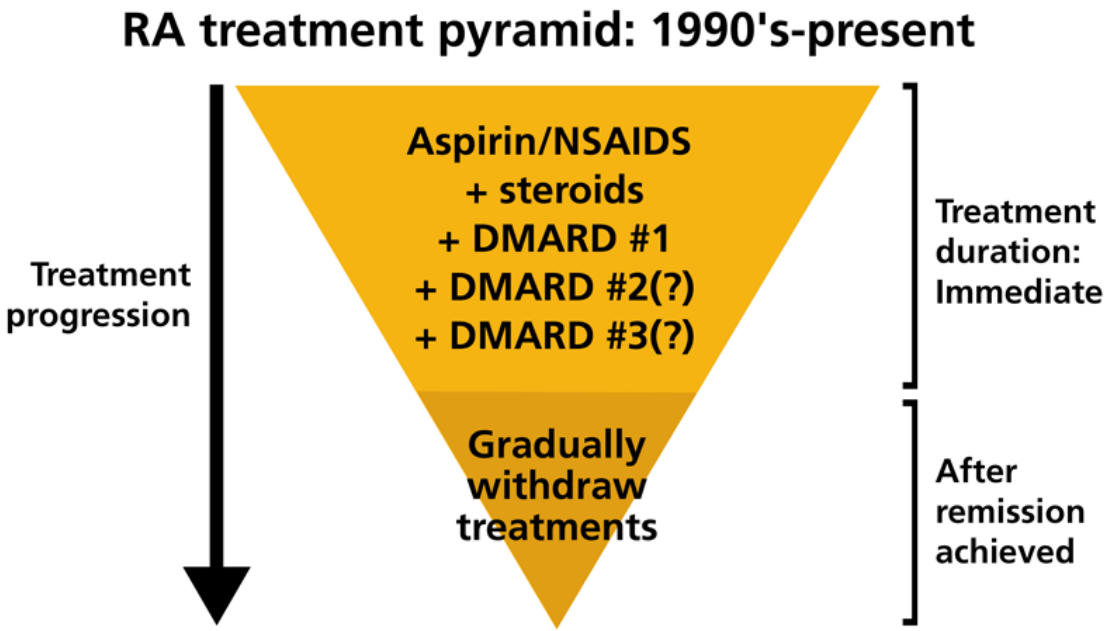
Goals of RA Therapy: Remission



Rheumatology. Evolution of treatment for rheumatoid arthritis. Volume 51, Issue suppl 6. Sept. 14, 2012.

- ~15-30% of patients can achieve remission
- Remission is more likely if we start treatment early

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Choosing Biologic & Targeted Synthetic DMARDs in RA

- Serious Infections
- Opportunistic Infections
- Malignancy
- Cardiovascular Disease
- Special Situations
  - Elective Surgery
  - Vaccinations

Individualizing Rheumatoid Arthritis Treatment

- **For inflammation**
  - use DMARDs

- **For damage**
  - use analgesics, physical therapy, assistive devices, surgery

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Limitations of RA Treatment in 2019

- Treatment not curative
- Balance drug efficacy vs risks
- Lack of accurate markers of efficacy or toxicity
- Goal of treatment
- Likelihood of disease progression
- Optimal dose
- Improvement in symptoms may not completely alter disease course (radiographic damage, extra-articular manifestations)

Rheumatoid Arthritis: Case Study 1/2

- 45 year old woman with seropositive RA for 1 year
- Methotrexate 20mg/week, prednisone 10mg/day
- Improved, still with active disease
  - Tender joint count = 8
  - Swollen joint count = 6
- Rheumatologist recommended addition of a biologic (anti-TNF therapy)

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Case Study 2/2

- She finds out that anti-TNF therapy
  - Doubles the risk of serious infections*
  - Increases risk for TB 12-fold**
  - Is associated with PML***, a severe, sometimes fatal disease for which few if any effective therapies exist
  - Is associated with death
- She declines biologic therapy

* Curtis JR, et al., Arthritis Rheum 2007; 56(4):1125-33;
** Tubach F et. al., Arthritis Rheum 2009 Jul;60(7):1884-94.
*** Kumar et. al. Arthritis Rheum. 2010 Nov;62(11):3191-5

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Biologic Safety is Difficult to Study

- Biologic use associated with disease severity
- Biologics frequently used with prednisone or other immunosupressive agents
- Clinical trials not powered to detect adverse events
- High rate of comorbidities in real-world patients
- Methodologic issues in analysis
  - Duration of exposure of some biologics unclear
  - Drug switching common

Infection Risk Due To RA Severity and Activity

- 609 RA patients and 609 controls matched on age, residence, sex* residing around Rochester, Minnesota
  - Greater than 12 years of follow-up, 1955 - 1994
  - Risk for hospitalized infection associated with RA: hazard ratio = 1.83 (1.52-2.21)
- CORRONA registry**
  - More than 25,000 RA patients
  - More active RA → higher rate of infection

Doran et al. Arthritis Rheum 2002; 46(9):227-2293

Doran et al. Arthritis Rheum. 2002 Sep;46(9):2294-300.

Au et. al. Ann Rheum Disease May 2011;70(5):785-91

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Confounding Due to Concomitant Glucocorticoids

Mean daily dose of glucocorticoids (no. of treatment episodes), outcome	Propensity score adjusted rate ratio (95% CI)
≤5 mg (n = 1,781)	
Pneumonia	0.88 (0.37-2.12)
Any bacterial infection	1.34 (0.85-2.13)
6-9 mg (n = 1.510)	
Pneumonia	2.01 (0.87-4.66)
Any bacterial infection	1.53 (0.95-2.48)
10-19 mg (n = 4,435)	
Pneumonia	2.97 (1.41-6.23)
Any bacterial infection	2.86 (1.80-4.56)
≥20 mg (n = 2,891)	
Pneumonia	6.69 (2.83-15.8)
Any bacterial infection	5.48 (3.29-9.11)

Schneeweiss S. Arthritis Rheum. 2007 Jun;56(6):1754-64

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Rates of Serious Infections Largely Driven by Disease, Comorbidities and Patient Factors, Not Biologics

	Rate of Serious Infections per 100 person-years
TOWARD (DMARD failure, **biologic naive**) (MTX +TCZ 8mg/kg) vs. (MTX + PBO)	5.9 vs. 4.7
RADIATE (TNF Failures, **refractory RA**) (MTX +TCZ 8mg/kg) vs. (MTX + PBO)	9.9 vs. 9.6

PBO = placebo; TCZ = tocilizumab

Genovese MC et al. Arthritis Rheum. 2008 Oct;58(10):2968-80
Emery P et al. Ann Rheum Dis. 2008 Nov;67(11):1516-23

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TB Risk for Those on Anti-TNF Therapy

Table 2 Numbers and rates of incident tuberculosis, switchers included **UK Biologic Registry**

Number of patients ever received the drug	DMARD (n = 3232)	All anti-TNF (n = 10 712)	ETA (n = 5521)	INF (n = 3718)	ADA (n = 4857)
*On drug**					
Person-years	7345	28 447	12 744	8069	7634
Cases of TB	0	27	5	11	11
Rate/100 000 person-years (95% CI)	0	95 (63 to 138)	39 (13 to 92)	136 (68 to 244)	144 (72 to 258)
IRR, adjusted for age, gender and entry year (95% CI)			Referent	3.1 (1.0 to 9.5)	4.2 (1.4 to 12.4)

Cochrane: TB rate 200/100,000 persons receiving drug

Dixon WG et al. *Ann Rheum Dis* 2010:69:522-528

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Vaccinations for Patients with Inflammatory Arthritis

	Inactivated Virus	Live Virus
PPSV23, PCV 13	✓	-
Influenza	✓	-
Herpes Zoster	??	✓*
Tetanus, diphteria	✓	-
Hepatitis B	✓	-
HPV vaccine	✓**	-

*** Age >50 years, live virus vaccines not recommended for patients on biologics or tofacitinib**

**** recommended up to age 26**

- Holding methotrexate 2 weeks after influenza vaccine may improve immunogenicity[1]
- 3% flares, 15% side effects in patients with RMD who received recombinant herpes zoster vaccine[2]

[1]Park J. et al. Ann Rheum Dis 2018; 77:898-904

[2]Stevens E. et al. EULAR 2019, Poster FRI0068

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Cancer Risk Associated with Biologics & Small Molecules

- Solid tumors: no excess risk
- Non-melanoma skin cancer: about 2-fold increase
- Risk does not appear to increase over time

	Biologics naïve (N=120)	TNFi treated (N=120)	
Total person-year follow up	550	592	
Recurrent breast cancer	9	9	
Rate/1000 person years (95% CI)	16 (7, 31)	15 (7, 29)	
HR recurrent breast cancer	1 (ref)	0.8 (0.3-2.1)	1.1 (0.4-2.8)*

* Adjusted for breast cancer characteristics (nodal state, surgery, chemotherapy), and comorbidies (DM, IHD, COPD, joint surgery).

Raaschou P et al, Ann Rheum Dis. 2015 Dec;74(12):2137-43.

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Lymphoma Risk and Incidence in RA

- Pre-biologic era – risk is at least double in RA than general population
  - most frequently diffuse large B cell lymphoma
- RA disease activity with continuous immunologic stimulation is probably the most established risk factor
- Treatment with Methotrexate and TNFi does not expose patients to a greater risk of lymphoma

Klein A. et al. Hematological Oncology 2018, 36:733-739.

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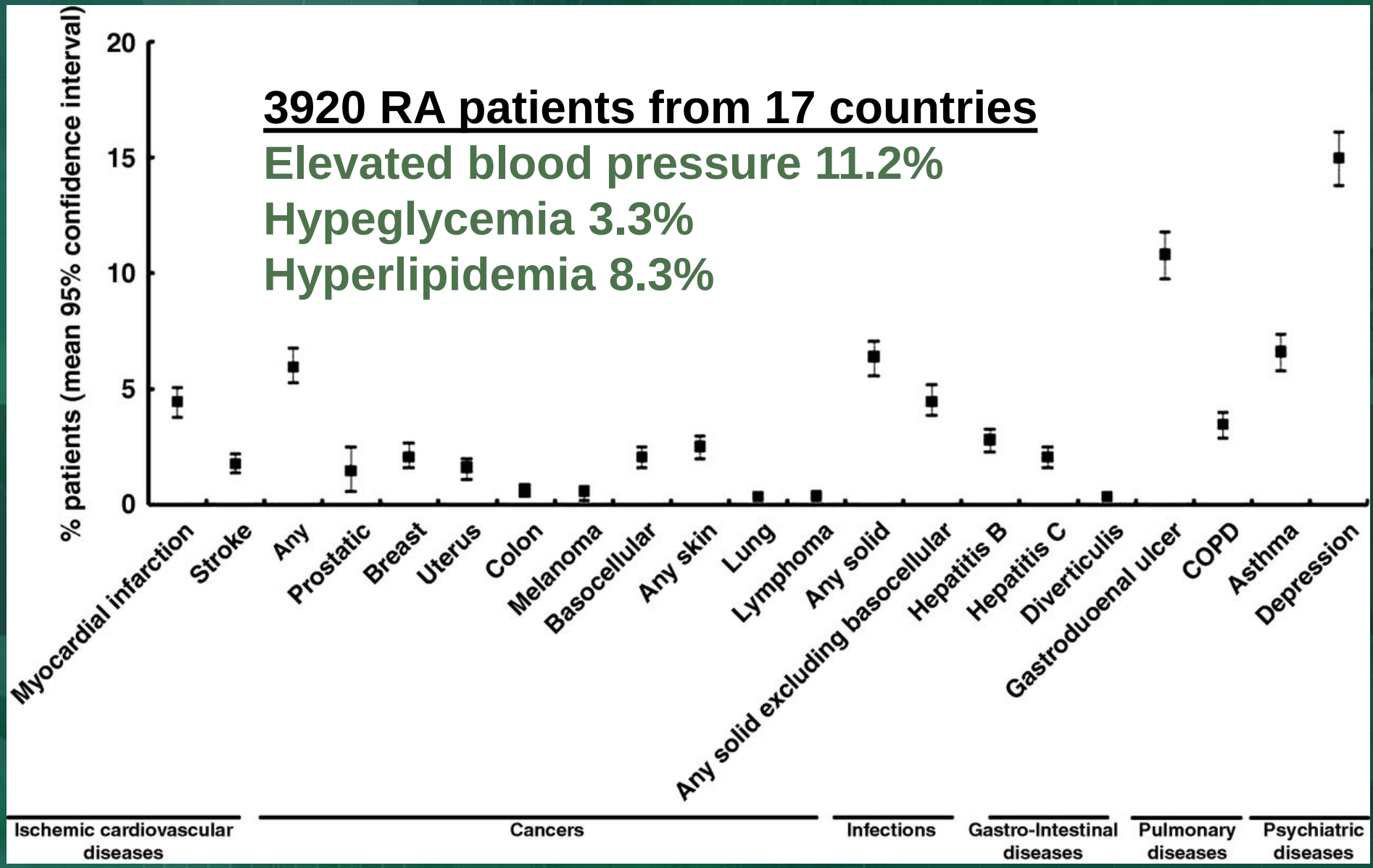
Joint Replacement Surgery in Patients with RMD

- Increased risk for periprosthetic joint infection following total hip arthroplasty and total knee arthroplasty
- Mitigate risk in the perioperative period
- Continue csDMARDs
- Withhold bDMARDs should be withheld as close to 1 dosing cycle as scheduling permits
- Restart bDMARDs after evidence of wound healing (14 days)
  - Patients off TNFi>28 days before surgery had ~60% reduction in infections

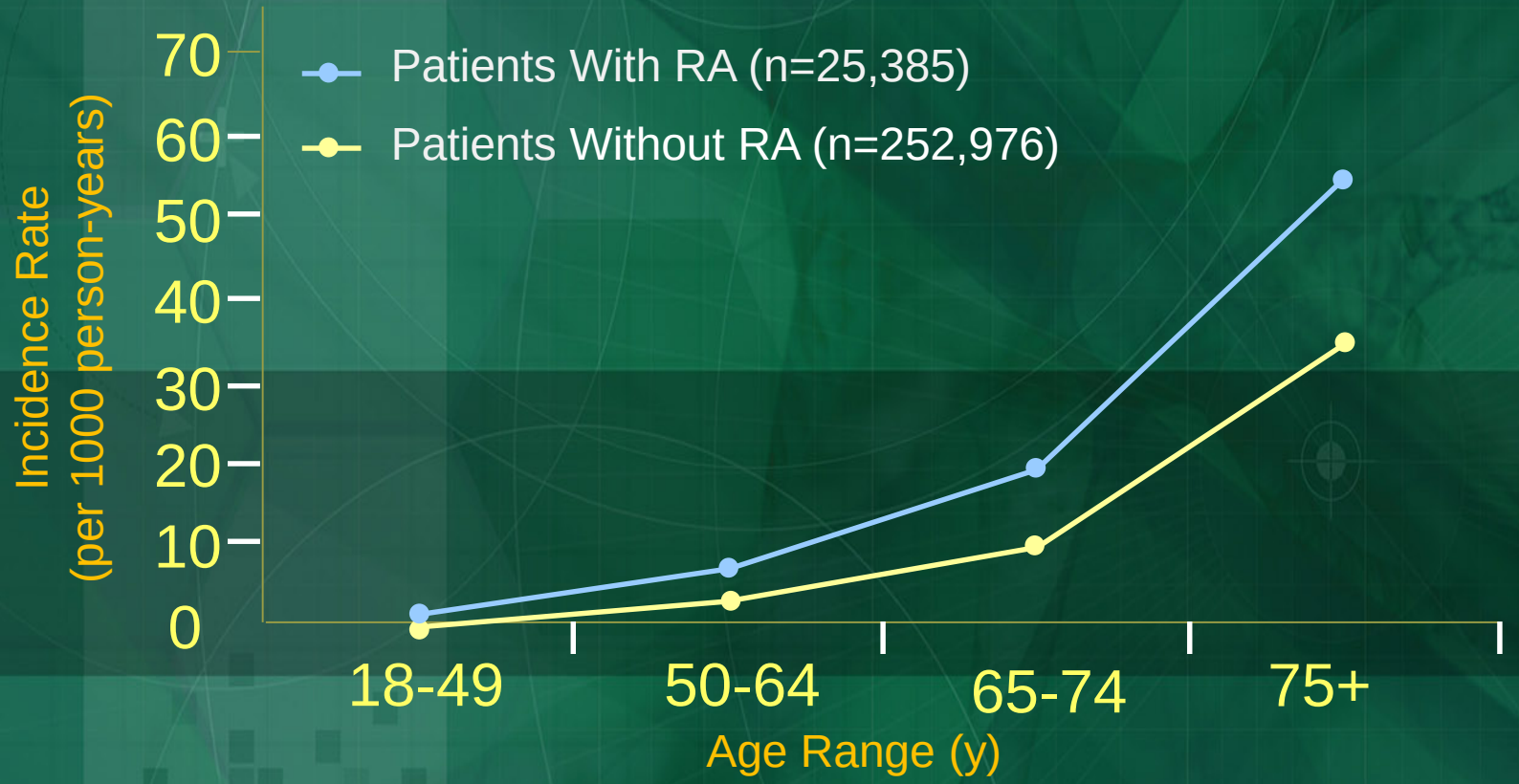
Goodman S et al. Arthritis Care and Research 2017

Comorbidities in RA



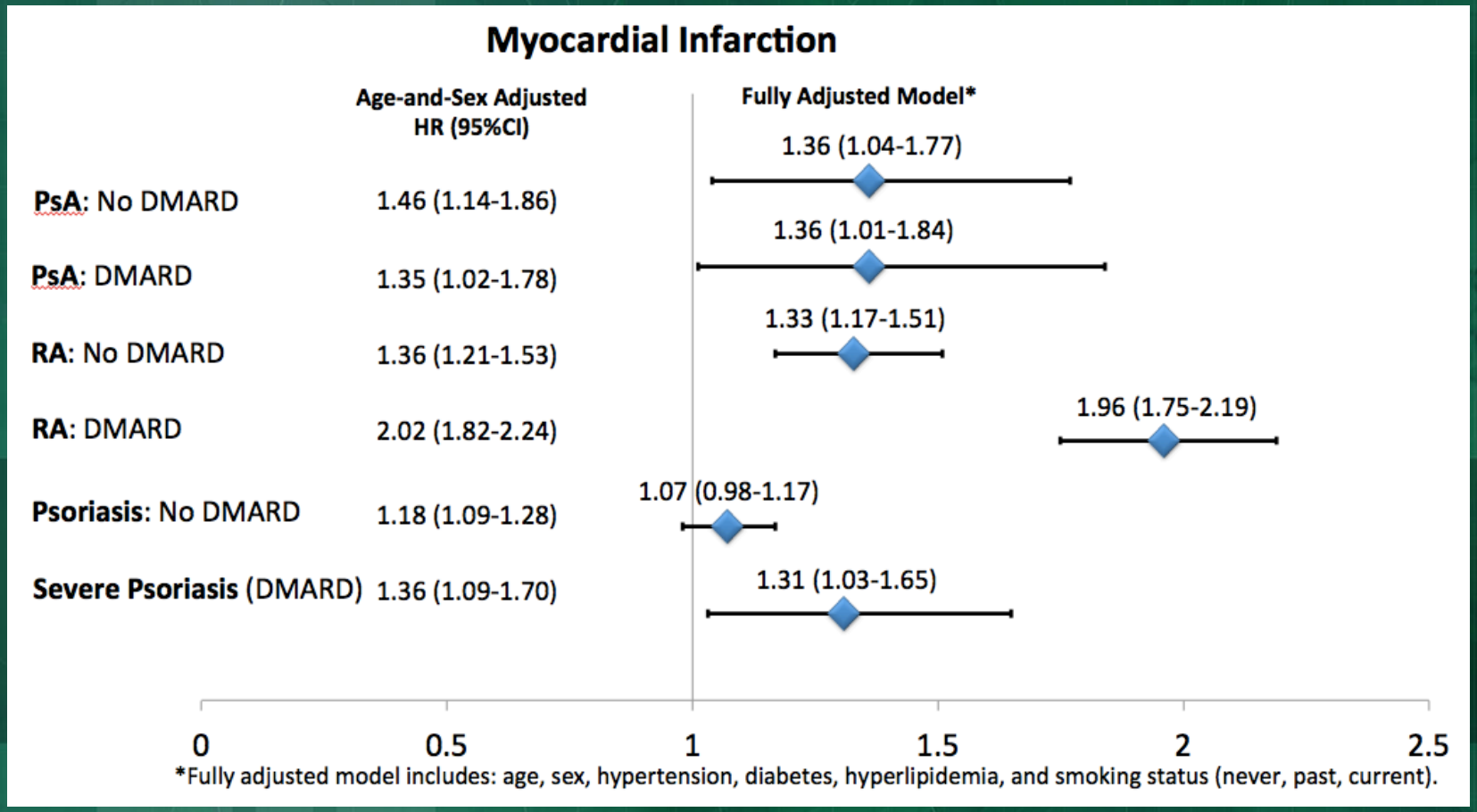
Dougados M. et al. An Rheum Dis. 2014 Jan; 73:62-8

RA Is an Independent Risk Factor for MI, Stroke



Solomon DH et al. *Ann Rheum Dis*. 2006;65:1608-1612.

PsA and Myocardial Infarction

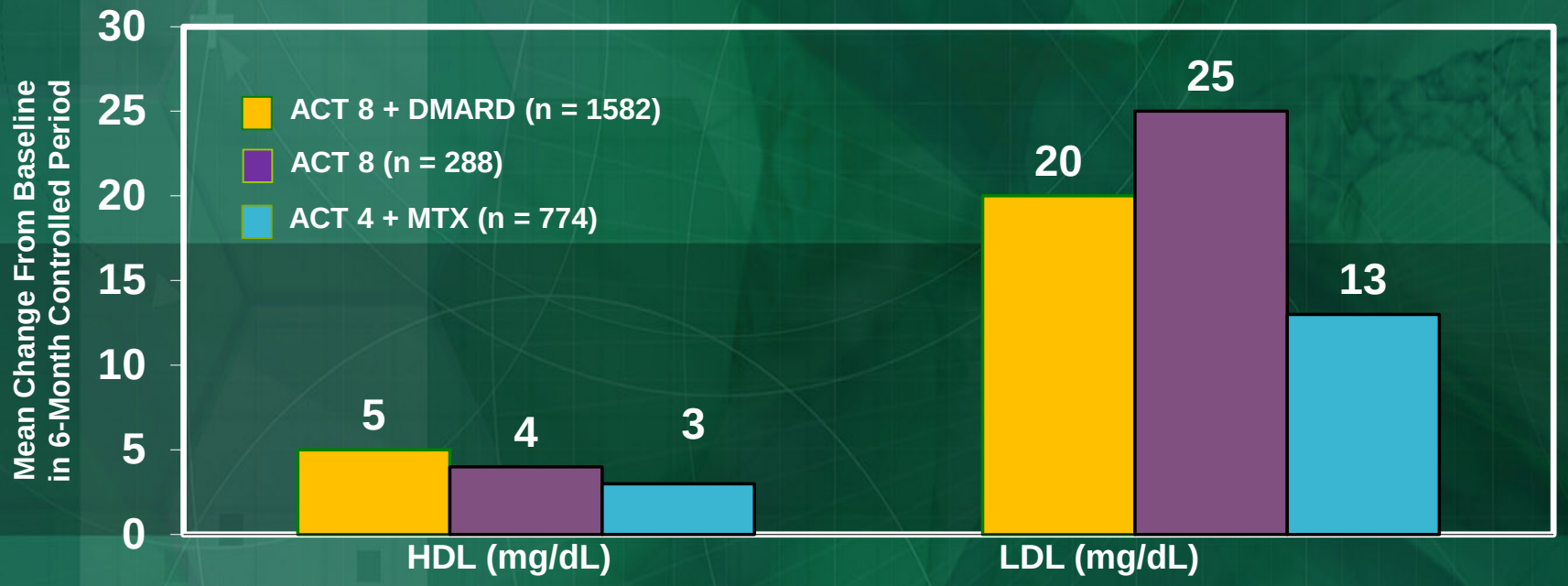


DMARD=Disease-Modifying Antirheumatic Drugs

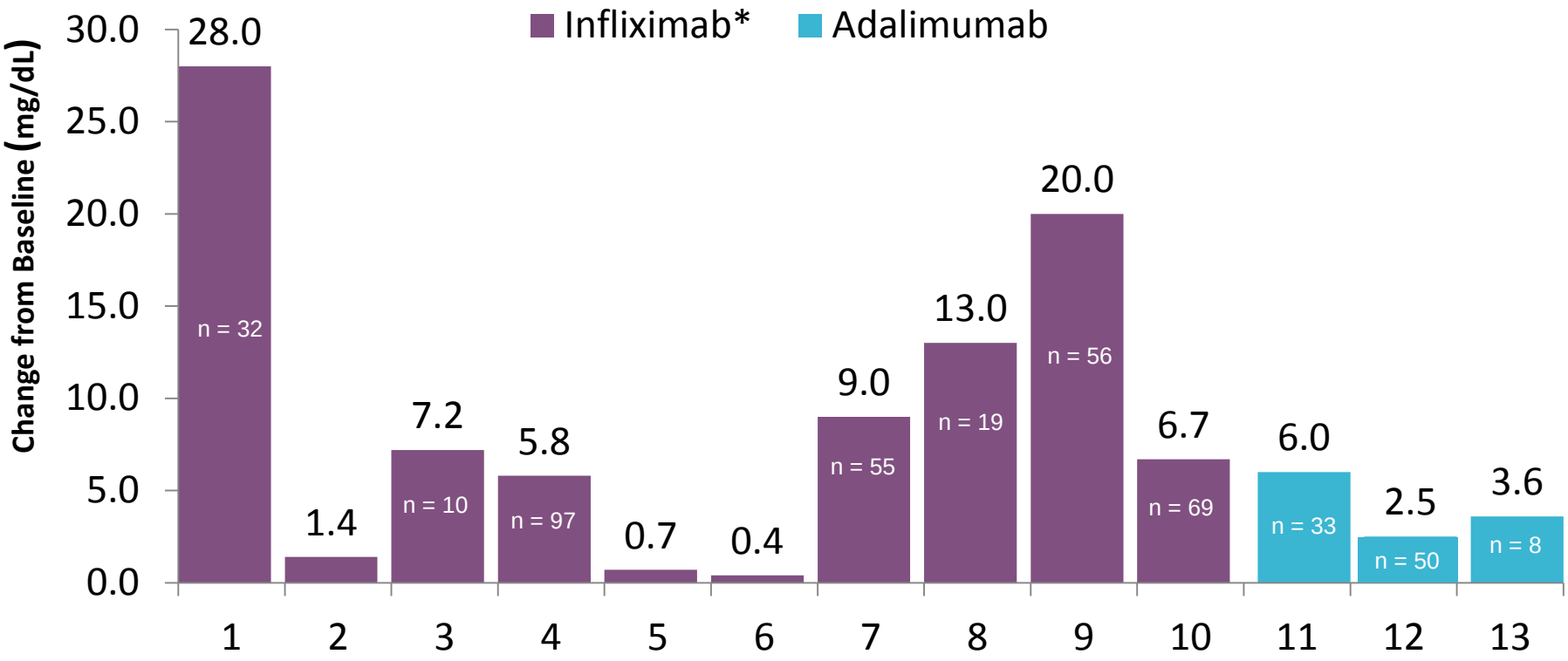
Ogdie A et al. *Ann Rheum Dis* 2015; 74:326–332.

Nissen et al. *N Engl J Med* 2016; :2519-2529.

Changes in Lipids Associated with Tocilizumab (IL-6Ra)



Increase in Total Cholesterol Associated with TNFi Therapy



Pollono EN. Clin Rheumatol. 2010; 29(9):947-55.

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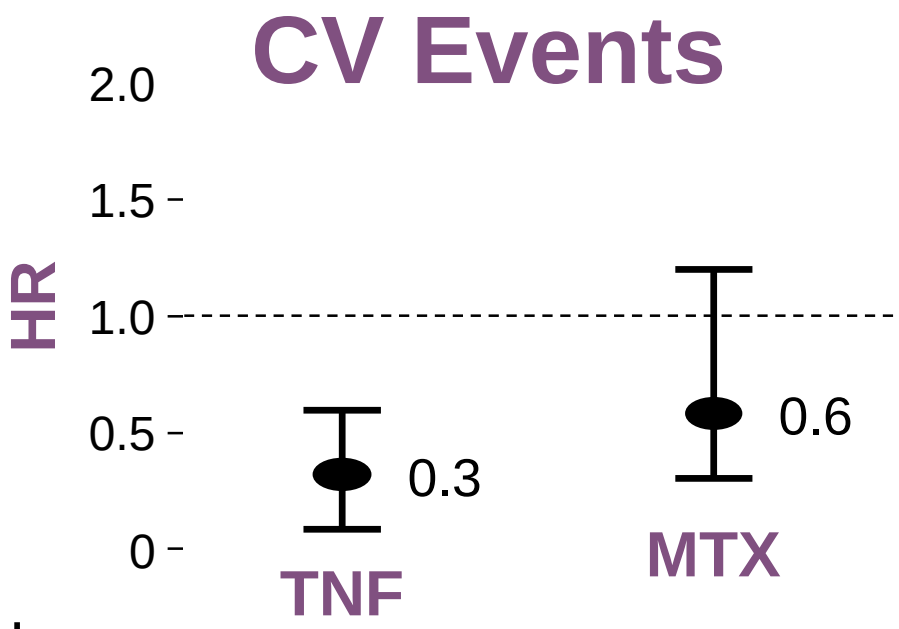
TNFi Therapy in RA and CV Outcomes

- N= 10,870 RA patients (CORRONA)
  - Median RA duration: 7 years
  - Median follow-up: 2 years
- Compared with non-biologics excluding methotrexate (MTX)
  - TNFi (RR 0.3)
  - MTX (RR 0.6)
- Prednisone an independent risk factor for CVD



Greenberg JD. Ann Rheum Dis. 2011 Apr;70(4):576-82.

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Individualizing DMARD Treatment in Autoimmune Arthritis

Comorbidity	Sulfasalazine	Methotrexate	Leflunomide	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Abatacept	Rituximab	Ustekinumab	Actemra	Sarilumab	Apremilast	Secukinumab	Tofacitinib	Baricitinib
CHF				A	A	A	A	A									
IBD															A		
Lymphoma				A	A	A	A	A									
Chronic HCV, untreated		A	A														
Depression														A			
Demyelinating Disease				A	A	A	A	A									
Diverticulosis												A	A				
Recurrent Infections				A	A	A	A	A									

DMARDs preferred in skin cancer

A= avoid

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bDMARDs Treatment Safety: Summary

- **Safety vs expected benefits of treatment**
  - Reduced damage
  - Reduced disability
  - Reduced death?
  - Undertreating autoimmune disease has risks (e.g. lymphoma)!
- **Infections**
  - Increased risk of infections, largely early after starting
  - Risk difference vs non-biologics low (~1-4 /100patient years)
  - Appears similar for low vs. high risk patients
  - Biologics confer no greater risk than moderate dose steroids (prednisone > 20 mg)

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bDMARD Treatment Safety: Summary

- No apparent increase in primary or recurrent malignancy except possibly non-melanoma skin cancer
- Absolute risk (not relative risk) likely to be most informative
- Increases in lipids but neutral or even reduced CV risk
- Risk-benefit profile of biologics likely favorable
- High dose prednisone likely more dangerous than DMARDs

Management of Autoimmune Arthritis: Summary

- Treat to target
- Encourage adherence to “treat-to-target”
- Offer coping strategies, physical/occupational therapy
- Encourage exercise, healthful diet
- Minimize corticosteroid use
- Evaluate fracture risk
- Screen for comorbidities and CVD risk factors
  - Hyperlipidemia, hypertension, diabetes, smoking cessation
- Preventative Care
  - Vaccinations

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Crystal Arthritis

Jasvinder Singh, M.B.B.S., M.P.H.

Professor of Medicine and Epidemiology, Division of Clinical Immunology and Rheumatology, The University of Alabama at Birmingham

Director, UAB Cochrane Musculoskeletal Group Satellite Center

Director, Gout clinic, University of Alabama Health Services Foundation

Staff Physician, Birmingham Veterans Affairs Medical Center

Kenneth Austin Rheumatology Symposium April 7th, 2018

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Disclosures

- Research Funding: Gout & other rheumatic diseases
  - Patient Centered Outcomes Research Institute (PCORI)
  - NIAMS: UAB Gout and Hyperuricemia Center for Research Translation (CoRT)
  - NIH: U10 CA 149950
  - NIA: R01 AG 028359, U01 AG18947
  - AHRQ: U19 HS021110
  - VA: Health Services Research & Development
  - Industry: Takeda, Savient
- Consultant: Takeda, Savient, Regeneron, Allergan, Iroko, Merz, Bioiberica, Crealta
- Stock/equity: Amarin, Viking

Overview

- Spectrum of Gout
- Diagnosis of Gout
- Treatment of Gout Flares
  - What's new?
- Treatment of Gout: Hyperuricemia
  - Allopurinol, Febuxostat, Probenecid
  - What's new in Gout treatment?
    - Pegloticase
    - Lesinurad-XOI combination
- Treatment Guidelines
  - 2012 ACR and 2017 ACP
- Hyperuricemia, gout and heart disease
- Gout Epidemiology

Spectrum of Gout

- **Most common inflammatory arthritis in adults: 8.3 million Americans[1]**
  - **Chronic polyarticular arthritis**
  - **Acute, intermittent, markedly painful monoarticular or oligoarticular inflammation**
  - **Tophaceous gout**
  - **Uric acid renal calculi**
- **Common associated comorbidities[2-4]**
  - **Hypertension, Chronic kidney disease**
  - **Heart disease, hyperlipidemia**

[1]Zhu Arthritis Rheum. 2011;63(10):3136-41 ; [2]Zhu Y, Am J Med. 2012;125(7):679-87 e1; [3]Kuo Ann Rheum Dis. 2016;75(1):210-7; [4]Primatesta BMC Musculoskelet Disord. 2011;12:103.

Gout: How bad could it be?

- **“**When I have an attack it shuts down my whole life. I can’t function. I will stay in the bed three to four days while I wait for it to pass.”
- “Have to have wheel chair close to me during an attack.”
- “I have to keep my crutches by the bed so that I can get to the bathroom.”
- “My whole life changed. I had to accept a lot of things that I did not want to.”
- “I broke my leg an year ago, I swear gout hurt worse than my fracture.”
- “I have been shot- I’ d rather be shot again than have the pain due to gout.”

Singh J Arthritis Res Ther. 2014;16(2):R82; Singh J Arthritis Res Ther. 2014;16(3):R132

Chronic Polyarthritis

Acute Mono- or Oligoarticular Gout

Tophaceous Gout

Gout is associated with synovitis and joint damage: Visualization

- Radiographs
  - Punched out erosions with “overhanging margins”
- Dual-energy CT (DECT)
  - Urate deposits
  - Bony erosions
- Ultrasound
  - Double contour sign
- MRI
  - Synovitis

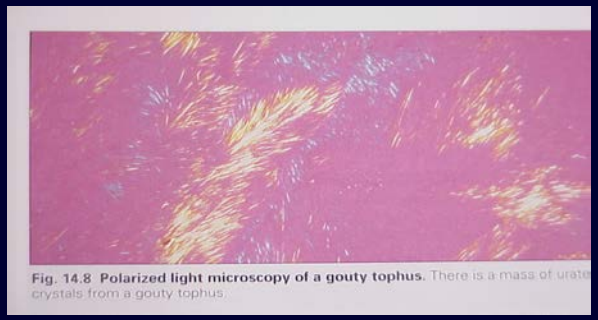
Diagnosis of Gout

Definitive Diagnosis: Joint Aspiration & Polarized Microscopy

Top, Urate crystals from a tophus are viewed under high-power polarized microscopy.

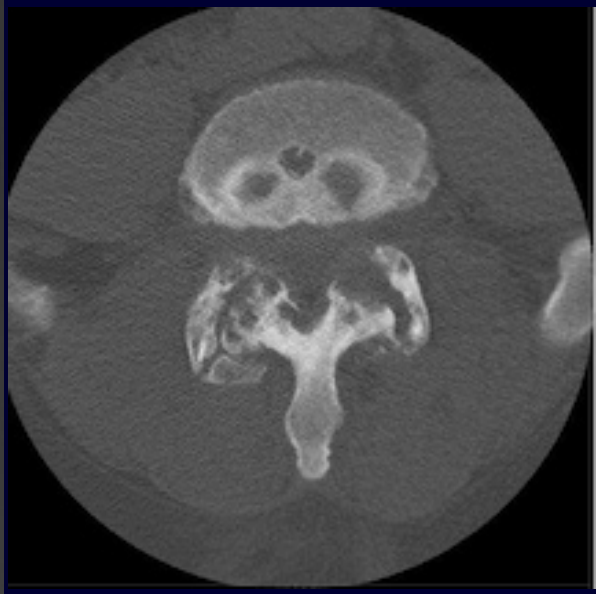
Bottom, Urate crystals from the same field are viewed under high-power compensated polarized light microscopy.

Monosodium urate monohydrate crystals are strongly negatively birefringent. They are bright yellow when parallel to the orienting line (slow vibration orientation) of the microscope's compensator and bright blue when perpendicular to this line. The crystals are almost always in a fine needle shape.

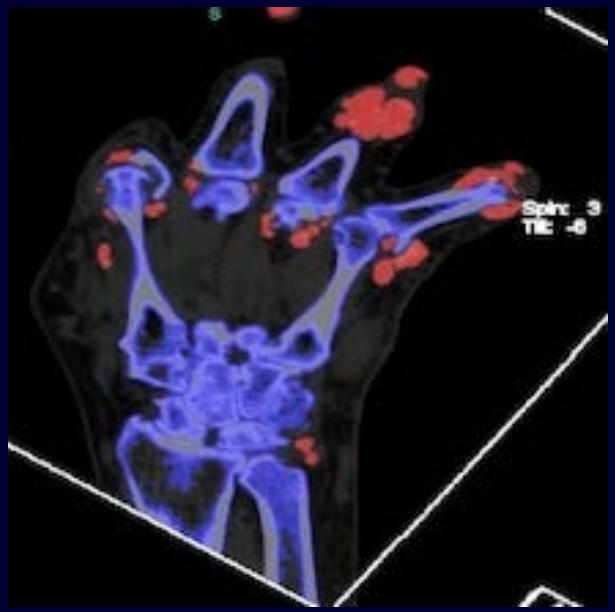


Tophus under high-power compensated polarized light microscopy

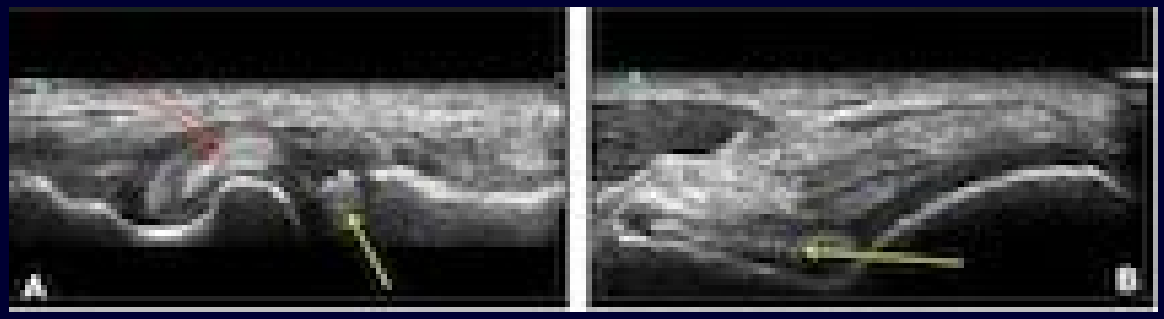
Gout is a destructive Arthritis



Gouty Erosions and Urate Tophi



Musculoskeletal Ultrasound



- Multiple hyperechoic aggregates (snow storm effect).
- A double-contour sign, formed by hyperechoic signal from crystal deposition on the articular cartilage surface combined with normal signal from the underlying bone.
- The combination of hyperechoic aggregates and the double contour sign is highly specific for gouty arthritis

NOTIONS OF THE AGREEABLE

N° 42.

Here's a dreadful situation! Murder! Betty! Here's the poker fell out! I shall be scalded to death! Oh this infernal gout!

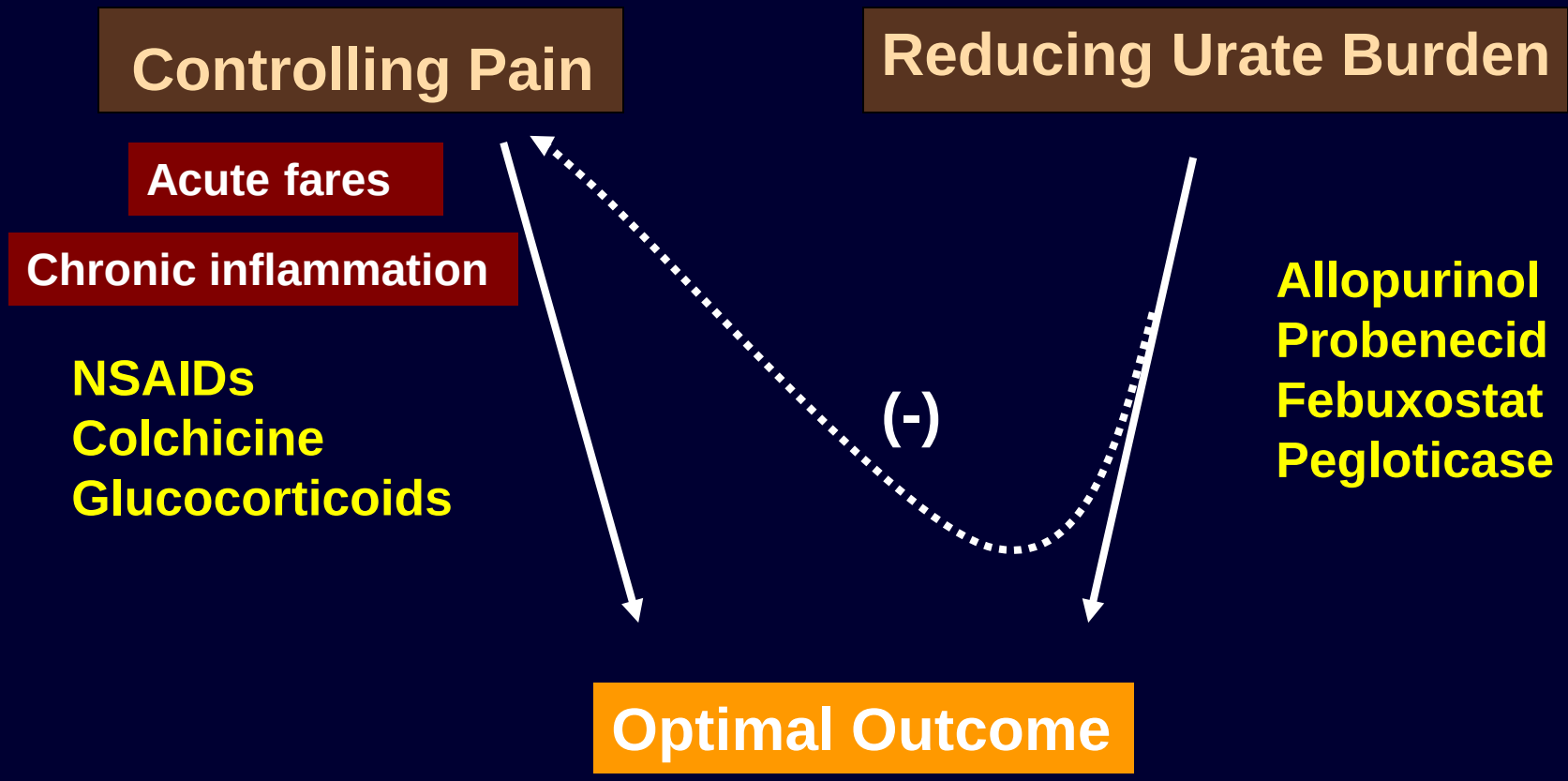
London. Published by William Spooner, 377 Strand.
Printed by W. Wells, 1st Dorset St. Fleet St.

Management Goals

- **Minimize chronic inflammation by urate-lowering**
  - **Urate-lowering therapy (ULT) to achieve target urate (sUA) < 6 mg/dl: ⬇flares, ⬇tophi, ⬇cost[1-3]**
- **Reduce/eliminate gout flares**
  - **Anti-inflammatory treatment of acute flares**
  - **Anti-inflammatory prophylaxis 6 months after new ULT**
- **Improve quality of life**
- **Reduce deformities due to tophi**

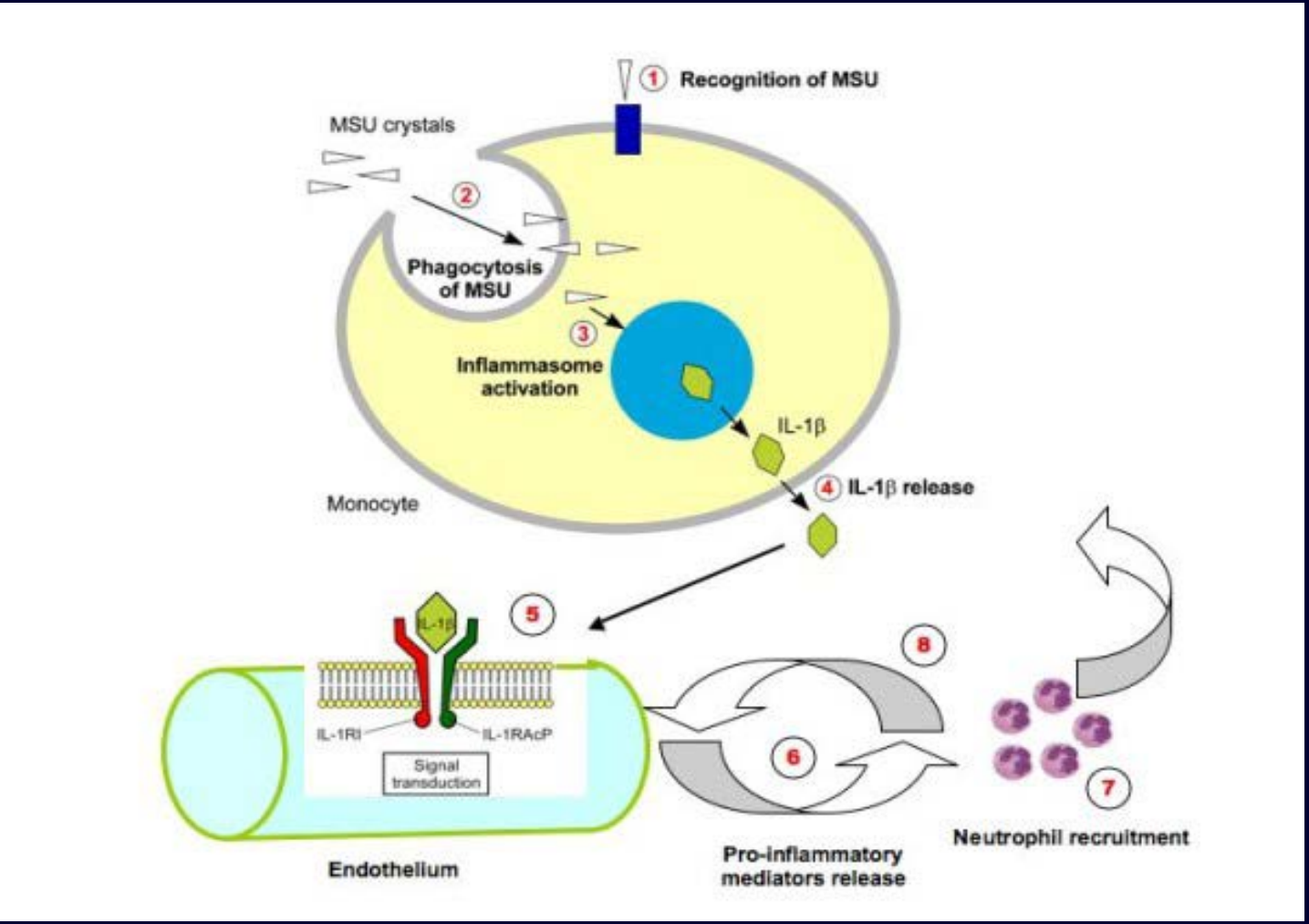
[1]Shoji Arthritis Rheum. 2004;51(3):321-5 ; [2]Becker J Rheumatol. 2009;36(6):1273-82; [3]Halpern J Clin Rheumatol. 2009;15(1):3-7.

Approach to Gout Management



Treatment of Gout Flares

Mechanism of Gout Flares



Arthritis Res Ther. 2010; 12(2): 206. Published online 2010 April 26.

Current Options for Acute Gouty Inflammation

First-line Choices

- NSAIDs : several are approved; all are effective
- Oral Colchicine: low dose
- Oral Glucocorticoids: comparable to NSAIDs
- IA Glucocorticoids

Other choices

- IM or IV Glucocorticoids
- Off Label: ACTH gel subcutaneous
- Off Label: IL-1 inhibitors
- Topical ice

Terkeltaub R, AR&T, 2009

Gout Treatment

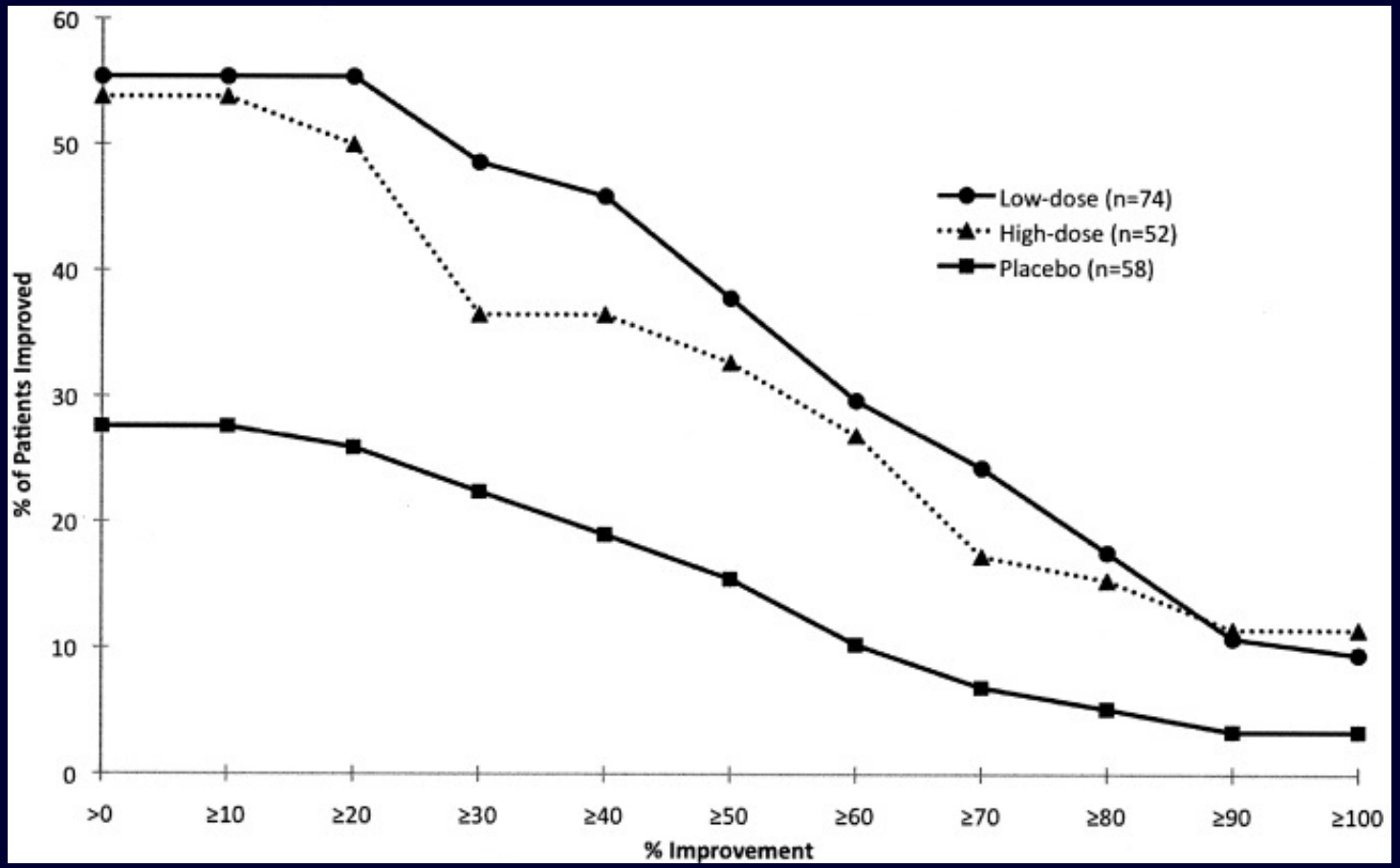
WHAT'S NEW?

PO Colchicine for Gout Flares : AGREE trial[1]

- Multicenter, randomized, double-blind, placebo-controlled, parallel-group study, N=184
- Primary Outcome: ≥50% pain reduction at 24 hours without rescue medication
- Self-administered for acute gout
  - low-dose colchicine (1.8 mg total over 1 hour)
  - high-dose colchicine (4.8 mg total over 6 hours) vs.
  - placebo

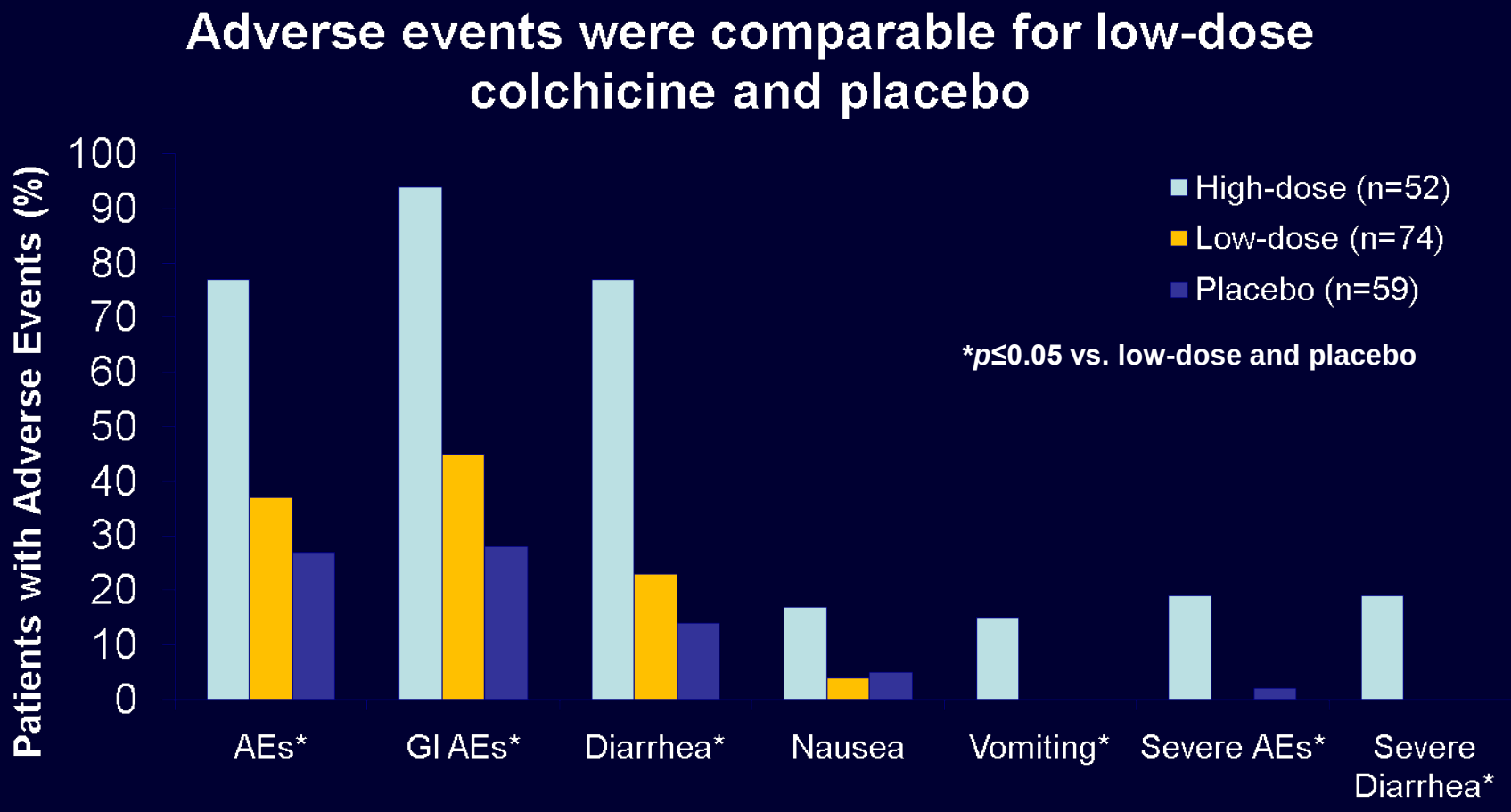
Terkeltaub et al. Arthritis Rheum 2010;62:1060-8

High versus low dosing of oral colchicine for early acute gout flare: 24-hour Outcome



Terkeltaub et al. Arthritis Rheum 2010;62:1060-8

Adverse Event with High dose and Low Dose Colchicine in the AGREE Trial



Terkeltaub RA, et al. Arthritis Rheum, 2010.

Treatment of Gout: Hyperuricemia

Treatment of Hyperuricemia in Gout

- **Lowering Uric Acid**
  - **Lifestyle Changes**
    - **Weight loss**
    - **Substitution of Thiazide diuretic with another anti-hypertensive agent**
    - **Stop Drinking Alcohol**
  - **Pharmacological therapy: Urate-lowering therapy (ULT)**
    - **Xanthine oxidase inhibitors: Allopurinol and Oxypurinol**
    - **Uricosuric drugs: Probenecid and Sulfinpyrazone; Benzbromarone (not available in U.S.)**
    - **Lesinurad: Taken off U.S. market by the company (low sales)**

Treatment of Hyperuricemia in Gout

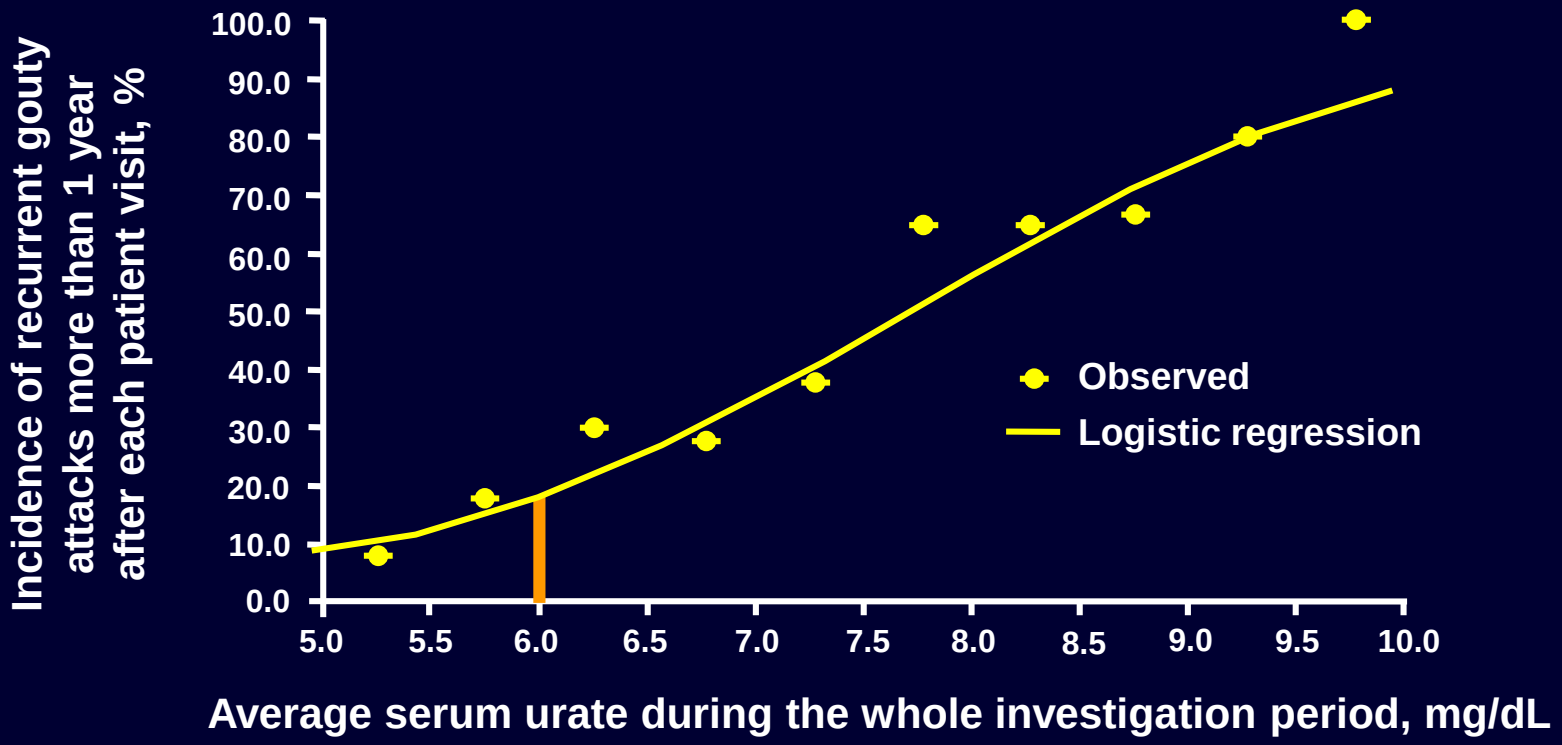
- **Prophylactic therapy is needed with new ULT use**
  - **NSAID prophylaxis**
    - **Sparse evidence in support**
    - **Usually low-dose, i.e., Naproxen 250 mg BID**
  - **Colchicine prophylaxis**
    - **First 6-months of anti-hyperuricemic therapy vs. 3-6 months after target sUA achieved ??**
    - **0.6 mg QD to BID – reduce dose in elderly and renal failure**

Long Term Pharmacological Anti-hyperuricemic therapy

- ***Fallacy*: No reason to check serum urate after starting Allopurinol**

- **Fact: A follow-up serum urate is needed for patients who start urate-lowering therapy to achieve target serum urate < 6 mg/dl**

Lowering Serum Urate Decreases Acute Flares

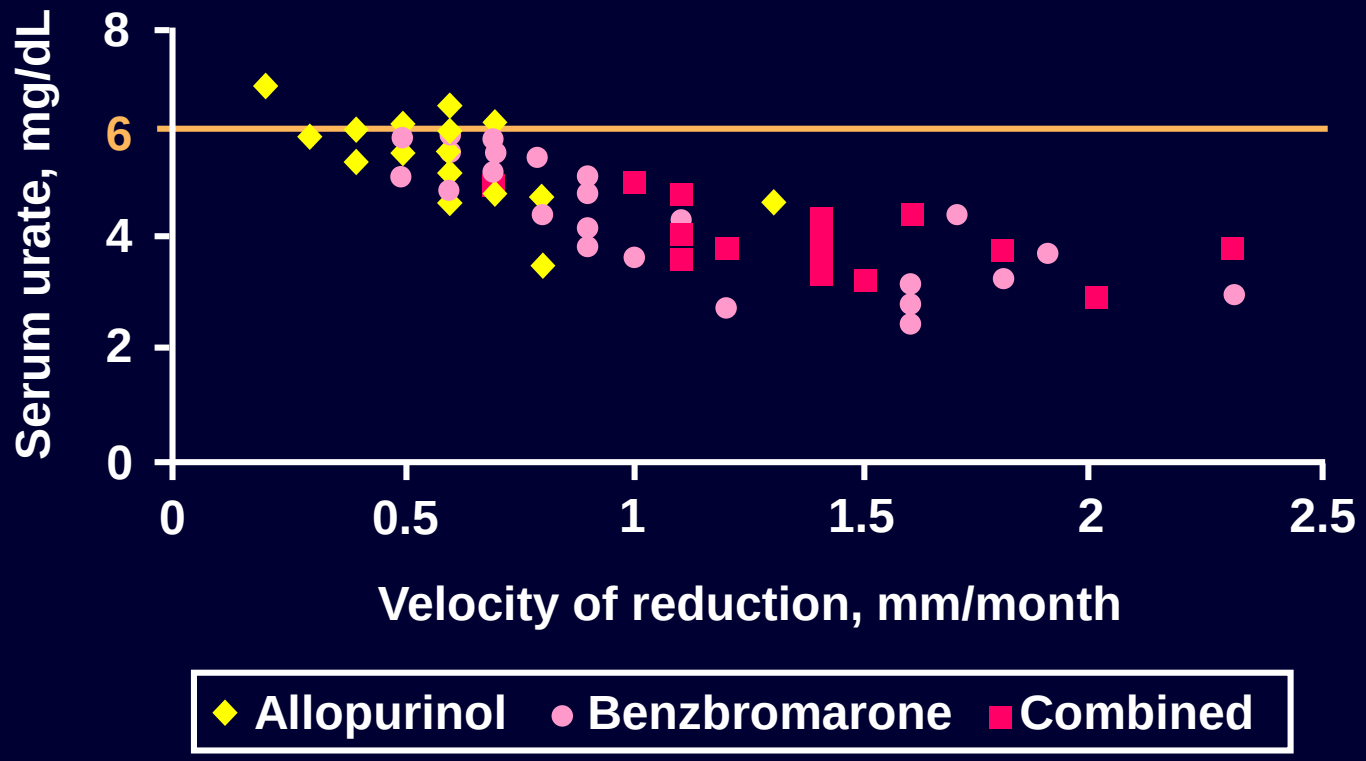


- 86% (71/81) of patients who had serum urate <6.0 mg/dL did not experience an acute flare during the study period

Shoji et al. *Arthritis Care Res*. 2004;51:321-325.

Lowering Serum Urate Decreases Tophi Size

The lower the serum urate, the faster the velocity of tophi reduction



63 patients followed for a mean of 5 years

Perez-Ruiz et al. *Arthritis Rheum*. 2002;47:356-360.

Tophaceous Gout

Treatment of gout: Allopurinol

- Most frequently used agent
- Reduces serum urate and shrinks tophi
- Reduction of recurrences of acute gouty arthritis
- Renal dose adjustment fails to achieve therapeutic serum urate lowering[1]
- Low-fixed Dosing succeeds in <50% patients[2,3]
- Advantages
  - Convenient once daily dosing
  - Effective irrespective of cause of hyperuricemia
  - Efficacious in patient with renal failure: only starting dose is lower, not the final dose

[1]Dalbeth N. J Rheumatol 2006 Aug;33(8):1646-50; Singh JA Ann Rheum Dis 2009;68:1265-70; Sarawate CA Mayo Clin Proc 2006;81:925-34

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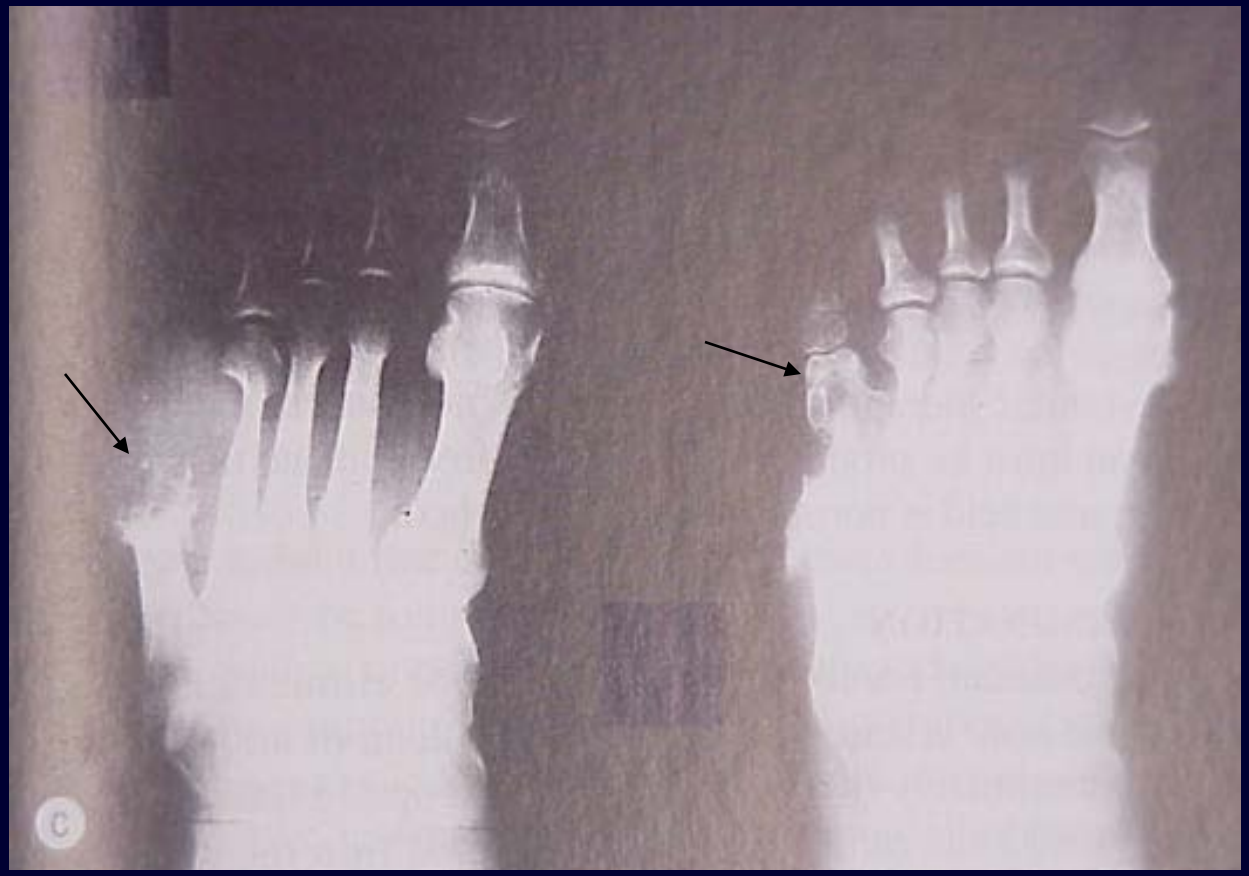
Treatment of gout: Allopurinol

- **Side Effects**
  - **Pruritus, mild rash, mild hypersensitivity reactions**
    - **Oxypurinol**
    - **Desensitization similar to penicillin**
  - **Rare severe hypersensitivity syndrome: HLA-B*5801[1, 2]**
  - **Drug interactions**
    - **Azathioprine and 6-mercaptopurine – reduce dose to ½ - 1/3**
    - **Warfarin – potentiation of anticoagulation**
- **Fallacy: Give allopurinol 300 mg to patients with normal and 100 mg to those with reduced renal function**
- **Fact: Doses 300-1200 mg are needed for higher BMI; FDA-approved doses up to 800 mg/day in 1968**

Tassaneeyakul W_ Pharmacogenet Genomics 2009 Sep;19(9):704-9; [2]Singh JA Nature rev Rheum 2013;9:200-2

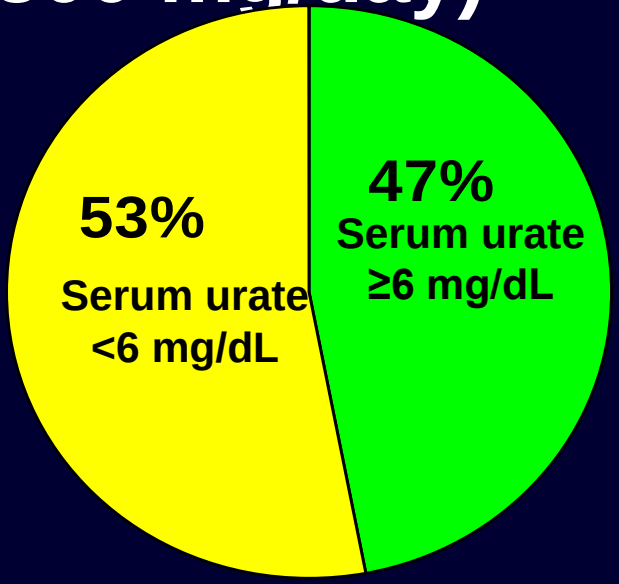
Allopurinol may heal gouty erosions: 8-year FU of a patient



Target Serum Urate Levels Not Always Achieved Even with 300 mg of Allopurinol

- Allopurinol given to patients with gout[1]
- 49 patients given standard doses of allopurinol (300 mg/day)

Results



1. Perez-Ruiz *F. Ann Rheum Dis*. 1998;57:545.

Febuxostat

- Approved in 2009
- Non-purine selective inhibitor of xanthine oxidase
- Minimal effects on other enzymes involved in purine and pyrimidine metabolism
- Metabolized mainly by glucuronide formation and oxidation in the liver

Febuxostat: Dosing

- Dosing
  - Initial: 40mg once daily
  - Usual: 40mg – 80mg once daily
    - Increase to 80mg if sUA is not < 6 mg/dL after 2 weeks
  - Max: 80mg daily (120 mg/day approved in Europe)
- Cost: 40 mg $140 (AAFP) versus allopurinol 300 mg $4 prescription at discount pharmacies

Febuxostat: FACT trial

Proportion of Subjects with sUA <6.0 mg/dL (ITT Subjects)

	Febuxostat 80 mg	Febuxostat 120 mg	Allopurinol 300 mg
Last 3 sUA <6.0 mg/dL	53% (136/255)*	62% (154/250)*	21% (53/251)
Wk 52 sUA <6.0 mg/dL	81% (129/159)*	82% (119/145)*	39% (70/178)

*p<0.05 for each febuxostat group vs. allopurinol group

Therapeutic doses of febuxostat are more effective in lowering serum urate than sub-therapeutic doses of allopurinol at 300 mg/day

Becker et al. NEJM 2005;353:2450-61

Febuxostat vs Allopurinol: RCT

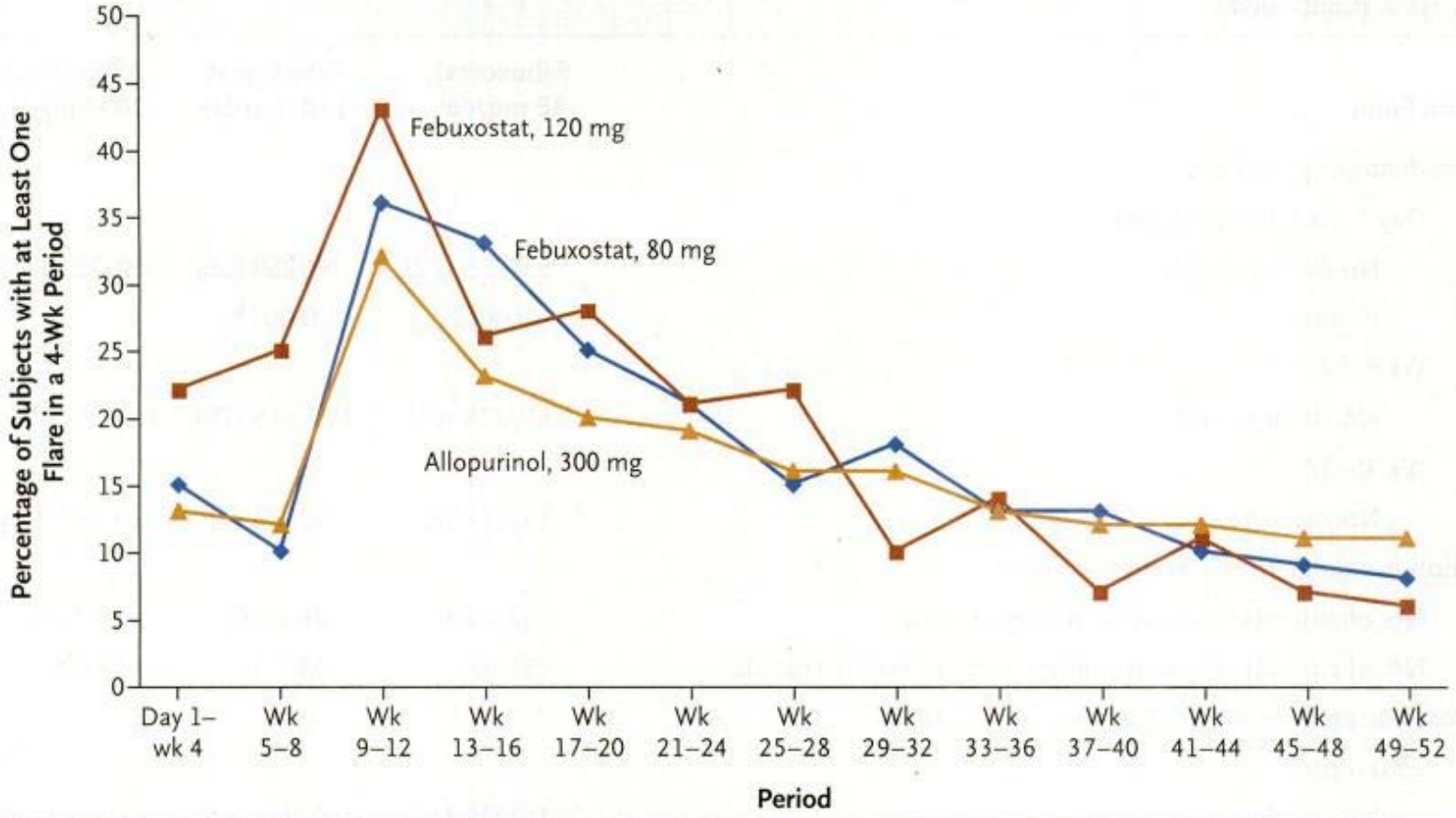


Figure 2. Subjects Requiring Treatment for Gout Flares.

The percentage of subjects in each interval is calculated by dividing the number of subjects with at least one gout flare in that interval by the number of subjects exposed to at least one dose of drug in that interval. Subjects may be counted in more than one interval. The subjects received prophylaxis during the period from day 1 to week 8. The results for the 80-mg febuxostat group are shown in blue, those for the 120-mg febuxostat group in pink, and those for the allopurinol group in yellow.

Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial

- 6,190 patients with gout and history of cardiovascular event and a serum urate level of at least 7.0 mg/dL (420 µmol/L), or of at least 6.0 mg/dL (360 µmol/L) with inadequately controlled gout, after a 1-to-3-week washout period
- CV event: myocardial infarction, hospitalization for unstable angina, stroke,

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Febuxostat (N=3098)	Allopurinol (N=3092)
Median age (interquartile range) — yr	64.0 (58–71)	65.0 (58–71)
Age ≥65 yr — no. (%)	1514 (48.9)	1586 (51.3)
Male sex — no. (%)	2604 (84.1)	2592 (83.8)
Duration of gout — yr	11.8±11.4	11.9±11.2
Baseline serum urate level — mg/dl	8.7±1.7	8.7±1.7
Presence of tophi — no. (%)	668 (21.6)	650 (21.0)
Median body weight (interquartile range) — kg	97.7 (84–113)	97.3 (84–113)
Body-mass index†	33.6±7.0	33.4±6.9
Race or ethnic group — no. (%)‡		
White	2160 (69.7)	2140 (69.2)
Black	552 (17.8)	593 (19.2)
Asian	92 (3.0)	96 (3.1)
American Indian or Alaska Native	262 (8.5)	234 (7.6)
Native Hawaiian or other Pacific Islander	13 (0.4)	14 (0.5)
Other	19 (0.6)	15 (0.5)
Cardiovascular risk factors and history — no. (%)		
Diabetes mellitus with small-vessel disease	1193 (38.5)	1213 (39.2)
Hypertension	2864 (92.4)	2851 (92.2)
Hyperlipidemia	2678 (86.4)	2702 (87.4)
Myocardial infarction	1197 (38.6)	1231 (39.8)
Hospitalization for unstable angina	855 (27.6)	869 (28.1)
Coronary revascularization	1129 (36.4)	1182 (38.2)
Cerebral revascularization	69 (2.2)	54 (1.7)
Congestive heart failure	622 (20.1)	631 (20.4)
Stroke	460 (14.8)	410 (13.3)
Peripheral vascular disease	412 (13.3)	375 (12.1)
Median estimated creatinine clearance — ml/min§		
Stage 1 or 2 chronic kidney disease	75.0	73.0
Stage 3 chronic kidney disease	46.0	46.0
Stage of chronic kidney disease — no./total no. (%)		
Stage 1 or 2	1456/3092 (47.1)	1459/3090 (47.2)
Stage 3	1636/3092 (52.9)	1631/3090 (52.8)

* Plus–minus values are means ±SD. There were no significant differences between the two groups with regard to any baseline characteristic. To convert the values for urate to micromoles per liter, multiply by 59.48.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race or ethnic group was reported by the patient.
§ Estimated creatinine clearance was calculated with the use of the Cockcroft–Gault formula and was corrected for ideal body weight. A value of 60 ml per minute or more indicated stage 1 or 2 chronic kidney disease, and a value of at least 30 but less than 60 ml per minute indicated stage 3 chronic kidney disease.

CARES Study: Results

Table 2. Major Safety End Points (Modified Intention-to-Treat Analysis).*

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value†
	no. of patients (%)			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87–1.23)‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03–1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72–1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73–1.41)	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59–1.26)	0.44
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92–1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01–1.47)	0.04

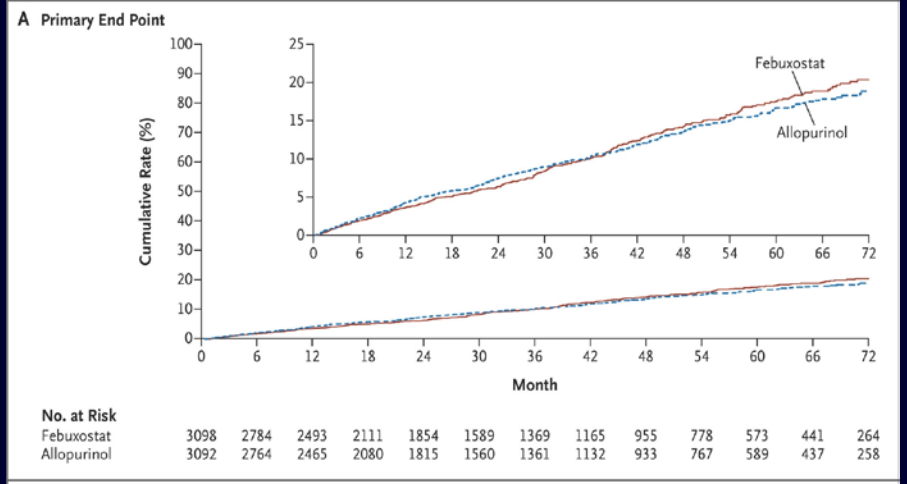
* The modified intention-to-treat analysis included all patients who underwent randomization with the exception of the 8 patients who never received febuxostat or allopurinol.

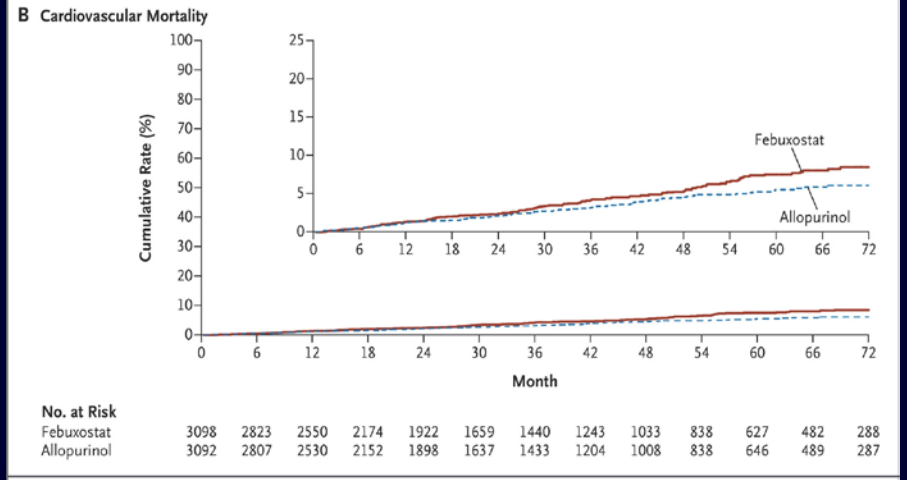
† The P value in parentheses is for test of the null hypothesis that the hazard ratio is at least 1.3 versus the one-sided alternative (noninferiority). All other P values are values for the test of superiority of febuxostat to allopurinol and were calculated with the use of a Cox regression analysis.

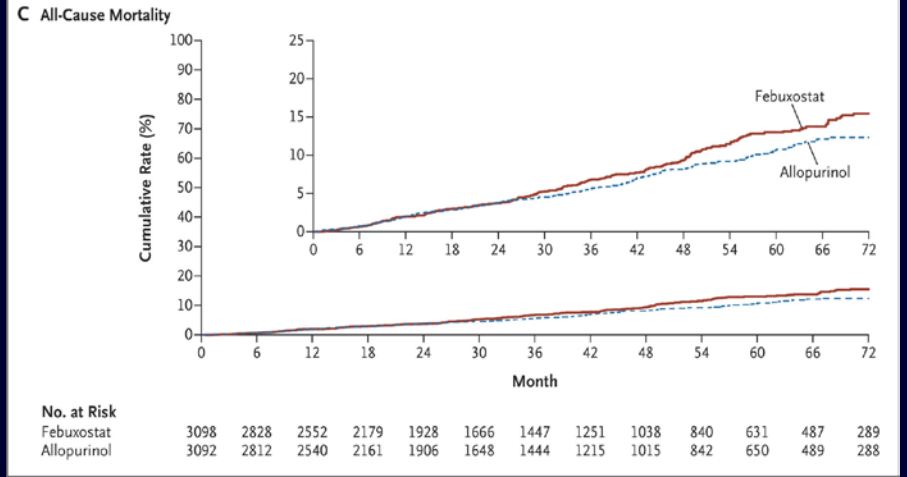
‡ The 97% confidence interval is provided here.

CARES trial

- Median FU: 32 months
- 57% discontinued trial regimen
- 405 discontinued follow-up
- Modified ITT analysis: primary end-point occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group
  - HR, 1.03; upper limit of the 1-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority.
- All-cause and cardiovascular mortality were higher in the febuxostat vs. allopurinol group
  - hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]
  - hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]



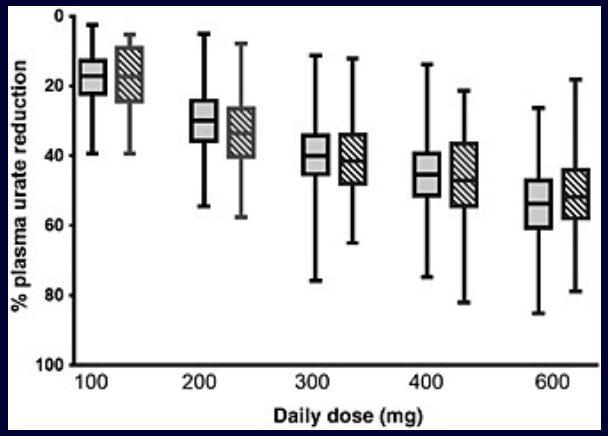




Gout Treatment: Urate-Lowering

WHAT'S NEW?

How to Dose Allopurinol Correctly?

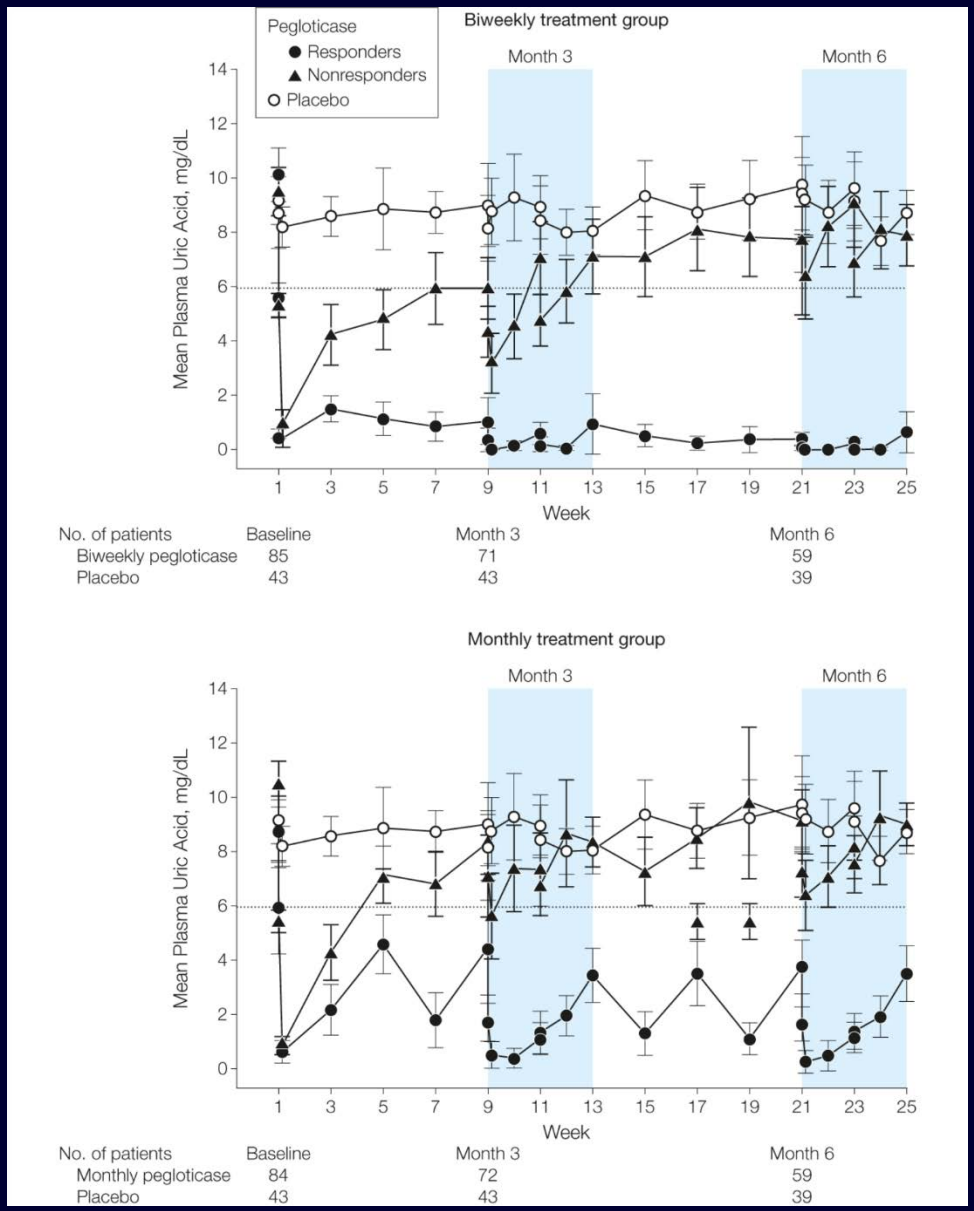


	Body weight					
CL_{cr} (ml min^{-1})	50 kg	70 kg	90 kg	110 kg	130 kg	150 kg
No diuretics						
>15–30	250 mg	350 mg	400 mg	450 mg	500 mg	550 mg
>30–50	250 mg	350 mg	400 mg	450 mg	500 mg	550 mg
>50–70	300 mg	350 mg	400 mg	450 mg	500 mg	550 mg
>70–90	300 mg	350 mg	400 mg	500 mg	550 mg	600 mg
>90	300 mg	400 mg	450 mg	500 mg	600 mg	600 mg
Taking diuretics						
>15–30	700 mg	800 mg	900 mg	950 mg	1000 mg	1000 mg
>30–50	450 mg	550 mg	600 mg	700 mg	800 mg	850 mg
>50–70	400 mg	500 mg	550 mg	650 mg	750 mg	800 mg
>70–90	400 mg	500 mg	550 mg	650 mg	750 mg	800 mg
>90	400 mg	500 mg	550 mg	650 mg	750 mg	800 mg

Wright D. Br J Clin Phar 2016 Feb; 81(2): 277–289.

Pegloticase

- Approved in 2010
- Recombinant, polyethylene glycol (PEG)–conjugated mammalian uricase
- Converts urate to allantoin
- Given IV: 8 mg IV biweekly
- Adverse events: Anaphylaxis (6%), infusion reactions (26%), heart failure exacerbation
- Caution: G6PD def. hemolysis
- Cost: $60,000/year vs. $100 for Allopurinol X 1 year
- **Check sUA before infusion**: If >6 mg/dl X2, do not infuse



Sundy JS. JAMA. 2011;306 (7):711-720

Primary: SUA <6 mg/dl >80% of time

	Pegloticase Biweekly	Pegloticase Monthly	PLACEBO
Pooled	42% (32-54%)	35% (24-46%)	0% (0-8%)
	<0.001	<0.001	
C0405	47% (31-62%)	20% (9-35%)	0% (0-17%)
	<0.001	0.04	
C0406	38% (24-54%)	49% (33-65%)	0% (0-15%)
	0.001	<0.001	

Secondary: >=1 tophi resolved

	Pegloticase Biweekly	Pegloticase Monthly	PLACEBO
Pooled	40% (29-53%)	21% (11-35%)	7% (1-24%)
	0.02	0.002	

Sundy JS. JAMA. 2011;306 (7):711-720

Table 3. Number of Pooled Replicate Modified Intent-to-Treat Group Patients Experiencing Treatment-Emergent Adverse Events[a]

Event	No. (%) of Patients		
	Pegloticase Biweekly (n = 85)	Pegloticase Monthly (n = 84)	Placebo (n = 43)
Any AE	80 (94)	84 (100)	41 (95)
Any serious AE	20 (24)	19 (23)	5 (12)
Death[b]	2 (2)	1 (1)	0
Discontinuation owing to AE	15 (18)	16 (19)	1 (2)
Most commonly reported[c]			
Gout flare	65 (76)	71 (85)	35 (81)
Infusion reaction	22 (26)	35 (42)	2 (5)
Headache	8 (9)	9 (11)	4 (9)
Nausea	10 (12)	6 (7)	1 (2)
Back pain	3 (4)	7 (8)	2 (5)
Nasopharyngitis	6 (7)	4 (5)	1 (2)
Dyspnea	4 (5)	5 (6)	2 (5)
Vomiting	4 (5)	5 (6)	1 (2)
Chest pain	5 (6)	4 (5)	1 (2)
Pruritus	3 (4)	5 (6)	0
Contusion	7 (8)	0	1 (2)
Pyrexia	2 (2)	5 (6)	1 (2)
Constipation	5 (6)	2 (2)	2 (5)
Blood pressure increased	0	6 (7)	0
Adjudicated CV events			
APTC events	2 (2)	1 (1)	0
CV death	2 (2)	0	0
Nonfatal MI	0	1 (1)[d]	0
Non-APTC events	3 (2)[e]	6 (7)	0
CHF	2 (2)	1 (1)	0
Arrhythmia	1 (1)	1 (1)	0
DVT	0	1 (1)	0
TIA	0	1 (1)	0
Unstable angina	0	1 (1)	0
Coronary revascularization	0	1 (1)	0

Abbreviations: AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; CHF, congestive heart failure; CV, cardiovascular; DVT, deep vein thrombosis; MI, myocardial infarction; TIA, transient ischemic attack.

[a] A treatment-emergent AE was defined as any event (except death) reported with a start date occurring on or after the date of the first dose or any pre-existing condition that worsened on or after the first dose. Adverse events were categorized according to codes used in the Medical Dictionary for Regulatory Activities (MedDRA version 9.0) and listed in descending order of total AEs for each item.

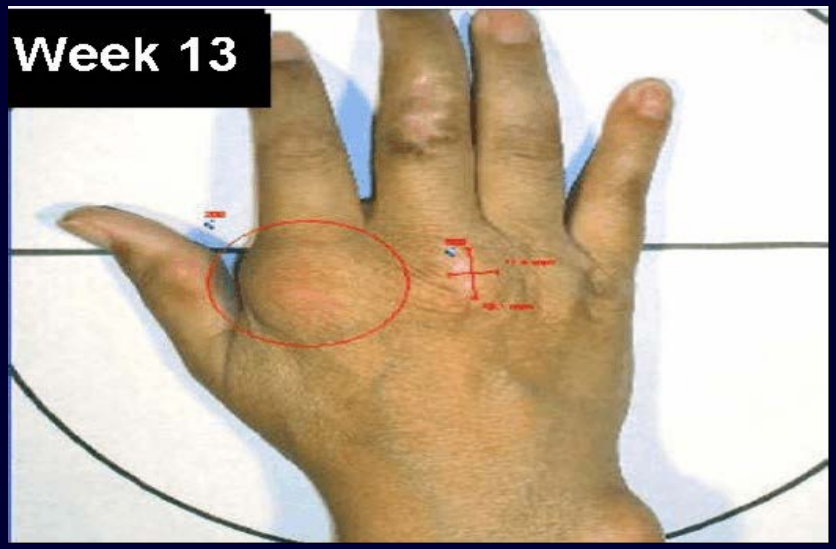
[b] Deaths recorded are those occurring during the 25-week treatment period. Additional deaths occurring in randomized patients outside the treatment period are described in the "Results" section.

[c] The most commonly reported AEs were defined as those occurring in ≥5% of patients in any treatment group and at least 1% more frequently in patients treated with pegloticase compared with patients receiving placebo.

[d] One patient had an APTC event (nonfatal myocardial infarction) and a non-APTC event (coronary revascularization), both recorded here.

[e] One patient had 2 non-APTC events (CHF and arrhythmia) and is not counted twice in the total percentage of affected patients.

Tophi “Debulking” with Uricase Therapy

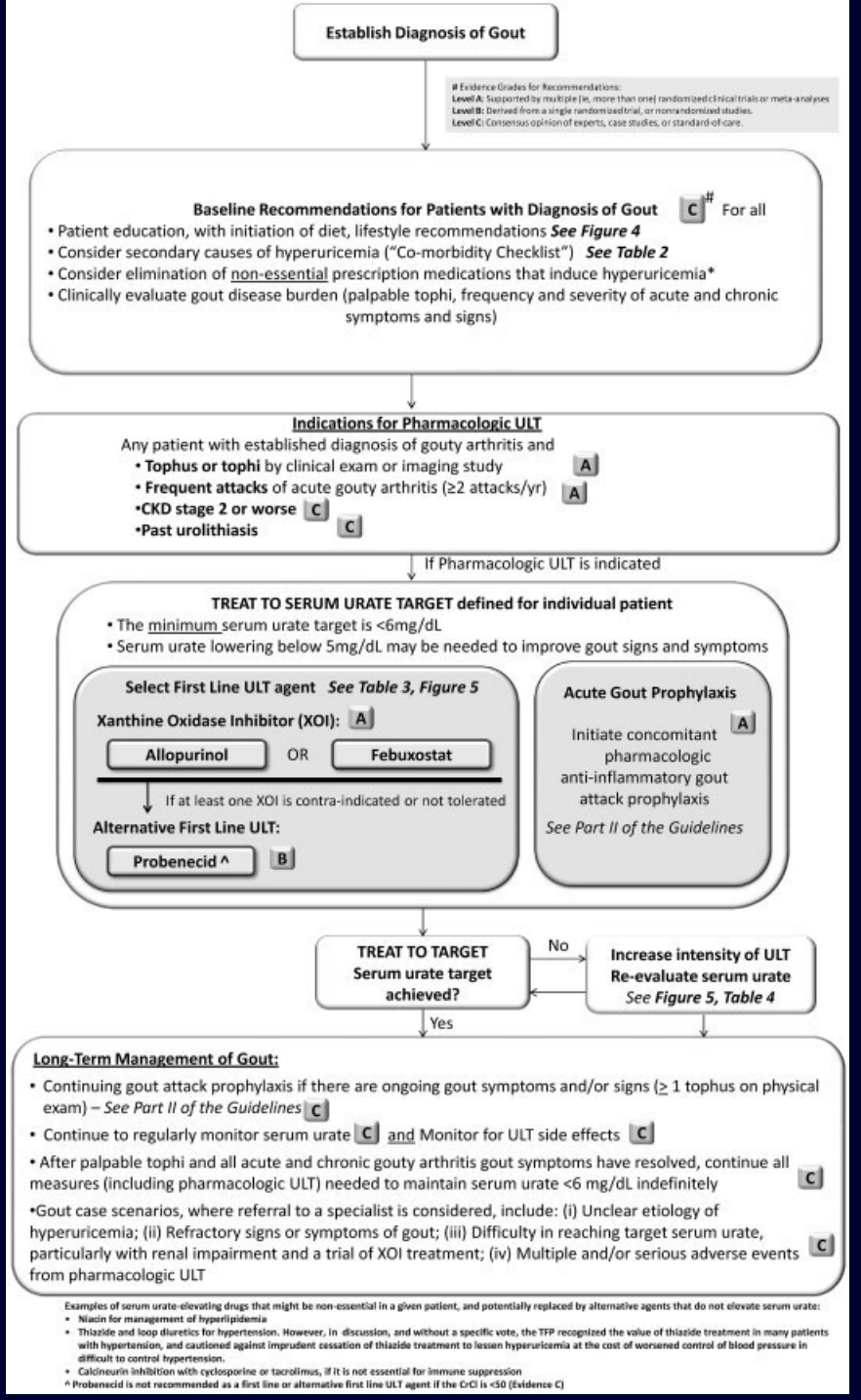


8 mg Pegloticase q 2 wks

Baraf , ACR, 2008

TREATMENT GUIDELINES: HOW CAN THEY HELP US?

2012 American College of Rheumatology Gout Guideline



2012 American College of Rheumatology Gout Guideline

Specific Recommendations:

GENERAL HEALTH, DIET, AND LIFESTYLE MEASURES FOR GOUT PATIENTS#:

Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, more than one) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies.
Level C: Consensus opinion of experts, case studies, or standard-of-care.

- **Weight loss for obese patients, to achieve BMI that promotes general health**
- **Healthy overall diet ^**
- **Exercise (Achieve physical fitness)**
- **Smoking cessation**
- **Stay well hydrated**

C

Avoid	Limit	Encourage >
• Organ meats high in purine content (eg, sweetbreads, liver, kidney) B	Serving Sizes of: • Beef, Lamb, Pork • Seafood with high purine content (eg, sardines, shellfish) B	• Low-fat or non-fat dairy products B
• High fructose corn syrup-sweetened sodas, other beverages, or foods C	• Servings of naturally sweet fruit juices • Table sugar, and sweetened beverages and desserts • Table salt, including in sauces and gravies C	• Vegetables C
• Alcohol overuse (defined as more than 2 servings per day for a male and 1 serving per day for a female) in all gout patients B • Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control C	• Alcohol (particularly beer, but also wine and spirits) in all gout patients B	

^Without a specific task force panel (TFP) vote, adherence to diets for cardiac health and control of co-morbidities such as obesity, metabolic syndrome, diabetes, hyperlipidemia, and hypertension was stressed for gout patients, as appropriate.

> The TFP recommendation to "encourage" intake was not intended to advocate excesses in consumption of specific dietary items. There was a lack of TFP voting consensus on: Cherries and Cherry Products, Ascorbate (In Supplements or Foods), Nuts, Legumes. The TFP did not specifically vote on the question of limits on consumption of purine-rich vegetables and legumes.

2017 ACP Gout Guideline

- **Recommendation 1: ACP recommends that clinicians choose corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine to treat patients with acute gout. (Grade: strong recommendation, high-quality evidence)**
- **Recommendation 2: ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout. (Grade: strong recommendation, moderate-quality evidence)**
- **Recommendation 3: ACP recommends against initiating long-term urate-lowering therapy in most patients after a first gout attack or in patients with infrequent attacks. (Grade: strong recommendation, moderate-quality evidence)**

Qaseem et al. Ann Intern Med. 2017;166:58-68.

2017 ACP Gout Guideline

- **Recommendation 4: ACP recommends that clinicians discuss benefits, harms, costs, and individual preferences with patients before initiating urate-lowering therapy, including concomitant prophylaxis, in patients with recurrent gout attacks. (Grade: strong recommendation, moderate-quality evidence)**

Qaseem et al. Ann Intern Med. 2017;166:58-68.

HYPERURICEMIA, GOUT AND HEART DISEASE

Potential Associations with Hyperuricemia Cardiovascular Events and Mortality

Finding	Supportive Studies
Hyperuricemia ↑ development of cardiovascular disease, ischemic heart disease, and/or coronary heart disease	✓ **Breckenridge et al.** (*Lancet*, 1966) ✓**Santos et al** ***(Am J Cardiol, 2007)***
Hyperuricemia ↑ risk of Cardiovascular events	✓ **SHEP** (*J Hypertens*, 2000) ✓ **Worksite Treatment Program** (*J Hypertens*, 1998) ✓ **PIUMA** (*Hypertension*, 2000) ✓ **LIFE 2003** (*Kidney Int*, 2000) ✓ **Darmawan et al.** (*J of Rheum*, 2003) ✓ **Lehto et al.** (*Stroke*, 1998)
Hyperuricemia ↑ mortality from coronary heart disease, ischemic heart disease, and overall mortality	✓ **NHANES** (*JAMA, 2002)* ✓ **Bickel et al.** (*Am J Cardiol*, 2002) ✓ **Darmawan et al.** (*J of Rheum*, 2003)

Hyperuricemia and CVD Framingham vs. NHANES

Framingham (n = 6763)

- Serum urate NOT associated with CVD after adjustment for other risk factors
- Diuretics most responsible for eliminating statistical significance of urate

Culleton F. *Ann Int Med* 1999;131:7:2404

NHANES I (n = 5926)

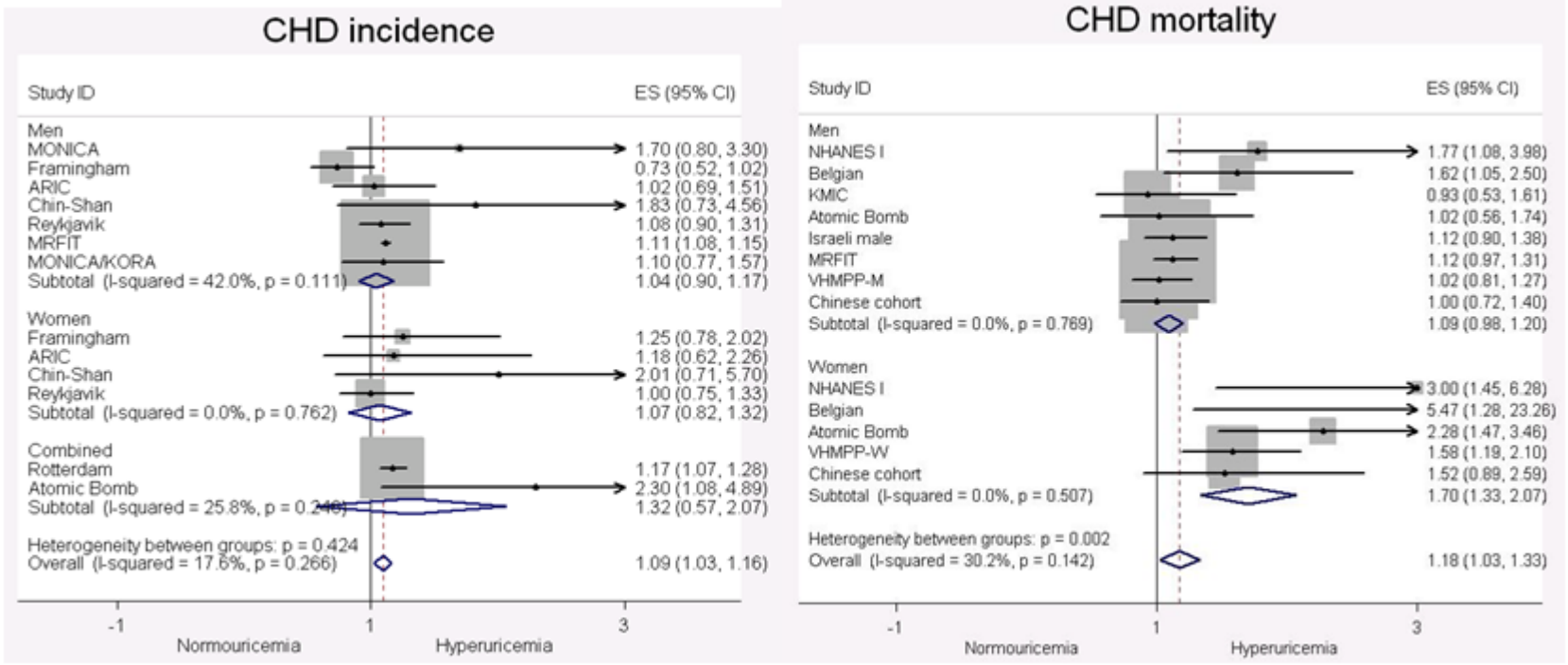
- 60 µmol/L ↑ in serum urate → 48% ↑ IHD risk in women
- Better external validity (generalizability) than Framingham
- Critique- serum urate may be confounder for hypertension, diuretic use, dyslipidemia, disordered glucose metabolism or renal insufficiency

Fang J. *JAMA* 2000;283:2404

Hyperuricemia and CHD Meta-analysis

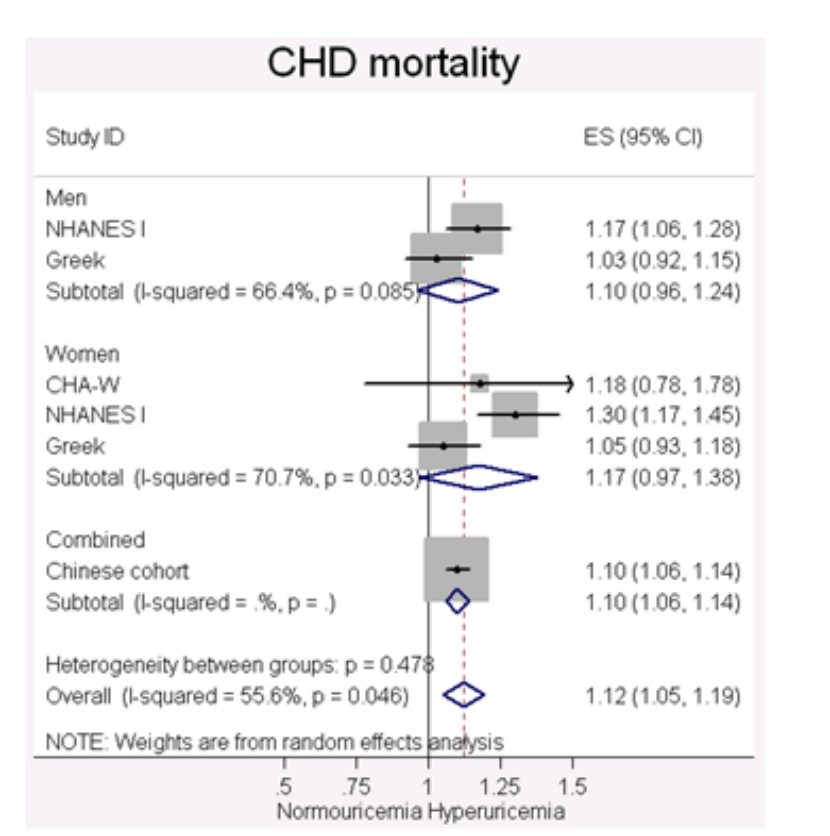
(n = 26 studies - 402,997 adults)

- **Pooled *unadjusted* risk ratio (RR)**
  - **1.34 (95%CI: 1.19-1.49) for CHD incidence**
  - **1.46 (95% CI: 1.20-1.73) for CHD mortality**
- **Pooled *multivariate* RR**
  - **1.09 (95% CI: 1.03-1.16) for CHD incidence**
  - **1.18 (95% CI: 1.03-1.33) for CHD mortality**



Kim SY Arth Care Res 62:170, 2010

Hyperuricemia and CHD: Gender Effect



- Each increase of 1 mg/dl in uric acid leads to overall pooled multivariate RR for CHD mortality = 1.12 (95% CI: 1.05-1.19)

- Subgroup analyses showed no significant association between hyperuricemia and CHD incidence/mortality in men, but a significant risk for CHD mortality in women (RR 1.70; 95% CI: 1.33-2.07)

Kim SY Arth Care Res 62:170, 2010

Is Gout a Risk for Myocardial Infarction?

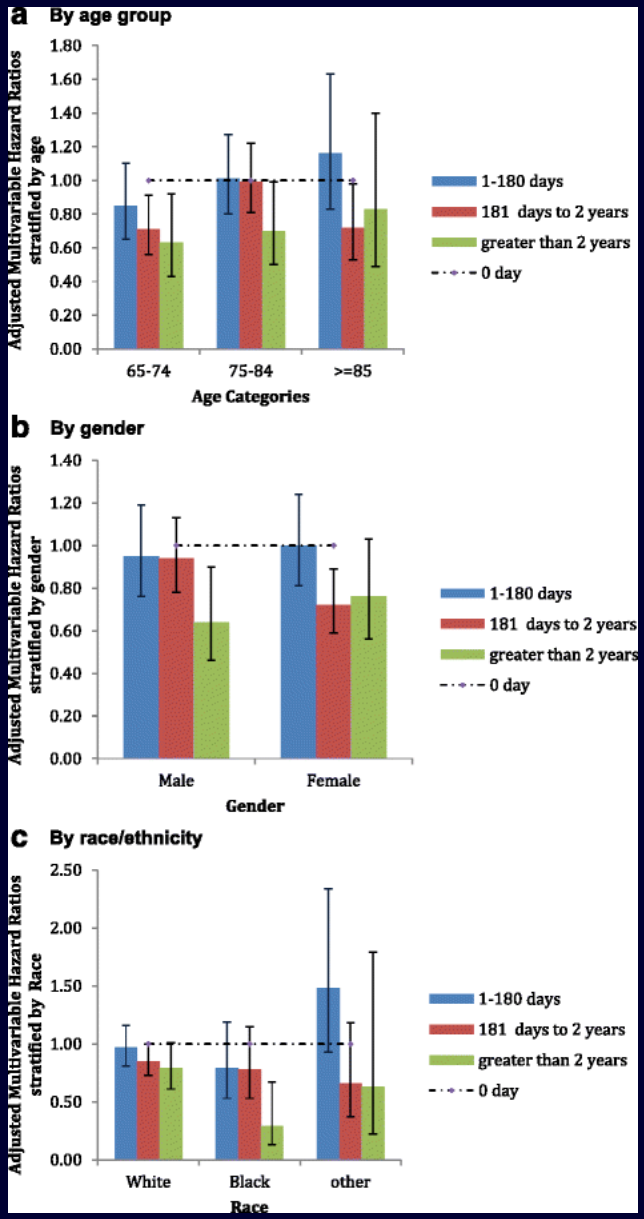
- 12,866 men followed for a mean of 6.5 years in MRFIT trial[1]
- MI events: Gout patients: 10.5%
  Non-gout patients: 8.43%
- Hyperuricemia independent risk factor for acute MI (OR=1.11 [95% CI, 1.08–1.15], p<0.001)
- Gout risk present in non-users of:
  - Alcohol
  - Diuretics
  - Aspirin
  - Those without metabolic syndrome, diabetes and obesity[1]

- 51,297 men followed prospectively over 12 years -Health Professionals Follow-Up Study
- Men with gout have a higher risk of death from all causes
- Relative Risk 1.55 of cardiovascular deaths[2]

[1]Krishnan et al, Arthritis Rheum 2006; 54: 2688–96
[2]Choi et al, Circulation 2007; 116: 894–900

Allopurinol reduces MI Risk in Elderly

- 5% random Medicare Claims data 2006-2012[1]
- ≥365 days baseline without MI and allopurinol
- 29,298 episodes of incident allopurinol use
- 1544 episodes (5.3%) had incident MI
- Hazard Ratio of MI with Allopurinol:
  - Use (vs. no use): **0.85 (95% CI, 0.77 to 0.95)**
  - longer allopurinol use durations →lower HR of MI (vs. 0 days):
    - 180 days-2 years, **0.83 (95% CI, 0.72 to 0.95)**
    - >2 years, **0.70 (95% CI, 0.56 to 0.88)**
    - <180 days, **0.98 (95% CI, 0.84, 1.14)**



[1]Singh JA. Arthritis Res Ther 2016;18:209.

HOSPITALIZED GOUT

Gout in Hospitalized patients

- Risk of gout flares is increased 4-fold with hospitalizations[1]
- Single-center hospitalization study[2]
  - 2002-2004: all hospitalized with diagnosis of gout
  - Leading causes of hospitalization
    - Acute gout: 19%
    - Heart failure: 19%
    - Chest pain: 9%
    - DVT, stroke, infections, GI bleed: 4-5% each
  - 27% were receiving allopurinol prior to admission
  - Urate was checked in 27% of all patients
  - 86% colchicine-treated and 80% NSAID-treated had renal failure
  - >50% took combination anti-inflammatory therapy

[1]Debruil M. AJM 2013;126(12); [2]Petersel D 2007; J Rheumatol 2007;34:1566–8

Tips for treatment of hospitalized gout

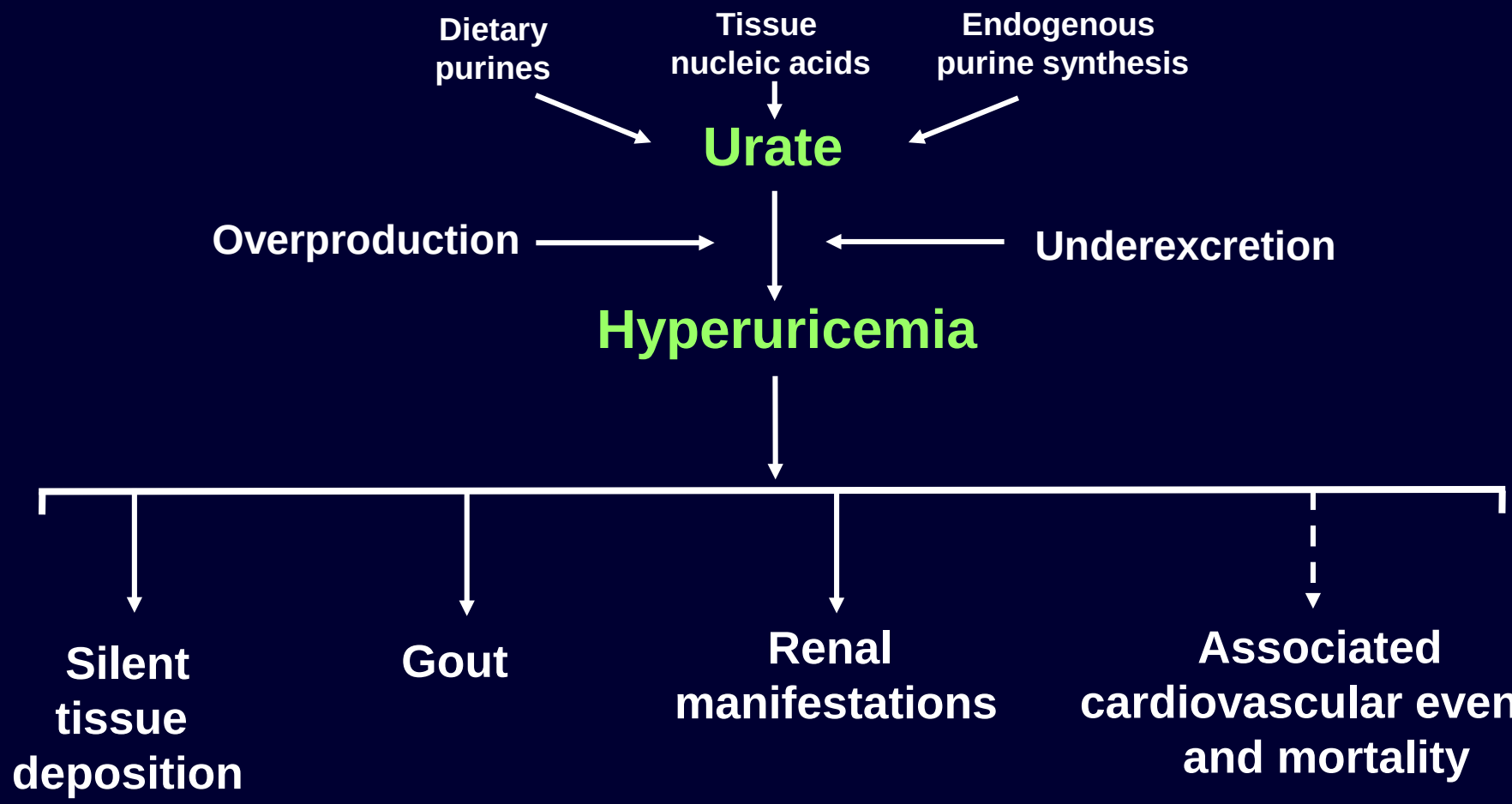
- Confirm gout diagnosis by aspiration
- Treat promptly; get rheum consult, if needed
- Intra-articular glucocorticoids (GCs) are usually the safest
- Parenteral GCs can be used except in severe diabetes, sepsis, uncontrolled systemic/organ infection
- ACTH can be used, when GCs are contraindicated
- Reserve NSAIDs and colchicine for cases where GCs can not be used
- Avoid combination anti-inflammatory treatment: NO evidence to support superior efficacy, and a clear evidence for harm

Conclusions

- Gout is common and the problem is increasing
- Hyperuricemia associated with prevalent comorbidities such as hypertension, CVD, hyperlipidemia, and insulin resistance
- Gout impairs quality of life and imparts considerable societal burden
- Treatment resistant gout creates unmet need
- Despite the evidence and guidelines, significant problems exist with gout quality of care
- Safer use of old and newer treatments may emerge
- New data on old and new risk factors

Gout Epidemiology

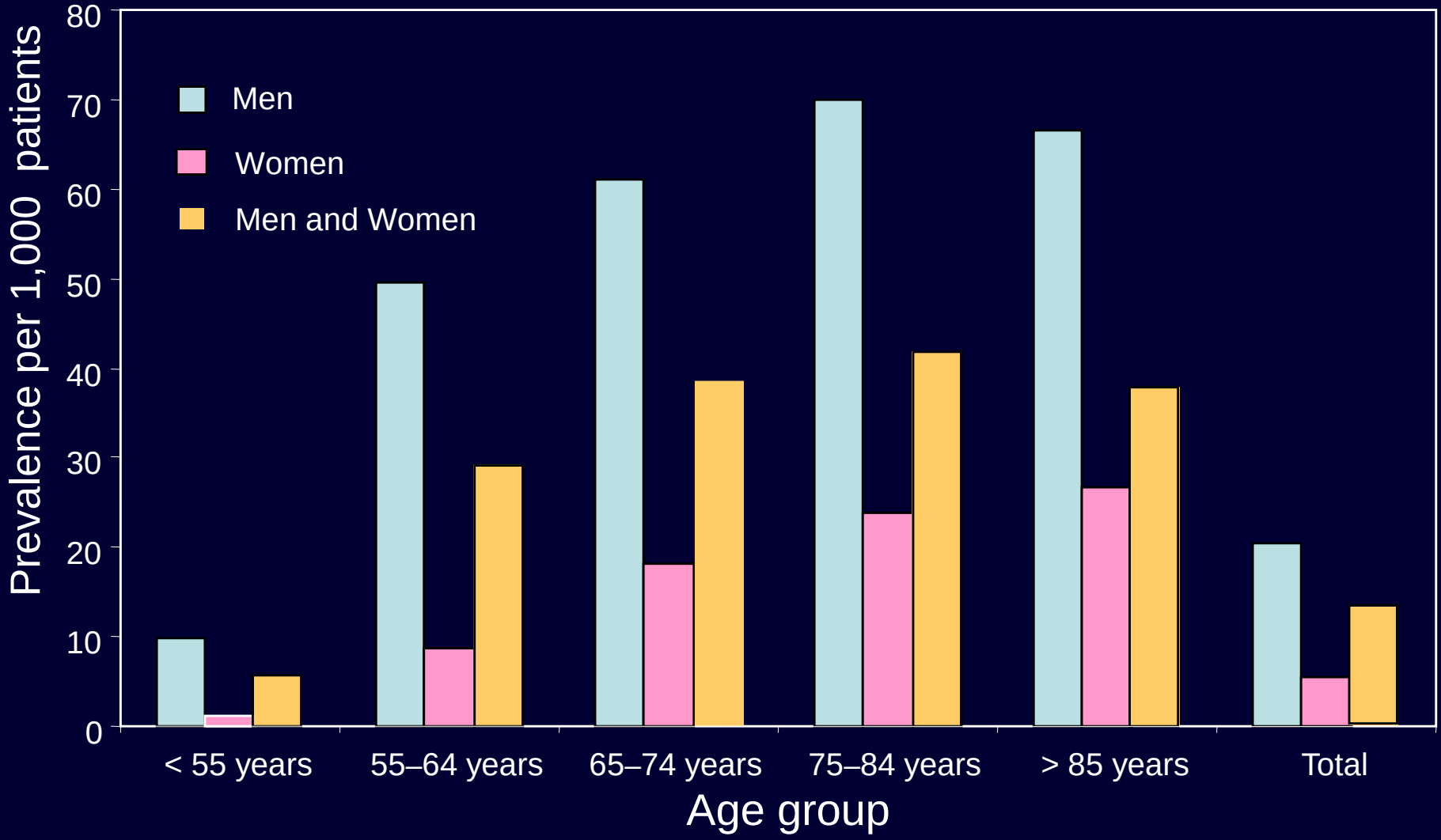
The Hyperuricemia Cascade



Gout = Uricase Gene Deficiency

- Almost all mammals possess urate oxidase (uricase) which oxidizes uric acid to allantoin, a highly soluble compound
- Inactivation of the uricase gene in humans and great apes results from several mutations
- The evolutionary advantage of hyperuricemia remains unknown

Gout Prevalence, GPRD 1999



Mikuls T. *et al. Ann Rheum Dis*, 2005;64:267.

Overall, Gender-Specific, and Age-Specific Prevalence (%) of Gout: NHANES III and 2007–2008

	NHANES III 1988–1994	NHANES 2007–2008	Difference (95% CI)
Gout Overall Prevalence	2.7	3.9	p<0.05
Male	3.8	5.9	p<0.05
Female	1.6	2.0	
Age groups			
20–39	0.7	0.8	
40–59	2.6	3.5	
60–79	6.8	8.5	
80+	5.9	12.6	p<0.05

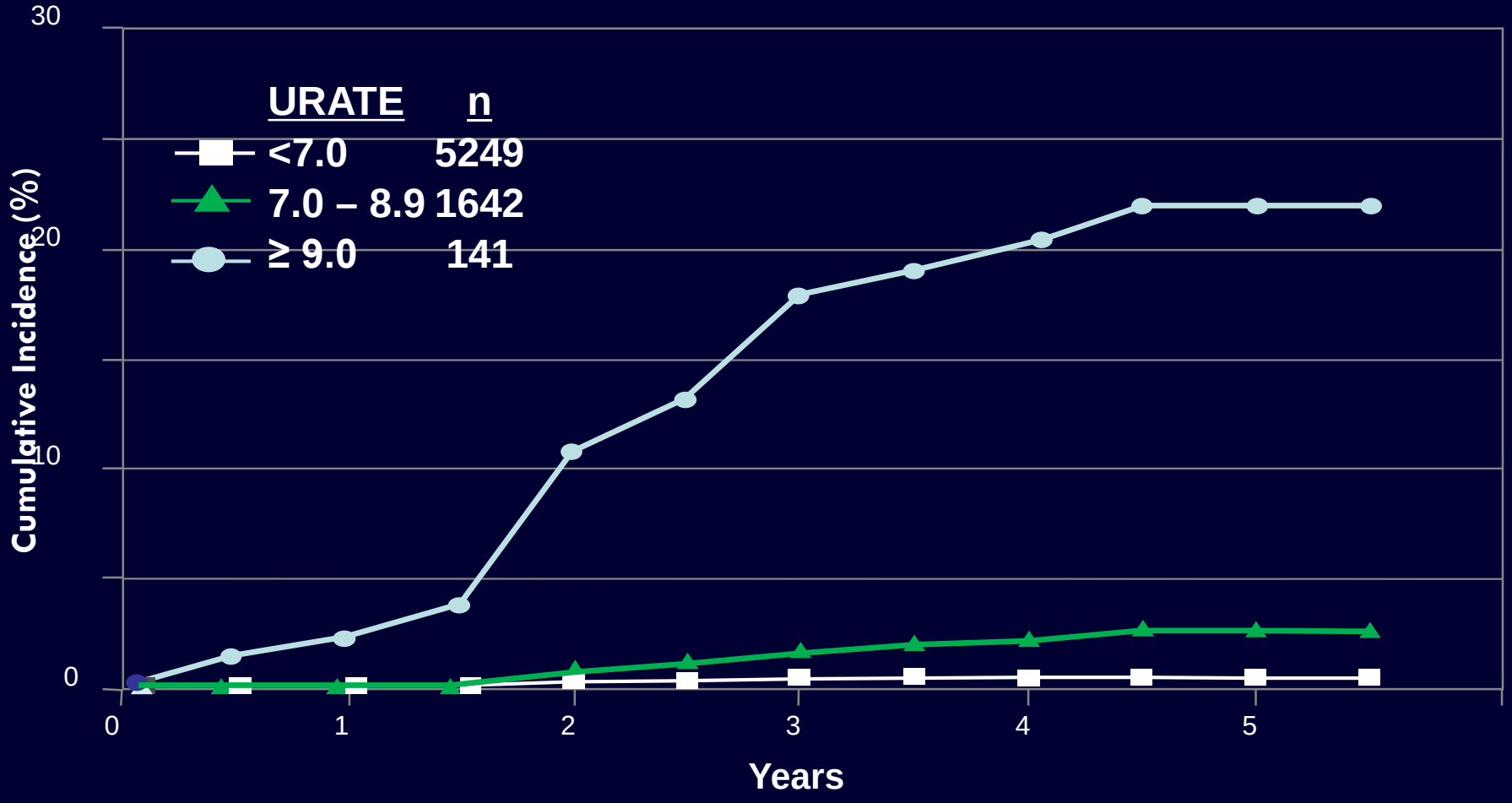
Zhu Y, Arthritis Rheum 2011;63:3136-41

Limitations of Data on Gout Epidemiology

- Data on incidence are limited, with broad geographic variability
- Variable methods of reporting
  - Self-reported prevalence may over- or under-estimate true prevalence up to 2-fold
    - 44% of patients in the Sudbury study claimed to have gout and could not be confirmed[1]
  - Physician under/over diagnosis
  - Crystal diagnosis not practical at population level

1. O'Sullivan JB. *Ann Rheum Dis* 1972;31:166.

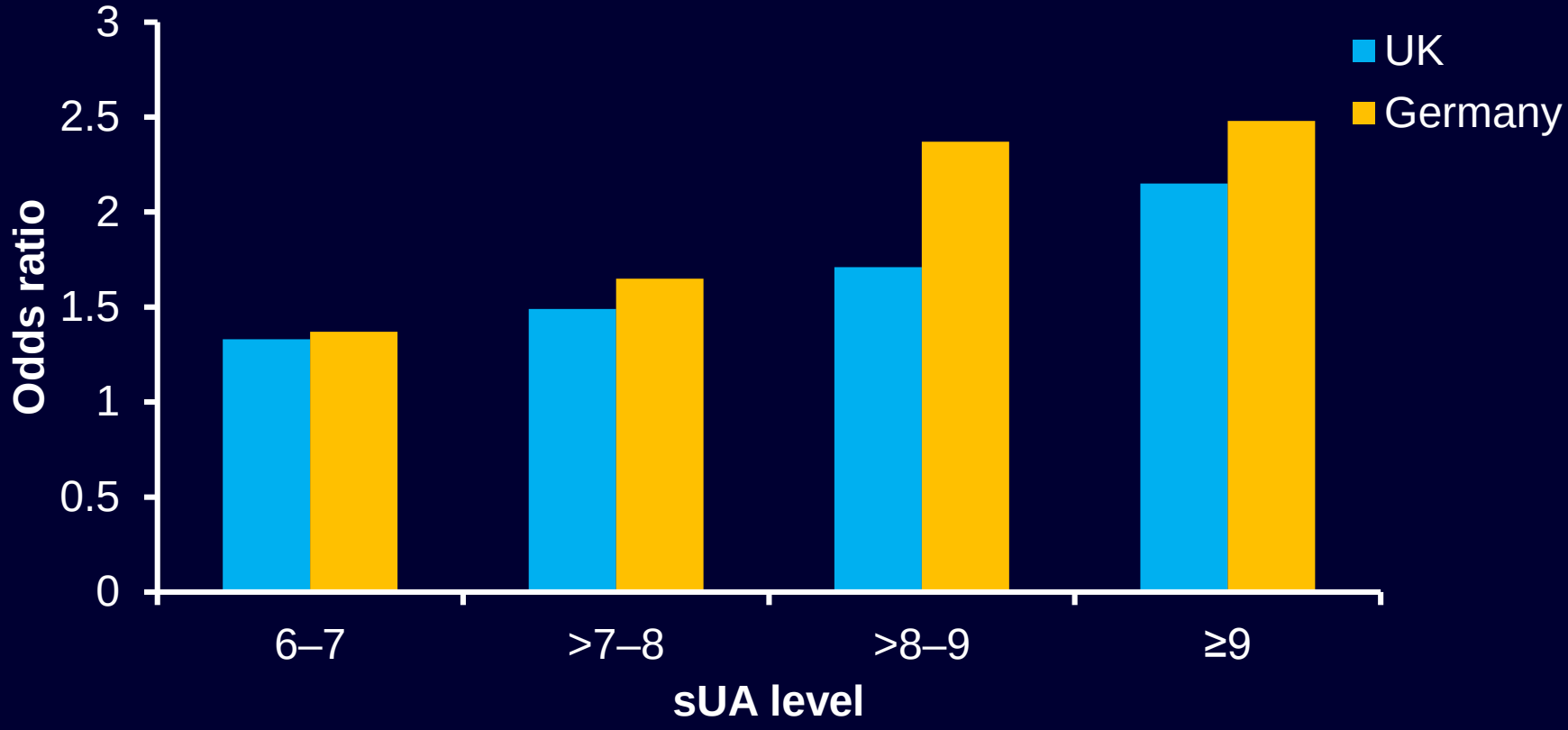
Incidence of Gout Based on Urate Levels



- In a study of men with hyperuricemia, 22% with serum urate levels ≥9 mg/dL developed gouty arthritis over 5 years[1]

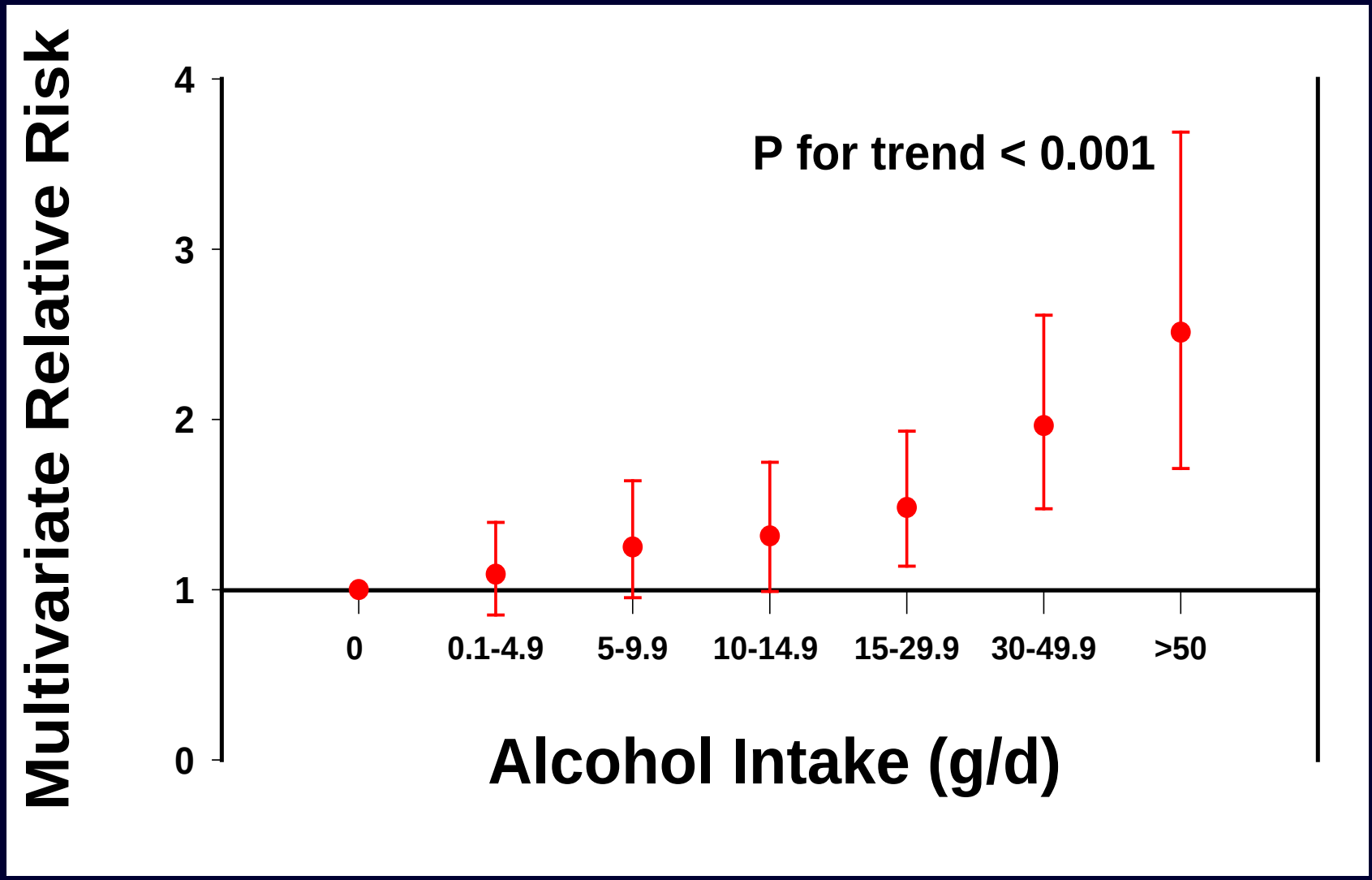
1. Campion EW, *et al*. *Am J Med*. 1987;82:421–426

Association Between sUA Level and Odds of Gout Flares



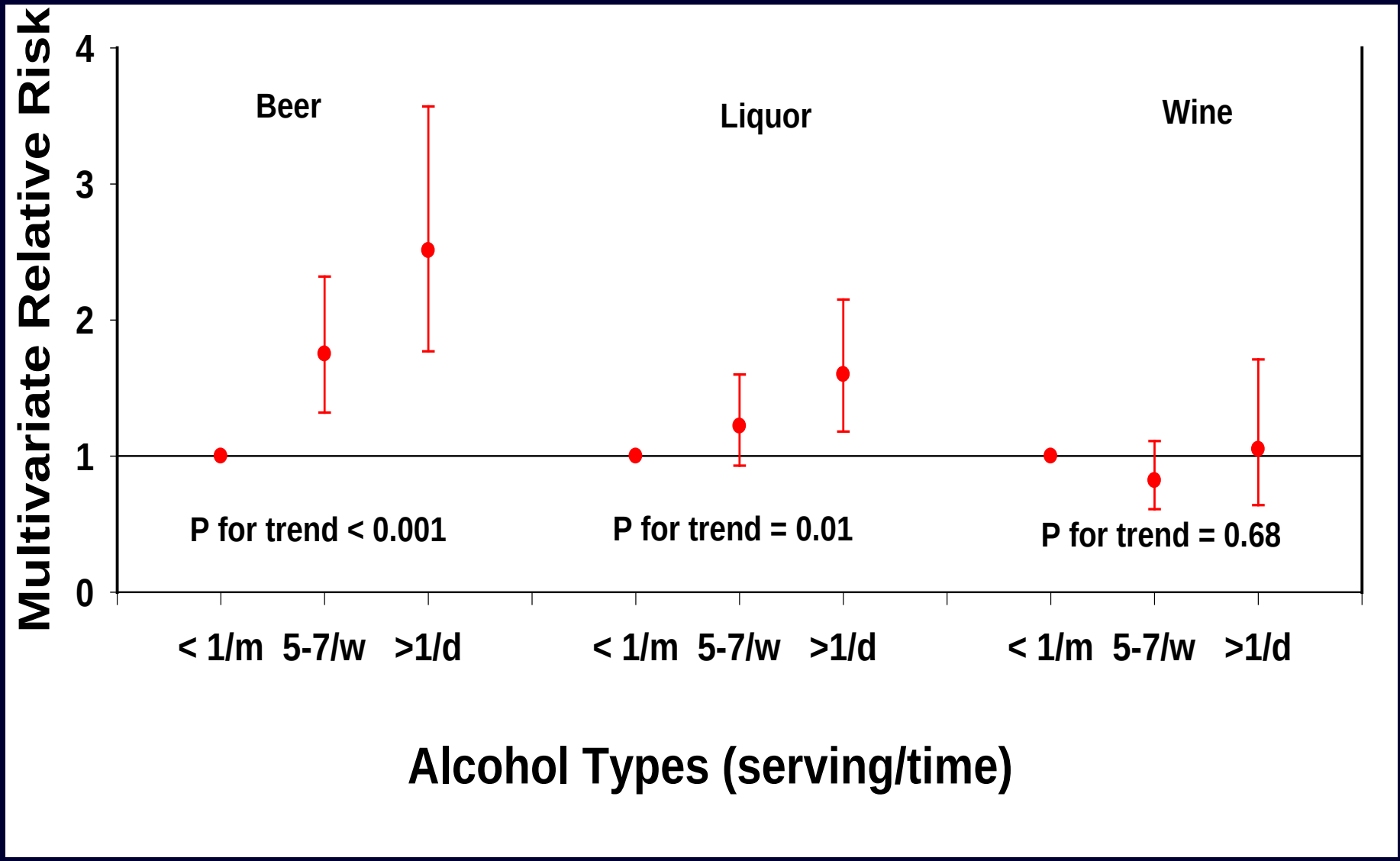
Annemans L. *et al. Ann Rheum Dis* 2008;67:960–966.

Alcohol Intake and Gout - HPFS



Choi H et al *Lancet*. 2004;363:1277

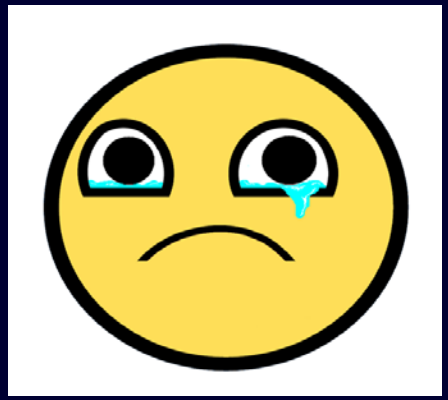
Alcoholic Beverages and Gout - HPFS



Choi H et al *Lancet*. 2004;363:1277

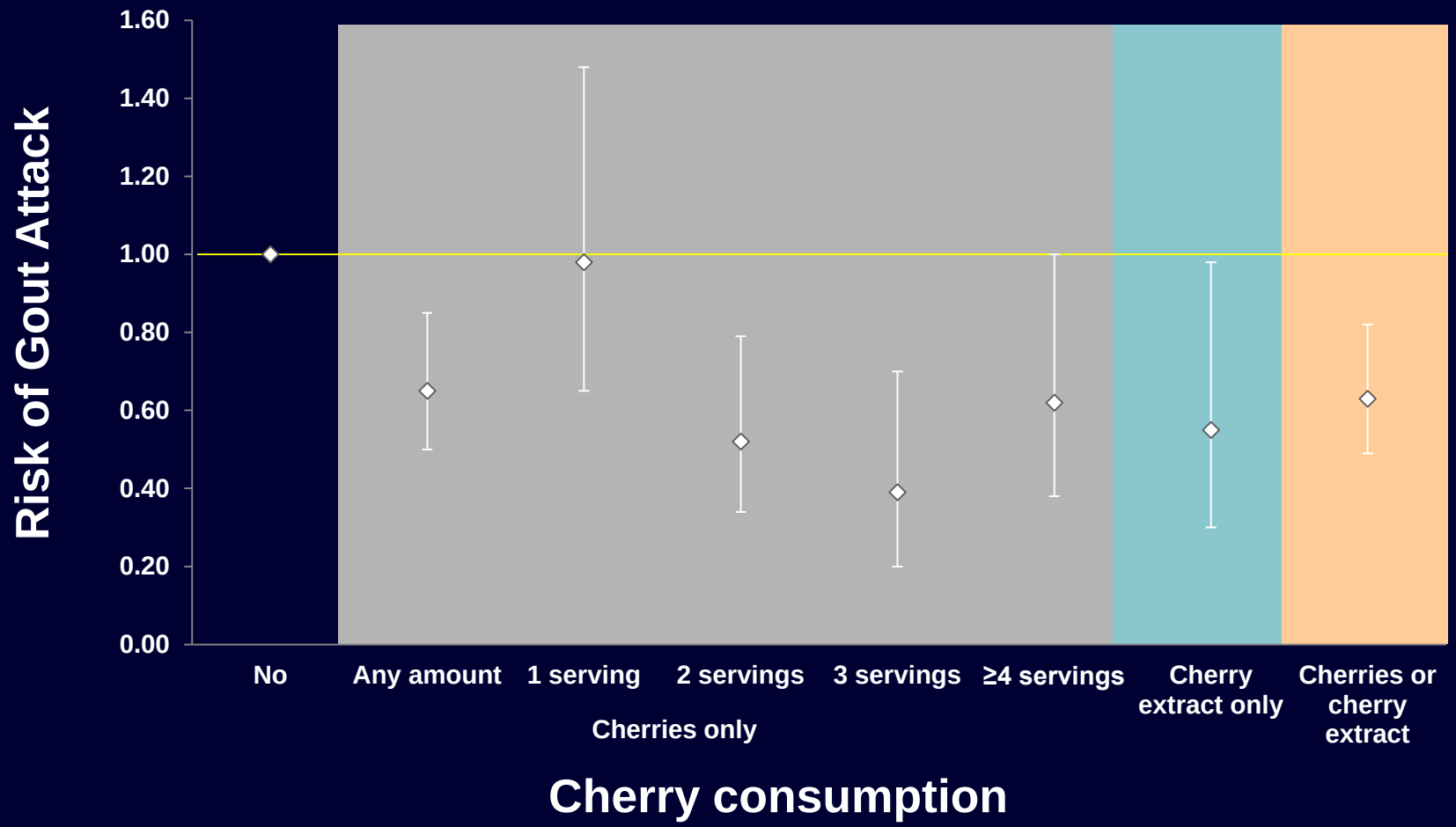
Is Wine Safer for Gout?

- Internet-based case crossover study of US participants with ≥ 1 attack per year
- Dose response relationship between amount of alcohol and recurrent attack
- Consuming wine, beer and alcohol all associated with increase risk



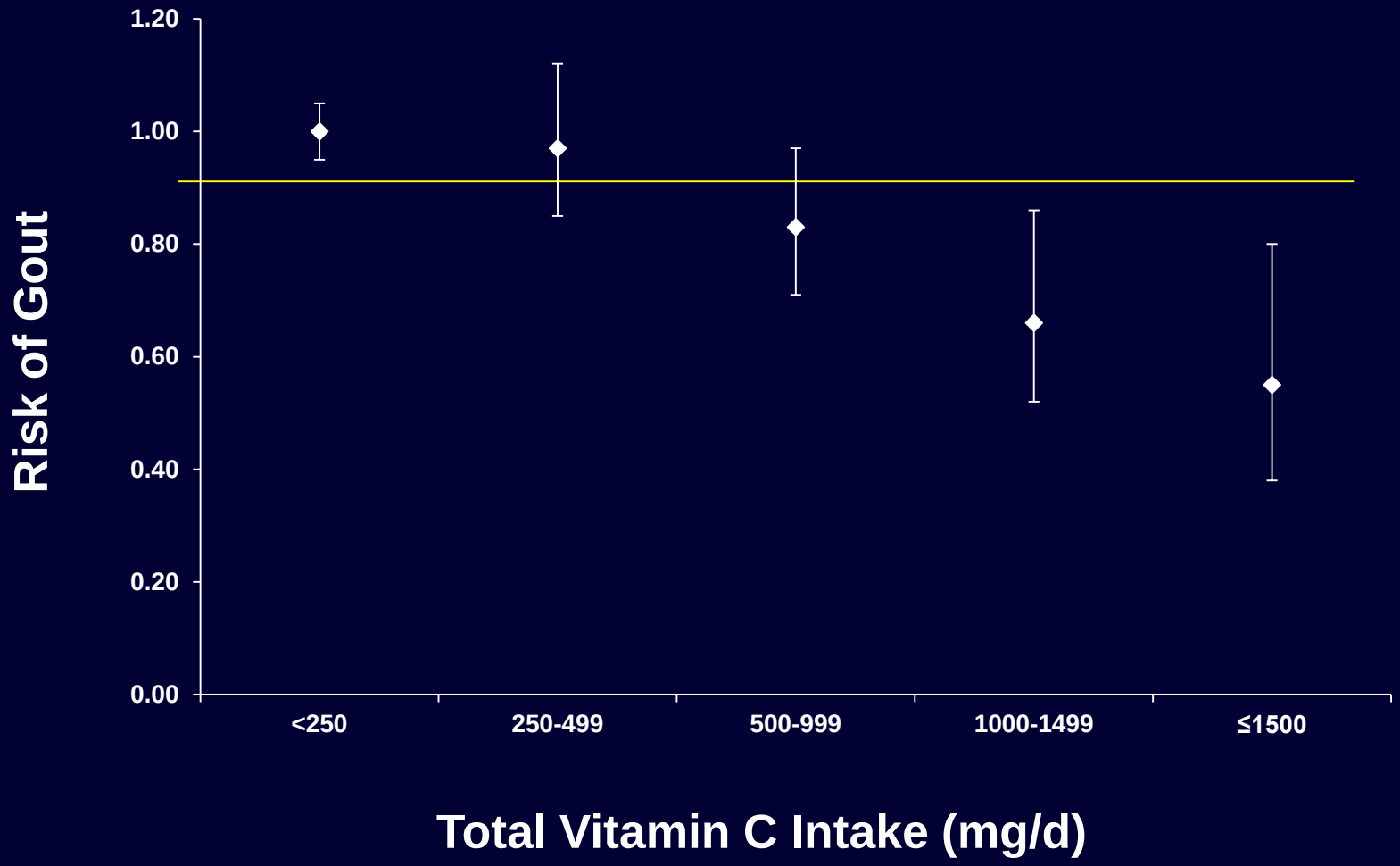
Neogi T. Am J Med 2014; 127:311

Cherries and Risk of Gout Attack



Zhang Y. et al. Arth Rheum 2012

Risk of Gout Decreases with Vitamin C Intake



Choi, HK, Arch Intern Med 2009;169:502

Thank You

Questions, Comments

Email: jasvinder.md@gmail.com

Osteoporosis: Evaluation and Treatment 8/24/19

Sarah L Morgan, MD, RD, CCD, FACP
Professor of Nutrition Sciences and Medicine
Medical Director, University of Alabama at Birmingham Osteoporosis Clinic and Bone Densitometry Unit

UAB MEDICINE

Knowledge that will change your world

- I have no relationships with pharma
- I am a past president of the International Society for Clinical Densitometry (ISCD) and a member of the ISCD Board

Outline

1. Definition of osteoporosis
2. Making the diagnosis of osteoporosis
3. Osteoporosis work-up
   - History/Physical Exam
   - Lab workup/Bone markers
   - DXA
4. Is there more I need to know about DXA besides looking at the report?
5. Treatment guidelines
   - Nonpharmacological treatments
   - Pharmacological therapies
   - Who to treat
   - AFF and ONJ
   - Drug holidays

Sample Patient Clinic Schedule
a.k.a – "The Bone Spa"

- 10:00 – DXA scan
- 11:00 – Physical Therapy Screen
- 11:00-1:00- "Tone Your Bones Class"
- 1:00 - 1:45 - Physician visit
- 2:00 - Check-out and f/u with patient educator, laboratory, other radiology tests

Patient Education Class

Counseling of Patients on Medication/Compliance, Nutrition

Tone Your Bones Exercise and Nutrition Class (TYBONE)

QUESTIONS?

TYB ToneYourBones

UAB Osteoporosis Prevention and Treatment Clinic

Search This Site Go

About Us Site Map

A Multidisciplinary Approach to Preventing and Treating Osteoporosis

Preventing and treating osteoporosis takes a team of specialists, including registered dietitians, physical therapists, pharmacists and physicians. We explain this approach here and hope this site will empower you to help yourself or someone you know who is also concerned about osteoporosis.

Virtual Clinic Visit - click on each of the steps below to learn more.

Step 1
Self Evaluation

Learn more about your risk factors.

Step 2
Bone Density Testing

How strong are your bones?

Step 3
Specialist Examination

Prepare for your doctor visit.

Step 4
Nutrition and Supplements

Feed your bones.

Step 5
Strength, Balance and Posture

Protect your bones.

Step 6
Personal Treatment Plan

Develop your life plan.

Reference and Research

- About Osteoporosis
- Prepare for Your Doctor Visit
- Related Links

more

News • April 2006

- Success Story
- Free Bone Density Screening
- Calcium Recipe of the Month

more

Staying In Touch

- Call the free Tone Your Bones Hotline, 1-888-934-BONE(2663), to speak to a health professional.
- Take the Tone Your Bones class.

more

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http://www.uab.edu/shp/toneyourbones/

"Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality."

Osteoporosis prevention, diagnosis, and therapy. JAMA 285: 785-795, 2001.

- **Diagnosis made by:**
  - **Presence of a fragility fracture**
  - **FRAX® (fracture risk) criteria**
  - **Bone mineral density criteria**

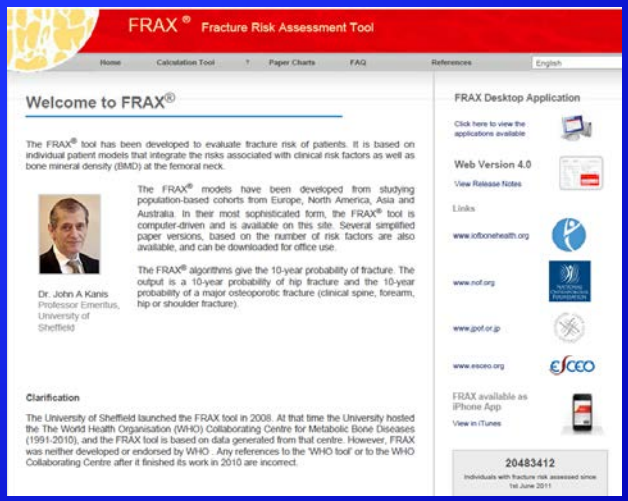
Definition of a Low Trauma Fracture

- Most people say a fall from a standing height
- Does not include fractures of the face, skull, hand/fingers, foot/toes, ankle (?)
- Is a fracture associated with low BMD that increases with age
- Low trauma fractures have been seen in individual with normal or near normal BMD, suggesting bone quality abnormalities (Malluche HH et al. Low energy fractures without low T-scores characteristic of osteoporosis J Bone Joint Surg Am 95: e139, 2013)

FRAX® Diagnosis of Osteoporosis

In postmenopausal women and mean ≥ age 50, osteoporosis may be diagnosed by

- **T-score ≤ -2.5 at the lumbar spine, total hip or femoral neck**
- **Low trauma hip fracture regardless of BMD**
- **T-score between -1.0 and -2.5 and low trauma vertebral, proximal humerus, pelvis, or some distal forearm fractures**
- **FRAX® major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥3%**



https://www.sheffield.ac.uk/FRAX

Siris ES. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group Osteoporos Int 25: 1439-43, 2014.

WHO Classification of Postmenopausal Osteoporosis

	T- score
Normal	Equal to -1.0 or higher
Low Bone Mass (Osteopenia)	Between -1.0 and -2.5
Osteoporosis	Equal to -2.5 or lower
Severe Osteoporosis	Equal to -2.5 or lower with fracture

- A T-score should not be used for everybody – i.e. premenopausal women and men < age 50 and children - use a Z-score instead
- A T-score ≤ -2.5 might not be osteoporosis – i.e. osteomalacia
- A T-score > -2.5 may still be osteoporosis - i.e. osteomalacia

World Health Organization. Technical Report Series 843
WHO, Geneva.1994.

The History and Physical Exam Evaluate for Common Secondary Causes of Low Bone Mass and Fracture (Not an exhaustive list)

Nutritional Vitamin D deficiency Eating Disorders (anorexia nervosa)	**Autoimmune** Rheumatoid Arthritis Systemic Lupus Ankylosing Spondylitis GIOP
Gastrointestinal Malabsorption Inflammatory bowel disease Gastric Bypass Liver Disease	**Renal** Hypercalciuria and Nephrolithiasis Renal tubular acidosis Chronic kidney disease (CKDMB)
Endocrine Hypogonadism Hyperparathyroidism Diabetes Mellitus	**Hematologic** MGUS Multiple Myeloma Systemic Mastocytosis
Medications Glucocorticoids Anticonvulsants Aromatase inhibitors or GnRH agonists SSRIs, PPIs, TZDs	**Pulmonary** COPD/Asthma with Steroids Cystic Fibrosis

How Common Are Secondary Causes?

- 204 postmenopausal women studied (mean age 64.9 years)
- DXA, spine x-ray, iPTH, 25-OH D, TFTs, urinary NTx, 24-hour urine for calcium and cortisol
- 82% had 25-OH D < 30 ng/ml and 57% had 25-OH D < 20 ng/ml
- 35% had elevated iPTH level
- 20% had hypercalciuria
- If Z-score < -2.0 had higher iPTH levels
- 41% had increase urinary NTx levels
- **The authors concluded that secondary causes of low BMD are common and contribute to the severity of disease**

Cerdá Gabaroi D et al. Search for hidden secondary causes in postmenopausal women with osteoporosis. Menopause 17: 135-139, 2010.

Medical History and Physical Exam

- History- fracture symptoms- pain & deformity (not all fractures are symptomatic)
- Weight and height changes (> 2 cm prospectively), medications, smoking, alcohol use, family history (parental history of hip fracture) USE A STADIOMETER
- Review of systems – dental issues, musculoskeletal, GI issues
- Clinical risk factors are predictive of fracture and not BMD (i.e. increasing age, female, family history and/or personal history of fractures as an adult, Caucasian or Asian, normal or early menopause, inactive lifestyle, cigarette smoking, inadequate calcium intake, certain medications, such as glucocorticoids)
- Physical Findings of fracture – Height loss, kyphosis, chest deformity, protuberant abdomen, dental health
- Physical findings may suggest increased fracture risk such as poor vision or hearing, orthostatic hypotension, gait disturbance, poor balance, (Get Up and Go Test, gait, and tandem gait)
- Some physical findings may suggest a diagnosis (i.e. blue sclera with osteogenesis imperfecta)
- < 2 fingerbreadths rib-pelvis distance is associated with spinal fractures (Olszynski WP et al. BMC Musculoskeletal Disorders 3: 22, 2002)
- >5 cm occiput to wall distance also raises clinical suspicion of spinal fracture (Green AD et al. JAMA 292: 2890-2900, 2004 and Siminoski K et al. J Bone Miner Res 16 (Suppl): S274, 2001).

Laboratory Work-up

- **Ruling out secondary causes**
  - **CBC**
  - **CMP (creatinine, alkaline phosphatase and LFTs) – make sure you have a phosphorus**
  - **24 hour urine for calcium and creatinine (spot urine?)**
  - **25-OH vitamin D**
- **Additional lab tests in selected patients (if clinically indicated)**
  - **Intact PTH**
  - **Serum thyrotropin**
  - **TTG – for suspected celiac disease (IgA)**
  - **Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma**
  - **Urinary free cortisol**
  - **Serum tryptase, urine-N-methylhistidine**
  - **Bone marrow aspirate**
  - **Bone biopsy with double tetracycline labelling.**

Camacho PM et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis -2017 Endocrine Practice 22: 1-42, 2016

Bone Markers

BONE RESORPTION

- **Collagen degradation products – telopeptides of type I collagen C-terminal – CTX and N-terminal - NTX**
- **Osteoclast enzymes – tartrate resistant acid phosphatase, cathepsin K**

BONE FORMATION

- **Collagen synthesis by products – propeptides of type I procollagen C-terminal PICP N-terminal PINP**
- **Matrix proteins –osteocalcin**
- **Osteoblast enzymes – alkaline phosphatase (total alkaline phosphatase and BSAP)**

- **Tartrate resistant acid phosphatase (TRAP5b) and bone specific alkaline phosphatase are not excreted by the kidney, the trimer of P1NP (the assay of total monomer and trimer is cleared by the kidney) (Miller, PD Bone disease in CKD: A focus on osteoporosis diagnosis and management. Am J Kidney Dis 64: 290-304, 2014)**

Naylor K, Eastell R. Bone turnover markers: use in osteoporosis. Nat Rev Rheumatol 8: 379-389, 2012.

Bone Biopsy

- Consider in special situations
  - Renal osteodystrophy
  - Unexplained osteoporosis in a young person
  - Extremely low bone mass?
  - Fragility fractures and normal BMD
  - Non-responders to osteoporosis therapy
- Typical method: non-decalcified double tetracycline labeled trans-iliac biopsy

DXA

- Dual-energy x-ray absorptiometry (DXA)
- Currently the standard in epidemiologic and pharmaceutical trials
- 2 different keV peaks
- 30-50 keV – Bone attenuation > soft tissue attenuation
- > 70 keV Bone attenuation = soft tissue attenuation
- Via a mathematical formula the differences in attenuation make it possible to quantitate bone mineral density
- Major manufacturers are Hologic, General Electric (Lunar), and Norland
- Same patient scanner on different brand scanners will have different BMD!!!

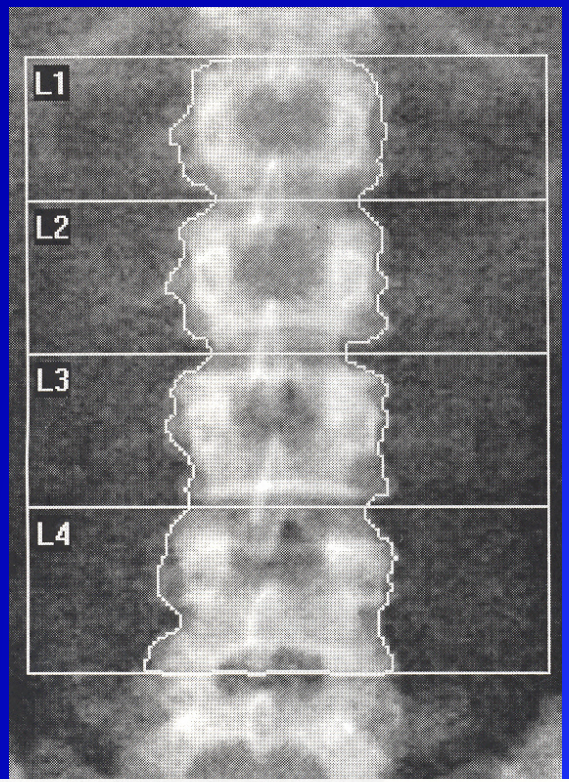
Radiation Safety
Effective Radiation Doses

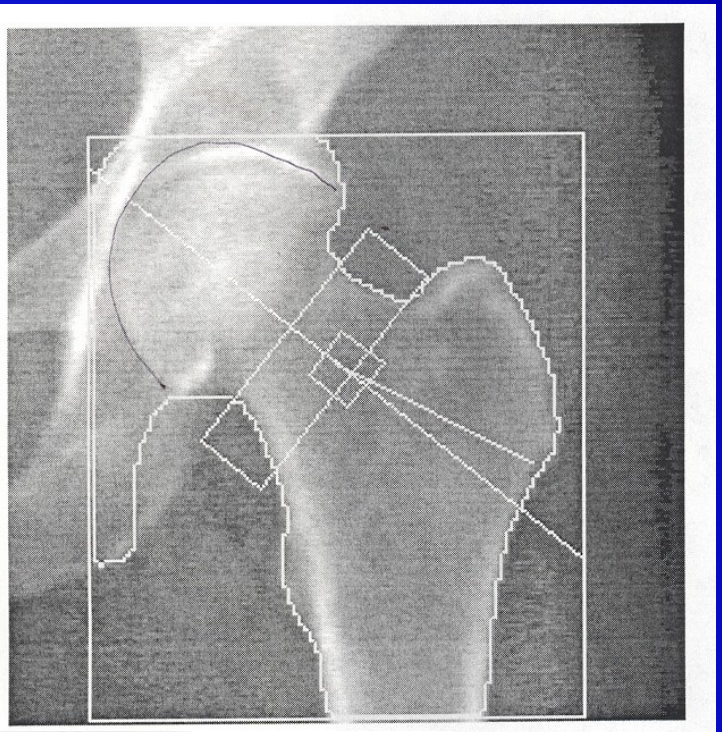
- Background: 5-8 µSv/day
- For general public maximal permissible dose is 5,000 µSv per year
- For occupational exposure maximal permissible dose is 50,000 µSv/year
- Lumbar Spine x-ray: 700 µSv
- DXA: 1-5 µSv
- pDXA: < 1 µSv
- QCT: 50-60 µSv
- pQCT: 1- µSv
- QUS:- none
- Less radiation than flying from York to Los Angeles and back (approximately 40 µSieverts)
- Not to be done in anybody pregnant or who thinks they are pregnant.

Clinical Uses of Bone Densitometry

- Diagnosis
- Fracture risk prediction –FRAX®
- Monitoring
- Applications include additional data such as hip axis length, vertebral fracture assessment (VFA) trabecular bone score (TBS), radiograph of femur to look for AFF

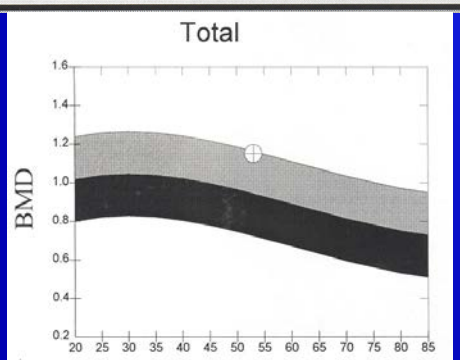
Hologic





DXA Results Summary:

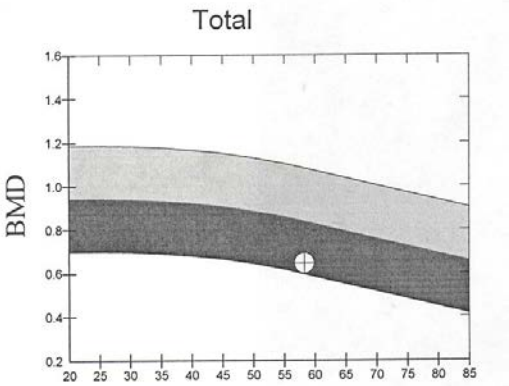
Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T - Score	Z - Score
L1	13.26	13.52	1.020	0.9	1.7
L2	14.37	16.81	1.170	1.3	2.2
L3	14.79	18.11	1.225	1.3	2.2
L4	18.27	21.46	1.174	0.5	1.5
Total	**60.69**	**69.90**	**1.152**	**1.0**	**1.9**



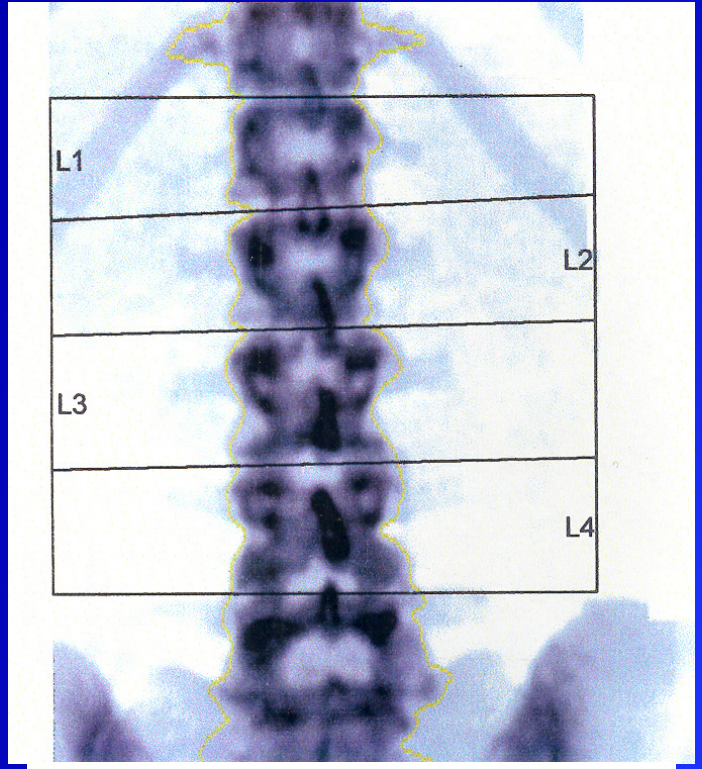
DXA Results Summary:

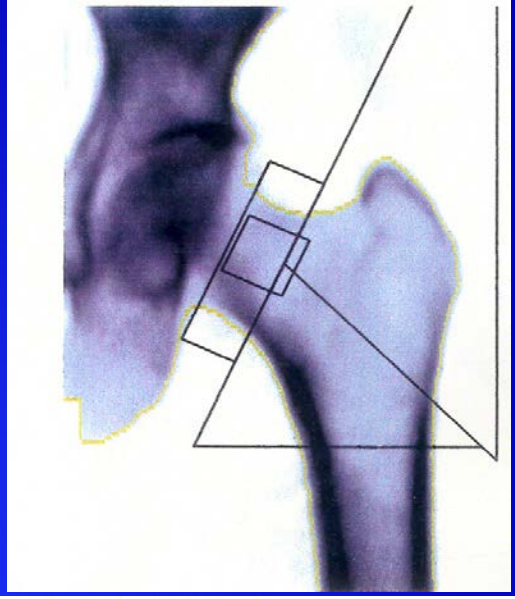
Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T - Score	PR (%)	Z - Score	AM (%)
Neck	5.12	3.08	0.602	-2.2	71	-1.0	84
Troch	9.38	4.47	0.477	-2.2	68	-1.4	77
Inter	21.05	15.37	0.730	-2.4	66	-1.8	73
Total	**35.55**	**22.93**	**0.645**	**-2.4**	**68**	**-1.6**	**77**
Ward's	1.13	0.40	0.359	-3.2	49	-1.3	70

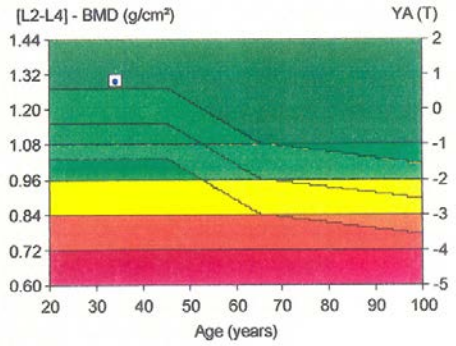
Total BMD CV 1.0%, ACF = 1.019, BCF = 1.055, TH = 5.905
WHO Classification: Osteopenia
Fracture Risk: Increased



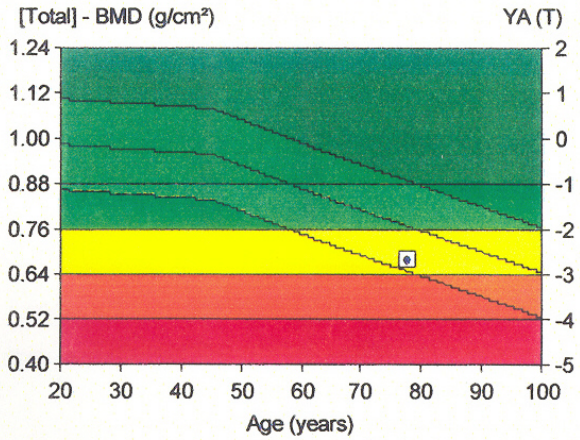
GE Healthcare (Lunar)







Region	BMD (g/cm²) [1, 6]	Young-Adult (T) [2]	Age-Matched (Z) [3]
L1	1.057	-0.6	-0.2
L2	1.254	0.4	0.8
L3	1.313	0.9	1.3
L4	1.329	1.1	1.5
L2-L4	1.302	0.9	1.2



Region	BMD (g/cm²) [1, 6]	Young-Adult (T) [2]	Age-Matched (Z) [3]
Neck	0.652	-2.7	-0.7
Wards	0.524	-3.0	-0.4
Troch	0.552	-2.2	-0.8
Shaft	0.841	-	-
Total	0.679	-2.7	-0.8

Medicare Guidelines for Bone Density Test Coverage

- An estrogen deficient woman at clinical risk for osteoporosis
- An individual with vertebral abnormalities as demonstrated by x-ray to be indicative of osteoporosis, low bone mass or vertebral fracture
- An individual receiving long-term glucocorticoid therapy
- An individual with primary hyperparathyroidism
- An individual being monitored to assess the response to or efficacy of an FDA-approved osteoporosis drug therapy

https://www.medicare.gov/coverage/bone-density.html

ISCD Indications for BMD Testing

- Women aged 65 and older
- Postmenopausal women < age 65 having risks factors: Low body weight, prior fracture, high risk medication use, disease or condition associated with bone loss
- Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication
- Men aged 70 and older
- For men < 70 years of age a DXA is indicated if they have a risk factor such as low body weight, prior fracture, high risk medication use, disease or condition associated with bone loss
- Adults with a fragility fracture
- Adults with a disease or condition associated with low bone mass or bone los
- Adults taking medications associated wit low bone mass or bone loss
- Anyone being considering for pharmacological therapy
- Anyone being treated, to monitor treatment affect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment.
- Women discontinuing estrogen should be considered for bone density testing according to the indications listed above

- Also see reference below for Vertebral Fracture Assessment guidelines

https://www.iscd.org/official-positions/2015-iscd-official-positions-adult/

NOF Guidelines for BMD Testing

- In women age 65 and older and men aged 70 and older
- In postmenopausal women and men above age 50-69, based on risk factor profile
- In postmenopausal women and men age 50 and old who have had an adult age fracture, to diagnose and determine degree of osteoporosis
- At dual-energy X-ray absorptiometry (DXA) facilities using quality assurance measures

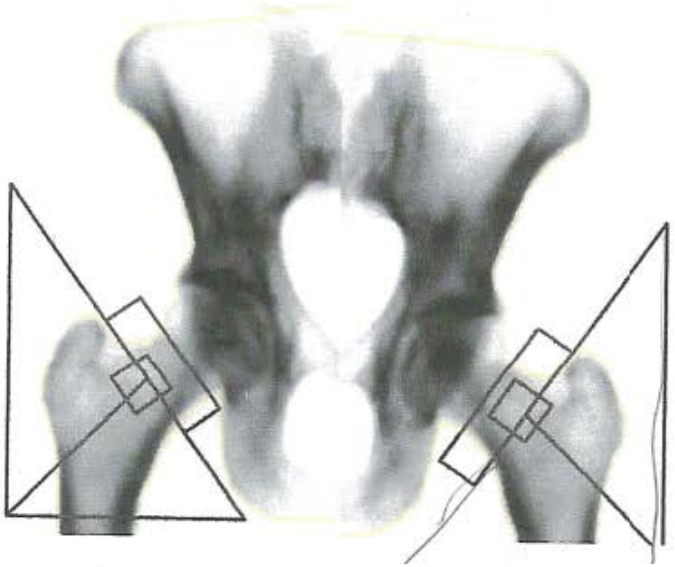
- Also see reference below for vertebral imaging guidelines

Cosman F et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25: 2359-2381, 2014.

Is There More to DXA Than Reading the Report?

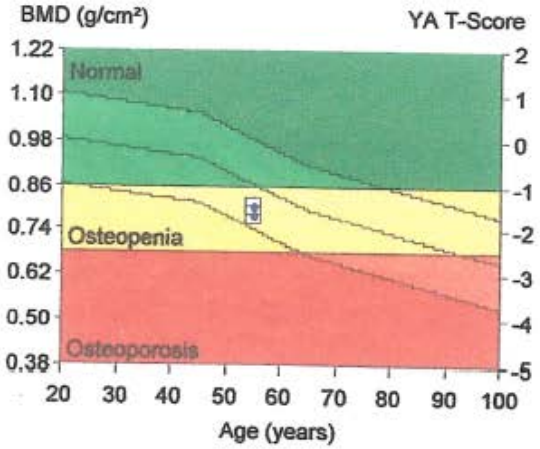
- **YES!!** – In my opinion there is a crisis related to DXA Quality
- Numerous studies have documented errors affecting patients in DXA analysis and reporting
- (Morgan and Prater Quality in dual-energy x-ray absorptiometry scan. Bone 2017 Nov;104:13-28. doi: 10.1016/j.bone.2017.01.033. Epub 2017 Jan 31.017)
- You must look at the images and evaluate/understand technical aspects!

65-year old male with a history of fracture sent for your evaluation



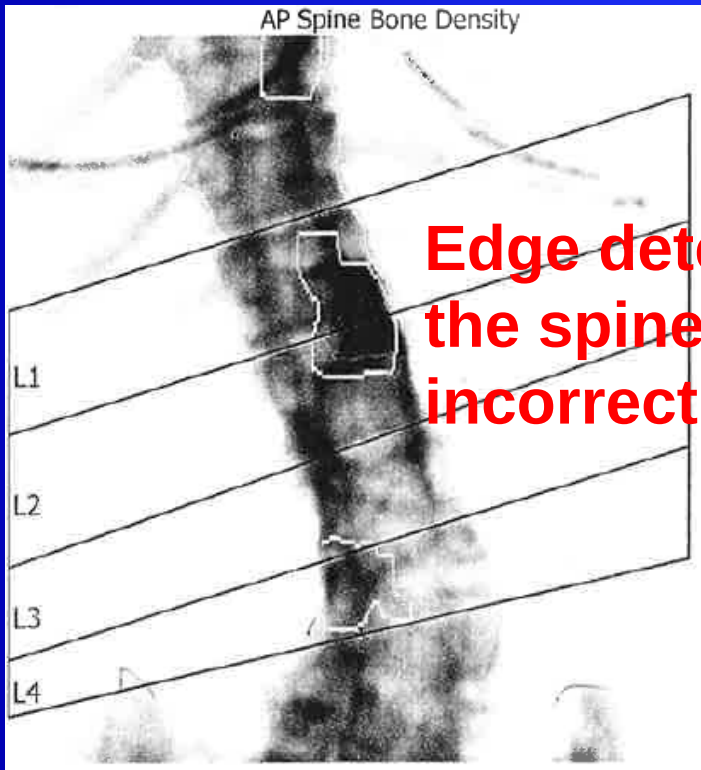
They did not scan far enough down into the left femur – so total left hip can't be reported.

Reference: Neck

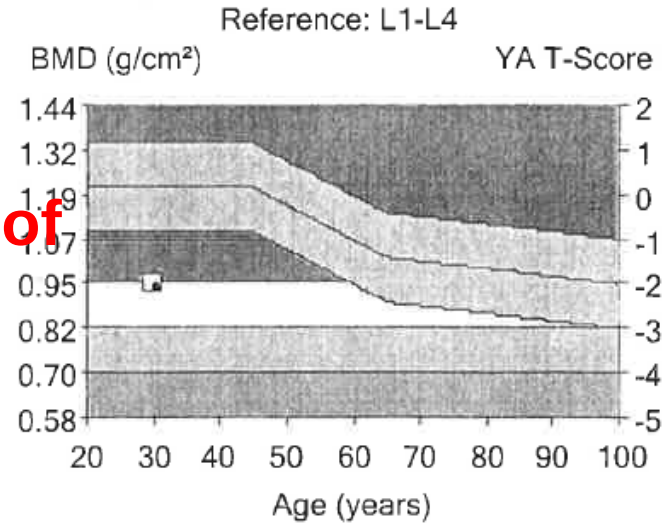


	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
Neck			
Left	0.780	-1.7	-0.7
Right	0.806	-1.4	-0.5
Mean	0.793	-1.6	-0.6
Difference	0.026	0.2	0.2

34 year old AA female, in an automobile accident – slammed into a bridge and forearm caught and twisted in the steering wheel – spiral forearm fracture - DXA ordered because of fracture and patient told that she likely has osteogenesis imperfecta



Edge detection of the spine is incorrect



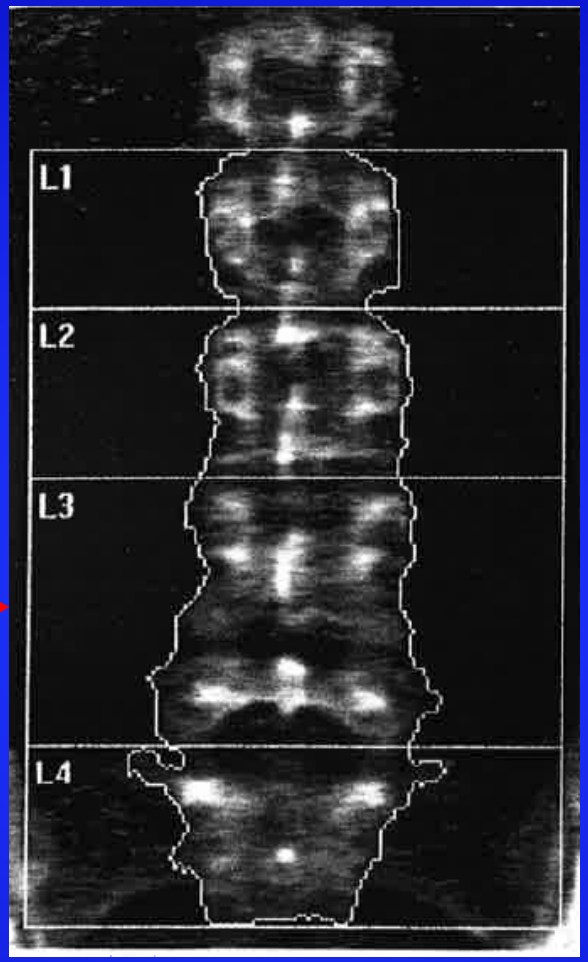
Region	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
L1	0.954	-1.5	-1.7
L2	1.123	-0.7	-0.9
L3	0.966	-2.0	-2.2
L4	0.652	-4.4	-4.6
L1-L4	0.948	-2.0	-2.1

35 year old Premenopausal Caucasian Female Sent with a Request to Order Denosumab

Right hip data:
Femoral neck Z score = -0.1
Total hip Z-score = -0.4
Hip scan is technically adequate

Referring physician concerned about Z= -3.8

2 vertebral bodies in this ROI

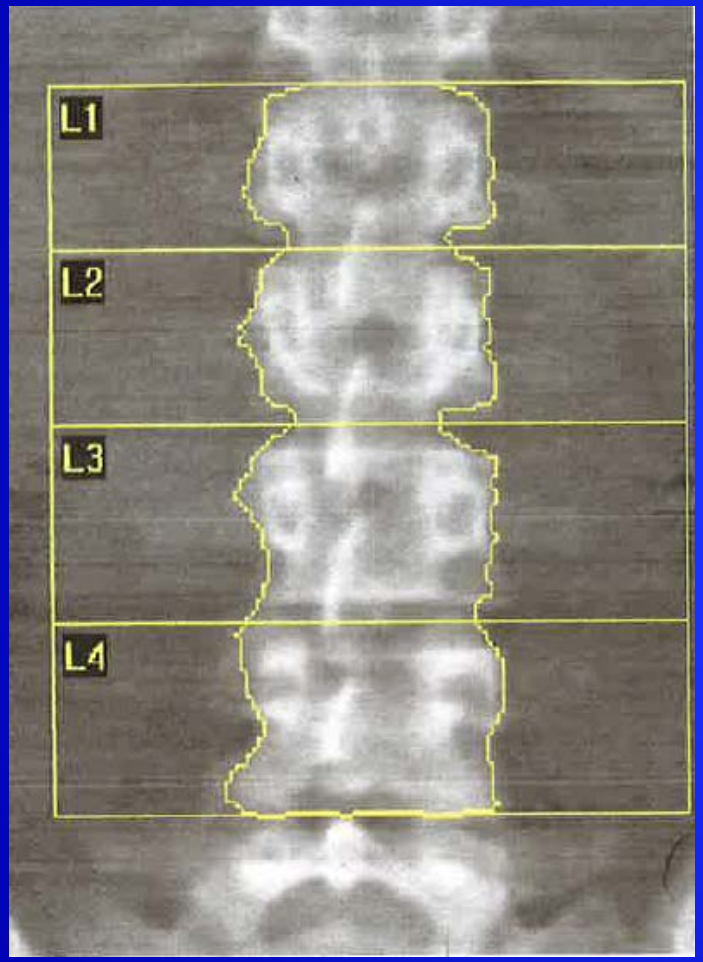


The correct lumbar spine ROI was not scanned - they have L2 – sacrum in the L1-L4 ROI

This is the sacrum – L4 drawn in the sacrum

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	Z - score
L1	13.31	13.40	1.007		0.8
L2	15.22	14.59	0.958		-0.6
L3	29.55	27.77	0.940		-1.3
L4	17.95	12.46	0.694		-3.8
Total	**76.03**	**68.21**	**0.897**		**-1.3**

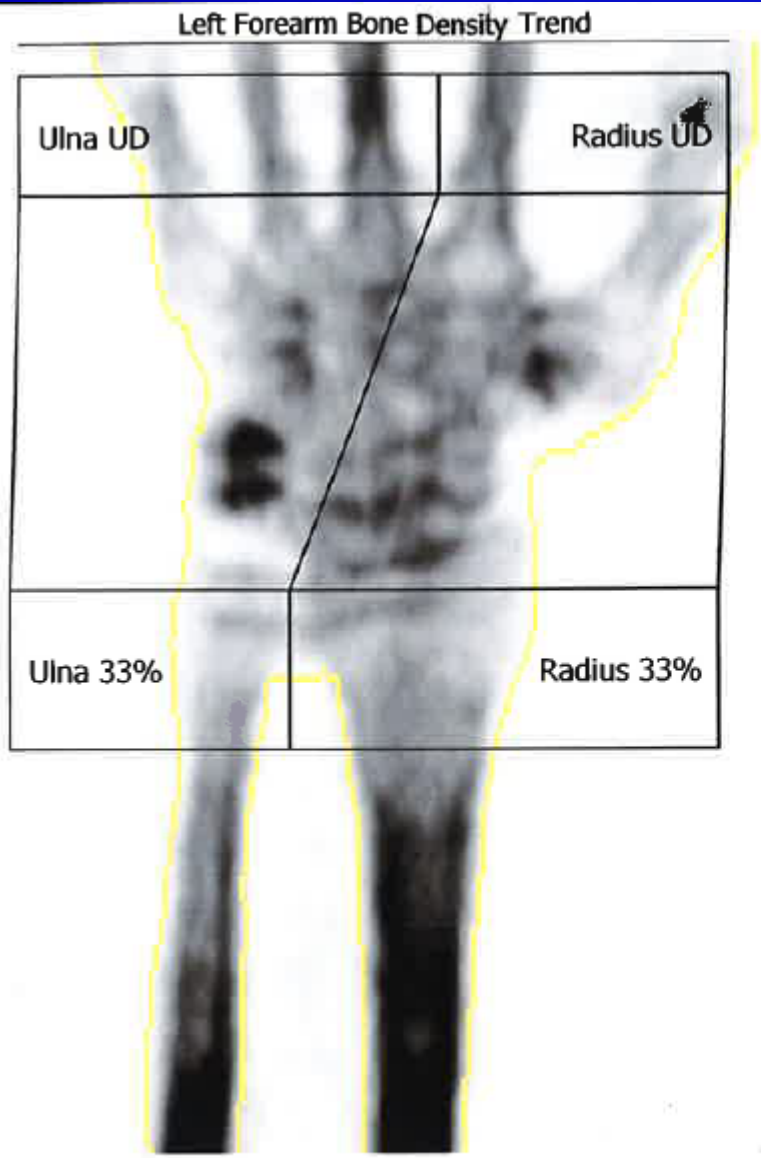
Repeat DXA at UAB

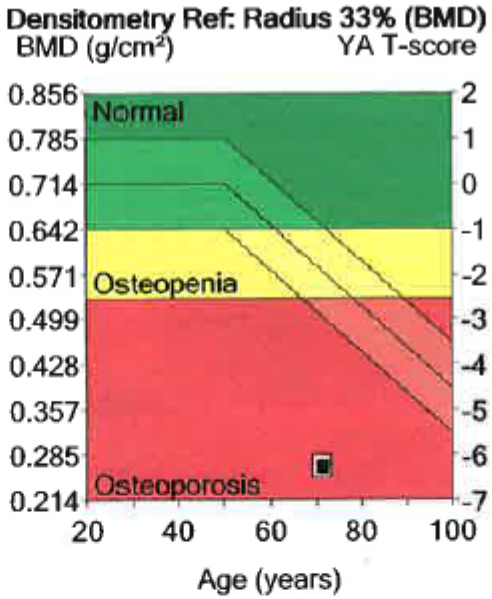


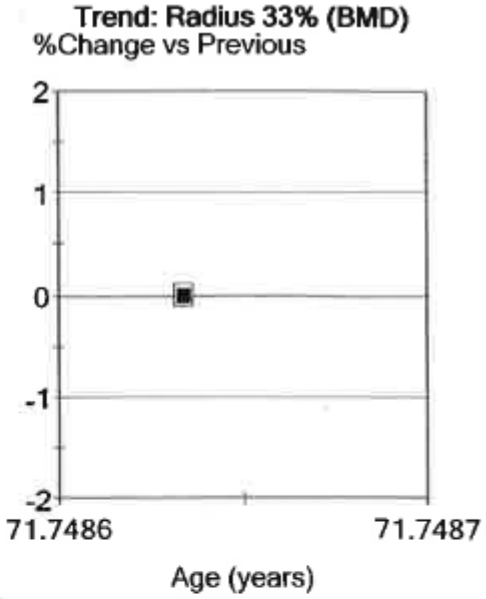
Femoral neck Z-score = -1.0
Total hip Z-score = -0.4

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	PR (%)	Z - score	AM (%)
L1	12.00	10.98	0.915	-0.7	92	-0.7	93
L2	13.04	13.36	1.025	0.0	100	0.0	100
L3	14.94	14.53	0.972	-1.0	90	-1.0	90
L4	16.12	14.77	0.917	-1.3	86	-1.3	87
Total	**56.10**	**53.64**	**0.956**	**-0.8**	**91**	**-0.8**	**92**

Repeat DXA scan – using "Z-scores – bone mineral density within the expected range for age"
Denosumab was <u>not</u> ordered







Region	BMD [1,9] (g/cm²)	Young-Adult [2] (%)	Young-Adult [2] T-score	Age-Matched [3] (%)	Age-Matched [3] Z-score
Radius UD	0.162	43	-5.9	53	-3.9
Ulna UD	0.203	-	-	-	-
Radius 33%	0.264	37	-6.3	46	-4.3
Ulna 33%	0.198	-	-	-	-
Both UD	0.183	-	-	-	-
Both 33%	0.242	-	-	-	-
Radius Total	0.244	44	-6.2	54	-4.2
Ulna Total	0.240	-	-	-	-
Both Total	0.242	-	-	-	-

Trend: Radius 33%

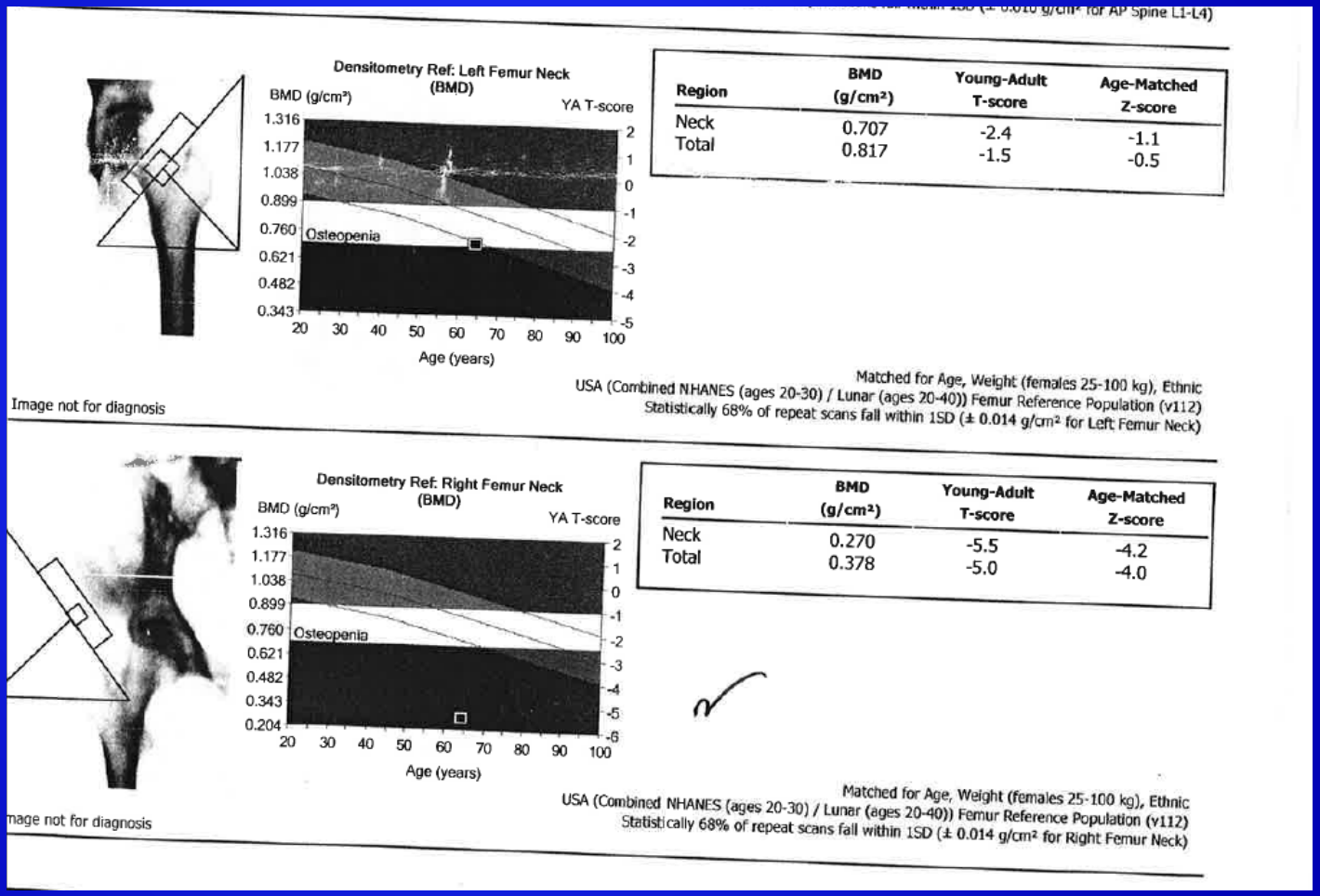
Measured Date	Age (years)	BMD [1,9] (g/cm²)	Change vs Previous (g/cm²)	Change vs Previous (%/yr)
03/23/2015	71.7	0.264	-	-

The ROI is incorrect – they are scanning the hand instead of the radius

COMMENTS:

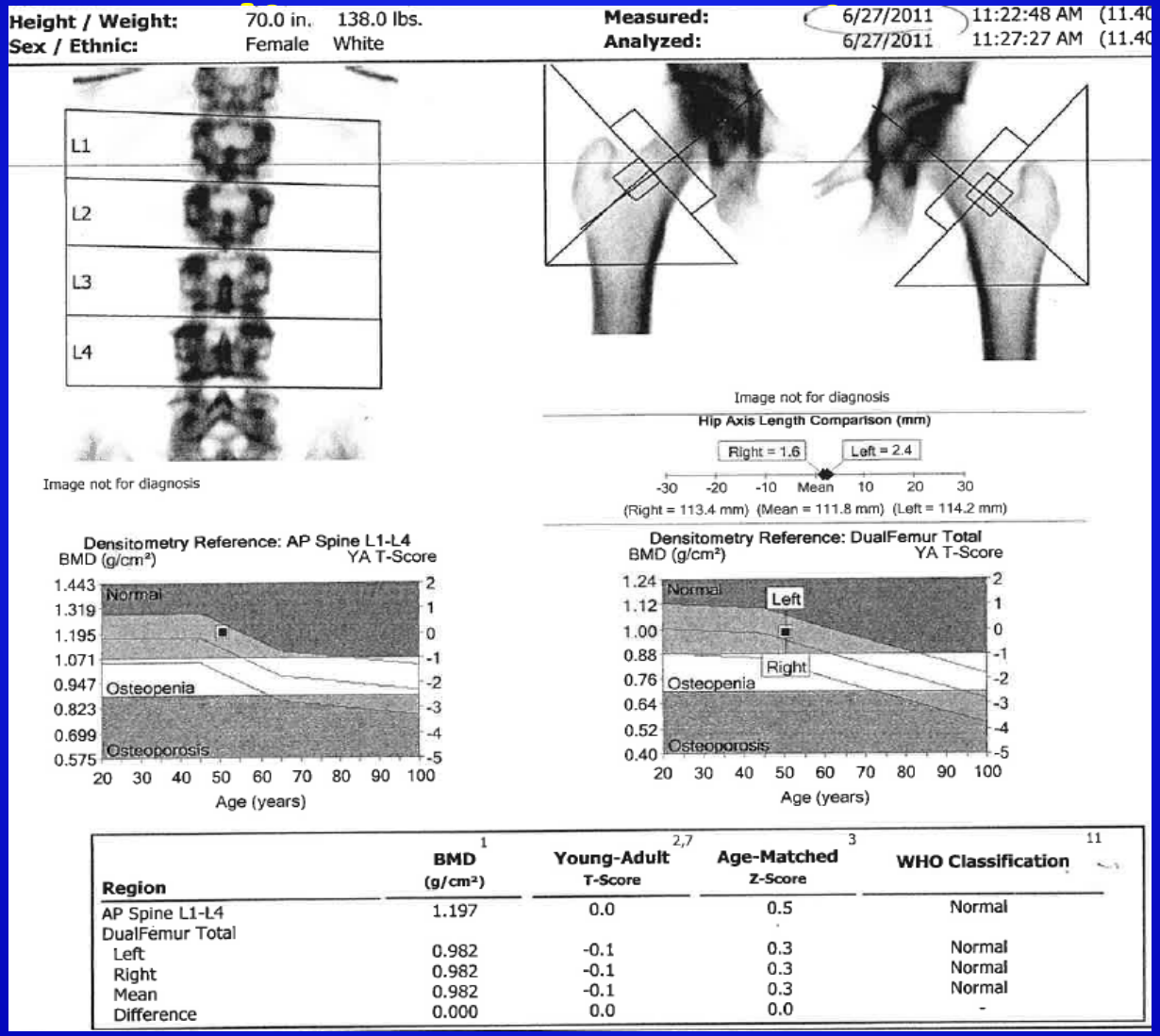
68-year old woman sent because of concerns that “her right hip might crumble”

The right hip ROI boxes are incorrectly placed



Patient sent for loss of BMD from 2011 to 2017

2011 Scan

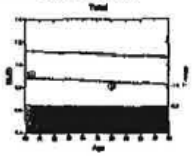


Region	BMD [1] (g/cm²)	Young-Adult [2,7] T-Score	Age-Matched [3] Z-Score	WHO Classification [11]
AP Spine L1-L4	1.197	0.0	0.5	Normal
DualFemur Total				
Left	0.982	-0.1	0.3	Normal
Right	0.982	-0.1	0.3	Normal
Mean	0.982	-0.1	0.3	Normal
Difference	0.000	0.0	0.0	-

Follow-up Scan in 2017

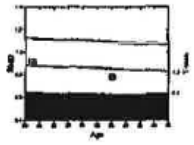
Age: 56 Date o

Scan Date: January 13, 2017
Scan ID: A01131708



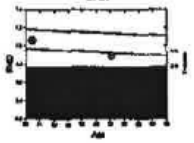
Scan Type: f Left Hip

Scan Date: January 13, 2017
Scan ID: A01131709



Scan Type: f Right Hip

Scan Date: January 13, 2017
Scan ID: A01131707



Scan Type: f Lumbar Spine

Results:

	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
Left Hip (Neck)	0.728	-1.1	86	0.0	100
Left Hip (Total)	0.813	-1.1	86	-0.3	95
Right Hip (Neck)	0.789	-0.5	93	0.6	109
Right Hip (Total)	0.782	-1.3	83	-0.6	92
Spine (Total)	0.893	-1.4	85	-0.3	97

Total BMD CV 1%

Summary:

Classification	
Left Hip BMD (Neck)	Osteopenia
Left Hip BMD (Total)	Osteopenia
Right Hip BMD (Neck)	Normal
Right Hip BMD (Total)	Osteopenia
Spine BMD (Total)	Osteopenia

A spine fracture indicates 5X risk for subsequent spine fracture and 2X risk for subsequent hip fracture.

World Health Organization criteria for BMD impression classify patients as Normal (T-score at or above -1.0), Osteopenia (T-score between -1.0 and -2.5), or Osteoporosis (T-score at or below -2.5).

HOLOGIC®

Previous Exams:

Region	Exam Date	Age	BMD (g/cm²)	T-score	BMD Change vs. Baseline	BMD Change vs. Previous
Total Hip(Right)	01/13/2017	56	0.782	-1.3	-0.135 (-14.7%)#	-0.135 (-14.7%)#
	06/27/2011	50	0.917	-0.2		
Femoral Neck(Right)	01/13/2017	56	0.789	-0.5	-0.128 (-14.0%)#	-0.128 (-14.0%)#
	06/27/2011	50	0.917	0.6		

**Denotes significance at 95% confidence level, LSC for AP Spine = 0.022 g/cm², LSC for Total Hip = 0.027 g/cm²*

 # Denotes dissimilar scan types or analysis methods

This case is a comparison of GE vs. Hologic – you can't compare unless cross calibrated - even using standardize BMD values can't always fix the problem.

Fan B Does standardized BMD still remove differences between Hologic and GE-Lunar state-of-the art DXA systems? Osteoporos Int 21: 1227-1236, 2010

What Can Be Done Related to the DXA Quality Crisis?

- Pay for performance related to DXA
- Certification of bone density technologists (CBDT)
- Certification of clinicians (CCD)
- Accreditation of DXA facilities
- Quality Assurance, best practice guidelines and SOPs are important

(Lewiecki EM et al. Best practices for dual-energy x-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance J Clin Densitom 19: 127-40, 2016)

Therapies of Osteoporosis

- Fall Prevention
- Physical Therapy and Exercise
- Calcium and Vitamin D
- Pharmacological Therapies

Fall Prevention

- **Preven**
  - Safe st
  - Bathro
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  - Arrang
  - Careful
  - Proper
  - Safe fo
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  - Use wa
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Fall Prevention Guidance

- Falls exact a large toll in older individuals/ER visits
- STEADI toolkit - https://www.cdc.gov/steadi/index.html – also has patient education resources
- I use the CDC fall risk questionnaire in my clinic (Rubenstein et al. J Safety Res 42: 493-499, 2011.)
- Various tests Timed Up and Go (TUG – www.RehabMeasures.org), 30 Second Chair Stand, Four Stage Balance test

Physical Therapy
Neutral Spine

Neutral spine kinetics is important with osteoporotic scores at the lumbar spine and a history of compression fractures.

Weight Bearing Exercise

- Exercise that forces your body to support your full weight – walking is probably not enough, need strength and balance training also
- http://www.americanbonehealth.org/what-you-should-know/exercise
- Poster called: “Do it Right and Prevent Fractures” by American Bone Health
- I am a great proponent of physical therapy referral for balance, strengthening, posture and neutral spine kinetics

Calcium Requirements

- Most abundant mineral in the body - in bones and teeth
- Necessary for blood clotting, nerve transmission, heartbeat regulation
- Calcium concentrations are carefully controlled by numerous mechanisms (parathyroid axis, vitamin D)
- Net absorption is inefficient
- Vitamin D increases calcium absorption
- IOM guidance:
  - Tolerable upper level intake 2,500 mg/day for ages 19-30, 2,000 mg/day for age 51 - >70
- For most patients 1200-1500 mg/day from food and supplements (no kidney stones)

http://iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx

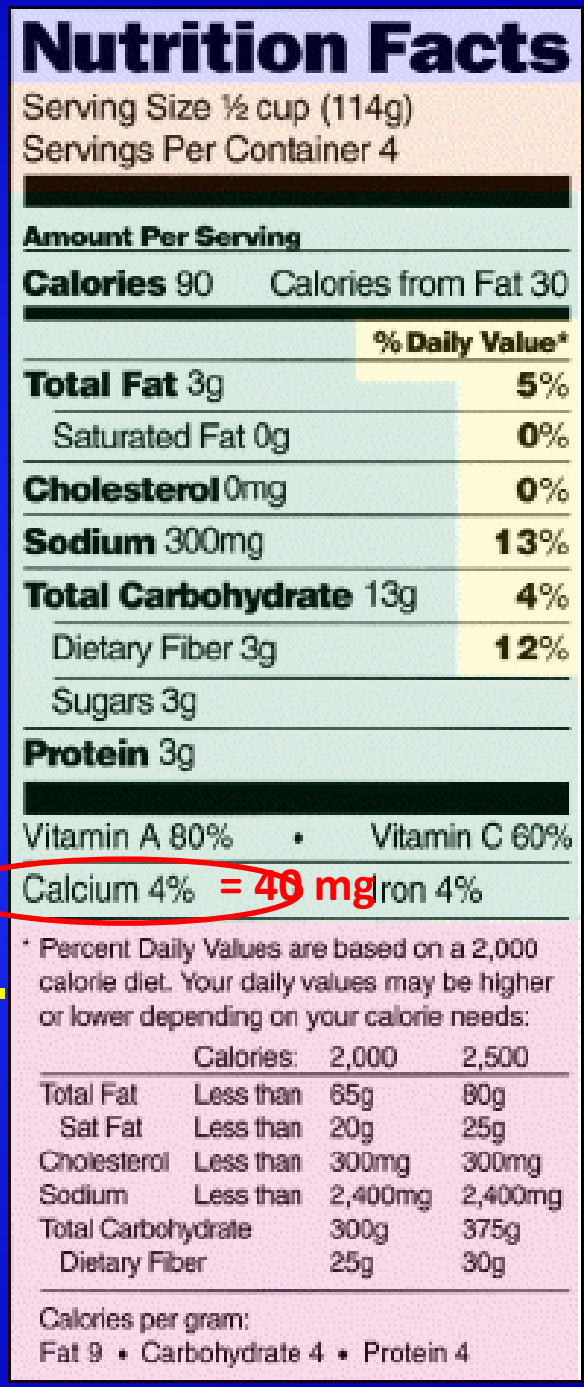
Sources of Calcium

- Dairy foods
  - 8 oz. Milk: 300 mg
  - 8 oz. Yogurt: 300 – 400 mg
  - 1 oz. Cheese: 200 mg
- Some Vegetables
  - ½ cup, canned turnip greens: 135 mg
  - 1 cup raw broccoli: 45 mg
- Fortified foods
  - 1 cup calcium fortified orange juice: 300 mg (need to shake/settling)
  - 1 oz. Fortified cereals: 100 – 1000 mg

  - Online calcium calculator at:

http://www.uab.edu/shp/toneyourbones/step-4-nutrition-and-supplements/why-calcium-is-important/calcium-calculator

Add a zero to the calcium % and it will give you mg per serving indicated –only works for calcium! - the new label will tell mg of calcium



Nutrition Facts

Serving Size ½ cup (114g)
Servings Per Container 4

Amount Per Serving

Calories 90 Calories from Fat 30

	% Daily Value*
Total Fat 3g	**5%**
Saturated Fat 0g	**0%**
Cholesterol 0mg	**0%**
Sodium 300mg	**13%**
Total Carbohydrate 13g	**4%**
Dietary Fiber 3g	**12%**
Sugars 3g	
Protein 3g	

Vitamin A 80% • Vitamin C 60%

Calcium 4% = 40 mg Iron 4%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

Calcium Supplements

Type	% ElementalCalcium
Calcium carbonate	40
Calcium citrate	21
Calcium lactate	13
Calcium gluconate	9
Calcium glubionate	6.5

- There are a variety of forms (liquid, chews, crystals, pills) – bariatric preparations can be useful
- The data suggests that both calcium carbonate and calcium citrate, taken with meals, have equivalent bioavailability
- Avoid supplements with hypercalciuria or nephrolithiasis
- Studies suggest that calcium citrate has been availability than Ca carbonate after roux-en-Y gastric bypass (Obes Surg 19:1256-61, 2009).
- The addition of magnesium with calcium may help if constipation is a problem
- Calcium supplements are not associated with cardiovascular disease

(Kopecky SL et al. Lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults; A clinical guidelines from the National Osteoporosis Foundation and the American Society for Preventive Cardiology Ann Intern Med 165: 867-868, 2016)

Vitamin D

- D_2 – ergocalciferol
- D_3 –cholecalciferol - naturally occurring form in humans
- RDI for individuals > 3 years old is 600 IU per day, UTL = 4000 IU per day

http://iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx

There is Disagreement About Target 25-OH Vitamin D Levels and Therefore Optimal Intakes

- Institute of Medicine

Target levels for 25-OH vitamin D: "Serum 25OHD levels of 16 ng/ml (40nmol/L) cover the requirements of approximately 50% the population and levels of 20 ng/ml (50 nmol/L) cover the requirements of at least 95% of the population" http://www.iom.edu/Reports/s010/Dietary-Reference-Intakes-for-Calcium-and-vitamin-D.aspx

- American Association of Clinical Endocrinologists

"….use a range from 30-50 ng/mL for most patients as an optimal and safe range." (www.aace.com/alert/alert11302010.php)

Why is there a Controversy about Optimal 25-OH Vitamin D Status?

- Problems with vitamin D assays (immunoassay picking up D2? – does your lab participate in a quality control program ? https://ods.od.nih.gov/Research/VitaminD.aspx
- Vitamin D supplements vary in potency (Leblanc ES, Perrin N, Johnson JD, Ballatore A, Hiller T. Over-the counter and compounded vitamin D: Is Potency what we expect? JAMA Intern Med 173: 585-6, 2013 .
- I recommend using USP supplements.
- To link a nutrient outcome to something like fracture, there is bigger observed effect with a deficient than a sufficient individual (Heaney RP. NEJM 367:77-78, 2012
- Also see: http://www.vitamindwiki.com/Defining+normal+level+of+vitamin+D+-+Heaney+Spring+2013)
- It is hard to study nutrients in isolation (i.e. calcium and vitamin D)
- We generally measure 25-OH vitamin D levels, but there are many metabolites that may be important

Vitamin D Bottom Line

- Studies in people making vitamin D cutaneous generally show a mean 25(OH) level of ~ 36 ng/mL [1,2,3]
- Autopsy study did not find an evidence of osteoid in bone biopsies if 25-OH vitamin D level was > 75 nmol/L = 30 ng/ml
- "We suggest that clinicians target ~ 40 ng/mL (100 nmol/L) as a 25 (OH)D goal for their patients with osteoporosis and use an amount of vitamin D supplementation necessary to reach this level. This suggestion is consistent with what is known of physiologically achievable serum levels, variability in commercially available 25(OH)D assays, and safety."[5]
- "We suggest that the 'Goldilocks principle' of not too much, not too little, but just right, applies to vitamin D". [5]
- I generally find that around 2000 IU per day from food and supplements is adequate to maintain at 25-OH vitamin D level > 30 ng/ml
- Make sure the assay in your institution is traceable to NIST standards

[1]Tangpricha V et al. Am J Clin Nutr 80: 1645-1649, 2004.
[2]Barger-Lux MJ, Heaney RP J Clin Endocrinol Metab 92: 2130-2135, 2002.
[3]Binkley N et al. Clin Chim Acta 411: 1976-1982, 2010.
[4]Priemel M et al.. J Bone Min Res 25: 305-12, 2010.
[5]Binkley N, Lewiecki EM J Clinical Densitometry 14: 95-99, 2011.

How Much to Supplement to Fix Deficiency?

- Individual responses to standard doses vary widely (Binkley N et al. Evaluation of ergocalciferol or cholecalciferol dosing, 1,600 IU daily or 50,000 IU monthly in older adults. J Clin Endocrinol Metab 96: 981-988, 2011.
- I generally treat vitamin D deficiency with 4000-5000 IU of cholecalciferol per day for 12 weeks
- Because of concerns of falls with high dose vitamin D supplementation, I generally don't use high dose supplements (Dhaliwal R and Aloia JF. Effect of vitamin D on falls and physical performance. Endocrinol Metab Clin N Am 46: 919-933, 2017).
- Malabsorption and bariatric surgery patients require higher doses

National Osteoporosis Foundation Guidelines on Who to Treat

- Postmenopausal women and men ≥ 50 years of age
  - T-score of ≤ -2.5 at the femoral neck, total hip, or lumbar spine
  - Vertebral or hip fracture
  - Low bone mass (T-score between -1.0 to -2.5) at the femoral neck or lumbar spine and a 10-year probability of hip fracture ≥ 3% or major osteoporotic fracture ≥ 20% by FRAX®

Cosman F et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 25: 2359-2381, 2014.

2016 AACE/ACE Guidelines on Who to Treat

- Postmenopausal women ≥ 50 years of age
  - T-score ≤ -2.5 at the lumbar spine, femoral neck, total hip, and/or distal 1/3 radius
  - Low trauma spine and hip fracture (regardless of BMD)
  - Osteopenia and fragility fractures (proximal humerus, pelvis, distal forearm) in the absence of other metabolic bone disorders
  - Osteopenia (T-score between -1.0 and -2.5) and increased fracture risk by FRAX®

Medications FDA-Approved for Prevention and Treatment of Osteoporosis

- Miacalcin® (calcitonin salmon) Nasal Spray
- Evista® (raloxifene HCl)

- Actonel® (risedronate sodium tablets)
- Boniva ® (ibandronate sodium)
- Fosamax® (alendronate sodium tablets)
- Reclast ® (zoledronic acid)

- Prolia ® (denosumab)

- Forteo® (teriparatide injection)
- Tymlos ® (abaloparatide injection)

- Evenity ® (romosozumab)

- **Multiple medications now available for prevention and treatment of osteoporosis**
  - All have been shown to decrease spine fracture. Effect on non-vertebral and hip fractures variable
  - All current medications except teriparatide and abaloparatide are antiresorptive – block action of osteoclasts
  - Teriparatide and abaloparatide are anabolic– increases activity of osteoblasts and osteoclasts
- **Choosing appropriate therapy for an individual patient requires consideration of risk/benefit ratio**

Summary of Current FDA Drug Indications

Medication	Postmenopausal Osteoporosis		Glucocorticoid-Induced Osteoporosis		Male Osteoporosis
	Prevention	Treatment	Prevention	Treatment	Treatment
Calcitonin		X			
Bazedoxifene/CEE	X				
Estrogen	X				
Raloxifene	X	X			
Alendronate	X	X		X	X
Risedronate	X	X	X	X	X
Ibandronate	X	X			
Zoledronic Acid	X	X		X	X
Denosumab		X			X
Teriparatide		X		X	X
Abaloparatide		X			
Romosozumab		X			

What About ONJ and AFF?

Discussing Risk vs Benefits with Patients

- I use Figure 3 (page 29) out of the AACE guidelines (Camacho PM. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2016. Endocrine Practice 22: 1-42 , 2016.)
- For example in women age 65-69:
  - Risk of a hip fracture is 387/100,000 people per year
  - Death by motor vehicle accident is 11/100,00 people per year
  - Death by murder – 6/100,000 people per year
  - ONJ in an osteoporosis patient 0.7/100,000 people per year
  - Death by lightening strike in New Mexico 0.6/100,000 people per year

- Another table compares 10- year probabilities of fractures, treated and untreated with ONJ
- Another table compares the benefits and risks of fractures, treated and untreated with ONJ and AFF

Osteonecrosis of the Jaw (MRONJ)

- Definition – Long-term presence of exposed nonhealing bone lesion in the oral cavity not healing after 6-8 weeks (Khosla S et al, ASBMR 23: 159-65, 2008)
- Etiology is not yet known – may involved local problems (dental extraction, exostoses, periodontal disease, infection, poorly fitting dentures) and systemic factors (bisphsophonates, cancer, steroids, chemotherapy, age, nutrition, smoking diabetes) Khosla S et al. JBMR 23: 159-65, 2008
- Risk is 1 per 10,000 to 1 per 100,000- Khosla S et al. JBMR22: 1479-91, 2007. (higher in oncology patients)
- Taskforce on ONJ: Khan AA et al. Case-based review of osteonecrosis of the jaw (ONJ) and Application of the International recommendations for management rom the International Task Force on ONJ. J Clin Densitom 20: 8-24, 2017. This publication contains a ONJ patient brochure.
- Risk factors for ONJ – suppuration, dental extraction, oral bisphosphonates, denosumab – (Khan et al. J Clin Densitom 20: 8-24, 2017>
- Vitamin D deficiency may increase the prevalence of MONJ (Heim n et al. Vitamin D (25-Oh) deficiency may increase the prevalence of medication-related osteonecrosis of the jaw. J Craniomaxilofac Surg 45: 2068-2074, 2017.
- Use of corticosteroids or immunosuppresants might be risk factors (Aljohan S et al. What is the effect of anti-resorptive drugs (ARDs) on the development of medication-associated osteonecrosis of the jaw (MRONJ) in osteoporosis patients: A systematic review J Cranio-Maxilofac Surgery 45: 1493-1502, 2017).
- Using sCTX as a marker is not supported by evidence – (Baim S, Miller PD JBMR 24: 561-74, 2009.
-

American Dental Association Council on Scientific Affairs

Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis

Executive summary of recommendations from the American Dental Association Council on Scientific Affairs

John W. Hellstein, DDS, MS; Robert A. Adler, MD; Beatrice Edwards, MD; Peter L. Jacobsen, PhD, DDS; John R. Kalmar, DMD, PhD; Sreenivas Koka, DDS, PhD; Cesar A. Migliorati, DDS, MS, PhD; Helen Ristic, PhD; for the American Dental Association Council on Scientific Affairs Expert Panel on Antiresorptive Agents

This executive summary is based on a report developed by an advisory committee of the American Dental Association Council on Scientific Affairs following an appraisal of the literature identified by means of a systematic search.[1]

The purpose of this report is to help dentists make treatment decisions based on the current best evidence when available, and on expert opinion when necessary, for patients being treated with antiresorptive agents (Table 1[2]). In an effort to improve the quality and efficiency of oral health care, the advisory committee compiled this report as an educational tool to assist dentists when discussing oral health with patients receiving antiresorptive therapy, as well as when treating these patients. This executive summary focuses on patients receiving antiresorptive therapy for low bone mass rather than on patients receiving antiresorptive therapy for cancer treatment. The committee chose this focus because patients with low bone mass are seen routinely by

ABSTRACT

ARTICLE 1

Background. This narrative review of osteonecrosis of the jaw in patients with low bone mass receiving treatment with antiresorptive agents is based on an appraisal of the literature by an advisory committee of the American Dental Association Council on Scientific Affairs. It updates the committee's 2008 advisory statement.
Methods. The authors searched MEDLINE for literature published between May 2008 (the end date of the last search) and February 2011.
Results. This report contains recommendations based on the findings of the literature search and on expert opinion that relate to general dentistry; periodontal disease management; implant placement and maintenance; oral and maxillofacial surgery; endodontics; restorative dentistry and prosthodontics; orthodontics; and C-terminal telopeptide testing and drug holidays.
Conclusions. The highest reliable estimate of antiresorptive agent–induced osteonecrosis of the jaw (ARONJ) prevalence is approximately 0.10 percent. Osteoporosis is responsible for considerable morbidity and mortality. Therefore, the benefit provided by antiresorptive therapy outweighs the low risk of developing osteonecrosis of the jaw.
Clinical Implications. An oral health program consisting of sound hygiene practices and regular dental care may be the optimal approach for lowering ARONJ risk. No validated diagnostic technique exists to determine which patients are at increased risk of developing ARONJ. Discontinuing bisphosphonate therapy may not lower the risk but may have a negative effect on low-bone-mass–treatment outcomes.
Key Words. Oral and maxillofacial pathology; alveolar bone; antiresorptive agent–induced ostenecrosis of the jaw; bisphosphonate-associated osteonecrosis; jaw; oral and mandibular diseases; oral pathology.
JADA 2011;142(11):1243-1251.

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TABLE 2

Prevention strategies for patients receiving antiresorptive therapy* (absent evidence of ARONJ†).

VARIABLE	CONSIDERATIONS FOR MANAGING PATIENTS' ORAL HEALTH
Duration of Antiresorptive Therapy	
Before therapy	▬ Optimal time to establish lifetime oral health awareness, as the long-term nature of antiresorptive therapy is associated with ever-increasing ARONJ risk ▬ Optimal period to remove unsalvageable teeth and perform invasive dentoalveolar procedures, although a less stringent requirement than that for patients being treated with these drugs as part of cancer therapy ▬ On assessment of the overall caries risk, periodontal disease risk and "dental intelligence quotient" of the patient, the dentist is best qualified to establish an appropriate treatment plan in coordination with the patient and the patient's physician
< 2 years	▬ Above discussions and assessments often are not performed or even possible before start of antiresorptive therapy, but all remain applicable after treatment has begun ▬ Risk during this period is very low; however, a few cases of ARONJ have been reported‡ ▬ Dentoalveolar procedures involving periosteal penetration or intramedullary bone exposure (for example, extractions, apicoectomies, periodontal surgeries, implants or biopsies) seem to carry a
	▬ Although the trial segmental or sextant approach to surgical procedures has not been studied in a prospective fashion, this approach should help limit the extent of ARONJ in a given patient
Emergency Dental Therapy	▬ All extractions or dentoalveolar surgeries required on the basis of dental or medical emergencies are appropriate, regardless of the number of extractions or surgeries and multifocality
Routine Dental Care	▬ Good oral health and routine dental care always are recommended

* Limited data suggest similar levels of risk for patients treated with oral bisphosphonates, intravenous bisphosphonates and subcutaneous denosumab in the treatment of low bone density. Similar prevention strategies appear appropriate for each of these modalities, with comparable modification according to duration of drug therapy. This does not mean that no differences exist between these treatment modalities, and further studies are needed. Sources: Aghaloo and colleagues[4]; Grbic and colleagues.[18]
† ARONJ: Antiresorptive agent–induced ostenecrosis of the jaw.
‡ Source: Mavrokokki and colleagues.[8]

Discontinuation of antiresorptive therapy should be a medical decision based primarily on the risk of experiencing skeletally related events (for example, fractures) secondary to low bone density, not the potential risk of developing ARONJ.

JADA 142: 1243-51, 2011

Ruggiero Suggested Guidelines

- No alteration in surgery plan is necessary if on the bisphosphonate for < 4 years
- BP < 4 years with steroids or antiangiogenic drugs consider stopping for 2 months prior to surgery and wait until healing to restart
- Bisphosphonate for > 4 years, stop for 2 months if possible and restart after total healing
- Dental implants require informed consent, consider drug holiday, alternative dosing, an alternative to a bisphosphonate

Ruggiero SL, et. al., American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg. 2014; 72: 1938-1956

ONJ cont

- I include an oral exam in the evaluation for low BMD and talk to patients about their oral health and assure dental follow-up
- A variety of dental disorders are more common in patients with osteoporosis – i.e. tooth loss
- I agree with the ADA's statement: "An oral health program consisting of sound hygiene practices and regular dental care may be the optimal approach for lowering ARONJ risk" (JADA 14: 1243-1251, 2011). I send the JADA article to dentists.
- I prefer to wait to start bisphosphonates/denosumab until invasive dental work is completed, if possible.

ATYPICAL FEMORAL FRACTURES

- **Key features: fracture in diaphysis or subtrochanteric region, transverse rather than spiral, often begins with a stress reaction or stress fracture of lateral femoral shaft and may be bilateral, prodromal pain in thigh or groin is common, pts are often on other drugs such as steroids**

PERSPECTIVE

JBMR

Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research

Elizabeth Shane,* David Burr,* Peter R Ebeling, Bo Abrahamsen, Robert A Adler, Thomas D Brown, Angela M Cheung, Felicia Cosman, Jeffrey R Curtis, Richard Dell, David Dempster, Thomas A Einhorn, Harry K Genant, Piet Geusens, Klaus Klaushofer, Kenneth Koval, Joseph M Lane, Fergus McKiernan, Ross McKinney, Alvin Ng, Jeri Nieves, Regis O'Keefe, Socrates Papapoulos, Howe Tet Sen, Marjolein CH van der Meulen, Robert S Weinstein, and Michael Whyte

Author affiliations appear on pp. 2288–2289

ABSTRACT

Reports linking long-term use of bisphosphonates (BPs) with atypical fractures of the femur led the leadership of the American Society for Bone and Mineral Research (ASBMR) to appoint a task force to address key questions related to this problem. A multidisciplinary expert group reviewed pertinent published reports concerning atypical femur fractures, as well as preclinical studies that could provide insight into their pathogenesis. A case definition was developed so that subsequent studies report on the same condition. The task force defined major and minor features of complete and incomplete atypical femoral fractures and recommends that all major features, including their location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete, and absence of comminution, be present to designate a femoral fracture as atypical. Minor features include their association with cortical thickening, a periosteal reaction of the lateral cortex, prodromal pain, bilaterality, delayed healing, comorbid conditions, and concomitant drug exposures, including BPs, other antiresorptive agents, glucocorticoids, and proton pump inhibitors. Preclinical data evaluating the effects of BPs on collagen cross-linking and maturation, accumulation of microdamage and advanced glycation end products, mineralization, remodeling, vascularity, and angiogenesis lend biologic plausibility to a potential association with long-term BP use. Based on published and unpublished data and the widespread use of BPs, the incidence of atypical femoral fractures associated with BP therapy for osteoporosis appears to be very low, particularly compared with the number of vertebral, hip, and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been established. However, recent observations suggest that the risk rises with increasing duration of exposure, and there is concern that lack of awareness and underreporting may mask the true incidence of the problem. Given the relative rarity of atypical femoral fractures, the task force recommends that specific diagnostic and procedural codes be created and that an international registry be established to facilitate studies of the clinical and genetic risk factors and optimal surgical and medical management of these fractures. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Research directions should include development of animal models, increased surveillance, and additional epidemiologic and clinical data to establish the true incidence of and risk factors for this condition and to inform orthopedic and medical management.
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KEY WORDS: OSTEOPOROSIS; BONE; PAIN; FRACTURE; ATYPICAL; SUBTROCHANTERIC; FEMORAL DIAPHYSIS; BISPHOSPHONATES

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*Co-Chairs.
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Journal of Bone and Mineral Research, Vol. 25, No. 11, November 2010, pp 2267–2294
DOI: 10.1002/jbmr.253
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Shane E. JBMR 25; 2267-94, 2010.

Summary and Conclusions

BPs are highly effective at reducing the risk of spine and nonspine fractures, including typical and common femoral neck and intertrochanteric fractures. However, there is evidence of a relationship between long-term BP use and a specific type of subtrochanteric and femoral shaft fracture. These fractures are characterized by unique radiographic features (ie, transverse or short oblique orientation, absence of comminution, cortical thickening, stress fracture or stress reaction on the symptomatic and/or contralateral side, and delayed healing) and unique clinical features (ie, prodromal pain and bilaterality). The apparent increased risk for atypical femoral fractures in patients receiving GCs is a concern because BPs are the mainstay for prevention of GC-induced osteoporotic fractures. Bone biopsies from the iliac crest and/or fracture site generally show reduced bone formation consistent with BP action. Paradoxically, some patients show biopsy evidence of enhanced bone resorption. Biochemical BTMs are often normal but may be increased. These fractures can occur in patients who have not been treated with BPs, and their true incidence in both treated and untreated patients is unknown. However, they appear to be more common in patients who have been exposed to long-term BPs, usually for more than 3 years (median treatment 7 years). It must be emphasized that these fractures are rare, particularly when considered in the context of the millions of patients who have taken BPs and also when compared with typical and common femoral neck and intertrochanteric fractures. It also must be emphasized that BPs are important drugs for the prevention of common osteoporotic fractures. However, atypical femoral fractures are of concern, and more information is urgently needed both to assist in identifying patients at particular risk and to guide decision making about duration of BP therapy. Physicians and patients should be made aware of the possibility of atypical femoral fractures and of the potential for bilaterality through a change in labeling of BPs. Given the relative rarity of atypical femoral fractures, to facilitate future research, specific diagnostic and procedural codes should be created for cases of atypical femoral fractures, an international registry should be established, and the quality of case reporting should be improved. Research directions should include development of animal models, increased surveillance, and additional epidemiologic data to establish the true incidence of and risk factors for this condition and studies to address their surgical and medical management.

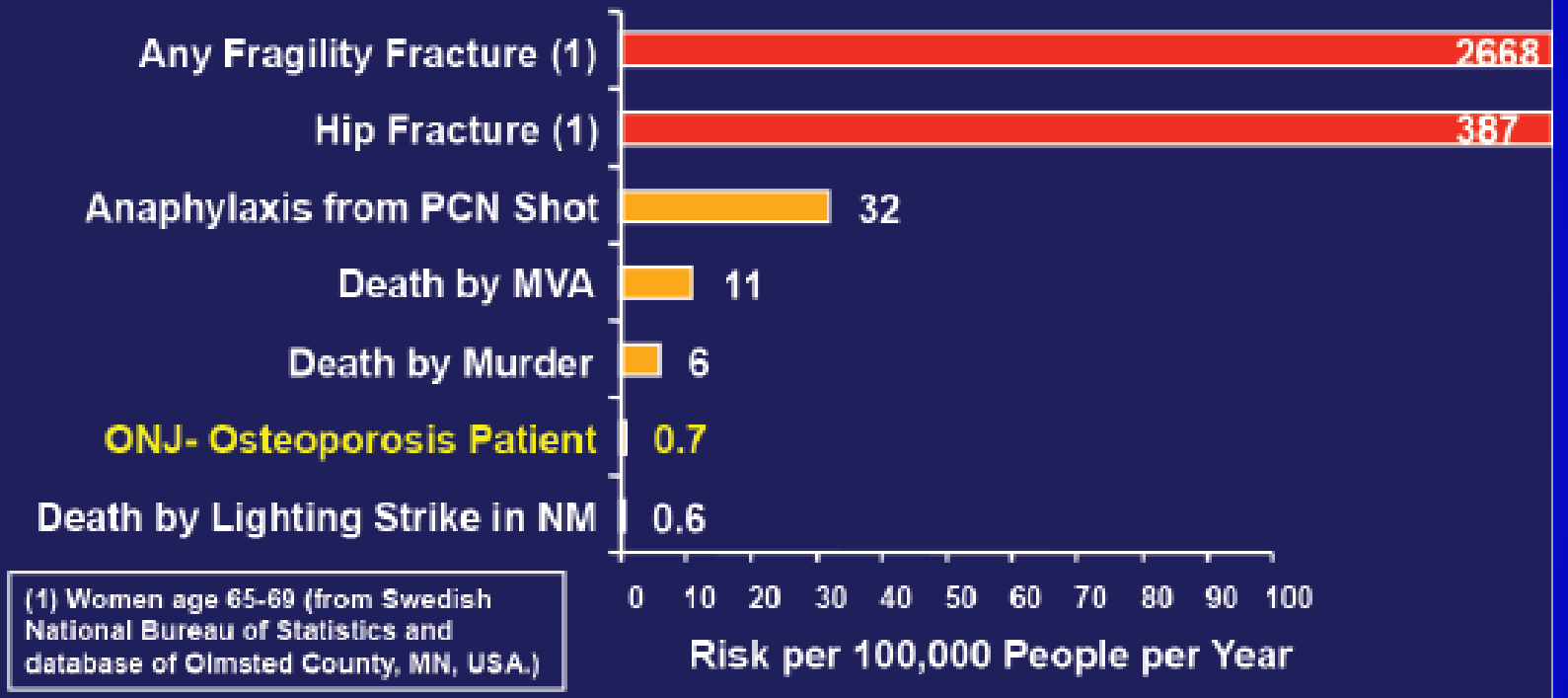
AFF

- Subtrochanteric fractures also occur in patients not taking antiresorptive medications
- Population estimates are approximately 0.01% after 3 years and 0.1% after 10 years (Rizzoli R et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. Osteoporos Int 2011;22:373-90
- Wang, Z and Bhattacharyya T. Trends in incidence of subtrochanteric fragility fractures and bisphosphonate use among the US elderly, 1996-2007. Bone Miner Res, 2011;26:553-60)

Discussing Risk vs Benefits with Patients

A

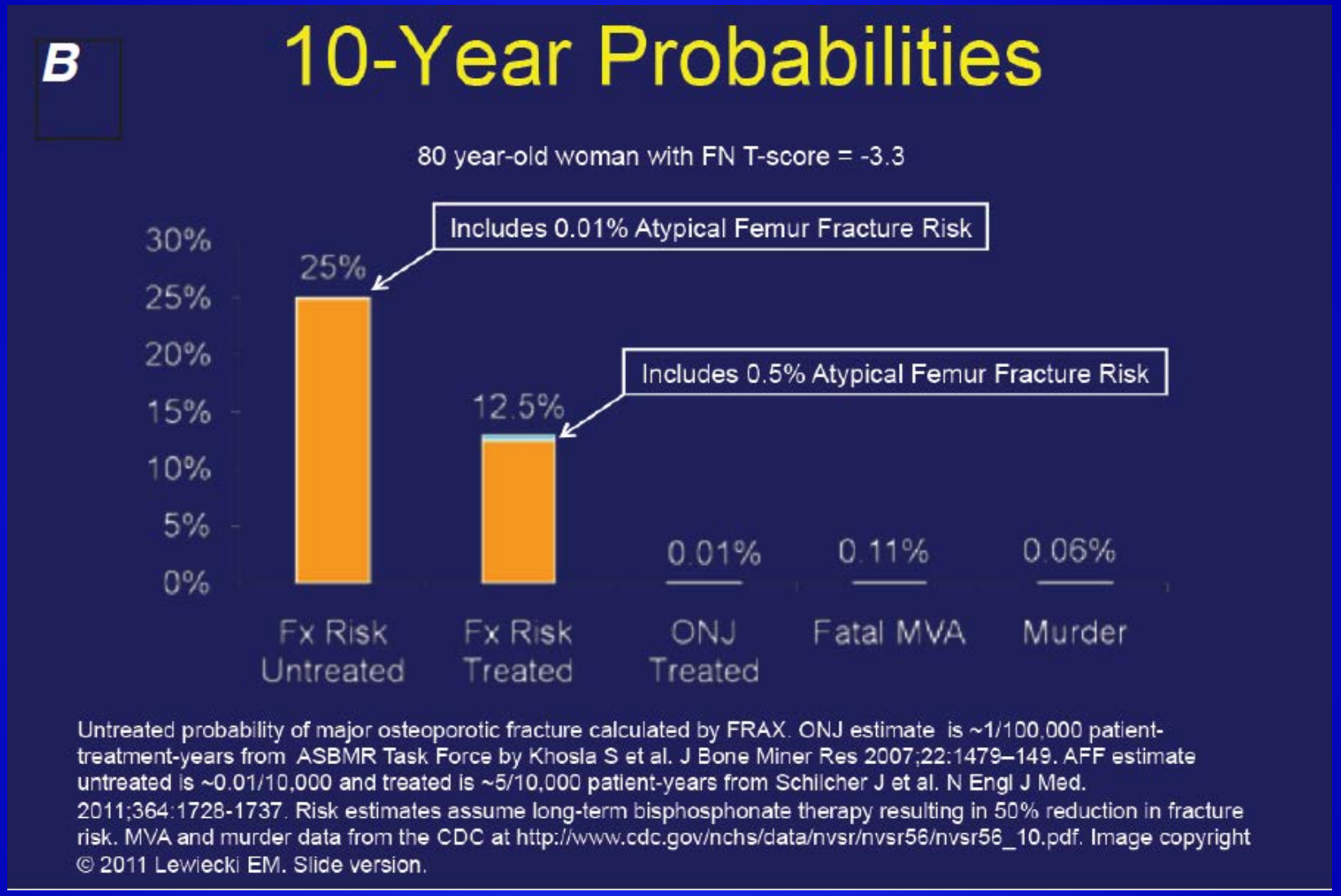
Comparative Risks



(1) Women age 65-69 (from Swedish National Bureau of Statistics and database of Olmsted County, MN, USA.)

Kanis JA et al. Osteoporos Int. 2001;12:417-427. Pharmcoepidemiol Drug Saf. 2003;12:195-202. National Center for Health Statistics. JADA. 2006;137:1144-1150. www.nssl.noaa.gov/papers/techmemos/NWS-SR-193/techmemo-sr193-4.html

Camacho PM. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2016. Endocrine Practice 22: 1-42 , 2016



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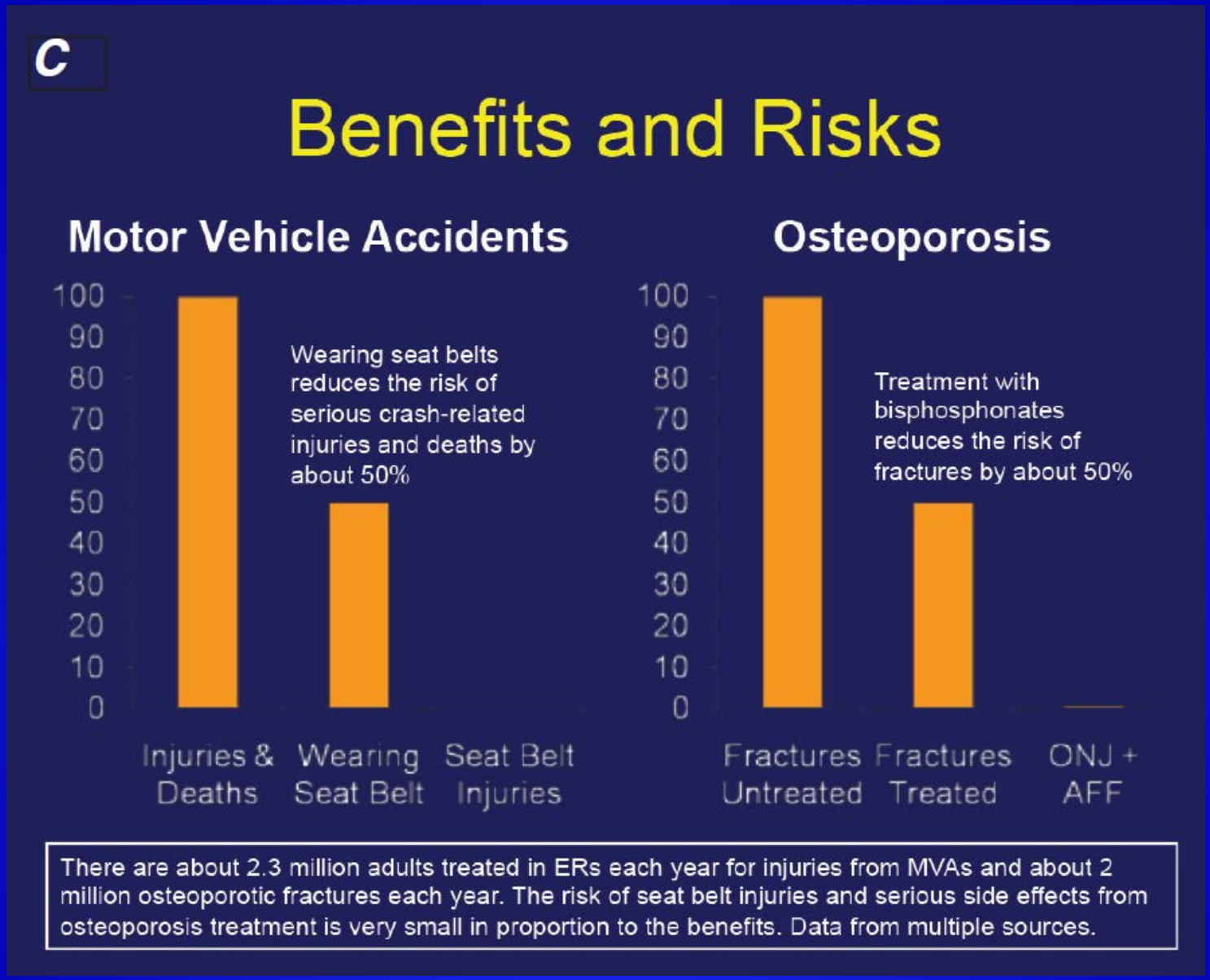
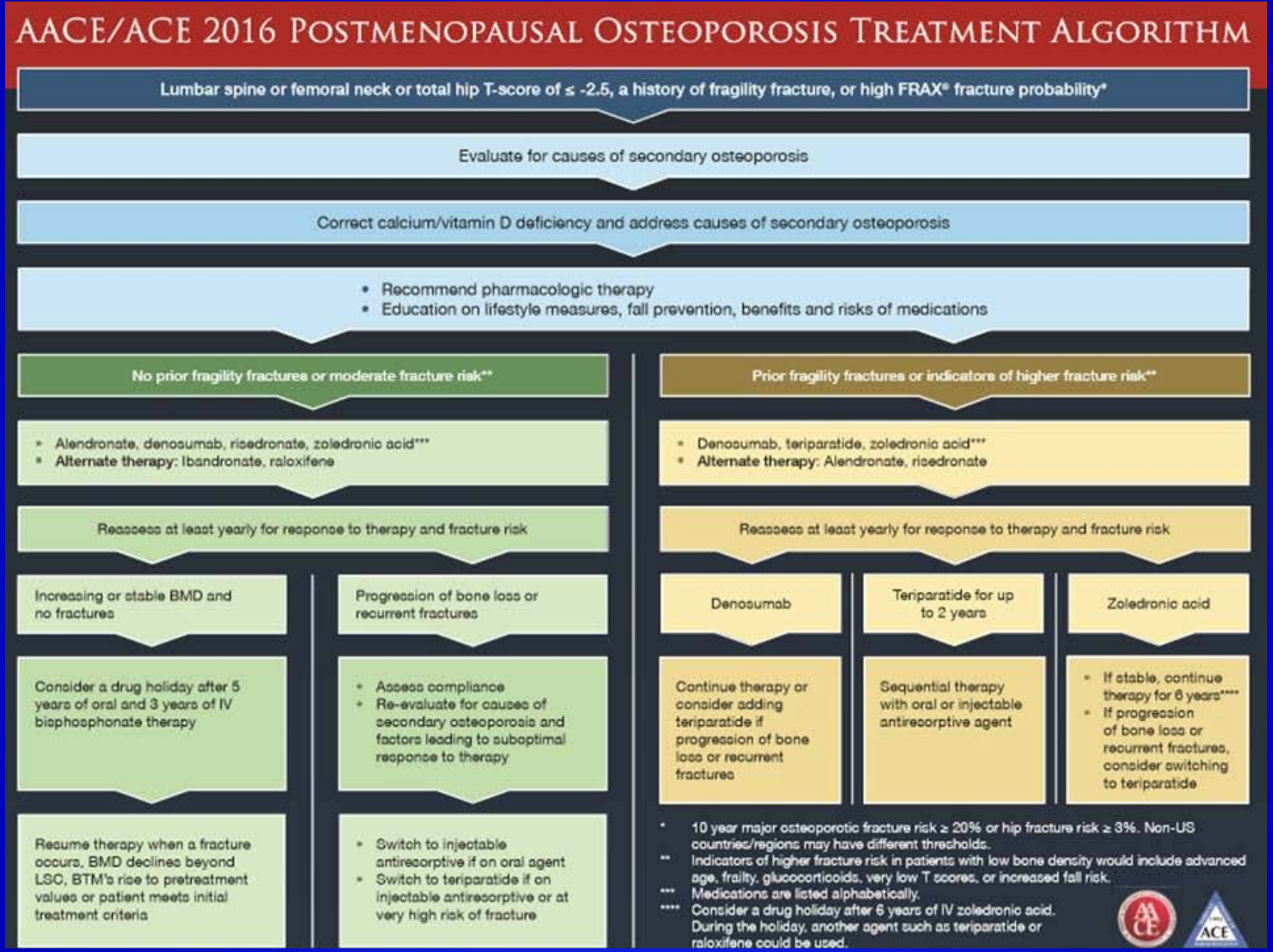


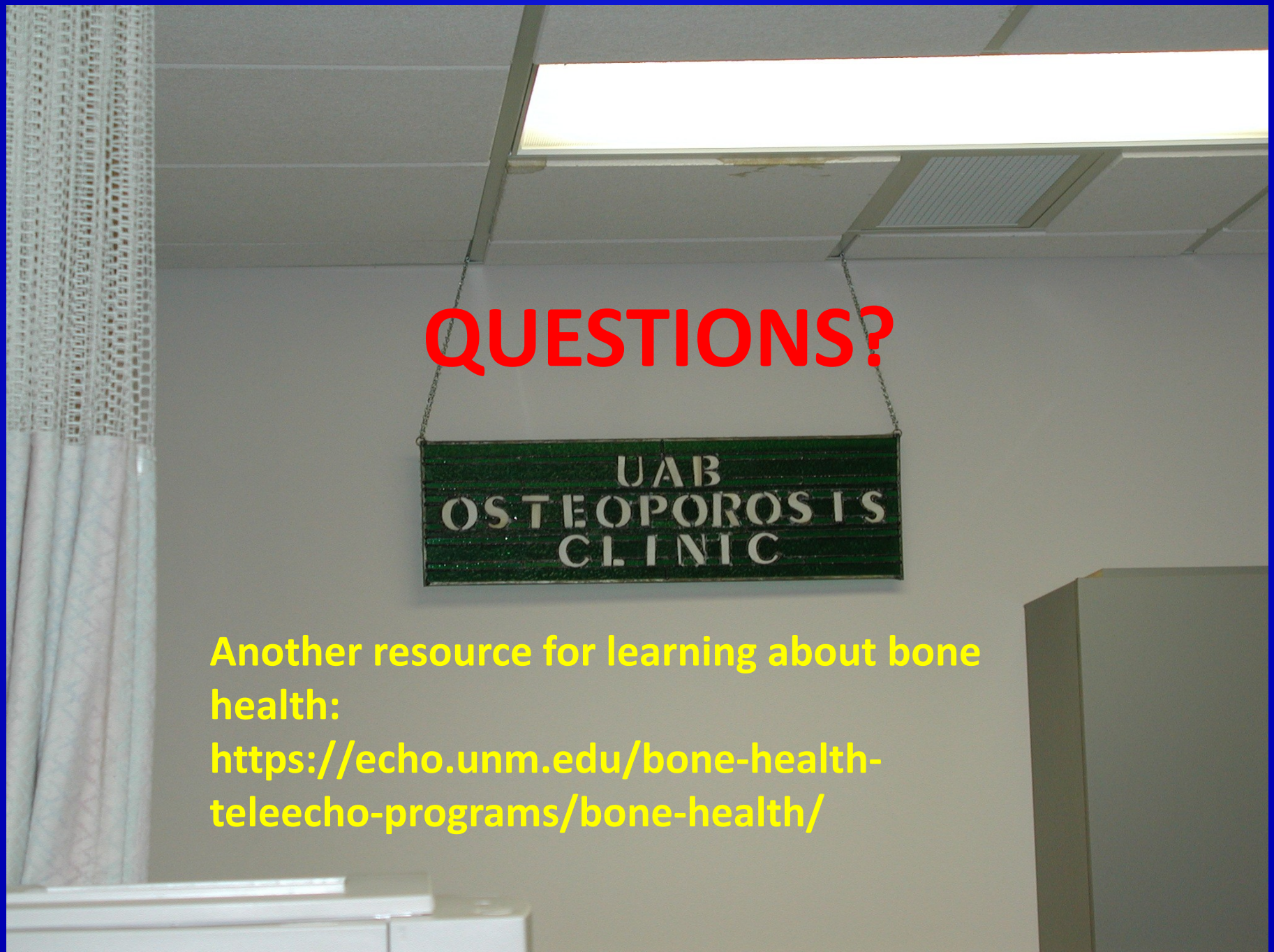
Camacho PM. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2016. Endocrine Practice 22: 1-42 , 2016

Drug-Free Holiday

- Because of the real or perceived side-effects of bisphosphonates the concept of a drug-free holiday has been popularized
- Drug free holiday concept does not apply to denosumab
- Good references related to when to do drug free holidays
  - Adler RA et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research J Bone Miner Res 31: 16-35, 2016.



Camacho PM. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2016. Endocrine Practice 22: 1-42 , 2016.


QUESTIONS?
UAB
OSTEOPOROSIS
CLINIC
Another resource for learning about bone health:
https://echo.unm.edu/bone-health-teleecho-programs/bone-health/

Lupus: Clinical Presentations and Current Management

W Winn Chatham MD

Disclosures

- Grant support from GSK, Janssen, BMS for lupus clinical trials

SLE

- Multi-system disorder associated with autoimmunity
- Prevalence 1-8/1000
  - females: males 10:1
  - higher prevalence among African-Americans
- Morbidity--
  - 80-85%: fatigue, arthralgia, skin rashes
  - 15-20%: visceral organ or CNS complications: nephritis, pneumonitis, pleuritis/pericarditis, seizures, psychosis, stroke syndromes

Patient ML

History:

22 yo AA female presented with a two month history of edema, fatigue, fevers. mild anemia and proteinuria. Exam was notable for hypertension [160/106 mmHg], mild alopecia, and tibial/pedal edema.

PMH:

pregnancy [term] one year earlier cx by proteinuria [1.2 gm]

Labs:

WBC 5.6K, Hct 25/Hgb 8.6 mg/dl, PLts 166K

Creat 0.9 mg/dl; nl LFTs, Albumin 2.9 gm/dl

4+ protein on U/A 30 RBC/casts, 5 WBC

24 hr Urine protein/creat = 4.8

Neg HIV, Neg HCV Ab

Patient ML

Serologic evaluation:

+ANA >1:1280

+ anti-dsDNA

+ anti-Smith, neg anti-SSA, neg anti-CLAb

+ IgG Coombs test

C3 57 [nl > 88], C4 14 [nl > 16]

Patient ML

Renal Biopsy:

H&E: diffuse focal proliferative lesions with one cellular crescent

EM: large mesangial and subendothelial immune deposits

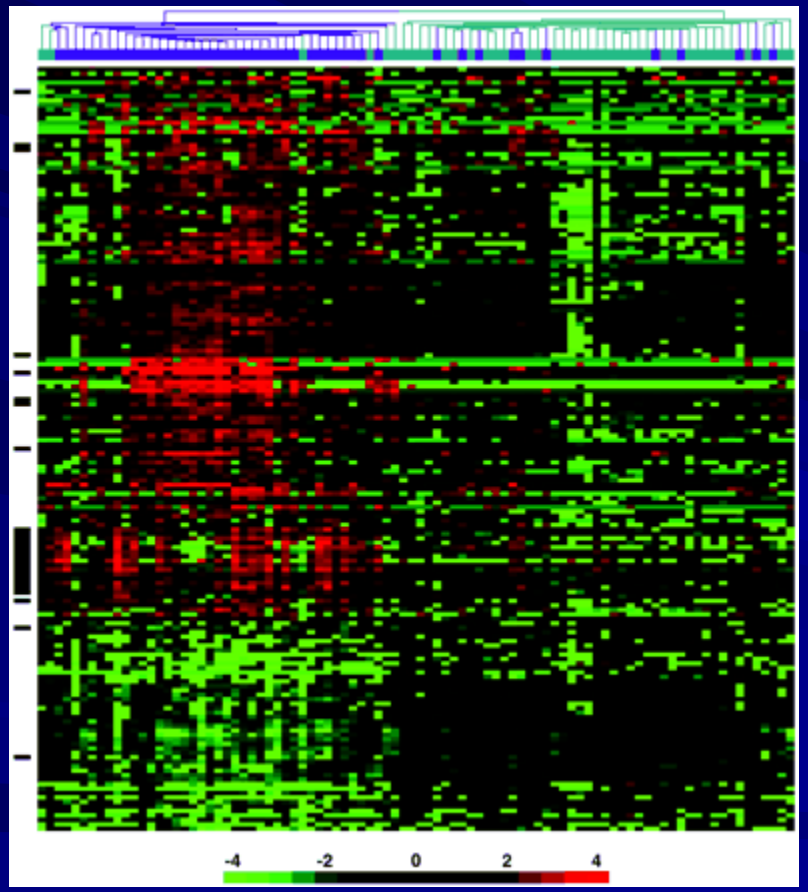
Dx: SLE with nephritis [proteinuria/IC GN], AIHA, high titer +ANA, +anti-dsDNA/Sm

SLE: Cardinal Features

- Profound constitutional symptoms
- Autoantibodies
  - specificities for nucleoproteins
- Immune complex mediated tissue lesions
  - immune mediated cytopenias
  - IC mediated glomerulonephritis, other vascular lesions

Immuno-Pathophysiology of Lupus

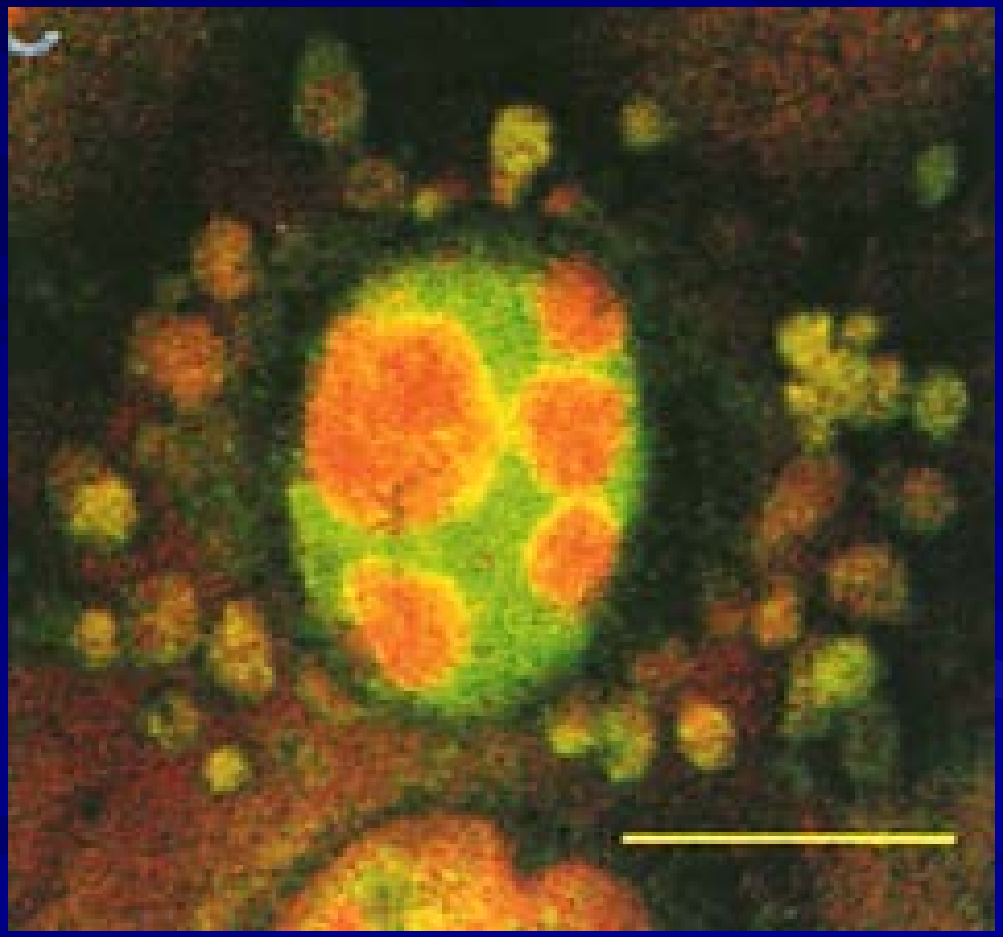
SLE Constitutional Symptoms: *“I feel like I always have the flu”*



‘Interferon Signature’

Baechler EC, Batliwalla FM, Behrens TW et al. 2003 PNAS 100(5): 2610

Autoantibodies in SLE: specificty primarily for nucleoproteins apoptotic blebs/bodies



Casciola-Rosen LA, Anhalt G, Rosen A. 1994 J Exp Med 179(4) : 1083

SLE: Immuno-pathophysiology

Aberrant responses to nucleoprotein products of cell death/apoptosis

- Production of type-1 interferons by APCs
- Production of BLyS/BAFF by APCs

Survival and proliferation of autoreactive B cells

Decreased number/function of regulatory T cells

Cellular and humoral autoimmunity

known genetic determinants impacting all of these

Diagnosing Lupus

ACR Criteria for SLE (any 4)

- Malar erythema
- Discoid skin lesions
- Photosensitivity
- Mouth ulcers
- Arthritis with synovitis
- Pleuritis, Pericarditis
- Seizures/psychosis]
- Renal disorder
- Cytopenia
- Positive ANA
- Immunologic disorder
  [anti-dsDNA Ab]
  [anti-Smith Ab]
  [anti-cardiolipin Ab]
  [false+ STS]

SLICC Criteria for SLE

4 (at least one clinical, at least one immunologic)

Clinical

- Acute cutaneous
- Chronic cutaneous
- Oral/Nasal ulcers
- Alopecia
- Arthritis with synovitis
- Pleuritis, Pericarditis
- Seizures, Psychosis
- Nephritis
- Cytopenia

Immunologic

- Positive ANA
- Positive anti-dsDNA
- Positive anti-Smith Ab
- Positive aPLAb
  - LAC, aCLAb, aB2GP1
- Low C3, C4, or CH50
- +Coombs/DAT

Nephritis + ANA or anti-dsDNA

A 32 year old Caucasian female complains of fatigue and generalized joint pain. Unable to complete tasks at work; weekends spent “recovering”

ROS: Occasional mouth ulcer, dry mouth. Feels ill after being outside with erythema on arms; recent flares of urticaria, frequent sinus infections

PMH: Sulfa allergy [rash]

Family Hx: M Cousin MS, M aunt SS

PE: Tender PIP joints, multiple tender points torso/extremities, otherwise normal

- *TSH:* normal
- *WBC:* 5200 [72 neut, 15 mono, 13 lymph]
- *Hct:* 34%
- *Plts:* 210,000/mm3
- *U/A:* normal
- *Chem Profile:* normal

- *ANA:* +1:320, homogeneous pattern

- *anti-dsDNA:* negative
- *anti-Smith:* negative
- *anti-SSA:* negative
- IgG 710 mg/dL, IgA 110 mg/dL, IgM 60 mg/dL

ACR/SLICC Criteria for SLE

- Acute Photosensitive rash
- Mouth ulcers
- Positive ANA

Does this patient have/should we treat for SLE ?

ACR/SLICC Criteria for SLE

- SLICC criteria more sensitive
  - Incorporate more skin mnaifestions
  - Incorporate low complement levels
- Still primarily for research purposes
- Treatment decisions should ***NOT*** be based upon ACR criteria for lupus
  - Patients with just 2 or 3 criteria may have severe SLE requiring Rx

SLE—other common clinical features

- Fever and/or increase fatigue level
- Sicca/Xerostomia sx
- Raynaud's
- Intolerance to sulfa drugs

SLE: Family Hx

*A family history of **any** autoimmune disorder may be an important clue to the early diagnosis of SLE*

Diagnosing Lupus: Early Recognition

- Cutaneous Presentations
- Articular Presentations
- Clinical Laboratory Presentations

SLE: Cutaneous manifestations

- Malar rash/papules
- Phototoxic erythematous rashes
- Cutaneous ulcers
- Panniculitis
  - inflammation of fat/adipose tissue
  - Erythema nodosum, Erythema induratum
- Subacute cutaneous lupus
- Urticarial vasculitis

SLE: Cutaneous Manifestations

Subacute Cutaneous Lupus

Subacute Cutaneous Lupus

- Often occurs in absence of other visceral disease manifestations
- ANA may be negative
- Most patients have anti-SSA/Ro
- Often accompanied by sicca, xerostomia
- Favorable response to antimalarials

SLE: urticarial vasculitis

- Most common form of cutaneous vasculitis in SLE
  - May be a presenting feature of lupus
- Association with:
  - Low complement levels
  - anti-C1q antibodies

Chilblains

- Onset typically in cold weather
- 25% of patients go on to develop SLE

Chilblain lupus Chilblain lupus characterized by reddish-blue nodules (in this case, on the fingers) occurring in cold weather. The lesions improved after the administration of nifedipine. Courtesy of Samuel Moschella, MD.

Panniculitis (lupus profundus)

- Up to 25% of patients with panniculitis will go on to develop SLE

Lupus profundus Sclerotic plaque with central depression (arrow) consistent with lupus profundus (panniculitis); this lesion was originally misdiagnosed as morphea which typically causes hyperpigmentation. There is also a scarring discoid lesion on the earlobe. Courtesy of Samuel Moschella, MD.

Hyperglobulinemic Purpura Leukocytoclastic Vasculits

Digital Vasculitis

SLE: articular presentations

- Symmetric, non-erosive arthritis
  - Distribution similar to RA
    wrists, MCPs, PIPs, elbows, knees, ankles

  Late:
  - Cartilage loss with loss of range [wrist, elbow]
  - Lax ligaments/deformity may develop [fingers]
- Osteonecrosis
  - Loss of blood supply to bone adjacent to joint
  - Rapidly progressive degenerative arthropathy may ensue [hips, knees, shoulders, ankles]

SLE: Cytopenias

- Leukopenia (WBC<3,000)
- Anemia
  - Immune hemolytic anemia
  - Microangiopathic hemolytic anemia
  - Renal disease
- Thrombocytopenia
  - Immune mediated [anti-platelet Ab]
  - Anti-phospholipid antibodies
- Pancytopenia
  - Aplastic anemia
  - Macrophage Activation Syndrome

MAS in Lupus

- Pancytopenia
- Coagulopathy
  - elevated INR
  - elevated d-dimer
  - low fibrinogen
- AST/ALT elevations
- Ferritin > 2000 ng/ml

= MAS

Anti-phospholipid antibodies in SLE

- APL Ab not uncommon in SLE
  - *[not exclusive to SLE]*
- Manifest by:
  - elevated PTT, “lupus anticoagulant”
  - anti-cardiolipin antibodies,
  - anti-β2 glycoprotein 1 Ab
- Predisposition to Thrombosis
  - arterial or venous
  - multiple organs, CNS affected
- Associated thrombocytopenia
- Increased risk for osteonecrosis

Diagnosing Lupus: Serologic Tests

Supporting Laboratory Tests:

- ANA [anti-nuclear antibodies] in high titer
  - Some are specific for lupus:
    - anti-dsDNA, anti-Smith
- Low complement levels (C3, C4, CH50)
- Other autoantibodies
  - Antibodies to platelets, red cells

ANA testing: ELISA (“direct”)

- Limited repertoire of nucleoproteins affixed to ELISA well
- Significant frequency of false negatives (same sera yielding high titers ANA by IF)

Bottom line: *do not exclude consideration of SLE based upon negative ANA testing by ELISA methods*

Assessing “Lupus Flare”

- Attention to ‘Lupus ROS’:
  - Rash, oral/nasal ulcers, hair loss
  - Chest pain and/or dyspnea
  - Joint pain/swelling
  - Focal neurologic sx
- Attention to exam:
  - Skin, oral/ocular membranes
  - Chest: lung crackles, pleuro/pericardial rubs
  - Abdominal tenderness, hepatosplenomegaly
  - Joint tenderness, range
  - Sensorium, focal neuro deficits
- Lab:
  - CBC, Urinalysis with Up/c, AST/ALT, Creatinine
  - C3, C4, anti-dsDNA

Patient EY

24 yo CF with hx SLE (ANA, malar/photoS rashes, oral ulcers, arthritis) treated with HCQ. Presents with 2 week hx fevers, increased arthralgia, macular rash.

Exam:

Blanching circinate erythema on arms, torso

No joint swelling noted

No mucosal ulcers

Lungs clear

Neuro exam: no focal deficits, normal sensorium

Labs: WBC 2900,Hct 32, Plts 180,000

AST 120, ALT 90 IU/ml, o/w nl CMP, creatinine; nl U/A

Normal C3, Normal C4, ESR 65 mm/hr

Treat for lupus flare?

SLE: Therapeutic Strategies

- Treatment of acute flares
  - corticosteroids
- Maintain suppression of acute flare
  - steroid sparing agents
    - Methotrexate: arthritis, subacute/discoid skin lesions
    - Dapsone: skin lesions
    - Leflunomide
    - Azathioprine
    - Mycophenolate
    - Cyclophosphamide
- Flare prevention
  - Antimalarials
  - Immunomodulating biologic agents (Belimumab)

Antimalarials in SLE

- Inhibit TLR signaling in pDCs, B cells
- Dosing: ≤ 6 mg/kg/day
- Prevent flares of disease

  The Canadian Hydroxychloroquine Study Group N Engl J Med 1991; 324:150-154

- Favorably impact CV morbidity in SLE
- Tolerance (GI) often preparation dependent
  - Quinacrine often better tolerated

Lupus Nephritis: Initial Management
Goal: preserve renal function

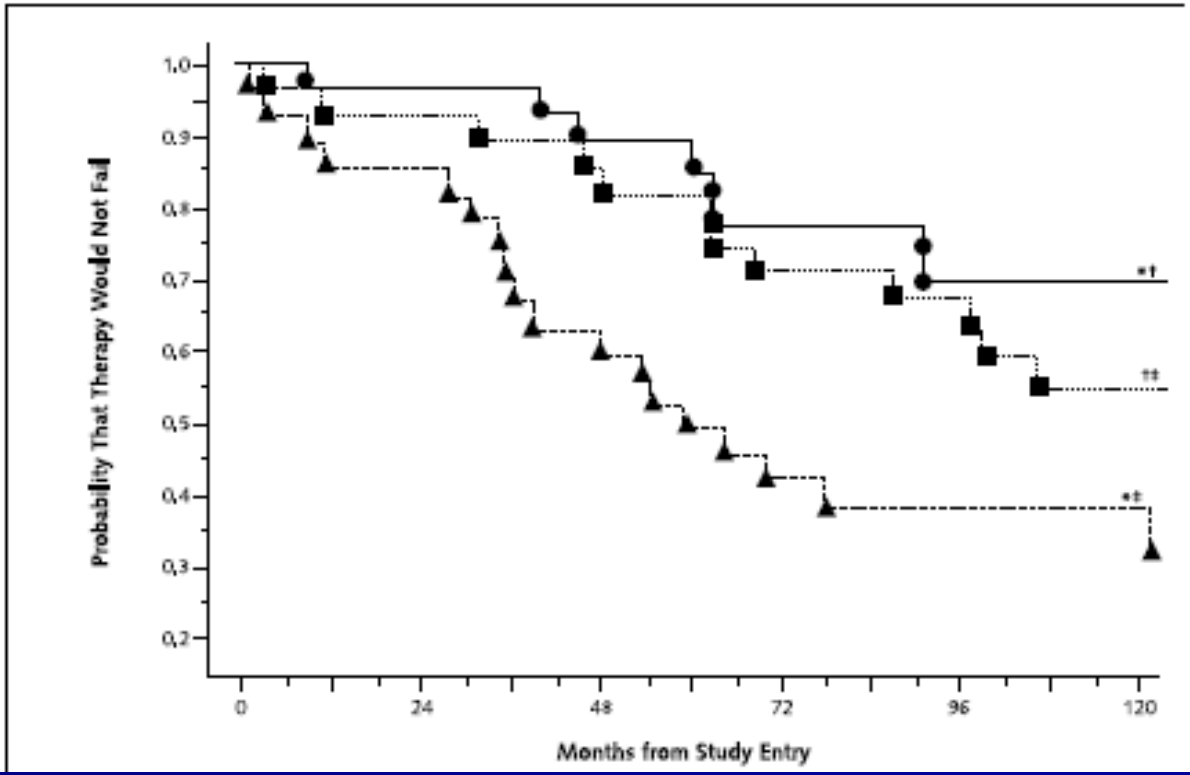
- Treat acute flares aggressively:

  Corticosteroids 1 mg/kg/day

  Pulse iv cyclophosphamide q 2-4 wks or mycophenolate for proliferative lesions
- Control BP!!!
- ACE inhibitors/ARBs if significant proteinuria
- Education
- Frequent F/U:
  - BP, U/A, creatinine, spot urinary protein/creatinine

Lupus Nephritis: Cyclophosphamide Use

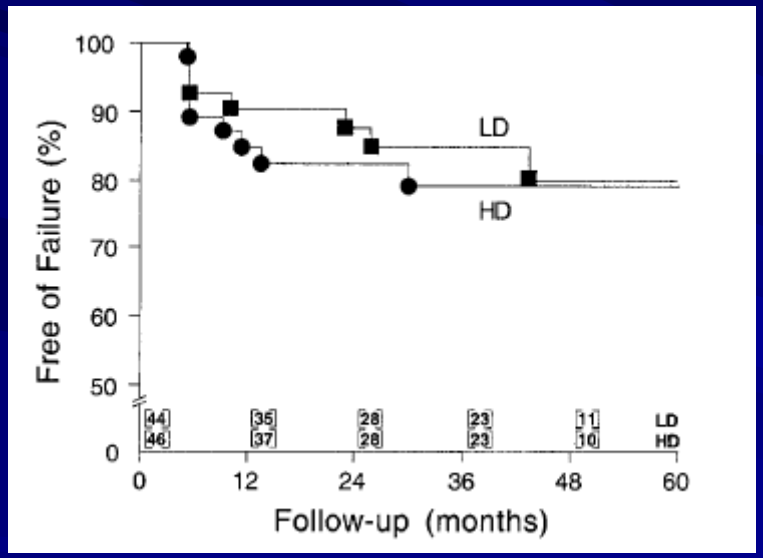
Figure. Kaplan–Meier analysis of failure of therapy with cyclophosphamide plus methylprednisolone (*circles*), cyclophosphamide only (*squares*), or methylprednisolone only (*triangles*).

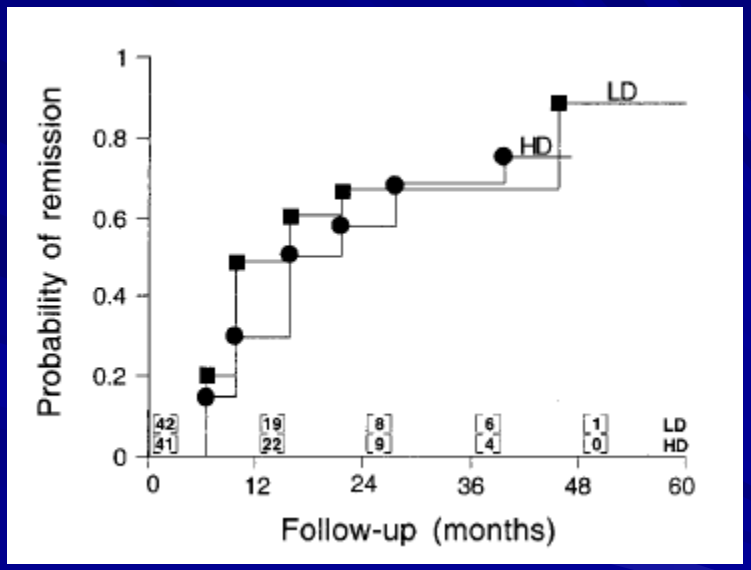


Illei GC ete al. Ann Intern Med. 2001 Aug 21;135(4):248-57

EuroLupus Nephritis Trial

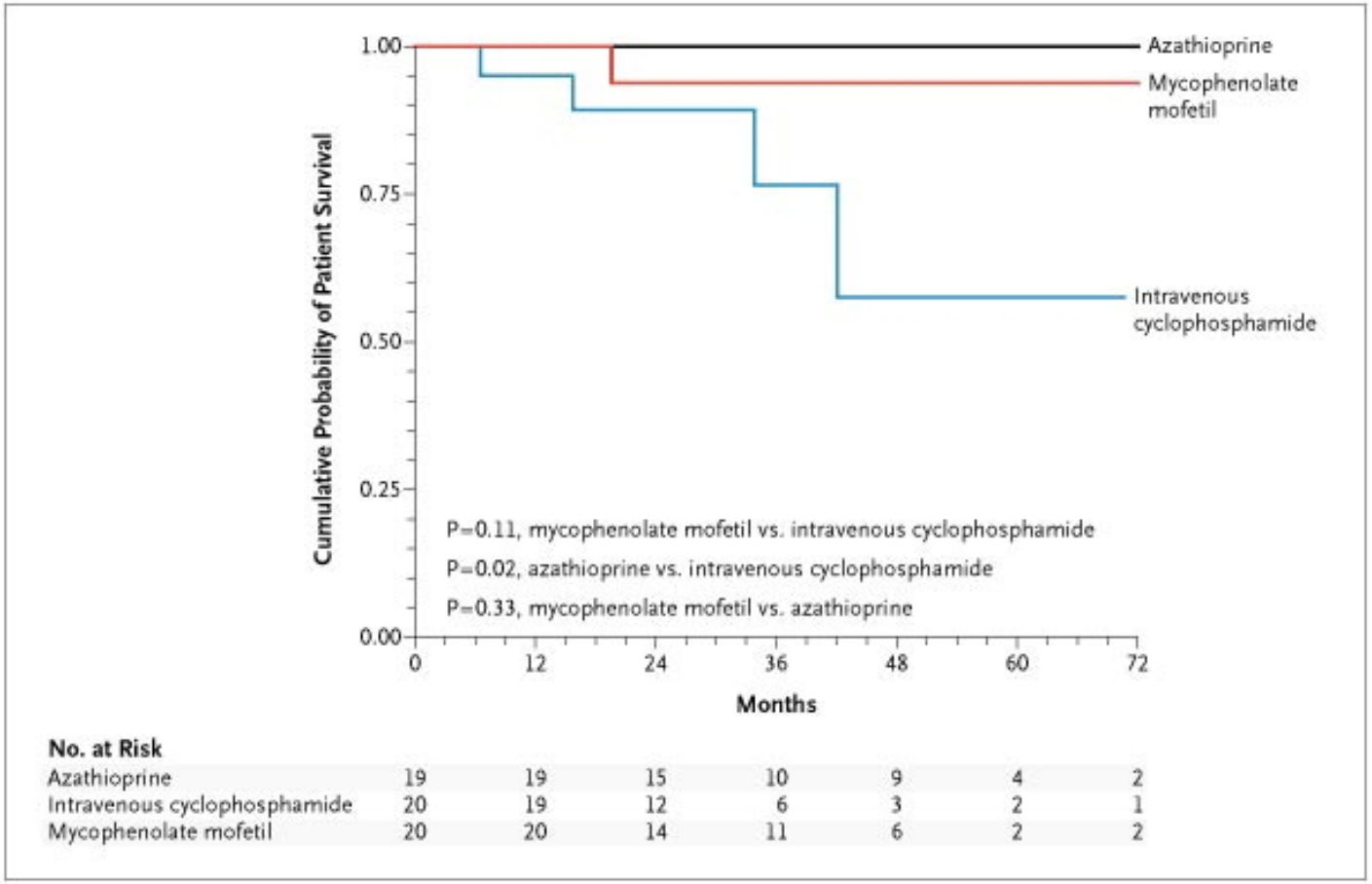
Houssiau FA et al Arthritis Rheum. 2002 Aug;46(8):2121-31





LD: 500 mg iv CTX q 2 wks x 6; then daily azathioprine (responders)
HD: 500 mg/m2-1500 mg iv CTX q 4wks x 6, then q 3 mos

LN: Optimizing Maintenance Rx



Contreras G et al. N Engl J Med 2004;350:971-980.

SLE Nephritis (ASPREVA trial): Mycophenolate vs CTX vs azathioprine

Acute renal flare:

- Monthly iv CTX vs daily Mycophenolate x 6 mos

Final analysis: MMF no better, but not inferior @ 6 mos

Month 6-24:

- Daily Mycophenolate vs Azathioprine

Final analysis: MMF outcomes better [fewer relapses]

Acute Lupus Pneumonitis

- Fever, cough, CXR infiltrates
- Exclude infection
- Alveolitis [HRCT and/or BAL]
- +/- Hemoptysis [alveolar hemorrhage]

Treatment--concomitantly:

- initiate high dose corticosteroids
- *exclude infection [bronchoscopy/BAL]*

LUPUS: CNS Complications

- Seizures
  - *Rx anti-convulsants (levetiracetam, lamotrigine*
- Psychosis [often with hallucinations]
  - *Rx anti-psychotics (risperdal)*
- Altered sensorium, confusion
  - *Rx corticosteroids +/- CTX, mycophenolate*
- Focal neurologic deficits
  - Stroke syndromes from vascular lesions
  - Focal inflammation in brain
  - *Rx corticosteroids +/- CTX; anticoagulation if +APLAb*

SLE: Rx Immune Hemolysis & Thrombocytopenia

- Corticosteroids 1-2 mg/kg/day
- Failure to respond:
  - IVIg
  - IV cylcophosphamide
  - Rituximab [anti-CD20 mAb]
- Splenectomy seldom required
  - Increased infection risk in SLE

SLE: New Therapies

- Belimumab: monoclonal antibody to BLyS/[BAFF]

  FDA approved 3/2011

  Decrease SLE activity, flares, steroid use added to SoC

  Best Responders: low C3, C4, + high-titer autoAb

  – *Upsides*:

    No significant toxicity

  – *Downsides*:

    Uncertainties re: optimal duration/dosing Rx

    Delayed onset of clinical response (6-12 mos)

    Cost ($30-$35K/year)

Evolving New Therapies for SLE

Targeting of innate responses:

- anti- interferon-α, INFR mAb
- anti-pDC mAb
- TLR blocking agents
- Jaki, Tyk2i
- Anti-IL12/23 mAb (ustekinumab)

Targeting of B cells and B cell activation

- anti-CD 20 mAb [rituximab]
- Anti-BlyS/BAFF reagents [belimumab]

Treg enhancement strategies

Primary Care and SLE

ensuring the best outcomes

- Mild Lupus: fatigue, rashes, arthritis
  - antimalarial Rx
- Moderate-Severe Lupus: visceral disease
  - Co-manage with rheumatologist
- Minimize premature CV morbidity
  - attention to CV risk factors
- Mitigate infection risk
  - Minimize corticosteroid use, UTD immunizatiosn
- Mitigate malignancy risk
  - Appropriate cancer/lymphoma screening,

Scleroderma/Myositis

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Assistant Professor
Clinical Immunology and Rheumatology
University of Alabama at Birmingham

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Conflict of Interest Disclosure

- I have no current conflicts of interest, financial or otherwise.

Scleroderma

Recognition and management for the Internist

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Scleroderma

Localized

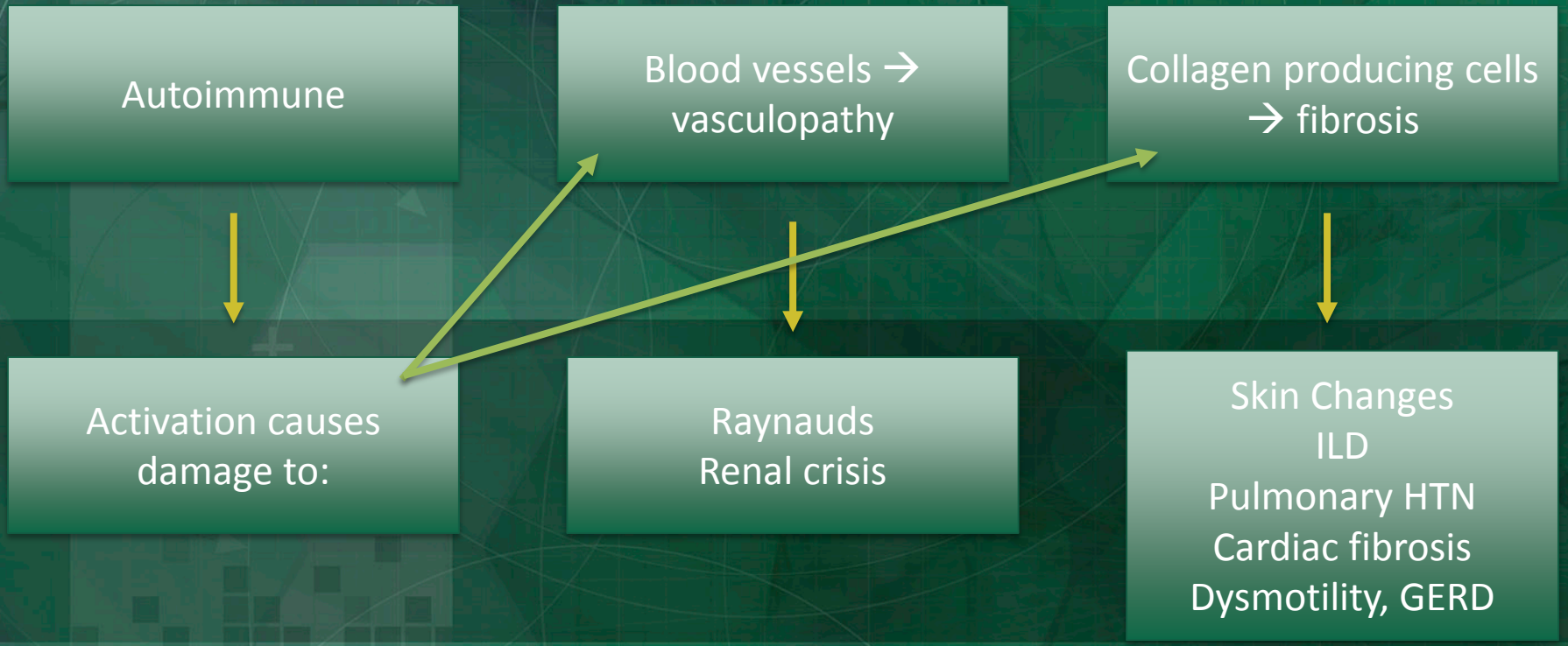
- Morphea
- Linear scleroderma
- Scleroderma en coup de sabre

Systemic (involving internal systems)

- Limited (CREST)
- Diffuse
- Scleroderma sine sclerosis

Adapted from *The Scleroderma Book*

- Pathogenesis



Adapted from *The Scleroderma Book*

Typical presentation

- Development of Raynauds
- Puffiness of the hands and feet
- More frequent heartburn
- Patient sees PCP for finger ulcer that won’t heal

Associated Features to be on the lookout for-

- Raynauds
  - Digital pits/ulcers
- Telangiectasias
- GERD

Raynauds

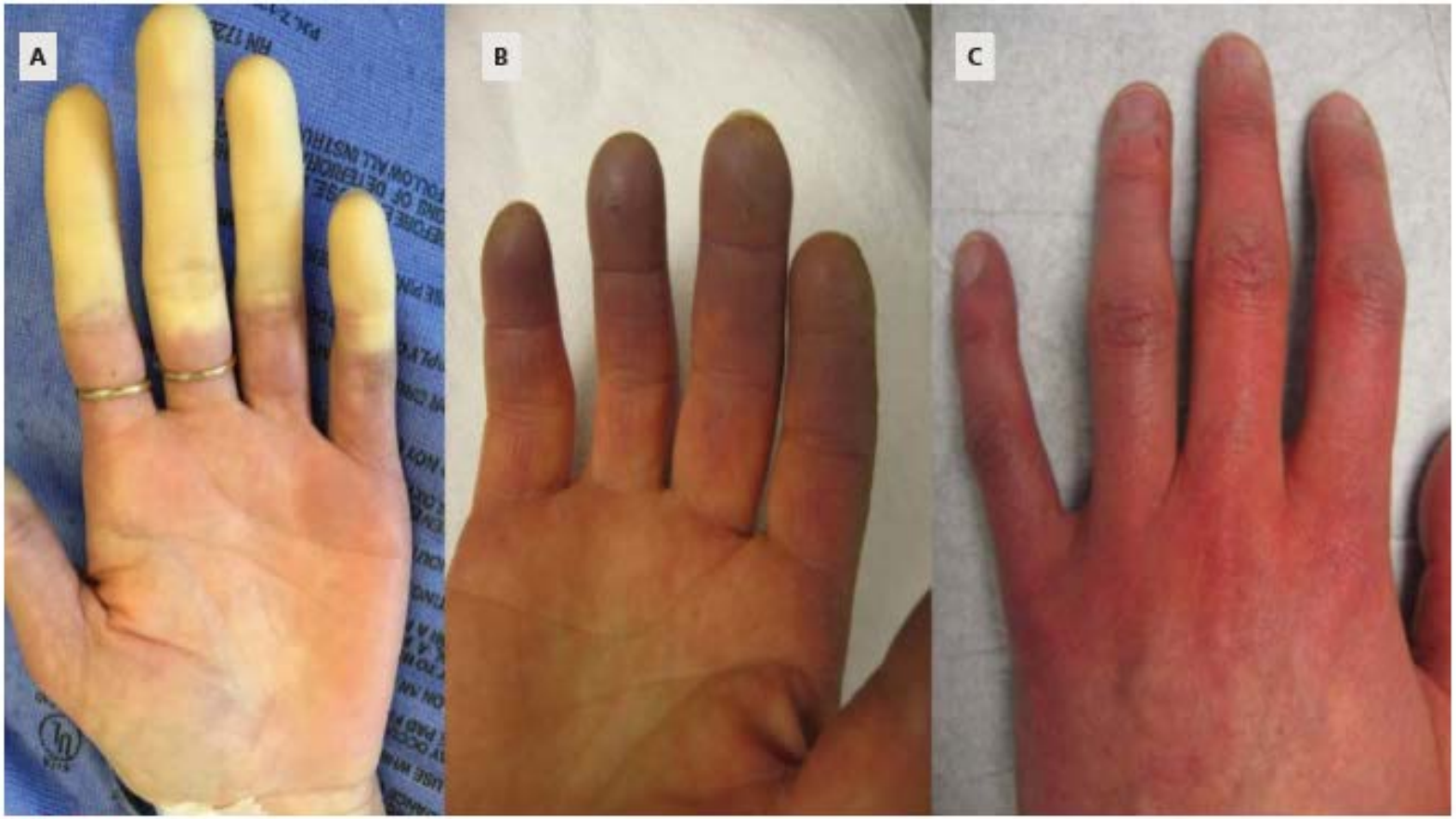
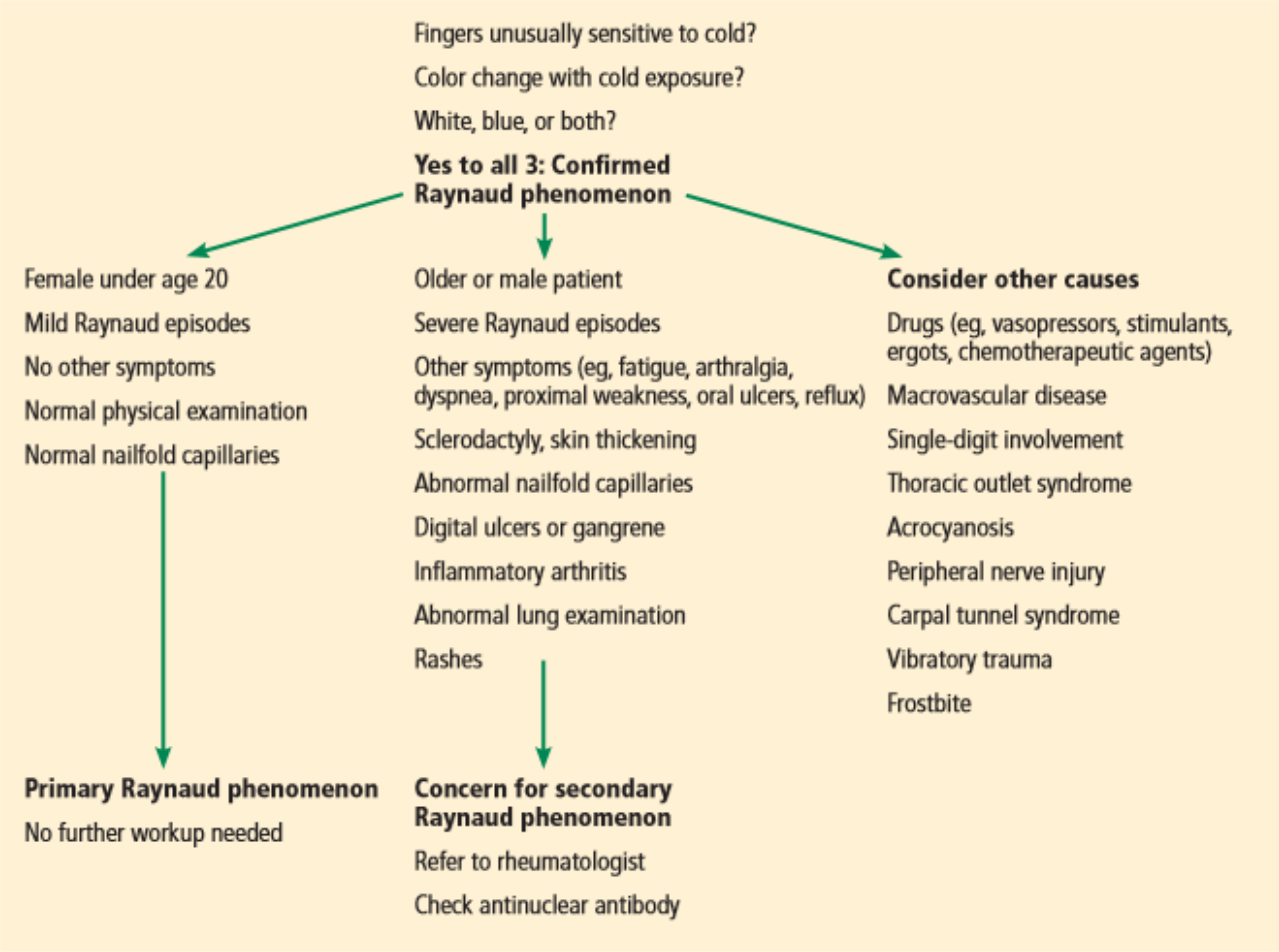


FIGURE 1. (A) White digits with intense vasoconstriction in Raynaud phenomenon; (B) blue digits with hypoxemic venous stasis; (C) red digits with hyperemic reperfusion.

Shapiro & Wigley. Cleveland Clinic Journal of Medicine (2017) 83:797-804

Raynauds – may be primary or secondary to autoimmune disease



Shapiro & Wigley. Cleveland Clinic Journal of Medicine (2017) 83:797-804

Digital pits/ulcers

Fig. 138.4 Digital pits on the fingertip of a patient with scleroderma.

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Raynauds Treatment

TABLE 1

Stepwise therapy for Raynaud phenomenon

Step 1	Cold avoidance
	Emotional regulation
Step 2	Dihydropyridine calcium channel blocker in maximum tolerated dose
	Phosphodiesterase type 5 (PDE5) inhibitor substituted for or added to a calcium channel blocker
Step 3	Topical nitrate (contraindicated in a patient already taking a PDE5 inhibitor due to risk of hypotension)
	Prazosin
	Fluoxetine
	Pentoxifylline
	Atorvastatin
For acute digital crisis	Calcium channel blocker plus topical nitrate or calcium channel blocker plus PDE5 inhibitor
	Intravenous prostacyclin
	Localized digital sympathectomy

Shapiro & Wigley. Cleveland Clinic Journal of Medicine (2017) 83:797-804

Telengiectasias

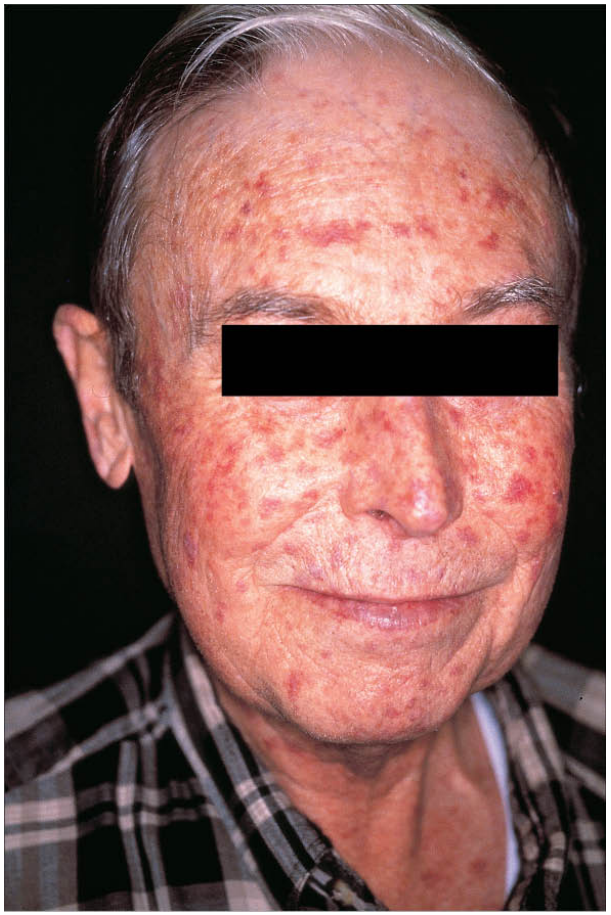

Fig. 138.11 Extensive facial telangiectasia in a man with limited cutaneous SSc.

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GERD

- Education about standard non-drug measures
  - Small, frequent meals
  - Avoiding food/liquid intake 2 hrs before bedtime
  - Elevating the head of the bed at night
  - Eliminating foods that aggravate symptoms
- PPI – mainstay in treatment; may use H2 blocker, but can be less effective

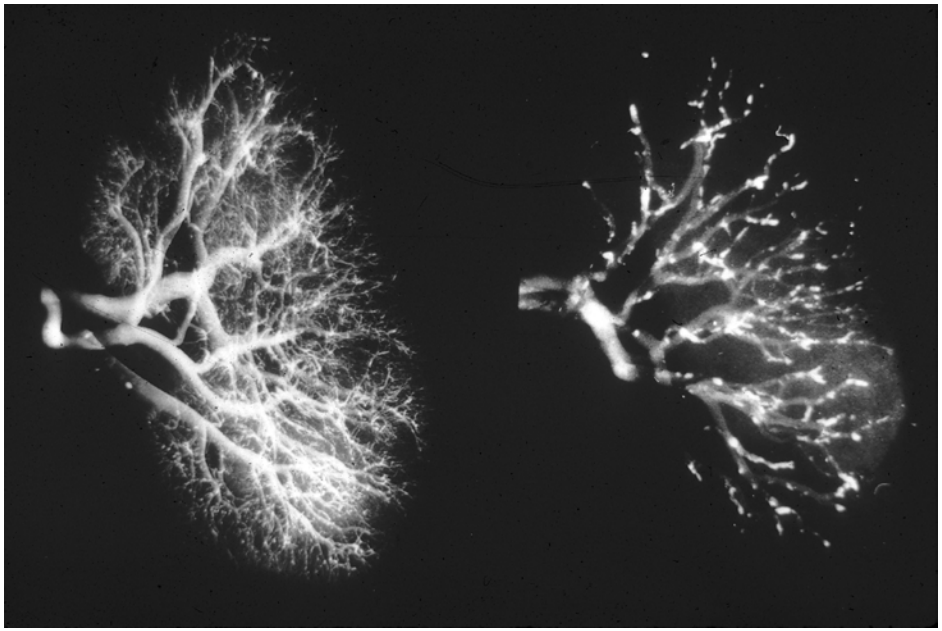
Shah & Wigley. Mayo Clin Proc. (2013). 88(4):377-393

Steroids and Scleroderma

- Though low dose steroids may play a small role in improving pain, they generally carry significant risk for renal crisis at higher doses.

Scleroderma Renal Crisis

- RISK FACTORS:
  - diffuse skin disease
  - tendon friction rubs
  - the presence of anti-RNA polymerase III Ab
  - new-onset anemia
  - pericardial effusion.
  - **Prednisone >15mg per day**
- Clinical Presentation
  - New hypertension >150/85 mmHg or significant increase over patient's baseline measured at least 2x over 24hours.
  - Rising creatinine
  - Proteinuria, and an active urinary sediment including RBCs and/or RBC casts
  - MAHA(when in doubt think TTP)
    - **Schistocytes- Critical to the diagnosis**
    - **Increased** concentration of serum indirect bilirubin
    - **Increased** LDH
    - **Decreased** serum haptoglobin.
    - Consider ADAMTS13 antibody test which will be **negative**
  - Retinal pathology consistent with malignant hypertension
- Treatment
  - ACEi



Typical return visit for patient with scleroderma

- Subjective: Any changes
  - Breathing/Exercise Capacity
  - Raynaud's Phenomenon
  - Reflux disease or other GI issues
  - Pain
- Objective
  - Blood Pressure: Note any changes with historical values(ANY SUDDEN INCREASE of 20-30 point systolic or 10-15 diastolic warrants a call).
  - Cardiopulmonary Exam
  - Evaluate fingers for digital ischemia
- Assessment
  - Appreciate how they are doing globally. Trends in Weight, Functional Capacity, Etc. Are they off the curve?
- Plan
  - Labs: CBC to track blood loss and side effects of medications. CMP to watch for renal issues or hepatotoxic side effects of medications.
  - PFT's, 6 minute walk and Echocardiogram at least once a year.

Myositis

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Case

- 20 y/o male with no significant past medical history was transferred from an outside hospital for concern for ALS
- Four months prior, he started having diffuse body aches, nausea, vomiting, decreased energy
- He had progressive muscle weakness for 4 months with > 20 lb weight loss and difficulty swallowing
- Prior to 4 months ago, he was healthy and worked in manufacturing

Case

- Upon arrival to our hospital:
  - Muscle strength was 4/5 in the proximal upper and lower extremities and with neck extension/flexion
  - Erythema was noted over the dorsal MCPs and around the cuticles. Erythematous patches were noted on the elbows
- Prior imaging:
  - Normal MRI of brain and C-spine

Case

- What would you do next?

Case

- Work-up
  - Labs: CK 168 Aldolase 8.6
  - EMG: inflammatory myopathy – more prominent in the upper limbs
  - Muscle biopsy: perivfascicular preponderance of structural abnormalities & extensive peri-mycelial perivascular inflammatory collections → consistent with dermatomyositis

Case

- Treatment
  - High dose glucocorticoids (1 g solumedrol IV x 3 days)
  - IVIG
  - DMARD therapy
    - MTX

Idiopathic inflammatory myositis

- Idiopathic inflammatory myositis/myopathies (IIM) are characterized by inflammatory infiltration of the skeletal and sometimes cardiac muscle.

- IIM manifests with muscle weakness, and often associated with a series of extra-muscular manifestations.

Lazarou et al. J Rheumatol. 2013 May;40(5):550-64

Idiopathic inflammatory myositis

- Worldwide incidence of inflammatory myopathies ranges from 1.16 to 19/million/year; Prevalence from 2.4 to 33.8/100,000 *(1)*
- USA incidence of adult IIM 66/million/year; Prevalence 14 to 17.4/100,000 *(2).*
- F>M, 2:1
- 40-50 years

1. *Rheumatology (Oxford). 2015 Jan;54(1):50-63.*
2. *BMC Musculoskelet Disord. 2012 Jun 15;13:103,2474-13-103.*

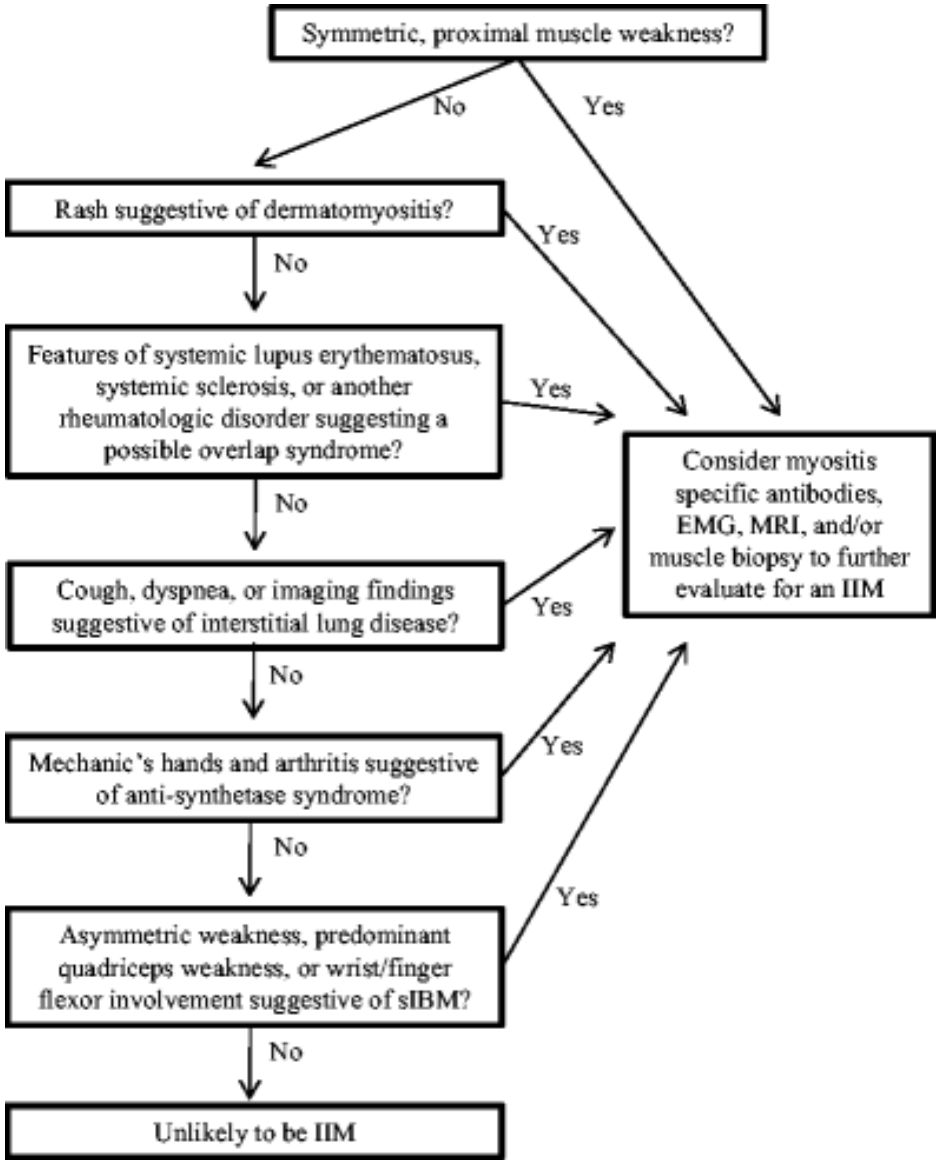
Classification

- Idiopathic inflammatory myopathies (adult forms) include:
    1. Dermatomyositis (DM)
    2. Polymyositis (PM)
    3. Immune mediated necrotizing myopathy (IMNM)
    4. Inclusion body myositis.
    5. Overlap myositis

- DM sine dermatitis (no skin rash, typical histology)
- Amyopathic DM (no muscle disease, typical skin rash)
- Non specific myositis (non specific histology)

Clinical features

- Proximal symmetrical muscle weakness
- Myalgia in 25-50%, mild
- Extra-muscular features:
  - Skin lesions
  - Lung disease
  - Esophageal disease
  - Cardiac disease
  - Malignancy



Leverenz et al. Clin Rheumatol (2016) 35: 1541

Dermatomyositis

Heliotrope rash in Dermatomyositis

Courtesy ACR image bank

Typical rash of dermatomyositis

Specific skin manifestations in dermatomyositis

- *Photosensitive*

A. *Heliotrope rash*

B. *Shawl sign*

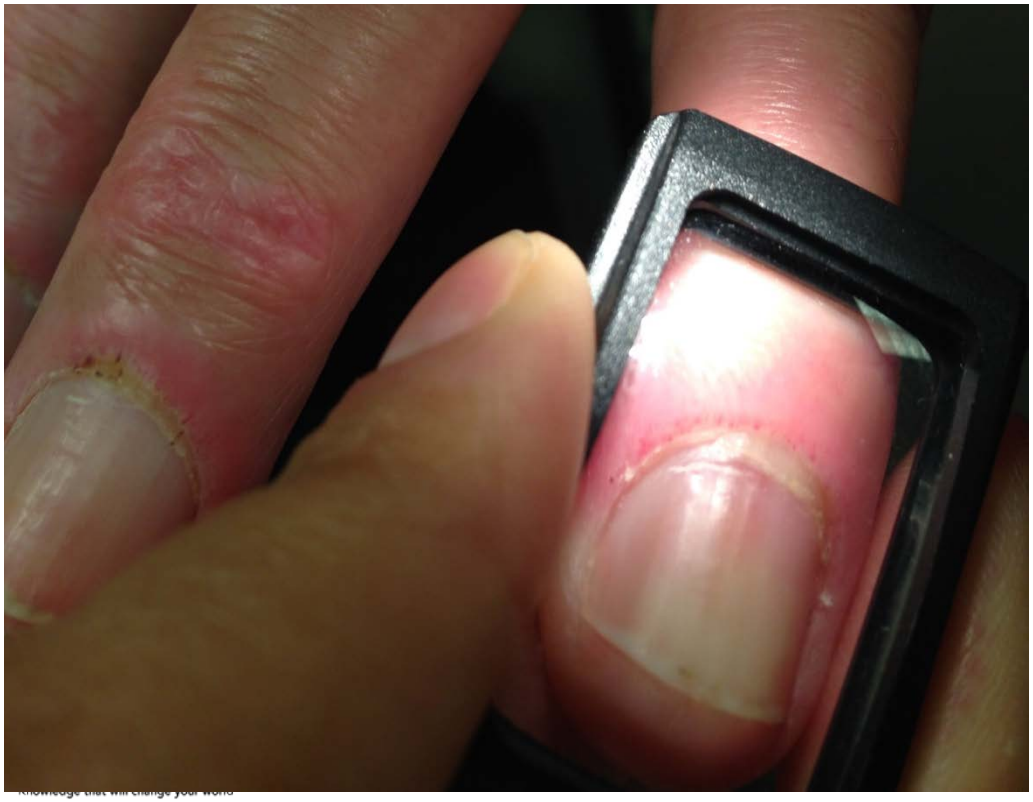
C. *Gottron sign*

D. *Mechanic's hands*

Lazarou et al. J Rheumatol. 2013 May;40(5):550-64.

Dermatomyositis

- Subcutaneous calcinosis (juvenile DM)
- Periungual telangiectasia (bottom)



Anti-synthetase antibodies

- Antisynthetase syndrome is a distinct entity – presence of anti-ARS antibodies, myositis, ILD, fever, arthritis, Raynaud's phenomenon and mechanic's hands.

Image: Courtesy ACR image bank

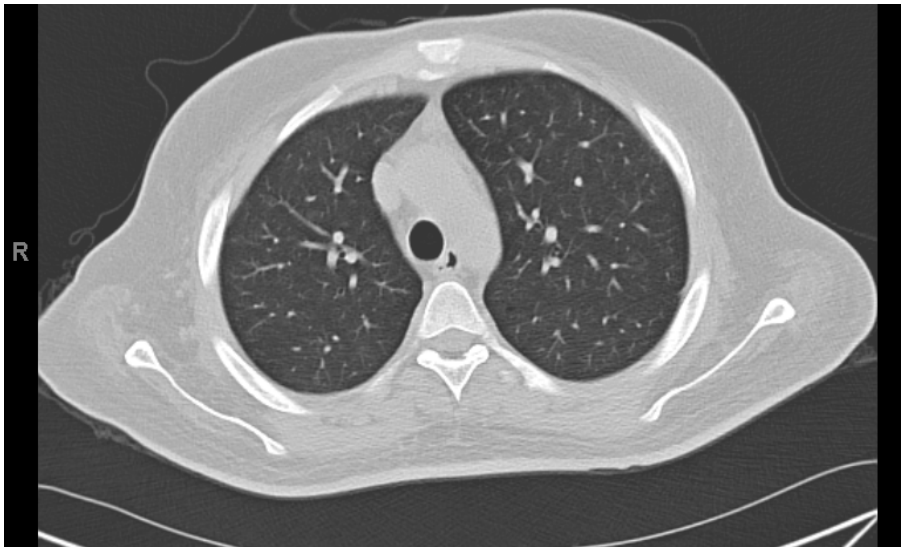
Myositis associated ILD

The prevalence of ILD in PM/DM patients has been reported to be 5-46%.

In patients with anti synthetase syndrome the prevalence of ILD has been reported to be >50%.

Presence of ILD in these patients can significantly affect the prognosis.

Takada et al. Autoimmunity. 2005 Aug;38(5):383-92.
Johnson C et al. Assessment of Mortality in Autoimmune Myositis With and Without Associated Interstitial Lung Disease. Lung. 2016 May 11.



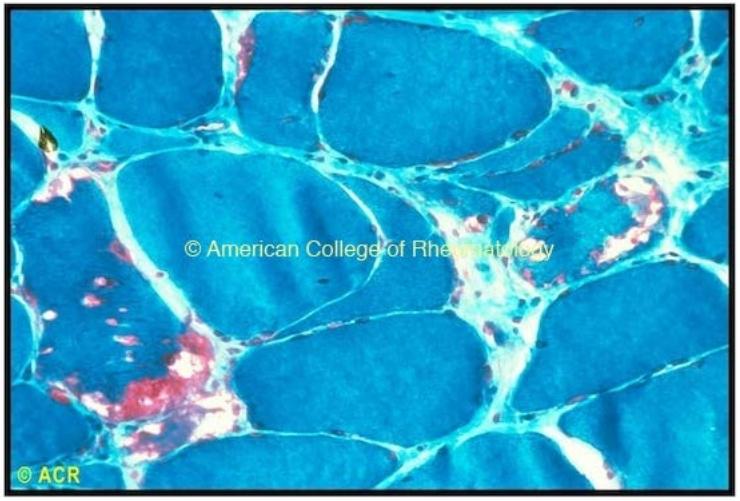
Polymyositis and Dermatomyositis

Diagnosis

- Laboratory abnormalities – elevation of CK, aldolase, LDH, AST/ALT, CK-MB
- Myositis specific antibodies and myositis associated antibodies
- Characteristic Electromyographic (EMG) findings showing myopathic changes (irritable myopathy)
- Magnetic resonance imaging (MRI)
- Histopathology
- PET scan

Inclusion body myositis

- >50 years old
- M>F
- Asymmetric muscle weakness
- Both proximal and distal muscle weakness
- Atrophy of quadriceps and forearms, facial and axial muscles
- Dysphagia
- CK is normal or slightly elevated
- Inclusion bodies on the biopsy



Colafrancesco S, Priori R, Valesini G. Best Pract Res Clin Rheumatol. 2015 Dec;29(6):810-25

Amato AA, Barohn RJ. 2009 Nov;80(11):1186-93

Immune-mediated necrotizing myopathy

- Patients treated with statins who do not recover following drug withdrawal
- Subacute or acute onset
- Severe muscle weakness
- Very high serum CK values
- Histology – predominant necrosis, lack of significant inflammation
- Anti-HMGCR antibodies

Overlap myositis

- Scleroderma
- SLE
- Sjogren's syndrome
- Rheumatoid arthritis

Differential diagnosis

- Endocrine
  - Hypothyroidism
  - Cushing's syndrome
- Rhabdomyolysis
  - Crush injuries
  - Seizures
  - Alcohol abuse
  - Heavy exertion
  - Surgery
  - Malignant hyperthermia
- Myocardial injury
- Infections
  - Viral – Influenza, HIV, CMV, EBV, Coxsackie
  - Bacterial – pyomyositis, lyme myositis
  - Fungal
  - Parasitic – trichinosis, toxoplasmosis

Differential diagnosis

- Drugs
  - Illicit drugs – cocaine, heroin
  - Alcohol
  - Corticosteroids
  - Other – colchicine, antimalarials, statins, penicillamine, zidovudine
- Myotonic disorders (myotonic dystrophy type I/II or myotonia congenital)
- Muscular dystrophies (Duchenne's or Becker's disease)
- Metabolic myopathies (carbohydrate, lipid or purine metabolism)
  - Exercise induced myalgia

Clin Rheumatol. 2016 Apr 4. [Epub ahead of print]

Causes of creatine kinase levels greater than 1000 IU/L in patients referred to rheumatology.

Leverenz D[1], Zaha O[1], Crofford LJ[1], Chung CP[2].

Author information

Abstract

Patients with severely elevated creatine kinase (CK) concentrations are commonly referred to rheumatologists to evaluate for the presence of an idiopathic inflammatory myopathy (IIM). However, no studies have evaluated the frequency with which IIMs are encountered in this clinical scenario. The Vanderbilt Synthetic Derivative, a de-identified copy of over 2 million patient records, was searched to identify adult patients with a CK greater than 1000 IU/L who had been evaluated by a rheumatologist. Each patient was assigned a diagnosis using a pre-determined algorithm. The records were then reviewed for pertinent demographic data and clinical characteristics. A total of 192 patients were included for analysis. Of these patients, 105 (55 %) were diagnosed with an IIM. The non-IIM causes were drug/toxin exposure (n = 16, 8 %), infection (n = 12, 6 %), trauma (n = 10, 5 %), myocardial injury (n = 5, 3 %), hypothyroidism (n = 4, 2 %), muscular dystrophy (n = 4, 2 %), neuropsychiatric disorder (n = 3, 2 %), metabolic myopathy (n = 2, 1 %), idiopathic CK elevation (n = 11, 6 %), and other diagnoses (n = 20, 10 %). Several characteristics were found to be significantly different between IIM and non-IIM cases. In particular, patients with an IIM were more likely to be female, have a positive ANA, have interstitial lung disease, and have proximal, symmetric weakness. This study found that approximately half of patients referred to our division of rheumatology with a CK greater than 1000 IU/L were diagnosed with an IIM. Given the importance of prompt diagnosis and treatment of these disorders, rapid assessment by the consulting rheumatologist for these patients is recommended.

KEYWORDS: Creatine kinase; Dermatomyositis; Idiopathic inflammatory myopathies; Myositis; Polymyositis

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Knowledge that will change your world

Myositis and associated cancers

Dermatomyositis

- Western countries – **ovarian, lung**, pancreatic, gastric, colorectal cancers, melanoma
- Asian – **nasopharyngeal cancer**

Polymyositis

- Has strongest association with non-Hodgkin lymphoma, lung, bladder cancer

- Adenocarcinoma is most common
- Meta-analysis shows that the risk of malignancy remains for many years after diagnosis of myositis but is the highest in the first year.

Screening for underlying malignancy

- Screening for underlying malignancy in patients with new diagnosis of inflammatory myositis is mandatory
- No consensus on how extensive screening work-up should be
- Careful history, complete physical exam, appropriate lab tests, age-appropriate cancer screening
- Risk of malignancy persists up to 5 years after initial diagnosis

Idiopathic Inflammatory Myositis

- Treatment of PM/DM depends on:
  - The severity of myositis
  - Presence of myositis specific antibodies
  - Presence of extra-muscular features:
    - Interstitial lung disease
    - Skin rash
    - Cardiac involvement
    - Dysphagia

Conventional treatment

- Glucocorticoids
  - Prednisone 1mg/kg/day
  - Pulse intravenous methylprednisolone - severe muscle weakness, ulcerative DM skin lesions, severe dysphagia, rapidly progressive interstitial lung disease (ILD)

- Steroids sparing agents
  - Methotrexate
  - Azathioprine (1.5 – 2.5 mg/kg/day)
  - Mycophenolate mofetil
  - Leflunomide
  - Adrenocorticotropic (ACTH) hormone gel
  - Rituximab
  - IVIG
  - Calcineurin inhibitors (cyclosporine, tacrolimus) – usually add-on therapy

Valiyil et al. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1328-34.

Oddis CV. J Intern Med. 2016 Apr 20.

Summary

- Idiopathic Inflammatory myositis is a group of rare, heterogenous disorders.
- Wide differential diagnosis
- Early diagnosis and prompt initiation of treatment can certainly help in improving the overall survival rate
- Glucocorticoids is the mainstay treatment.
- Very frequently steroid sparing immunosuppression, alone or in combination is required.

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Thank you! Questions?

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Knowledge that will change your world

POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS

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2019 RHEUMATOLOGY UPDATE FOR PRIMARY CARE AND HOSPITAL MEDICINE
August 24th 2019

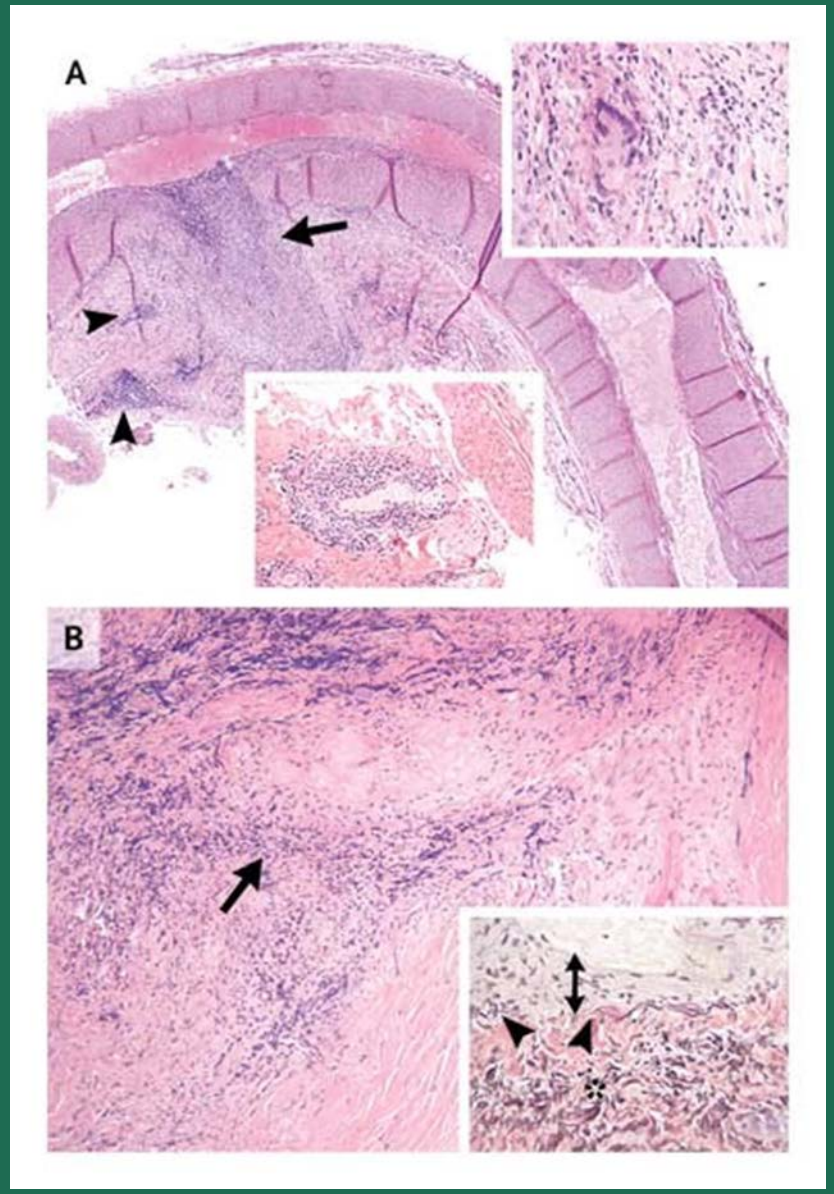
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
VA U.S. Department of Veterans Affairs

DISCLOSURES

- None

- 72 yo Veteran
- Seen in March 2018
  - 2 months of sore throat, no URI Symptoms
  - Initial evaluation - amoxicillin + prednisone 10 mg/day – resolution
  - Recurrence when prednisone completed
  - Pain progressed to involve jaw, ears, both frontotemporal regions
  - 3 weeks prior – ESR is 60 mm/h
  - 1 weeks before evaluation – horizontal diplopia
- Physical exam: uncomfortable, scalp/neck tenderness on palpation. Ocular movements intact

- Started on prednisone 60 mg/day
- Scheduled for temporal artery biopsy concurrently – happened 3 days after visit
- Rapid resolution of all symptoms after prednisone initiation


A
B

PMR & GCA

- Different manifestations of shared disease process
- PMR: bursitis/periarthritis/arthritis version
- GCA: Vasculitic version plus or minus PMR

POLYMYALGIA RHEUMATICA – ILLNESS SCRIPT

- Age > 50 yo – Peak incidence 70-80
- Higher incidence/prevalence in Caucasians/Whites – however, can occur in all races/ethnic groups
- Symmetrical aching and stiffness about the shoulders, hip girdle, neck, and torso

POLYMYALGIA RHEUMATICA – ILLNESS SCRIPT

- Gelling or morning/inactivity stiffness is severe and disabling
- Peripheral arthritis is common
- Pain on palpation and restricted range of motion muscle groups in shoulder and hip girdle
- Elevation in ESR<CRP common (70-80%) but not universal

GIANT CELL ARTERITIS – CLASSICAL ILLNESS SCRIPT

- Universal over age 50
- New onset headaches/scalp tenderness
- Jaw claudication
- Visual disturbance: blurry/vision loss, diplopia, hallucinations

GIANT CELL ARTERITIS – ADDITIONAL PRESENTATIONS

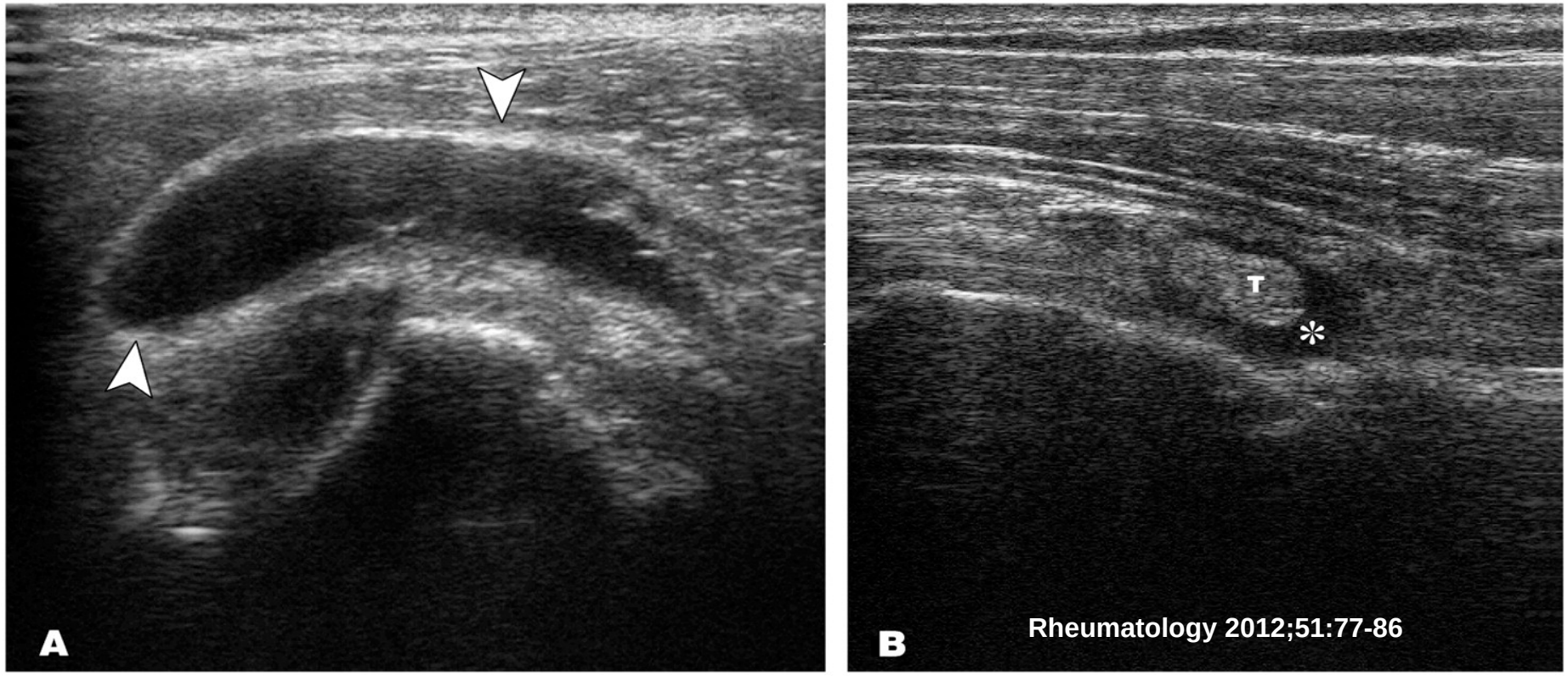
- FUO-like: fever, weight loss, malaise
- Aortitis/Vasculitis: chest pain, abdominal pain, limb claudication
- PMR symptoms can overlap with any of the presentations
- Elevation in ESR<CRP common (90%) but not universal

DIFFERENTIAL DIAGNOSIS PMR & GCA

Polymyalgia Rheumatica	Giant Cell Arteritis
Seronegative inflammatory arthritis	Other vasculitides: WG, MPA, PAN, etc
Fibromyalgia	Atherosclerosis
Cervical and hip osteoarthritis	Dental problems
Hypothyroidism	Subacute thyroiditis
Viral and chronic infections	Infections
Polymyositis	Trigeminal neuralgia
Cancer	Cancer
Amyloidosis	Amyloidosis
Parkinson’s disease	Non-arteritic ischemic optic neuropathy (NAION)
	Viral infections: Zoster

DIAGNOSTIC WORKUP PMR

- Clinical diagnosis
- Increased inflammatory markers helpful
- Ultrasound can be supportive



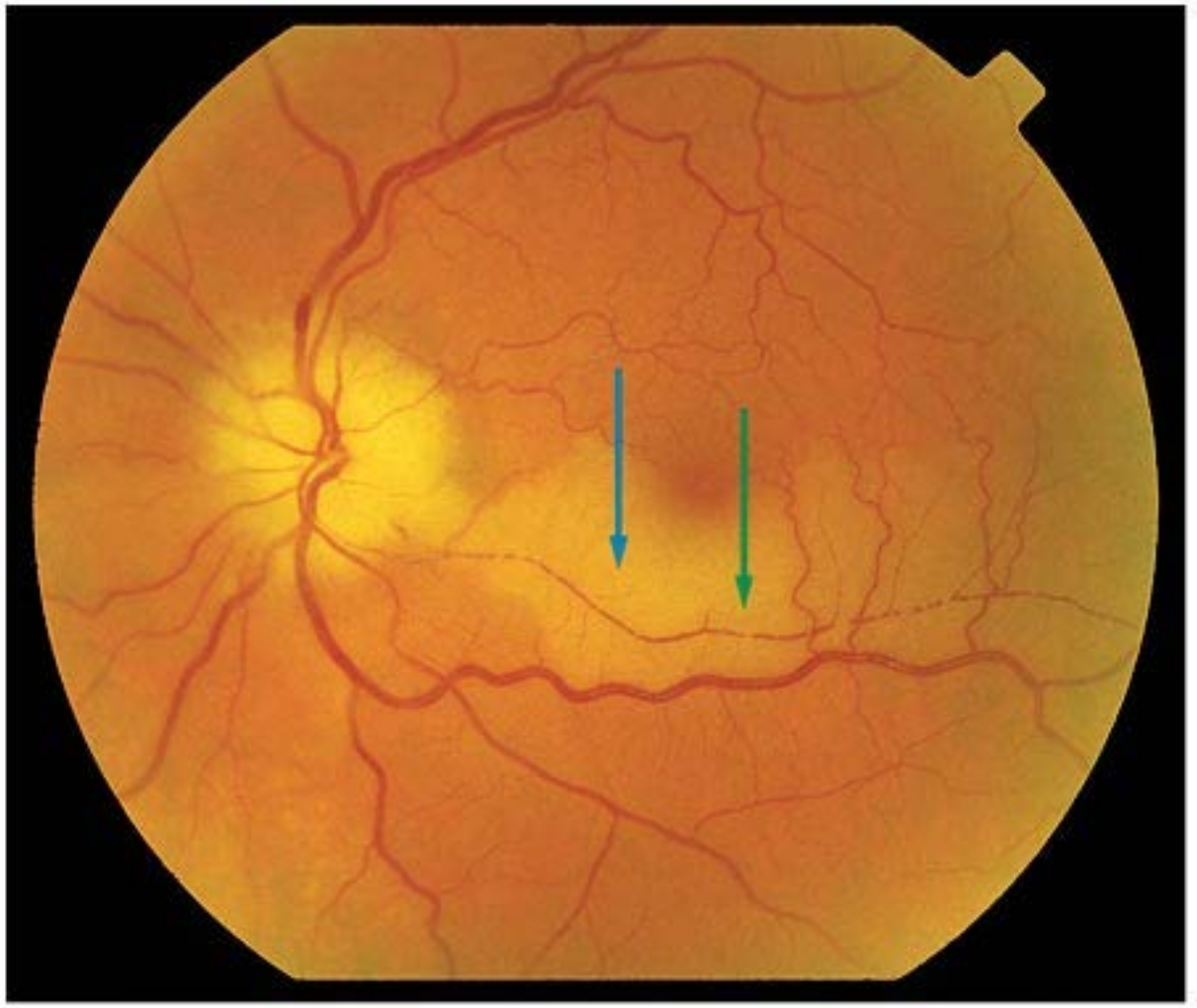
US of the shoulder in a patient with PMR showing (A) subdeltoid bursitis and (B) tenosynovitis with effusion (*) circumferential to the biceps long head tendon (T).

DIAGNOSTIC WORKUP GCA – TEMPORAL ARTERY BIOPSY

- Should be pursued for diagnosis when possible
- Some patients (~40%) will not have any TA involvement
- Obtain a generous segment of the artery for study (> 1 cm)
- Do not delay therapy for biopsy

DIAGNOSTIC WORKUP GCA - OPHTALMOLOGY

- If cranial symptoms involve ophthalmologist early
- Vision loss in GCA is irreversible
- Disk edema (cupping)/Arteritic ischemic optic neuropathy (ANION)



ADDITIONAL IMAGING TECHNIQUES

- Ultrasound can be helpful in guiding biopsy/supporting diagnosis

- CT angiography/MRI/PET scan useful for evaluation of aortitis/peripheral vasculitis

CASE # 2

- 68 yo AA Veteran
- 2 month of new onset headaches, bilateral shoulder pain, malaise, blurry vision
- On physical exam: diffuse muscle and bone pain on palpation
- Labs: Hg 9 mg/dL, Plt 135 K, Cr 2.6 (from baseline 1.4), Ca 11.5, UA + 2 protein

CASE # 2

- Started on prednisone 1 mg/kg with improvement in symptoms
- Scheduled for temporal artery biopsy: negative
- SPEP, UPEP, IFE, K/L chains: serum IgG monoclonal protein, K/L > 100, + Urine monoclonal protein
- Diagnosis: multiple myeloma

INITIAL TREATMENT CONSIDERATIONS FOR PMR

- Treatment goal is symptom relief
- Glucocorticoids (still) are the mainstay of therapy
- Doses of glucocorticoids needed are lower than in GCA
- Typical stating dose of prednisone is 15 mg (range 7.5-20 mg)

TREATMENT CONSIDERATIONS IN PMR

- Response is usually rapid
- Lack of response → reconsider diagnosis or ? GCA
- If response, initial dose should be continued until symptoms resolve and continued for 2-4 weeks
- Progressive taper of 2.5-5 mg at a time every 2-4 weeks

COMMON QUESTIONS DURING PMR TREATMENT

- Symptoms are resolved, but sed rate/CRP still high?
  - Reconsideration of diagnosis, GCA?
  - Do not go back up on GCs, but do not taper further/slower taper

- Symptoms return when tapering GCs, now what?
  - If prednisone daily dose ≤ 5 mg/day might need prolonged therapy, very slow taper (by 0.5-1 mg/month)
  - If prednisone dose > 5 mg/day consider steroid sparing agent (Methotrexate)

INITIAL TREATMENT CONSIDERATIONS FOR GCA

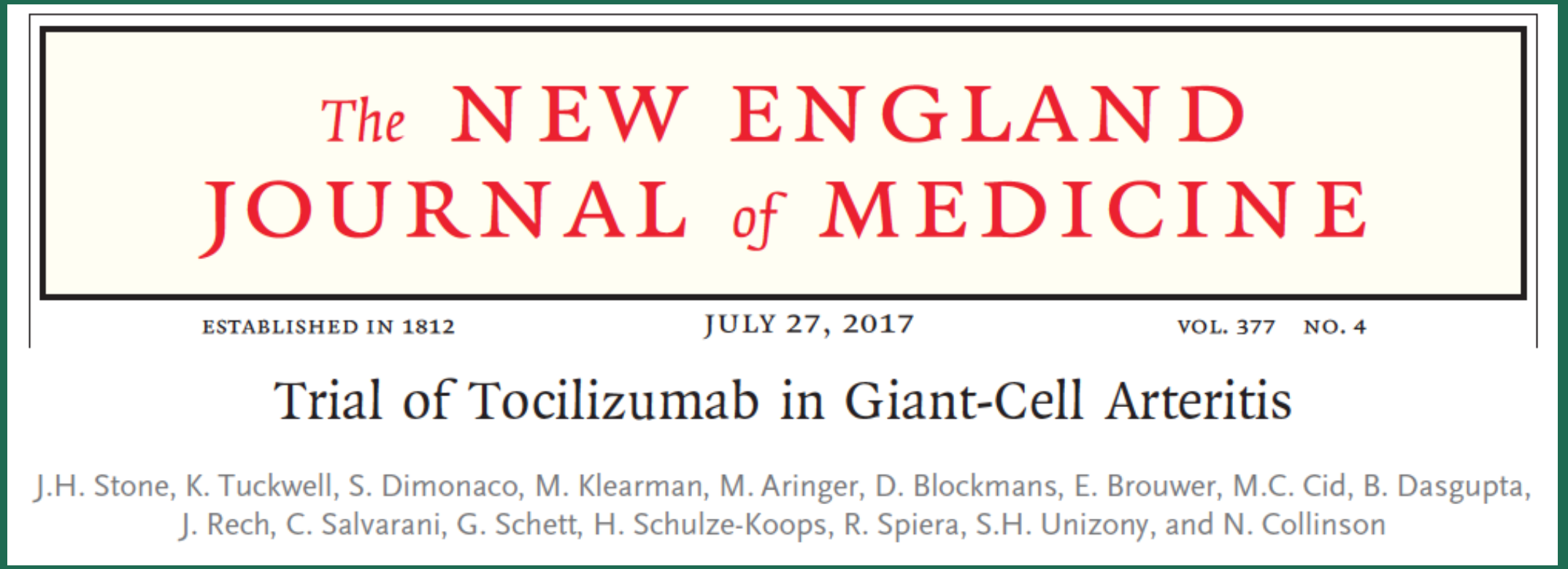
- Treatment goal is symptoms relief and prevention of vascular events
- If suspicion is high DO NOT wait for temporal artery biopsy
- Initial treatment strategy:
  - No vision loss/deficit or vascular event = 1 mg/kg/day up to 60 mg/day of prednisone
  - Vision loss/deficit or vascular event = pulse dose high dose IV GCs x 3 days followed by treatment above

CONVENTIONAL TREATMENT APPROACH FOR GCA

- After resolution of symptoms and ESR/CRP normal, continue initial GC dose for 2-4 weeks
- Taper of GC by 10 mg/day every 2-4 weeks until 20 mg/day
- Taper of GC by 5 mg/day every 2-4 weeks until 10 mg/day, then follow scheme for PMR (HIGH RELAPSE RISK PERIOD)
- If relapse
  - Vascular or vision loss/deficit: increase back to 1mg/kg of prednisone
  - If PMR symptoms: increase by 5-10 daily mg of prednisone

CONSIDERATION/PRECAUTIONS DURING HIGH DOSE GC TREATMENT FOR GCA

- Infection risk/PJP
- Weight gain/Edema
- Depression/Psychosis
- Hyperglycemia
- Osteoporosis
- Adrenal suppression
- Hypertension/Hyperlipidemia/CV risk
- Increased appetite
- Sleep disturbance

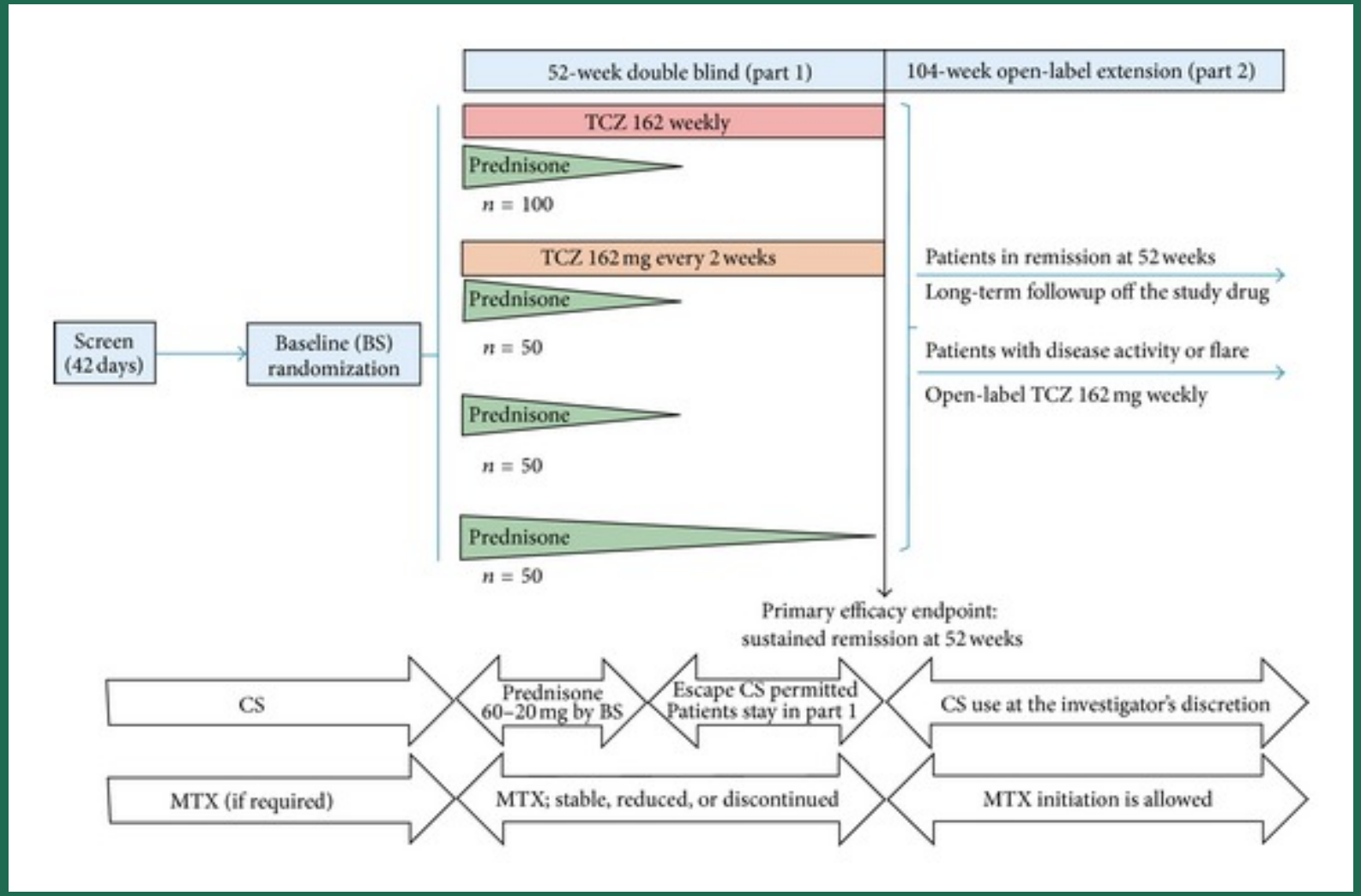


- Randomized, double-blind, placebo-controlled, phase 3 trial
- Research question: does tocilizumab result in higher rates of sustained glucocorticoid-free remission in giant cell arteritis than placebo through a period of 52 weeks?

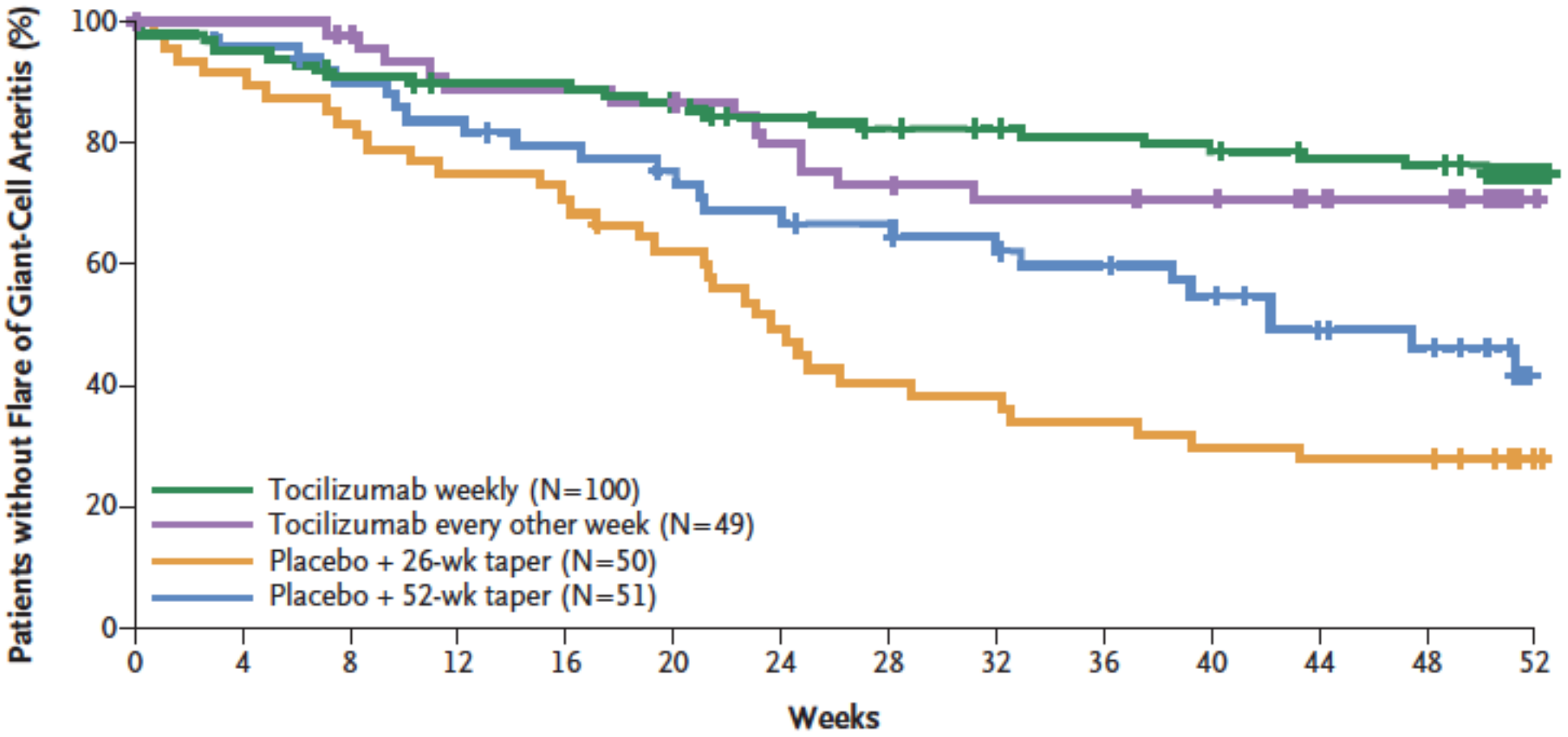
STUDY OUTCOMES

- Primary: % of patients on sustained prednisone-free remission (no flare and CRP < 1 mg/dL) from week 12-52
  - Flare: recurrence signs/symptoms of GCA or ESR > 30 attributable to GCA + necessity for an increase in the prednisone dose
- Secondary outcomes: cumulative prednisone dose, QOL
- Safety

TOCILIZUMAB IN GIANT CELL ARTERITIS TRIAL



Unizony S. International Journal of Rheumatology Volume 2013, Article ID 912562



No. at Risk

Tocilizumab weekly	100	93	88	85	85	81	77	74	71	69	67	64	63	5
Tocilizumab every other week	49	47	45	40	40	39	35	32	30	30	29	26	24	2
Placebo + 26-wk taper	50	44	40	36	34	29	23	19	18	16	14	13	13	3
Placebo + 52-wk taper	51	48	44	41	38	35	32	30	28	25	22	17	15	0

Figure 2. Time to First Flare after Clinical Remission of Giant-Cell Arteritis in All Patients.

GIACTA TRIAL CONCLUSIONS

- Both tocilizumab regimens were (very) superior to placebo with respect to sustained remission (absence of flares) and prednisone cumulative dose

- Adverse events where similar across groups, expect neutropenia ↑ tocilizumab (4%)

TREATMENT APPROACH FOR GCA AFTER GIACTA (TOCILIZUMAB) STUDY

- Initial treatment approach is the same - high dose GCs
- When possible, I follow GIACTA study paradigm after initial treatment
- Insurance/coverage/logistic issues with tocilizumab can be complex → rheumatologist needed at this stage
- Tocilizumab allows for faster GC tapering – off by 3-6 months

MY PRACTICE POINTERS (1)

- Racial/Ethnic considerations for GCA are important
  - Quite rare in African-Americans and non White/Caucasian groups
  - Consider alternative diagnoses more strongly
  - Less inclined to empiric high dose GCs
- PMR also has a racial/ethnic higher frequency in Whites/Caucasians but not nearly as pronounced as GCA

MY PRACTICE POINTERS (2)

- Sedimentation rate has age /gender adjustment
  - Men = Age/2
  - Women = (Age/2) + 10
- GCA is not only a cranial disease, older adult with FUO/high ESR/CRP and:
  - Unexplained chest pain/cough
  - Unexplained abdominal pain
  - Unexplained extremity pain or claudication / pulse deficit-assymetry

CONCLUSIONS

- Both PMR and GCA are disease of older adults
- Elevated inflammatory markers are supportive of diagnosis, not universal
- Both are more prevalent (GCA>>>PMR) in Caucasians of Northern European descent
- In both conditions consideration of differential diagnosis is paramount

CONCLUSIONS

- PMR largely a clinical diagnosis
- GCA is supported by histopathology, novel techniques are in development
- Glucocorticoids are still the preferred initial treatment in both
- IL6 inhibition (tocilizumab) has markedly improved outcomes in GCA

THANKS FOR YOUR ATTENTION

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