MAYO CLINIC

Mayo Clinic Rheumatology Update

April 17-18, 2015

Sawgrass Marriot
Ponte Vedra Beach, Florida

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CME Activity Description

This two-day course provides internists and general practitioners with an up-to-date focus on rheumatologic disorders. This course aims to help participants gain a better understanding of how to recognize and diagnose common rheumatologic disorders, as well as identify which patients can be managed within their own practice and which need referral to a specialist. Residents and fellows will have the opportunity to participate by submitting original studies for poster presentations. This course is seeking to offer optional CME and self-assessment credits available online after the course.

CME Activity Objectives

Upon conclusion of this program, participants should be able to:
• Review basic clinical and therapeutic aspects of rheumatologic conditions
• Improve interpretation skills for common rheumatology laboratory testing
• Identify patients that can be managed in primary care practices and patients that need to be referred to rheumatology
Attendance at this Mayo course does not indicate nor guarantee competence or proficiency in the performance of any procedures which may be discussed or taught in this course.

Intended Audience

This course aims to educate primarily internists and general practitioners, but will be applicable to Rheumatologists, as well as allied health staff working in the afore mentioned areas.

Continuing Education Credit

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Faculty evaluation forms were offered to a sampling of the registrants. Completed faculty evaluation forms should be returned to the registration desk at the conclusion of the CME activity. If you wish to participate in evaluating the faculty, please stop at the registration desk to inquire if extra evaluation forms are available.

Your feedback is very important to us and will be used for planning future programs, as well as identifying faculty strengths and opportunity for growth.

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Faculty

Course Director(s)

Andy Abril, M.D.; Benjamin Wang, M.D.

Guest

Guest Faculty
Gurjit S. Kaeley, M.D.
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John M. Davis, III, M.D.
W. Leroy Griffing, M.D.
Thomas G. Mason, II, M.D.
Lester E. Mertz, M.D.
Clement J. Michet, M.D.
Kevin G. Moder, M.D.
Thomas D. Rizzo, Jr., M.D.
Jason C. Sluzevich, M.D.
Benjamin Wang, M.D.
Kenneth J. Warrington, M.D.

Faculty, Planning Committee and Provider Disclosure Summary

Mayo Clinic Rheumatology Update
April 17-18, 2015

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Relevant financial relationship(s) with industry:

Name	Nature of Relationship	Company
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Leroy Griffing, M.D.	Grant/ Research	Bayer HealthCare

No relevant financial relationship(s) with industry:

Name	
Florentina Berianu, M.D.	Clement J. Michet, M.D.
Ronald Butendieck, M.D.	Kevin G. Moder, M.D.
Kenneth T, Calamia, M.D.	Thomas D. Rizzo, Jr., M.D.
Gurjit S. Kealey, M.D.	Jason Sluzevich, M.D.
Thomas G. Mason, M.D.	Benjamin Wang, M.D.
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References to off-label and/or investigational usage(s) of pharmaceuticals or instruments in their presentation:

Name	Manufacturer/Provider	Product/Device
Kenneth T. Calamia, M.D.	Anti TNF agents	Multiple

Rheumatology Update

Marriott Sawgrass, Ponte Vedra Beach, Florida

April 17-18, 2015

Friday, April 17, 2015	
7:15 a.m.	Continental Breakfast and Registration
7:45	Introductions/Pre-Test
8:00	Approach to the Patient with MSK Symptoms Kevin G. Moder, M.D.
8:30	Fibromyalgia Benjamin Wang, M.D.
9:00	Rheumatoid Arthritis-Preventive Care for RA Patients John M. Davis, III, M.D.
9:30	Questions and Answers
9:45	Break
10:00	Crystaline Arthropathies Benjamin Wang, M.D.
10:30	Gout Management W. Leroy Griffing, M.D.
11:00	Back Pain Thomas D. Rizzo, Jr., M.D.
11:30	Questions and Answers
11:45	Lunch
12:45 p.m.	Rheumatoid Arthritis-Update on Treatment John M. Davis, III, M.D.
1:15	Autoantibodies in Rheumatology Kevin G. Moder, M.D.
1:45	Scleroderma W. Leroy Griffing, M.D.
2:15	Questions and Answers
2:30	Break
2:45	Systemic Lupus Gen. Concepts Ronald R. Butendieck, Jr., M.D. ACPE UAN: 0853-0000-15-048-L01-P Contact hours: 0.5
3:15	Polymyalgia Rheumatica Florentina Berianu, M.D.
3:45	Sjögren's Syndrome Ronald R. Butendieck, Jr., M.D. ACPE UAN: 0853-0000-15-049-L01-P Contact hours: 0.5
4:15	Questions and Answers
4:30	Adjourn
4:30 – 6:00 p.m.	Poster Presentation

Program schedule is subject to change without notice.

Rheumatology Update

Marriott Sawgrass, Ponte Vedra Beach, Florida

April 17-18, 2015

Saturday, April 18, 2015

7:30 a.m.	Continental Breakfast
7:45	Announcements
8:00	Vasculitis Overview Andy Abril, M.D. ACPE UAN: 0853-0000-15-047-L01-P Contact hours: 0.5
8:30	Primary Raynaud's Phenomenon Thomas G. Mason, II, M.D.
9:00	Inflammatory Myopathies Lester E. Mertz, M.D.
9:30	Questions and Answers
9:45	Break
10:00	Update on GCA Andy Abril, M.D.
10:30	Juvenile Inflammatory Arthritis Thomas G. Mason, II, M.D.
11:00	Cutaneous Manifestations of Rheumatologic Disorders Jason C. Sluzevich, M.D.
11:30	Questions and Answers
11:45	Lunch
12:45 p.m.	Psoriatic Arthritis Gurjit S. Kaeley, M.D.
1:15	Spondyloarthropathies Clement J. Michet, M.D.
1:45	Hip Pain Thomas D. Rizzo, Jr., M.D.
2:15	Questions and Answers
2:30	Break
2:45	Musculoskeletal Ultrasound in Rheumatology Gurjit S. Kaeley, M.D.
3:15	Behcet's Disease Kenneth T. Calamia, M.D.
3:45	Auto Inflammatory Syndromes Lester E. Mertz, M.D.
4:15	Questions and Answers
4:30	Post-Test
4:45 p.m.	Closing Remarks/Adjourn

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Approach to the Patient with Musculoskeletal Complaints

Kevin G. Moder, MD
Mayo Clinic
Rochester, Minnesota

CP1194588-1

Assessment

- Age
- Gender
- History
- Physical

CP1194588-2

Return to Program Schedule

Age & Gender

- Fibromyalgia more common in younger patients
- PMR/GCA occur in patients over age 50 and usually over age 60
- OA more common in older patients
- RA can occur at any age
- Most rheumatic diseases and FM are more common in females than males but can occur in both

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History & Physical Exam: What are You Looking For?

- Articular?
- Is there true joint swelling?
- Distribution of joints
- Time course
- Associated symptoms
- PMH, recent history

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CP1194588-4

History & Physical Exam: Inflammatory or Not?

- Warmth
- Erythema
- Synovitis
- AM stiffness
- Lab evaluation
- Response to Rx

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CP1194588-3

Key Clue

- “Hurts all over”
- Muscles and joints
- Fibromyalgia

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CP1194588-5

Monoarthritis Acute/Subacute

Inflammatory
- Infection
- Crystalline
- Evolving inflammatory oligo/ polyarthritis

Noninflammatory
- Fracture
- Int derangement
- Hemearthrosis
- AVN

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CP1194588-6

Chronic Monoarthritis

Inflammatory
- Inflam arthritis
- Atypical infections
- Crystalline

Noninflammatory
- DJD
- Tumor
- AVN

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CP1194588-7

Case 1

- 39-year-old cardiologist
- Runner
- 10 weeks of R knee pain and swelling
- Initial evaluation x-ray negative
- Rx with NSAIDs

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Case 1 Exam

- R knee effusion
- Not warm nor erythematous
- Tender over medial joint space
- Knee stable

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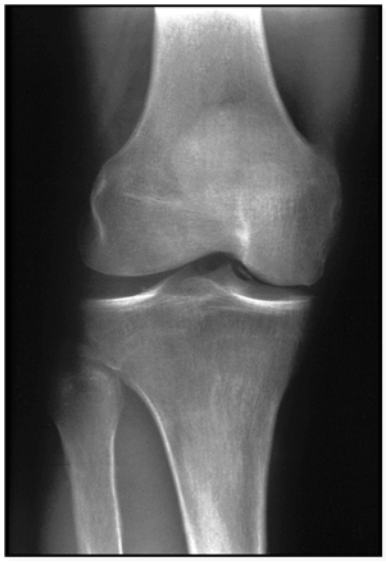

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CP1194588-10

Evaluation of Monoarthritis

- X-ray
- If inflammatory
  - CBC, ESR, Ca, uric acid, Lyme, others
- Aspiration
  - Cell count, crystals, cultures

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CP1194588-12

More than one joint

- Oligoarthritis vs polyarthritis
- Distribution
  - Symmetric
  - Large and/or small
  - Spine
  - Weight bearing only
- Associated Sx

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CP1194588-15

Oligoarthritis

- Spondyloarthropathies
  - Psoriasis
  - IFBD
  - Reactive arthritis
  - Ank spondylitis
- Evolving polyarthritis
- Other
  - Noninflammatory – DJD

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CP1194588-16

Spondyloarthropathies

- Young males > females
- Females may have less axial involvement and more peripheral arthritis
- Asymmetric
- Large > small joints
- Spine involved
- Often associated with HLA B27
- Associated conditions
    - Uveitis/iritis, IFBD, Psoriasis

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CP1194588-17

Case 2

- 35-year-old male
- 6 weeks of arthralgia/arthritis
    - Knees, wrists, ankles, hips
- Recent exposure as flood-relief worker
- PMH severe cystic acne
- Associated features: Fatigue

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CP1194588-18

Case 2a

- Saw LMD, Rx with NSAID, some relief
- Initial eval seronegative, ESR 35
- Synovitis in wrists and ankles
- AM stiffness of 1 hour

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Case 2b

- Differential Dx wide
- Seronegative inflammatory polyarthritis
- Not asymmetric without back involvement
- No small joints
- Little other associated symptoms
- Need more extensive evaluation

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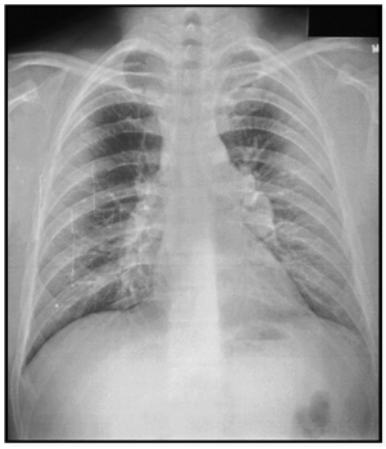

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CP1194588-21

Answer Case 2

- Acute Sarcoidosis
  - Lofgren's syndrome
- During evaluation developed E nodosum on legs
- Did well with resolution of Sx over 3 months on Rx with NSAIDs only

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CP1194588-24

Evaluation of Polyarthritis

- CBC, ESR
- RF, ANA, CCP
- Chemistries – Uric acid, CA, Cr, AST
- CXR
- Urine
- If acute- parvovirus

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Case 3

- 57-year-old male
- Refer by neuro
- PMH of OA, LBP
- 6 mos h/o hand pain (PIPs, MCPs, wrists)
- 1 hour am stiffness
- Tried celebrex without benefit
- FH of RA

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Physical Exam

- Heberden's and Bouchard's nodes
- Tender over multiple PIPs, MCPs
- Tenosynovitis R wrist
- Synovitis MTPs 2-4 both feet
- Positive "squeeze test" hands and feet

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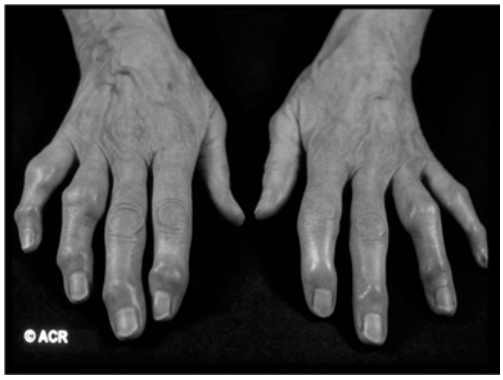
CP1194588-30

Heberden's and Bouchard's nodes



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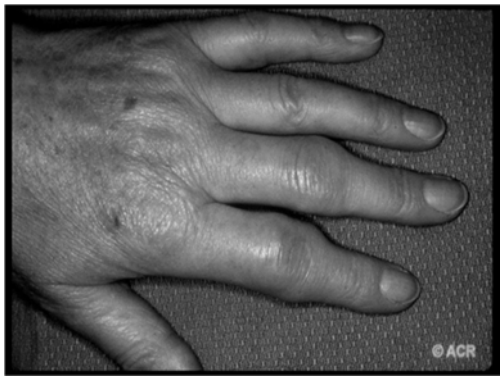
Rheumatoid Arthritis



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Diagnostic Evaluation

- CBC, esr, CRP normal
- Rheumatoid Factor strongly positive
- CCP (cyclic citrulinated peptide) strongly positive
- Xrays without erosions

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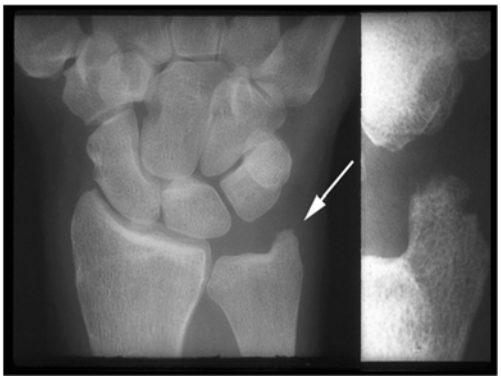
Early changes Are Seen in the Hand or Wrist



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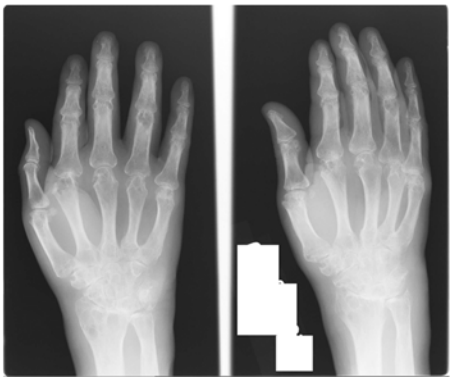
Erosions



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RA Classification Criteria

Table 3 The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)**	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)††	5
B. Serology (at least 1 test result is needed for classification)‡‡	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)§§	
Normal CRP *and* normal ESR 0	0
Abnormal CRP *or* normal ESR 1	1
D. Duration of symptoms¶¶	
<6 weeks	0
≥6 weeks	1

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Ann Rheum Dis 69:1580, 2010

RA treatment Guidelines

- Based on duration of disease
- Disease activity
- Prognostic factors
  - RF and/or CCP positive
  - Functional limitation
  - Extra articular disease
  - Erosions on XRAY

Arthritis Rheum 59(6):762, 2008

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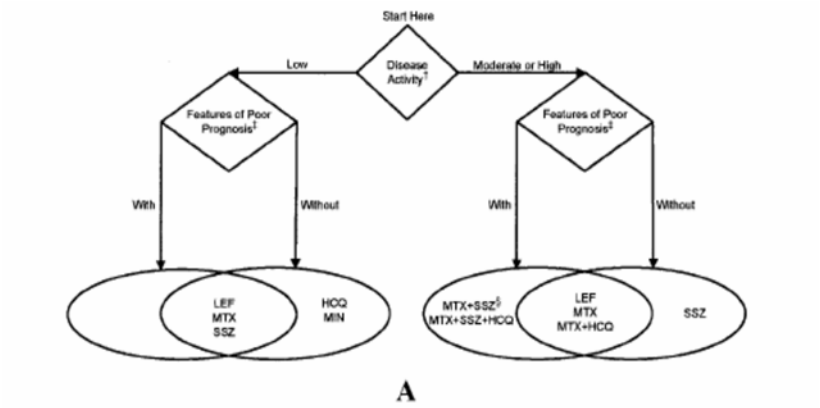
Initial Treatment



A

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Case 4

- 33 year-old female with 10 year history or myalgias, arthralgias, and fatigue
- Tenderness over multiple muscle areas
- No synovitis or weakness on examination
- Has tried NSAIDs without relief
- Is requesting narcotic analgesics for relief

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CP1104125-36

Case 4 Labs

- CBC normal
- ESR, CRP normal
- CA, AST, CR, vitamin D normal
- Urinalysis normal
- STSH normal

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Fibromyalgia

- A condition characterized by chronic diffuse musculoskeletal pain
- Associated with psychosocial stress, depression and anxiety
- Pain above and below the waist on both sides of the body
- Present x 3 months or more
- Characteristic tender points 11/18

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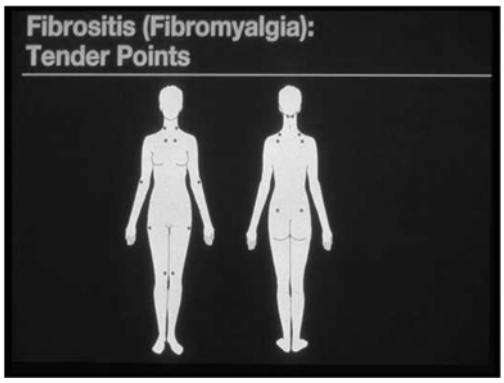

Slide from ACR slide collection

2010 FM Criteria

- Replaces the 1990 criteria
- No longer requires tender points
- Based on widespread pain index
- Symptom severity score

Widespread Pain Index
19 body areas

- Shoulder girdle R & L
- Upper arm R & L
- Lower arm R & L
- Hip R & L
- Upper leg R & L
- Lower leg R & L
- Jaw R & L
- Upper back R & L
- Chest
- Neck
- Abdomen

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Symptom Severity (SS)

- Fatigue
- Waking unrefreshed
- Cognitive symptoms
- Somatic symptoms
- Each scored 0-3

  0=none 2= moderate

  1=mild 3= severe

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2010 Fibromyalgia Classification Criteria

- Widespread Pain Index ≥7 and
- Symptom Severity Score ≥ 5

  or
- WPI 3-6, SS ≥9
- Symptoms present > 3 months
- No other disorder present to explain pain

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FM demographics

- Most commonly young adults
- Women are 75-95% of patients
- Present in 2-10% of the population
- Often have had “growing pains” in childhood
- Many other associated somatic complaints

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FM Evaluation

- There is no test for fibromyalgia
- Simple screening labs to exclude other disorders
  - ESR, CBC, TSH, Calcium, Vitamin D
- Do not need autoantibodies in all pts
- Consider sleep apnea in older pts with new onset symptoms

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FM Treatment

- Exercise
- Tricyclic antidepressant for sleep
- Education
- Medications
  - Duloxetine (Cymbalta) in females - SNRI
  - Pregabalin (Lyrica) – GABA analogue
  - Pramipexole (Mirapex) - DRA
  - Milnaciprin (Savella) - SNRI

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Case 4 Summary

- No features of SLE
- Fatigue and tender points are consistent with fibromyalgia

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Case 5

- 24 year old female referred for 3 week h/o joint pains
- Bilateral hands, wrists, ankles, feet
- Patient notes swelling
- Morning stiffness of > 1 hour
- Gelling
- Took NSAIDs with mild relief

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Examination

- Synovitis bilaterally in multiple PIPs and MCPs
- Can't fully flex or extend fingers
- Tenosynovitis in wrists
- R>L knee effusion
- Synovitis in ankles and MTPs of both feet

Initial Workup

- Saw Primary Care MD
- CBC, ESR, CR normal
- CRP elevated
- RF, ANA negative

What would you do next?

Results

- CCP negative
- CXR negative
- HLA B27 negative
- CCP negative
- Positive IgM parvovirus serology

Parvovirus

- Acute arthritis in adults
- Fifth's disease in kids
- More frequent infection in late winter/early spring but can occur anytime of year
- May last 6 weeks to 6 months
- Rarely has been reported before the onset of Rheumatoid Arthritis
- Different virus from the canine parvovirus
- Treatment with NSAIDs but may require low dose prednisone in tapering course

Case 6

- 73 year old female
- 6 week history of aching in groin bilaterally as well as shoulders
- Am stiffness for several hours
- Gelling
- Took ibuprofen with minimal relief
- On examination no synovitis
- ESR elevated at 35 mm/hr

Polymyalgia Rheumatica

- Age over 50 years, usually over 60 years old
- Hip/shoulder girdle aching
- No or little synovitis
- Can be associated with GCA
- Elevated ESR and/or CRP >90%
- Dramatic and prompt response to prednisone in doses 5 mg TID within 48 hours
- Usually runs its course over 1-2 years, rare cases more chronic
- RS3PE variant

Summary

Most important to classify type of arthritis

- Mono vs oligo vs polyarthritis
- Inflammatory vs noninflammatory
- Acute, subacute, chronic
- Distribution

With polyarthritis beware of systemic illnesses

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CP1194588-34

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Fibromyalgia:
A Disorder of Sensory Processing

Benjamin Wang, M.D., FRCPC
Division of Rheumatology
Mayo Clinic
Jacksonville, Florida

Disclosures

- Financial relationships: None
- Off-label uses of drugs/devices: None

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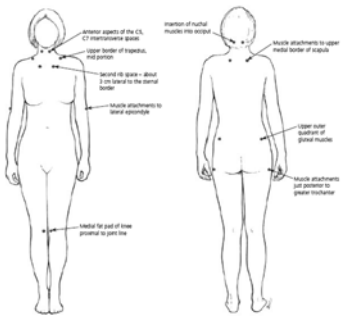
Fibromyalgia: Broadly Defined

- A common and complex condition of widespread musculoskeletal pain accompanied by nonrestorative sleep, fatigue, psychological dysfunction, and regions of localized tenderness
- More recent insights have suggested that fibromyalgia is a disorder to the processing of sensory information by the nervous system



MAYO CLINIC Wolfe, et al, Arthritis Rheum 1990;33:160–72

Fibromyalgia: Common and Commoner

- Using ACR criteria, the prevalence of fibromyalgia in most studies from industrialized nations ranges from 0.5 to 4%
- Chronic widespread pain (CWP) diagnosed in the absence of tender points has a 10-11% prevalence in industrialized nations
- FMS may be diagnosed without requisite numbers of tender points; they do not capture the complexity of FMS
- TP may add specificity to diagnosis, but improved diagnostic criteria are being sought

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Symptoms are typical, even stereotypical

- Pain and sensory
  - Generalized symptoms, articular and non-articular
  - Aching, deep, sore, bruised, “lactic acid”
  - Hypersensitive to: light, sound, temperature, humidity, odors etc.
- Fatigue
  - Poor stamina
  - Poor recovery from efforts
- Sleep disturbance
  - Nonrestorative: waking up tired
  - Problems in both induction and maintenance phases of sleep
- Cognitive
  - Poor memory, especially short-term
  - Poor focus/concentration
  - Word-finding problems
  - Forgotten facts/events/conversations
- Affective: depression, anxiety
- Pain behaviors

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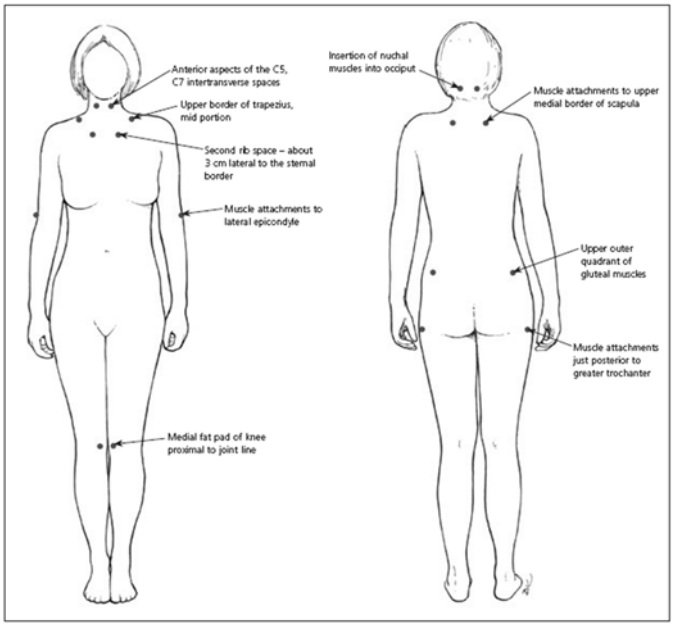

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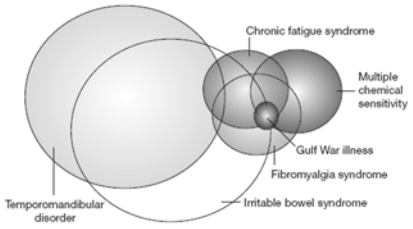
The Broader Context of Fibromyalgia



Primary diagnosis	Degree of overlap with secondary condition (%)[67,68]				
	FMS	CFS	IBS	TMD	MCS
FMS	NA	70	32–80	75	55
CFS	35–70	NA	58–92	20	41–67
IBS	32–65[a]	58–92[a]	NA	32–65[a]	ND
TMD	13–18	20	64	NA	ND
MCS	33–55	30	ND	ND	NA

Figure 1 Central pain syndromes that have symptoms overlapping with those of fibromyalgia syndrome. There is overlap of a number of prevalent systemic and regional chronic pain and abnormal sensory conditions that share common mechanisms and effective treatments.[16,65–68] Abbreviations: CFS, chronic fatigue syndrome; FMS, fibromyalgia syndrome; IBS, irritable bowel syndrome; MCS, multiple chemical sensitivity; NA, not applicable; ND, not determined; TMD, temporomandibular disorder. [a]Not numerically represented on diagram.

Dadabhoy D and Clauw D. Nat Clin Prac Rheum 2006; 2(7):364.

Fibromyalgia: We are not alone

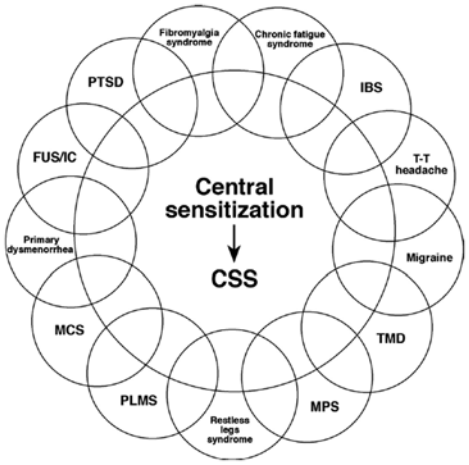


Figure 1 Currently proposed members of the CSS family with overlapping relationships and a common pathophysiological link of CS. IBS, irritable bowel syndrome; T-T headache, tension-type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; RSTPS, regional soft-tissue pain syndrome; PLMS, periodic limb movements in sleep; MCS, multiple chemical sensitivity; FUS, female urethral syndrome; IC, interstitial cystitis; PTSD, posttraumatic stress disorder. Depression may also be a member (see text). Modified from reference 198.

Yunus MB. Semin Arthritis Rheum 2007; 36:339-356

Changing Concepts

- Beginning in the 19th century: predominately muscular and connective tissue – “muscular rheumatism” (Virchow, 1852), “fibrositis” (Gowers, 1904), “nodular fibromyositis” (Kelly, 1945)
- Early 20th century: FMS as a psychological disorder - “psychogenic rheumatism” and “psychosomatic rheumatism”
- Late 20th century: evolution of specific criteria, centering on pain manifestations
- Early 21st century: neuroscience-based concepts, neuroendocrine models, genetic factors

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Recent Insights in Physiology

- Disordered pain and sensory processing: central sensitization, “**myalgic encephalomyelopathy**” (revival in 2015)
  - Peripheral neuronal dysfunction
  - Spinal sensitization
  - Supraspinal abnormalities
  - Autonomic dysfunction
- Neuroendocrine influences
- Genetic predisposition

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Sensory Processing in Fibromyalgia: More Facilitation, Less Inhibition

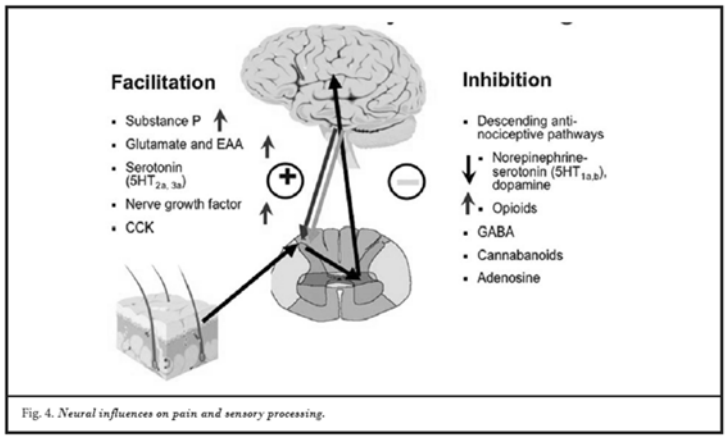

Fig. 4. *Neural influences on pain and sensory processing.*

Clauw D, et al. Mayo Clinic Proc 2011; 86(9): 907-911.

Where does fibromyalgia begin?

- Chronic illnesses
  - Inflammatory diseases including autoimmune connective tissue disorders (e.g. SLE, Sjogren's, rheumatoid arthritis)
  - Infections (Lyme, viral) – debated; recent XMRV "myth"
- Trauma (surgical, motor vehicle accident)
  - 7.8% incidence of widespread pain within 12 months of MVA (Wynne-Jones, 2006)
  - Risk factors: older age, post-collision physical symptoms, pre-collision health-seeking behavior, pre-collision somatization, perceived initial injury severity
- Teleologic explanation? – survival advantage? (Voss, 2002)

Peripheral Nerve Dysfunction

- Importance of acid-sensing ion channel 3 (ASIC3) in chronic pain induction
  - In ASIC3 knockout mice, secondary mechanical hyperalgesia does not develop (Benson, 2007)
  - Re-expression of ASIC3 in muscle tissue (but not skin) of ASIC3 knockout mice restores the development of hyperalgesia (Ikeuchi, 2008)
  - In parallel, central sensitization of dorsal horn neurons, measured as a bilateral spread of receptive fields and increased mechanical sensitivity, does not develop in ASIC3 knockout mice (Sluka, 2003)
- Calcium channel subunit α2-δ is abnormally upregulated
  - Binds small molecules that reduce pain (e.g. gabapentin, pregabalin)
  - Affects function of main α1 subunit of calcium channel

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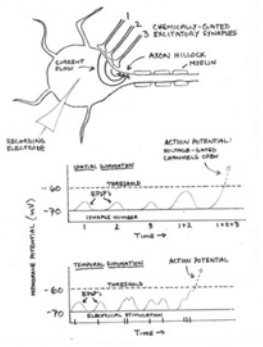
A Key Mechanism: Spinal sensitization

- **Amplification of second-order neuron sensory impulses in spinal cord**
- **Promoted by abnormal calcium channel activity**
- **Receptor to NMDA (N-methyl-D-aspartate) upregulated in spinal cord of experimental FMS**
  - **Normally inactive but is upregulated after repeated stimulation by glutamate and substance P**
  - **Generates wind-up (temporal summation) to amplify and perpetuate afferent nociceptive signals**
  - **Blocked by ketamine and dextromethorphan; latter has not shown clinical benefit in early trials**
- **Spinal activation of the cAMP pathway**
  - **produces mechanical hyperalgesia and increases the response of spinothalamic tract neurons to noxious but not innocuous mechanical stimuli**



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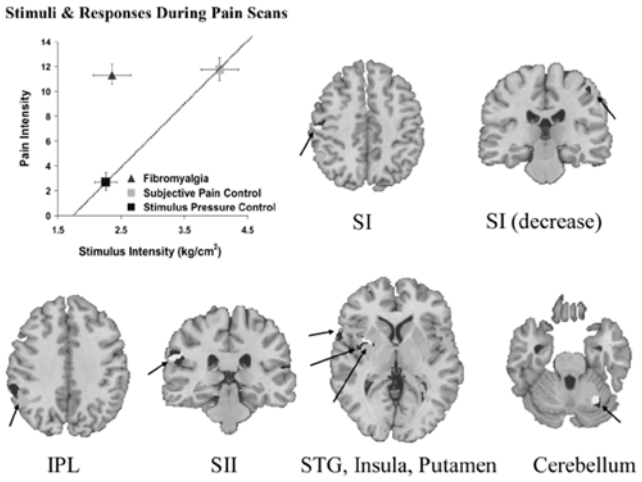
Functional MRI



Gracely RH et al. Arthritis Rheum 2002; 46(5): 1333-1343.

SPECT can localize and quantify areas of brain activation and inhibition in fibromyalgia

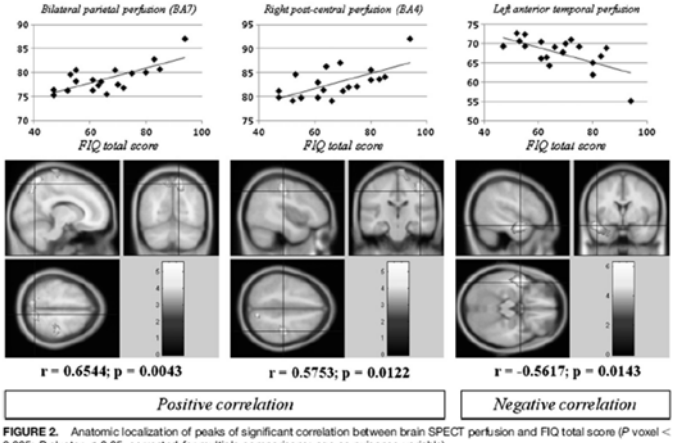
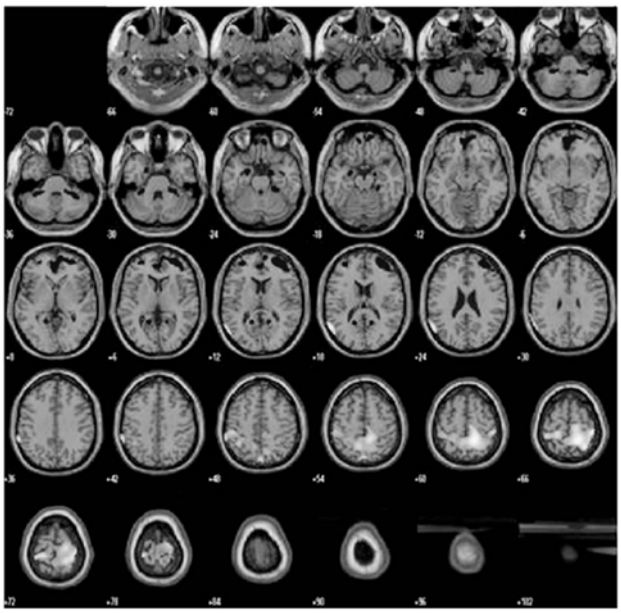


FIGURE 2. Anatomic localization of peaks of significant correlation between brain SPECT perfusion and FIQ total score (P voxel < 0.005; P cluster < 0.05, corrected for multiple comparisons; age as nuisance variable).

Guedj E et al. J Nucl Med 2008; 49:1798–1803



Guedj E. Eur J Nucl Med Mol Imaging (2007) 34:130–134

Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in Rostral Anterior Cingulate Cortex during provoked pain

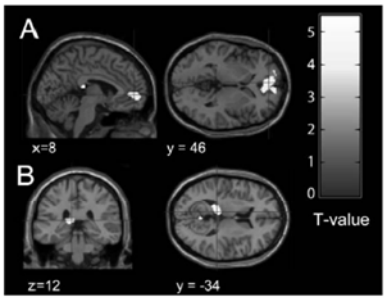


Fig. 2. Regions of the brain where healthy controls have higher activity than FMS patients during subjectively calibrated painful stimulation minus sensory stimulation. Clusters corresponding to (A) the rACC, and (B) the pulvinar nucleus of thalamus. The exact anatomical locations (x, y, z) are given in MNI coordinates.

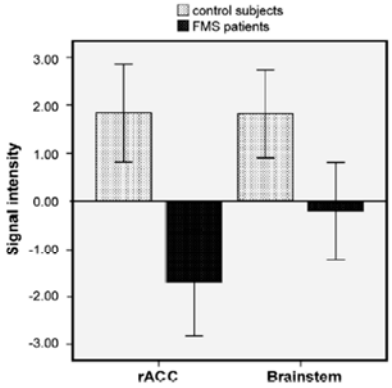
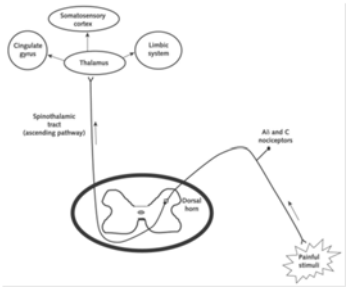


Fig. 3. Representation of neuronal activity in the rACC and the brainstem during subjectively calibrated painful stimulation minus sensory stimulation in patients and controls. The bars represent the signal intensity for the same coordinate in the rACC ($x = -8$, $y = 46$, $z = 4$) and the brainstem ($x = 4$, $y = -22$, $z = 40$). The signal intensity for the contrast pain minus sensory stimulation was recorded for every individual and bars represent the mean intensity. Error bars represent the standard error. The exact anatomical location (x, y, z) is given in MNI coordinates.

Jenson KB et al. Pain 144 (2009) 95–100

The Mind-Body Connection

- The spinothalamic tract, provides nociceptive information to thalamic nuclei as well as to the primary and secondary somatosensory cortices
  - Involved in **sensory discriminative aspects** of pain as well as in the anticipation of painful stimuli
- Spinothalamic tract projections also facilitate nociceptive input to the insular cortex which has interconnections with the amygdala, prefrontal cortex, and anterior cingulate cortex
  - Involved in **affective, cognitive, and autonomic responses** to nociception
- Chronic pain processing reflects decreased sensory processing in somatosensory regions in favor of enhanced activation of regions
  - Associated with cognitive, emotional, and introspective processing of events (Apkarian, 2005)



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The Influence of Brain and Body Hormones

- Hypothalamic-pituitary-adrenal axis abnormalities
  - Increased sympathetic outflow with decreased parasympathetic tone results in visceral hyperactivity
  - May impact sleep
  - Systemic norepinephrine release with increased sympathetic tone reduces pain inhibition
  - This may explain the responsiveness of patients to short-term conrticosteroids – not an anti-inflammatory benefit, but a hormonal one!

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Genetic Factors

- Some genes have been identified that may be important as risk factors for fibromyalgia
- Polymorphisms of gene encoding catechol-O-methyltransferase (COMT) described. Low enzymatic haplotypes more frequent in FMS patient samples and may account for some of the neuroendocrine abnormalities

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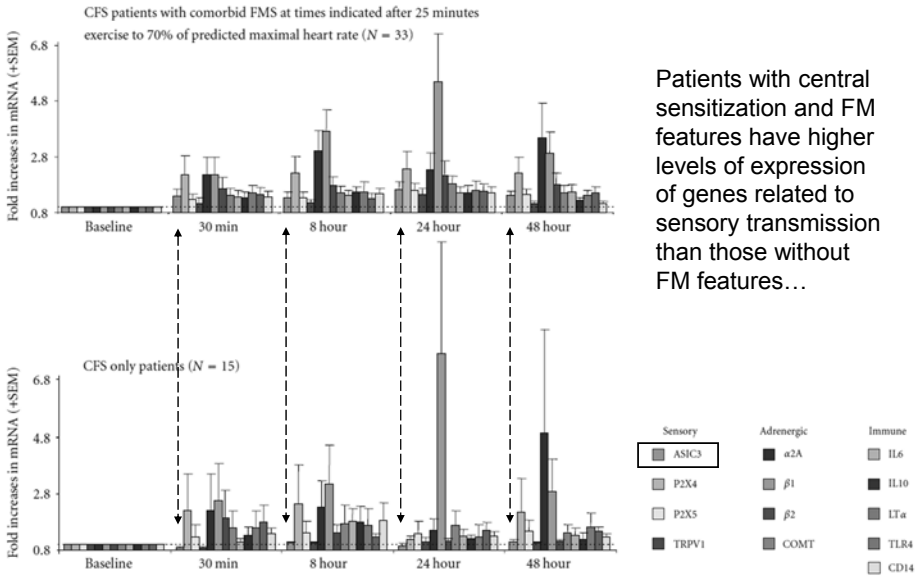

Patients with central sensitization and FM features have higher levels of expression of genes related to sensory transmission than those without FM features…

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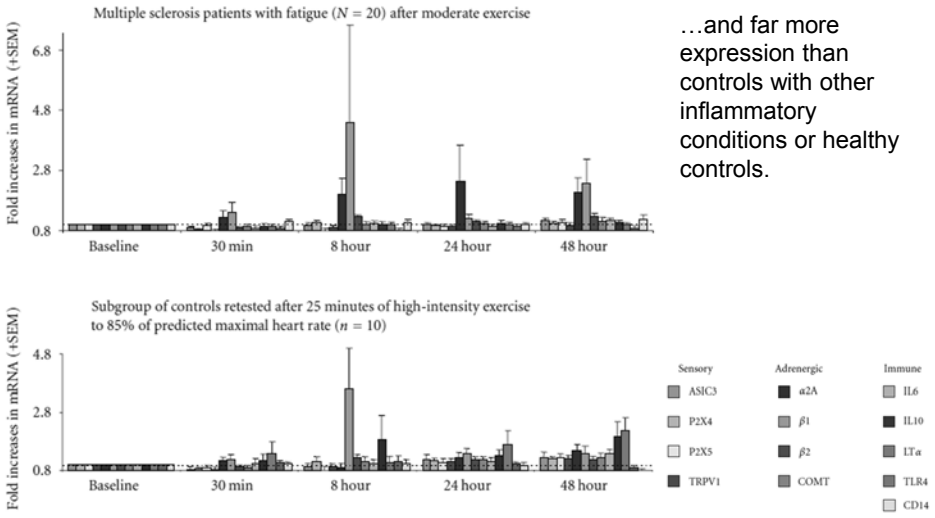
Light KC, White AT, et al. *Pain Res and Treatment* (2012)



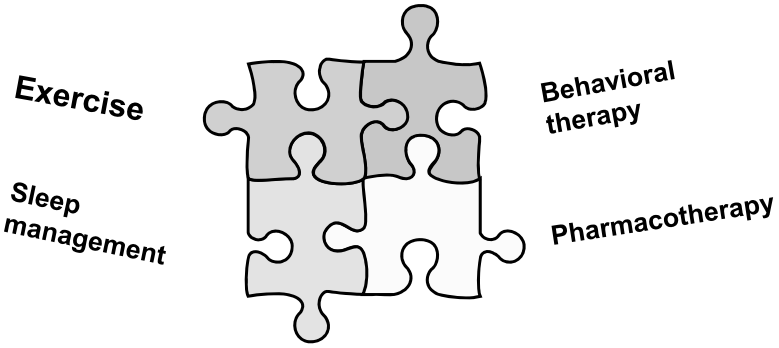
…and far more expression than controls with other inflammatory conditions or healthy controls.

MAYO CLINIC

Light KC, White AT, et al. *Pain Res and Treatment* (2012)

Treatment

- Evidence supports a multimodality approach that addresses pain management, sleep quality, behavioral and psychological issues, and physical exercise and rehabilitation



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- **Efficacy of *Multicomponent Treatment* in Fibromyalgia Syndrome: A Meta-Analysis of Randomized Controlled Clinical Trials**

Total treatment ≥30 hours					
Pain	2	52	SMD (Fixed)	−0.36 (−0.78, −0.05)	0.09
Fatigue	1	38	WMD (Fixed)	−1.20 (−2.20, −0.20)	0.02
Sleep	ND				
Depressed mood	1	38	SMD (Fixed)	−1.07 (−2.73, 0.60)	0.26
Quality of life	1	38	SMD (Fixed)	−0.58 (−1.08, −0.07)	0.02
Self-efficacy pain	1	38	SMD (Fixed)	0.63 (0.13, 1.14)	0.01
Physical fitness	1	38	SMD (Fixed)	0.44 (−0.06, 0.94)	0.09
Total treatment <30 hours					
Pain	3	84	SMD (Fixed)	−0.38 (−0.68, −0.07)	0.02
Fatigue	2	48	WMD (Fixed)	−0.59 (−1.45, 0.27)	0.18
Sleep	ND				
Depressed mood	3	84	SMD (Fixed)	−0.84 (−1.16, −0.52)	< 0.0001
Quality of life	2	54	SMD (Fixed)	−0.60 (−1.00, −0.19)	0.004
Self-efficacy pain	3	74	SMD (Fixed)	0.50 (0.16, 0.84)	0.004
Physical fitness	3	74	SMD (Fixed)	0.24 (−0.10, 0.57)	0.16

* MT = multicomponent therapy; 95% CI = 95% confidence interval; SMD = standardized mean difference; WMD = weighted mean difference; ND = no data.

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Hauser W et al. Arthritis & Rheumatism (Arthritis Care & Research) 2009; 61:216–224

Exercise: Effect on Pain

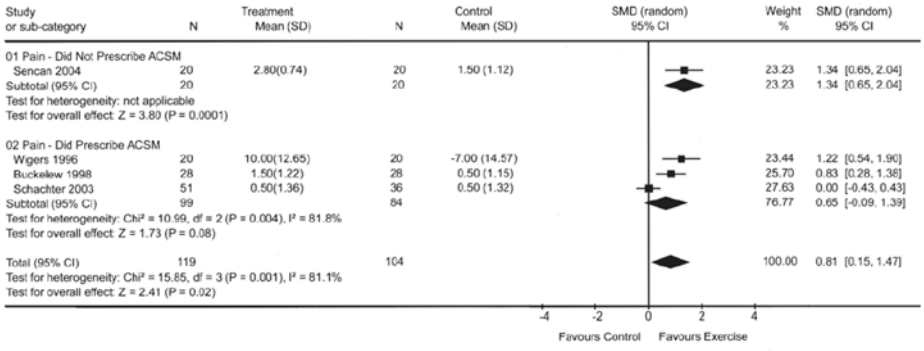

Figure 1. Metaanalysis for effect of aerobic exercise on pain (01: exercise programs did not meet ACSM standards; 02: exercise programs met ACSM standards). SMD: standardized mean difference. From The Cochrane Library 2007, Issue 4, with permission.

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Busch AJ et al. J Rheumatol 2008;35:1130–44)

Exercise: Effect on Depression

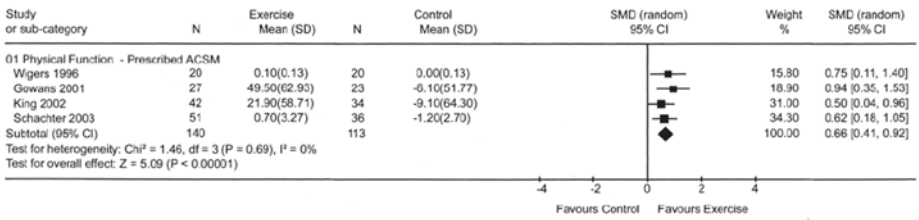

Figure 4. Metaanalysis for effect of aerobic exercise on depression (01: exercise programs did not meet ACSM standards; 02: exercise programs met ACSM standards). SMD: standardized mean difference. From The Cochrane Library 2007, Issue 4, with permission.

- Submaximal levels of exertion appear to be most sustainable
- Most common mistake: overexercise

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Busch AJ et al. J Rheumatol 2008;35:1130–44)

Treating Sleep

- Sleep-related problems almost universal in fibromyalgia syndrome, and are strongly predictive of pain, fatigue, and difficulty with social functioning (Theadom, 2007)
- Increased airways resistance without overt apnea is frequently observed and may respond to positive airways pressure (Gold, 2005)

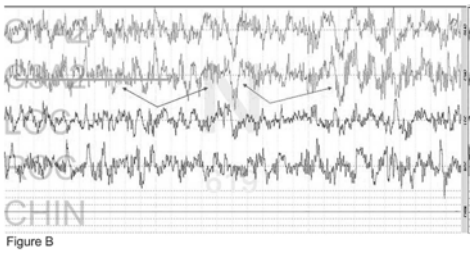

Figure B

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Drug therapy does not provide significant relief of symptoms or lasting benefits

- Most evidence for efficacy
  - Amitryptiline: long-term efficacy data lacking
  - Cyclobenzaprine
  - Tramadol
- Moderate evidence for efficacy
  - SSRI: fluoxetine, buproprion, etc.
  - SNRI: **duloxetine**, **milnacipran**
  - **Pregabalin**, gabapentin, topiramate

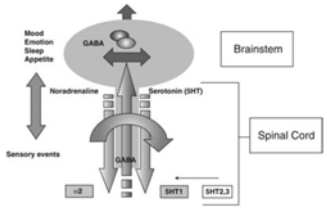

Figure 2. Neurotransmitter-modulated spinal-brain loop interference. GABA, gamma-aminobutyric acid; 5HT, serotonin.

- No evidence for efficacy: opiate analgesics, NSAIDs, corticosteroids, benzodiazepines, thyroid hormone, calcitonin, magnesium.

[Bold = FDA approved for fibromyalgia**]**

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Behavioral Therapy: Key Elements

- Education
- Goal setting
- Behavioral pacing
- Relaxation training
- Identification of dysfunctional thought patterns such as catastrophizing
- Communication skills and strategies for acquisition, maintenance, and generalization of skills
- Strategies for relapse prevention and for managing flare-ups
- Use of multidisciplinary teams

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Bennett R. Nat Clin Pract Rheum 2006; 2:416-424.

Summary

- Fibromyalgia is a common disorder of chronic widespread pain associated with many symptoms such as fatigue and sleep disorder
- The physiology involves abnormal sensory processing and central sensitization
- Treatment should involve multiple components to address pain, deconditioning, sleep disorders, and psychological aspects

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Return to Program Schedule

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Rheumatoid Arthritis

Preventative Care for RA Patients

John M. Davis III, M.D., M.S.

Mayo Clinical Rheumatology Update
April 17-18, 2015
Sawgrass Marriott, Ponte Vedra Beach, Florida, USA

Disclosure

- Research support
  - Site investigator (Roche, Pfizer)
  - Grant support (Pfizer)
- No off-label treatments will be discussed.

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Return to Program Schedule

Background

Comorbidities of Rheumatoid Arthritis

Cardiometabolic syndrome

Depression

Infections

Heart Disease

Cancers

Asthma
Obstructive lung disease

Osteoporosis

Gastrointestinal ulcers and perforations

Background

- Who should be providing preventative care to patients with RA?
  - Known gaps in preventative care[1,2]
  - Evidence of better preventative care in patients with regular PCP visits[1]
  - Increasingly complex guidelines
- Timely debate about our health care system
  - Local, regional and national systemic change
  - Patient-centered medial home/neighborhood
  - Issues of cost and reimbursement

Learning Objectives

After this lecture, learners will be able to assess risk and implement preventative strategies for:

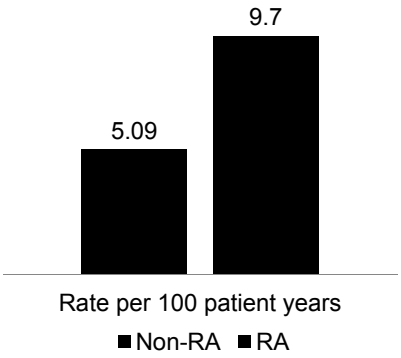
1. Infectious diseases
2. Cardiovascular disease
3. Glucocorticoid-induced osteoporosis

Infection Risk Assessment and Prevention

Serious Infections in the Pre-Biologic Era

Hospitalized Infections

RR = 1.88 *(95% CI: 1.71 – 2.07)*



Infection Type

Type	Risk Ratio
Septic arthritis	21.6
Osteomyelitis	10.6
Skin/soft tissue	2.8
Other	2.4
Pneumonia	1.8
Lower respiratory	1.6

*Prospective cohort study performed using the resources of the Rochester Epidemiology Project. Cohorts recruited 1955 to 1994 and followed through 2000.
N = 609 RA subjects and 609 matched non-RA

Infection Risk Assessment and Prevention

Patient Factors

1. Personal history of infections
   - Frequency
   - Severity
2. Comorbidities
   - Aging[1]
   - Diabetes, chronic lung disease, alcoholism[2]
3. Laboratory abnormalities
   - Leukopenia, T- or B-cell lymphopenia
   - Hypogammaglobulinemia
4. Disease severity
   - Higher disease activity scores[2]
   - ACR Functional Status[2]
   - Extra-articular manifestations, joint damage, foot ulcers
5. Surgeries
   - Prosthetic joints, hardware, central lines, etc.

[1]Doran et al. Arthritis & Rheumatism 2002
[2]Au et al. Annals of the Rheumatic Diseases 2011

Infection Risk Assessment and Prevention

Treatment Factors - Biologics and Corticosteroids

Safety of Biology Therapy (SABER) Study

- Retrospective cohort study
  - Large US databases (US Medicare, Tennessee Medicaid, New Jersey, Kaiser Permanente)
  - Predominantly low-income, vulnerable patients
  - Included 139,611 patients with RA
- Study design features
  - New user design with propensity-score matching
  - Drug exposure by pharmacy data
  - Validated definitions for hospitalized infections
  - Follow-up 365 days after drug start

Infection Risk Assessment and Prevention

SABER Study Results: All Serious Infections

Exposures	Events, No.	Person-Years, No.	Rate, per 100 PY	Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)
Non-biologic drugs	326	4192	7.78	1 (Ref.)	1 (Ref.)
TNF antagonists	497	6089	8.16	1.05 (0.91-1.21)	1.05 (0.91-1.21)
Baseline glucocorticoid use, prednisone					
None					1 (Ref.)
>0-<5 mg/d					1.32 (1.10-1.21)
5-10 mg/d					1.78 (1.47-2.15)
>10 mg/d					2.95 (2.41-3.61)

Shown here are results for 139,611 patients with RA

*Propensity-score matched cohorts plus adjustment for baseline glucocorticoid use

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Infection Risk Assessment and Prevention

SABER: Non-viral Opportunistic Infections

Non-viral opportunistic infections (n = 80)	Frequency (%)
Pneumocystosis	16 (20%)
Nocardiosis/actinomycosis	12 (15%)
Tuberculosis	10 (12.5%)
Histoplasmosis	9 (11.3%)
Non-tuberculous mycobacteria	9 (11.3%)
Salmonellosis	8 (10%)
Listeriosis	4 (5%)
Legionellosis	4 (5%)
Cryptococcosis	3 (3.8%)
Endemic fungal infection	1 (1.3%)
Toxoplasmosis	1 (1.3%)
Coccidioidomycosis	1 (1.3%)
Blastomycosis	1 (1.3%)
Aspergillosis	1 (1.3%)

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Infection Risk Assessment and Prevention

SABER: Non-viral Opportunistic Infections

Exposures	Events	Person-years	Crude rate (per 1000 person years, 95% CI)	Adjusted Hazard Ratio
Non-biologic DMARDs	13	7188	1.8 (1.1 to 3.1)	1.00 (ref)
New TNFi users	67	22,213	3.0 (2.4 to 3.8)	1.6 (0.9, 3.1)
Any baseline glucocorticoid use				1.7 (1.0, 2.8)

Infliximab and adalimumab posed the greatest risk of non-viral opportunistic infections compared to etanercept and non-biological DMARDs.

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Infection Risk Assessment and Prevention

SABER Study Results: Summary

- Higher absolute rates of serious infections than previously reported in this USA cohort
- No increased risk of serious infections at the group-level for TNF antagonists compared to comparator non-biologic drugs
- Non-viral opportunistic infections (PCP, TB) was increased in new users of TNF antagonists
- Infliximab-based therapies regimens associated with higher risk of infections than other TNFi
- Glucocorticoid use associated with strong, dose-dependent increase in the risk of serious infections

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Infection Risk Assessment and Prevention

Preventative Strategies

1. Assess infection risk
2. Educate patients at high risk
3. Administer recommended vaccinations
4. Screen for latent infections prior to biologics
5. Triage patients with acute febrile illnesses
6. Manage DMARDs during infections

KL Winthrop. Rheumatic Disease Clinics of North America 2012

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Infection Risk Assessment and Prevention

1-Year Risk Score for Serious Infections

Predictor, level	Coefficient
Age	
<60 years	0
60 to ≤80 years	0.404
>80 years	0.857
Previous history	
Never or >3 years ago	0
In the past 2-3 years	1.67
In the past year	2.138
Extra-articular disease	0.620
ESR	
<30 mm/hour	0
30 to ≤50 mm/hour	0.180
>50 mm/hour	0.611
Corticosteroid dosage	
None	0
≤10 mg/day	0.553
>10 mg/day	1.281
Comorbidities	
None	0
1	0.675
2 or more	1.024

One-year risk of serious infection (%) = [1 – 0.989 (exp[A])] 100%, where A 0.404 (if age 60 to 80 years) 0.857 (if age 80 years) 2.138 (if serious infection in the past year) 1.670 (if serious infection in the past 2–3 years) 0.620 (if extraarticular RA) 0.180 (if ESR 30 to 50 mm/hour) 0.611 (if ESR 50 mm/hour) 0.553 (if corticosteroids 10 mg/day) 1.281 (if corticosteroids 10 mg/day) 0.675 (if 1 comorbidity) 1.024 (if 1 comorbidity).

Score of ….

1.53 = 5% risk

2.25 = 10% risk

2.69 = 15% risk

3.00 = 20% risk

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Infection Risk Assessment and Prevention

Use of Infection Risk Scores

- Three RA person-specific infection risk scores have been published.[1-3]
- All three combine:
  - Age
  - Comorbidities (e.g., diabetes, lung disease, renal disease)
  - Previous serious infection
  - Treatment with glucocorticoids
  - Treatment with biologic agents (e.g., TNF inhibitors)
- All three have been found to have good calibration and discrimination with observed risk.

[1]Crowson et al. Arthritis & Rheumatism 2012
[2]Curtis et al. Arthritis Care & Research 2012
[3]Zink et al. Annals of the Rheumatic Diseases 2014

Infection Risk Assessment and Prevention

Risk Communication and Education

- Tell patients about their risk factors for infection
- Convey absolute vs. relative risk
- Emphasize importance of seeking care early
- Recommend vaccinations
- Emphasize need to minimize steroids

Infection Risk Assessment and Prevention

Recommended Vaccinations

- The American College of Rheumatology recommends the following vaccinations in all patients with RA (evidence level C):
  - Influenza (intramuscular)
  - Pneumococcal
  - Herpes zoster virus*
  - Hepatitis B virus
  - Human papillomavirus
- Vaccinations ideally should be done <u>before</u> starting synthetic or biologic DMARDs

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Infection Risk Assessment and Prevention

Vaccine Safety and Effectiveness

Safety

- Vaccines due not increase the risk of RA[1]
- HZV vaccine was not associated with short-term rise in HZV incidence in Medicare patients exposed to biologics[2]

Effectiveness

- Effects of DMARDs on humoral responses to influenza and pneumococcal vaccines:

<u>Reduced:</u>

methotrexate[3]
rituximab[3,4]
abatacept[4]
tofacitinib[5]

<u>Unchanged:</u>

TNF inhibitors[3]
tocilizumab[6]

[1] Bengtsson et al. Annals of the Rheumatic Diseases 2010
[2] Zhang et al. Journal of the American Medical Association 2012
[3] Hua et al. Arthritis Care & Research 2014
[4] Crnkic Kapetanovic et al. Arthritis Research & Therapy 2013
[5] Bingham et al. Annals of the Rheumatic Diseases 20144Kapetanovic et al. Arthritis Research & Therapy 2013
[6] Windthrop et al. Annals of the Rheumatic Diseases 2014

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Infection Risk Assessment and Prevention

Pneumococcal Vaccination

Summary of the ACIP Recommendations for pneumococcal vaccines in adult patients with immunocompromising conditions such as RA:

Prior PPSV-23	Recommendation
None	Give PCV-13 followed by PPSV-23 at least 8 weeks later
One prior PPSV-23	Give PCV-13 (>1 year from last PPSV-23) Give booster PPSV-23 (5 years after the last PPSV-23)
Two prior doses of PPSV-23	If >1 year from last PPSV-23, then give PCV-13 Patients who are under age 65 are eligible to receive one further PPSV-23 after turning 65 years old

Perry et al. Current Rheumatology Reports 2014

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm

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Infection Risk Assessment and Prevention

Herpes Zoster Vaccination

- Risk of HZV infection is significantly increased in patients with RA
- Live-attenuated vaccine approved for use in individuals age 50 years or older
- ACIP and ACR recommend this vaccine in patients taking:
  - methotrexate (<0.4 mg/kg/week, e.g. 25 mg/week)
  - glucocorticoids (prednisone <20 mg/day or equivalent)
  - azathioprine (<1.5 mg/kg/day)
- HZV vaccination is considered contraindicated in patients taking TNF or non-TNF biologics

Perry et al. Current Rheumatology Reports 2014

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Infection Risk Assessment and Prevention

Screen for Latent Infections

- Treatment with TNF and non-TNF biologic therapies for RA can increase the risk of reactivation of latent tuberculosis infection (LTBI) and hepatitis B virus (HBV) infection.
- Screen all patients prior to starting therapy:
  - Tuberculin skin test, or
  - Interferon-γ release assay (IGRA)
  - Hepatitis B surface antigen (HBsAg)
  - Hepatitis B surface antibody (HBsAb)
  - Hepatitis B core IgG antibody (HBcAb)
- Follow guidelines for management if any positive.

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Infection Risk Assessment and Prevention

Management of Latent Infections

- If LTBI is detected, must treat with isoniazid for 9 months, ideally at least 1 month before starting a TNF or non-TNF biologic agent
- If positive HBsAg or HBcAb, must consult Hepatology for recommendations about antiviral therapy (tenofovir).

http://www.gastro.org/practice/medical-position-statements/Technical_Review_HBVr_07-07-2014.pdf

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Learning Objectives

After this lecture, learners will be able to assess risk and implement preventative strategies for:

1. Infectious diseases
2. Cardiovascular disease
3. Glucocorticoid-induced osteoporosis

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CV Risk Assessment and Prevention

Background on CV risk in RA

- Mortality is significantly increased in RA[1]
- 40 – 50% of deaths in RA are due to cardiovascular causes[2]
- Incidence of CVD is 50% higher in persons with RA than their peers in the general population[3]
- The increased risk of CVD is not fully explained by traditional CV risk factors[4]

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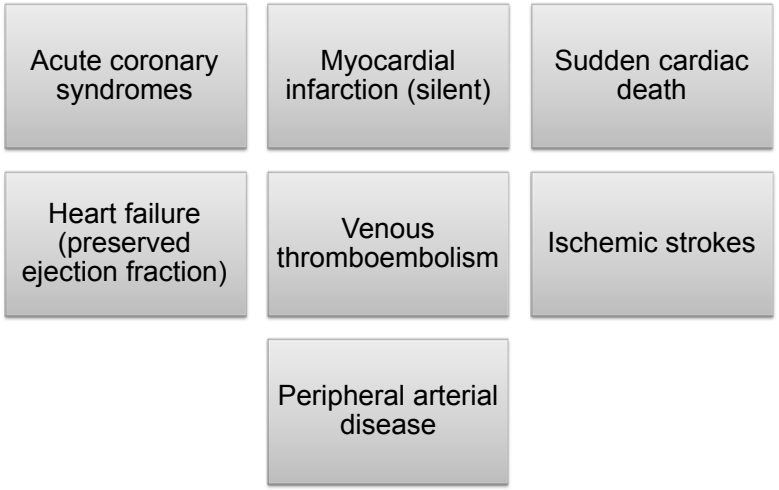
CV Risk Assessment and Prevention

Types of CVD that are increased in RA



Crowson et al. American Heart Journal 2013

CV Risk Assessment and Prevention

High 10-Year CV Risk in newly diagnosed RA

- Compelling data from a population-based incidence cohort of subjects with RA compared to matched non-RA cohort
- The absolute CV risk in RA subjects was similar to that of non-RA subjects 5 – 10 years older.
- More than half of 50-59 year old patients with newly diagnosed RA and all of those >60 years had a 10% or greater risk of CV disease over the next 10 years.

Maradit Kremers et al. Arthritis & Rheumatism 2008

CV Risk Assessment and Prevention

Preventative Strategies

1. Screen for CV risk factors
2. Estimate absolute 10-year CV risk
3. Implement lifestyle modifications
4. Initiate pharmacologic therapies
5. Periodically reassess control and compliance

CV Risk Assessment and Prevention

What are the risk factors for RA patients?

Traditional

- Age
- Tobacco smoking
- Hypertension
- Dyslipidemia
- Family history
- Diabetes
- Metabolic syndrome

Disease-Specific

- Disease activity scores
- Physical disability
- Rheumatoid factor
- Anti-CCP antibodies
- Rheumatoid nodules
- Extra-articular manifestations
- Erosive joint damage

CV Risk Assessment and Prevention

Role of the primary care provider

- The frequency of primary lipid screening has been reported to be only 45% among Medicare patients with RA.
- Lipid screening was significantly better among patients who saw their PCP at least annually.
  - Only 22% of patients who did not see their PCP annually had documented lipid screening (adjusted risk ratio 0.78, 95% CI: 0.71 – 0.84).
- These data underscore the need to have good partnership between PCP and rheumatologists to ensure adequate lipid screening.

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Bartels et al. Arthritis & Rheumatism 2011

CV Risk Assessment and Prevention

Screening for CV risk factors

- Measure blood pressure at every RA visit
  - Goal should be <130/85 as in diabetes
  - Often are confounding factors, i.e., NSAIDs or steroids, but take seriously
- Lipid screening
  - Measure fasting lipid profile in 1st year and then every 3 – 5 years if okay
- Measure high-sensitivity C-reactive protein
- Treat diabetes and metabolic syndrome according to standard guidelines

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CV Risk Assessment and Prevention

Assess absolute 10-year CV risk

- Recommend the ASCVD risk score using pooled cohort equations[1]
- Input the following variables:
  - Gender
  - Age
  - Race
  - Total cholesterol
  - HDL cholesterol
  - Systolic blood pressure
  - Treated or not for hgih blood pressure
  - Diabetes
  - Smoker

Output:

10-year risk of ASCVD

10-year risk in a similar patient with optimal risk factors

"elevated risk" is 7.5%

[1]Stone et al. Journal of the American College of Cardiology 2014

CV Risk Assessment and Prevention

Assess absolute 10-year CV risk

- We generally follow the current AHA/ACC guidelines for treatment of blood cholesterol[1]
- These guidelines recommend statin therapy for the following groups:
  1. Patients with clinical ASCVD
  2. LDL-C ≥190 mg/dL
  3. Patients with diabetes and LDL-C 70 – 189 mg/dL
  4. Patients without diabetes, age 40 – 75 years, LDL-C 70 – 189 mg/dL and ≥7.5% 10-year ASCVD risk.
- These guidelines do not take into account RA-specific risk factors

[1]Stone et al. Journal of the American College of Cardiology 2014

CV Risk Assessment and Prevention

Estimate 10-year CV risk

- Problems with CV risk scores (i.e., Framingham, new ASCVD risk score)[1]
  - Under-estimation of risk
  - Poor calibration and discrimination
- Current EULAR guidelines to use 1.5X modifier[2]
  - Disease duration ≥10 years
  - Positive RF or anti-CCP antibodies
  - Erosions
- But, modifier does not help …[1]

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CV Risk Assessment and Prevention

Individualizing CV risk management

- Consider RA specific risk factors
- Cardiology consultation
- Shared decision-making about statin therapy
- Goals and preferences of the patient
- Contraindications or prior intolerance of statins
- Non-invasive imaging to detect early ASCVD?(coronary calcium score, carotid ultrasonography, peripheral endothelial function)

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CV Risk Assessment and Prevention

When to refer to Cardiology?

- Severe disease with persistent disease activity
- Extra-articular disease manifestations (nodules, scleritis, vasculitis, lung disease, Felty's)
- Multiple CV risk factors in setting of RA
- Personal history of ASCVD

Learning Objectives

After this lecture, learners will be able to assess risk and implement preventative strategies for:

1. Infectious diseases
2. Cardiovascular disease
3. Glucocorticoid-induced osteoporosis

Glucocorticoid-Induced osteoporosis Background

- The World Health Organization (WHO) FRAX score includes RA as a fracture risk factor
- Glucocorticoid use in 40 – 50% of patients
- Glucocorticoids are associated with a significantly increased risk of fractures
- Doses as low as 2.5-7.5 mg daily associated with increased risk

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Grossman et al. Arthritis Care & Research 2010

Glucocorticoid-Induced osteoporosis Risk factors

- Low body mass index
- Parental history of hip fracture
- Current smoking
- ≥3 alcoholic drinks per day
- Higher daily glucocorticoid dose
- Higher cumulative glucocorticoid dose
- Intravenous pulse glucocorticoid therapy
- Declining central BMD exceeding least significant change

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Grossman et al. Arthritis Care & Research 2010

Glucocorticoid-Induced osteoporosis Preventative Approach

- To whom do these recommendations apply?
  - Post-menopausal women and men age >50 years
  - Anticipated or prevalent duration of glucocorticoid use for ≥3 months

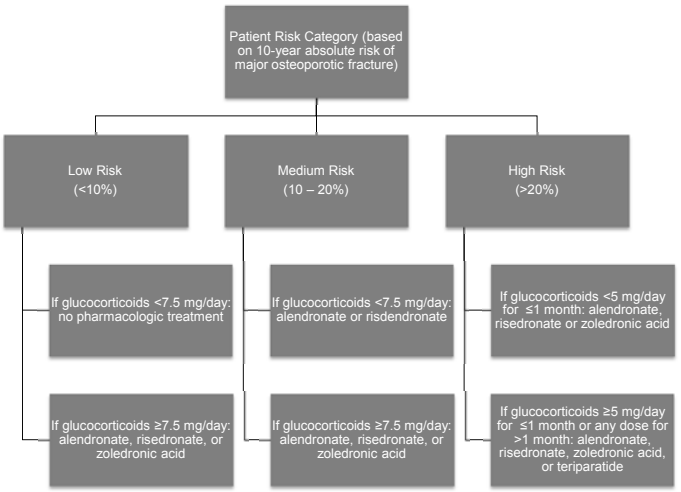
1. Counsel and assess risk factors of those patients starting or on prevalent glucocorticoid therapy
2. Determine patient risk category based on FRAX and other risk factors
3. Monitor patients on prevalent glucocorticoid therapy

Glucocorticoid-Induced osteoporosis Fracture Risk Assessment

- Use FRAX to estimate 10-year risk of major osteoporotic fracture and hip fracture:
- Input:
  - Age
  - Sex
  - Weight
  - Height
  - Previous fracture
  - Current smoking
  - Glucocorticoid use (5 mg for 3 months)
  - rheumatoid arthritis
  - Secondary osteoporosis
  - Alcohol 3 or more units/day
  - Femoral neck BMD (g/cm^2)

http://www.shef.ac.uk/FRAX/tool.aspx?country=9

Glucocorticoid-Induced osteoporosis Preventative Approach



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Grossman et al. Arthritis Care & Research 2010

Glucocorticoid-Induced osteoporosis Limitations

- Premenopausal women or men age <50 years without previous fracture?
- How long to treat?
- How to monitor?

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Grossman et al. Arthritis Care & Research 2010

Glucocorticoid-Induced osteoporosis Lifestyle and nutritional assessment

- Weight-bearing exercise
- Smoking cessation
- Avoidance of excessive alcohol intake
- Calcium and vitamin D intake
- Fall risk assessment
- Serum 25-hydroxyvitamin D level
- Calcium intake (supplement plus oral) 1,200 – 1,500 mg/day
- Vitamin D supplementation (800 – 1000 IU/day)

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Grossman et al. Arthritis Care & Research 2010

Summary and Conclusions

- The learner should be able to implement risk assessment and management strategies to prevent infection, ASCVD and glucocorticoid-induced osteoporosis.
- We discussed the importance of being pro-active and individualizing assessment.
- Shared decision-making is key given incomplete evidence base.
- Collaborative care approaches are often valuable to improve preventative care.

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Return to Program Schedule

CRYSTALLINE ARTHROPATHIES

WITH A FOCUS ON THE NON-URATE ARTHROPATHIES

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Division of Rheumatology
Mayo Clinic in Florida

Disclosures

- Financial relationships: None
- Off-label uses of drugs/devices: None

Return to Program Schedule

Objectives

- Know when to suspect crystal-induced arthritis in your differential diagnosis
- Recognize the clinical and radiographic features of the non-gout crystal arthropathies
- Differentiate between benign crystal arthropathy vs. potentially destructive forms
- Offer initial diagnostic workup and treatment

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Overview of the Crystal Arthropathies

- Major forms
  - Uric acid
  - Calcium pyrophosphate dihydrate (CPPD)
  - Basic calcium phosphate (BCP, incl. hydroxyapatite)
- Most frequent presentation is monoarthritis
- May also present as tendonitis and periarthritis
- Varied clinical acuity
  - Intensely inflammatory – all crystals may produce this
  - Indolent or asymptomatic –CPPD

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Case Study

- 79 year old Caucasian female
- Breast cancer survivor – mastectomy, chemotherapy 1994
- Acute right wrist pain with swelling, warmth x 3 days
- No other joints involved
- No history of trauma, no changes in medications
- Examination reveals warm, tender right wrist, decreased flexion, extension, lateral deviation with pain; joint examination features non-inflammatory OA changes in the hands; no tophi
- CBC, creatinine, AST, ALT, alkaline phosphatase, total calcium, albumin, RF, ESR, SPEP normal

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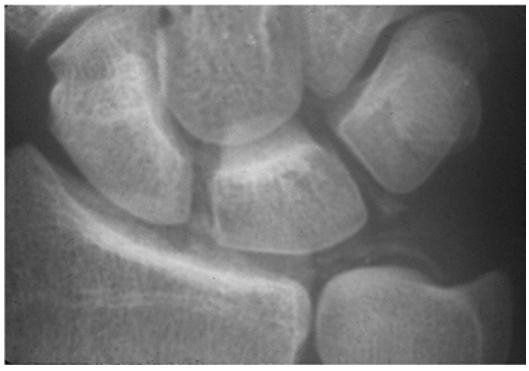
Case, cont.



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Case, cont.

- Joint aspiration performed in office – no crystals seen on polarized microscopy
- Single injection of 40 mg methylprednisolone to the wrist effective within 2 days; no recurrent symptoms
- Provisional diagnosis: CPPD deposition disease, pseudogout, osteoarthritis

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Common Clinical Syndromes

Common clinical syndromes associated with the deposition of calcium crystals

Periarticular deposits of BCP crystals	Asymptomatic, incidental finding Acute calcific periarthritis Chronic periarticular pain and/or joint dysfunction
Intra-articular deposits of BCP crystals	Asymptomatic, incidental finding Acute synovitis Severe OA Destructive arthropathy (eg, Milwaukee shoulder syndrome)
Intra-articular CPP crystals	Asymptomatic, incidental finding Acute CPP crystal arthritis (pseudogout) Chronic CPP inflammatory arthritis OA with CPP

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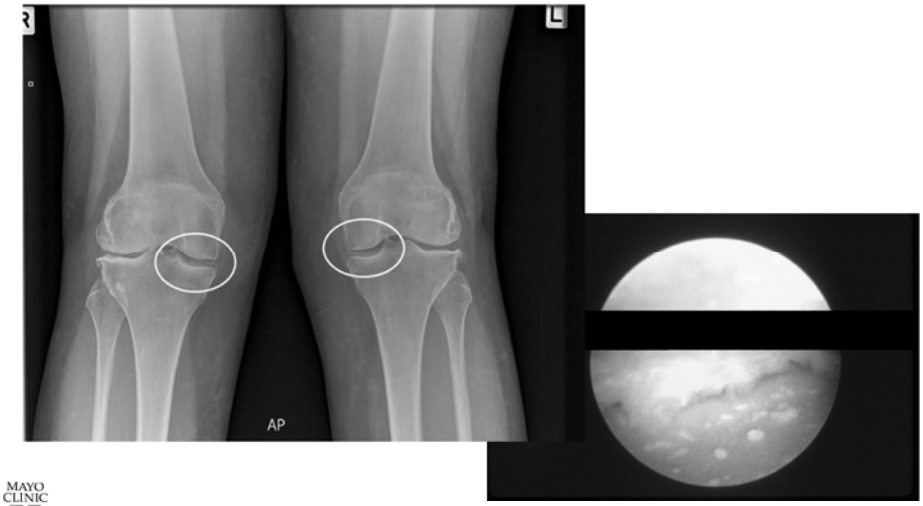
Durcan L, et al. Rheum Dis Clin N Am 40 (2014) 311–328

Asymptomatic CPPD with Osteoarthritis



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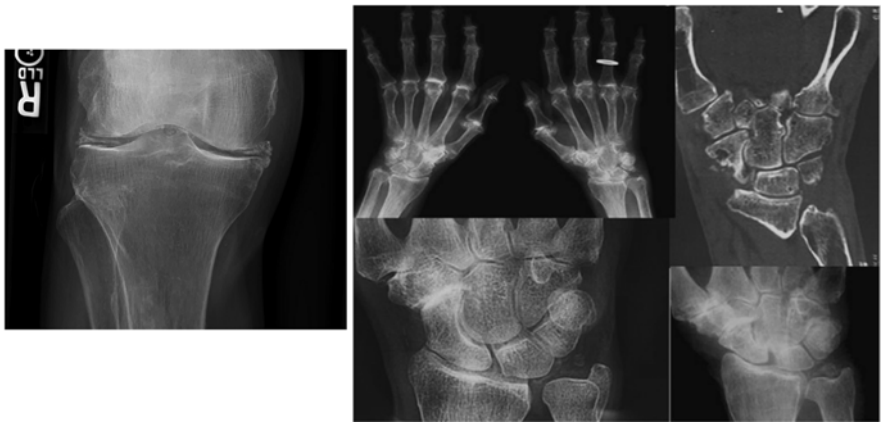
CPPD with Osteoarthritis



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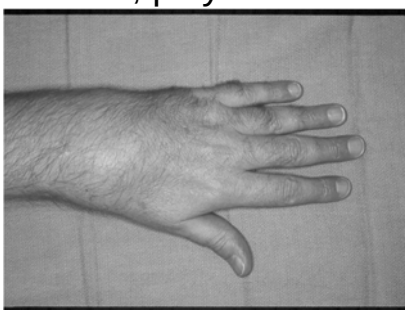
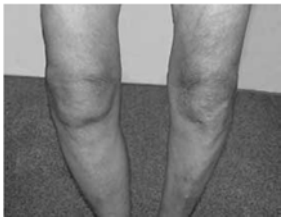
Ea H-K and Lioté F. Rheum Dis Clin N Am 40 (2014) 207–229

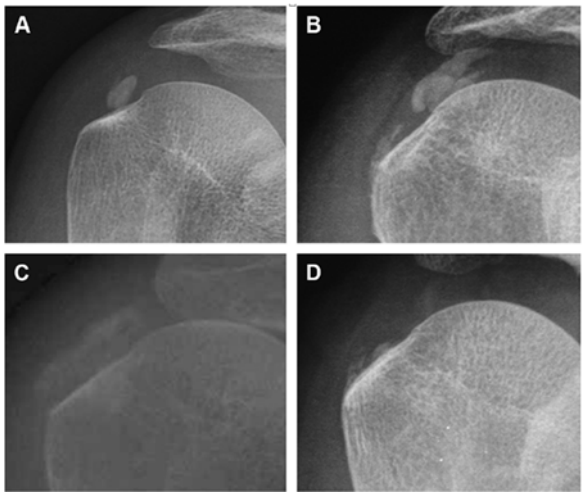
Acute Arthritis

- Clinical patterns
  - Pseudogout – monoarticular, polyarticular (rare)
  - Pseudo-RA
  - Pseudo spondylitis





Calcific Tendonitis



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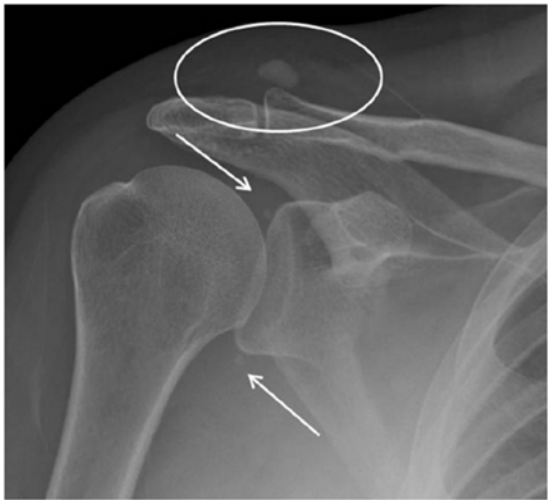
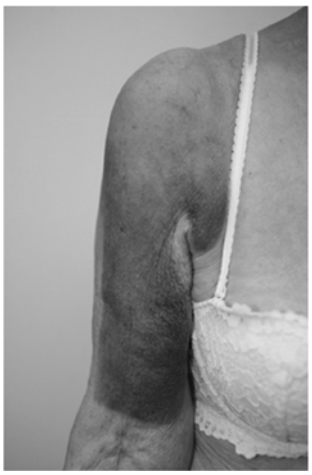
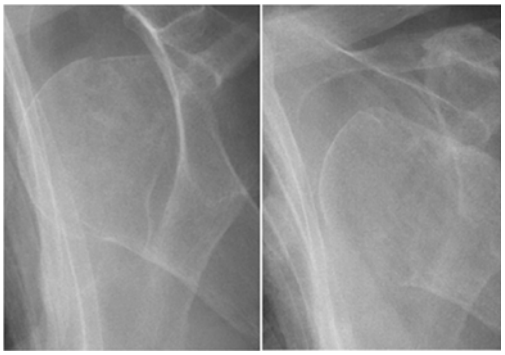
Calcific Periarthritis



McQueen FM et al. Rheum Dis Clin N Am 40 (2014) 231–249

Milwaukee Shoulder





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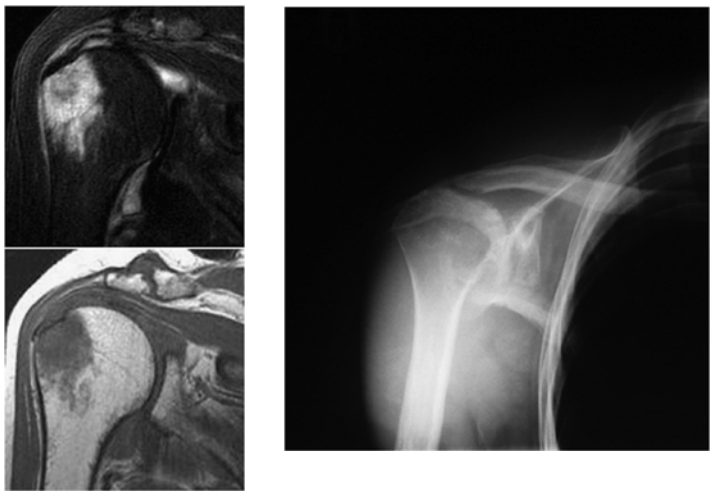
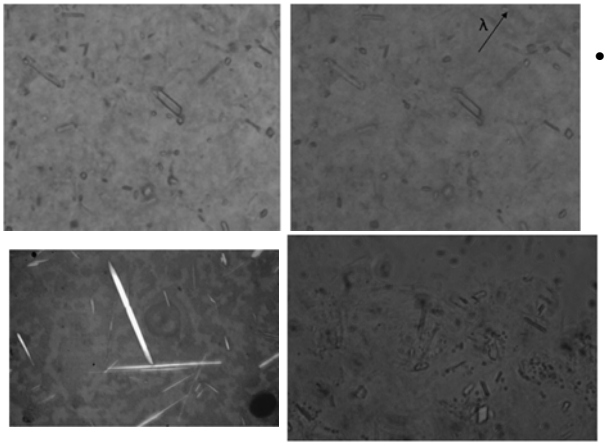


Durcan L et al. Rheum Dis Clin N Am 40 (2014) 311–328

Diagnosis

- Synovial fluid analysis: polarized light microscopy
- Radiology
  - Plain x-ray
  - CT
  - MRI
  - Ultrasound
- Electron microscopy
- X-ray difraction

Microscopic Crystal Analysis



- WEAK positive birefringence (purple-violet when parallel to the axis of the polarizer)

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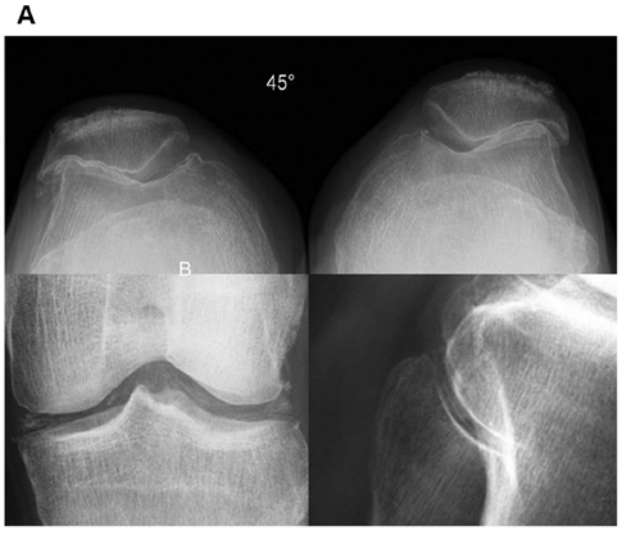
Plain Radiography



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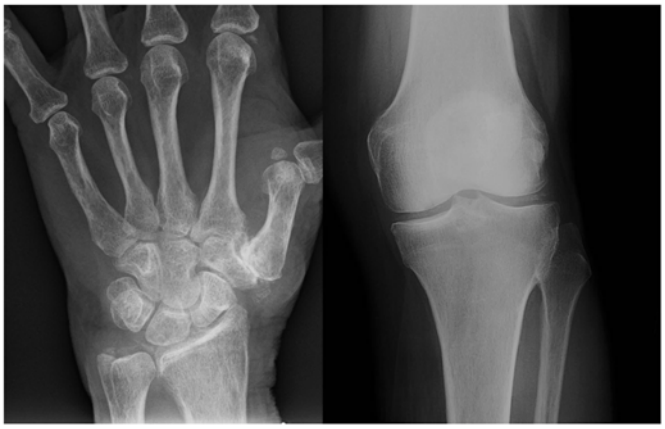
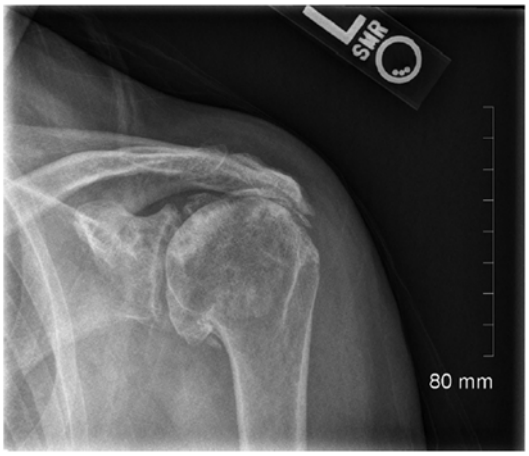
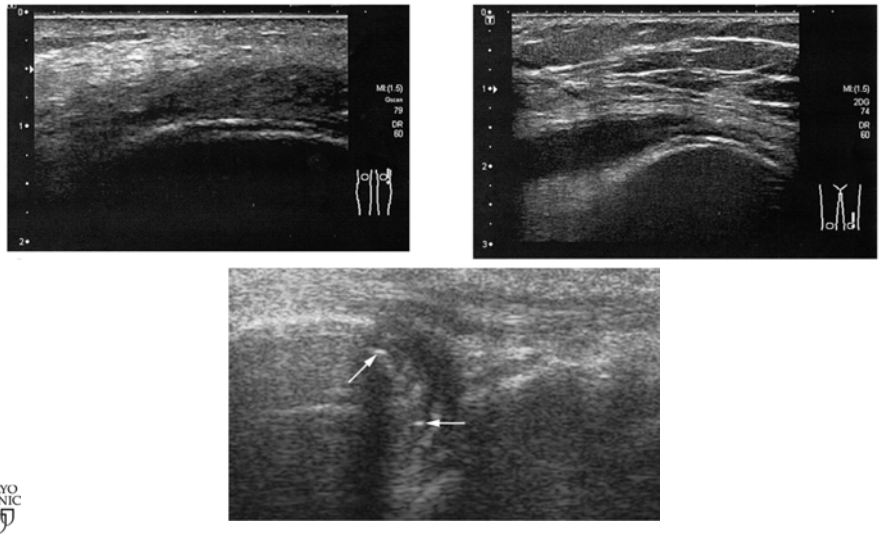
Plain Radiography



Miksanek J and Rosenthal AK. Curr Rheumatol Rep (2015) 17:20

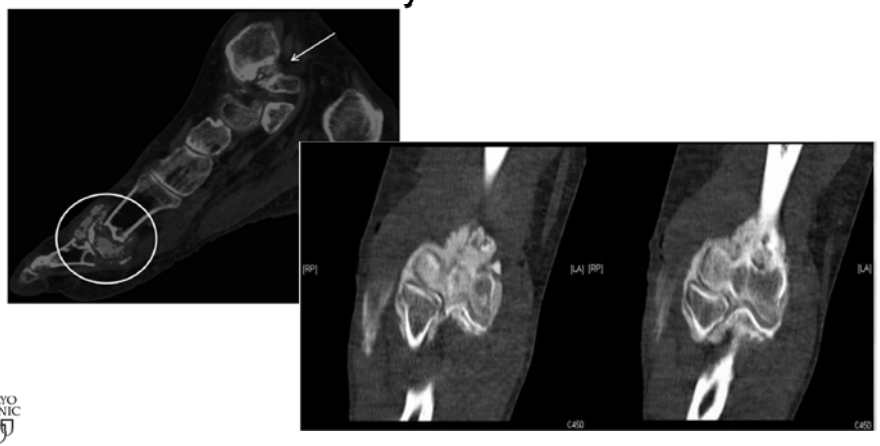


Ultrasound

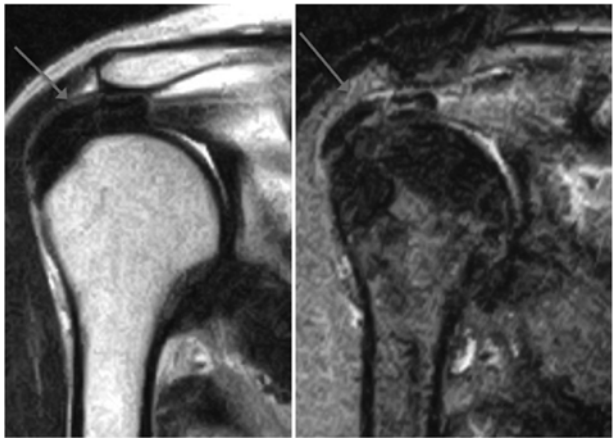


CT Scan

- Dual-energy CT scan for urate will not detect calcium crystals



MRI



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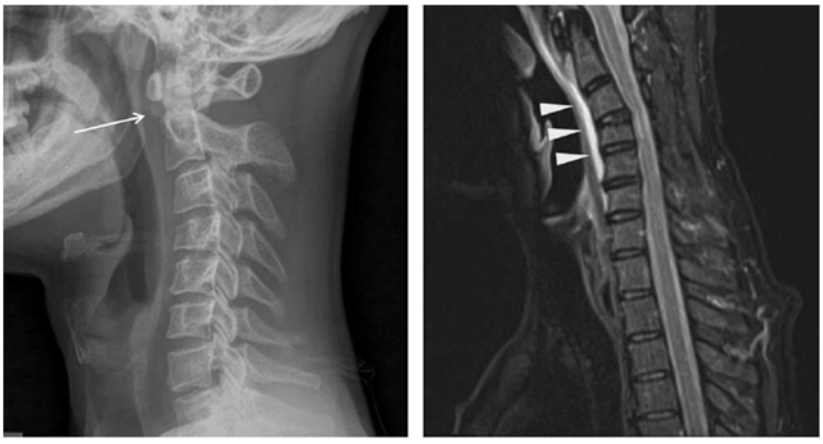
MRI



McQueen FM et al. Rheum Dis Clin N Am 40 (2014) 231–249

Risk Factors for CPPD

- Age >55
- Osteoarthritis
- Primary genetic syndrome: ANKH gene mutation*
- Endocrinopathies and metabolic disorders*
  - Hyperparathyroidism
  - Hypomagnesemia
  - Hypophosphatasia
  - Chronic kidney disease stage 5
  - Hemachromatosis

*Screen if polyarticular disease or younger age of onset

Treatment

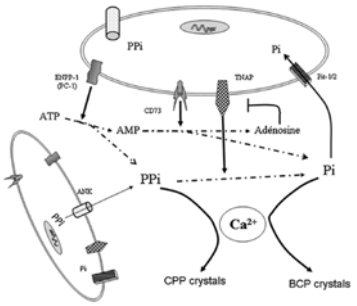
- No therapy for calcium crystal disease has been rigorously evaluated or compared
- Acute CPPD arthritis, periarthritis – treat like acute gouty arthritis
  - NSAIDs
  - Colchicine
  - Corticosteroids – oral or intra-articular
  - ACTH
  - Anti-IL-1 biologic therapy – anakinra, canakinumab
- Acute calcific tendonitis
  - As above
  - *Barbotage,* or needling of acutely inflamed tendon to reduce intratendinous pressure
  - Extracorporeal shock-wave therapy (ESWT)

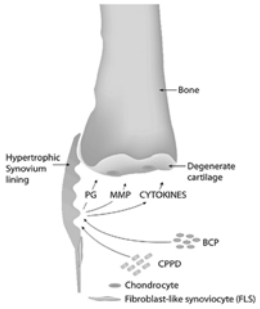
Treatment

- Chronic inflammatory CPPD
  - Long-term corticosteroids
  - Colchicine (weak evidence)
  - Methotrexate
  - IL-1 antagonism
  - Hydroxychloroquine, long term NSAIDs, magnesium, probenecid
- Milwaukee shoulder syndrome
  - Repeated joint aspiration and corticosteroid injection
  - Joint arthroplasty

Pathogenesis

- Genetic predispositions: ANKH gene leading to overexpression of ANK protein (pyrophosphate transport)





Kachewar SG and Kulkarni DS. J Clin Diagn Res 2013; 7(7):1482–5.
Markello TC et al. Mol Genet Metab 2011;103(1):44–50

Common Clinical Syndromes

Common clinical syndromes associated with the deposition of calcium crystals	
Periarticular deposits of BCP crystals	Asymptomatic, incidental finding Acute calcific periarthritis Chronic periarticular pain and/or joint dysfunction
Intra-articular deposits of BCP crystals	Asymptomatic, incidental finding Acute synovitis Severe OA Destructive arthropathy (eg, Milwaukee shoulder syndrome)
Intra-articular CPP crystals	Asymptomatic, incidental finding Acute CPP crystal arthritis (pseudogout) Chronic CPP inflammatory arthritis OA with CPP

MAYO CLINIC

Durcan L, et al. Rheum Dis Clin N Am 40 (2014) 311–328

Summary

- Calcium crystal disorders are a common yet under-recognized cause of acute arthritic syndromes
- Very commonly asymptomatic and found on plain x-rays
- Suspect calcium disorders in an older individual with
  - acute monoarthritis in an older individual
  - acute tendinitis
  - acute or refractory shoulder monoarthritis
- Management
  - Plain radiography is the most helpful imaging modality
  - Perform synovial fluid analysis when possible, but yield is lower
  - Screen for metabolic or genetic disorders in a younger patient
  - Treatment is largely empiric and based on acuity of presentation

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Return to Program Schedule

Gout Management

Rheumatology Update 2015
Ponte Vedra Beach, Florida
April 17, 2015

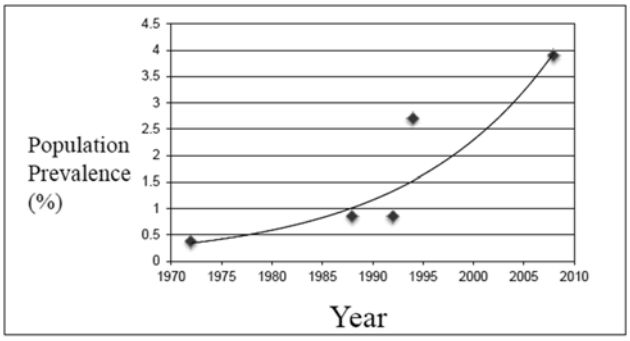
Leroy Griffing MD
Mayo Clinic Arizona
lgriffing@mayo.edu

Disclosures

- Bayer HealthCare - study site PI
- Off-label medications in presentation
  - Lesinurad

Return to Program Schedule

Gout



Zhu et al. Arthritis Rheum 2011;10:3136-41

MAYO CLINIC

Case 1

A 52 y/o mildly obese male presents with a 2 day history of awakening with his right big toe painful, red, and swollen. No trauma, but he recalls 8 months ago his left big toe became sore and modestly swollen for 4 days that he blamed on a piece of lumbar falling on his work boot at his construction job. He drinks 2 beers nightly and more on weekends. With suspicion for possible gout, a serum uric level is obtained (male: 3.7-8.0 mg/dl).

Gout can be clinically excluded from further consideration if the result is:

a) 9.7
b) 7.5
c) 5.2
d) B and C above
e) none of the above

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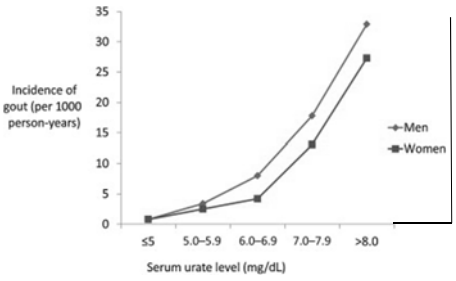
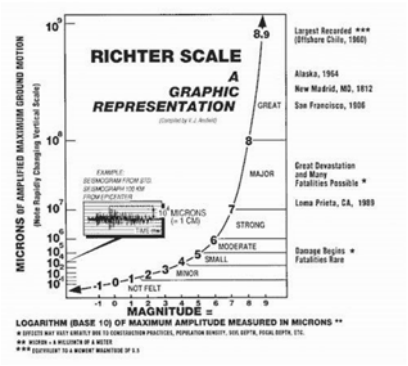
Hyperuricemia

- For gout purposes:
  - Is defined as a serum urate level ≥ 6.8 mg/dl
    - Upper limit of urate solubility at physiologic temperature and pH.
    - Population-based normals are misleading (M: 3.7-8.0; F: 2.7-6.1).
  - Is necessary but not sufficient to cause gout
    - Asymptomatic hyperuricemia
  - May not be apparent during an acute attack (12-43%)
    - Serum level may transiently drop by 1.5-2.0 mg/dl.
    - Retest after the acute attack is treated.

MAYO CLINIC

Hyperuricemia



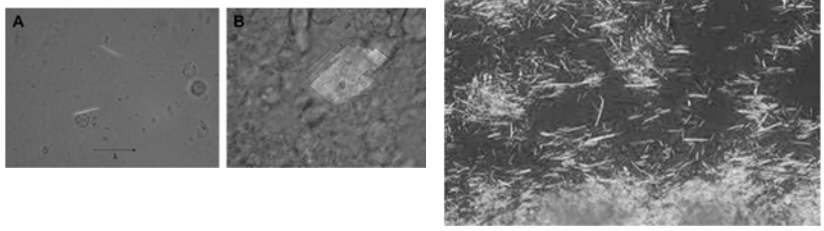


MAYO CLINIC

Roddy, et al. Rheum Dis Clin N Am 2014;40: 155-75

Diagnostic Standard

Aspiration of joint synovial fluid or a tophus with monosodium urate (MSU) crystals confirmed by polarized microscopy



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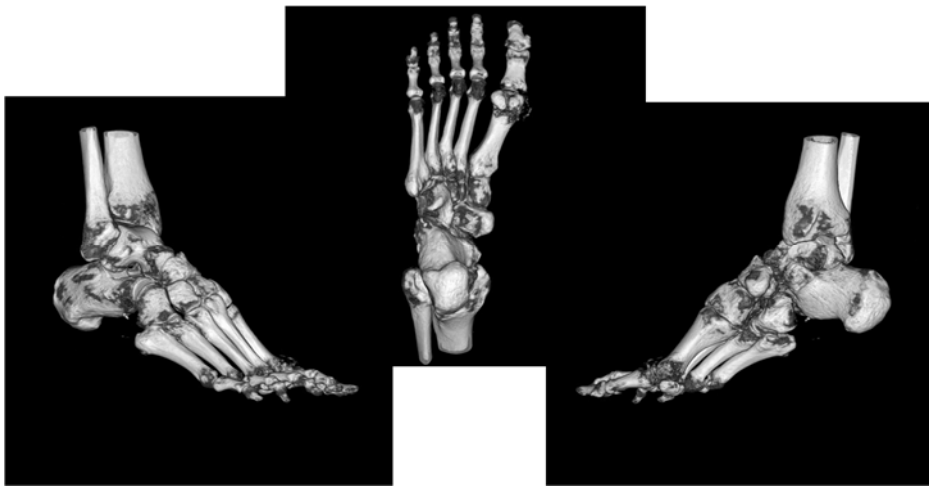
Dual Energy CT Scan (DECT)



MAYO CLINIC

Dalbeth et al. Curr Rheumatol Rep 2013;15:301

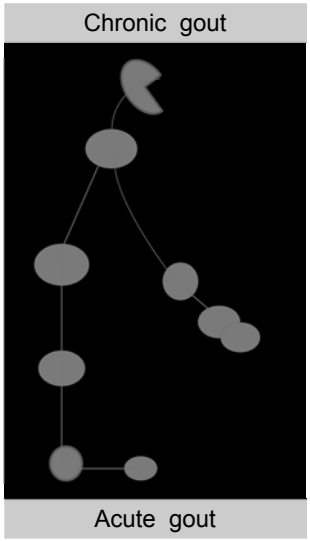
Diagnosis

- Clinical Triad
  - Acute monoarticular arthritis
    - Severe pain, erythema, swelling
    - Nocturnal onset
    - Maximum intensity reached within 24 hours
    - Resolves after 4-10 days
  - Hyperuricemia
  - Responsive to colchicine
- Limitations
  - Other etiologies may mimic
  - Hyperuricemia (depends)
  - Other acute arthritis may respond to colchicine

MAYO CLINIC

Diagnosis

- Acute Gout
  - 1st attack involves a single joint (90%)
    - 1st MTP (90%)
  - Subsequent attacks predominantly involve lower extremity joints
    - 1st MTP (90%)
    - Next, in order of frequency;
      - instep, ankles, knees
  - Frequency increases with time
  - Later attacks in upper extremity joints
    - fingers, wrists, elbows
- Chronic Gout
  - Attacks polyarticular and continuous
  - tophi
  - fever



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Management of Acute Attacks

Aim: rapid relief of pain and disability

Ideally, treat within 24 hours of onset

Assess Severity and Context

Supplement with topical ice as needed.

Monotherapy — Pain <7/10 or 1-2 joints

Combination therapy — Pain ≥7/10 or polyarticular

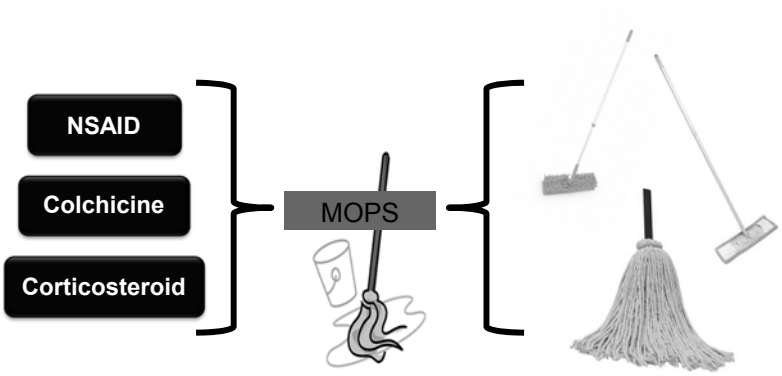
NSAID	Corticosteroid	Colchicine	1. NSAID + colchicine 2. Corticosteroid + colchicine
Full dose until the attack resolves – with an option to taper	Prednisone 0.5mg/kg daily X 5-10 days or, 2-5 days, then taper 7-10 days Or, Medrol dose pack Optional: IA triamcinolone acetonide (larger joints) IV methylprednisolone	Best if attack < 36 hrs duration Loading dose 1.2mg orally followed by 0.6mg 1 hr later 12 hrs later, begin 0.6mg 1-2X daily until attack resolves	Optional (larger joints) IA triamcinolone acetonide

MAYO CLINIC

Adapted from Khanna et al. Arthritis Care & Res 2012;64:1447-61

Management of Acute Attacks

Aim: rapid relief of pain and disability



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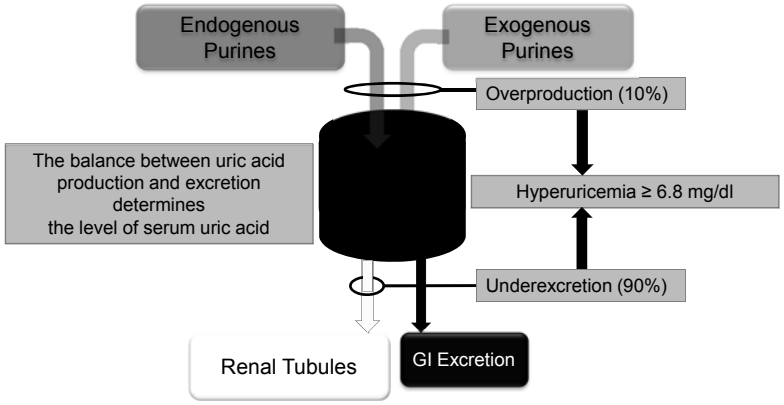
Hyperuricemia



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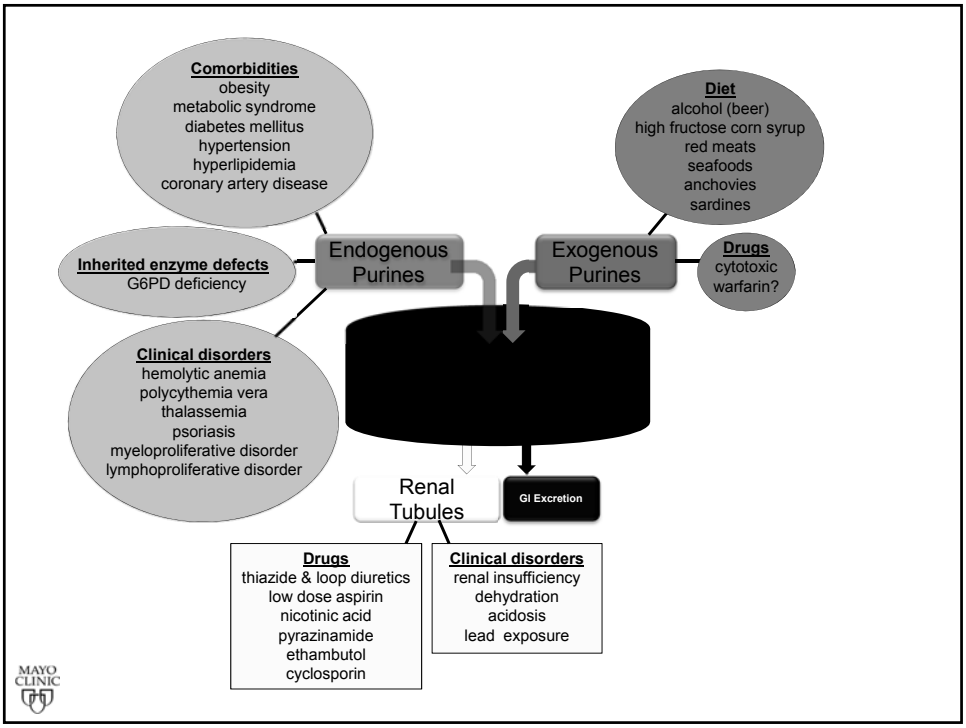

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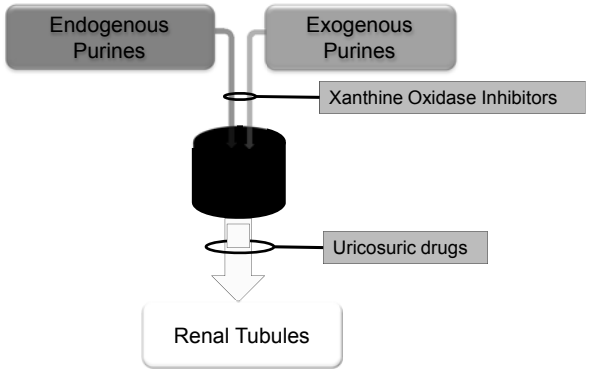
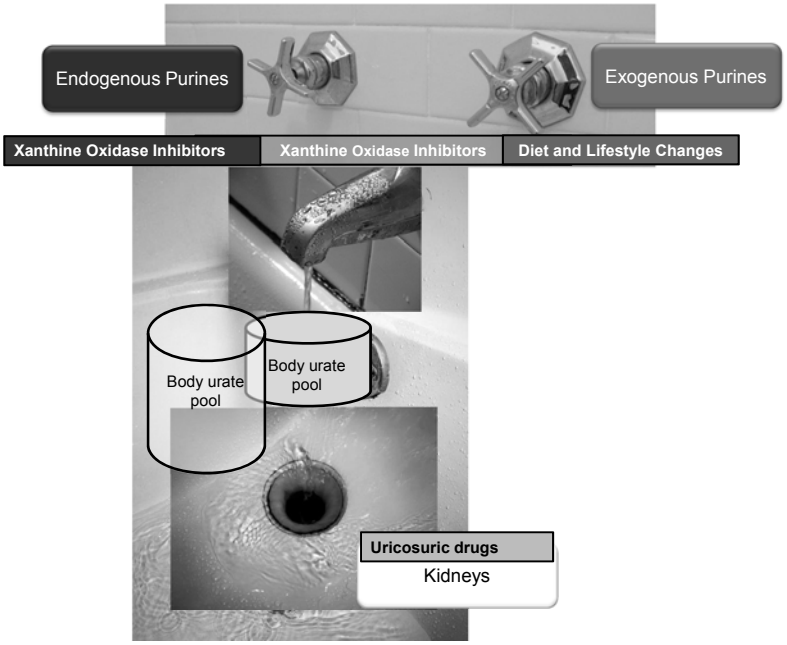
Urate Lowering Therapy



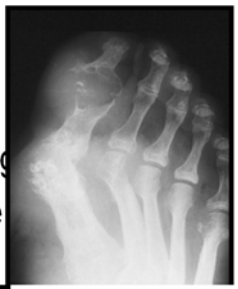
Urate Lowering Therapy

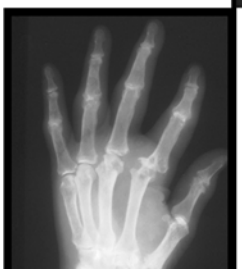
- Xanthine Oxidase Inhibitors
  - Allopurinol
  - Febuxostat
- Uricosuric Agents
  - Probenecid
  - Modest potency
    - Losartan
    - Fenofibrate
    - Vitamin C

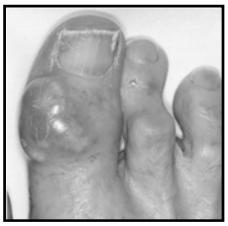


Urate Lowering Therapy

- Indications
  - History of ≥ 2 attacks
  - Tophus by examination or imag
  - Chronic kidney disease (stage
  - Prior urolithiasis
  - Joint damage







Urate Lowering Therapy

- Xanthine Oxidase Inhibitors
  - Allopurinol
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- Uricosuric Agents
  - Probenecid
  - Modest potency
    - Losartan
    - Fenofibrate
    - Vitamin C

MAYO CLINIC

Urate Lowering Therapy

- Xanthine Oxidase Inhibitors
  - Allopurinol
  - Febuxostat

Characteristics	Allopurinol	Febuxostat
Action	Nonspecific XO inhibition	Selective XO inhibition
Elimination	Renal	Hepatic
Daily Dose	(50mg), 100-800mg	40mg or 80mg
Cautions	Severe CKD	Hepatic failure; eGFR< 30ml/min
Interactions	Azathioprine, mercaptopurine, warfarin	Azathioprine, mercaptopurine
DRESS (drug reaction with eosinophilia and systemic symptoms)	Rare	Rare

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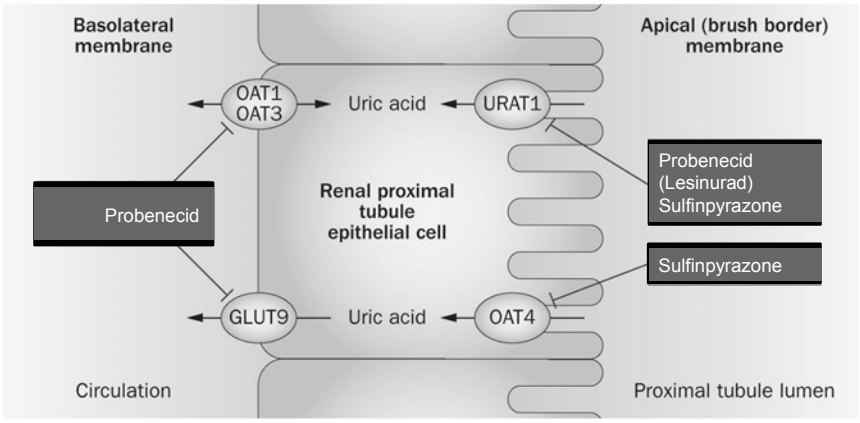
Rees et al. Nat Rev Rheumatol 2014;10:271-283

Urate Lowering Therapy

- Uricosuric agent: Probenecid
  - Least commonly used approach
    - Requires confirmation of urate underexcretion (<800 mg/24 hr)
    - TID dosing
    - 9% develop nephrolithiasis (K citrate prophylaxis)
    - Frequent drug-drug interactions
  - Contraindicated
    - Cr cl <50 ml/min
    - Prior nephrolithiasis
  - More often is added to a XO inhibitor if refractory disease

Mechanism of Action of Uricosuric Drugs



Adapted from Rees et al. Nat Rev Rheumatol 2014; 10: 271-283

Case 2

A 62 y/o obese male with a history of 3 attacks of gout in the past 2 years involving each of his big toes presents with another severe attack starting yesterday in his left ankle. Colchicine is prescribed as in the past and lab tests obtained while his is in the office. He returns 2 days later to go over the results and reports the attack is 50% better. His serum uric acid level is 9.9 mg/dl (male nl: 3.7-8.0) and creatinine 1.2 mg/dl. Unlike the past, this visit he is willing to consider allopurinol.

The best advice is to:

a) continue colchicine and start now allopurinol 300 mg/day
b) continue colchicine and start now allopurinol 100 mg/day
c) continue colchicine for 2 weeks; then start allopurinol 300 mg/day
d) continue colchicine for 2 weeks; then start allopurinol 100 mg/day

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Urate Lowering Therapy

Introducing Allopurinol

- Timing
  - Problem:
    - Acute urate lowering during an attack may intensify or prolong the attack
  - Strategy:
    - Wait 2 weeks after the attack has resolved before initiating
    - Initial dose ≤ 100 mg/day (50 mg/day if CKD)

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Urate Lowering Therapy

Introducing Allopurinol

Mop first and Go Low - Avoid the Splash

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Urate Lowering Therapy

Introducing Allopurinol

- Safety
  - Problem:
    - Acute urate lowering may cause allopurinol hypersensitivity syndrome/DRESS
      - 1:1000 with 20-25 % mortality
      - Within first few months of use
      - Risk factors
        - » Higher initial dosing!
        - » Age and female gender
        - » Thiazide diuretics
        - » CKD
        - » Risk haplotype HLA-B*5801 in Korean pts with stage ≥3 CKD, and in all Chinese or Thai pts
  - Strategy:
    - Initial dose should be ≤100 mg/day (50 mg/day if CKD stage 4-5)
    - If risk haplotype, use alternative urate lowering approach

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Case 3

A 68 y/o obese, hypertensive, diabetic female has a history of 4 attacks of gout in the past 5 years involving her big toes and one foot. Two of these attacks have been within the past year. She was seen two weeks ago with a severe attack in her right knee beginning 2 days earlier. Her serum creatinine is 1.4 (eGFR 45 cc/min). Colchicine was felt to be the safest choice and she completed the 2 weeks of treatment with resolution of the attack. Her serum uric acid is now 9.4. Allopurinol is advised and started 100 mg/day. After 2 weeks at this dose, the next step(s) in her care should be:

a) increase allopurinol to 300 mg/day maximum
b) increase allopurinol by 100 mg increments every 2 weeks to 300 mg/day maximum.
c) increase allopurinol by 100 mg increments every 2 weeks to the lowest dose (≤800 mg/day) that achieves a serum urate 8.0 mg/dl.
d) same as (C) but achieves a serum urate of 6.8 mg/dl.
e) same as (C) but achieves a serum urate of 6.0 mg/dl.

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Adequately Addressing Hyperuricemia

- Serum uric acid
  - Achieve target
    - ≤ 6 mg/dl at a minimum
    - < 5 mg/dl if extensive disease including tophi
  - Laboratory normal ranges – do not rely on
    - Male: 3.7-8.0 mg/dl
    - Female: 2.7-6.1 mg/dl

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Urate Lowering Therapy

Effective and Safe Use of Allopurinol

- Initiation
  - ≤100 mg/day
  - 50 mg/day if CKD stage 4-5
- Titration
  - Gradually in 50-100 mg increments every 2-4 weeks
  - Get to lowest dose that achieves target serum urate level
    - » 50-800 mg/day
    - » 300 mg/day achieves target level in only 21-55% of individuals
    - » Dose can be >300 mg/day in CKD if accompanied by
      - Patient education on lifestyle changes
      - Monitoring for drug toxicity
        - Rash, fever, pruritus, LFT's, anemia, cytopenias

Stamp et al. Arthritis Rheum 2011;63:412-21

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Urate Lowering Therapy

Effective and Safe Use of Allopurinol

- Initiation
  - Wait - mop the floor first
  - Go low - avoid the splash and the rash
- Titration
  - Allopurinol often started too high and sustained too low
  - Go slow
  - But go the distance – Get to target serum urate level
- The lower the serum urate level, the faster the reduction of tophi

3 T's

Timing Titration Target

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Urate Lowering Therapy

- Pegloticase
  - Pegylated mammalian (porcine-like) recombinant uricase
    - 8 mg IV every 2 weeks
  - Profound reduction
    - serum uric acid level to <1 mg/dl within 24-72 hrs.
    - tophi
  - Pegloticase antibody - 90%
    - Loss of effect
    - Infusion reactions (50-75%)
    - Anaphylaxis (5%)
  - Reserved for symptomatic advanced tophaceous gout

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Case 4

A 58 y/o hypertensive male with a history of at least 5 attacks of gout in the past 3 years had another attack most recently 9 weeks ago in his right foot which was treated with successfully with colchicine for two weeks. His serum uric acid level was then 8.6 mg/dl and creatinine 1.3 mg/dl. Allopurinol 100 mg/day was started and titrated in increments of 100 mg every two weeks up to 300 mg/day as of last week when his serum uric acid level was 6.8 mg/dl. Because the level was still above target, the allopurinol dose was increased to 400 mg/day. He calls today as he thinks the allopurinol must not be working after all because another attack came on last night in his left ankle.

The best advice is:

a) take colchicine for 2 weeks and continue allopurinol at 400 mg/day.
b) take colchicine and reduce allopurinol back to 300 mg/day for 2 weeks; then resume allopurinol 400 mg/day
c) stop allopurinol; take colchicine for 2 weeks; then resume allopurinol 400 mg/day.
d) stop allopurinol; take colchicine for 2 weeks; then switch to febuxostat 40 mg daily.

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Urate Lowering Therapy and Acute Attacks

- Newly introduced urate lowering therapy (< 6 months)
  - Prophylaxis against acute attacks
    - Advised for all patients simultaneous with initiating urate lowering treatment
    - Most often colchicine or NSAID
    - Duration
      - If no tophi: 3-6 months after target uric acid level achieved (≤ 6 mg/dl at a minimum)
      - Tophi or extensive disease: 6 months after target uric acid level achieved (≤ 5 mg/dl)
  - Prophylaxis failures
      - Do not reduce or stop urate lowering therapy!
      - Brief course of prednisone or Medrol dose pack
      - Resume prophylaxis for appropriate remaining duration
      - Assure target serum urate level gets achieved.

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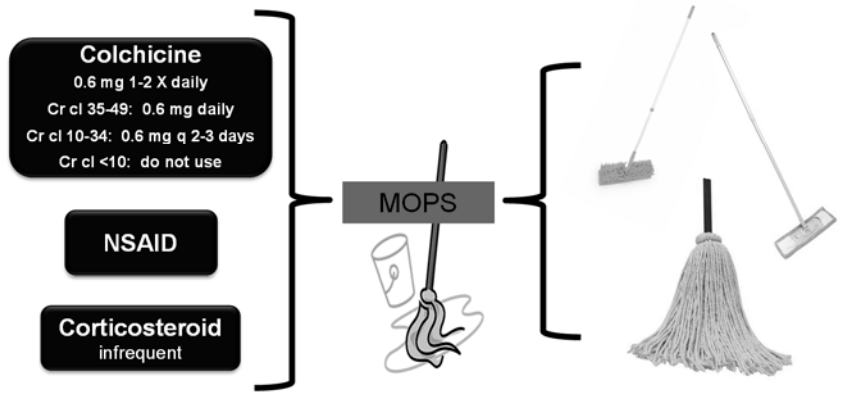
Prophylaxis Against Acute Attacks

Keeping the floor dry for 3-6 months while the tub drains



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Urate Lowering Therapy and Acute Attacks

- Established urate lowering therapy (> 6 months-years)
  - Acute attacks
    - Do not reduce or stop urate lowering therapy!
    - Treat with a “mop”
      - Colchicine
      - NSAID
      - Brief course of prednisone or Medrol dose pack
  - After the acute attack
    - Re-evaluate: Has target serum uric acid level been maintained?
    - If not:
      - Compliance?
      - Change in renal status?
      - New medication?
      - Other illness or event?

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Return to Program Schedule

Back Pain

Thomas D. Rizzo, Jr., M. D.
Department of Physical Medicine and Rehabilitation
Mayo Clinic
Jacksonville, Florida

Mayo Clinic Rheumatology Update
April 17, 2015

Disclosures

- I will not speak about any off-label use of medications
- I do not receive payments from Big Pharma or Device Manufacturers
- I am not beholden to The Man.

Return to Program Schedule

Objectives

- Red Flags: What are they and what do they mean
- How to evaluate
- Differential Diagnosis
- Imaging and Testing
- When to refer and to whom

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Why am I seeing Back Pain?

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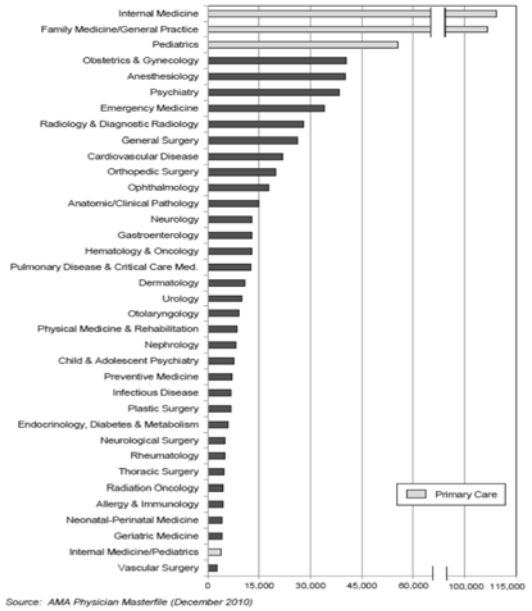
Figure 3. Specialties with the Largest Number of Active Physicians, 2010



Source: AMA Physician Masterfile (December 2010)

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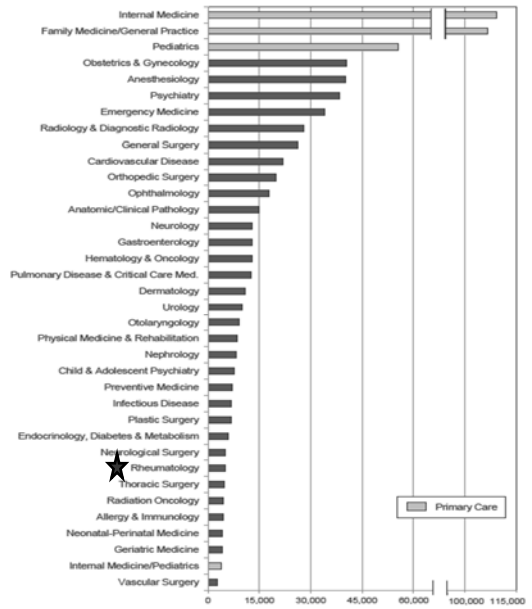
Figure 3. Specialties with the Largest Number of Active Physicians, 2010



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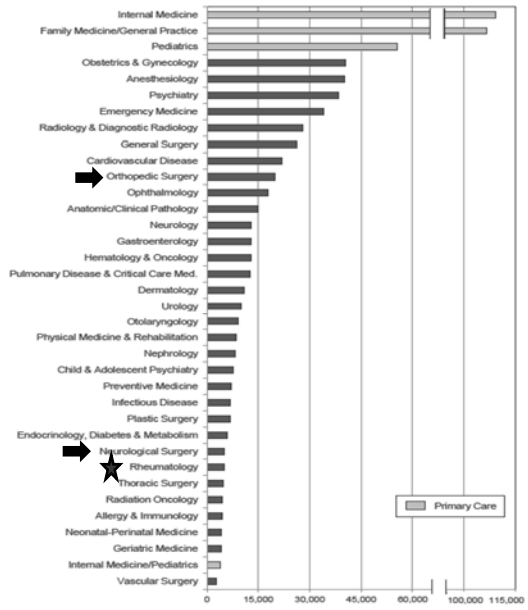

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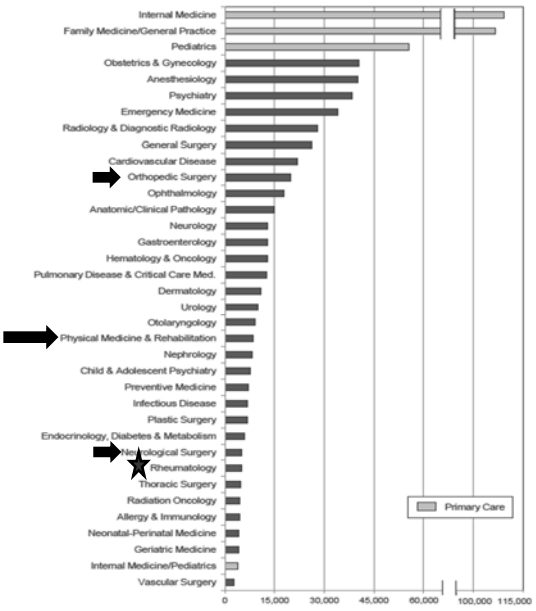

Source: AMA Physician Masterfile (December 2010)

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Why Patients Visit Their Doctors

- Skin disorders
- Osteoarthritis/joint disorders
- Back problems
- Cholesterol problems
- Upper respiratory conditions (not including asthma)
- Anxiety, depression and bipolar disorder
- Chronic neurologic disorders
- High blood pressure
- Headaches/migraine
- Diabetes
- Why Patients Visit Their Doctors: Assessing the Most Prevalent Conditions in a Defined American Population St. Sauver J L., Warner D O., et al., Mayo Clinic Proceedings Volume 88, Issue 1 , Pages 56-67, January 2013

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Low Back Pain
Impact

- 80% of people will have low back pain at some time
- 80% will resolve spontaneously in 3 months
  - 20% take longer than 3 months (chronic)
- 80% of patients with pain > 3 months will get better with other interventions

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Low Back Pain Impact

- 96 % of people with LBP will get better with time or conservative measures
- 4% don't

Challenges

- Who is in the 4%?
- Can you make the 4% less?
- How can you keep the 4% happy?

Red Flags

- Who doesn't get imaging
  - No trauma
  - Activity related pain that resolves with rest
  - No constitutional symptoms
  - No concern of systemic disease
  - Recent onset/intermittent symptoms

Red Flags

- History
  - Age > 50
  - Drug or alcohol abuse
  - Significant trauma
  - Previous malignancy
  - Use of corticosteroids
  - Intended litigation or compensation
- Physical Examination
  - Fever
  - Findings suggestive of Anklylosing Spondylitis
  - Significant Weight loss
  - Motor neurologic deficits

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Evaluation

- Begin with the end in mind
- Death or Irreparable harm
- History
- Physical Exam
- Testing
- Referral

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Physical Exam

- Logic
- Movement
- Symmetry of findings
  - Muscle spasm or tightness
- Neurologic exam
  - Asymmetry rather than “normal”
  - Sensation? Who knows?
  - If yours is not reliable, refer

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Other Causes of Back Pain

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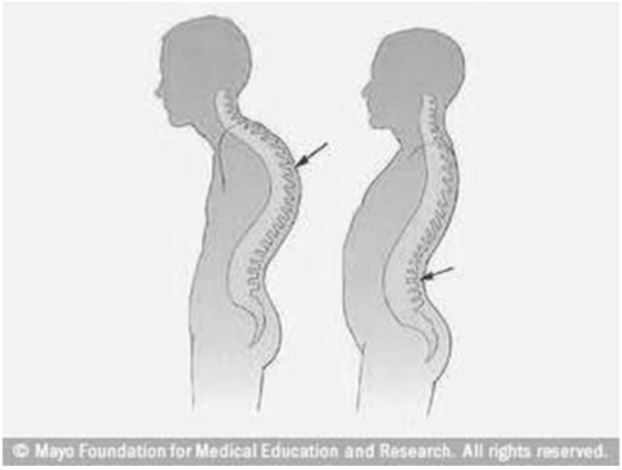
Posture and Back Pain

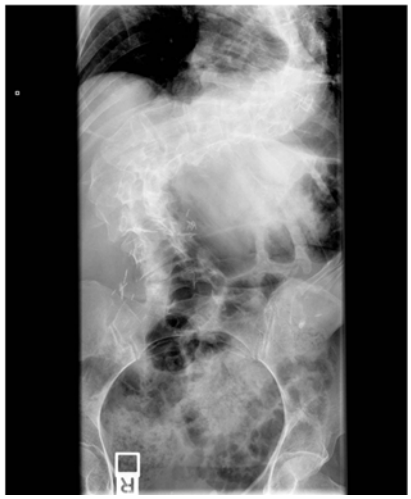


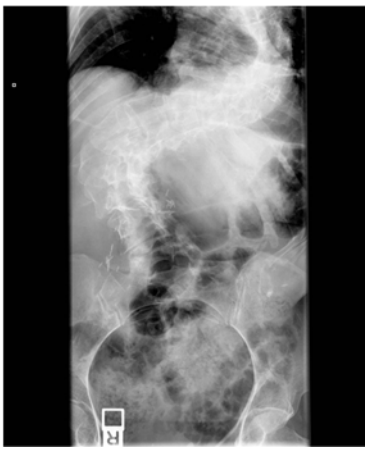
Physical Exam

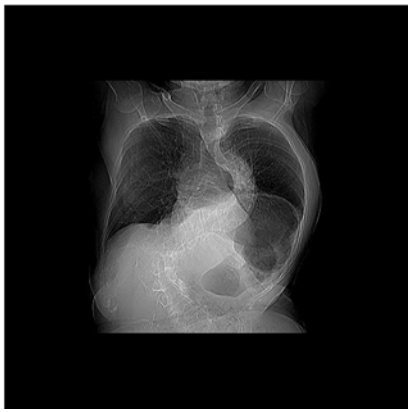
- Discogenic Pain (and no muscle spasm)
  - Sharp pain in mid range of combination motions
- Vertebral body pathology
  - Pain increases with flexion
- Facet/posterior element pathology
  - Pain with extension
- Systemic illness or fracture
  - Pain at rest

Testing patients with Low Back Pain

- Imaging
- Electrodiagnostics
- Provocative







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Differential Diagnosis
Low Back Pain
"Typical Presentation"

Acute Presentation

- **Specific Event**
- **Localized or radiating**
- **Loss of function**

Be aware of

- **Loss of bowel or bladder control**
- **Weakness without pain**

Chronic Presentation

- **Remote event with intermittent recurrence**
- **"Aching" sensation**
- **Activity related**
- **Better with rest**

Be aware of

- **Constant pain**
- **Pain that is better tolerated with movement or worse with rest**

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Differential Diagnosis
Low Back Pain

- Degenerative disc disease
- Facet joint arthropathy
- Lumbar radiculopathy
- Sacroiliac joint syndrome
- Acute vertebral compression fracture
- Sacral stress fracture
- Referred pain from abdomen or pelvis
- Occult lesions in the spine, such as metastasis or infection

Low Back Strain or Sprain Omar El Abd and Joao E.D. Amadera, Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation, Ch 48, 244-248

Differential Diagnosis
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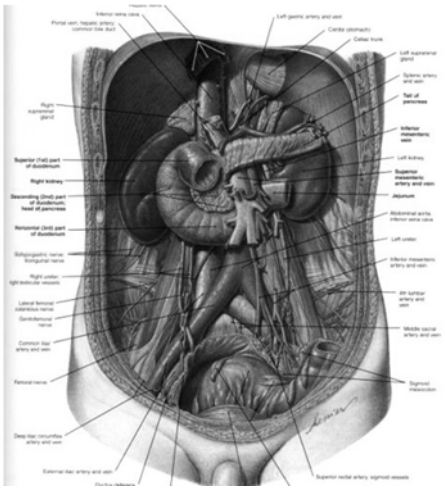
Low Back Strain or Sprain Omar El Abd and Joao E.D. Amadera, Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation, Ch 48, 244-248

Referred Pain from Abdomen or Pelvis



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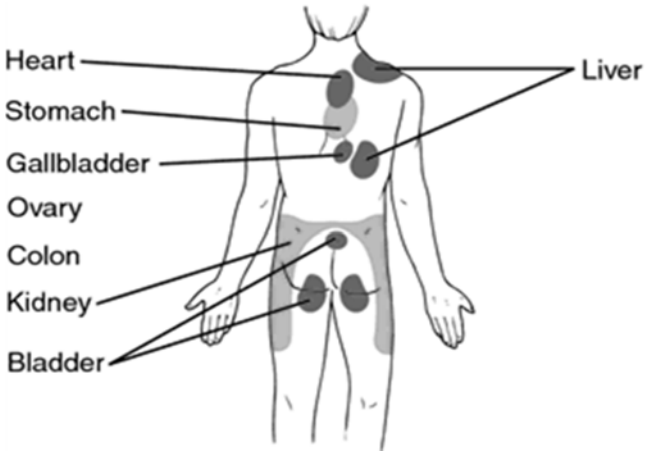
Referred Pain Patterns



http://medical-dictionary.thefreedictionary.com/chronic+pain

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Management

- Advance the Treatment Process
  - Establish a diagnosis based on History and Physical
  - Testing to confirm if necessary
  - Establish treatment approach
  - Re-evalualate
    - New finding
      - new differential/new or repeat testing
    - No change and no response to treatment
      - New testing or referral

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Management: Sample approach

- Plan A
  - Symptomatic treatment: Medications and Rest
- Plan B
  - Imaging/tests: add therapy
- Plan C
  - Axial Imaging: add injections
- Plan D
  - Discogram: Consider IDET
- Plan E
  - No Change: Pain Management Program

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Low Back Pain

Pain Relief

Low Back Pain

Pain Relief

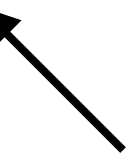
- Rest
- Medications
- Physical Modalities
- Injections
- Manipulation
- Acupuncture

Low Back Pain

Pain Relief

Low Back Pain

Flexibility



Pain Relief

Low Back Pain

Flexibility

- Back Rehab 101
- William's Flexion exercises
  - Knee to chest
  - Pelvic tilt
  - Bridging
  - Lower limb stretching

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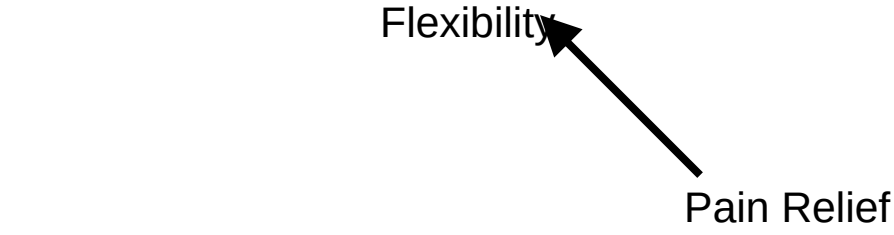
Low Back Pain



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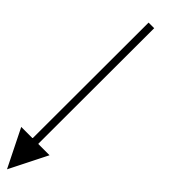
Low Back Pain



Strengthening

Pain Relief

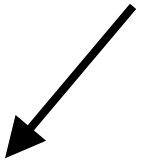
Low Back Pain

Strengthening

- Sit-ups
- Dynamic Lumbar Stabilization
- Pilate's
- Functional Exercises with good technique

Low Back Pain

Flexibility



Strengthening

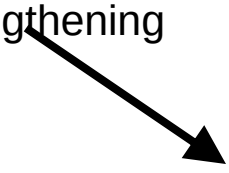
Pain Relief

Low Back Pain

Flexibility

Strengthening

Pain Relief



Return to Function

Physical Therapy

- Pain Control
- Re-establish Motion/ Posture
- Improve strength
- Return to desired activities

Physical Therapy

- May be difficult but shouldn't be painful
- Post exercise discomfort for less than 2 hours
- Takes 2 months for significant change in strength
- If this is not working, consider re-assessment

Physical Therapy
Reasons it won't work

- Wrong Diagnosis
- Wrong Treatment
- Not long enough treatment
- Patient doesn't "get it"

New Treatments

- VAX-D
- MED-X
- IDET
- Artificial Discs
- Vertebroplasty
- Kyphoplasty
- Prolotherapy
- Plasma Rich Protein Injections (PRP)

VAX-D
Vertebral Axial Decompression

- Variation on Traction ("It's not traction, it's VAX-D)
- Can create negative intra-discal pressure

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MED-X

- Strengthening System
- Reproducible
- Effective(?)
- Compared to what?


MED X Cervical Extension Unit


MED X Lumbar Extension Unit

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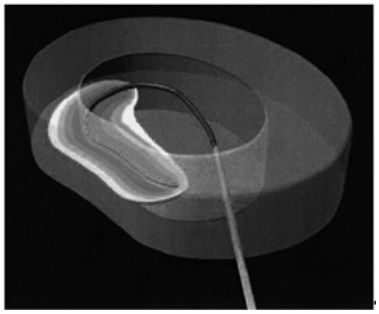
IDET

Intradiscal Electrothermal Therapy

- “Hot wire” technique
- Alternative to fusion
- Typically done in Lumbar region
- Typically requires positive/provocative discogram
- Patient should have failed a trial of Therapy



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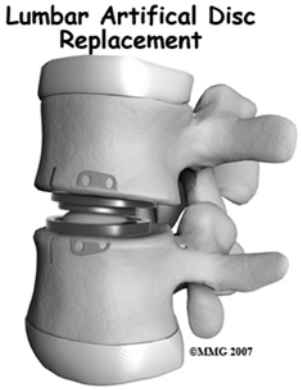
Artificial Discs

- Coming to a patient near you.
- Where’s the pain?
- How long will this take?
- What happens if it doesn’t work?



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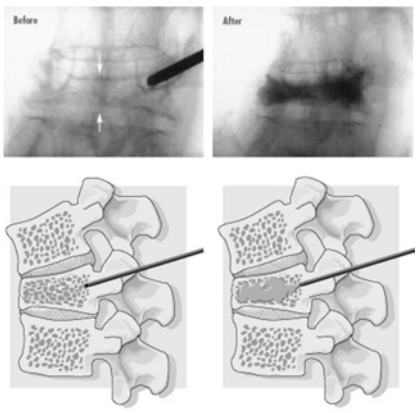
Vertebroplasty
Kyphoplasty

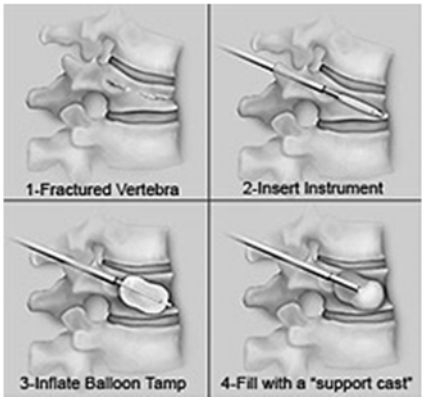
- Treatment for vertebral fractures
  - No fracture, no treatment
- Vertebroplasty: Cement them where they lay
- Kyphoplasty: We can make you taller
- Evaluation includes MRI and Bone Scan

Vertebroplasty



- www.advancedorthopain.com/

Kyphoplasty



- www.vancouverspinedoctor.com

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Prolotherapy

- Decreasing Pain by strengthening ligaments
- Strengthening ligaments by depositing collagen (e.g. inducing scar tissue)

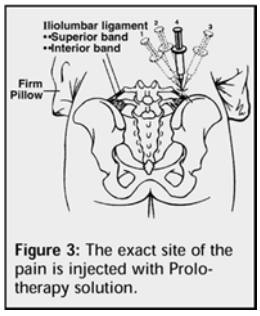
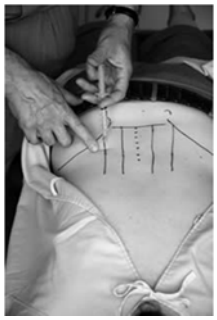


Figure 3: The exact site of the pain is injected with Prolo-therapy solution.

www.kerakemas.com



www.altmedicinezone.com

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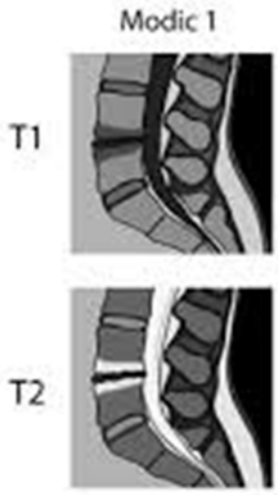
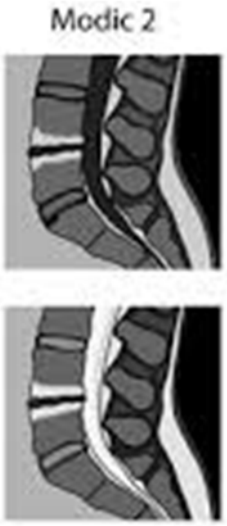
Modic Changes on MRI

- **Modic type I**
  - **T1:** low signal
  - **T2:** high signal
  - represents bone marrow edema and inflammation
- http://radiopaedia.org/articles/modic-type-endplate-changes



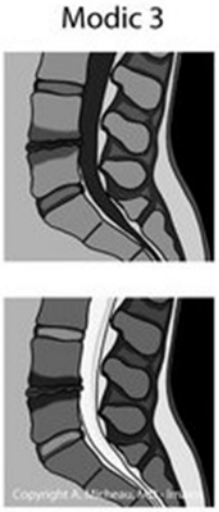
Modic Changes on MRI

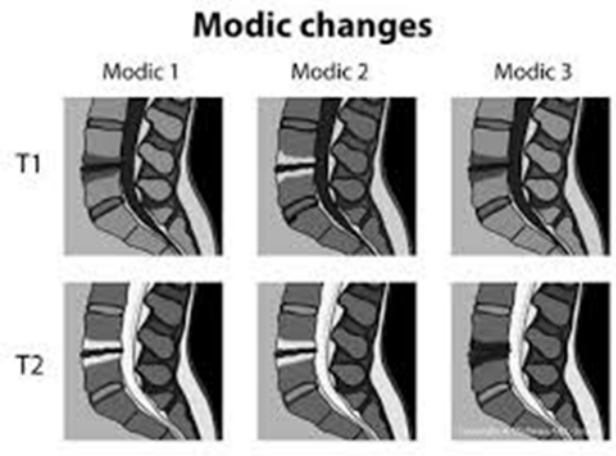
- **Modic type II**
  - **T1:** high signal
  - **T2:** iso to high signal
  - represents normal red hemopoietic bone marrow conversion into yellow fatty marrow as a result of marrow ischaemia
- http://radiopaedia.org/articles/modic-type-endplate-changes



Modic Changes on MRI

- **Modic type III**
  - **T1:** low signal
  - **T2:** low signal
  - represents subchondral bony sclerosis
- http://radiopaedia.org/articles/modic-type-endplate-changes





Antibiotics to Treat Low Back Pain

- Cultures done on discs following surgical removal showed bacteria.
- MRIs showed Modic I changes.
  - Modic I
    - **T1:** low signal
    - **T2:** high signal
    - represents bone marrow edema and inflammation

Antibiotic treatment in patients with chronic low back pain

- 162 Pts w/ 6 months LBP and Modic I changes
- Randomized
- Treatment group: 100 days of amoxicillin–clavulanate 500 mg/125 mg (Bioclavid) either 1 or 2 tabs, TID
- F/U in one year
- Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy, HB Albert, JS Sorensen, BS Christensen, C Manniche, Eur Spine J (2013) 22:697–707

Antibiotic treatment in patients with chronic low back pain

Symptoms	Baseline	1 year after treatment
Had LBP	100%	67.5%
Constant pain	75.3	19.5
Disturbed sleep	74	29.9
Pain with valsalva	75.3	41.6
Pain with flexion	96.1	49.4
Pain with extension	87	51.9

Antibiotic treatment in patients with chronic low back pain

- Adverse effects
  - 67% of treatment group
  - 27%--loose BM > 3 weeks (moderate adverse effect)
  - 21%--serious adverse effect
  - 1 serious adverse event in placebo group

References

- Deyo RA, “Early Evaluation of Low Back Pain” J of General IM Vol 1(Sept/Oct) 328-38, 1986
- Pengel LH, et al., “Acute low back pain: systemic review of its prognosis” BMJ, Vol 327 p323, Aug 2003.
- Yelland MJ, et al. “Prolotherapy injections for chronic low-back pain” The Chochrane Library, Vol 4.2004.

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Return to Program Schedule

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Rheumatoid Arthritis

Update on Treatment

John M. Davis III, M.D., M.S.

Mayo Clinical Rheumatology Update
April 17-18, 2015
Sawgrass Marriott, Ponte Vedra Beach, Florida, USA

Disclosure

- Research support
  - Site investigator (Roche, Pfizer)
  - Grant support (Pfizer)
- No off-label treatments will be discussed.

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Return to Program Schedule

Learning Objectives

1. Understand the importance of early recognition and treatment of RA
2. Outline fundamental concepts of the 'treat-to-target' approach for RA
3. Be able to implement initial treatment for RA in primary care settings
4. Approach to the patient with inadequate treatment response

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Background

Rheumatoid Arthritis, or RA

- Definition
  - Inflammatory rheumatic disease
  - Features of autoimmunity
  - Systemic involvement
- Epidemiology
  - 0.24% prevalence worldwide[1]
  - Lifetime risk: 3.7% of women, 1.7% of men[2]
- Economic burden of RA in the U.S.[3]
  - Annual incremental cost per patient = $2,085
  - Total US expenditure = $22.3 billion (2008 USD)

[1]Cross et al. Annals of the Rheumatic Diseases 2014
[2]Crowson et al. Arthritis & Rheumatiology2011
[3]Kawatkar et al. Arthritis Care and Research (Hoboken) 2012

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Background

Recent Paradigm Shifts

- Improved diagnostics (anti-CCP, RA criteria)
- Advent of biologic therapies
- Goal-directed treatment strategies
- Improved outcomes of disease
- Decreased severe extra-articular disease
- Rising costs of care

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Learning Objectives

1. **Understand the importance of early recognition and treatment of RA**
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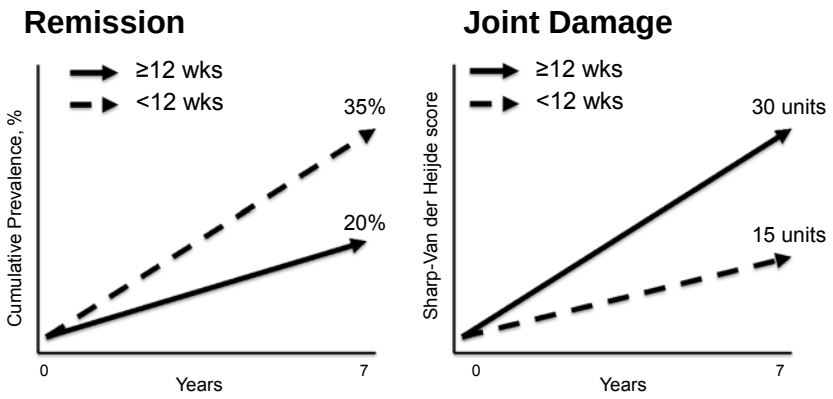
Early Diagnosis and Treatment

The Impact of Delay in Assessment



n = 598 patients with RA
Leiden Early Arthritis Clinic
1993 – 2006

van der Linden, et al. Arthritis & Rheumatism 2010

Early Diagnosis and Treatment

Positive Outcomes

- Control of signs and symptoms[1]
- Improved quality of life[1]
- Better work productivity[2]
- Less joint damage[3]
- Decreased cardiovascular risk[4]
- Improved survival[4]
- Probably lower costs[2]

[1]Vermeer et al. Arthritis Care & Research (Hoboken) 2013
[2]Hone et al. Arthritis Care & Research (Hoboken) 2013
[3]Smolen et al. Annals of the Rheumatic Diseases 2009
[4]Roubille et al. Annals of the Rheumatic Diseases 2015

Early Diagnosis and Treatment

2010 ACR Classification Criteria for RA

Classification as RA requires definite clinical swelling in ≥ 1 joint, plus a score of ≥ 6 among the following domains:

Tenderness or swelling

Joint Involvement	
1 large joint	0
2 – 10 large joints	1
1 – 3 small joints	2
4 – 10 small joints	3
>10 joints (1 sm jt)	5

Serology	
Negative RF and anti-CCP	0
Abnormal RF or anti-CCP	2
Abnormal RF or anti-CCP*	3

* ≥ 3X upper limit of normal

Acute Phase Reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

Disease Duration	
< 6 weeks	0
≥ 6 weeks	1

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Aletaha et al. Arthritis & Rheumatism 2010

Early Diagnosis and Treatment

Two Patients with Definite Clinical Synovitis

Example: Seropositive RA	
Both wrists are tender and swollen	2 points
Anti-CCP ≥ 250 units RF < 14 IU/mL	3 points
Normal CRP and ESR	0 points
Duration of 8 weeks	1 points
	6 points

Example: Seronegative RA	
12 joints (MCPs, wrists, shoulders, ankles, MTPs)	5 points
Anti-CCP <15.9 units RF < 14 IU/mL	0 points
CRP 19.1 mg/L	1 point
Duration of 12 weeks	1 point
	7 points

In order to meet criteria for definite RA, other possible causes for the arthritis must be excluded.

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Learning Objectives

1. Understand the importance of early recognition and treatment of RA
2. **Outline fundamental concepts of the 'treat-to-target' approach for RA**
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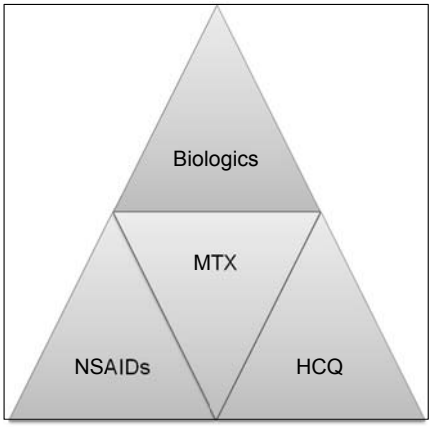
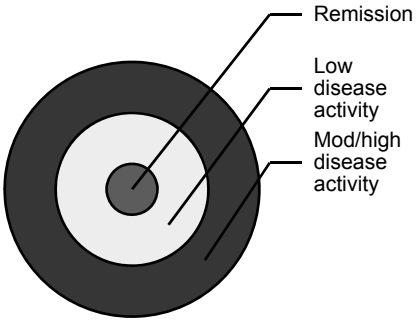
Treat-to-Target Strategy

Paradigm Shift in RA Therapy

Old Paradigm



New Paradigm



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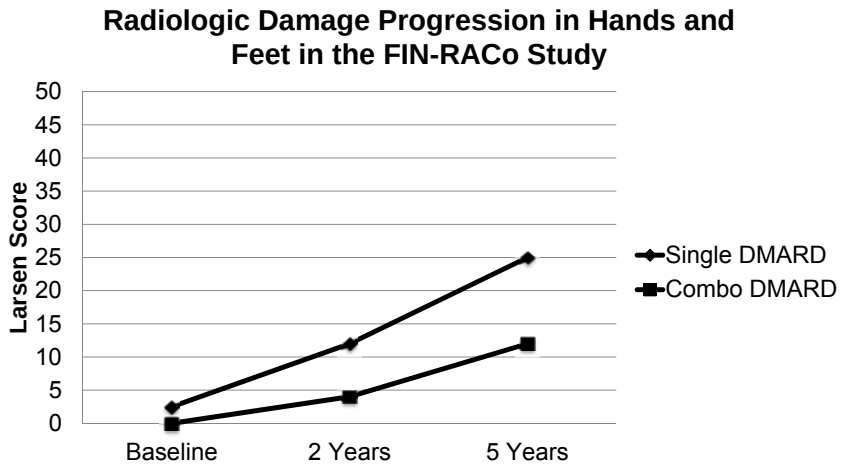
Singh JA et al. Arthritis Care & Research 2012

Treat-to-Target Strategy

Value of Combination Therapy

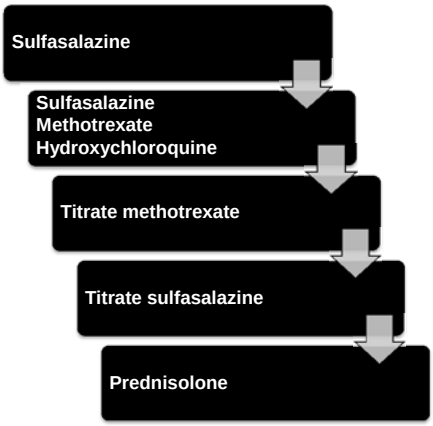


Korpela et al. Arthritis & Rheumatism 2004

Treat-to-Target Strategy

Value of Intensive Therapy and Tight Control

Treatment Algorithm



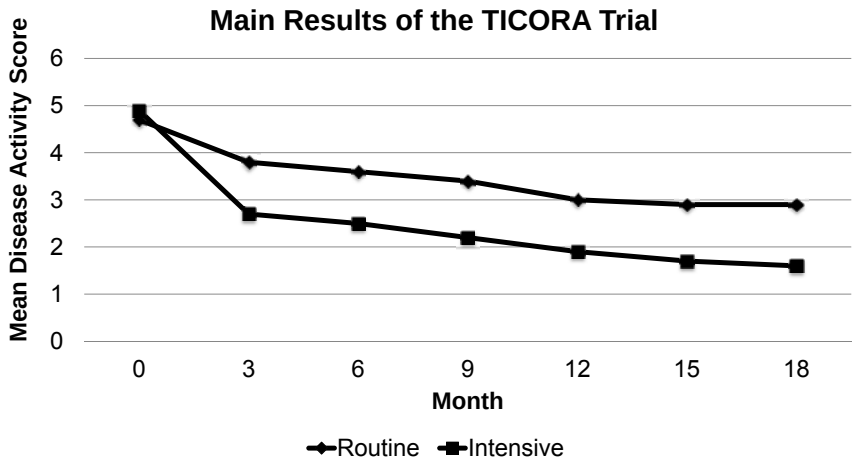
TICORA Trial[1]

- Single-blind RCT
  - Intensive Therapy
    - Algorithm
    - Q 1 month visits
    - Steroid injections
  - Usual Care
    - Q 3 month visits
- Early RA pts, high activity

[1]Grigor et al. The Lancet 2004

Treat-to-Target Strategy

Value of Intensive Therapy and Tight Control



[1]Grigor et al. The Lancet 2004

Treat-to-Target Strategy

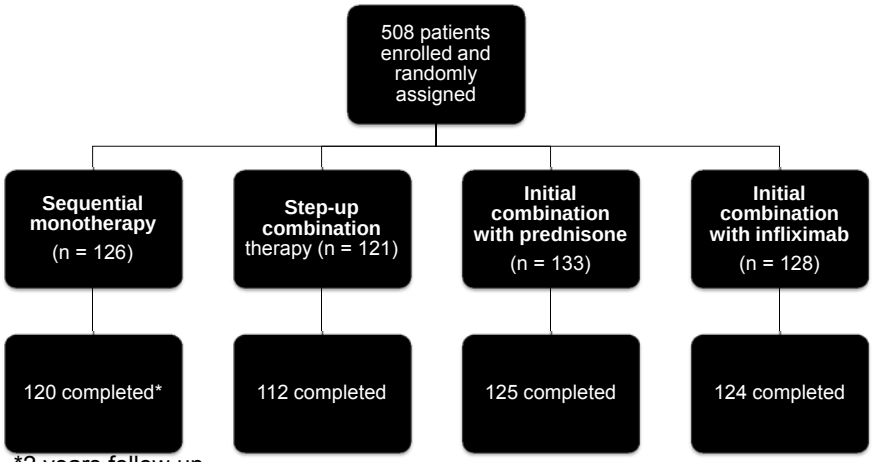
The BeSt Study[1,2]

- Randomized, controlled clinical trial
  - Comparison of 4 treatment strategies
    - Sequential monotherapy
    - Step-up combination therapy
    - Initial combination therapy w/ prednisone
    - Initial combination therapy w/ infliximab
  - Only the nurse joint assessor was blinded
  - Treatment adjusted q 3 months according to the Disease Activity Score (DAS)
    - Target: ≤ 2.4

[1]Goekoop-Ruiterman et al. Arthritis & Rheumatism 2005
[2]Goekoop-Ruiterman et al. Annals of Internal Medicine 2007

Treat-to-Target Strategy

The BeSt Study[1,2]



*2 years follow-up

[1]Goekoop-Ruiterman et al. Arthritis & Rheumatism 2005
[2]Goekoop-Ruiterman et al. Annals of Internal Medicine 2007

Treat-to-Target Strategy

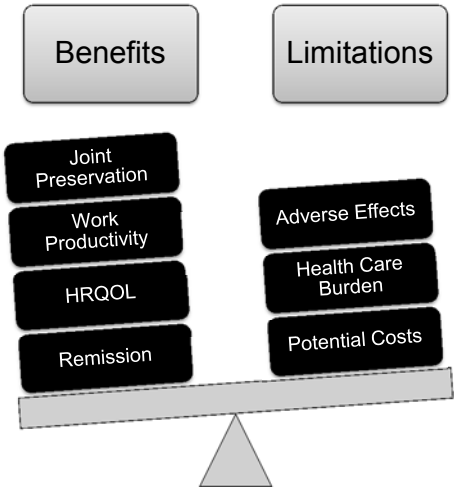
The BeSt Study: Major Lessons[1,2]

- Similar clinical outcomes at the end of two years
- Sequential and step-up therapy arms cycled through more medications
- Faster improvement with initial combinations
- Lower erosive disease progression with initial combination therapy
- Post-hoc study: Better outcomes in DAS-directed vs. routine treatment strategies[3]

[1]Goekoop-Ruiterman et al. Arthritis & Rheumatism 2005
[2]Goekoop-Ruiterman et al. Annals of Internal Medicine 2007
Goekoop-Ruiterman et al. Annals of the Rheumatic Diseases 2009

Treat-to-Target Strategy

Value Equation



Treat-to-Target Strategy

How to Do It

- Frequent appointments (q1-3 months)
- Monitor patient-reported outcomes (PROs)
- Assess clinical disease activity (next slide)
- Modify treatment to achieve the target
- Reassess 1-3 months after modification

Treat-to-Target Strategy

Disease Activity Assessment

Simplified Disease Activity Index (SDAI)

Summation of 5 variables:

Tender joint count (0 – 28)

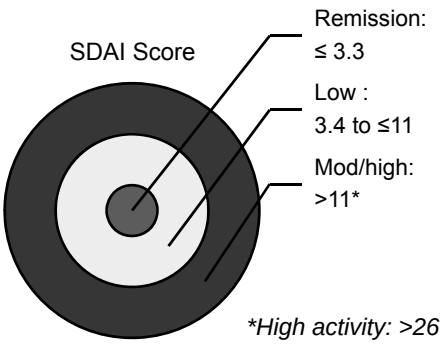
Swollen joint count (0 – 28)

Patient global (0 – 10)

Provider global (0 – 10)

C-reactive protein (mg/dL)

Thresholds:



**High activity: >26*

Anderson J et al. Arthritis Care & Research 2012

Learning Objectives

1. Understand the importance of early recognition and treatment of RA
2. Outline fundamental concepts of the 'treat-to-target' approach for RA
3. **Be able to implement initial treatment for RA in primary care settings**
4. Approach to the patient with inadequate treatment response

Initial Treatment Approach

Disease-Modifying Antirheumatic Drugs (DMARDs)

Conventional Synthetic

oral
- Methotrexate
- Hydroxychloroquine
- Sulfasalazine
- Leflunomide
- Azathioprine
- Cyclosporine
- Minocycline

Biologic

subcutaneous
- TNF inhibitors
  - Adalimumab
  - Certolizumab
  - Etanercept
  - Golimumab
  - Infliximab
- Anakinra (IL-1ra)
- Abatacept (CTLA-4:Ig)
- Rituximab (anti-CD20)
- Tocilizumab (anti-IL-6R)

Targeted Synthetic

oral
- Tofacitinib (JAK inhibitor)

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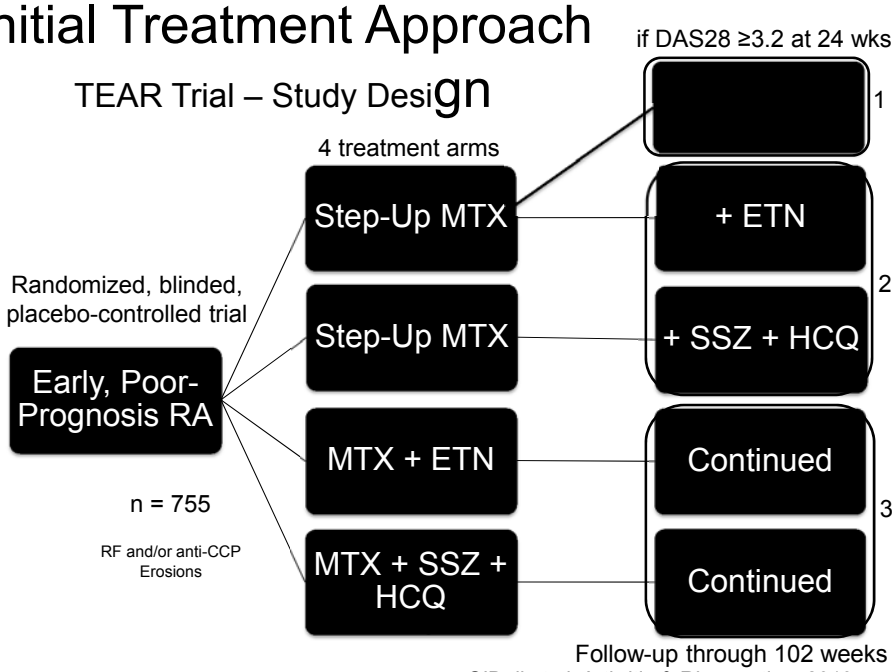
Initial Treatment Approach

TEAR Trial – Study Design



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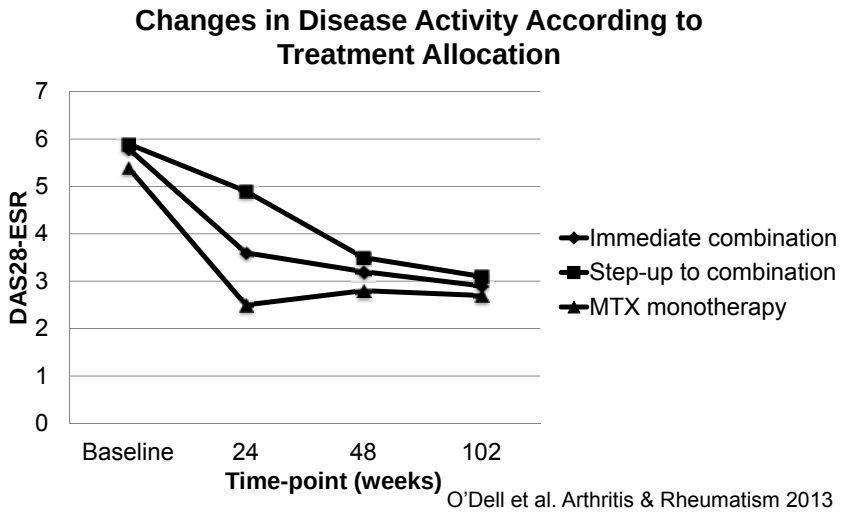
O'Dell et al. Arthritis & Rheumatism 2013

Initial Treatment Approach

Methotrexate is the First-line DMARD



O'Dell et al. Arthritis & Rheumatism 2013

Initial Treatment Approach Other Data

- SWEFOT Trial[1]
  - RCT comparing +infliximab vs. +SSZ + HCQ in MTX-inadequate responders
- Interpretation differed: 12 vs. 24 months
  - Faster response in infliximab group
  - No differences after 24 months
    - Clinical disease activity[2]
    - Health-related quality of life[3]
  - Marginally higher radiographic progression in the infliximab group

[1]Van Vollenhoven et al. Lancet 2009
[2]Van Vollenhoven et al. Lancet 2012
[3]Karlsson et al. Annals of the Rheumatic Diseases 2012

Initial Treatment Approach

Glucocorticoid Therapy

- Value is rapid control of inflammation
- Systemic disease = systemic therapy
- Disease-modifying benefits in early RA, even in context of a treat-to-target strategy[1]
  - Inhibition of radiographic joint damage
  - Benefits maintained 5 years out
- In patients at high risk of joint damage, prednisone 30 mg/day similarly effective as 60 mg/day when added to methotrexate[2]

[1]Bakker et al. Annals of Internal Medicine 2012
[2]Verschuren et al. Annals of the Rheumatic Diseases 2015

Initial Treatment Approach

Initial Drugs

Initial DMARD R_X:

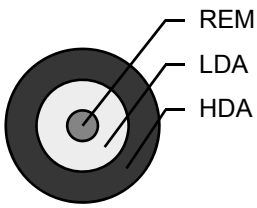
Methotrexate 10 – 15 mg PO Q week
Titrate to 20 – 25 mg Q week
Adjustments Q 2 weeks
Folic acid 1 mg PO QD
Prednisone 10 – 30 mg PO QD
Taper to 5 mg QD by 6 – 8 wks

*Leflunomide is alternative if intolerant of methotrexate.

Critical 3-Month Decision:

Target Achieved?

Low Disease Activity (LDA)
SDAI ≤ 11



Davis and Matteson. Mayo Clinic Proceedings 2012

Initial Treatment Approach Methotrexate is the First-line DMARD

- TEAR trial validated MTX-first strategy
- Similar clinical and radiographic outcomes
- Importance of blinding in trial design
- Still need personalized approach

Learning Objectives

1. Understand the importance of early recognition and treatment of RA
2. Outline fundamental concepts of the 'treat-to-target' approach for RA
3. Be able to implement initial treatment for RA in primary care settings
4. **Approach to the patient with inadequate treatment response**

Approach to Inadequate MTX Response

Differential Diagnosis

- Regional musculoskeletal syndromes
- Crystalline arthritis (i.e., gout or pseudogout)
- Severe degenerative joint disease
- Connective tissue disease
- Pain disorders (central pain sensitization)
- Depression, anxiety, or other psychosocial

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Approach to Inadequate MTX Response

Optimizing Conventional DMARD Management

- Key questions:
  - Compliance with MTX and folic acid?
  - Adequate dose of MTX?
  - Switch to subcutaneous route?
  - Adverse effects limiting treatment?
  - Adequate education about disease?
  - Adequate support by family / care providers?
  - Smoking cessation?
  - Weight management?

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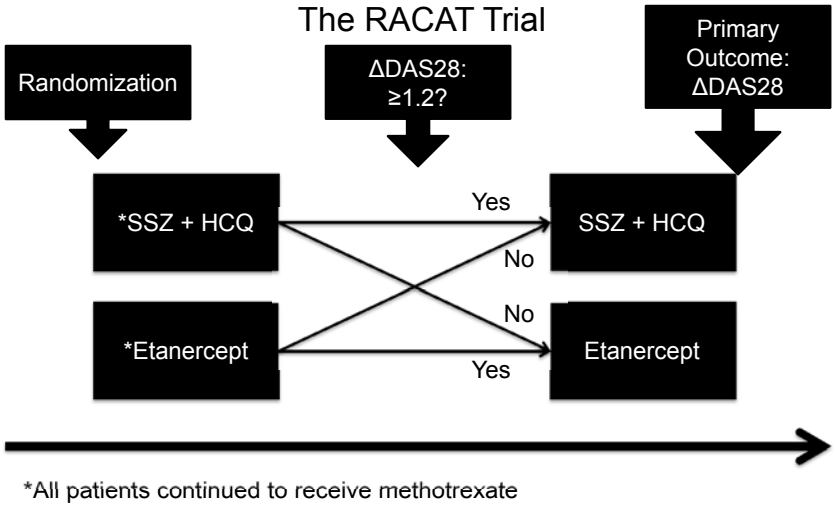
Initial Treatment Approach Options for MTX-Inadequate Responders

- Increase MTX to ≤25 mg Q week
- Switch MTX to SC injections (bioavailability)
- Add hydroxychloroquine ± sulfasalazine
- Add leflunomide (caution: liver toxicity)
- Add TNF inhibitor
- Add CTLA-4:Ig (abatacept)

Davis and Matteson. Mayo Clinic Proceedings 2012

Approach to Inadequate MTX Response

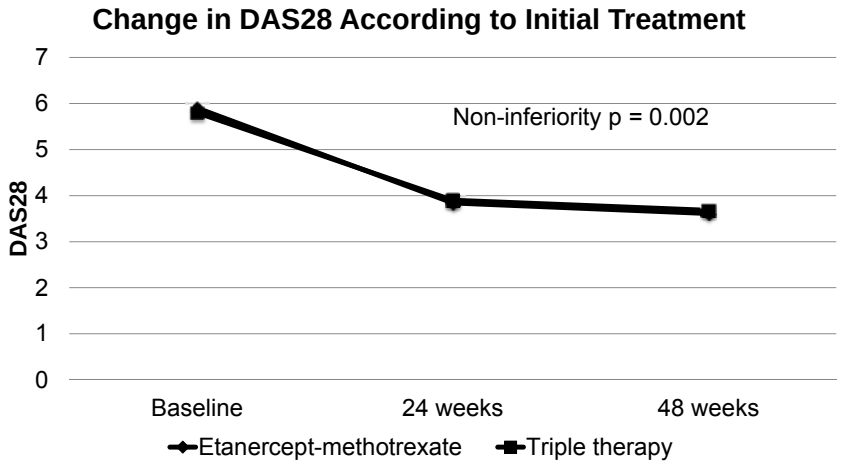
The RACAT Trial



O'Dell et al. New England Journal of Medicine 2013

Approach to Inadequate MTX Response

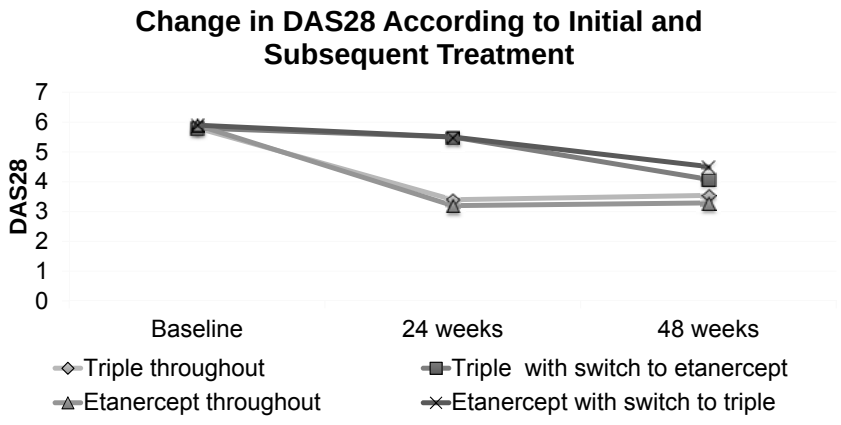
The RACAT Trial



O'Dell et al. New England Journal of Medicine 2013

Approach to Inadequate MTX Response

The RACAT Trial



O'Dell et al. New England Journal of Medicine 2013

Approach to Inadequate MTX Response

The RACAT Trial

- Addition of SSZ + HCQ to background MTX, with switch to etanercept by week 24 in non-responders, was non-inferior to adding etanercept to MTX in patients with inadequate response to methotrexate.
- Compliance between the regimens was similar (≈75%)
- No significant differences in
  - Patient-reported outcomes
  - Radiographic damage
- Adverse effects profiles
  - Infectious adverse events: etanercept
  - Gastrointestinal disorders: triple therapy

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O'Dell et al. New England Journal of Medicine 2013

Initial Treatment Approach Other Data

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[1]Van Vollenhoven et al. Lancet 2009
[2]Van Vollenhoven et al. Lancet 2012
[3]Karlsson et al. Annals of the Rheumatic Diseases 2012

Summary

- Apply current diagnostic tests and RA criteria to improve outcomes of early RA.
- Intensive treatment strategies targeting clinical remission optimize patient outcomes.
- Recent evidence has validated methotrexate as the first-line drug therapy for RA.
- In patients with inadequate response to methotrexate, adding the combination of SSZ + HCQ is non-inferior to adding etanercept.

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Return to Program Schedule

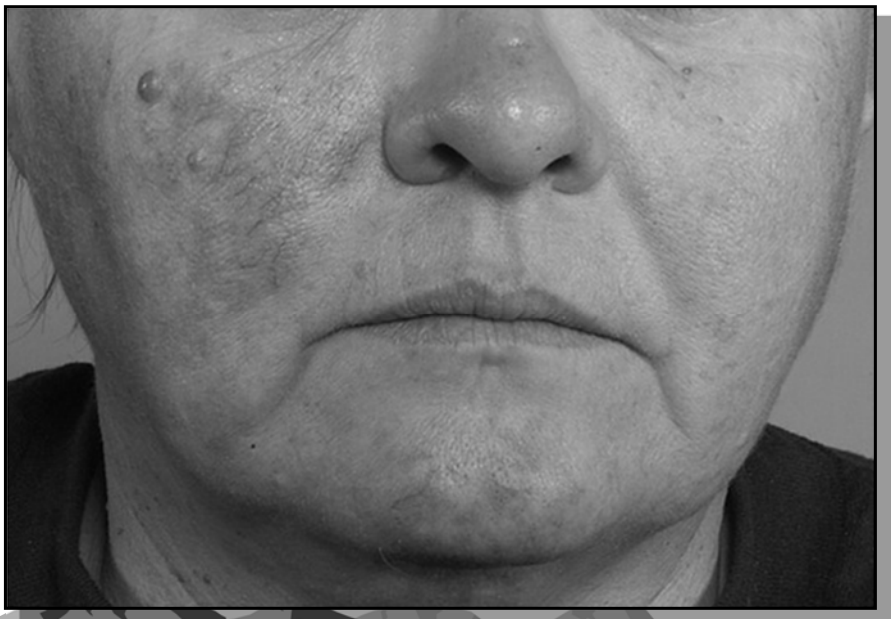
Use of Laboratory Tests in Rheumatology

Kevin G. Moder, MD
Consultant, Rheumatology
Mayo Clinic, Rochester, MN

Case 1

- 46-year-old woman with facial rash, myalgias, arthralgias, and fatigue
- Erythematous raised rash over cheeks and nose consistent with rosacea
- Tenderness over joints and multiple muscle areas; fibromyalgia tender points present

Return to Program Schedule



CP1104125-39

Case 1 Labs

- CBC normal
- Chemistry panel normal
- Urinalysis normal
- ANA (+) 2.3 (1:40, homogenous)
- ds-DNA (-)
- ENA (-)

CP1104125-37

Case 1 Question

- Which of the following is the most likely cause for this patient's MSK complaints?
  - A. SLE
  - B. Undifferentiated CTD
  - C. Fibromyalgia
  - D. MCTD
  - E. Polymyalgia Rheumatica

1982 ACR Classification Criteria for SLE

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis
- Renal disorder
- Neurologic disorder
- Hematologic disorder
- ANA
- Immunologic disorder

CP1104125-38

Case 1 Summary

- No features of SLE
- Rash is related to acne rosacea
- Fatigue and tender points are consistent with fibromyalgia
- ANA is weakly positive, but more specific serology tests are negative

So what does a positive ANA mean?

CP1104125-40

What is an ANA?

- Autoantibody directed against nuclear targets
- Produced in many autoimmune conditions, including SLE and other CTD
- Highly sensitive for SLE (good screening test)
- Not specific for SLE (not diagnostic of SLE)

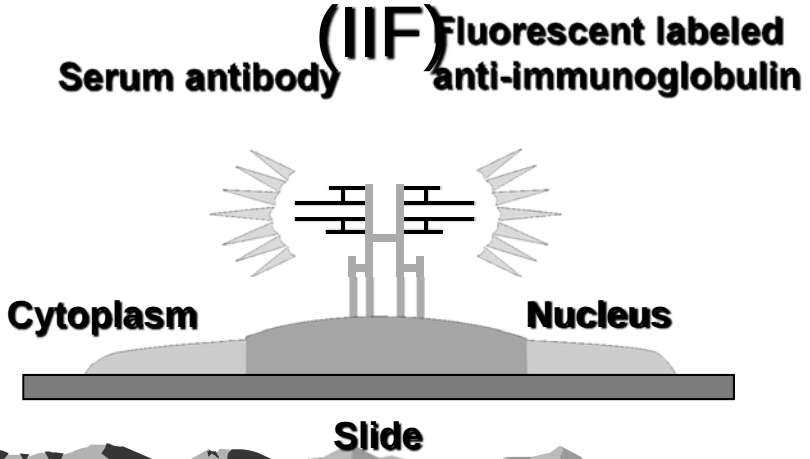
CP1104125-42

Antinuclear Antibody (ANA) Testing Techniques

- Immunofluorescence (IF) test
  - –Titer
  - –Pattern
- Enzyme immunoassay (EIA)
  - –Value

CP1104125-43

Principle of Indirect Immunofluorescence (IIF)



CP1104125-44

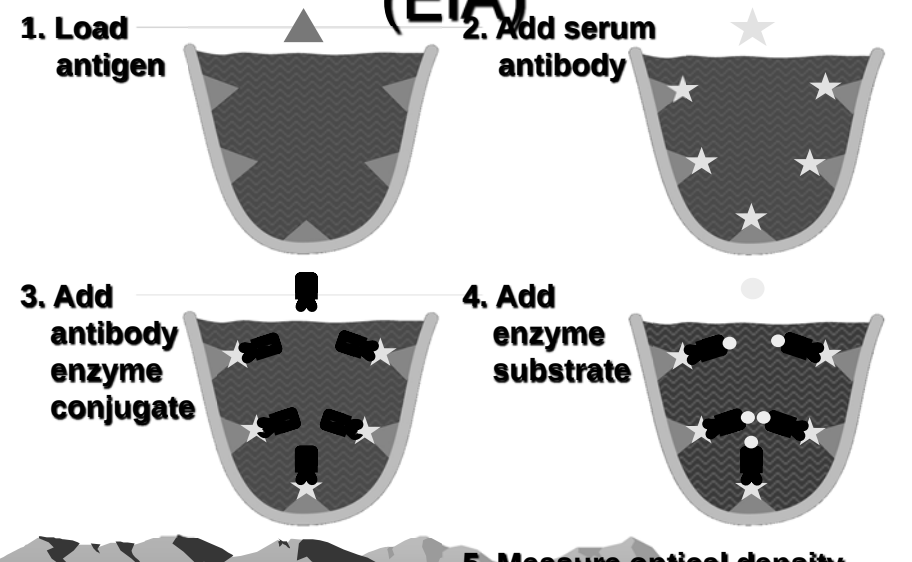
ANA Immunofluorescence Titers

Serial dilutions

- Low titer of less significance (<1:80)
- Titer not a good indicator of disease activity

CP1104125-47

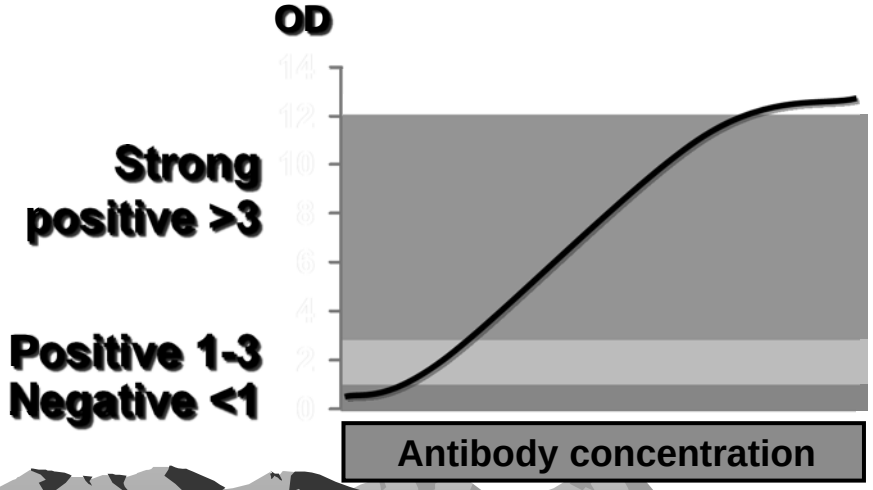
Enzyme Immunoassay (EIA)



CP1104125-50

ANA EIA Values

Results on a Linear Scale



CP1104125-51

Meaning of (+) ANA for SLE

Assume ANA sensitivity 100%; specificity 96%
100 people tested; SLE prevalence 1%

Diagnosis	Test	SLE	No SLE	Total
	ANA(+)	1	3	4
	ANA(-)	0	96	96
	Total	1	99	100

	No.	%
Sensitivity	1/1	100
Specificity	96/99	96
NPV	96/96	100
PPV	1/4	25

CP1104125-52

Causes of Positive ANA

- Connective tissue disorders
- Other autoimmune conditions
- Medications
- Infections
- Cancer
- Aging
- Normals

CP1104125-59

Summary of ANA+

- ANA is very sensitive for SLE (seen in 95-98% of patients who have active SLE)
- ANA is not specific for SLE
- ANA can be seen in many other conditions and must be interpreted in the clinical context

Key point: Joint pains and a positive ANA do not necessarily mean SLE

CP1104125-60

Case 2

- 26-year-old man with edema and joint pain for 2 weeks; fever to 39°C
- Exam demonstrates joint tenderness on motion and edema

CP1104125-70

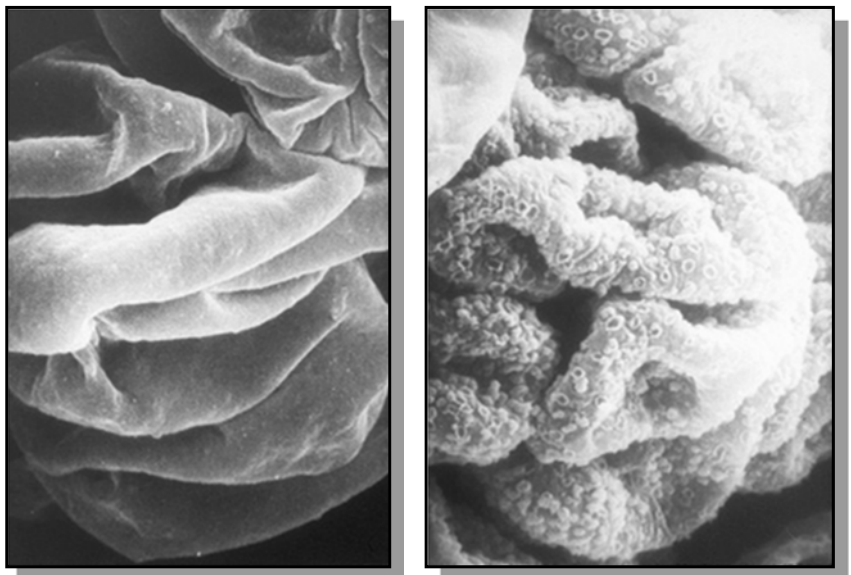
Case 2
Labs

- Creatinine 2.6
- Urinalysis: 3+ protein, 21-50 RBC, RBC casts
- ANA (+) >12.0 (1:2560, rim)
- ds-DNA 438
- ENA negative
- CH_{50}, C3 and C4 all suppressed

CP1104125-71

Question Case 2

- Which of the following abnormalities can be seen in patients with lupus nephritis?
  - A. hypocomplementemia
  - B. positive DSDNA antibodies
  - C. active urinary sediment
  - D. proteinuria
  - E. all of the above



CP1104125-78

ds-DNA Antibodies

- Antigen: Double-stranded (native) DNA
- Specific but not sensitive for SLE
- Positive in 30-60% of SLE patients
- Levels correlate with disease activity in some patients
- Often associated with nephritis
- Usually negative in drug-induced LE

CP1104125-114

ds-DNA and Complement

ds-DNA

- **Associated with renal disease**
- **Level varies with disease activity in some patients**

Complement levels

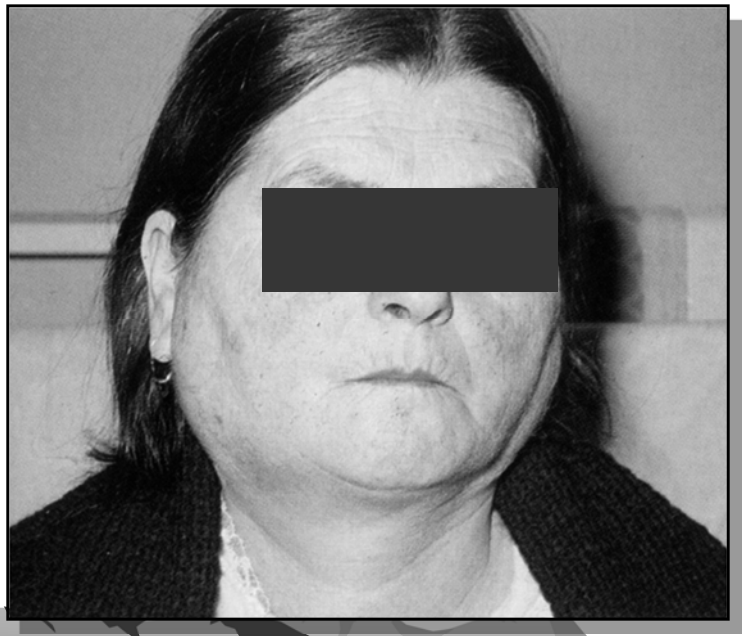
- **Total, C3 and C4**
- **May be low in some SLE pts**
- **Can vary with lupus activity**

CP1104125-74

Case 3

- 41-year-old woman with dry eyes and mouth
- Complains of fatigue, arthralgias and myalgias
- Exam shows dryness of conjunctivae and oral mucosa and prominent dental caries
- Also noted is parotid gland swelling

CP1104125-85



CP1104125-87

Case 3
Labs

- CBC normal
- ESR elevated (60)
- ANA (+) 9.4 (1:640, speckled)
- ds-DNA (-)
- ENA (+): SS-A/Ro, SS-B/La
- SPEP with polyclonal gammopathy

CP1104125-86

Question Case 3

- Which of the following autoantibodies are seen in patients with Sjogren's?

A. Anti U1 RNP
B. Anti SM
C. Anti DSDNA
D. Anti SSA and SSB
E. Anti centromere

ENA Antibodies

Extractable nuclear antigens (ENA) – RNA/protein complexes

Classic ENAs

SSA/Ro	**Sjögren's, SLE**
SSB/La	**Sjögren's, SLE**
Sm	**SLE**
U1-RNP	**MCTD, SLE**

2 additional antigens

Jo-1	**Myositis with ILD**
Scl-70	**Scleroderma**

CP1104125-89

Summary of Case

- Clinical features consistent with Sjogren's syndrome, not SLE
- ANA is positive in other CTD

CP1104125-90

Case 4

- 25-year-old man with lupus presents with right leg pain and swelling and pleuritic left chest pain
- Serositis and arthritis previously
- Exam shows swelling and tenderness of the right calf and thigh and a left pleural rub

CP1104125-91

Case 4
Studies

- ANA (+) >12.0
- ds-DNA (-)
- ENA (-)
- Lupus anticoagulant (+)
- IgG antiphospholipid antibody (+)
- Chest x-ray normal
- Spiral CT of chest – left pulmonary embolism

CP1104125-92

Question Case 4

- Appropriate treatment of this patient would include which of the following?
  - A. anticoagulation
  - B. ASA only
  - C. Prednisone 60 mg daily
  - D. Prednisone 20 mg daily and anticoagulation
  - E. Cyclophosphamide 100 mg daily PO

Antiphospholipid Antibodies

- Heterogenous group of antibodies
  - –Lupus anticoagulant (LAC)
  - –Anticardiolipin antibodies
- May be associated with the antiphospholipid antibody syndrome (APS) or cause no trouble
- Often the cause for the false-positive RPR or VDRL in SLE patients
- May occur in patients with or without CTD

CP1104125-93

Lupus Anticoagulant

Misnomer

- **Not exclusive to patients with lupus**
- **Associated with thrombosis, not bleeding**

Prolongation of phospholipid-dependent clotting assays

- **Activated partial thromboplastin time (APTT)**
- **Dilute Russell viper venom time (DRVVT)**

CP1104125-94

Anticardiolipin Antibodies

- Bind to cardiolipin and/or β2 glycoprotein-1 bound to phospholipids
- Test for these with ELISA assay
- Different isotypes
  - –IgM
  - –IgG

CP1104125-95

Clinical Findings Associated with APL

- Arterial and/or venous thrombosis
- Recurrent miscarriages
- Livedo reticularis
- Cutaneous ulcers
- Thrombocytopenia
- Marantic endocarditis

CP1104125-96

Treatment of Patients with Antiphospholipid Syndrome

- Agent and duration of therapy depends on the type and severity of event
- Life threatening thromboembolic events require life long anticoagulation with Coumadin
- INR usually >2.5- 3.0
- Asymptomatic patients – aspirin

CP1104125-98

Case 5

- 68 y Male with 9 month history of joint pain and swelling
- PMH of PMR 4 years ago resolved with short course of prednisone
- FH of RA in his mom
- PE- with synovitis of mulitple MCPs,wrists, L elbow, shoulders tender, R knee effusion, synovitis both ankles, MTPs feet

Labs and xrays

- Mild anemia
- Elevated ESR (92) and CRP (60)
- Positive CCP (> 250)
- Xrays without erosions
- What is your diagnosis?

CCP Antibodies

- antibodies to Cyclic citrulinated peptide (ACPA)
- Citrulinated peptides found in the synovium of RA patients
- Very specific for RA in high value
- Can be seen with negative RF
- Associated with more radiographic progression

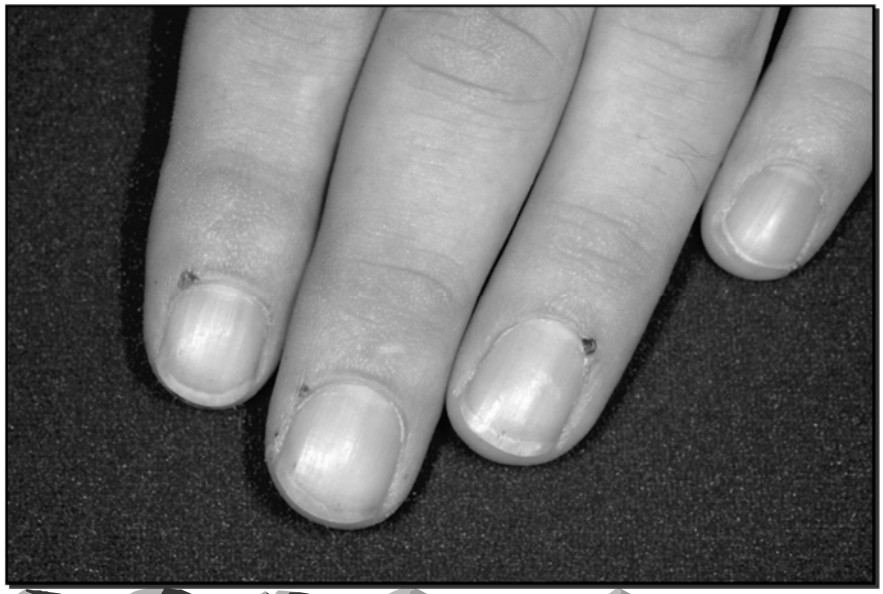
Case 6

- **36-year-old male**
- **2-month Hx inflammatory polyarthritis**
- **Symmetric, small and large joints**
- **RF positive**
- **Elevated ESR, mild anemia**
- **LMD Dx RA, Rx NSAIDs and low-dose pred and refer to rheum MD**

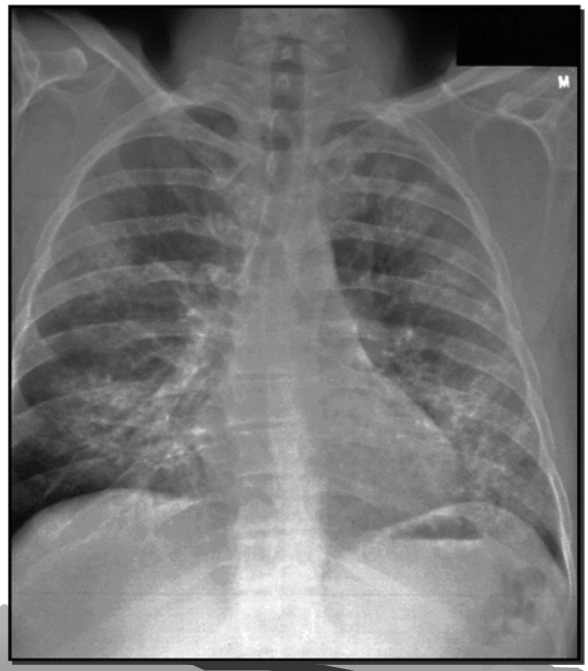
CP1194588-26

Before Visit

- Patient developed hemoptysis
- Spots near finger nails
- Increasing fatigue
- Came early for evaluation



CP1194588-27



CP1194588-29

Case 6

- CXR – alveolar hemorrhage
- Hemoglobin fell to 9
- Active urine sediment
- Positive C ANCA
- Dx: Wegener's granulomatosis
- Granulomatosis with Polyangitis

CP1194588-30

ANCA

- Anti-neutrophil cytoplasmic antibody
- Two patterns
  - C ANCA (cytoplasmic)
  - PR3 antibody
  - p ANCA (perinuclear)
  - MPO antibody
  - Others are not specific for vasculitis

Summary

- ANA is sensitive but not specific for CTD
- Elevated dsDNA and low complements are associated with SLE/nephritis
- SM is very specific for SLE
- RNP can be seen in SLE/MCTD
- SSA/SSB in Sjogren's, SLE
- APL can be associated with clotting
- ANCA can be seen with vasculitis

Return to Program Schedule

Scleroderma

Rheumatology Update 2015
Ponte Vedra Beach, Florida
April 17, 2015

Leroy Griffing MD
Mayo Clinic Arizona
Scleroderma Program
lgriffing@mayo.edu

Disclosures

- Bayer HealthCare - study site PI
- Off-label medications in presentation
  - everything

Return to Program Schedule

Scleroderma

- Localized Scleroderma
  - morphea
  - linear scleroderma
- Systemic Scleroderma
  - diffuse
  - limited / formerly called CREST

    (calcinosis, Raynaud's, esophagus, sclerodactyly, telangiectasia)
- Overlap syndrome
  - mixed connective tissue disease (MCTD)

    (systemic scleroderma, systemic lupus, polymyositis)

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Diagnosing Scleroderma

Modified Rodnan Skin Scoring (MRSS)

for

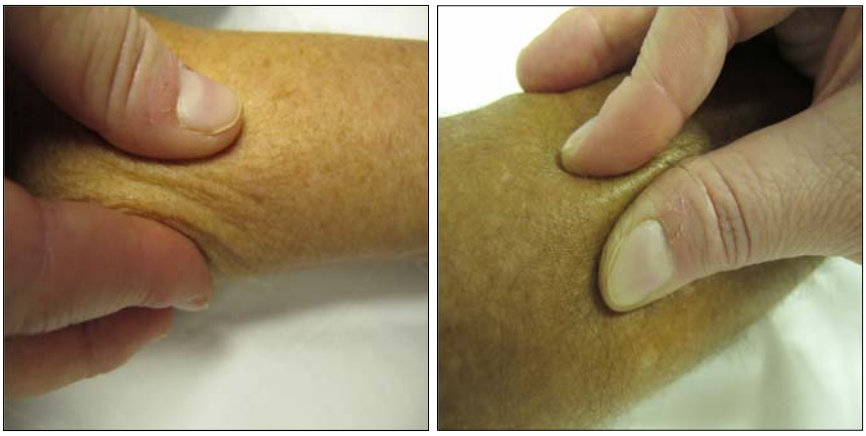
systemic scleroderma

clinically differentiates

limited vs. diffuse forms

MAYO CLINIC

Modified Rodnan Skin Scoring



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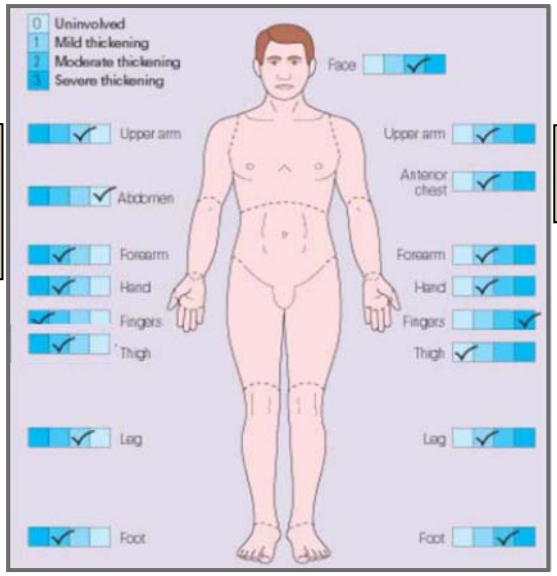
Modified Rodnan Skin Scoring

17 body areas are separately scored 0-3 for thickening



maximum score possible is 51

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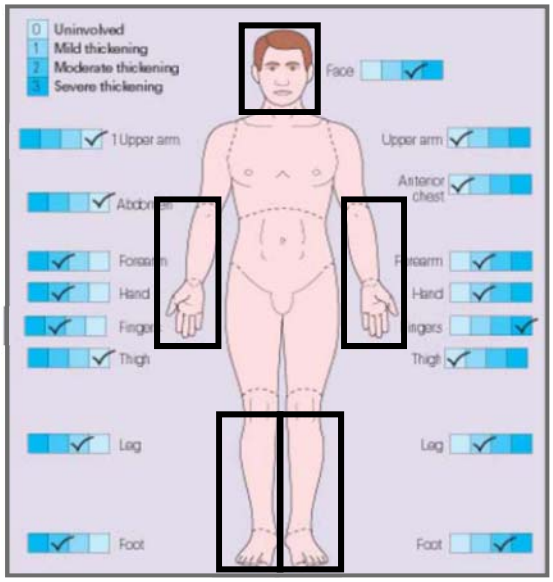
Modified Rodnan Skin Scoring

Limited Scleroderma



Only 11/17 areas potentially thickened

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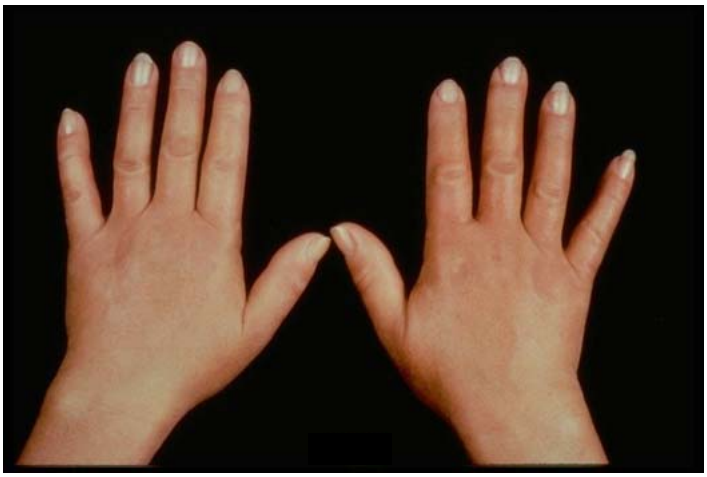
Limited Scleroderma

often remains edematous
(reflecting slow progression of skin fibrosis)



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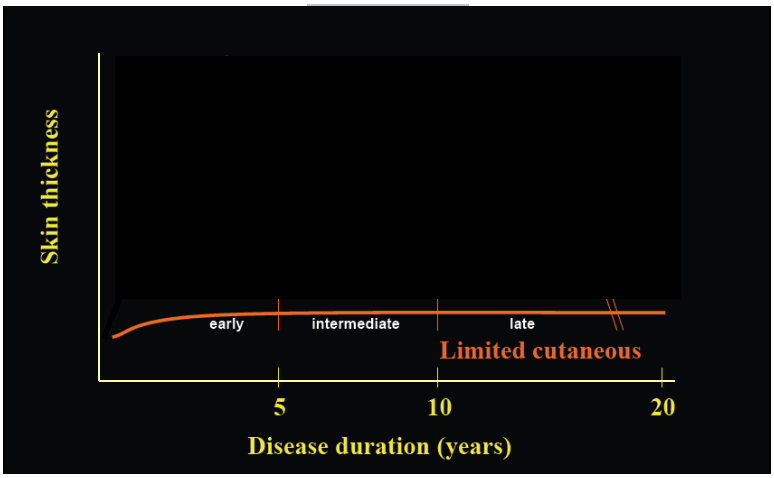
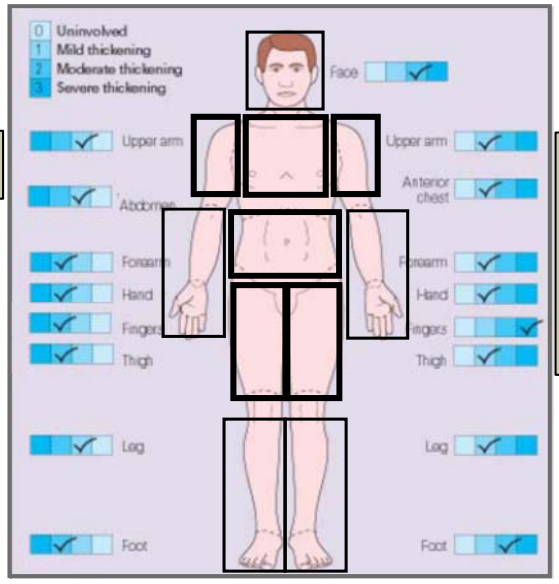
Evolution of Skin Thickening
MRSS



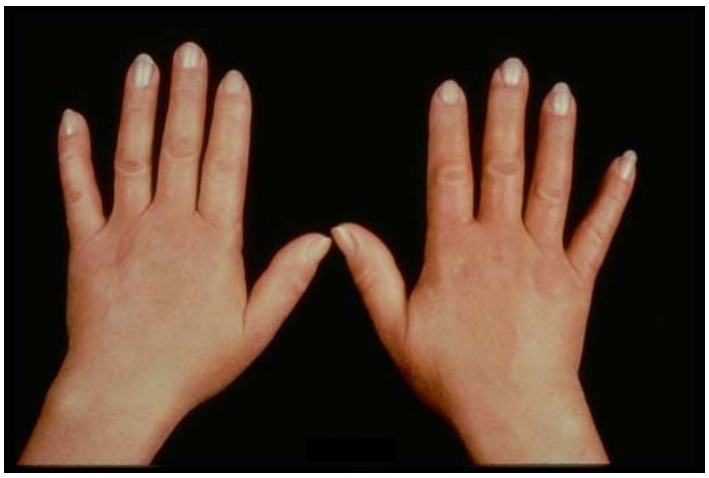
Modified Rodnan Skin Scoring

Diffuse Scleroderma



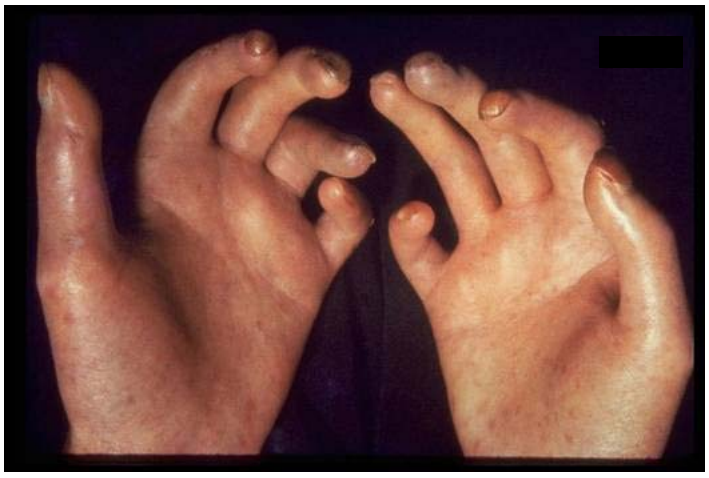
All 17 scored areas potentially thickened and must include proximal areas

Scleroderma
edematous phase



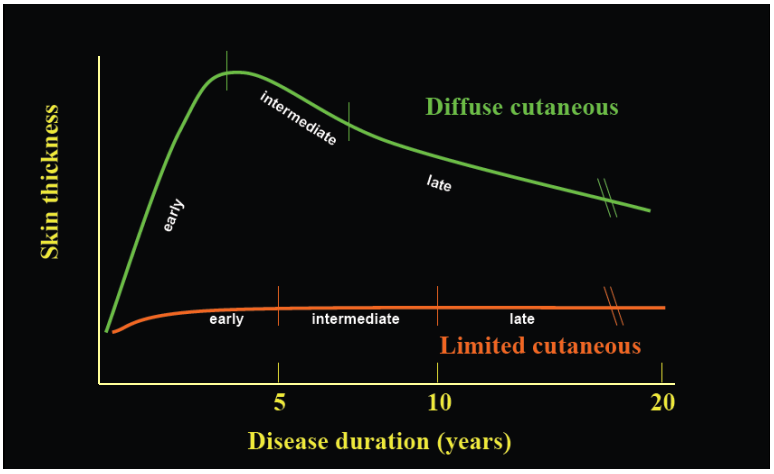
MAYO CLINIC

Scleroderma
fibrotic phase



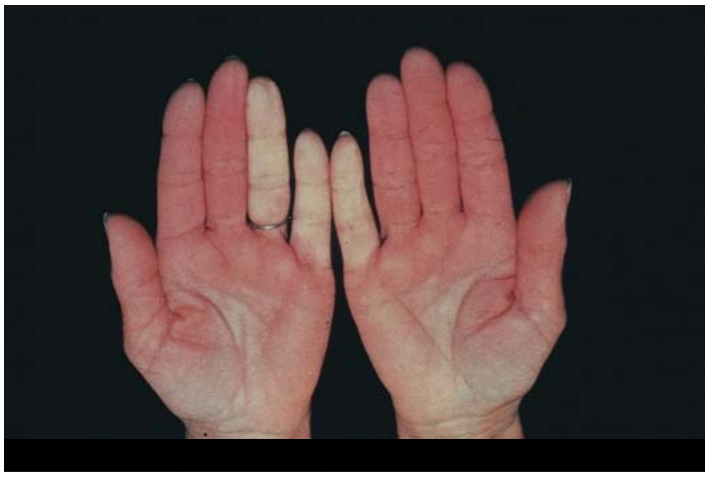
MAYO CLINIC

Evolution of Skin Thickening
MRSS



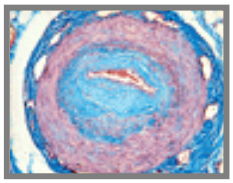
MAYO CLINIC

Scleroderma
Raynaud's phenomenon

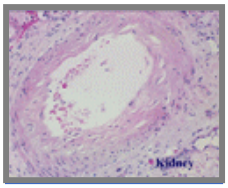


MAYO CLINIC

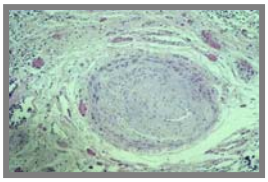
Scleroderma
obliterative vasculopathy



digit



kidney



lung

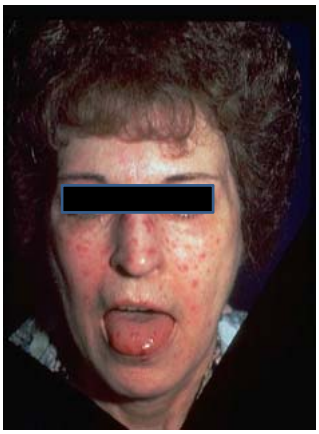
MAYO CLINIC

Raynaud's phenomenon
scleroderma vs. primary

- Scleroderma
  - more frequent and severe attacks
    - vasospasm
    - plus obliterative vascular disease
  - physical examination
    - absent ulnar artery pulses
    - telangiectasias
    - dilated nailfold capillaries
    - digital pitting, ulcers, and infarcts
  - scleroderma antibody

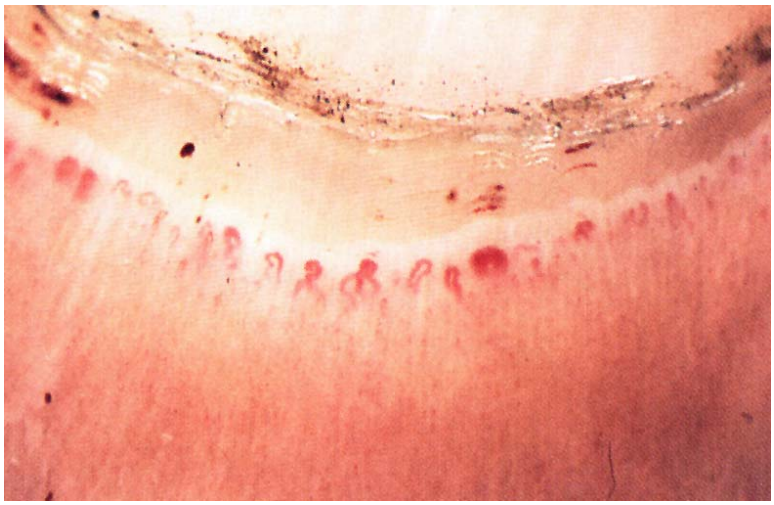
MAYO CLINIC

Scleroderma
telangiectasias



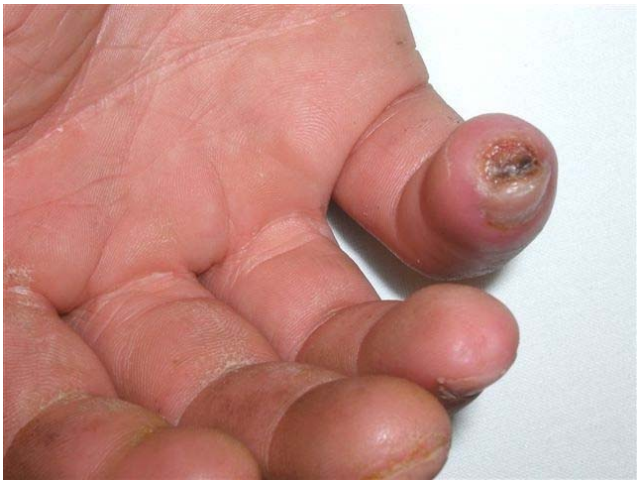
MAYO CLINIC

Scleroderma
nailfold capillary dilation and dropout



MAYO CLINIC

Scleroderma
digital pitting and ulcers



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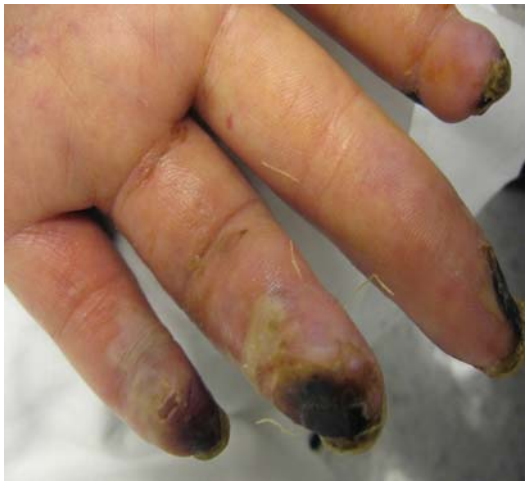
Scleroderma
digital infarction



MAYO CLINIC

Scleroderma
managing Raynaud's phenomenon

Avoid aggravating factors
COLD, STRESS, TRAUMA, SMOKING
SEROTONIN AGONISTS, AMPHETAMINES

↓

Add calcium channel blocker
NIFEDIPINE, AMLODIPINE

Lesser options
LOSARTAN, PRAZOSIN,FLUOXETINE

↓

Add phosphodiesterase inhibitor
PENTOXIFYLLINE, SILDENAFIL,TADALAFIL

MAYO CLINIC

Scleroderma
managing digital ulcers

Avoid aggravating factors
Treat Raynaud's phenomenon

↓

- atorvastatin
  - 84 pts, treated 4 months — New ulcers (mean)
    - 56 pts: atorvastatin 40 mg/day — 1.6
    - 28 pts: placebo — 2.5
    - Functional status favored statin group
      - SHAQ-DI, VAS for RP, ulcer severity, pain scales, VAS physician global
    - Endothelial activation markers favored statin group

Abou-Raya et al. Arthritis Rheum 2008;35:1801-08

↓

- topical nitroglycerin ointment 2%
- bosentan
  - 122 pts, treated 16 weeks — New ulcers (mean)
    - 79 pts: bosentan 62.5-125 mg BID — 1.4
    - 43 pts: placebo — 2.7
    - Improved hand function favoring bosentan
    - No difference in healing of existing ulcers
- Botox injections

Korn et al. Arthritis Rheum 2004;50:3985-93

MAYO CLINIC

New 2013 Classification

Item	Score
Skin thickening of fingers of both hands extending proximal to the MCP joints (sufficient criterion)	**9**
Skin thickening of the fingers *(only count the higher score)*	
Puffy fingers	**2**
Sclerodactyly (distal to the MCP but proximal to the PIP joints)	**4**
Fingertip lesions *(only count the higher score)*	
Digital tip ulcers	**2**
Fingertip pitting scars	**3**
Telangiectasia	**2**
Abnormal nailfold capillaries	**2**
Pulmonary arterial hypertension and/or interstitial lung disease	**2**
Raynaud's phenomenon	**3**
SSc-related autoantibodies (anticentromere, anti-Scl-70 (anti–topoisomerase I), anti–RNA polymerase III)	**3**

Sensitivity = 0.91
Specificity = 0.92

Maximum score = 19
Sufficient score = 9

MAYO CLINIC

van den Hoogen et al. Arthritis Rheum 2013;65:2737-47

New 2013 Classification

Sclerodactyly	Skin thickening proximal to MCPs	Criteria apply
--	+	no
+	--	yes
+	+	sufficient
--	--	yes

Scleroderma sine skin

MAYO CLINIC

van den Hoogen et al. Arthritis Rheum 2013;65:2737-47

Classification vs. Diagnosis

- Criteria
  - mirror those features used clinically in making a diagnosis.
  - are feasible to use in daily practice.
- Patients classified are a subset of patients diagnosed with scleroderma.
- Criteria may fall short in making diagnosis:
  - Raynaud's, +NFC, + anticentromere Ab = 8
  - Sclerodactyly, GERD/ +EMOT, renal crisis, +RNA pol III Ab = 7
- Clinical criteria that failed to make the classification list
  - calcinosis, tendon rubs, finger flexion contractures, esophageal dilation, renal crisis

MAYO CLINIC

van den Hoogen et al. Arthritis Rheum 2013;65:2737-47

Independent Predictive Factors for the Progression of Raynaud's Phenomenon to Systemic Sclerosis

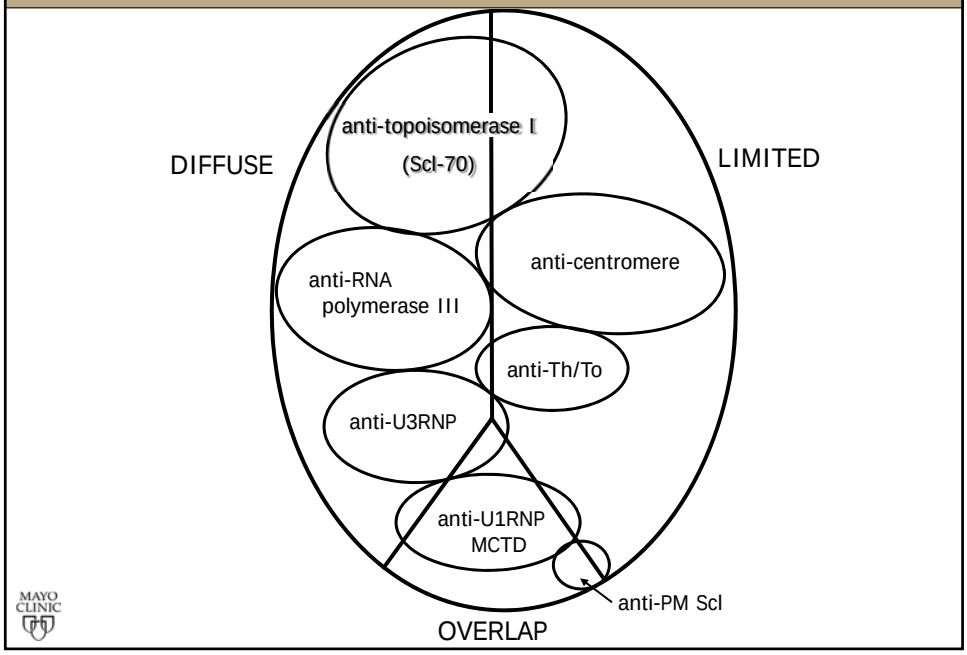
Predictors at first evaluation of RP		No. of Patients	Definite SSc Outcome		
NFC	SSc Ab		5 yrs	10 yrs	Last followup
--	--	446	6 (1.3)	7 (1.6)	8 (1.8)
+	--	31	7 (22.6)	7 (22.6)	8 (25.8)
--	+	65	14 (21.5)	21 (32.3)	23 (35.4)
+	+	44	29 (65.9)	32 (72.7)	35(79.5)
Total		586	56 (9.5)	67 (11.4)	74 (12.6)

NFC= nailfold capillary examination

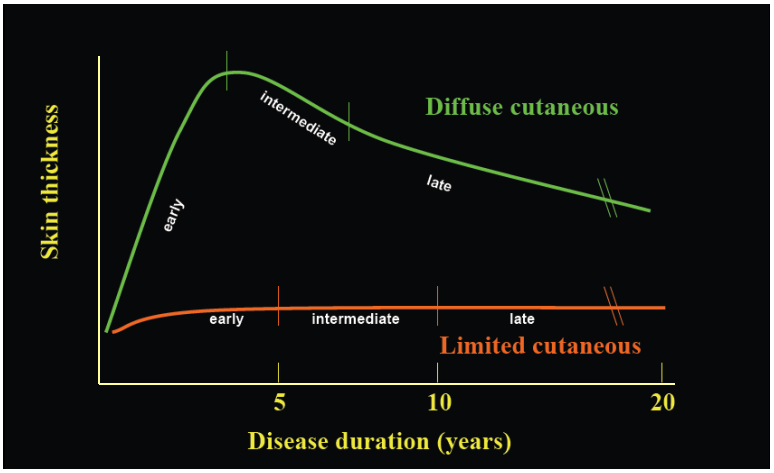
Koenig et al. Arthritis Rheum 2008;58:3902-12

MAYO CLINIC

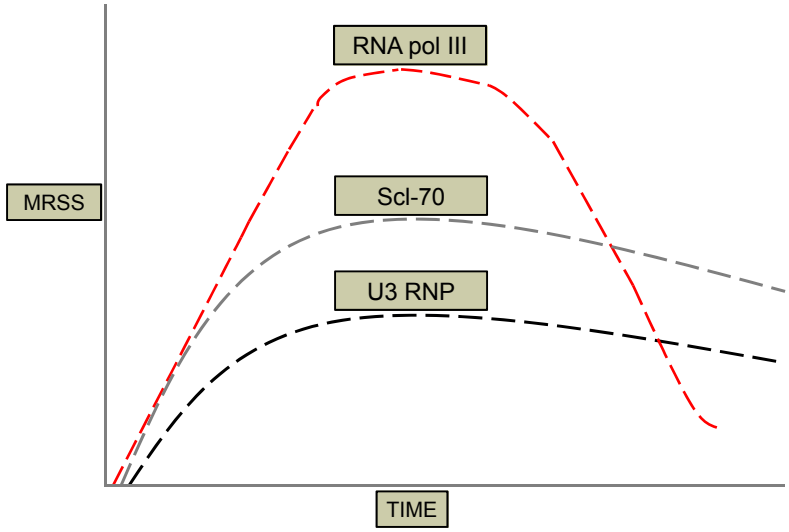
Clinical vs. Serologic Classification
SCLERODERMA



Evolution of Skin Thickening
MRSS



Evolution of Skin Thickening
MRSS



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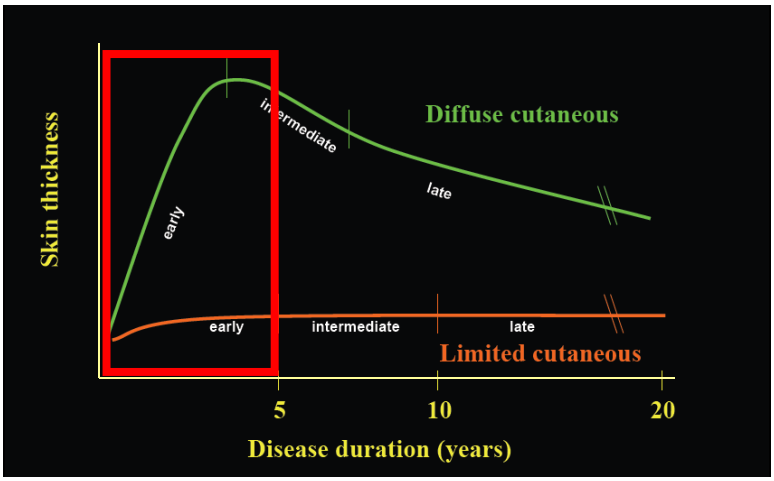
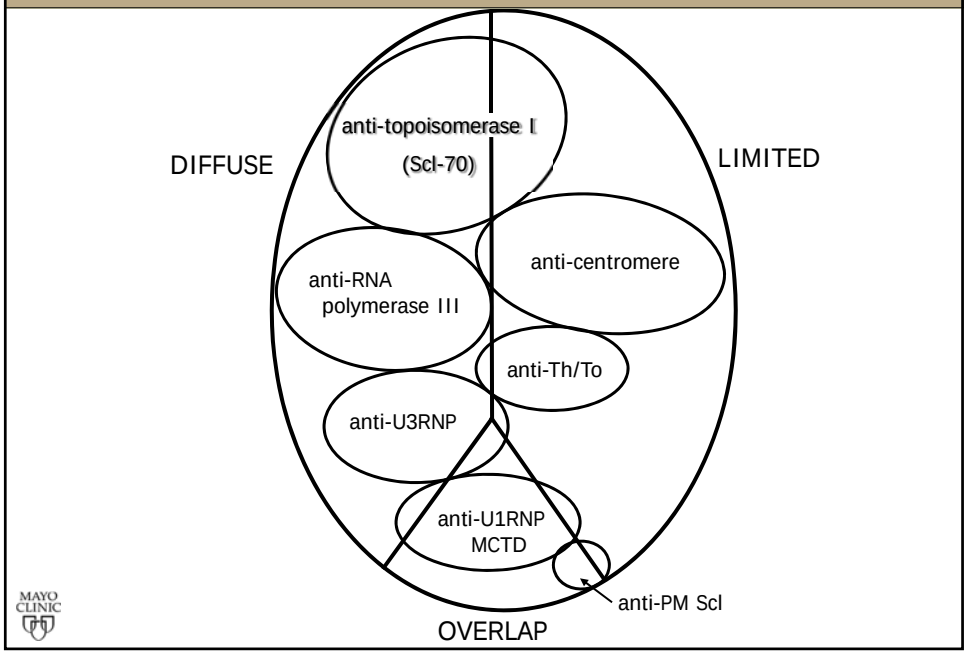
Visceral Involvement
kidney, interstitial lung disease, esophagus, heart



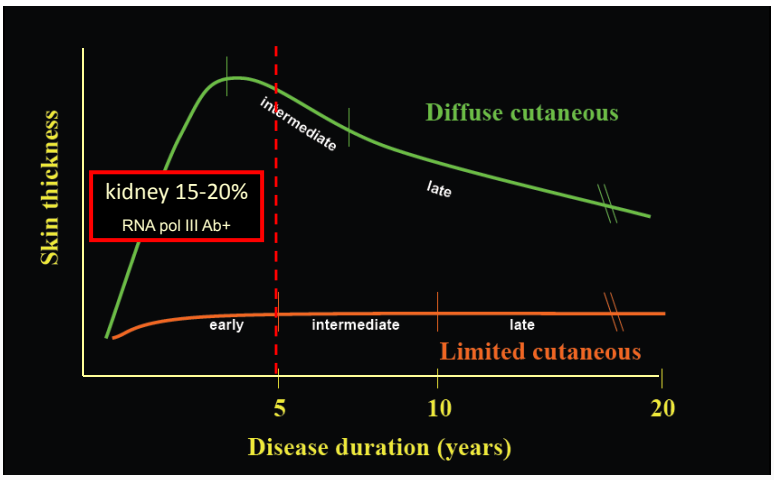
MAYO CLINIC

Clinical vs. Serologic Classification

SCLERODERMA



RENAL CRISIS



Scleroderma
renal crisis

- malignant hypertension
  - oliguric renal failure
  - microangiopathic hemolytic anemia - schistocytes
- usually diffuse systemic sclerosis 15- 20%
  - first 4-5 years of skin disease
  - rapidly progressive skin thickening (RNA polymerase III ab)
  - self monitor blood pressure daily
  - provoked with use of prednisone >15mg/day!
- outcome
  - 40% - no dialysis
  - 20% - temporary dialysis
  - 20% - permanent dialysis
  - 20% - early death
- treatment
  - angiotensin converting enzyme (ACE) inhibitors

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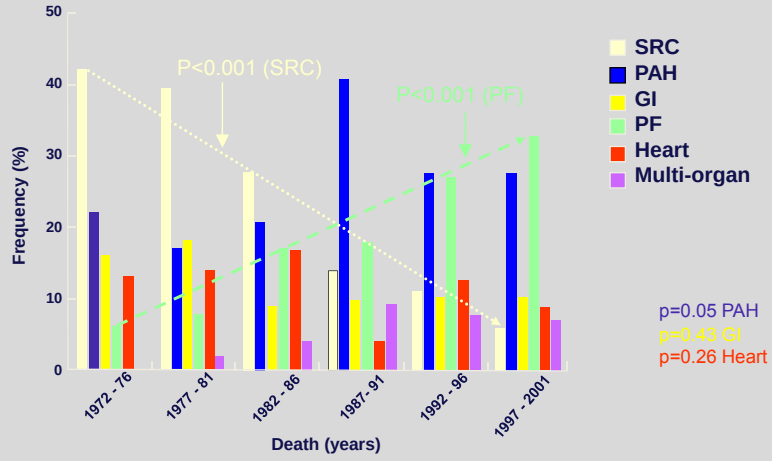
Causes of Systemic Scleroderma-related Deaths between 1972 and 2001



GI, gastrointestinal; PAH, pulmonary arterial hypertension; PF, pulmonary fibrosis; SRC, scleroderma renal crisis.

MAYO CLINIC

Steen et al. Ann Rheum Dis 2007;66:940-944

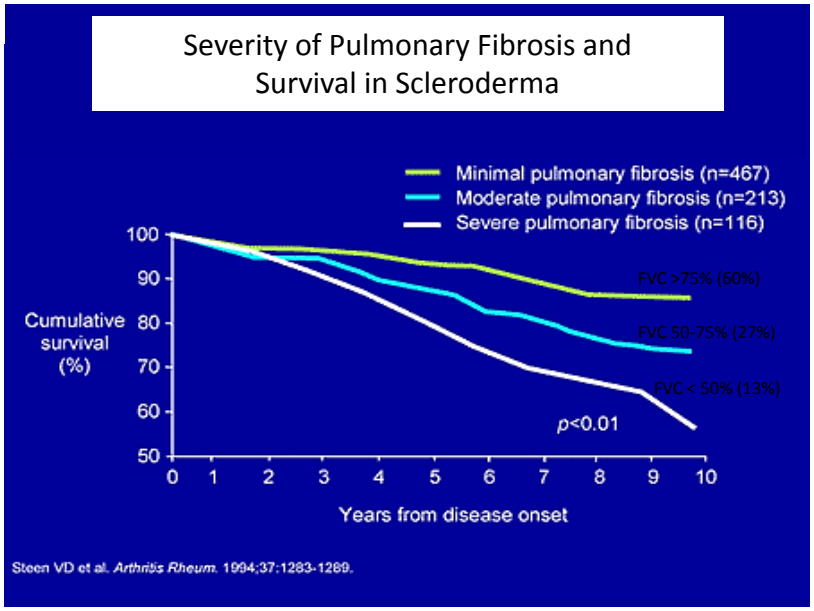
Scleroderma
Interstitial Lung Disease

- Type
  - NSIP: 77% (62/80)
  - UIP: 15% (12/80)
- Five year survival rate
  - NSIP 91% (cellular and fibrotic)
  - UIP 82%
- Mortality associated with:
  - lower FVC and/or DLCO
  - higher rate of deterioration in FVC and/or DLCO

Bouros et al. Am J Respir Crit Care Med 2002; 165:1581-86

MAYO CLINIC

Severity of Pulmonary Fibrosis and Survival in Scleroderma



Steen VD et al. *Arthritis Rheum.* 1994;37:1283-1289.

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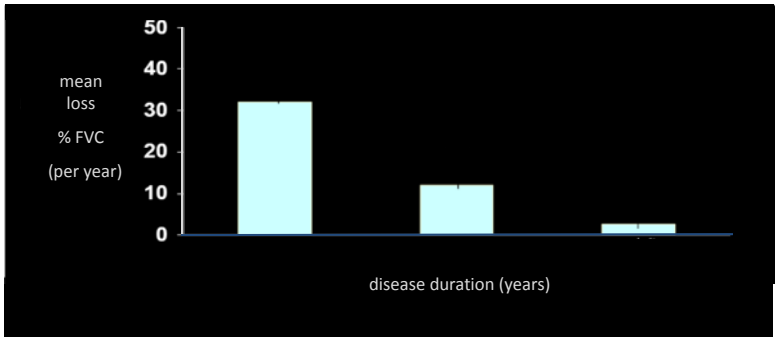
Severe Pulmonary Fibrosis
(FVC <50%)

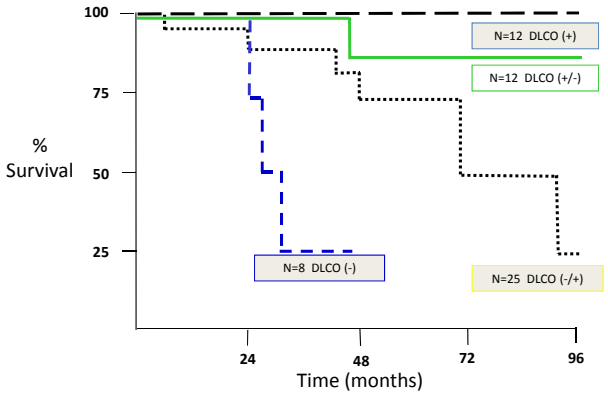
most rapid decline in first 2 years of ILD



Steen et al. Arthritis Rheum 1994; 37:1283-89

Scleroderma Survival
Linked to Change in DLCO over 3 Years

(+/-) & (-/+) = change within ≤ 15% of baseline
(+) & (-) = change > 15% of baseline



Bouros et al. Am J Respir Crit Care Med 2002; 165:1581-86

Scleroderma ILD
Worse Prognostic Factors

- scleroderma context:
  - onset relative to the skin thickening
    - within first 5 years
    - especially within first 2 years
  - Scl-70 antibody
    - 70% involved; 15% severe
    - monitor PFTs every 3-6 months
  - anti-centromeric antibody protective
- male gender
- African-American
- worsening FVC > 10%/year and/or DLCO>15%/ 3years
- baseline chest HRCT scoring

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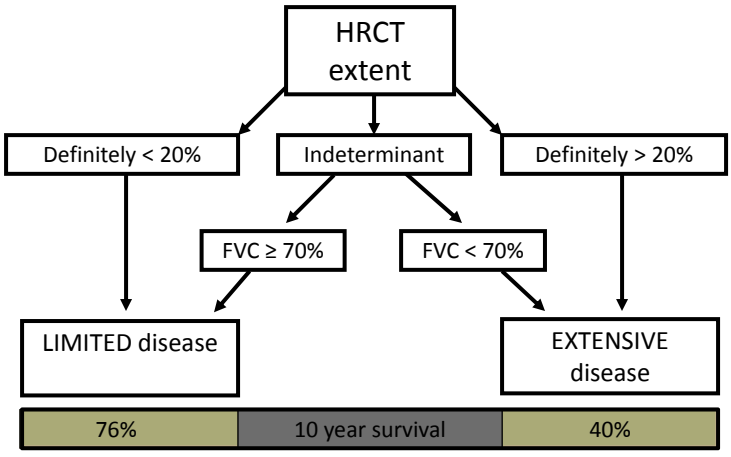
Scleroderma ILD Prognostic Algorithm



Goh et al. Am J Respir Crit Care Med 2008;177:1248

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Pulmonary Function Tests

FVC Result

70%

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Baseline Pulmonary Function Tests

120%

FVC normal range

80%

70%

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Dyspnea in Scleroderma

multiple causes may exist simultaneously

- interstitial lung disease
- pulmonary hypertension
- aspiration pneumonia
- obstructive lung disease
- thromboembolic disease
- heart failure
- anemia
- respiratory muscle weakness

Scleroderma Lung Study (SLS)

- patients
  - 158 patients: diffuse or limited SSc ≤ 7 years duration (mean of 3.1 years)
  - with scleroderma-related interstitial lung disease
    - mean FVC=68.1%
    - mean DLCO =47.4%
  - and active alveolitis (ground glass opacities on HRCT and/ or BAL fluid)
- study treatment for 1 year
  - CYC daily oral (≤ 2 mg/kg with adjustments for treatment-related toxicities)
  - or matching PLACEBO
  - prednisone up to 10 mg/ day permitted
- followed for an 1 additional year without further treatment

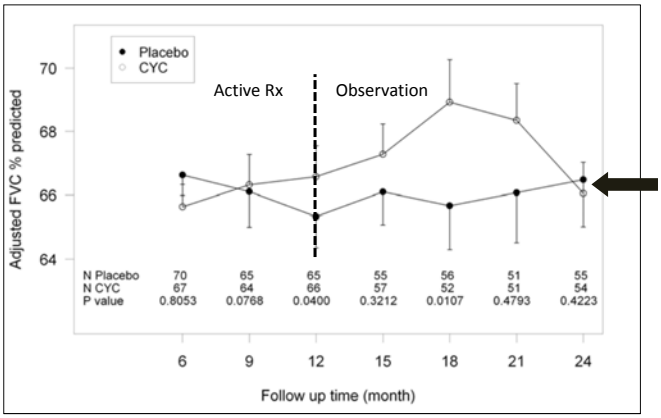
Tashkin et al. NEJM 2006; 354(25):2655-66

SLS: Outcome at 12 months

- FVC % predicted
  - adjusted mean difference of 2.53% ($p<0.03$)
  - statistically significant favoring CYC
- DLCO % predicted - no difference
- Secondary endpoints
  - self-reported dyspnea, HAQ-DI, SF-36 vitality and health-transition supported benefit
- Response was not predicted by:
  - baseline HRCT ground glass opacities
  - BAL results

Tashkin et al. NEJM 2006; 354(25):2655-66

SLS: FVC Outcome
months 12-24

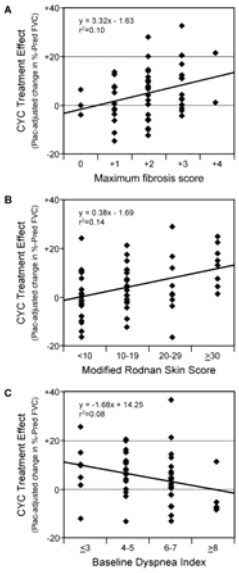


Significant difference no longer present at 24 months

Tashkin et al. NEJM 2006; 354(25):2655-66

Magnitude of CYC effect

- Correlates with baseline:
  - Maximum fibrosis score from HRCT = severity of reticular infiltrates
  - MRSS (≥ 23)
  - Mahler BDI (higher score = less dyspnea)
- No correlation with baseline:
  - % predicted FVC
  - % predicted DLCO
  - Disease duration



Roth et al. Arthritis Rheum 2011;63:2797-808

Mycophenolate

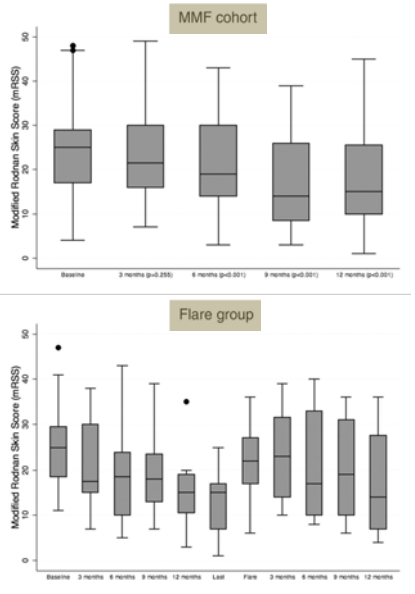
- 1 year
  - clinical care
  - primarily for active skin disease
- 98 pts
  - Diffuse SSc
  - Mean duration 21.9 months
  - Scl-70 = 24/94; ACMA =2/94
- Dose
  - 1500 mg BID = 52/98
  - 1000 mg BID = 41/98
  - 1000 mg/d = 2/98
  - 28/98 = additional immunosuppressive agent
- Outcomes:

	Baseline	3 mon	6 mon	9mon	12 mon
MRSS	24.4	23.4	21.4	17.5	17.5
FVC	79.4	--	--	--	80.7
DLCO	77.4	--	--	--	79.2

- MMF alone = 45/98:

	Baseline	3 mon	6 mon	9mon	12 mon
MRSS	23.9	21.8	19.8	14.6	13.9

- FLARE group= 20/98

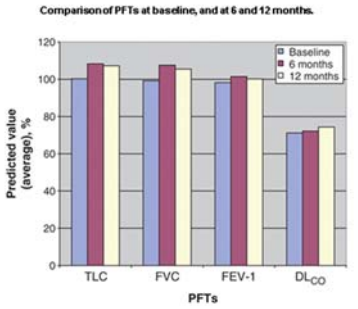


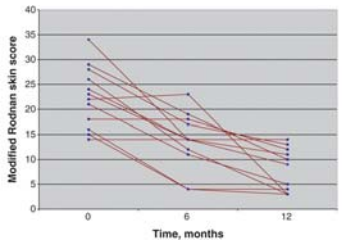
Le et al. Ann Rheum Dis 2011;70:1104-07

Mycophenolate

- 1 year, open-label prospective
- 15 pts
  - Diffuse SSc
  - Mean duration 13.4 months
  - Scl-70 =6/15; ACMA = none
- Dose
  - 1500 mg BID = 6/15
  - 1000 mg BID = 8/15
  - 1000 mg/d =1/15
- Outcomes:

	Baseline	6 mon	12 mon
MRSS	22.5	21.5	8.4
FVC	99.2	107.5	105.4
DLCO	71.2	72.1	74.3





Derk et al. Rheumatology 2009;48:1595-99

Scleroderma Lung Study II (SLS II)

- Patients
  - 142 patients, diffuse or limited disease, ≤ 7 years duration
  - scleroderma-related interstitial lung disease
- Study treatments for 2 years
  - CYC daily oral (≤ 2 mg/kg, adjusted for treatment-related toxicities) X 1 year, followed by 1 year placebo.
  - Mycophenolate ≤ 1500 mg BID for 2 years
- Results expected 2015

Hematopoietic Stem Cell Transplantation for Scleroderma

- 3 randomized, controlled trials
  - **ASSIST**: **A**merican **S**cleroderma **S**tem cell versus **I**mmune **S**uppression **T**rial
  - **ASTIS**: **A**utologous **S**tem cell **T**ransplantation **I**nternational **S**cleroderma
  - **SCOT**: **S**cleroderma: **C**yclophosphamide **o**r **T**ransplantation

MAYO CLINIC

ASTIS

Autologous Stem cell Transplantation International Scleroderma
HSCT vs. Cyclophosphamide (CYC)

- Accrual
  - 156 pts, 29 centers, March 2001-2009
- Treatments
  - 79 pts: HSCT – lymphocyte ablative
    CYC (200mg/kg over 4 days) and rbATG; reinfusion autologous CD 34+ stem cells
  - 77 pts: CYC
    12 successive monthly IV CYC (750mg/m²)

MAYO CLINIC

van Larr et al. JAMA 2014;311(24):2490-98

ASTIS

Autologous Stem cell Transplantation International Scleroderma
HSCT vs. Cyclophosphamide (CYC)

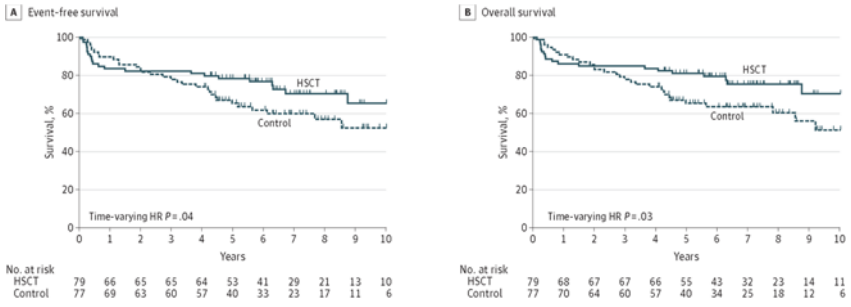
- HSCT group
  - Early treatment-related mortality 10.1%
    - All deaths occurred within first 60 days of transplant
  - More grade 3 and 4 adverse events
    - 62.9% (vs 37.0% CYC)
    - during the first 2 years of follow-up
  - More viral infections
  - Modest decrease in serum creatinine

MAYO CLINIC

van Larr et al. JAMA 2014;311(24):2490-98

ASTIS

Autologous Stem cell Transplantation International Scleroderma
HSCT vs. Cyclophosphamide (CYC)



MAYO CLINIC

van Larr et al. JAMA 2014;311(24):2490-98

ASTIS

Autologous Stem cell Transplantation International Scleroderma
HSCT vs. Cyclophosphamide (CYC)

- HSCT group
  - Better outcomes seen:
    - Skin score
    - Functional ability
    - Quality of life
    - Lung function (modest; baseline FVC 81.4% all pts)

van Larr et al. JAMA 2014;311(24):2490-98

Hematopoietic Stem Cell Transplantation for Scleroderma

- Relapses
  - **ASSIST**: 20%
  - **ASTIS**: 22.4 % required addition of immunosuppressive medication 12-24 months post transplant.
  - **SCOT**: ? (37% = Nash 2007, 34 pts)

SCOT

Scleroderma: **C**yclophosphamide **o**r **T**ransplantation
HSCT vs. Cyclophosphamide (CYC)

- Accrual
  - 114 pts, 14 centers, June 2005-2016 (final data collection)
- Treatments
  - Myeloablative: TBI 800 cGY, CYC 60mg/kg X 2 and eqATG; Reinfusion CD 34+ stem cells
  - CYC: 12 successive monthly IV CYC (500-750mg/m²)
- Results expected 2017

MAYO CLINIC

Scleroderma

esophageal involvement

"Esophageal manometry studies can document the hypomotility of GERD but are not usually required. It can be assumed that variably severe hypomotility is present at the time of diagnosis or soon after the diagnosis of scleroderma."

Textbook: SYSTEMIC SCLER

Editors: PJ Clements and DE Furst
second edition 2004

MAYO CLINIC

High Resolution Esophageal Manometry (HRM): Topographical Mapping of Esophageal Motor Function in Scleroderma (SSc)

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- *University of Cincinnati- Cincinnati, OH

MAYO CLINIC

High Resolution Esophageal Manometry (HRM): Topographical Mapping of Esophageal Motor Function in Scleroderma (SSc)

- Results 80 pts:
  - 55 (69%) "classic" scleroderma pattern.
  - 5 (6%) normal.
  - 20 (25%) varying patterns including multi-peaked contractions and spasm.

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Scleroderma
esophageal involvement

- Symptoms
  - 90-95% of pts
  - onset within first five years
  - dysphagia
  - GERD: heartburn, regurgitation, hoarseness
  - Recurrent aspiration pneumonia
- Management
  - slower eating
  - proton pump inhibitor
  - elevated head of the bed
  - avoidance of eating within 2-3 hr of bedtime

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New 2013 Classification

When the criteria don't apply:

- Skin thickening **sparing the fingers** is classified as **not** having SSc.
- Patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy)

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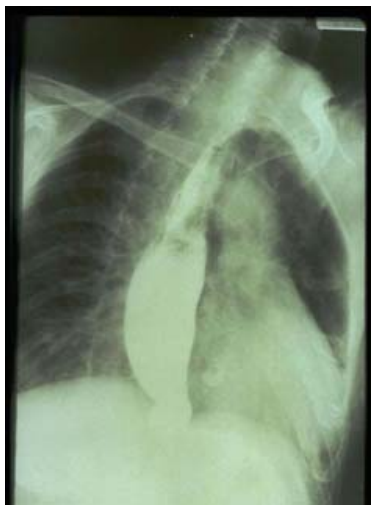
van den Hoogen et al. Arthritis Rheum 2013;65:2737-47

Scleroderma
esophageal involvement



ASTIS
Primary endpoint: Long-term event-free survival
53 total events

- HSCT - 79 pts
  - 22 events
    - 3 organ failures
    - 19 deaths
      - 8 treatment-related (1st year)
      - 9 disease progression
      - 2 other
- CYC - 77 pts
  - 31 events
    - 8 organ failures (7 deaths)
    - 23 other deaths
      - 0 treatment-related
      - 19 disease progression
      - 4 CVD
      - 5 malignancy
      - 2 other

van Larr et al. JAMA 2014;311(24):2490-98

ASTIS

Autologous Stem cell Transplantation International Scleroderma
HSCT vs. Cyclophosphamide (CYC)

- HSCT group
  - Early treatment-related deaths (10.1%)
  - Primary endpoint: Better long-term event-free survival

    Event = occurrence of death of any cause, or
    persistent major organ failure (heart, lung, kidney)
  - Better overall survival (median 5.8 years follow-up)

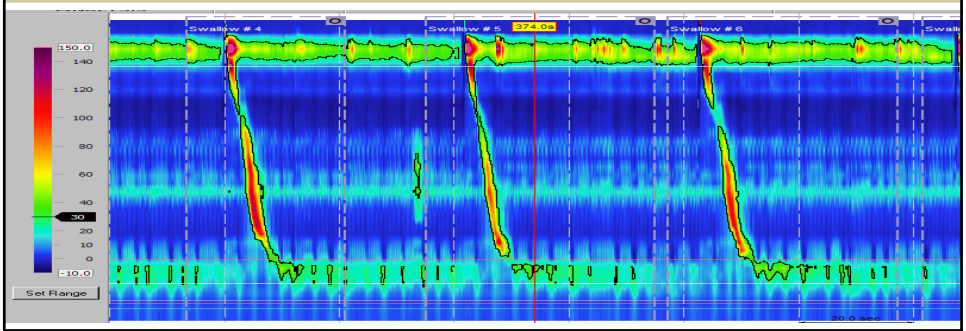
van Larr et al. JAMA 2014;311(24):2490-98

Hematopoietic Stem Cell Transplantation for Scleroderma

- Rapid and sustained improvement in skin score and function
- Stable lung function
- Possibly improved long term survival (?)
- Treatment mortality (6-10%)
  - Cardiac status, cardiac toxicity, capillary leak, infection, smoking history
- Selection of high risk patients who have failed to improve or have worsened on conventional immunosuppressive agents, yet don't have significant end organ disease and don't smoke.

Naraghi et al. Curr Rheumatol Rep 2013
Khanna et al. JAMA 2014;311(24):2485-87

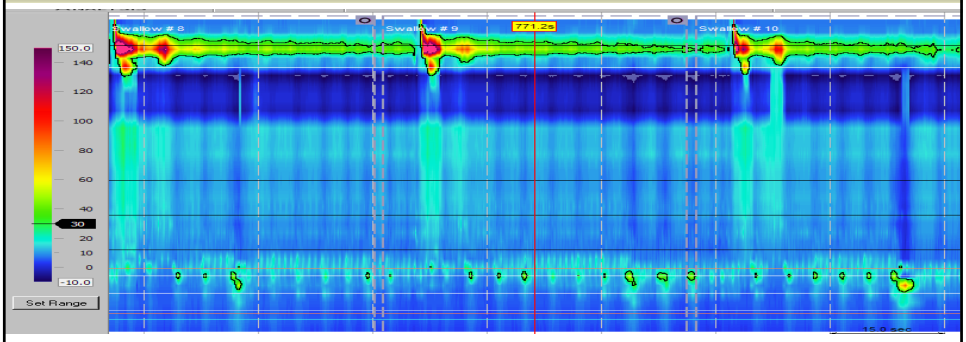
normal



Subtype	Gender F:M	Mean Age (yrs)	Mean LOI (yrs)	Mean Basal LES (mmHg)	Mean Wave Amplitude (mmHg)
Normal N=5 (6%)	5:0	51	4	20	81

Scleroderma Esophageal Involvement

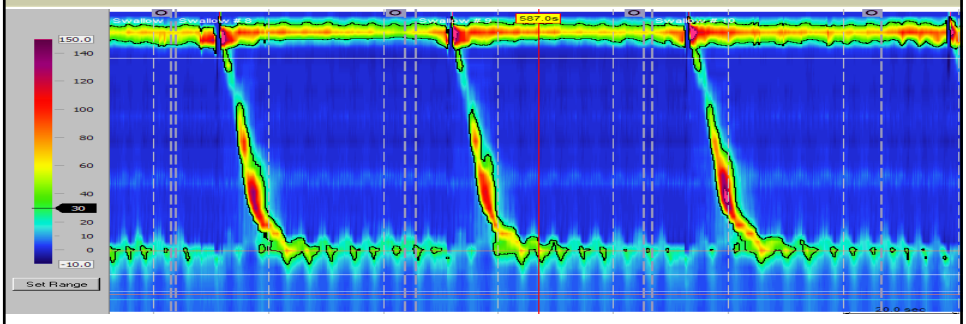
"classic" pattern



Subtype	Gender F:M	Mean Age (yrs)	Mean LOI (yrs)	Mean Basal LES (mmHg)	Mean Wave Amplitude (mmHg)
Classic SSc Pattern N=55 (69%)	45:10	54	10	6	6

Scleroderma Esophageal Involvement

reduced LES with multi-peaked contractions



Subtype	Gender M:F	Mean Age (yrs)	Mean LOI (yrs)	Mean Basal LES (mmHg)	Mean Wave Amplitude (mmHg)
Hypotensive LES+Sp/MPC N=4 (5%)	4:0	43	5	6	81

Return to Program Schedule

MAYO CLINIC

Systemic Lupus: General Concepts

Ronald R. Butendieck, M.D.
Division of Rheumatology

Conflict of Interest

- None

Return to Program Schedule

Educational Objectives

- Describe the clinical manifestations and laboratory findings included in making a diagnosis
- Define the classification criteria
- Discuss initial treatment management strategies for a variety of clinical presentations

Background

- Chronic autoimmune inflammatory disorder
- May affect virtually any organ
- Characterized prototypically by presence of autoantibodies with almost all patients being ANA positive
- Variety of clinical patterns may manifest leading to diagnostic challenge

Epidemiology

- Prevalence
  - 20-150 cases per 100,000
  - Urban > suburban
  - Higher among Asians, Afro-Americans, Afro-Caribbeans, Hispanic Americans, Asian Indians
- More common in females (estrogen effects)

Pons-Estel GJ, *Semin Arthritis Rheum*. 2010
Chakravarty EF, *Arthritis Rheum*. 2007
Petri M, *Best Pract Res Clin Rheumatol*. 2002

SLE: Gender and Age of Onset

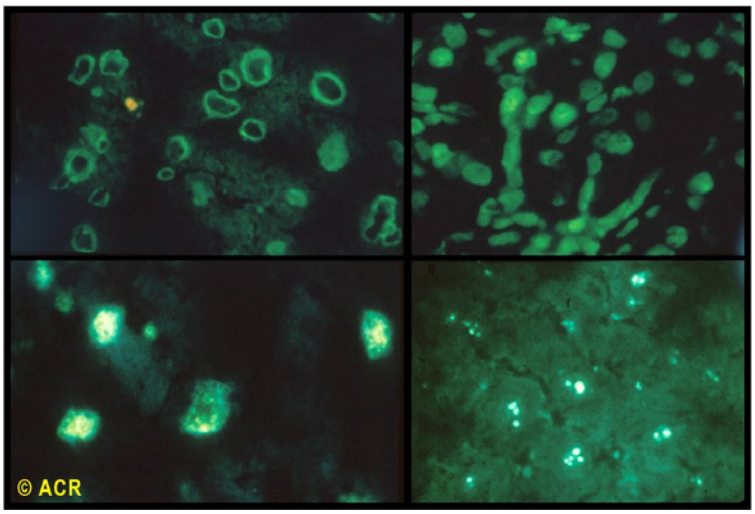
Age of onset	<16 years	16-55 years	>55 years
%SLE diagnosis	20%	65%	15%
FEMALE:MALE	8:1	10-15:1	3:1

2012 Systemic Lupus International Collaborating Clinics (SLICC) Criteria

- At least 4/17 criteria
  - ≥ 1 of the 11 clinical criteria
  - ≥ 1 of the 6 immunologic criteria
- OR
- Biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANA) or anti-double-stranded DNA (dsDNA) antibodies

SLICC

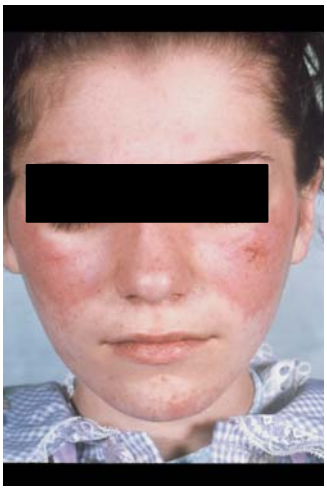
- Mucocutaneous: Rashes, ulcers, alopecia
- Joint disease: Synovitis or tenderness
- Serositis: Cardiopulmonary
- Renal: 500mg proteinuria/24 hr or RBC casts
- Neurologic: Seizures, psychosis, myelitis, mononeuritis multiplex, peripheral or cranial neuropathy, acute confusional state
- Cytopenias
- Serology: ANA, dsDNA, anti-Sm, APL, anti-B2GP1, low complements, direct Coombs



Case 1

- Mrs. T is a 34 yo healthy Caucasian female
- CC: Chest pain and facial rash
- HPI: Nonradiating pain along right anterior chest. Worse when taking deep breath. No cough, dyspnea, or lower extremity swelling. No trauma, new activities, or medications
- ROS: 2 year h/o arthralgias hands, wrists. Intermittent oral ulcers. “Sensitive to the sun.”

Case 1



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Case 1

- Labs:
  - Mild normocytic anemia
  - Normal CMP, U/A
  - Negative troponin
  - ESR 40
  - + ANA
  - + SS-A
  - Low C3

Case 1

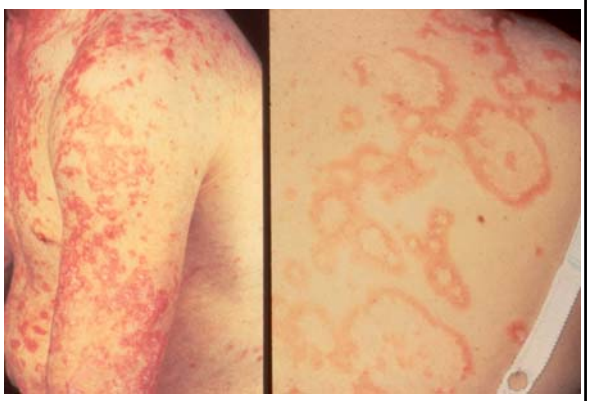
- Workup
  - EKG without abnormalities
  - CXR without effusion
  - Hand radiographs without erosive disease

Diagnosis?

1. Subacute cutaneous lupus
2. Chronic cutaneous lupus
3. Systemic lupus erythematosus
4. Drug induced lupus
5. Lupus profundus
6. Lupus tumidus
7. I didn't know there were so many types of lupus!

Subacute cutaneous lupus

- SS-A (>80%)
- 50% have SLE
- > 1/3 may be drug-induced



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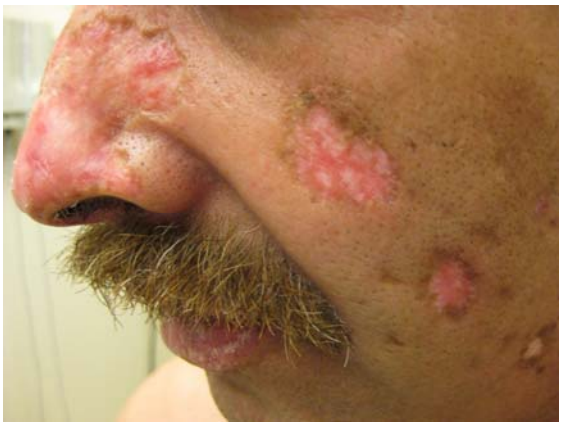
Grönhagen CM, *Sweden Br J Dermatol*. 2012
Marzano AV, *Br J Dermatol*. 2011
Stavropoulos PG, *J Eur Acad Dermatol Venereol*. 2008

Discoid lupus

- May be seronegative
- 10-15% risk of SLE
- Scarring



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Durosaro O, *Arch Dermatol.* 2009
Healy E, *Ir J Med Sci*. 1995

What would be your 1st line medication for her underlying condition?

1. Acetaminophen/NSAIDS
2. Hydroxychloroquine
3. Hydrocodone-acetaminophen
4. Topical corticosteroids
5. High dose steroids

Nonpharmacologic and Preventative Interventions

- Sun protection
  - Avoidance
  - Clothing
  - Sunscreen blocking UVA/UVB. SPF ≥55
- Check Vitamin D level
- Exercise
- Smoking cessation
- Chronic steroid toxicity prevention
- Cardiovascular disease prevention

Toloza SM, *Lupus*. 2010
Lehmann P, *Autoimmun Rev*. 2009
Hak AE, *Arthritis Rheum*. 2009
Urowitz MB, *J Rheumatol*. 2007
Formica MK, *J Rheumatol*. 2003
Ghaussy NO, *J Rheumatol*. 2003

Pharmacologic therapy

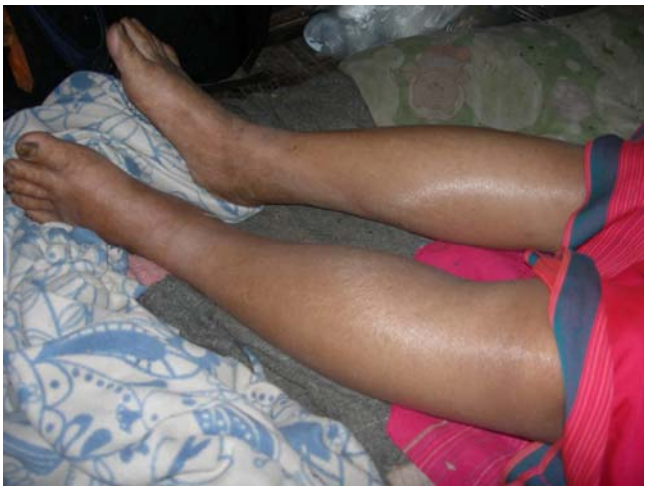
- Hydroxychloroquine
  - Constitutional symptoms
  - Arthralgias/arthritis
  - Mucocutaneous disease
  - Reduce flare rates
  - Decreased thrombotic events
  - Decrease organ damage accrual
  - Reduce mortality

Belmont HM, *Bull Hosp Jt Dis (2013)*. 2013
Akhavan PS, *J Rheumatol*. 2013
Ruiz-Irastorza G, *Ann Rheum Dis.* 2010
Pons-Estel GJ, *Arthritis Care Res (Hoboken)*. 2010
Jung H, *Arthritis Rheum*. 2010
Fessler BJ, *Arthritis Rheum*. 2005
The Canadian Hydroxychloroquine Study Group. *N Engl J Med*. 1991

Case 2

- Ms. S is an otherwise healthy 45yo AAF with h/o SLE x 5 years
- CC: New onset BLE swelling
- HPI: Dx SLE 5 years ago with mucocutaneous and musculoskeletal symptoms previously well-controlled on hydroxychloroquine 200 mg BID and prednisone 5 mg daily. BLE swelling progressive over last 3 months. Swelling lasts all day. No other symptoms.

Case 2



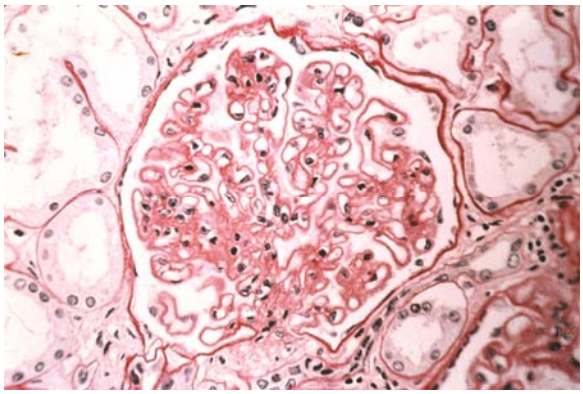
Case 2

- BP 145/75 bilaterally (Previously 118/65)
- Labs
  - Mild normocytic anemia (stable)
  - CMP WNL except albumin low (new)
  - ESR 20 (previously 12)
  - C3 and C4 WNL
  - + ANA, +SS-A, - dsDNA

What lab test would you order next to further evaluate the patient?

1. Anti-Sm antibody
2. Troponin
3. Anti-RNP antibody
4. Lupus anticoagulant
5. Urine studies
6. BNP

Case 2



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Rationale for Renal Biopsy in SLE

- Up to 60% SLE patients will have renal involvement
- Renal involvement is a major cause of morbidity
- Different subtypes require different management
- Renal biopsy can contain prognostic value
- Diagnosis of renal involvement based on tissue as clinical and lab tests are not conclusive

Beck LH, *J Am Soc Nephrol.* 2009

Indication for renal biopsy

- Protein excretion > 500 mg/day.
- Active urinary sediment
  - Hematuria (≥ 5 RBCs/HPF)
  - Cellular casts
- Time is of the essence
  - Prompt initiation of treatment with better outcomes in several studies

Faurschou M, *J Rheumatol*. 2006
Contreras G, *Lupus.* 2005
Esdaile JM, *J Rheumatol*. 1994

Membranous Lupus Nephritis (Class V)

- Up to 10-20% pts with lupus nephritis
- Can present with minimal clinical symptoms
- Can have normal/negative C3, C4, dsDNA
- May have normal or slightly elevated creatinine
- Better prognosis
  - 10 year renal survival of 72-98%

Bhinder S, *Am J Med Sci*. 2010
Beck LH, *J Am Soc Nephrol*. 2009
Sun HO, *Lupus*. 2008
Austin HA 3rd, *J Am Soc Nephrol*. 2009
Mercadal L, *Nephrol Dial Transplant*. 2002
Huong DL, *Medicine (Baltimore)*. 1999
Sloan RP, *J Am Soc Nephrol*. 1996
Neumann K, *Semin Arthritis Rheum*. 1995
Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL). *Am J Kidney Dis*. 1992

Membranous lupus nephritis Treatment

- Blood pressure optimization
  - 130/80 or lower
- Reduce proteinuria
  - < 1000 mg/day if possible
  - Otherwise reduce proteinuria by 50-60% baseline AND proteinuria < 3.5 g/day
- Lipid lowering
- Maximize ACE I, ARB, statins

Membranous Lupus Nephritis Treatment

- Indications for immunosuppressant meds
  - Persistent symptomatic nephrotic syndrome
  - Increased or rising serum creatinine
  - Mixed membranous and proliferative lesions on biopsy
- Cyclophosphamide
- Mycophenolate mofetil
- Azathioprine

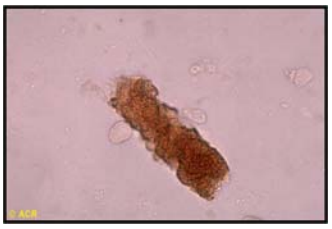
Austin HA, *J Am Soc Nephrol*. 2009
Appel GB, *J Am Soc Nephrol*. 2009
Ginzler EM, . *N Engl J Med*. 2005
Mok CC, *Am J Kidney Dis*. 2004

Case 3

- Ms. L is a 20 yo AAF previously healthy
- CC: Severe fatigue, weight loss, exercise intolerance
- HPI: Track runner with 2 mo h/o progressive fatigue/malaise and 6 lbs weight loss that is unexplained. No other symptoms. No new medications. Not depressed. Mother has SLE.

Case 3

- EKG negative
- CXR clear
- Labs:
  - Hgb 8.5, WBC 2.9
  - Creatinine elevated
  - +ANA, +dsDNA
  - Low C3, low C4
  - ESR 75
  - U/A with RBC casts and 2+ proteinuria



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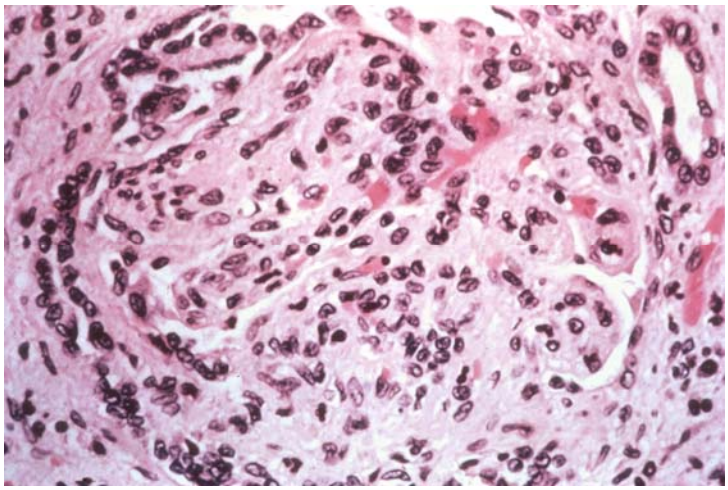
What diagnostic test is indicated?

1. CT abdomen/pelvis
2. ANCA panel
3. Renal biopsy
4. Bone marrow biopsy
5. Rheumatology consultation

Case 3



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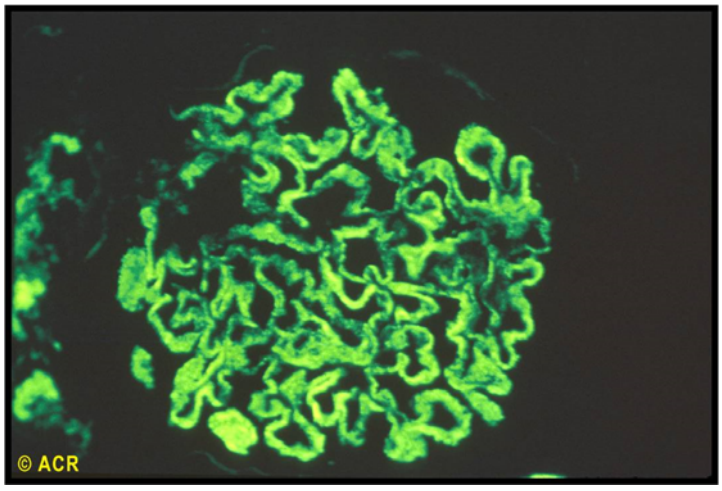
Case 3



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Lupus nephritis
Risk factors for progression

- Elevated serum creatinine
- Hypertension
- Nephrotic range proteinuria
- Anemia with hct < 26%
- Black and Hispanic race and ethnicity
- Delayed therapy
- Failing to achieve remission
- Relapses

Sisó A, *Medicine (Baltimore).* 2010
Faurschou M, *J Rheumatol*. 2006
Contreras G, *Lupus.* 2005
Korbet SM, *Am J Kidney Dis*. 2000
Austin HA 3rd, *Kidney Int.* 1994
Esdaile JM, *J Rheumatol*. 1994
Appel GB, *Am J Med.* 1987

The dsDNA

- Titers may fluctuate with SLE disease activity
- Associated with active glomerulonephritis
- Involvement in pathogenesis of lupus nephritis

Cortés-Hernández J, *Am J Med*. 2004
Kavanaugh AF, *Arthritis Rheum*. 2002
Borg EJ, *Arthritis Rheum*. 1990

Lupus Nephritis Class III/IV Treatment: Induction Therapy

- IV pulse MP (500-1000 mg) daily x 3 days, then switch to oral prednisone

PLUS

- IV CYC
  - High dose: 500-1000 mg/mo x 6 doses
  - Low dose: 500 mg q 2 weeks x 6 weeks
- MMF: 2-3 g/day x 6 months
  - Preferred over CYC in AA and Hispanic pts

MP: Methylprednisolone
CYC: Cyclophosphamide
MMF: Mycophenolate mofetil

Hahn BH, *Arthritis Care Res (Hoboken)*. 2012
Bertsias GK, *Ann Rheum Dis*. 2012

Lupus Nephritis Class III/IV Treatment: Maintenance Therapy

- MMF or azathioprine
  - No difference in morbidity or ESRD
  - No difference in side effects
- MMF
  - Lower rate of relapse
- Azathioprine
  - Women in complete remission who wish to become pregnant

Henderson LK, *Am J Kidney Dis.* 2013
Henderson L, *Cochrane Database Syst Rev*. 2012
Stoenoiu MS, *Nephrol Dial Transplant*. 2012
Dooley MA, *N Engl J Med*. 2011
Houssiau FA, *Ann Rheum Dis*. 2010
Contreras G, *N Engl J Med*. 2004

Case 4

- Ms. A is a 27yo AAF with 3 uncomplicated pregnancies
- ED CC: Dyspnea, chest pain, cough, generalized swelling
- HPI: 7-8 years arthralgias/mild arthritis bilateral hands/wrists controlled on OTC NSAIDS. Previously told “elevated ANA, but no lupus.” Otherwise previously healthy. No other meds. Severe fatigue, coughed up blood that day.

Case 4

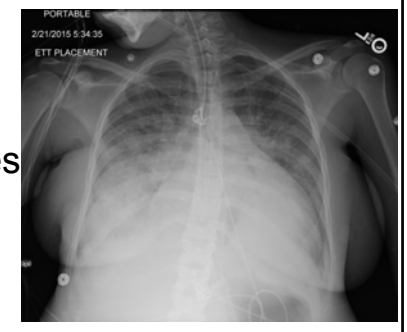
- Rapid shallow breaths
- Hypoxic requiring supplemental O2
- Pericardial friction rub
- Generalized anasarca

Case 4: Labs

- Hgb 5.1; MCV 86.5; WBC 12.5; Plt 360
- + ANA, anti-Sm-ab, low C3/C4
- ESR 120
- Negative dsDNA
- Renal function preserved
- LFTs WNL
- APL, lupus anticoagulant, anti-B2GP1 neg

Case 4: Initial Imaging

- Echo
  - EF 40-45% with ? RV thrombus
  - Moderate pericardial effusion
- CXR
  - Diffuse bilateral infiltrates
  - Small pleural effusions



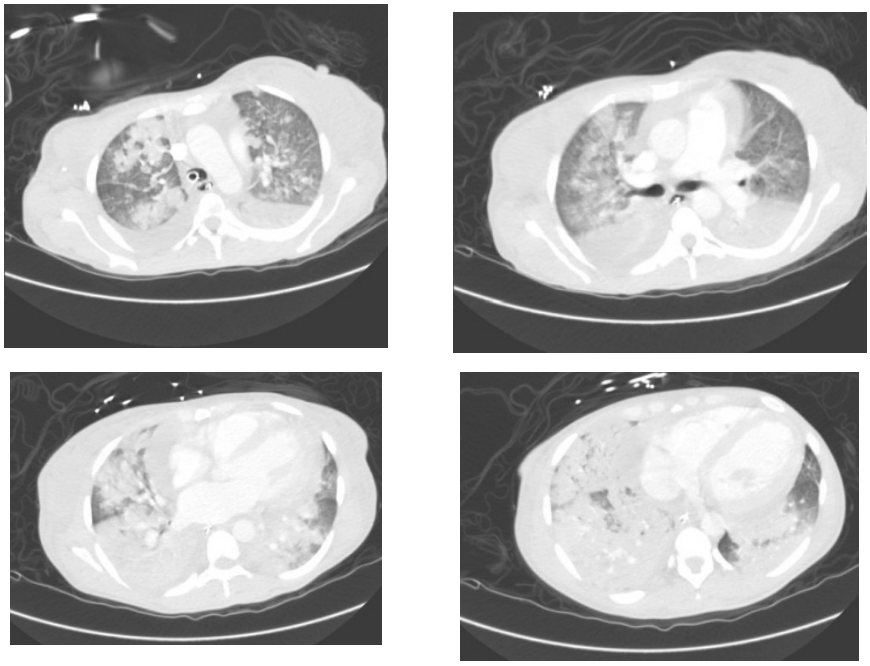
Case 4:
Initial Treatment and Clinical Course

- Lupus: MP 40mg TID
- RV thrombus: heparin ggt
- Decreased LF function: diuresis, BB

- Following day developed respiratory failure → intubation → PEA → hospital transfer

Case 4: Workup

- CTA chest
  - Diffuse GGO bilaterally.
  - No PE
  - Cardiomegaly with pleural effusions
- Bronchiolar lavage: progressively hemorrhagic aliquots with hemosiderin-laden macrophages
- Echo
  - EF 25% with severe global hypokinesis
  - No thrombus
  - Moderate circumferential pericardial effusion



Imaging/Workup Review

- Pleuropericardial effusions
- Myocarditis
- Diffuse alveolar hemorrhage

SLE: Diffuse Alveolar Hemorrhage (DAH)

- Relatively rare
- Can be 1st manifestation of SLE
- May occur with or without hemoptysis
- High association with SLE nephritis
- High mortality rates

Badsha H, *Semin Arthritis Rheum*. 2004
Zamora MR, *Medicine (Baltimore)*. 1997

DAH: Treatment

- MP 1000 mg IV daily x 3 days
- Plasmapheresis x 5 days
- Cyclophosphamide 1000 mg IV monthly

Zamora MR, *Medicine (Baltimore)*. 1997
Erickson RW, *Semin Arthritis Rheum*. 1994
Schwab EP, *Semin Arthritis Rheum*. 1993

SLE: Pulmonary disease

- Acute pneumonitis
- Interstitial lung disease
- Pulmonary hypertension
- Shrinking lung syndrome
- Pleural effusions
- Organizing pneumonia
- Pulmonary venoocclusive disease
- Adult respiratory distress syndrome

SLE: Myocarditis

- Up to 9% of SLE patients
- Echo with global hypokinesis
- Increased frequency in AA patients
- Association with SS-A, RNP and pericarditis
- Endometrial biopsy “gold standard” for dx
  - Mononuclear infiltrate
  - Fibrosis
- Rare causes: CYC, hydroxychloroquine

Apte M, *Rheumatology (Oxford)*. 2008
Nord JE, *Semin Arthritis Rheum*. 2004
Keating RJ, *J Am Soc Echocardiogr*. 2005
Wijetunga M, *Am J Med*. 2002
Moder KG, *Mayo Clin Proc*. 1999

Myocarditis: Treatment

- No controlled trials
- MP 1000 mg IV daily x 3 days
- Cyclophosphamide
- Azathioprine
- IVIG
- Treatment for heart failure

Barnado A, *Am J Med Sci*. 2014
Zawadowski GM, *Lupus*. 2012
Moder KG, *Mayo Clin Proc*. 1999

SLE: Cardiac disease

- Pericardial disease (most common)
  - NSAIDS
  - Prednisone
  - Colchicine
- Coronary artery disease
  - Strict control of risk factors
- Libman-Sacks endocarditis
  - 6-10% pts
  - Anticoagulation in select pts

Roldan CA, *J Rheumatol*. 2008
Moyssakis I, *Am J Med*. 2007
Doria A, *Lupus*. 2005
Guindo J, *Circulation*. 1990

Take Home Points

- SLE is a chronic, multisystem autoimmune disorder with a variety of clinical manifestations
- Specific clinical findings, serology, and pathology are relied upon to make a diagnosis
- Hydroxychloroquine should be used as foundational treatment in all patients with SLE
- Sun avoidance and management of cardiac risk factors are important in SLE
- Obtaining a timely renal biopsy is crucial in the management of lupus nephritis

Return to Program Schedule

Polymyalgia Rheumatica

Florentina Berianu, MD
Rheumatology, Mayo Clinic Jacksonville

I have nothing to disclose

Return to Program Schedule

Learning Objectives:

1. **Identify patients with the diagnosis of PMR**
2. **Review the differential diagnosis in a patient with PMR**
3. **To learn how to treat patients with PMR**

MAYO CLINIC

References:

- H.S. Barber: Myalgic syndrome with constitutional effects: polymyalgia rheumatica. Ann Rheum Dis. 16:230-237 1957 13445065
- C.S. Crowson, E.L. Matteson, E. Myasoedova, et al.: The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 63:633-639 2011 21360492
- B. Dasgupta, M.A. Cimmino, H.M. Kremers, et al.: 2012 provisional classification criteria for polymyalgia rheumatica. Arthritis Rheum. 64:943-954 2012 22389040
- K. Hagihara, I. Kawase, T. Tanaka, T. Kishimoto: Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. J Rheumatol. 37:1075-1076 2010 20439532
- C. Salvarani, F. Cantini, G.G. Hunder: Polymyalgia rheumatica and giant-cell arteritis. Lancet. 372:234-245 2008 18640460
- C. Salvarani, F. Cantini, I. Olivieri, et al.: Proximal bursitis in active polymyalgia rheumatica. Ann Intern Med. 127:270-331 1997
- C. Salvarani, P. Macchioni, C. Manzini, et al.: Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized controlled trial. Ann Intern Med. 146:631-639 2007 17470831

MAYO CLINIC

What is Polymyalgia Rheumatica?

MAYO CLINIC

PMR Definition:

- Reported by Dr. Barber in 1957 with 12 cases
- PMR is an inflammatory syndrome of older individuals characterized by pain and stiffness in the shoulder and/or pelvic girdles
- Constitutional symptoms are common (33%-50% of patients)

MAYO CLINIC

ACR and EULAR have established provisional classification (2012)

- Experts used a point system to help in research studies.

- All patients were **required to have the first three criteria:**
  - Age ≥50 years
  - Bilateral shoulder achiness
  - Abnormal ESR or CRP

ACR and EULAR have established provisional classification (2012)

The point system applied to:

Morning stiffness	2 points
Hip pain	1 points
Absence of RF/ACPA	2 points
Absence of other joint pain	1 points

ACR and EULAR have established provisional classification (2012)

- Diagnostic accuracy of required three criteria plus a score of at least 4 points for the other criteria yielded sensitivity of 68% and specificity of 78%
- Addition of shoulder ultrasound increased the diagnostic accuracy

Epidemiology

- PMR is the second most common autoimmune syndrome, with a lifetime risk of 2.4% for women and 1.7% for men
- PMR rarely affects those <50 years of age and becomes more common with increasing age
- Most patients are >60 years of age, with a mean age of onset of approximately 70 years
- Women are affected twice as often as men
- PMR, like GCA, largely affects whites and is uncommon in Blacks, Hispanic, Asian, and Native American individuals

Clinical Presentation

- Stiffness and pain are usually acute or subacute in onset
- Symmetric, profound involvement of more than one area (neck, shoulders, pelvic girdle). At times the initial symptoms are unilateral and then progress to symmetric involvement
- The shoulder is often (70% to 95% of patients) the first area to be affected. The neck and pelvic girdle are involved in 50% to 70% of cases.
- The magnitude of the pain limits mobility; stiffness and gelling phenomena are dramatic. Patients may complain of a sensation of muscle weakness due to the pain and stiffness.

MAYO CLINIC

Do we see inflammatory arthritis in PMR?

MAYO CLINIC

The Arthritis of PMR

- Approximately 50% of patients can have peripheral joint manifestations
- Knee effusions, wrist synovitis (often with carpal tunnel syndrome), and sternoclavicular arthritis are detected most frequently
- Ankle and metatarsophalangeal joint (MTP) arthritis are rare and should prompt consideration of another diagnosis

Findings on physical examination of patients with PMR

- **Physical findings are less striking than the history**
- Up to 33% of patients have constitutional symptoms/signs and appear chronically ill, with weight loss, fatigue, depression, and low-grade fever
- High, spiking fevers are unusual unless GCA is present
- Joint movement increases the pain, which is often felt in the proximal extremities, not the joints
- Strength is normal unless disuse atrophy has occurred

What is the source of the symptoms in PMR?

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Source of pain in PMR

- Systemic inflammatory syndrome, accounting for the constitutional symptoms
- It is believed that tenosynovitis (biceps) and bursitis (subdeltoid, subacromial, trochanteric, and interspinous muscles) rather than synovitis is the source of symptoms. Shoulder MRI has demonstrated this in patients
- Muscle biopsies are usually normal with no inflammation

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Do we see characteristic laboratory findings in PMR?

MAYO CLINIC

Laboratory results in PMR

- Elevated ESR
- PMR may occasionally (**7%) occur with normal or only mildly elevated ESR (<40 mm/h)**
- CRP is usually elevated.

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Other Commonly Encountered Laboratory Abnormalities

- Reflective of systemic inflammatory process
  - Normochromic normocytic anemia
  - Thrombocytosis
  - Increased gamma globulins
  - Elevated acute-phase reactants
- Elevated alkaline phosphatase
- Renal function, urinalysis, and serum creatine kinase levels are normal
- Tests for antinuclear antibodies, RF, and ACPAs are negative

MAYO CLINIC

How are PMR and GCA related?

- PMR and GCA frequently occur at the same time or sequentially in individual patients
- PMR has been noted in 40% to 60% of patients with GCA and may be the initial symptom complex in 20% to 40% of cases. Conversely, GCA may occur in 30% of patients with PMR.

MAYO CLINIC

Should a temporal artery biopsy be performed on a patient with PMR?

MAYO CLINIC

Temporal artery biopsy in PMR

- Temporal artery biopsy is usually **not necessary** unless symptoms or signs suggest the presence of GCA

Temporal artery biopsy is suggested:
- Patients with fever are more likely to have occult GCA
- Failure of prednisone (15 to 20 mg/day) to significantly improve symptoms
- Failure to normalize ESR/CRP within 1 month should suggest the presence of GCA

MAYO CLINIC

Differential diagnosis:

- Fibromyalgia syndrome: tender points, normal ESR
- Hypothyroidism: elevated TSH, normal ESR
- Shoulder osteoarthritis, rotator cuff, frozen shoulder: physical examination, x-rays, normal ESR
- Polymyositis: weakness predominates; elevated creatine kinase; abnormal EMG
- Malignancy
- Occult infection (TB, HIV, SBE): clinical suspicion of infection; cultures, and serologies
- Rheumatoid arthritis: positive RF, anti-CCP, small joint involvement, especially MTPs

MAYO CLINIC

How is PMR Distinguished from Rheumatoid Arthritis?

- It is often difficult to distinguish PMR from the onset of RA in older patients, in whom constitutional symptoms and morning stiffness often surpass joint manifestations
- Features that support the diagnosis of PMR are as follows
  - Absence of RF and anti-CCP antibodies
  - Lack of involvement of small joints (metacarpophalangeal and proximal interphalangeal joints, MTPs) of the hands and feet
  - Lack of development of joint damage
  - Absence of erosive disease during follow-up
- **The response to glucocorticoids is not a reliable distinguishing feature.**

MAYO CLINIC

Use of glucocorticoids in PMR

- Prednisone at a dose of 15 to 20 mg/day usually evokes a dramatic and rapid response
- Lean individuals may be treated with lower doses (10 to 15 mg/day) initially, whereas obese patients will need higher doses
- Most patients are significantly better within 1 to 2 days, although others may take longer (1 to 2 weeks) to respond completely
- A single daily dose is recommended

Use of glucocorticoids in PMR

- Tapering of an oral prednisone dose is based on the patient's clinical response
- PMR symptoms and ESR/CRP are the most reliable parameters. CRP normalizes more quickly than ESR, which should steadily decline to normal within 1 month.
- Failure to normalize these acute-phase reactants should prompt a search for occult GCA or an alternative diagnosis

Use of glucocorticoids in PMR

- Once ESR and CRP are normalized, the prednisone dose is decreased by 2.5 mg every 2 to 4 weeks until a dose of 10 mg/day is attained
- Further tapering is by 1 mg every 1 to 2 months while the patient and ESR or CRP are monitored
- During the tapering, an increase in ESR or CRP in an otherwise asymptomatic patient does not justify an increase in prednisone dosage. However, the dose should not be tapered any further until alternative causes of the elevated acute-phase reactant have been investigated.

MAYO CLINIC

The Course of PMR

- The course of PMR is long with recurrences
- Possible predictors of a poor clinical course
  - Older age at diagnosis
  - Female sex,
  - Very high ESR/CRP with failure to normalize CRP within 1 week of starting prednisone
- Overall, some 75% of patients are able to taper off their prednisone treatment within 2 years

MAYO CLINIC

The Course of PMR

- Between 25% and 35% of patients require low doses of glucocorticoids indefinitely because of a relapse each time the prednisone is tapered off
- In those who are able to stop taking glucocorticoids, PMR relapse can occur in 10% to 20% of patients some months or even years later

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Steroids sparing agents:

- In patients with steroid-dependent PMR, use of methotrexate can facilitate tapering of steroids
- Biologic therapy such as steroid-sparing agents has had mixed results
  - Controlled trial using infliximab did not show benefit
- It was recently reported that tocilizumab is effective, highlighting the prominent role of IL-6 in the pathogenesis

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Use of Methotrexate (MTX) as a Corticosteroid-sparing Agent

- Has been addressed in a randomized, doubled-blind and placebo-controlled trial
- Prednisone (25 mg/day starting dose) was tapered off within 24 weeks with dose adjustment in cases of flare-up
- Patients were randomized to receive 10 mg per week MTX or placebo for 48 weeks
- Outcome was assessed after 18 months
- MTX noted to assist with successfully tapering of steroids

- Caporali R, et al. Ann Intern Med. 141:493-500 2004 15466766

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Use of Methotrexate (MTX) as a Corticosteroid-sparing Agent

- Median cumulative prednisone dose was 2.1 g in the MTX group and 2.9 g in the placebo group
- Rate and severity of adverse effects were similar

- Remaining questions
  - If benefits from MTX are clinically meaningful?
  - Patients managed with the prednisone/MTX combination still underwent disease recurrences
  - Corticosteroid-sparing effect was modest at best
  - Adverse events remained unchanged

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Conclusion

- PMR is a common systemic inflammatory disorder in the elderly
- Patients present with subacute onset of severe pain and stiffness in proximal limbs and a high ESR
- PMR may appear simultaneously or sequentially in patients with GCA
- Patients typically respond dramatically to prednisone at 15 to 20 mg/day
- PMR treatment often extends for 2 years or more and relapses are frequent

MAYO CLINIC

Return to Program Schedule

Sjögren's Syndrome

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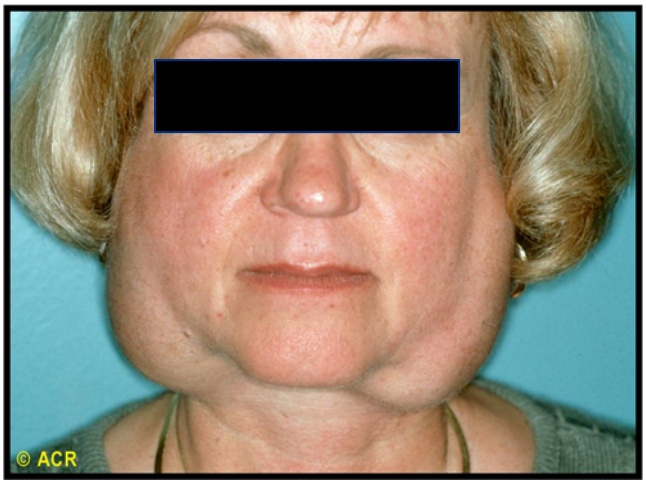
Conflicts of interest

- None to disclose

Return to Program Schedule

Sjögren's syndrome
Educational Objectives

- Describe the clinical manifestations and laboratory findings included in making a diagnosis
- Define the classification criteria (s)
- Discuss symptomatic management as treatment



Sjögren's syndrome

- Chronic, systemic autoimmune disease with lymphocytic infiltration of the exocrine glands, mainly salivary and lacrimal glands, resulting in functional impairment → sicca syndrome
- May result in extra-glandular manifestations with increased morbidity and mortality

Sjögren's syndrome

- Primary
  - No other underlying rheumatic disease
  - May preclude development of other rheumatic disease by years
  - Search for other autoimmune processes
- Secondary
  - Associated with other connective tissue disease (RA, SLE)

Peri Y, *Best Pract Res Clin Rheumatol.* 2012
Vitali C, *Ann Rheum Dis.* 2002

Sjögren's syndrome: Who and how common?

- Females between 4th-6th decade
- F:M 9:1 to 20:1 in some cohorts
- Estimated incidence between 3.9-5.3/100,000
- Estimated prevalence between 0.1% and 4.8%
  - Criteria dependent
  - More recent: between 0.01% and 0.9% (using AECG criteria)

Patel R, *Clin Epdemiol*. 2014

Sjögren's syndrome Concomitant autoimmunity

- Cross-sectional study of 410 patients
  - 134 (32.6%) patients with poly autoimmunity
    - Autoimmune thyroid disease (21.5%)
    - RA (8.3%)
    - SLE (7.6%)
    - IBD (0.7%)
    - Multiple autoimmune syndrome (8.5%)
- Screen for celiac disease (up to 5-10%)

Amador-Patarroyo MJ, *J Autoimmun.* 2012
Roblin X, *Arch Int Med.* 2004

Sjögren's syndrome Mimics

- Age-related sicca
- Benign lymphoepithelial sialadenitis and dacryoadenitis
- Contact lens irritation
- Poorly controlled diabetes
- Medications
- Vitamin A deficiency
- Blepharitis
- Viral infection

Sjögren's syndrome: Mimics

- Sarcoidosis
- Hepatitis C
- HIV infection
- Graft-versus-host-disease
- IgG4-related disease
- Systemic vasculitis
- Lymphoma and other hematologic malignancies
- Pemphigoid

Sjögren's syndrome: Classification Criteria (s)

- The European classification criteria (1996)
  - Revised by the American–European consensus group (AECG) in 2002
- The International Collaborative Clinical Alliances Cohort (2012)
  - Approved by the American College of Rheumatology

Shiboski SC, *Arthritis Care Res (Hoboken).* 2012
Vitali C, *Ann Rheum Dis.* 2002
Manthorpe R, *Scand J Rheumatol Suppl.* 1986

Revised AECG Criteria

- Ocular symptoms: positive response to one
  - Daily persistent trouble with dry eyes for > 3 months
  - Recurrent sensation of sand or gravel in the eyes
  - Use tear substitutes > three times per day?
- Oral symptoms: positive response to one
  - Daily feeling of dry mouth for > 3 mo
  - Recurrent or persistent swollen salivary glands as an adult
  - Frequently drink liquids to aid swallowing dry food?
- Ocular signs: + Schirmer's test (<5 mm/5 min) or positive rose bengal score (>4)
- Salivary gland involvement: a positive test on at least one
  - Unstimulated whole salivary flow (<1.5 mL/15 minutes) or parotid sialography showing the presence of diffuse sialectasis
  - Parotid gland sialography showing the presence of diffuse sialectasis without evidence of obstruction in the glands
  - Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
- Histopathology: minor salivary gland biopsy with focal score ≥ 1 focus/4 mm^2
- Autoantibodies: presence of anti-SSA (Ro) or anti-SSB (La) or both

Vitali C, *Ann Rheum Dis.* 2002

ACR Classification Criteria

- Serology
  - + SS-A and/or + SS-B
  - + ANA ≥ 1:320 and RF
- Biopsy
  - Labial salivary gland biopsy with focal lymphocytic sialadenitis with focal score ≥ 1 focus/4 mm^2
- Ocular staining score ≥ 3
- Need 2/3 to fit criteria

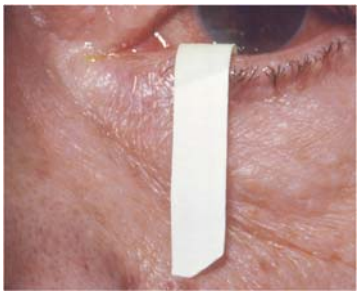
Shiboski SC, *Arthritis Care Res (Hoboken)*. 2012

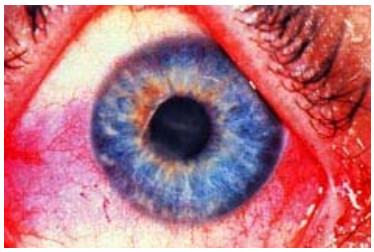
Sjögren's syndrome Serologic findings

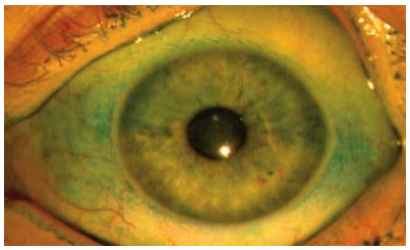
- Cohort of 400 patients
  - ANA – 74%
  - SS-A – 40%
  - RF – 38%
  - AMA – 35%
  - SS-B – 26%
  - Antiparietal cell gastric abs – 20%
  - MPO abs – 18%
  - TPO abs – 13%
  - Low CH50 – 12%
  - Low C4 – 8%
  - Cryoglobulinemia – 9%

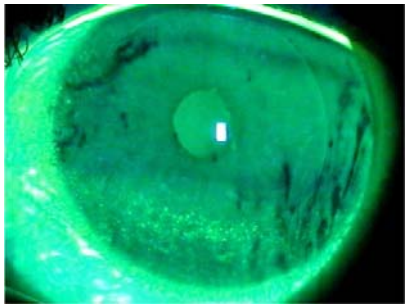
García-Carrasco M, *Medicine (Baltimore)*. 2002

Sjögren's syndrome: Lacrimal gland testing









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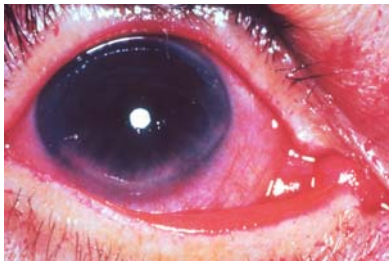
Sjögren's syndrome: Ocular Testing

- Schirmer's test
  - Positive test if <5 mm wetting in 15 minutes
- Staining tests
  - Lissamine green, Rose Bengal, fluorescence
  - Positive with score ≥ 3



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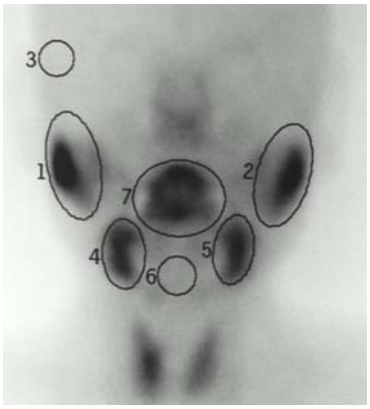
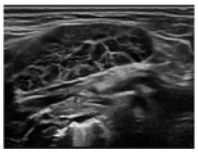
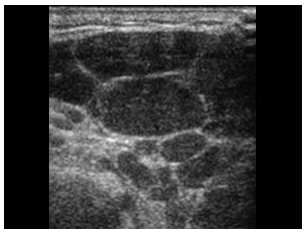
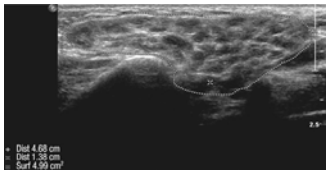
Vitali C, *BMJ.* 2012
Whitcher JP, *Am J Ophthalmol.* 2010
Afonso AA, *Ophthalmology.* 1999

Sjögren's syndrome: Salivary gland testing







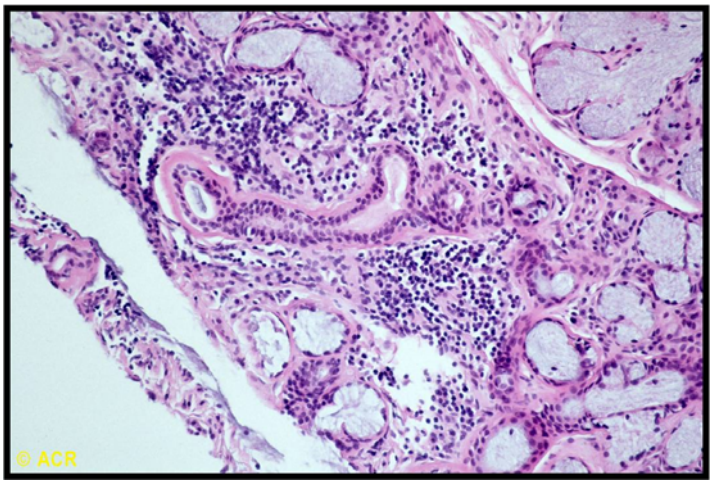


Sjögren's syndrome: Salivary gland testing

- Sialometry
  - Unstimulated salivary flow ≤1.5 mL/15 min
- Scintigraphy
  - About 34% positive in SS patients
- Ultrasonography
  - Improves diagnostic accuracy of criteria

Cornec D, *Arthritis Rheum*. 2013
Milic VD, *J Rheumatol*. 2009
Hermann GA, *Nucl Med Commun*. 1999

Sjögren's syndrome
Minor salivary gland biopsy



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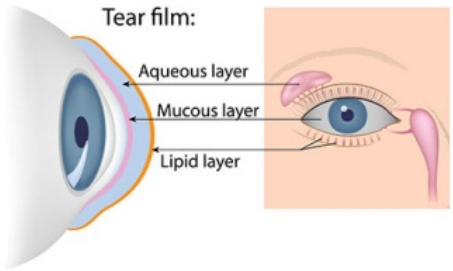
Sjögren's syndrome
Minor salivary gland biopsy

- Gold standard for diagnosis
- Lymphocytic foci: collection of 50 or more mononuclear lymphoid cells
- Biopsy with focus score ≥1 per 4 mm^2
- Persistent lip numbness in up to 6%

Varela Centelles P, *Rheumatology (Oxford)*. 2014
Shiboski SC, *Arthritis Care Res (Hoboken)*. 2012

Sjögren's syndrome: Ocular Manifestations

- Insidious onset
- Often worse in evening
- Hyposecretion of tear aqueous layer by lacrimal cells



Sjögren's syndrome: Ocular

- Symptoms
  - Irritation, 'grittiness,' foreign body sensation
  - Mucous filaments inner canthus in morning
  - Photophobia
- Exam
  - Punctate conjunctival and corneal damage
  - Reduced tear production
  - Mucous filaments
  - Dilation of the bulbar conjunctival vessels
  - Dullness of the conjunctiva and cornea

Sjögren's syndrome: Ocular Treatment

- Education
  - Environmental Management
  - Proper eyewear
- Avoid contributing medications
- Artificial tears
  - Preservative-Free if taking > 4x/day
- Lubricating gels/ointments
- Topical cyclosporine
- Punctal plugs

Pucker A, Cochrane Database Syst Rev. 2012
Akpek EK, Ophthalmology. 2011
Sall K, Ophthalmology. 2000

Sjögren's syndrome: Ocular Treatment

- No objective evidence for oral immunosuppressives
  - Systemic glucocorticoids
  - Methotrexate, leflunomide, azathioprine
  - Infliximab, etanercept, abatacept
  - Belimumab

Mariette X, *Ann Rheum Dis.* 2015
Meiners PM, *Ann Rheum Dis.* 2014
van Woerkom JM, *Ann Rheum Dis.* 2007
Mariette X, *Arthritis Rheum.* 2004
Zandbelt MM, *J Rheumatol.* 2004
Sankar V, *Arthritis Rheum.* 2004
Price EJ, *J Rheumatol.* 1998
Skopouli FN, *Clin Exp Rheumatol.* 1996
Fox PC, *Clin Exp Rheumatol.* 1993

Sjögren's syndrome: Xerostomia

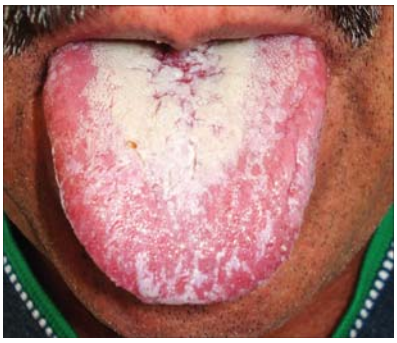
- Chronic dry mouth
- Adherence of food to buccal surfaces
- Problems with dentures
- Changes in taste
- Difficulty speaking continuously
- Dysphagia
- Difficulty consuming dry food

Sjögren's syndrome: Xerostomia Complications

- Dental caries up to 65%
- Gingival recession
- Bacterial infections of Stensen's duct
- Laryngotracheal reflux
  - Frequent throat clearing, cough, substernal pain, and nocturnal awakening that simulates panic attacks
- Chronic esophagitis
- Weight loss, nocturia

Sjögren's syndrome: Oral Candidiasis

- Can be present in over 1/3 of patients
- Facilitated by denture use
- More common in background of abx and immunosuppressant use



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van der Reijden WA, *Ann Rheum Dis*. 1999
Rhodus NL, *J Otolaryngol.* 1997
Tapper-Jones L, *J Clin Pathol.* 1980

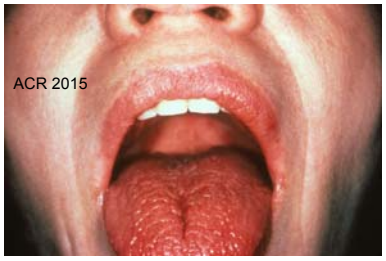
Sjögren's syndrome: Xerostomia Treatment

- Education
  - Environmental management
  - Hydration, but not excessive
  - Avoid mouth breathing at night (OSA?)
- Avoid contributing medications, oral irritants, and acidic drinks
- Sugar-free gums/liquids
- Hard candies
- Dental hygiene

Ramos-Casals M, *Nat Rev Rheumatol*. 2012
Furness S, *Cochrane Database Syst Rev*. 2011
da Silva Marques DN, *J Oral Pathol Med.* 2011
Ramos-Casals M, *JAMA*. 2010
Thanou-Stavraki A, *Semin Arthritis Rheum*. 2008
Wu AJ, *Rheum Dis Clin North Am.* 2008
Mavragani CP, *Nat Clin Pract Rheumatol.* 2006

Sjögren's syndrome: Xerostomia Treatment

- Salivary substitutes
  - Multiple RTCs
  - Beneficial as spray or mouthwash
  - No single agent preferred



Ramos-Casals M, *Nat Rev Rheumatol*. 2012
Furness S, *Cochrane Database Syst Rev*. 2011
Alpöz E, *Clin Oral Investig*. 2008
van der Reijden WA, *Arthritis Rheum.* 1996

Sjögren's syndrome: Xerostomia Treatment

- Muscarinic agonists
  - Several RTCs noted benefit
    - Increased salivary flow
    - Improvement in symptoms
    - No head-to-head trials
    - Cholinergic side effects
- Pilocarpine: 5 mg po 4-5x/day
- Cevimeline: 30 mg po TID

Ramos-Casals M, *JAMA*. 2010
Leung KC, *Clin Rheumatol.* 2008
Petrone D, *Arthritis Rheum.* 2002

SICCA Treatment: Hydroxychloroquine

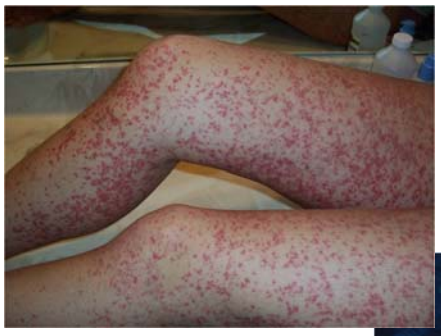
- Several small RCTs
  - No symptomatic benefit
  - Some improvement in ESR, CRP, hyperglobulinemia
- 3-year retrospective study of 40 pts
  - Improved oral dryness, pain, salivary flow rates
- Other small series
  - Conflicting outcomes

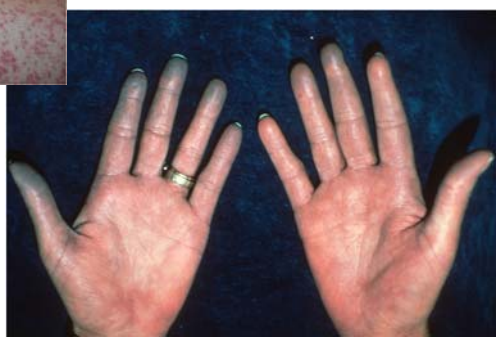
Gottenberg JE, *JAMA*. 2014
Yavuz S, *Rheumatol Int*. 2011
Cankaya H, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2010
Rihl M, *Rheumatology (Oxford)*. 2009
Tishler M, *Ann Rheum Dis*. 1999
Fox RI, *Lupus*. 1996
Kruize AA, *Ann Rheum Dis*. 1993

SICCA Treatment: Rituximab

- RCT with 30 pts over 1 year
  - Benefit corneal staining/subjective ocular dryness
- RCT with 19 pts over 120 weeks
  - Improvement in Shirmer testing
- RCT of 17 pts w/o benefit
- Several small series noting benefit in salivary flow, especially earlier in the course of disease.
- May decrease lymphocytic salivary gland infiltration

Carubbi F, *Arthritis Res Ther*. 2013
Meijer JM, *Arthritis Rheum*. 2010
Meijer JM, *Ann Rheum Dis*. 2009
Devauchelle-Pensec V, *Arthritis Rheum*. 2007
Ring T, *Clin Rheumatol*. 2006
Pijpe J, *Arthritis Rheum*. 2005





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Sjögren's syndrome: Cutaneous manifestations

- Xerosis
  - Stratum corneum dysfunction
- Cutaneous vasculitis (10%)
  - SS-A
  - Leukocytoclastic vasculitis lower extremities
- Raynaud's
- Annular erythema
  - SS-A, SS-B
  - Face, trunk, upper extremities

Kittridge A, *J Cutan Med Surg.* 2011
Bernacchi E, *Clin Exp Rheumatol.* 2004
García-Carrasco M, *J Rheumatol.* 2002

Sjögren's syndrome: Cutaneous treatment

- Mild disease: hydroxychloroquine
- Moderate/severe disease:
  - Steroids
  - MTX, mycophenolate, cyclophosphamide

Sjögren's syndrome: MSK Manifestations

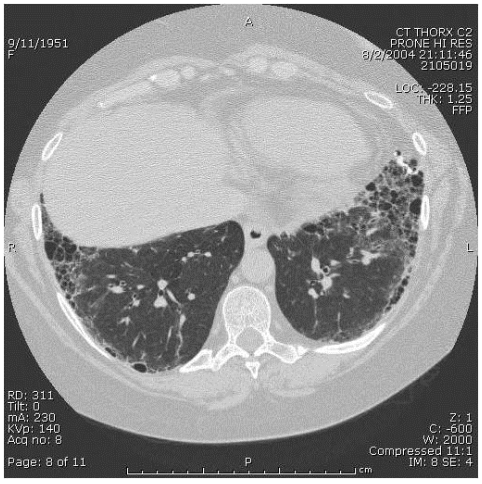
- Articular
  - About 50% with arthralgias w/ or w/o arthritis
  - Intermittent, prolonged morning stiffness
  - RF+ pts with increased symptoms/arthritis
  - CCP + rare
  - Nonerosive
- Muscle
  - Myalgias common
  - Inflammatory myositis rare
  - Discord between histopathology and symptoms

Kamali S, Clin Rheumatol. 2005
García-Carrasco M, *Medicine (Baltimore)*. 2002
Kraus A, *J Rheumatol*. 1994
Pease CT, *Br J Rheumatol*. 1993

Sjögren's syndrome: MSK Treatment

- Acetaminophen
- NSAIDS
- Hydroxychloroquine
  - A few uncontrolled studies noting benefit
  - One small double blind, placebo controlled study without benefit
- MTX for more aggressive arthritis
- Rituximab for inflammatory myositis

Easterbrook M, *J Rheumatol*. 1999
Fox R, *Lupus*. 1996
Kraus A, *J Rheumatol*. 1994
Kruize AA, *Ann Rheum Dis*. 1993



ACR 2015

Sjögren's syndrome: Cardiopulmonary Manifestations

- Interstitial lung disease
  - Usually NSIP and asymptomatic
  - Bibasilar and subpleural involvement
- Acute pericarditis
  - Very rare
  - Evidence for previous asymptomatic pericarditis and/or LF dysfunction noted

Palm O, *Rheumatology (Oxford).* 2013
Pérez-De-Lis M, *Lupus.* 2010
Dalvi V, *Clin Rheumatol.* 2007
Ito I, *Am J Respir Crit Care Med.* 2005
Gyöngyösi M, *Ann Rheum Dis.* 1996
Rantapää-Dahlqvist S, *Clin Rheumatol.* 1993
Mohri H, *J Rheumatol.* 1986

Sjögren's syndrome: Cardiopulmonary Treatment

- Based on severity
- No treatment if asymptomatic
- Mild serositis
  - Steroids, hydroxychloroquine
- Moderate/severe disease
  - Steroids, azathioprine, cyclophosphamide

Sjögren's syndrome: Renal manifestations

- Interstitial nephritis
  - Infiltrate → tubular damage
  - Distal Type 1 RTA (up to 25%)
- Nephrogenic DI
    - R/O chronic lithium use and hypercalcemia
- Isolated hypo-K
- MPGN and MN

Mavragani CP, *Annual Review of Pathology: Mechanisms of Disease.* 2014
Maripuri S, *Clin J Am Soc Nephrol*. 2009
Goules A, *Medicine (Baltimore). 2000*
Poux JM, *Clin Nephrol*. 1992

Sjögren's syndrome: Renal Treatment

- Typically asymptomatic
- Avoid nephrotoxic agents (NSAIDS)
- If glomerulonephritis is present
  - Treat like lupus nephritis
    - Steroids, glucocorticoids, cyclophosphamide, mycophenolate mofetil

Sjögren's syndrome: Hepatic manifestations

- Abnormal biochemical tests
- Biopsy may demonstrate
  - PBC
  - Portal tract fibrosis
  - Chronic active hepatitis
  - Autoimmune hepatitis (1.7 - 4%)
- Idiopathic noncirrhotic portal hypertension

Ebert EC, *J Clin Gastroenterol.* 2012
Kogawa H, *Clin Rheumatol. 2005*
Skopouli FN, *Br J Rheumatol*. 1994
Tsianos EV, *Hepatology*. 1990

Sjögren's syndrome: Hepatitis C

- Pts with HCV can look like SS
- Increase suspicion in pts with elevated liver enzymes
- Can cause + ANA, RF, cryoglobulinemia
  - Complications: joints, thrombocytopenia

Verbaan H, *J Intern Med*. 1999
García-Carrasco M, *Ann Rheum Dis*. 1997
Jorgensen C, *Arthritis Rheum*. 1996

Sjögren's syndrome: GI manifestations

- Upper dysphagia
  - Dry pharynx
- Lower dysphagia
  - Esophageal dysmotility
- Autoimmune cholangitis
  - Positive AMA
- Recurrent pancreatitis (<5%)

Ebert EC, *J Clin Gastroenterol.* 2012
Ramirez-Mata M, *J Rheumatol.* 1976
Palma R, *Dig Dis Sci.* 1994

Sjögren's syndrome: CNS manifestations

- Vasculopathy → CVA
- MS-like lesions
- CN V, VII, VIII defects
- Aseptic meningitis
- Longitudinal transverse myelitis and optic myelitis
  - SS-A
  - Frequent relapses

Chai J, *Curr Opin Neurol.* 2010
Rabadi MH, *J Neurol Neurosurg Psychiatry.* 2010
Rossi R, . *Clin Neurol Neurosurg.* 2006
Delalande S, *Medicine (Baltimore).* 2004

Sjögren's syndrome: CNS Treatment

- CNS vasculitis/myelopathy
  - IV glucocorticoids and cyclophosphamide
- CVA from vasculopathy
  - Check antiphospholipids, cardiolipins
  - Increased risk of atherosclerosis

de Seze J, *J Rheumatol*. 2006
Vaudo G, *Arthritis Rheum*. 2005

Sjögren's syndrome: Peripheral neurologic manifestations

- ~10% pts with SS
- Case series of 92 pts
  - Sensory ataxia (36)
  - Painful sensory neuropathy (18)
  - Pure sensory trigeminal neuropathy (15)
  - Mononeuritis multiplex (11)
  - Multiple cranial neuropathies (5)
  - Radiculoneuropathy (4)
  - Autonomic neuropathy (3)

Mori K, *Brain*. 2005

Sjögren's syndrome: Peripheral neuropathy Tx

- Asymmetric → mononeuritis multiplex
  - Glucocorticoids/immunosuppressives
- Symmetric → Typically sensory
  - Avoid anticholinergics
  - Gabapentin
- Peripheral motor
  - Difficult to treat
  - Use of IVIG

Mori K, *Brain*. 2005
Takahashi Y, *Neurology* 2003
Levy Y, *Ann Rheum Dis* 2003

Sjögren's syndrome: Autonomic dysfunction Tx

- Confirm with tilt-table test
- Fludrocortisone
- Midodrine

Andonopoulos AP, *Rheumatol Int.* 1995

Sjögren's syndrome
Fatigue

- Common
- Multifactorial
  - Disrupted sleep
  - Fibromyalgia
  - Hypothyroidism?
  - Autonomic dysfunction?
- Does not correlate with ESR/CRP, glandular or extra-glandular manifestations

Tishler M, *Clin Exp Rheumatol.* 1997
Bonafede RP, *J Rheumatol.* 1995

Sjögren's syndrome
Lymphoma

- Relative risk 4-40 fold
- Watch for
  - Salivary gland swelling
  - Decreased C4 level
  - Persistent cryoglobulinemia
  - SS-B positivity
  - Palpable purpura
  - Monoclonal gammopathy

Quartuccio L, *J Autoimmun.* 2014
Lazarus MN, *Rheumatology.* 2006
Zintzaras E, *Arch Intern Med.* 2005
Kassan SS, *Ann Intern Med.* 1978

Sjögren's syndrome
Take home points

- Systemic inflammatory disease with glandular and extra-glandular manifestations with quality of life and potentially life-threatening consequences
- Rule out mimics
- Treatment based on severity of symptoms and organ involvement
- Meticulous treatment for ocular and oral involvement is crucial
- Among autoimmune diseases, SS confers the highest risk for development of lymphoma

Assessment Question #1

True or False

1) Sjögren's syndrome may result in extra-glandular manifestations

   Answer: True

2) According to the revised American-European Consensus Group (AECG) classification criteria, the absence of anti-SSA (Ro) autoantibioties is indicative of Sjögren's syndrome

   Answer: False

3) Anticholinergics are an appropriate treatment option for Sjögren's syndrome patients experiencing peripheral neuropathy.

   Answer: False

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