PENNSYLVANIA
RHEUMATOLOGY
SOCIETY

Representing Pennsylvania Rheumatologists

ONSITE MATERIALS

7th ANNUAL SCIENTIFIC MEETING

SEPTEMBER 26-27, 2020 • VIRTUAL

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ACCREDITATION

For Physicians:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of the Pennsylvania Medical Society and the Pennsylvania Rheumatology Society. The Pennsylvania Medical Society is accredited by the ACCME to provide continuing medical education for physicians.

The Pennsylvania Medical Society designates this live activity for a maximum of **8.0 AMA PRA Category 1 Credits™**. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Faculty and all others who have the ability to control the content of continuing medical education activities sponsored by Pennsylvania Medical Society are expected to disclose to the audience whether they do or do not have any real or apparent conflict(s) of interest or other relationships related to the content of their presentation(s).

PURPOSE & TARGET AUDIENCE

Update Members, Rheumatologists, and non-MD/DO's who have an interest in Rheumatology with the most current and up-to-date treatments and scientific information regarding the field. Expand knowledge and competence in managing patients seen in daily practice.

WHAT IS THE PENNSYLVANIA RHEUMATOLOGY SOCIETY?

The Pennsylvania Rheumatology Society is the professional association organized and operated to serve the common professional interests of rheumatologists and their patients in Pennsylvania and the Pennsylvania region.

HOW CAN I BECOME A PRS MEMBER?

The Pennsylvania Rheumatology Society (PRS) is comprised of three different membership categories. An Active Membership is open to MD's and DO's only. These members can vote on important Society issues during the Annual Business Meeting. An Affiliate Membership is open to anyone interested in the practice of Rheumatology. Trainees in general medicine or rheumatology may join for the duration of their training for no fee.

If you would like to become a member of PRS, please visit our website
https://www.parheumatology.org/join-prs.html

AGENDAS

SATURDAY

Time	Lecture	Speaker
8:00 am – 8:10 am	**Presidential Welcome: Alfred Denio, III, MD** **Meeting Announcements & Introductions: Philip Dunn, DO**	
8:10 am – 9:10 am	**Gout & Metabolic Syndrome: What's the Connection?**	Michael Pillinger, MD
9:10 am – 10:10 am	**How to Bolster the Rheumatologic Workforce & Increase Rheumatologic Practice Efficiency**	John Tesser, MD, FACP, FACR
10:10 am – 10:40 am	**Break/Sponsors**	
10:40 am – 11:40 am	**Behcet's Disease**	Yusuf Yazici, MD
11:40 am – 12:40 pm 11:40 am – 11:55 am 11:55 am – 12:10 pm 12:10 pm – 12:25 pm 12:25 pm – 12:40 pm	**Thieves' Market Presentations** **Kirsten Koons, MD:** Slam Dunk Diagnosis – Or is Something Else Hiding in the Trenches? **Eva Rottmann, DO:** More Than Meets the Eye **Fabian Rodriquez, MD:** I Feel Hot, I Can't Walk and My Throat Hurts Voting	**Judges:** Anna Papazoglou, MD Christina Payne, MD Anupama Shahane, MD, MPH
12:40 pm – 1:00 pm	**ACR Update**	Angus Worthing, MD, FACR, FACP-ARAPC
12:55 pm – 1:40 pm	**Break/Sponsors**	
1:40 pm – 2:40 pm	**IGG4: Related Disease**	Zachary Wallace, MD, MSc
2:40 pm – 3:00 pm	**Annual Business Meeting/Closing Remarks**	Alfred Denio, MD

SUNDAY

Time	Lecture	Speaker
8:00 am – 8:10 am	**Meeting Announcements & Introductions: Alfred Denio, III, MD**	
8:10 am – 9:10 am	**Common Challenges in Image Interpretation of Arthritis**	Donald Flemming, MD, FACR
9:10 am – 10:10 am	**Systemic Sclerosis – A New Decade**	Christopher Derk, MD, MS
10:10 am – 10:40 am	**Break/Sponsors**	
10:40 am – 11:40 am	**Myositis**	Lisa Christopher-Stein, MD, MPH
11:40 am – 12:00 pm	**Closing Remarks**	Alfred Denio, III, MD

HOW TO JUDGE THE THIEVES' MARKET

You may rank each Thieves' Market presentation as:

- **Below Average**
- **Average**
- **Above Average**
- **Superb**

Each presentation will be judged on:

- **Scientific Merit**
- **Delivery**
- **Novelty**
- **Overall Impression**

We will be taking a poll at the end of the Thieves' Market presentations to determine the Ralph Schumacher, Jr., M.D. Fellows' Research Award (1st place), 2nd, and 3rd place winners. you for your participation!

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*** Designates a Thieves' Market Presenter**

+ Designated a Thieves' Market Judge

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Committee Member

Visit our Exhibitor Hub and complete the treasure hunt for a chance to win a $500 Apple Gift Card!

CME DISCLOSURE

Financial relationships reported by members of the Pennsylvania Rheumatology Society's Planning Committee are provided below. During all phases of planning for the Annual Meeting, areas of conflict were managed through a peer-review process and/or through individual recusal when appropriate.The Planning Committee has reviewed all presenter disclosure reports, identified potential conflicts of interest, and implemented strategies to manage those areas of conflict, where they exist.

Name	Company Name	Nature of Relationship
Jason Bankert, DO*	None	None
Lawrence Brent, MD*	None	None
Lisa Christopher-Stein, MD, MPH	Inova Diagnostics Royalties Dysimmune Diseases Foundation AbbVie	Consultant Advisory Board
Alfredo Denio, MD*	AbbVie BMS	Speaker Speaker
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Philip Dunn, DO*	None	None
Kirsten Koons, MD	None	None
Donald Flemming, MD, FACR	None	None
Anna Papazoglou, MD	None	None
Christina Payne, MD	None	None
Michael Pillinger, MD	Swedish Orphan Biovitrum Horizon Pharma	Consultant Consultant
Fabian Rodriguez, MD	None	None
Eva Rottman, DO	None	None
Lisabeth Scalzi, MD, MS*	None	None
Anupama Shahane, MD, MPH	None	None
Irene Tan, MD*	None	None
John Tesser, MD, FACP, FACR	None	None
Zachary Wallace, MD, MSc	Viela Bio Patients Like Me BMS	Grant Support/Consultant Employment Grant
Yusuf Yazici, MD	Amgen Celegene Sanofi	Consultant Consultant Consultant

**** Designates a Pennsylvania Rheumatology Society program committee member***

NOTICE OF DISCLAIMER

The information presented is that of the contributing faculty and does not necessarily represent the views of the Pennsylvania Rheumatology Society, the CME accreditor, Pennsylvania Medical Society, and/or any named commercial entity providing financial support.

The Pennsylvania Rheumatology Society makes every effort to ensure that speakers are knowledgeable authorities in their fields. Seminar attendees are nevertheless advised that the statements and opinions expressed by seminar speakers are those of the speakers, not that of Pennsylvania Rheumatology Society. The speakers' statements and/or opinions should not be construed as Pennsylvania Rheumatology Society policy or recommendations, and Pennsylvania Rheumatology Society disclaims any liability or responsibility for the consequences of any actions taken in reliance upon those statements or opinions.

PROGRAM OUTCOMES

Gout & Metabolic Syndrome: What's the Connection.
Treat gout earlier. Treat to urate target. Monitor and manage co-morbidities in gout patients.

How I Diagnose and Treat IgG4-RD in 2020
Learners should be able to identify patients with IGG4 related disease, review recently published IGG4 related disease criteria and properly treat these patients with the most up-to-date options.

Behcet's Disease
Correctly diagnose behcet. Start treatment early. Assess disease activity to recognize remission to potentially stop treatment.

How to Bolster the Rheumatologic Workforce & Increase Practice Efficiency
To encourage rheumatologists to consider bringing APCs into their employ. To utilize APCs to the top of their license and education to maximize rheumatology care to the community. To restructure their practice to achieve maximum efficiency and sustainability.

Common Challenges in Image Interpretation of Arthritis
Develop a deeper appreciation of challenges of image interpretation. Recognition of impact of cognitive bias on image interpretation. Understand limitations of advanced imaging on diagnosis.

Systematic Sclerosis – A New Decade
Improve early diagnosis both at the clinic level but also through education to effect referral patterns from primary care providers and dermatologists. Follow a regimented screening pattern with regular follow ups for early detection of organ specific involvement. To be up to date with recent therapeutic advances both disease and organ specific and know how to implement them in the individual patients.

Myositis 2020: Moving on From Poymyositis and Dermatomyositis
Early identification of myositis and prompt treatment for the best possible outcome. Identify myositis associated antibodies.

Thieves Market
Apply up-to-date clinical information on the diagnosis and management of patients with rheumatic and immunologic disorders. Describe the most current information regarding the pathophysiology underlying rheumatic disorders. Apply new diagnostic and management strategies.

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Speaker Slides Saturday

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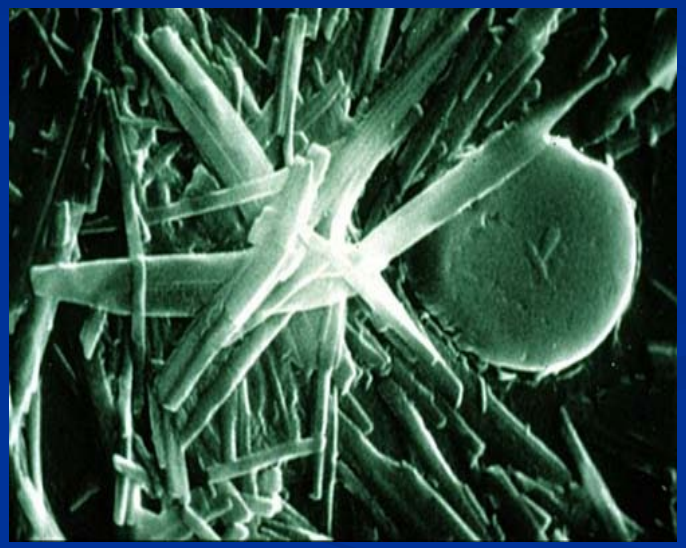
Gout and the Metabolic Syndrome: What's the Connection?



(The truth is out there….)

Michael Pillinger, MD
Professor of Medicine and Biochemistry and Molecular Pharmacology
Co-director, Crystal Diseases Study Group
NYU School of Medicine/NYU Langone Medical Center

Disclosures

Grants-Hikma, Horizon
Consultancy-Horizon, Sobi

What Is Gout?

The complex intersection of multiple intrinsically complex processes:

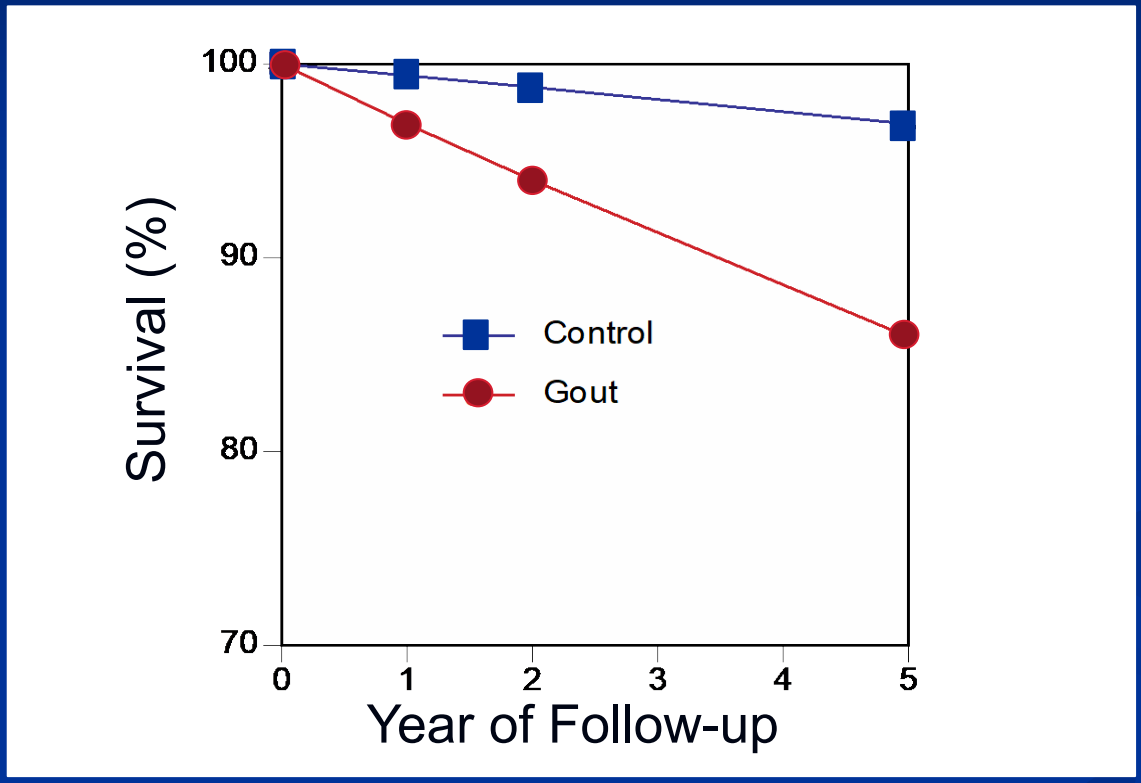
- Hyperuricemia (metabolic, excretory, dietary sources)
- Urate crystallization
- Inflammatory responses to crystallized urate

Why care about gout?

Gout is….

- Common-8-12 million Americans
- Painful
- Expensive, particularly when poorly managed
- Responsible for disability and lost work
- Associated with many co-morbidities

Gout Is a Marker for Increased Mortality



6631 patients, 53,048 patient-years

Kuo et al, Joint Bone Spine 2011

What is the Metabolic Syndrome?

Any three of five:

1. Abdominal (central, visceral) obesity
2. Hypertriglyceridemia
3. Low HDL
4. Hypertension
5. Elevated fasting plasma glucose/insulin resistance

Inflammatory markers:

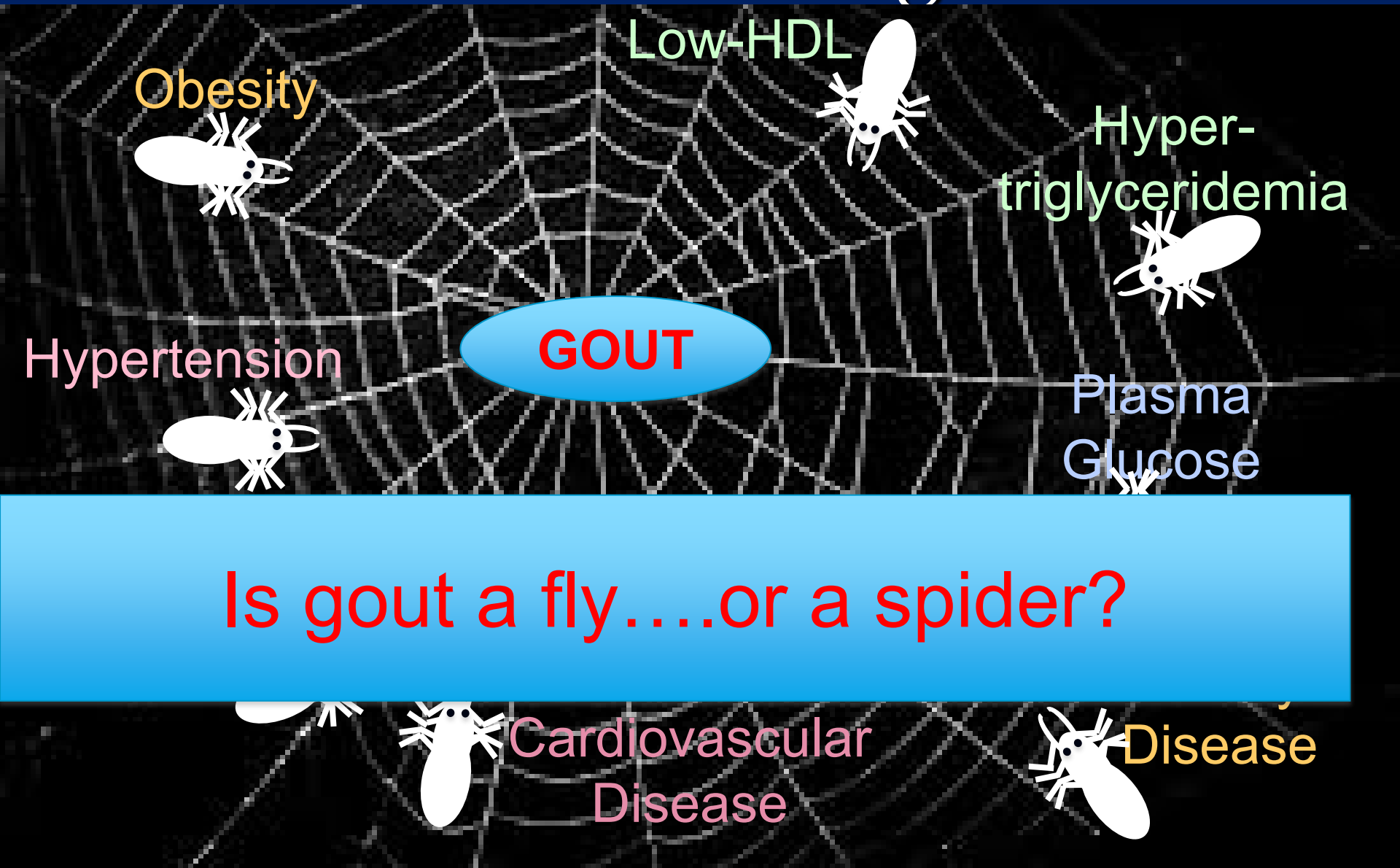
1. Elevated CRP, adipokines, others

Long-term consequences:

1. Type 2 Diabetes
2. Cardiovascular disease
3. Renal disease
4. Others

National Cholesterol Education Program Adult Treatment Panel III

The Metabolic Syndrome: A Web of Danger



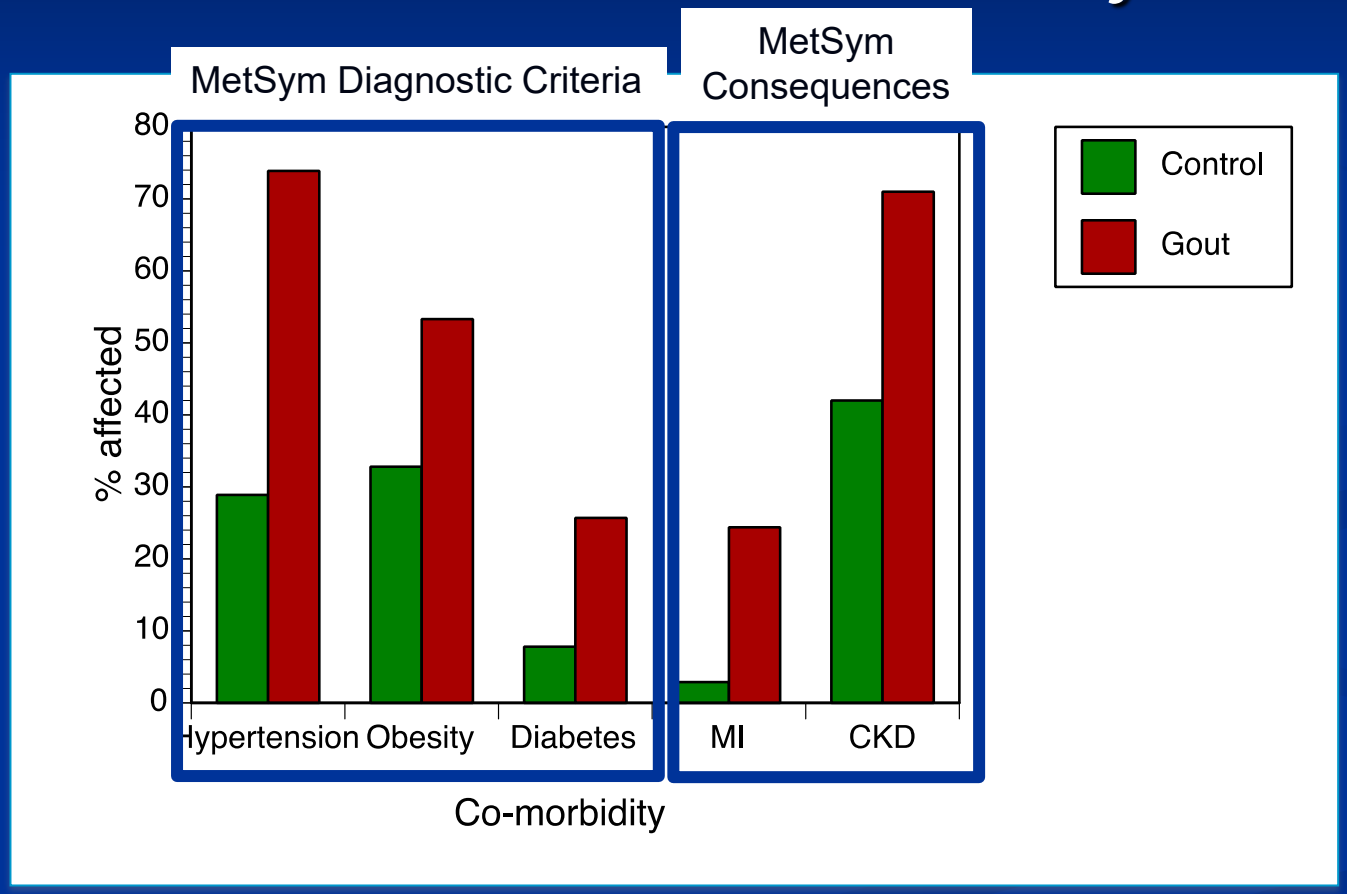
Gout, Hyperuricemia and Metabolic Syndrome: One Epidemic or Two?

Condition	NHANES III (1990s) % affected	NHANES (2010's) % affected	% Increase
Metabolic syndrome	25.3	34.2	22.2
Hyperuricemia	18.2	20.1	17.6
Gout	2.7	3.9	44.4

Hirode and Wong, JAMA 2020;323(24):2526-2528

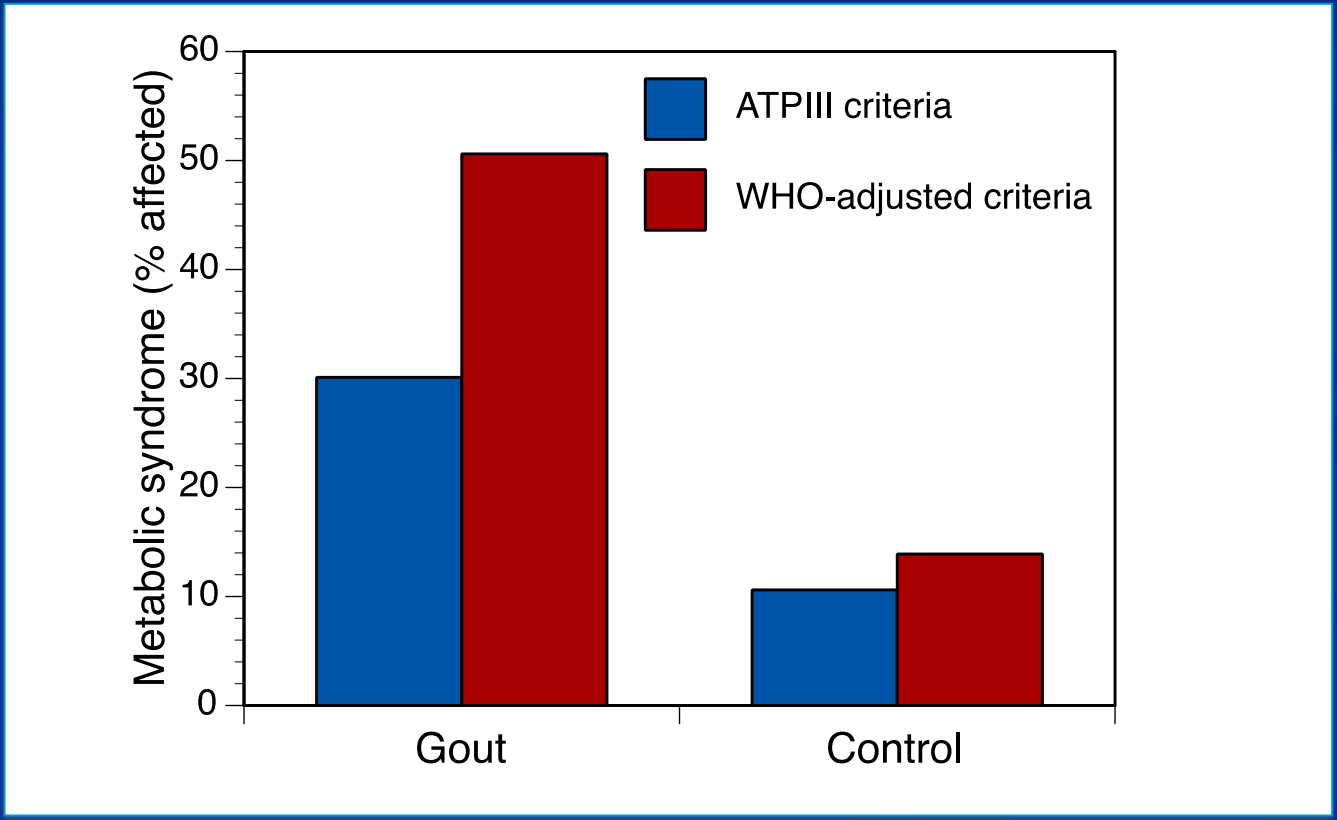
Zhu et al, Arthritis Rheum 2011;63(10):3136-3141
Chen-Xu et al, Arthritis Rheum 2019;71(6):991-999

Gout Co-morbidities Are Greater Than In The General Population and Reflect The Metabolic Syndrome



Zhu et al, Arthritis Rheum 2012;125(7):

Patients With Gout Have a Higher Prevalence of Metabolic Syndrome Than Non-gout Controls



Yoo et al, Rheumatology International 201;31(4):485-91

Gout, Hyperuricemia and Hypertension

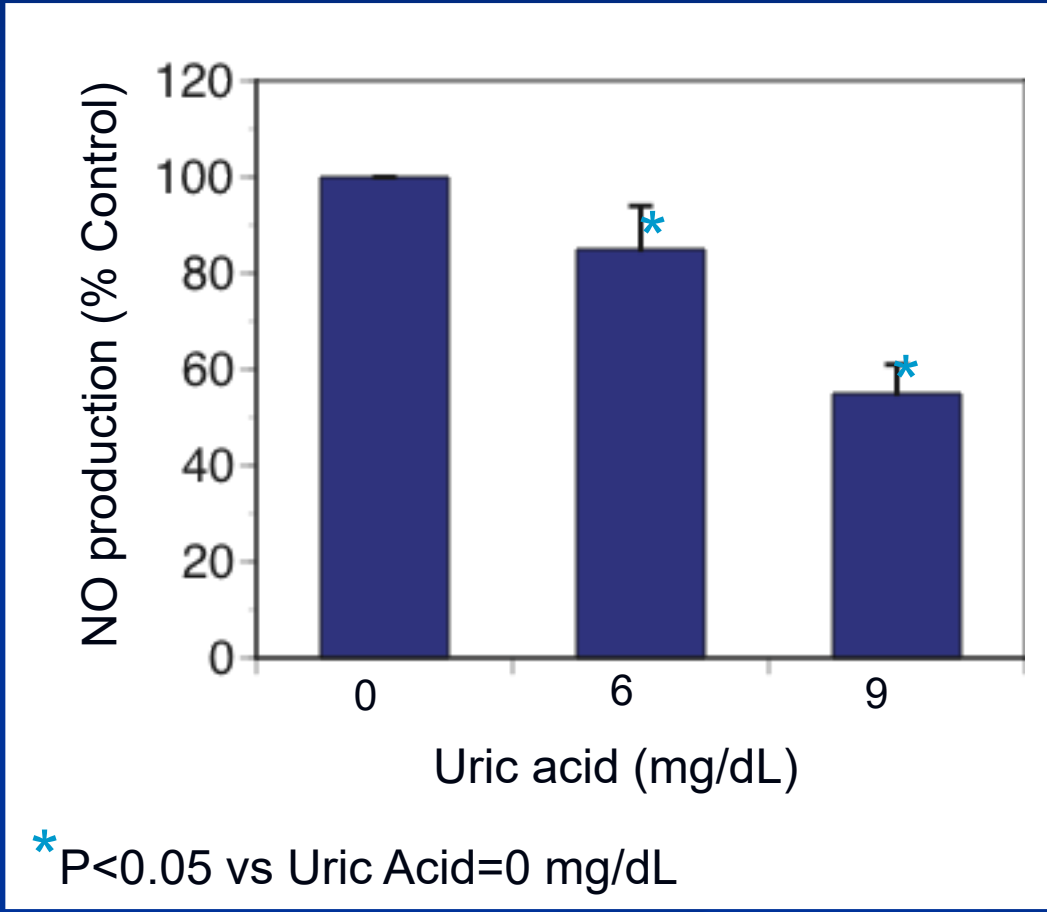
Gout and Hypertension?

"People who are subject to this high blood pressure frequently belong to gouty families or have themselves suffered from the symptoms of the diseases."

-Frederick Akbar Mohamed, 1879

Heinig and Johnson, Cleveland Clinic Journal of Medicine 2006; 73:1059

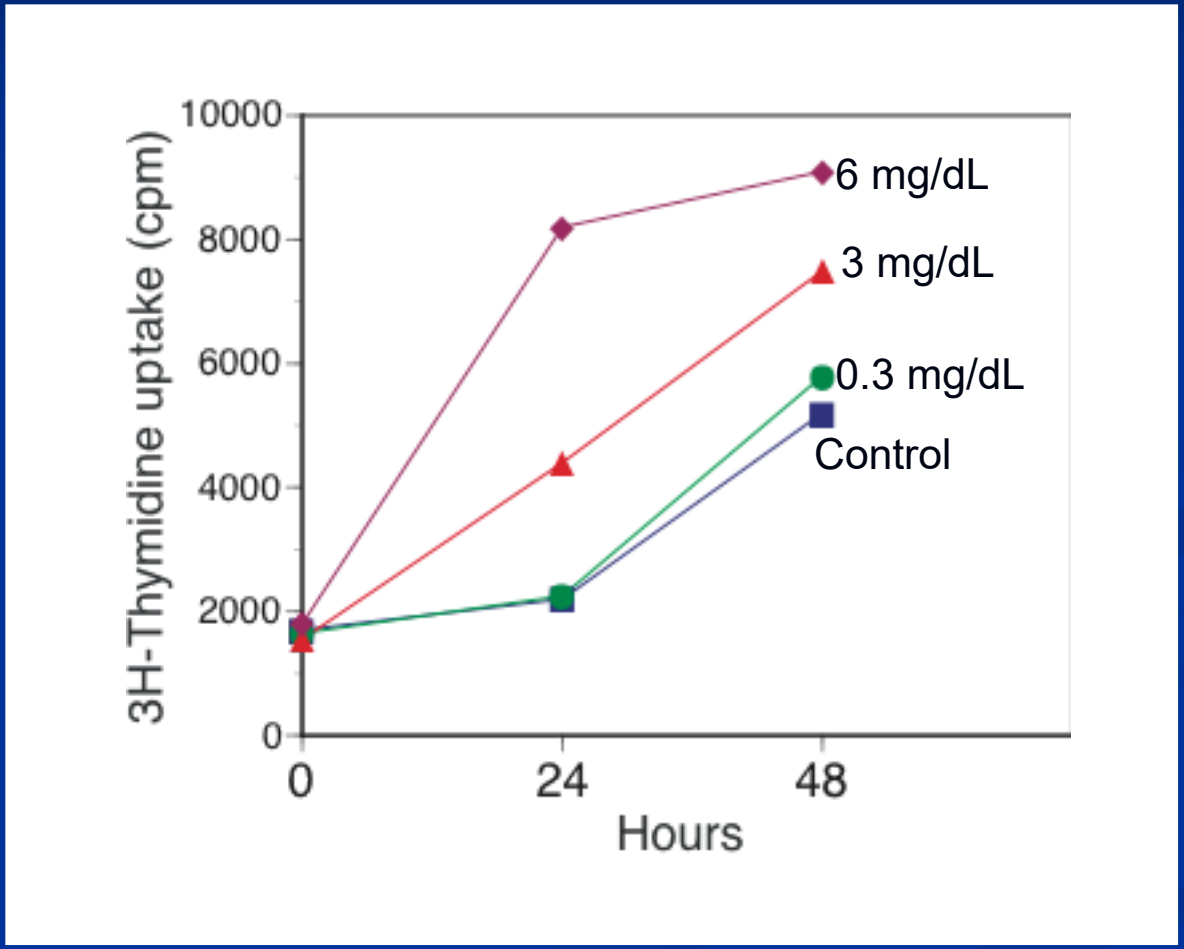
Can Hyperuricemia Raise Blood Pressure?
Urate Inhibits Nitric Oxide Synthesis by Vascular Endothelium



*P<0.05 vs Uric Acid=0 mg/dL

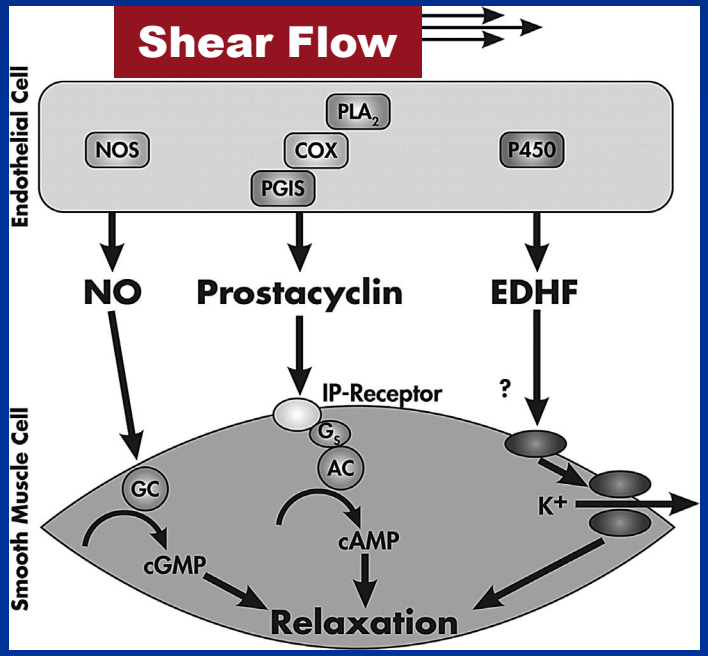
Kang Am J Nephrol 2005;25:425-433

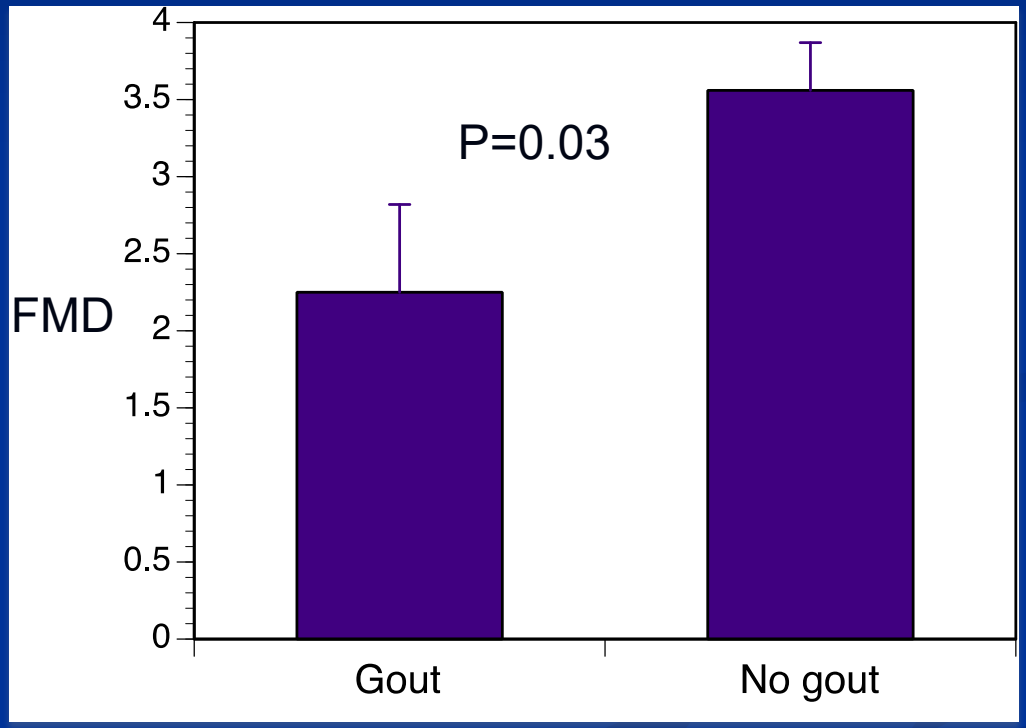
Can Hyperuricemia Raise Blood Pressure? Urate Induces Vascular Smooth Muscle Proliferation



Kang Am J Nephrol 2005;25:425-433

Gout Patients Have Impaired Arterial Function Compared with Health Controls: Flow-mediated Brachial Artery Dilation (FMD)





- 32 untreated gout patients
- 64 healthy controls

Clifford PS et al. Advan in Physiol Ed, 2011;35:5-15

Krasnokutsky et al, Clin Rheum 2018;37(7):1903-11

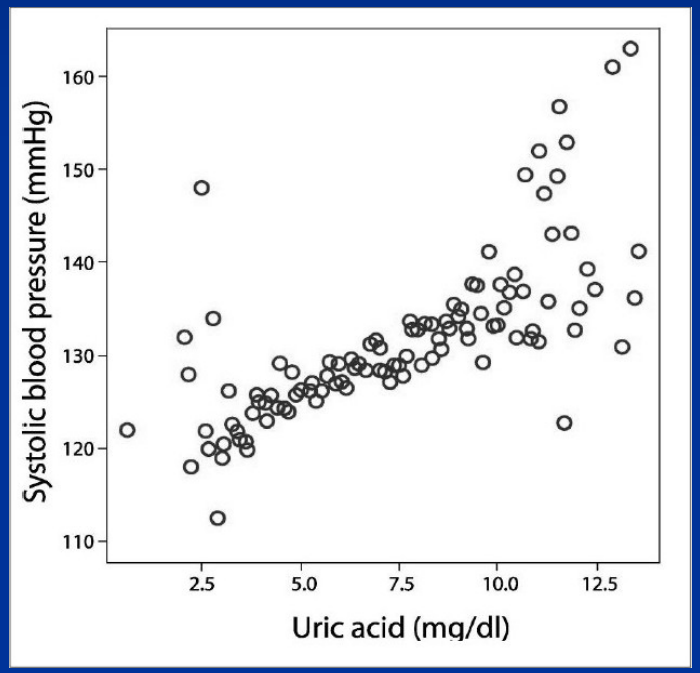
Can Hyperuricemia Raise Blood Pressure? Renal Effects

- Stimulation of renin-angiotensin
- Interstitial inflammation
- Induction of renal tubular injury

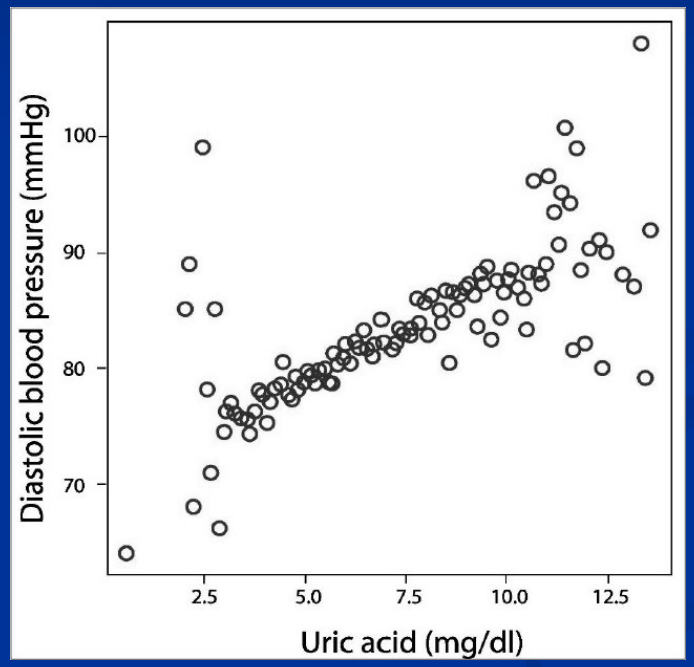
Mazzali et al; Hypertension 2001;
Watanabe et al; Hypertension 2003

Hyperucemia Predicts Hypertension

Systolic BP



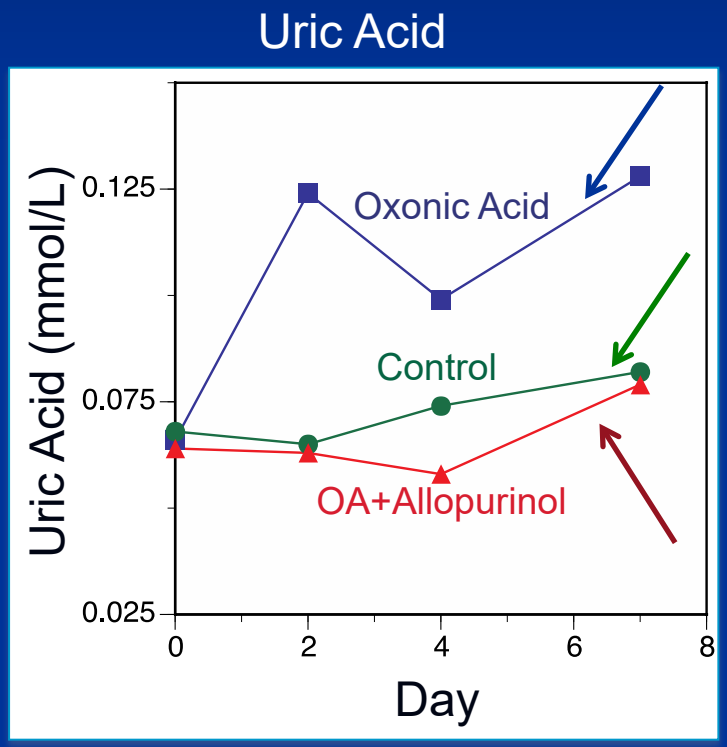
Diastolic BP

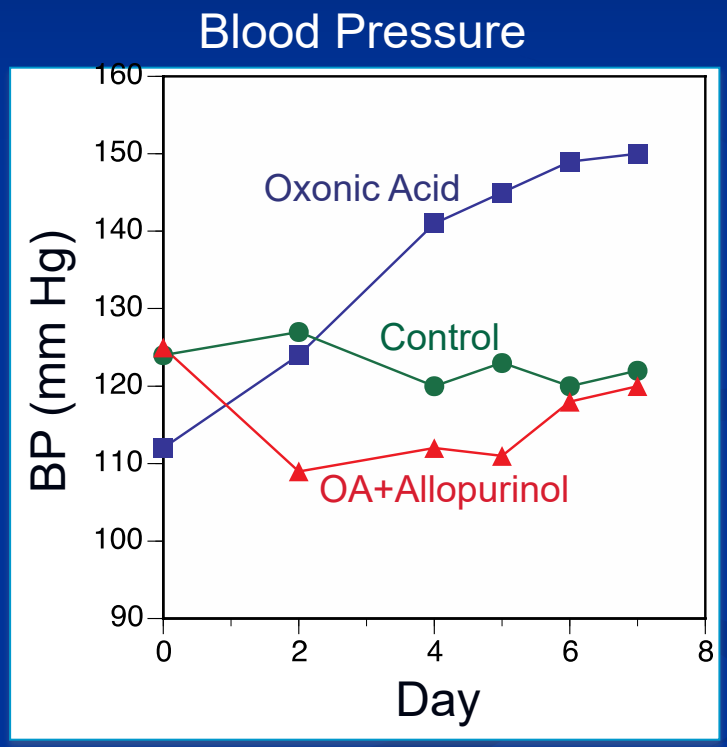


- Cross-sectional study; 5,564 members of the Thai armed forces
- *Hyperuricemia persisted as independent risk factor after multivariate analysis*

Ouppatham et al. J Postgrad Med 2008

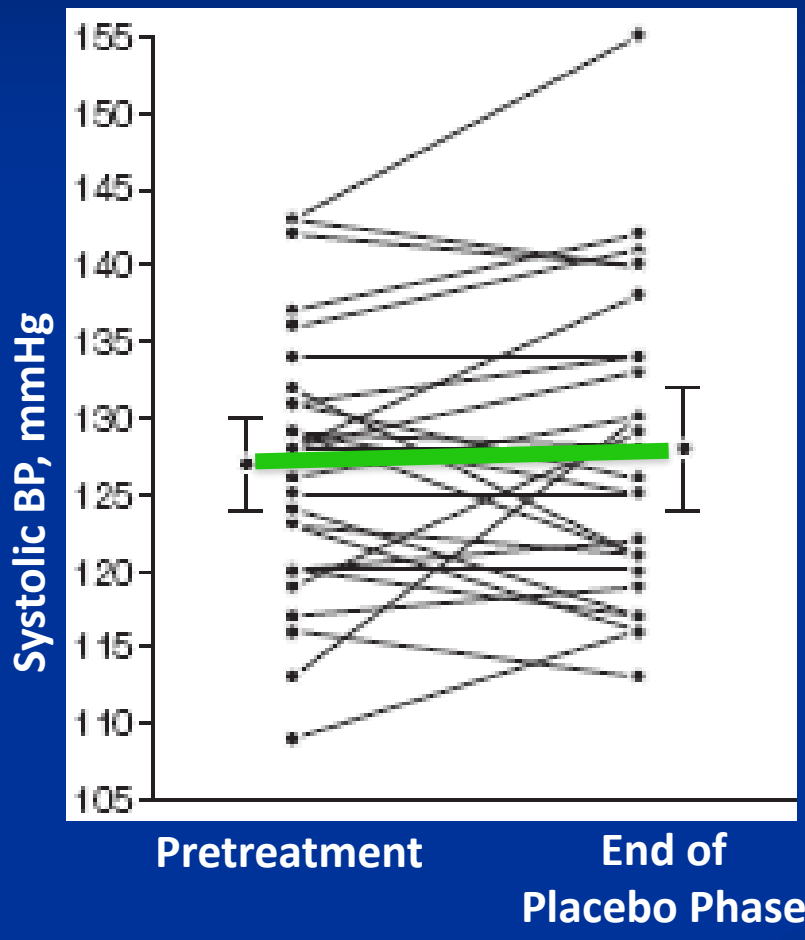
Hyperuricemia Elevates, and Allopurinol Lowers Blood Pressure in Rats

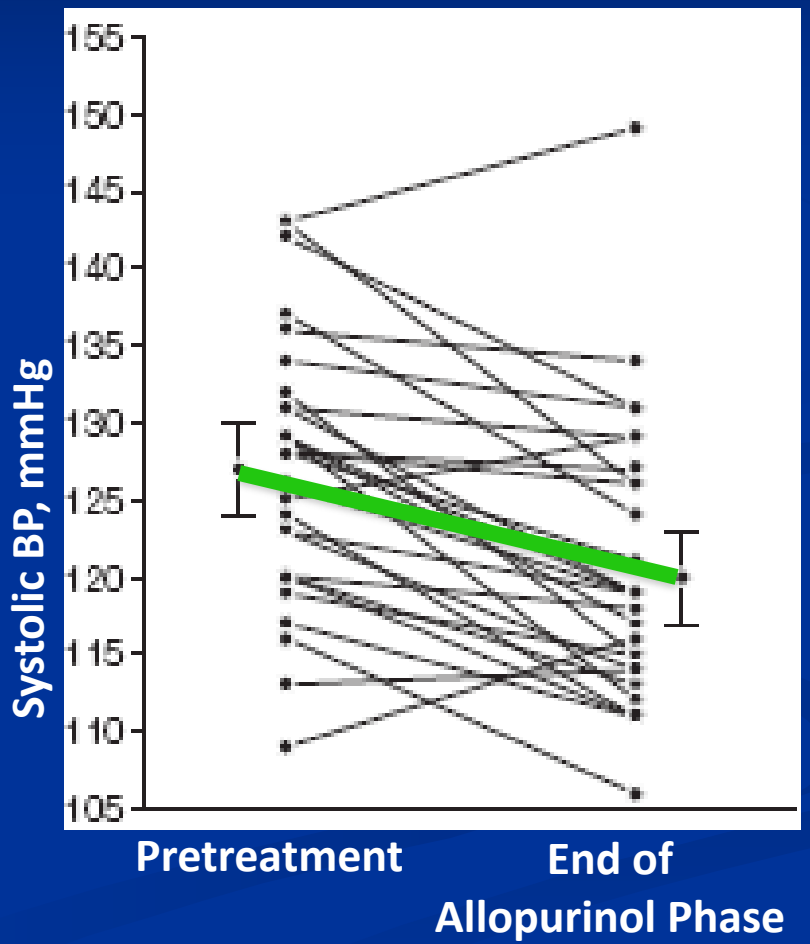




Mazzali et al, *Hypertension* 2001;38(5):1101-1106

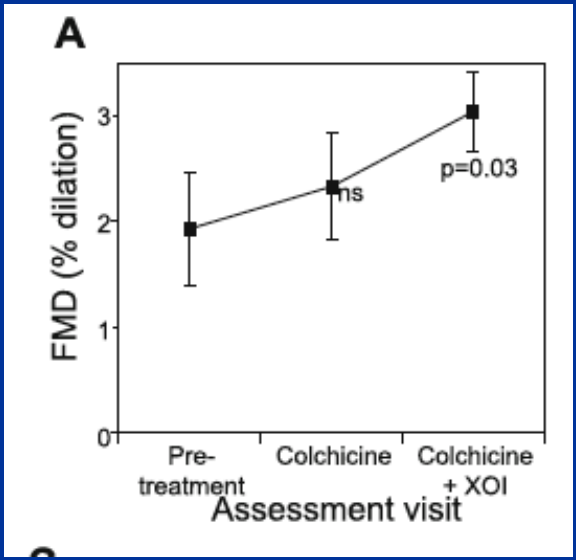
Uric Acid and Blood Pressure: Allopurinol Decreases Blood Pressure in Adolescents

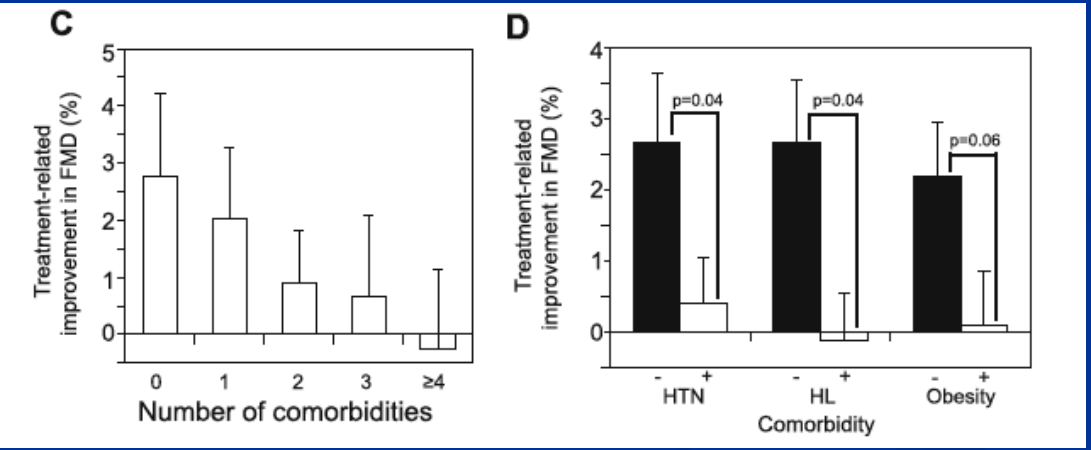




Feig DI, et al. JAMA. 2008 Aug 27;300(8):924-32.

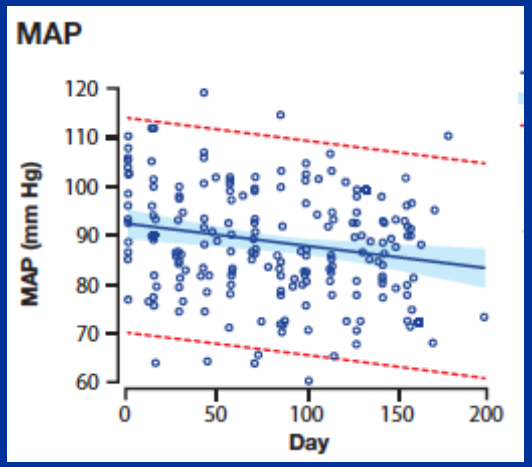
Urate Lowering Improves Endothelial Responsiveness in Gout Patients (But Works Better in Patients Without Established Co-morbidities)

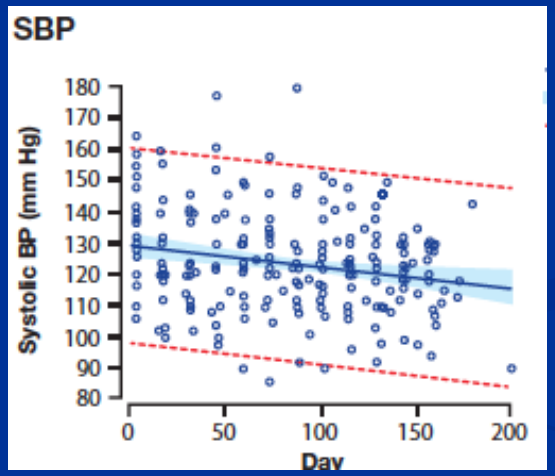


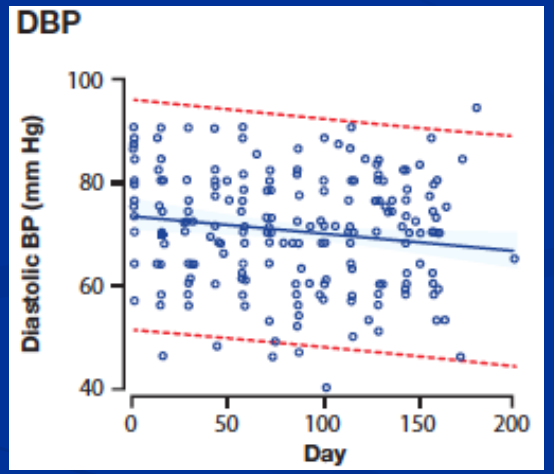


Toprover et al, Arth Res Ther 2020;22(1):169

Extreme Urate Lowering With Pegloticase May Lower Blood Pressure Even In Patients With Established Gout



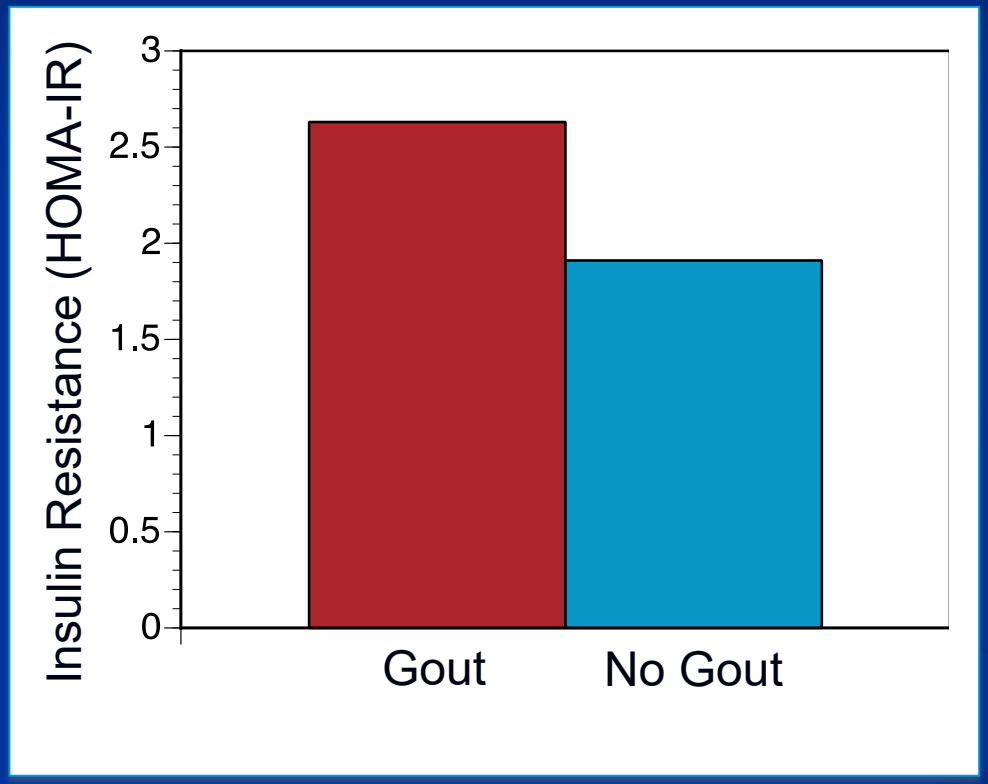




Johnson et al, *Hypertension* 2019;74:94-101

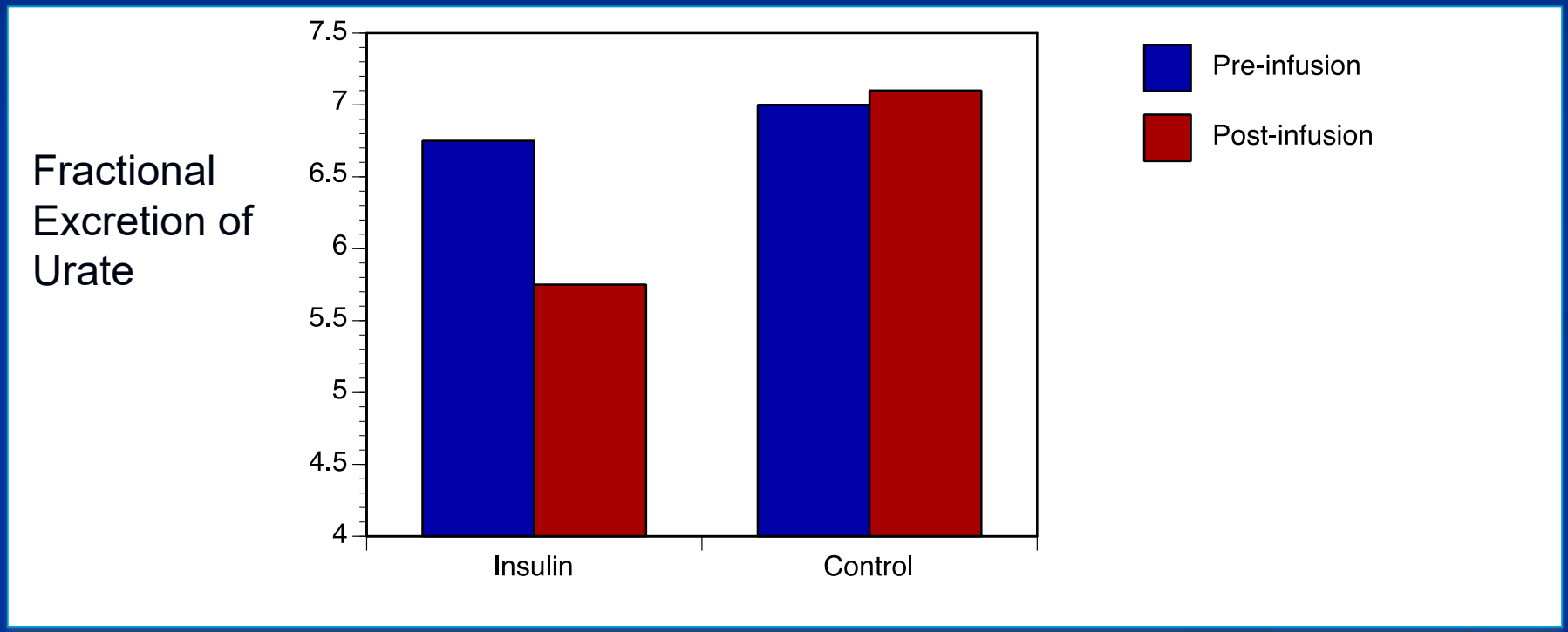
Hyperuricemia, Insulin Resistance and Diabetes: The Chicken or the Egg?

Patients with Gout Have an Increased Prevalence of Insulin Resistance



Yoo et al, Rheumatology International 201;31(4):485-91

Diabetes and Uric Acid: Insulin Infusion Promotes Renal Urate Retention



A Diagnosis of Gout Conveys a Risk for Future Incidence of Type II Diabetes: The MRFIT Study

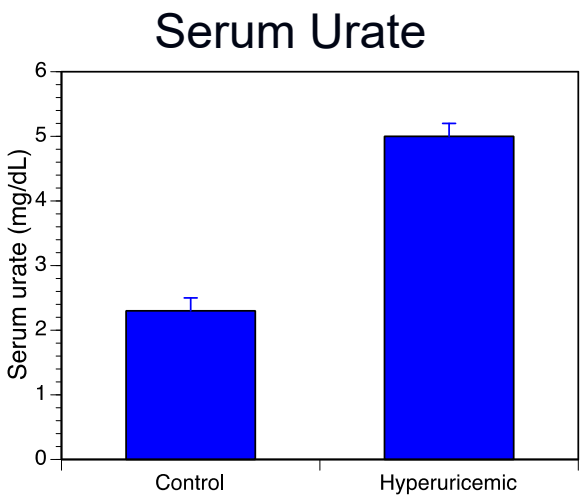
Diabetes Analysis	No Gout	Gout
Incidence/100 person-years	1.79	3.08
Age-adjusted		1.66 (1.37, 2.02)
Full r	1.0	1.34 (1.09, 1.64)

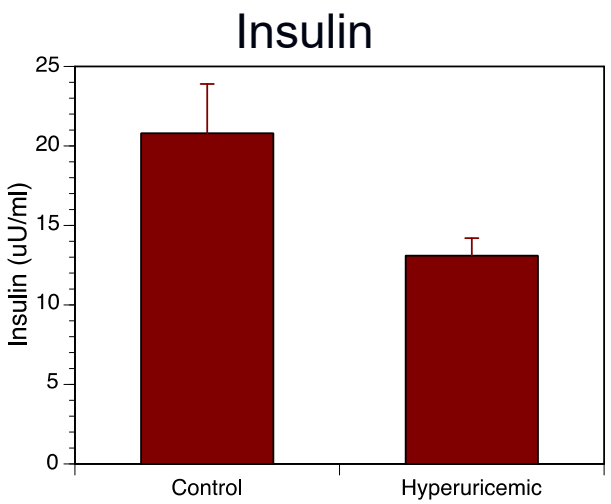
Individuals with diabetes may be at lower risk for future gout than individuals without diabetes! (UK Health Improvement Network Database)

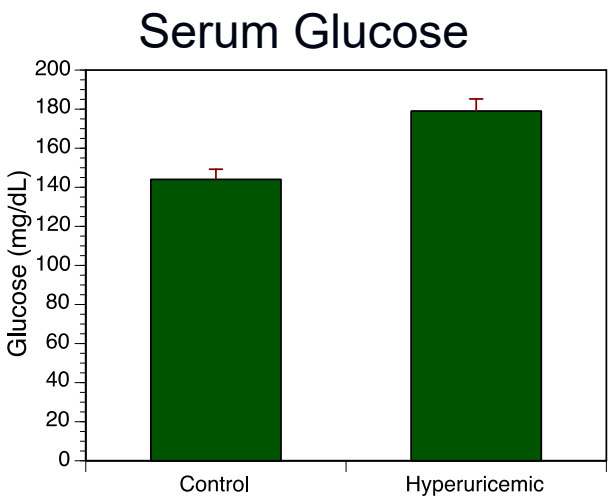
MRFIT-(Multiple Risk Factor Intervention Trial) Prospective study of 11,351 males with multiple cardiovascular risks

Choi et al, Rheumatology 2008;47(10):1567-1570
Rodriguez et al, Ann Rheum Dis 2010;69(10):2090-2094

Hyperuricemia Promotes Pancreatic Injury and Reduced Insulin Generation in a Mouse Model

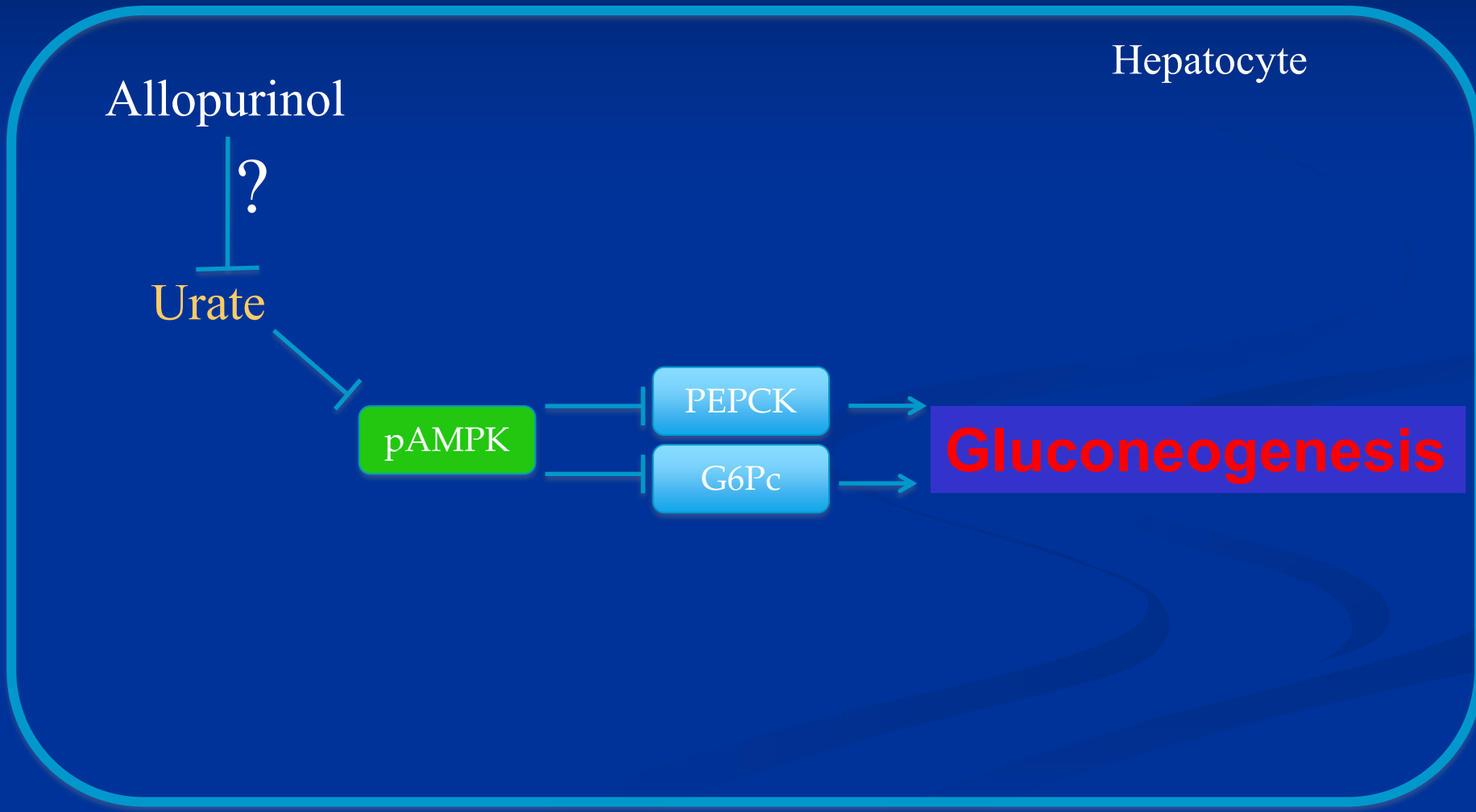






Scott et al, Experimental Biology and Medicine 1981;166(1):123-128

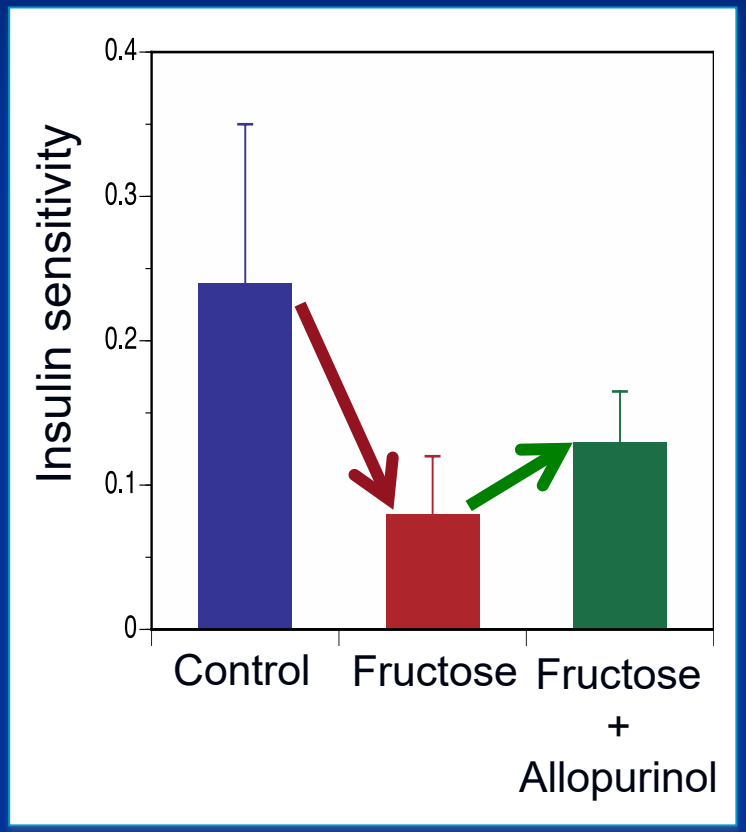
Hepatic Gluconeogenesis: Urate Inhibits the Inhibitor of Gluconeogenesis



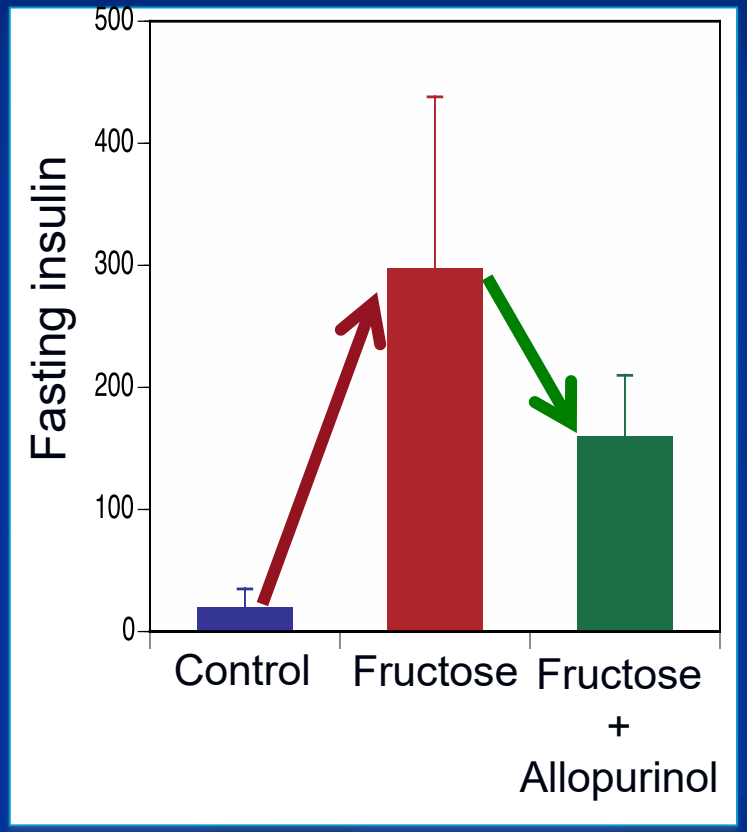
Cicerchi et al, FASEB Journal 2014;28:3339-3350

Can Hyperuricemia Induce Insulin Resistance? (A Fructose-fed Rat Model)

Insulin Sensitivity

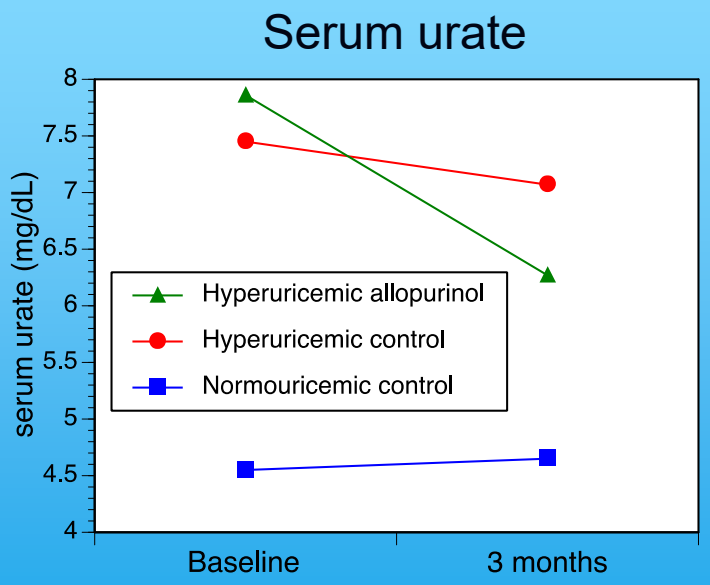


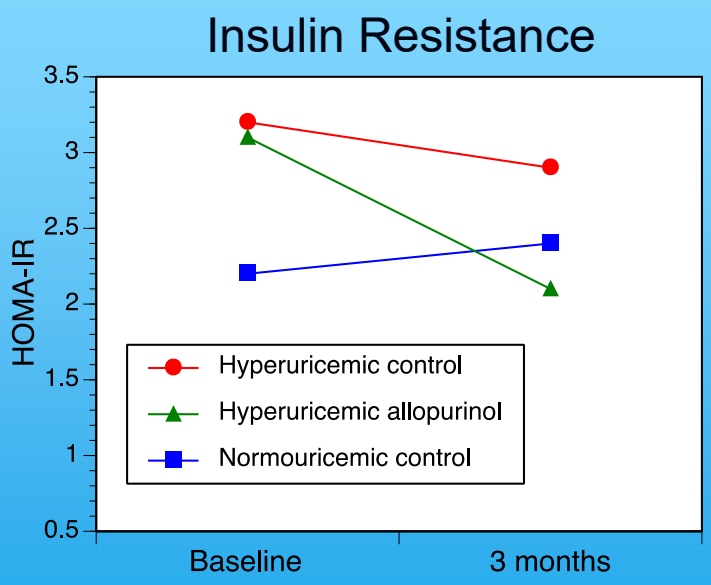
Serum Insulin Level



Nakagawa et al Am J Physiol Renal Physio 2006: 290:F625-631.

Can Allopurinol Improve Insulin Resistance in Humans?

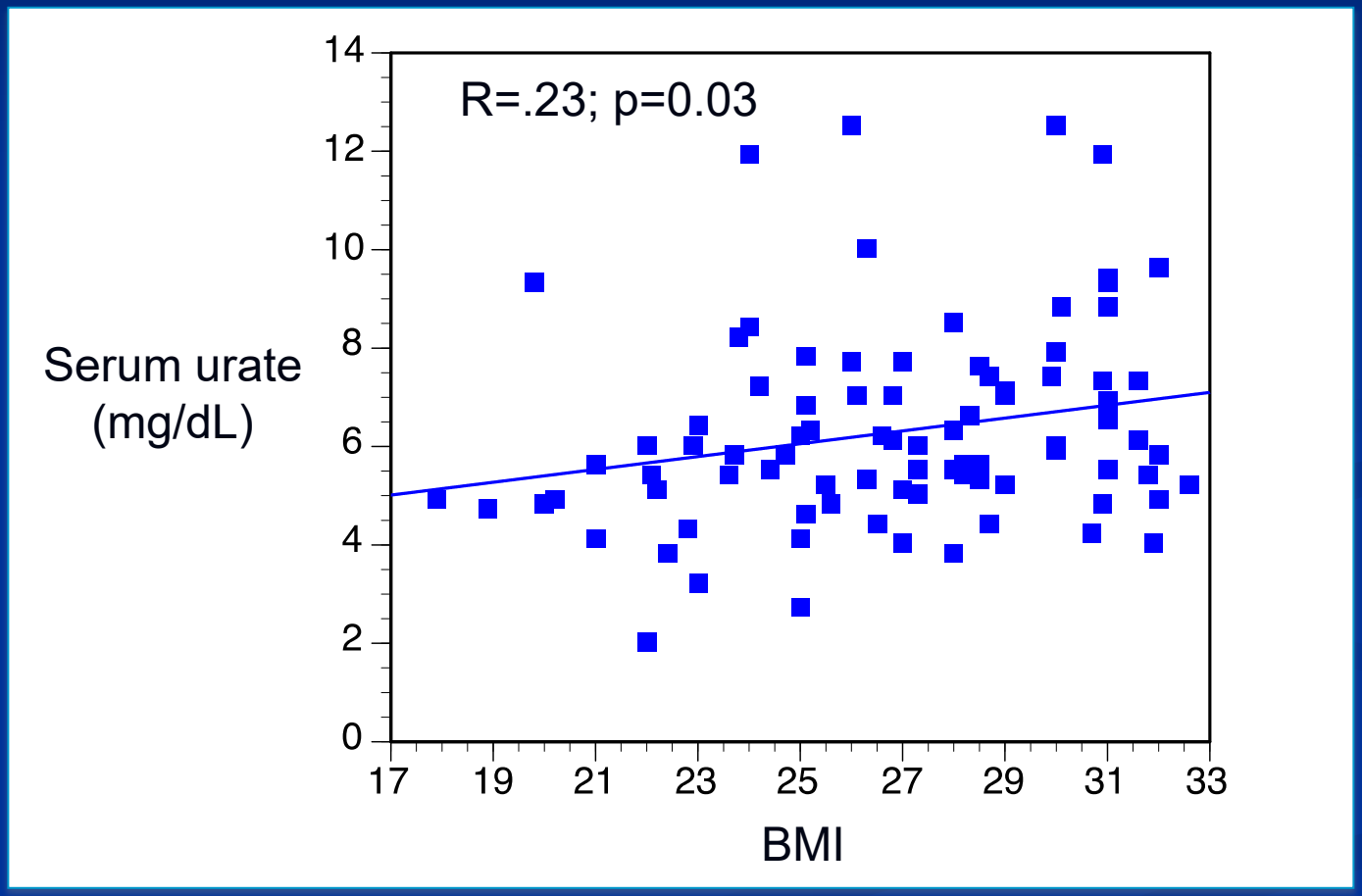




Kanbey et al J Inv Med 2015;63:924-929

Hyperuricemia, Gout, Obesity and Hyperlipidemia

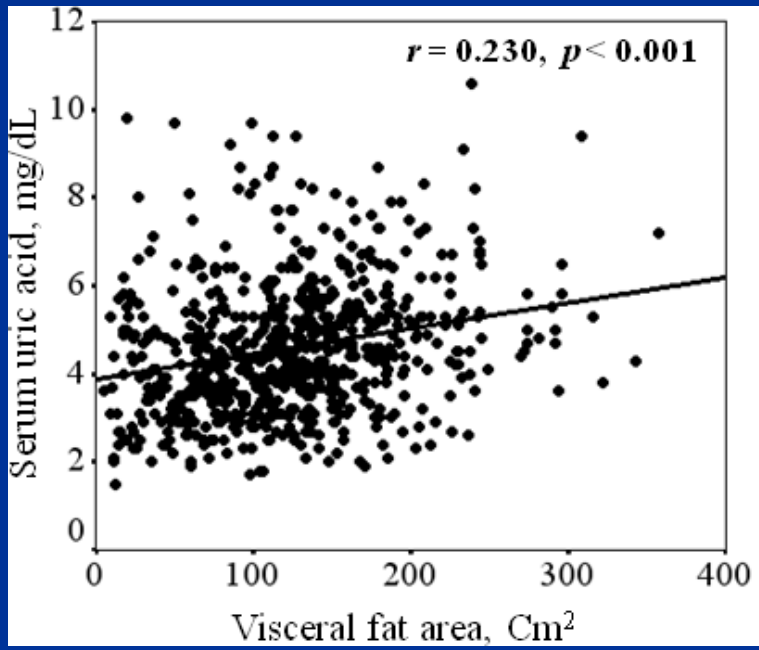
Serum Urate Correlates With Body Mass Index



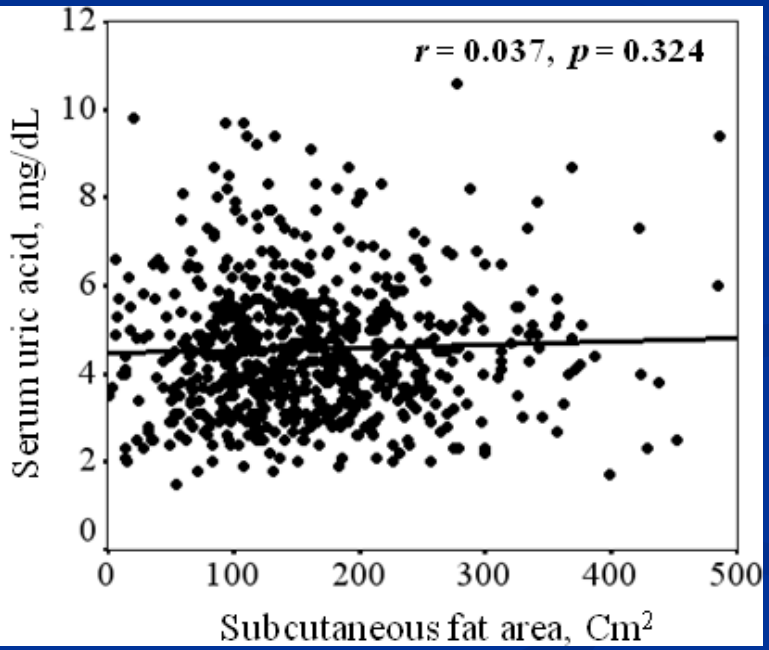
Pillinger et al, unpublished

Serum Urate Correlates With Visceral But Not Subcutaneous Fat

Visceral (Central)

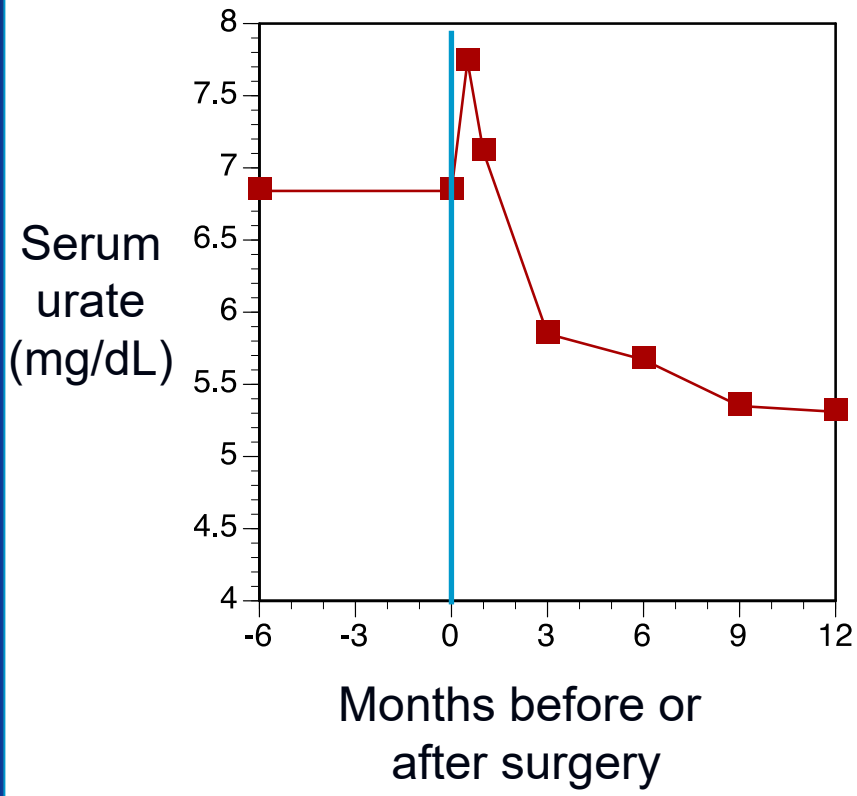


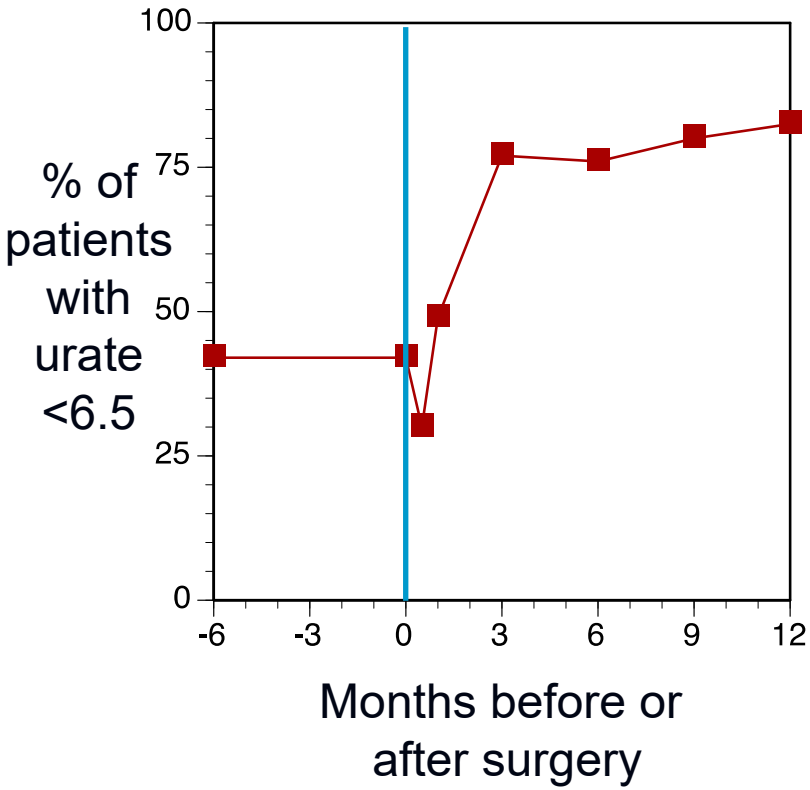
Subcutaneous (Non-visceral)



Kim et al, Diabetology & Metabolic Syndrome 2012;4(1):3-9

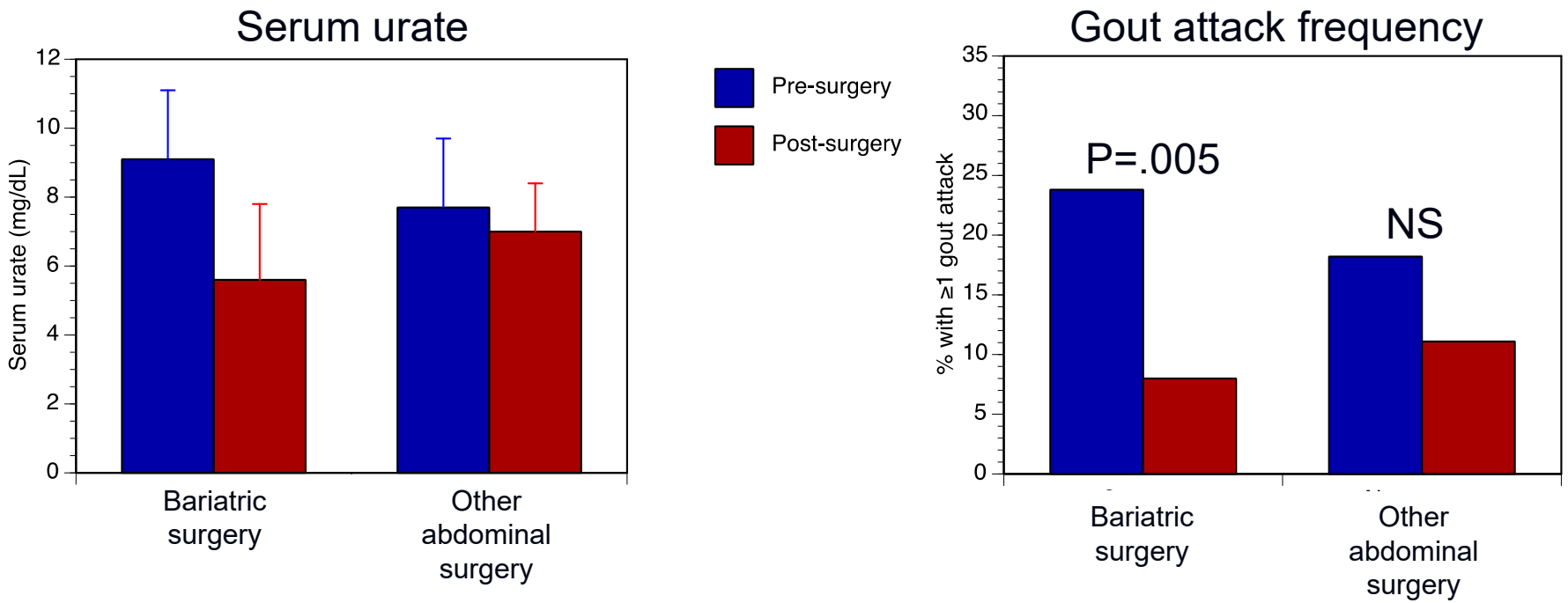
Bariatric Surgery Results In Serum Urate Decline





Dalbeth et al, Ann Rheum Dis 2014;73:797-802

Bariatric Surgery Results In Reduced Risk of Gouty Attacks



Romero-Talamas et al, Surgery for Obesity and Related Diseases 2014;10:1161-1165

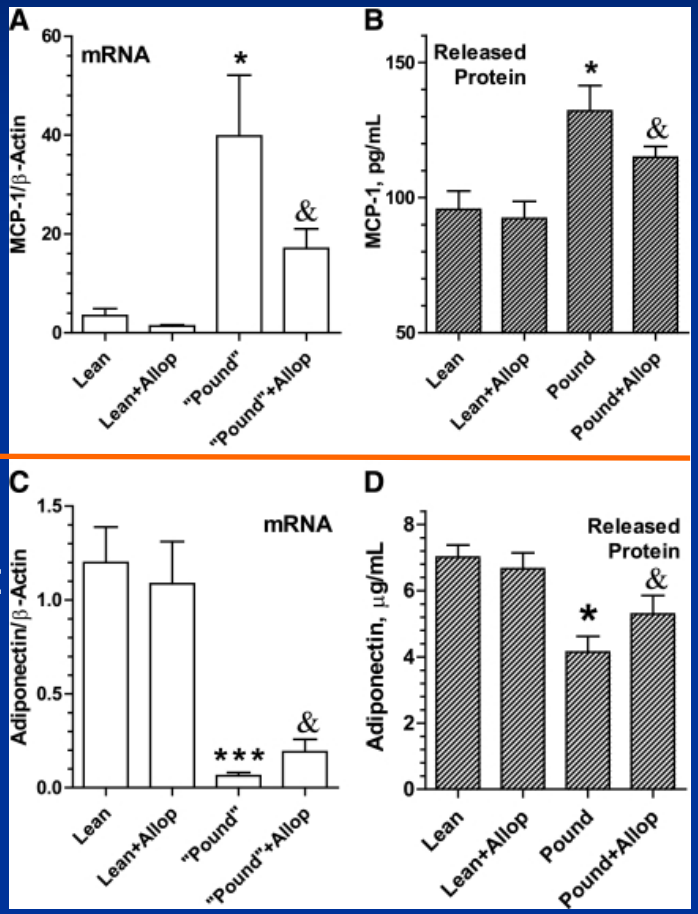
So Fat Can Regulate Urate…..But Can Urate Regulate Fat?

Urate Lowering With Allopurinol Improves the Inflammatory Profile of Adipose Tissue In The "Pound" Mouse: Adipokines

mRNA Protein

MCP-1: Pro-inflam-matory

Adiponectin: Anti-inflam-matory



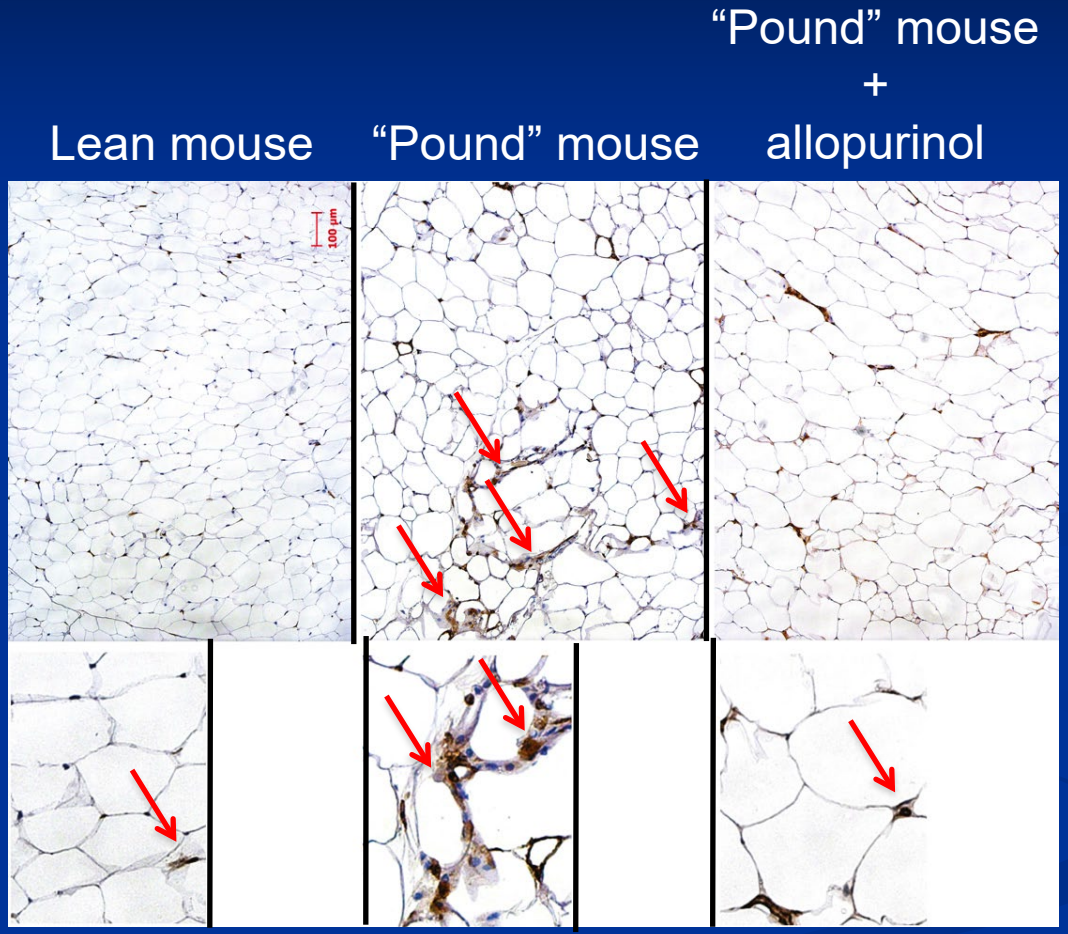
"Pound" mouse:

- Model of metabolic syndrome developing obesity, insulin resistance, dyslipidemia and fatty liver disease (leptin receptor mutation)
- Also develop hyperuricemia

Baldwin et al, Diabetes 2011;60(4):1258-1269

Urate Lowering With Allopurinol Improves the Inflammatory Profile of Adipose Tissue In The "Pound" Mouse: Macrophage Infiltration

Red arrows indicate macrophage staining

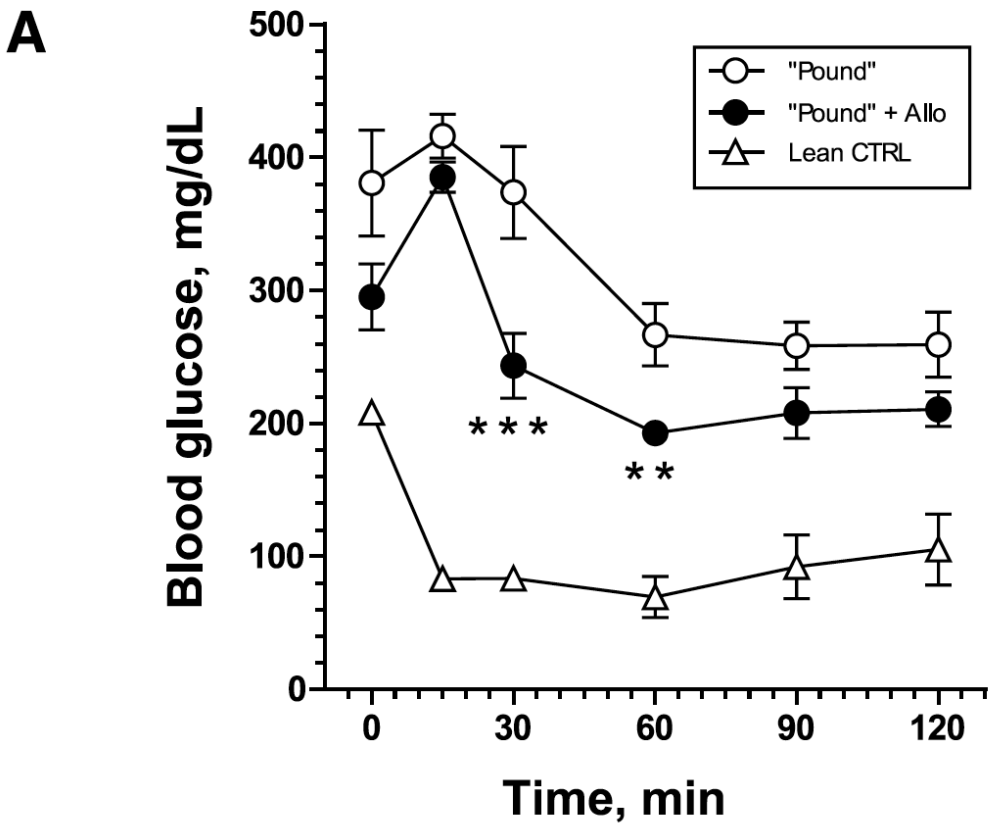


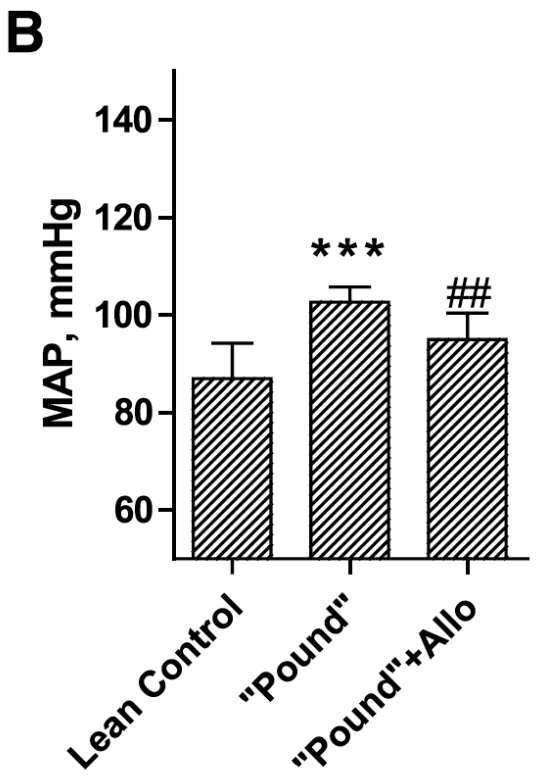
Baldwin et al, Diabetes 2011;60(4):1258-1269

Urate Lowering With Allopurinol Improves Insulin Resistance and Hypertension in the "Pound" Mouse

Insulin Resistance

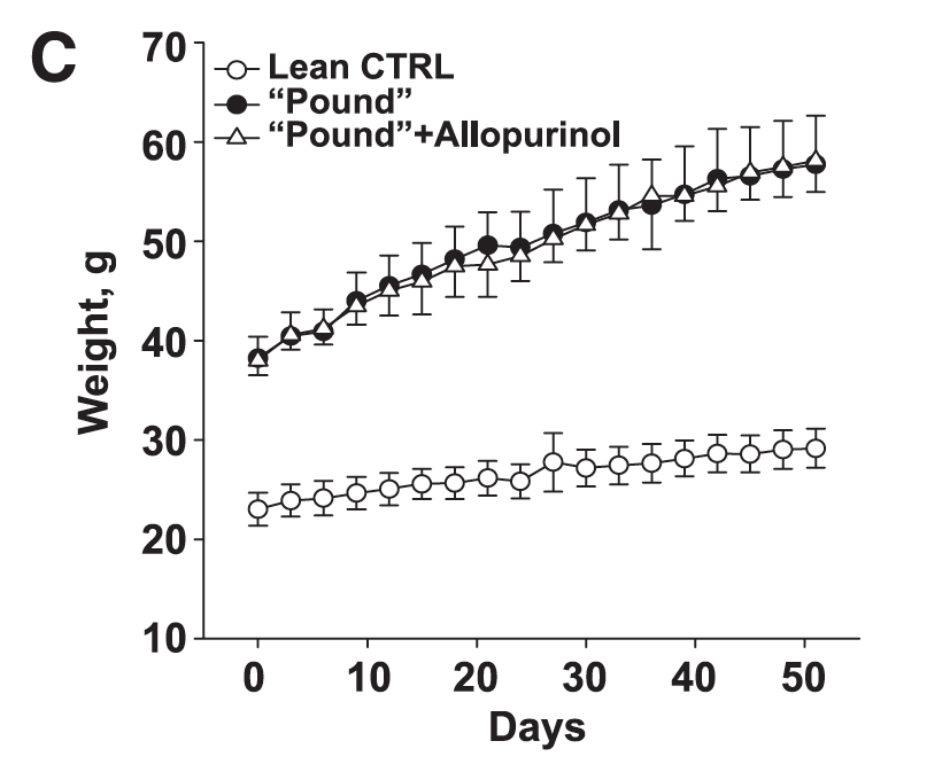
Hypertension





Baldwin et al, Diabetes 2011;60(4):1258-1269

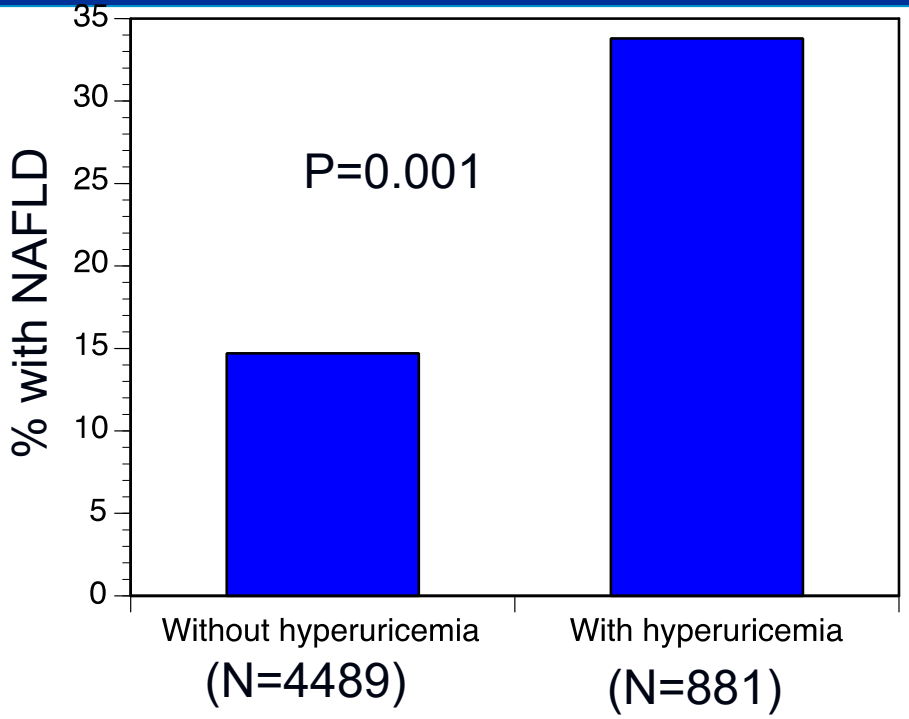
Can Urate Lowering Lead to Overall Fat Reduction? Not in the "Pound" Mouse!



Baldwin et al, Diabetes 2011;60(4):1258-1269

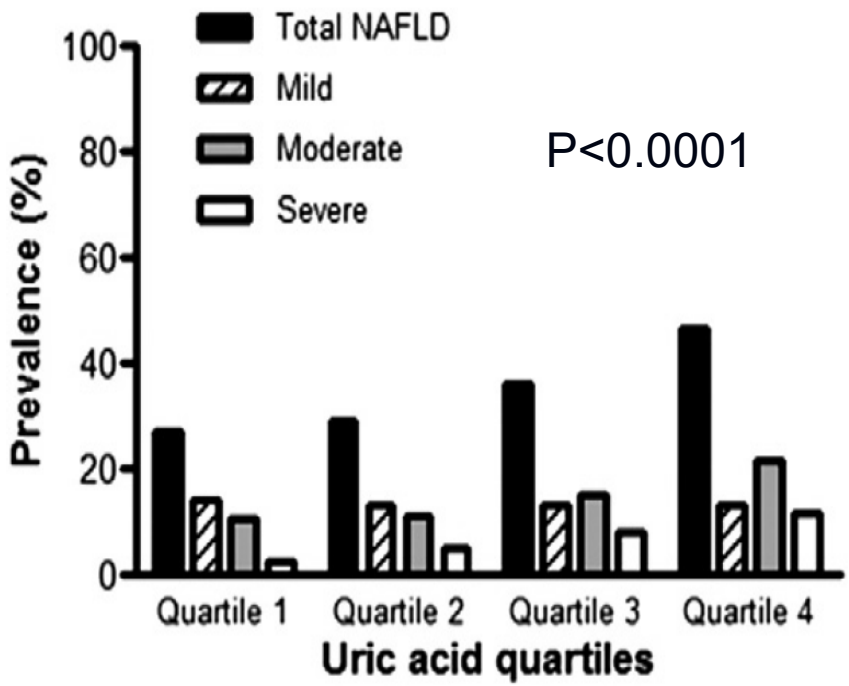
Serum Urate Levels in Humans Are Associated With Prevalence Of Non-alcoholic Fatty Liver

Overall



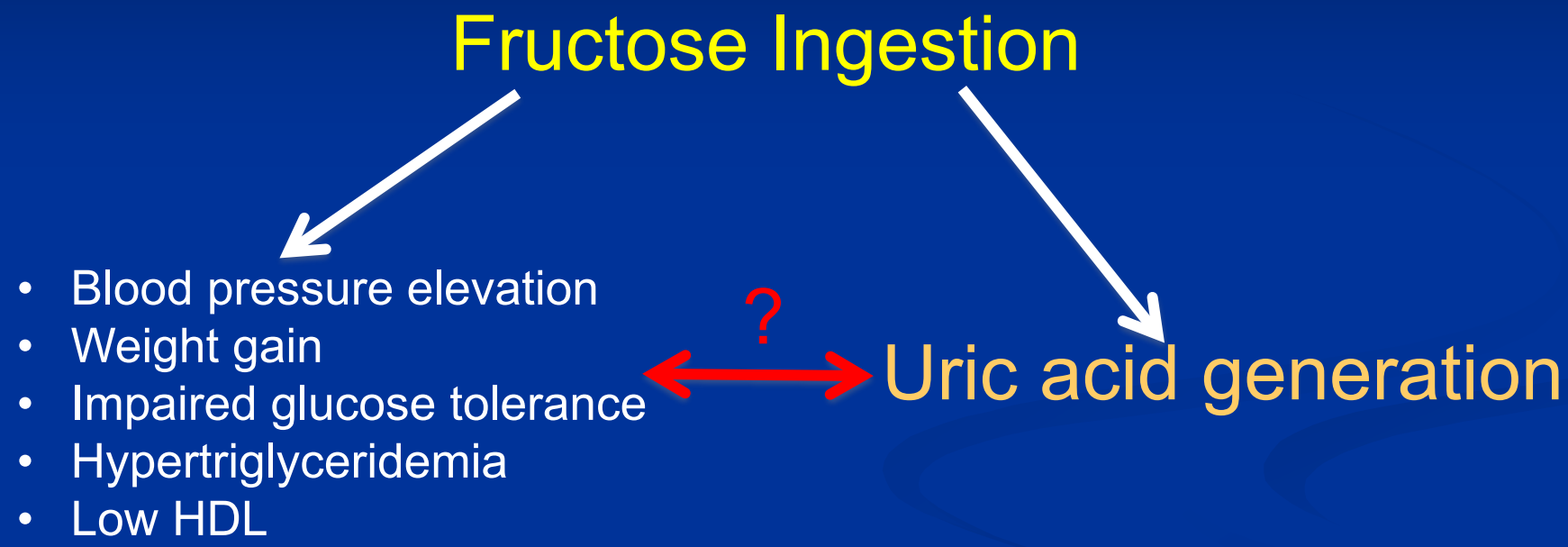
Shih et al, M Formos Med Assoc 2015;113(4):314-320.

NAFLD by severity and urate



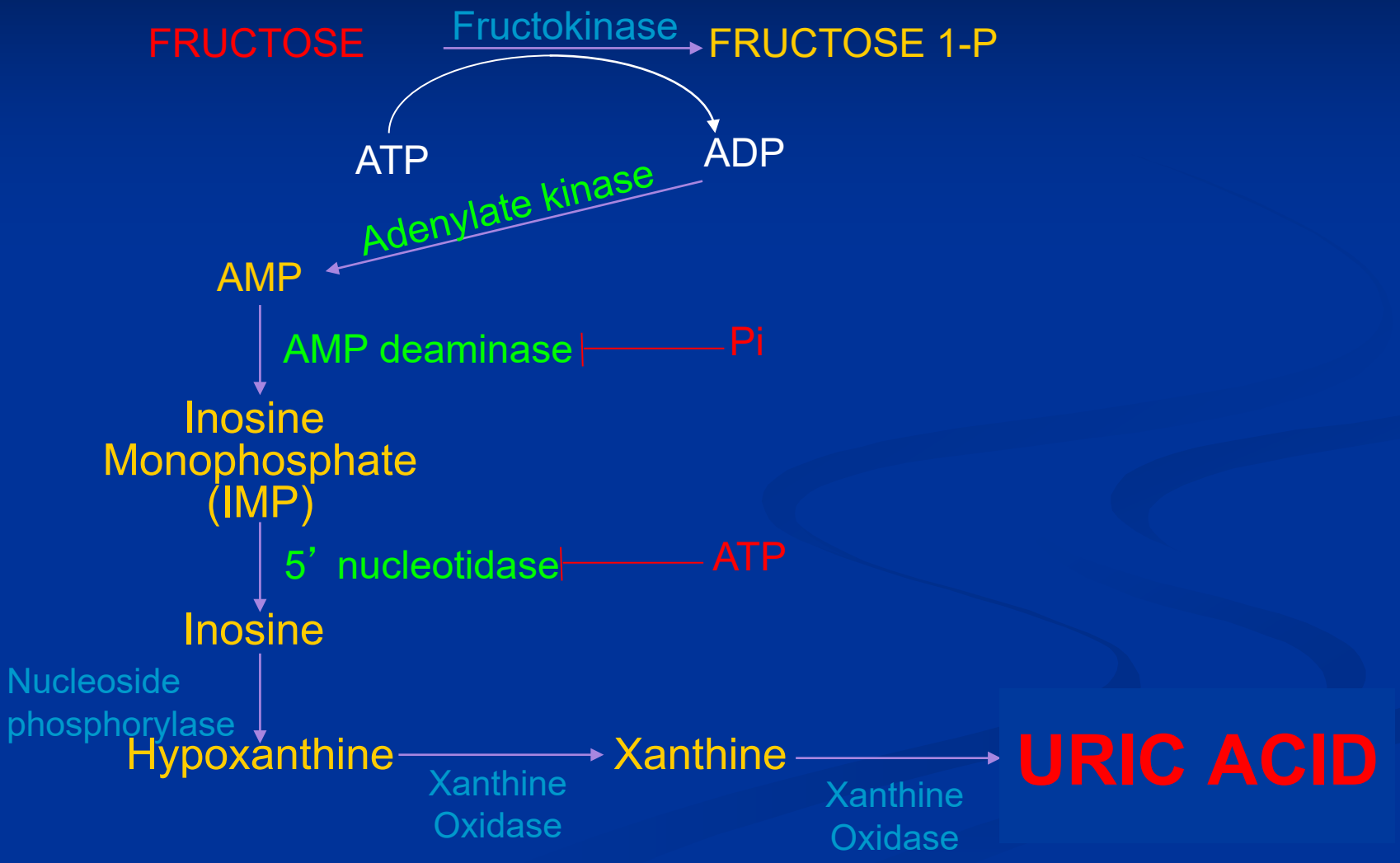
Sirota et al, Met Clin and Exp 2013;62:392-399

Fructose Ingestion: A Link Between Hyperuricemia, Gout and Metabolic Syndrome



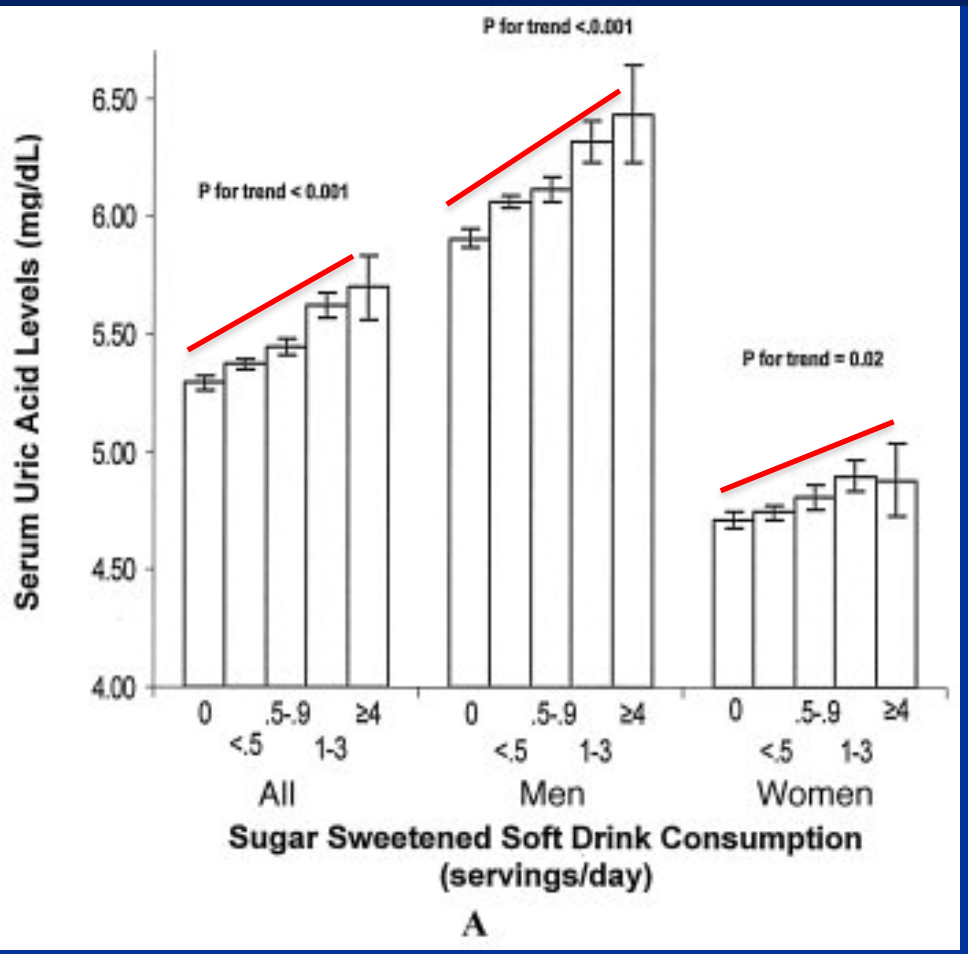
Johnson RJ et al. Endocr Rev 2009;30(1):96-116

Hepatic Metabolism of Fructose Results in Synthesis of Uric Acid



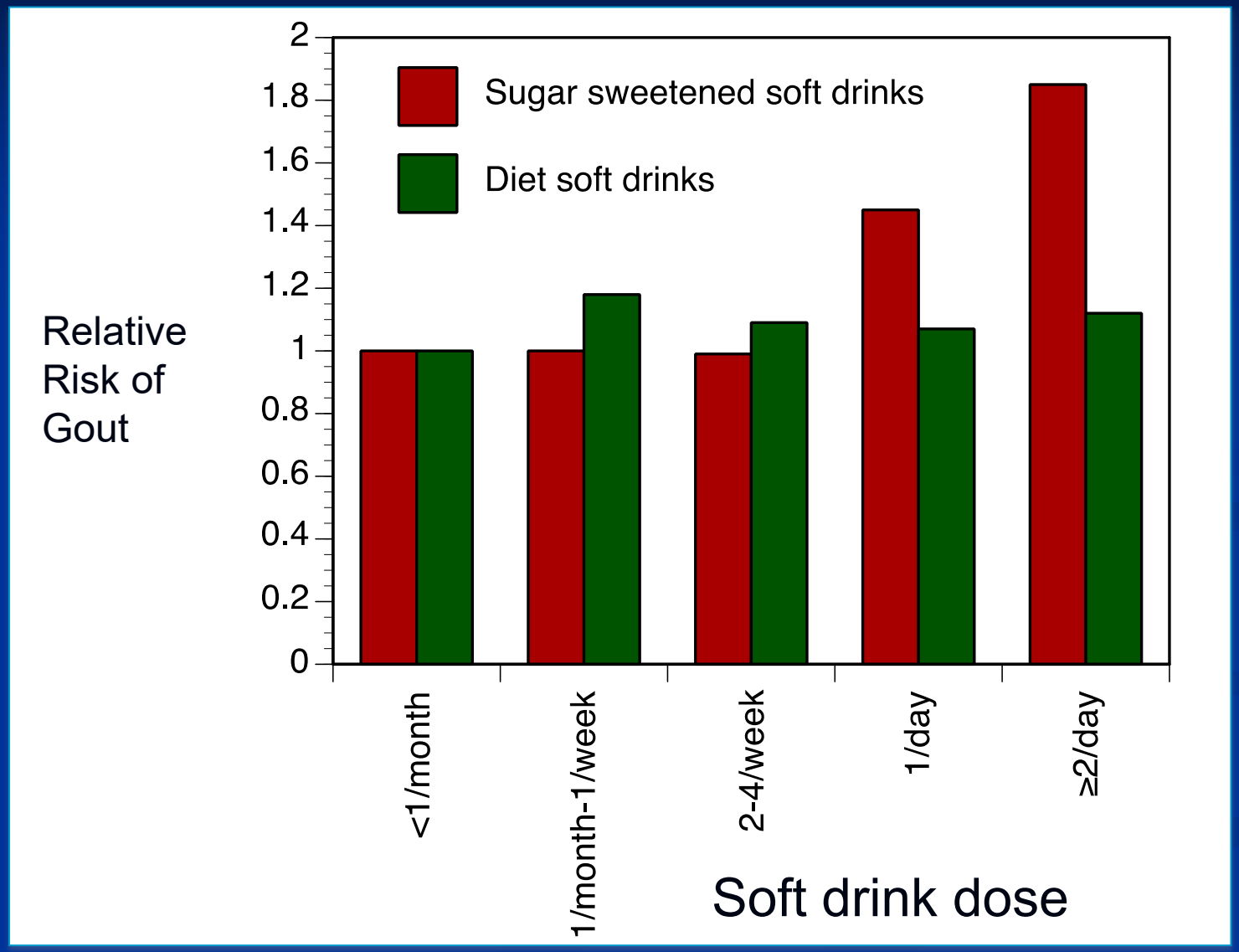
Mayes, Am J Clin Nutr 1993;58(suppl):754S-65S.

Ingestion of Fructose In The Form of Soft Drinks Correlates With Serum Uric Acid Levels



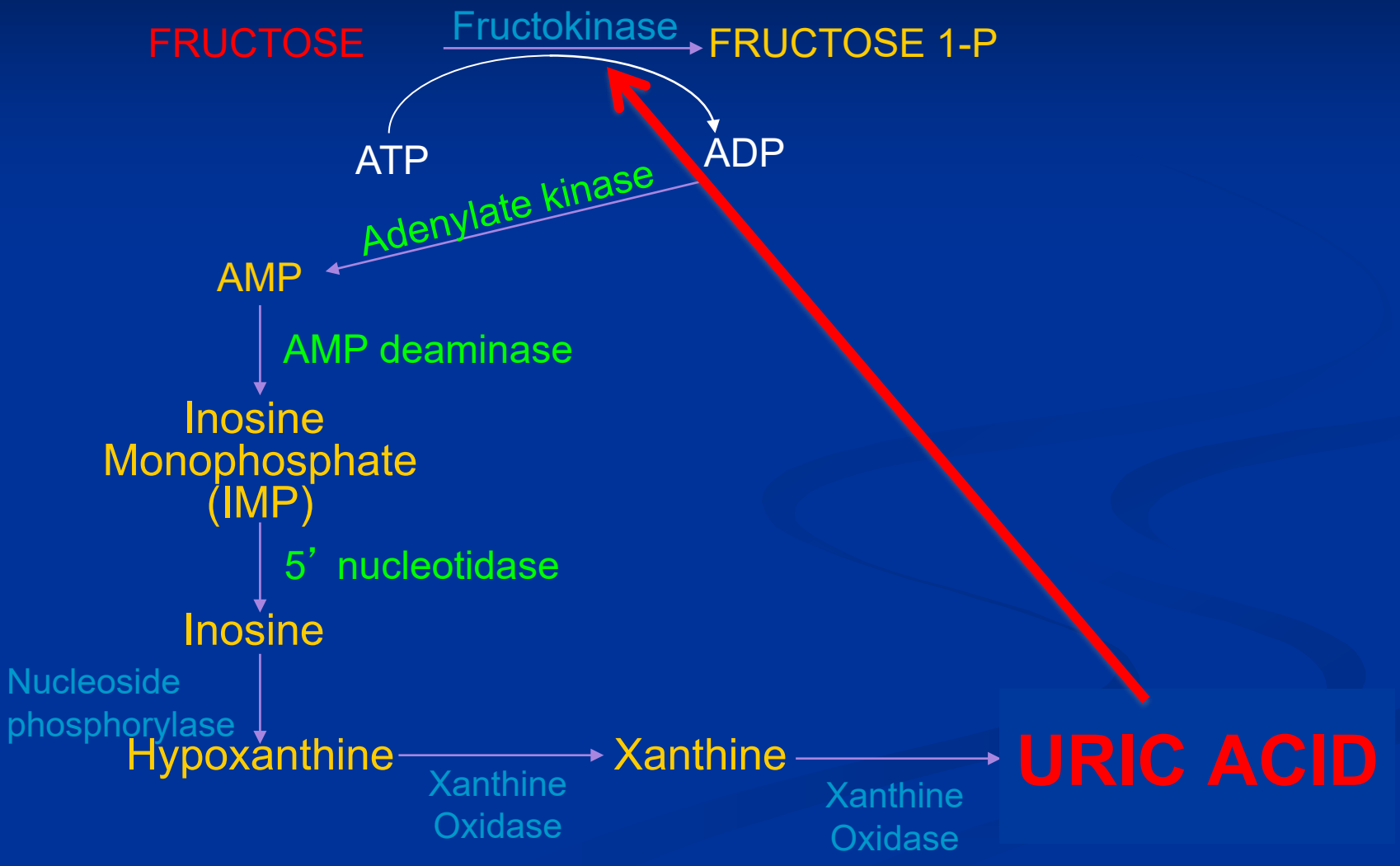
Choi et al, Arthritis Care & Research 2008;59(1):109-116.

Ingestion of Fructose In The Form of Soft Drinks Correlates With Risk for Gout



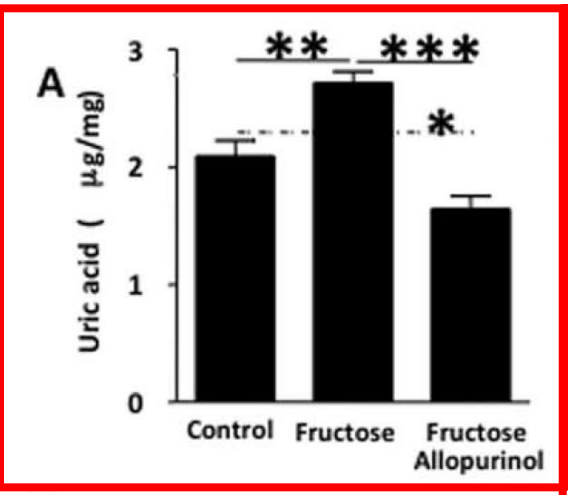
Choi and Curhan, BMJ 336(7639):309-312.

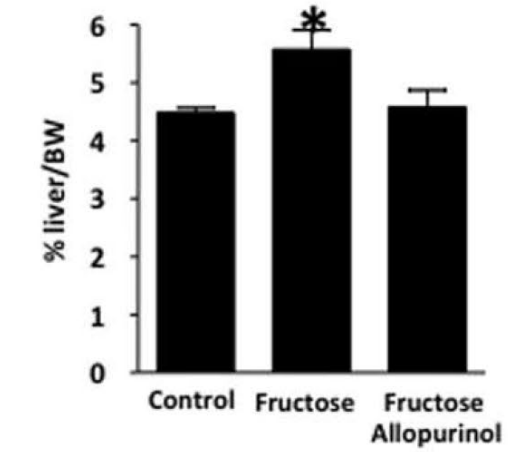
Hepatic Metabolism of Fructose Results in Synthesis of Uric Acid

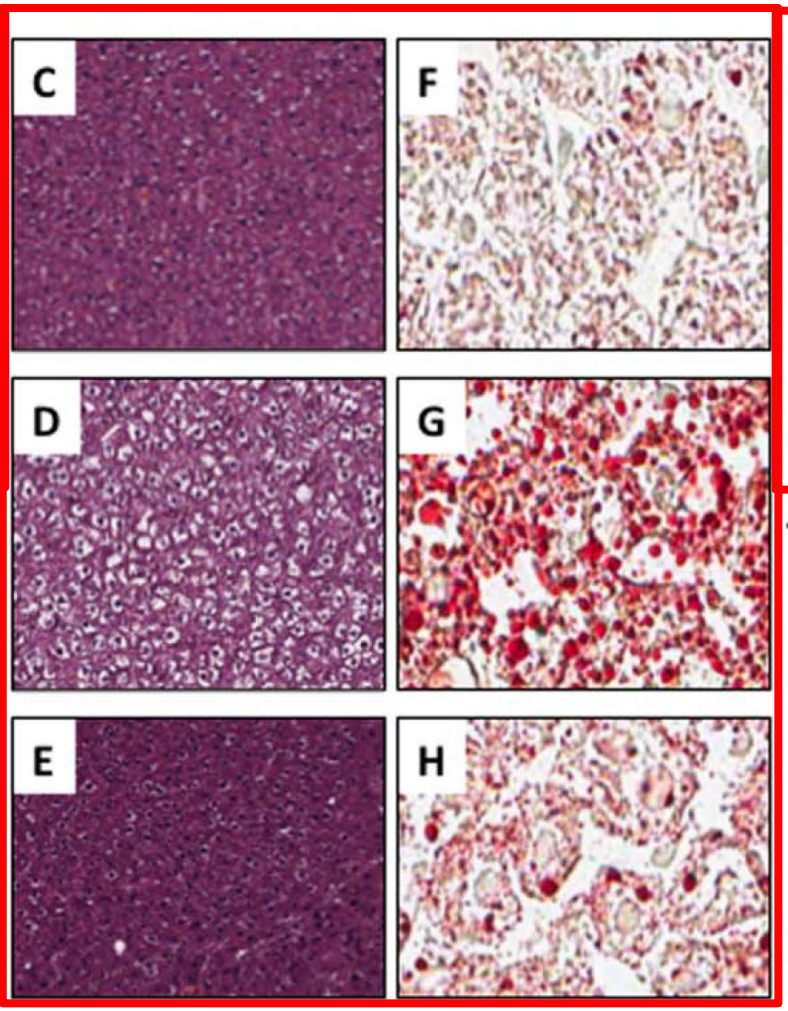


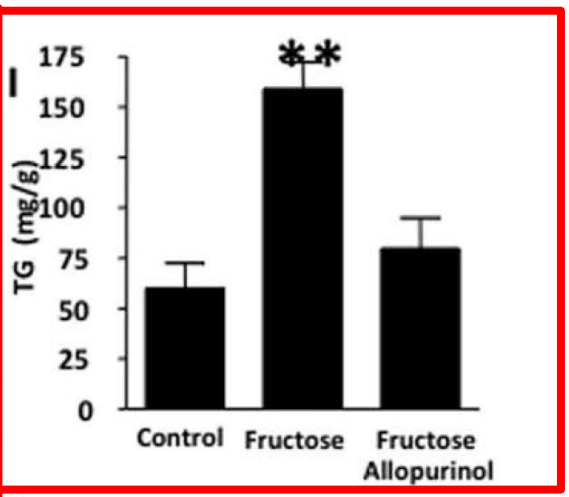
Mayes, Am J Clin Nutr 1993;58(suppl):754S-65S.

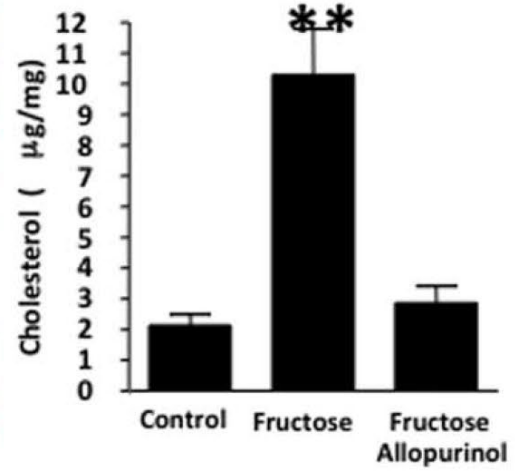
Another Role for Urate: Activating Fructokinase to promote Lipid Production In the Liver





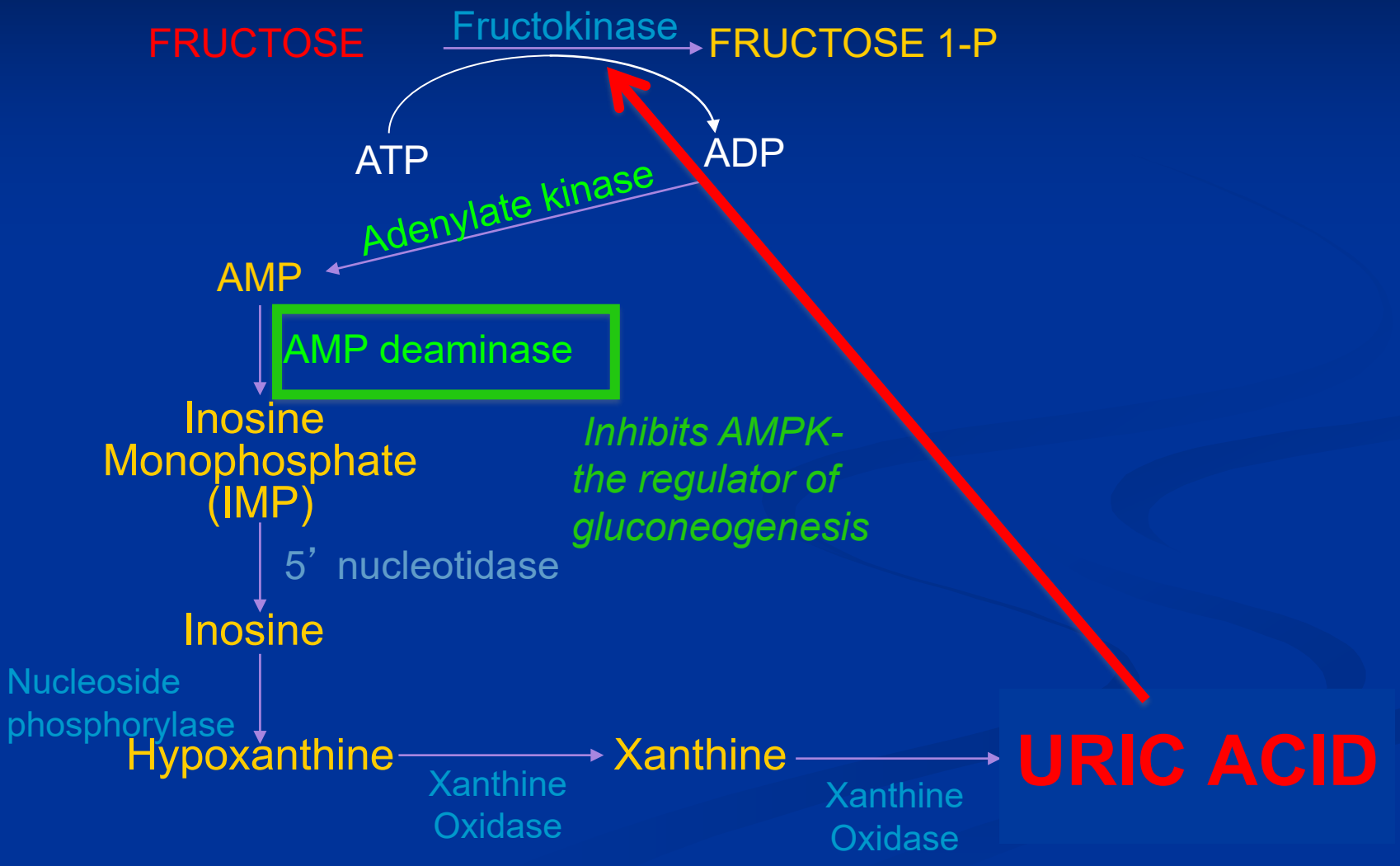






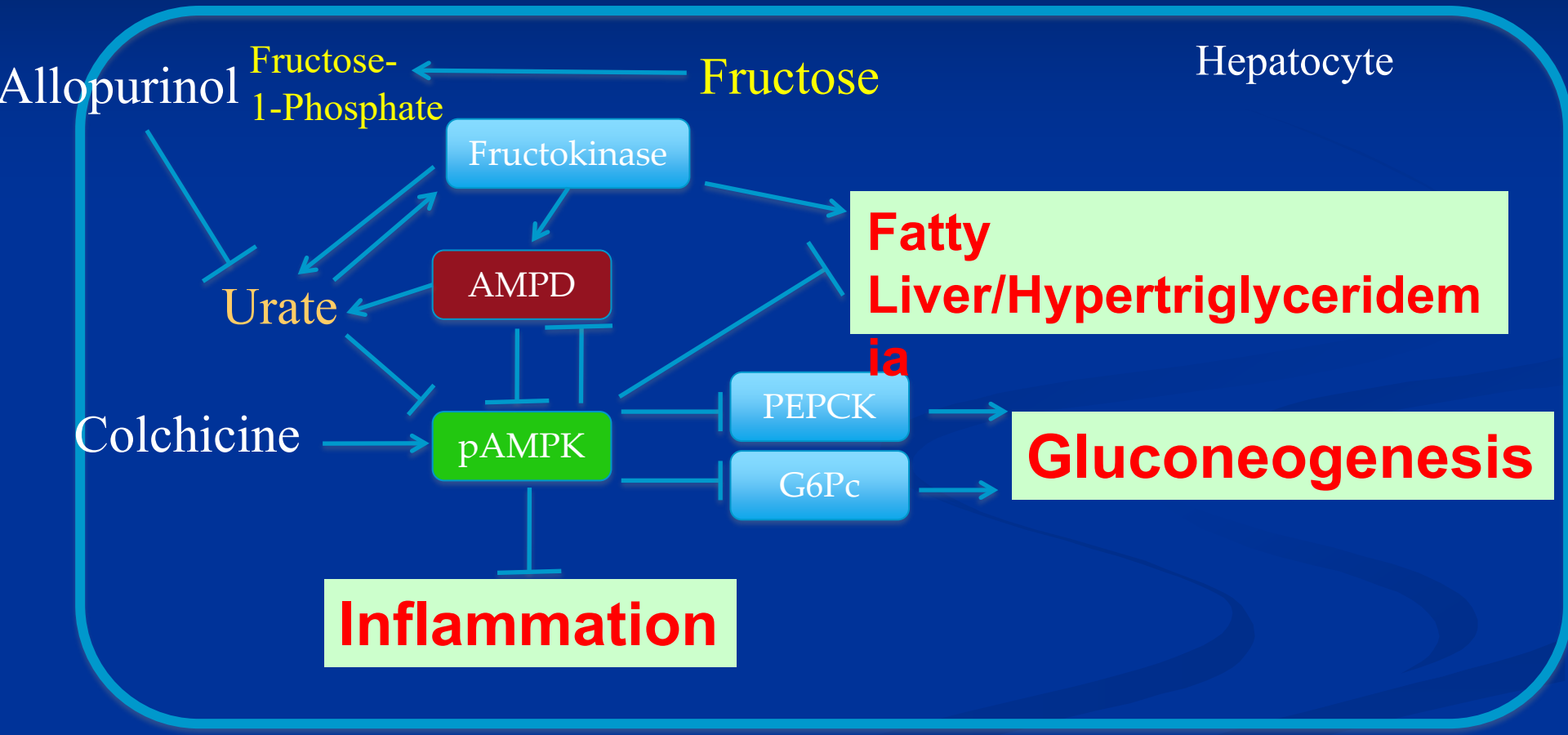
Lanaspa et al, PLOS ONE 2012;7(10);e47948

Hepatic Metabolism of Fructose Results in Synthesis of Uric Acid



Mayes, Am J Clin Nutr 1993;58(suppl):754S-65S;

Hepatic Gluconeogenesis: Urate Inhibits the Inhibitor of Gluconeogenesis

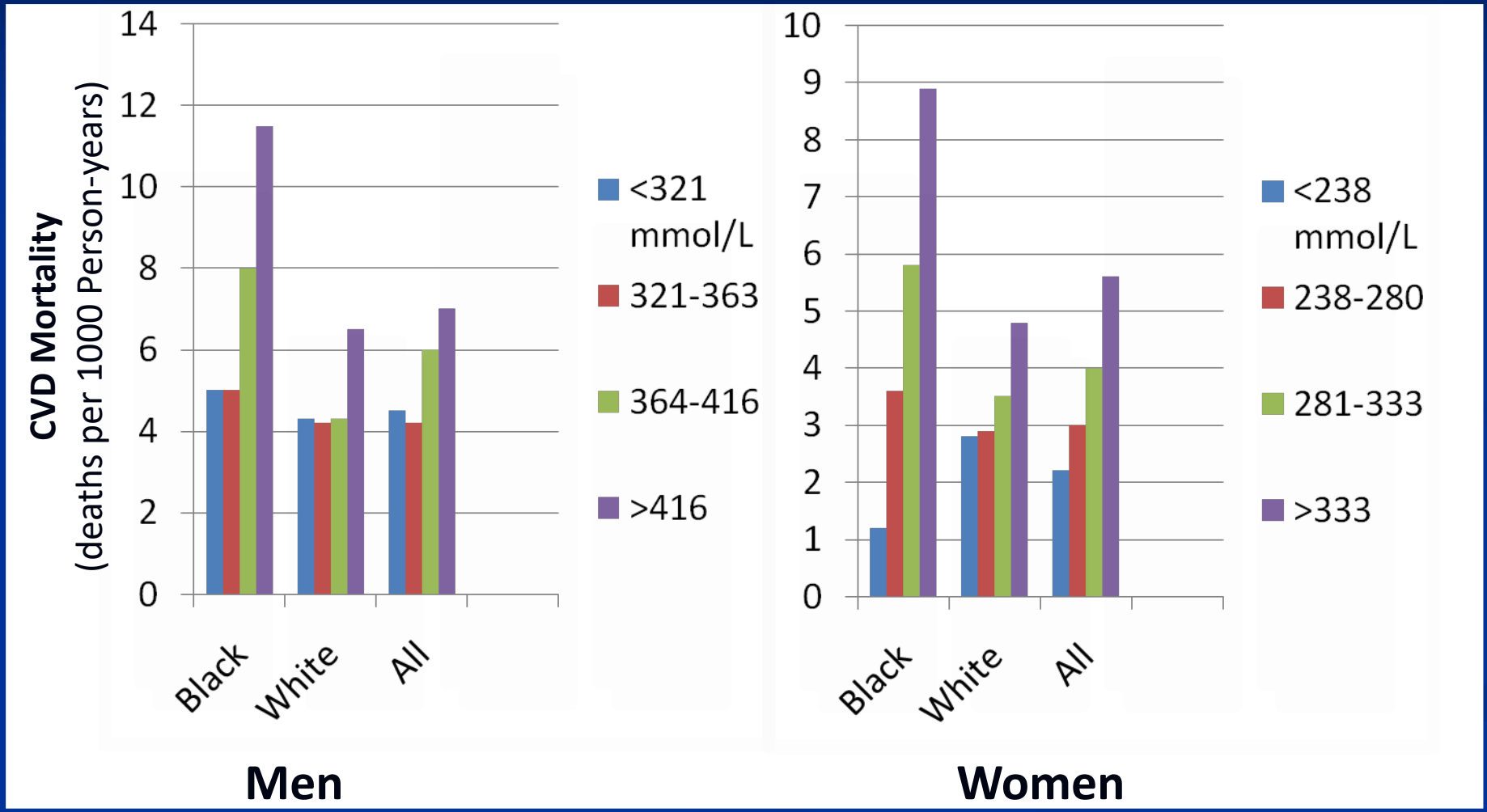


Terkeltaub et al, FASEB Journal 2014; Kanbey et al; Lanspa et al, PLoS One 2012;7(10):e47948

Hyperuricemia, Gout and Cardiovascular Disease

Hyperuricemia and Cardiovascular Disease:

Across many studies, hyperuricemia is consistently associated with cardiovascular disease…



NHANES I: Age-adjusted Cardiovascular Mortality Rates by Quartile of Serum Urate Level

Fang J, Alderman MH. JAMA;2000;283(18):2404-10

What About Gout and Cardiovascular Disease?

-Does gout represent a risk factor for cardiovascular disease?

-Is the risk conferred by gout independent of, or over and above that conferred by hyperuricemia?

The Health Professionals Follow-up Study: Gout Conveys an Independent Risk for MI and Cardiovascular Death

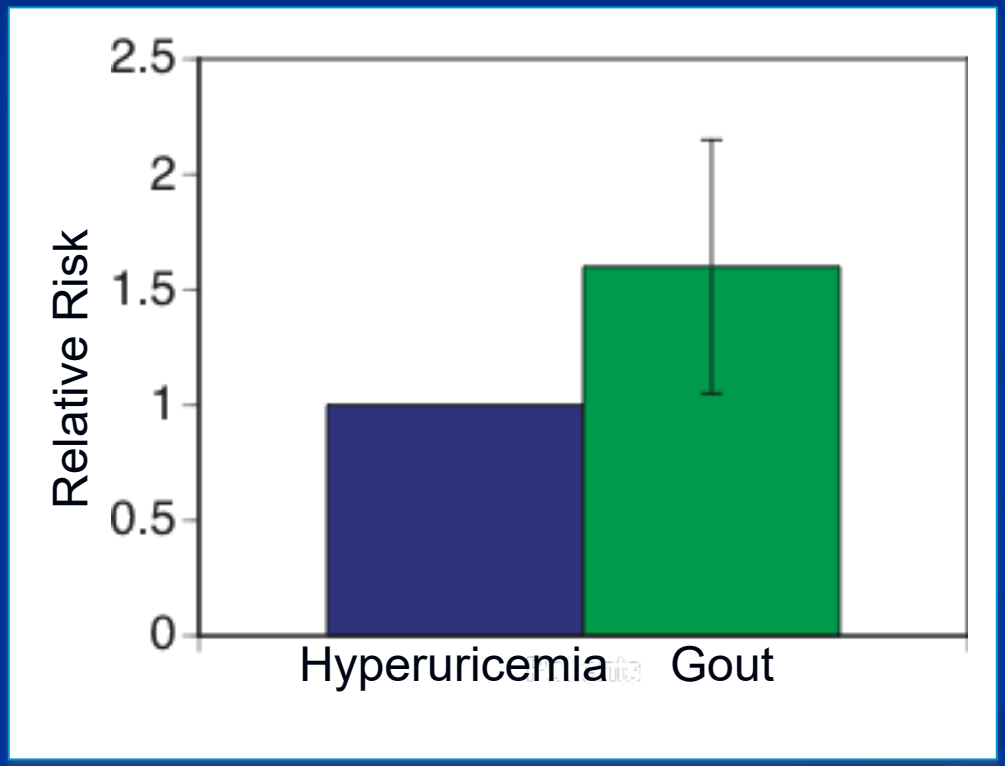
	No Gout	Gout	
Outcome	RR	RR	CI
***Non-fatal MI**	**1**	**1.59**	**(1.04 to 2.8)**
***CV Death**	**1**	**1.32**	**(1.09 to 1.6)**

Health Professionals Follow-up Study: 51,529 male health professionals followed prospectively for approximately 15 years.

*Multivariate adjusted

Choi et al, Circulation 2007

The Framingham Study: Gout Confers Risk For Cardiovascular Disease (Over and Above Hyperuricemia)



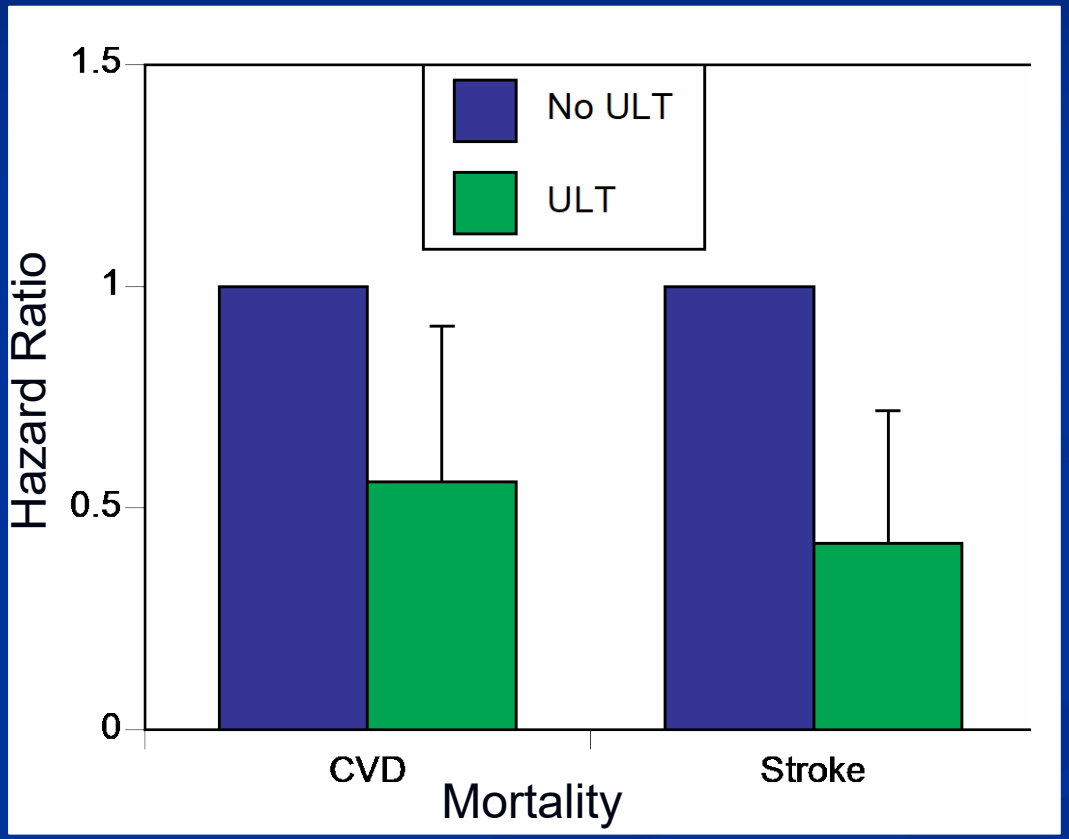
Abbott et al, J Clin Epidemiol 1988;41:237-42

Can Gout Cardiovascular Disease be Reduced Through Gout Treatment?

Does Urate Lowering Therapy Lower Cardiovascular Morbidity?

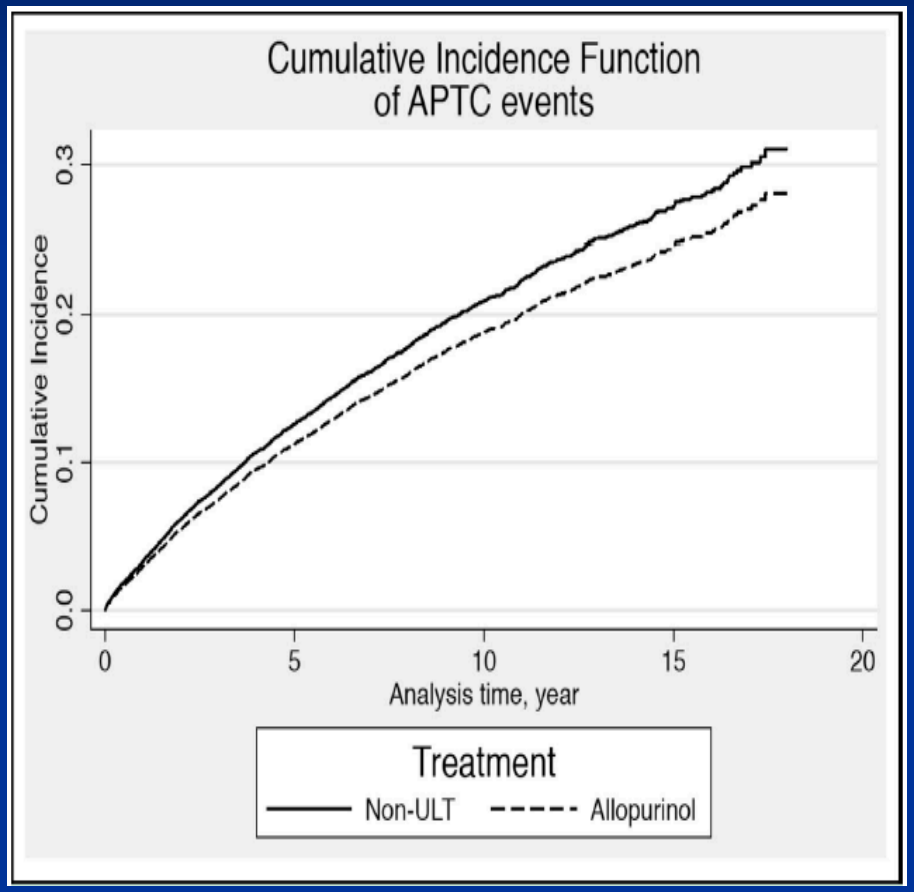
Taiwanese databases:
MH Health Clinical Center
National Health Insurance Drug Database
National Mortality Registry
N=45,215
Mean follow-up=11.3 years

Adjusted for:
Age
Sex
Hyperglycemia
Hypertriglyceridemia
Kidney disease
Heart disease
Smoking
Others



Chen J-H and Pan W-H, ACR Annual Meeting 2010

Does Urate Lowering Therapy Lower Cardiovascular Morbidity In Hyperuricemic Patients?



Hazard ratio 0.89 (0.81-0.97)

BUT:

- **No accounting for gout**
- **Confounding by indication**
- **Likely treated patients were gout patients, untreated were asymptomatic hyperuricemics**
- **So we don't' really know the effect of allopurinol on AH**

Larsen et al, Am J Med 2016

Does Lowering Serum Urate Reduce Cardiac Risk?

Limitations of study:

- Modest size
- Not blinded
- Allopurinol dose low
- Allopurinol has antioxidant effect

Goicoechea et al Clin J Am Soc Nephrol 2010;
Goicoechea et al Am J Kidney Dis 2015

Gout and Metabolic Syndrome: Implications For Treatment

2020 American College of Rheumatology Gout Treatment Guidelines: The Basics

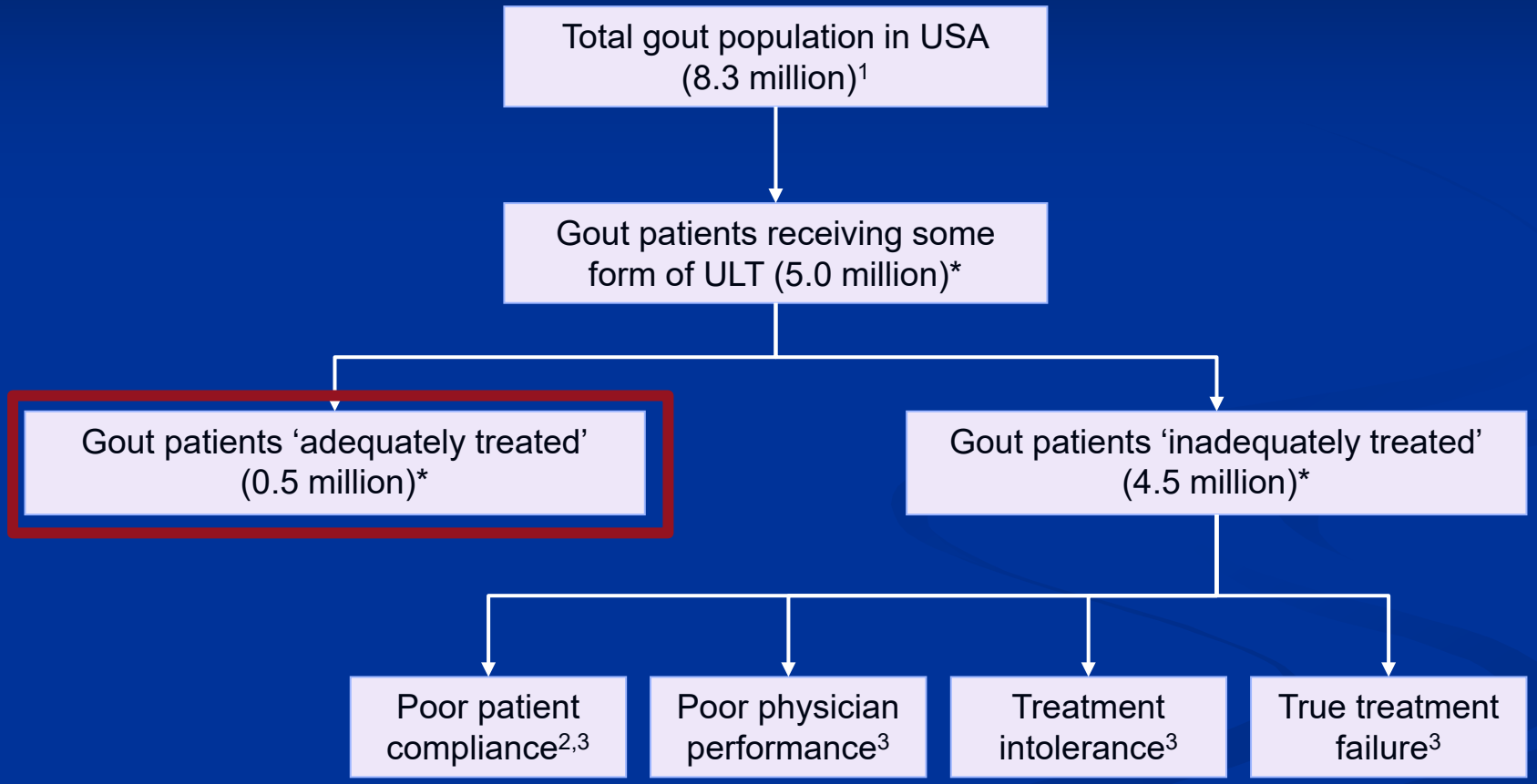
- Most patients with gout should receive TREATMENT WITH A URATE LOWERING AGENT
- Start low, titrate and TREAT TO TARGET!!!!!
  - <6.0 mg/dL in most cases
- ANTI-INFLAMMATORY PROPHYLAXIS during urate-lowering is mandatory!

Khanna et al, Arthritis Care & Res 2012;64(10):1431-1446;
Khanna et al, Arthritis Care & Res 2012;64(10):1447-1461;

Should We Be More Aggressive With Gout Treatment In the Face of Metabolic Syndrome Co-Morbidities?

In most cases, appropriate urate-lowering for gout, according to ACR guidelines, is probably appropriate and sufficient

Gout Treatment in the USA is Woefully Inadequate!!!!



*Data inferred from Zhu Y, *et al*. (2011) and Sarawate CA, *et al*. (2006).[3] ULT=urate-lowering therapy.

1. Zhu Y, *et al. Arthritis Rheum* 2011;63:3136–41. **2.** Riedel AA, *et al. J Rheumatol* 2004;31:1575–81. **3.** Edwards NL. *Curr Rheumatol Rep* 2011;13:154–9. **4.** Sarawate CA, *et al. Mayo Clin Proc* 2006;81:925–34.

Should We Treat "Asymptomatic" Hyperuricemia?

- Routine in Asia, not in US or Europe
- ACR declined to make a recommendation
  - Insufficient data to either support or refute
- Distinguish between hyperuricemics with and without metabolic syndrome co-morbidities?

Large prospective trials are needed!

Thank You/Acknowledgments

Crystal Diseases Study Group

Svetlana Krasnokutsky, MD, MSCI
Virginia C Pike, BA
Daisy Bang, MD
Aaron Garza, MD
Binita Shah MD, MSCI
Daria Crittenden, MD
Anastasia Slobodnick, MD
Susanna Jeurling, BA
Irina Dektiarev
Jonathan Samuels
Bruce Cronstein, MD
Steven Sedlis MD
David Goldfarb, MD
Steven Bernstein, MD

Gout Co-morbidities Project

Robert Keenan, MD, MPH
Mark Fisher, MD, MPH

Colchicine in Gout Project

Svetlana Krasnokutsky, MD, MSCI
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Steven Sedlis MD
Aaron Lehman, MD
Jeff Greenberg MD MPH
Craig Tenner MD
Chris Swearingen PhD
Binita Shah MD, MSCI

Colchicine PCI

Binita Shah, MD, MSCI
Bruce Cronstein, MD
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How to Bolster the Rheumatology Workforce

Optimizing the Deployment of Advanced Practice Clinicians

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Disclosure Statement

I have no financial disclosures.

References

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- **the-rheumatologist.org**/article/how-to-address-the-rheumatology-workforce-gap. May 17, 2019
- NPs vs PAs: What's the Difference? - Medscape - Aug 28, 2019.
- How Can Integrated Healthcare Contribute to Sustainable Healthcare in Rheumatology. B. Vrijhoef. DOI: 10.1136/annrheumdis-2018-eular.7841

Advanced Practice Clinicians

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- Three-year Master's program
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- General Education but then specialize in particular area

Both require:

- State licensing, National certification by exams and CME
- Autonomy varies by state
- Comparable Pay

Agenda

- Review the workforce shortage of rheumatology physicians and clinicians: current and projected
- Overview of rheumatologists perceptions of working with APCs
- APCs – who are they?
- APCs future in rheumatology
- The APC model in AARA

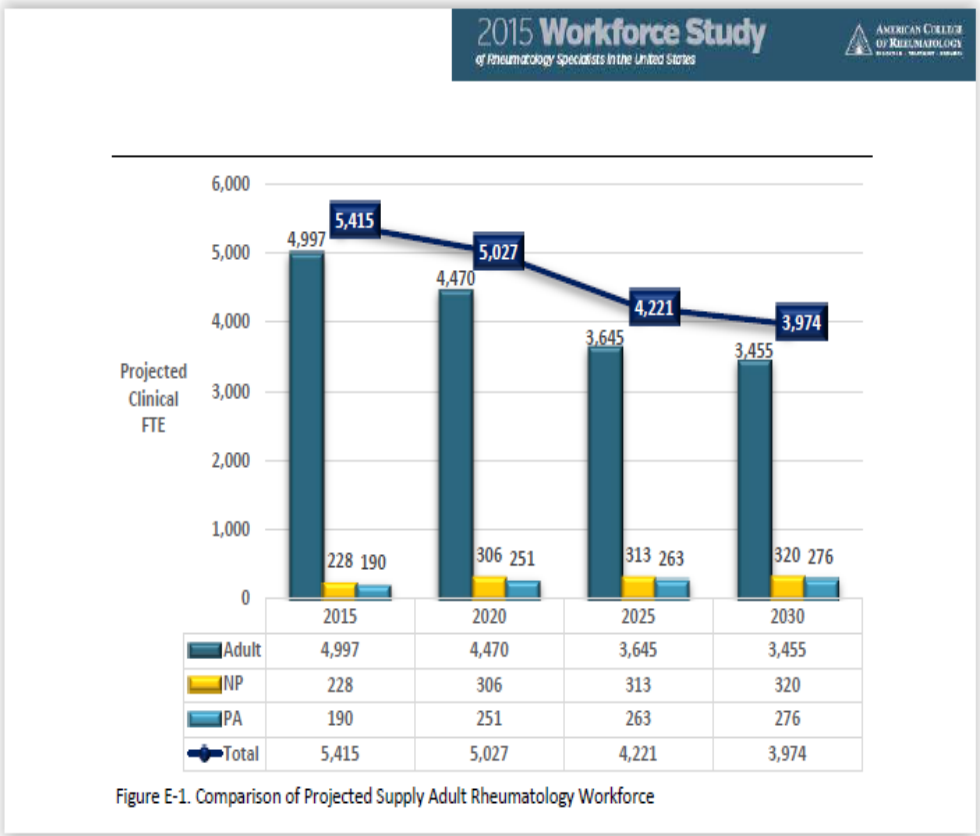


Figure E-1. Comparison of Projected Supply Adult Rheumatology Workforce

ACR 2015 Workforce Study Report

Total adult rheumatology workforce supply and demand projections

Supply	2015 Baseline (FTE)	2020 Projections		2025 Projections			2030 Projections		
		Total	% Diff. 2015–2020	Total	% Diff. 2020–2025	% Diff. 2015–2025	Total	% Diff. 2025–2030	% Diff. 2015–2030
Adult	4,997	4,470	-10.5	3,645	-18.6	-27.1	3,455	-5.2	-30.9
NP	228	306	+34.2	313	+2.3	+37.3	320	+2.2	+40.4
PA	190	251	+32.1	263	+4.8	+38.4	276	+4.9	+45.3
Total	**5,415**	**5,027**	**-7.8**	**4,221**	**-16.0**	**-22.6**	**4,051**	**-4.2**	**-25.2**

Demand	Baseline	2020	2025	2030
Projected workforce supply†	5,415	5,027	4,221	4,051
Projected need	6,115	6,796	7,490	8,184
Difference (excess demand)‡	700	1,769	3,269	4,133
Percent change excess demand	+12.9	+35.2	+77.5	+102.0
Number projected with disease§	22,500,000	25,421,467	28,571,024	36,361,586
Adults with disease/provider (supply)¶	4,155.1	5,057.0	6,768.8	8,976.0
Adults with disease/provider (need)#	3,679.5	3,740.7	3,814.6	4,443.0

Figure 3. Total adult rheumatology workforce supply and demand projections (clinical full-time equivalent [FTE]). Numbers include new graduating fellows entering the workforce annually. Assumes 1.0 FTE for adult rheumatologists working in nonacademic settings (~80% workforce), 0.5 FTE for adult rheumatologists working in academic settings (~20% of workforce), and 0.9 FTE for all nurse practitioners (NPs) and physician assistants (PAs). † = supply numbers include both physician and nonphysician providers; ‡ = number of excess demand compared to same-year supply projections; § = number of projected patients with rheumatic diseases plus 25% osteoarthritis patient load; ¶ = number of adults with disease per provider based on current projections; # = number of adults with disease per provider if projected need is met.

Arthritis Care & Research
Vol. 70, No. 4, April 2018, pp 617–626

The Maldistribution of Rheumatologists in the USA

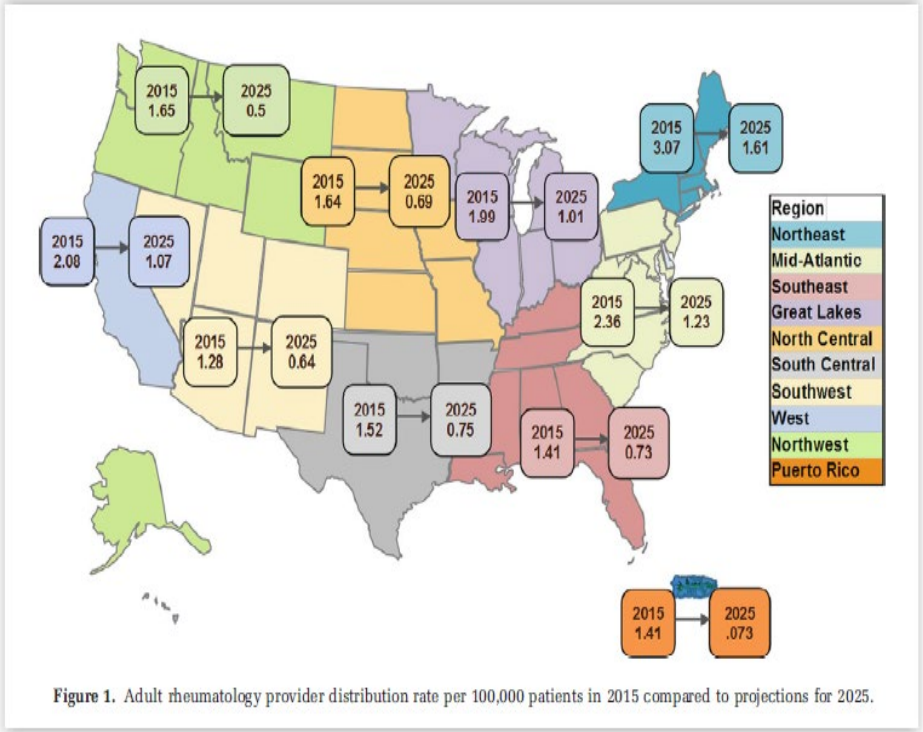


Figure 1. Adult rheumatology provider distribution rate per 100,000 patients in 2015 compared to projections for 2025.

Battafarano DF, et al. Arthritis Care & Research Vol. 70, No. 4, April 2018, pp 617–626 DOI 10.1002/acr.23518

Advanced Practice Clinicians

- Major organizations existent
  - AAPA
  - ACR/AHP
  - American Association of Nurse Practitioners
  - Rheumatology Nurses Society
- Why APCs in rheumatology
  - Projected workforce shortage of rheumatologists over the next 12 years
  - Extend expertise of the rheumatologist to larger rheumatic disease population in the community
  - Improve practice performance
  - Enhance the time efficiency of the rheumatologist

Rheumatology Workforce Challenges

- Lack of rheumatologists
- Maldistribution of rheumatologists
- More demand for adult rheumatology fellowship slots currently budgeted and allotted in US
  - About 100 more physicians applied for fellowships than available
  - Rheumatology Research Foundation partially funds 20-25 slots per year
  - Arthritis Foundation has new grant mechanism
- Less demand for pediatric fellowship slots than allotted
  - Less than 50% filled last year
  - Loan forgiveness programs

The Rheumatologist, March 2018

Seven Opportunities to Change

1. Increase training programs – especially underserved areas
2. Increase PAs and NPs into rheumatology
3. Better educate non-rheum providers in MS medicine
   - Empower them to manage primary care MS disease
4. Loan forgiveness to rheumatologists to work underserved areas
5. Embrace telemedicine to provide and triage rheum care
6. Engage physical and occupational therapists to provide more primary rheum care
7. Build interdisciplinary communities to provide additional support

Battafarano DF et al, Arthritis Care & Research Vol. 70, No. 4, April 2018, pp 617–626
DOI 10.1002/acr.23518

EULAR 2018: Sustainable Healthcare in Rheumatology and the Role of Healthcare Professionals

- The older model of rheumatologic care of decades past is no longer tenable
- Increasing fellowships and training new rheumatologists AND increasing NP and PA participation will not meet future needs
- Team-based care: **“Teamlets”**
  - Expand role of medical assistants to gather and record information, and post-visit education (ensure patient understands the visit)
  - Leveraging pharmacists and social workers
  - Increasing nursing involvement at all levels
  - The key is sustainable outcomes by improving healthcare outcomes, the patient experience, and societal cost

EULAR 2018: Sustainable Healthcare in Rheumatology and the Role of Healthcare Professionals

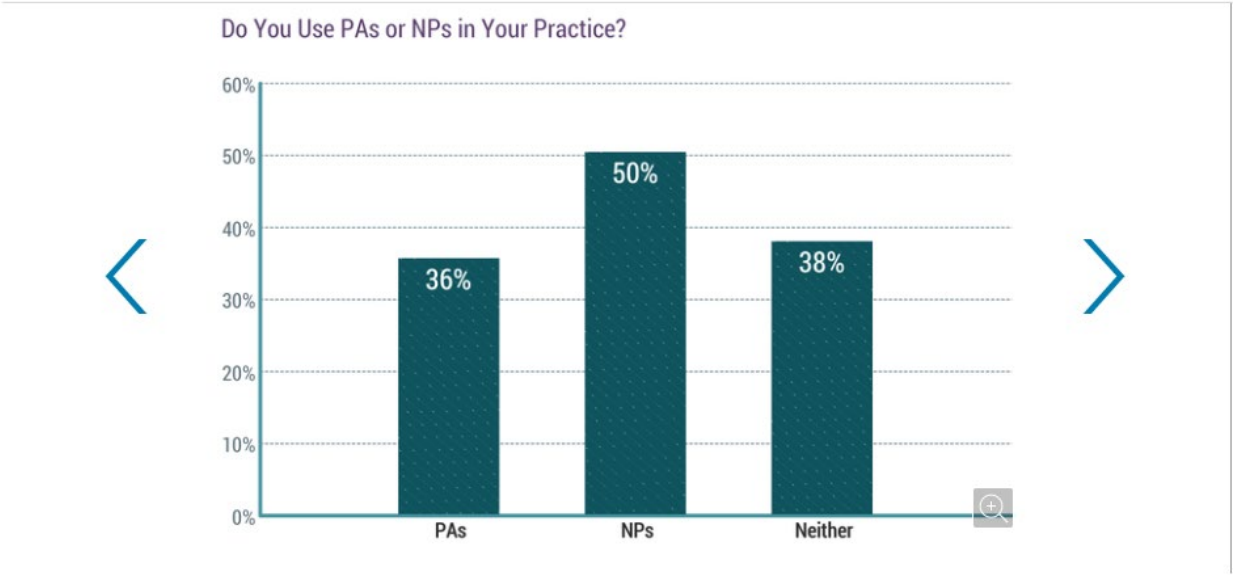
- Models of increase nurse and medical assistant and non-clinician health professionals in rheumatology to complement and leverage a team based approach
  - Include PT and OT in early diagnosis and triage to rheumatologists
  - Provide important OA, soft tissue and non-systemic inflammatory rheumatology care
- Literature review: 63 articles/53 systems/16 countries (B. Vrijhoef)
  - Heterogenous integrated healthcare models
  - No one size fits all
  - Systematic approach needed to understand and compare integrated care models

B. Vrijhoef. DOI: 10.1136/annrheumdis-2018-eular.7841

What per cent of Physicians Work with APCs?

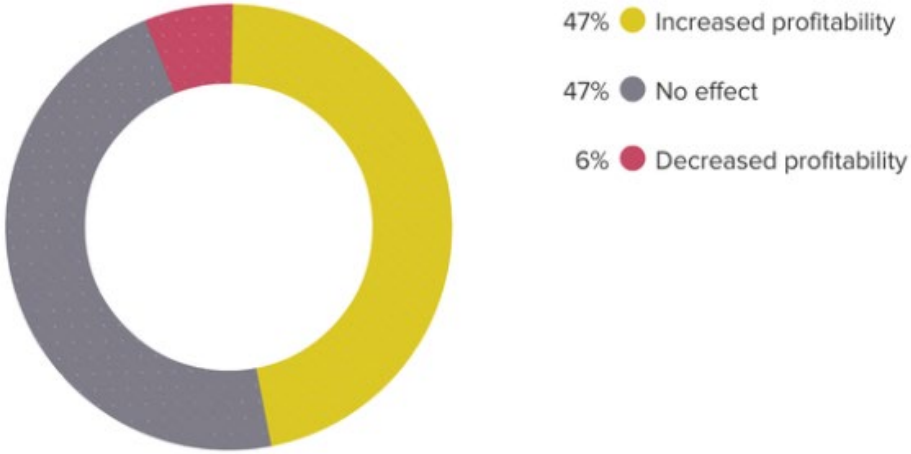
Medscape Physician Compensation Report 2020

21 / 33

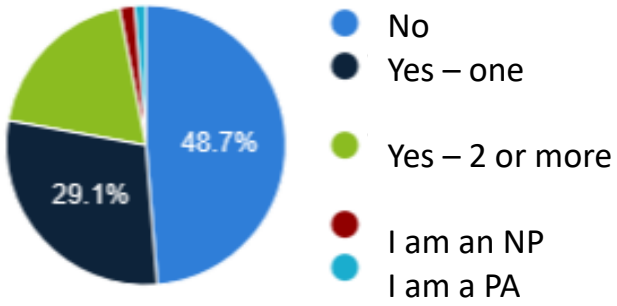


Medscape Physician Compensation Report 2020

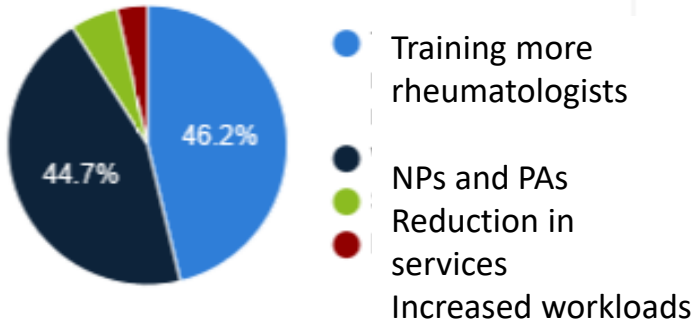
What Effect Have PAs or NPs Had on Your Practice's Profitability?



1. Do you employ or work with a NP or PA?

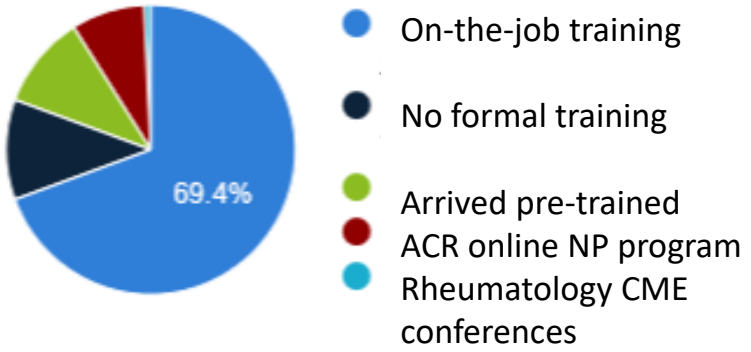


2. Future Rheum manpower shortages will need to be met by

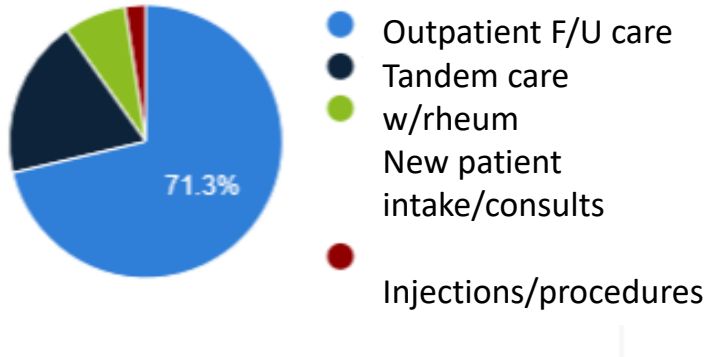


Cush, John J. Nurse Practitioner-Physician Assistant Manpower Survey. RheumNow Live Vote. Sep 2017.

3. How was your Rheumatology NP or PA trained ?

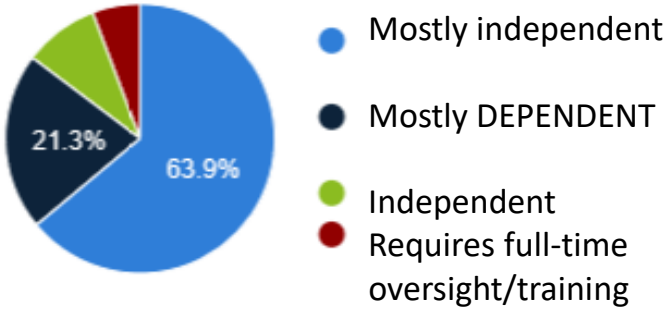


4. Your NP or PA primarily does which?

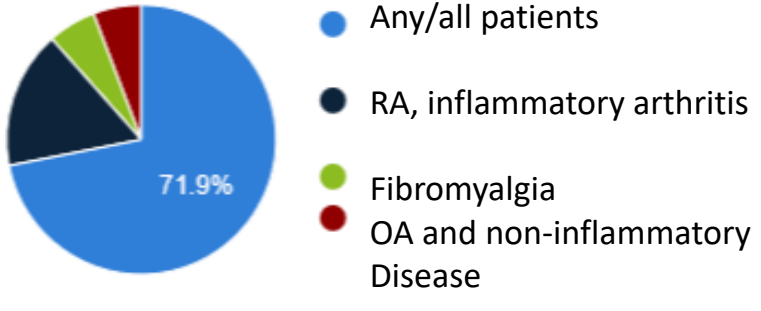


Cush, John J. Nurse Practitioner-Physician Assistant Manpower Survey. RheumNow Live Vote. Sep 2017.

5. How independent is your NP or PA?

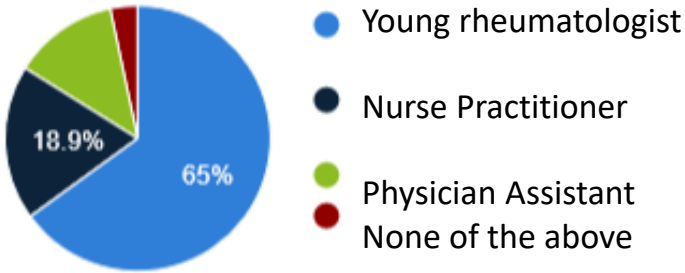


6. What kind of patients does your NP-PA see?

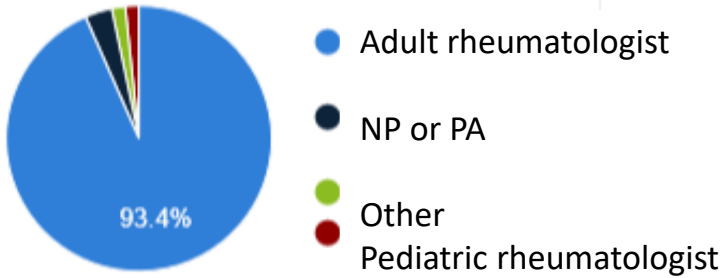


Cush, John J. Nurse Practitioner-Physician Assistant Manpower Survey. RheumNow Live Vote. Sep 2017.

7. I would prefer to hire & work with a:



8. I am a:



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Challenges to Rheumatology APC Workforce

- Attraction - How should the profession promote a career in rheumatology to APCs?
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- Deployment – What is the most effective working environment for APCs in rheumatology?
- Retention – What measures would drive APC career durability in rheumatology?
- What else should rheumatologists and the ACR be asking about APCs? What more should we know and understand?

NPs vs PAs: What's the Difference? - Medscape - Aug 28, 2019.

Pie in the Sky Proposal?

- Estimated rheumatologists employing APC's: 25-50%
- Estimated APC/rheumatologist ratio: 1:10
- AARA APC/rheumatologist ratio: 2:1
- Estimated total 2030 rheumatologist workforce: 3455
- Total rheumatology workforce need: 8184
- Potential total APC workforce (assume 2:1 ratio): 6910
- Assume APC productivity 0.9 of rheumatologist: 6220
- Total potential rheumatology workforce: 9675

Arthritis Care & Research
Vol. 70, No. 4, April 2018, pp 617–626

Caldron PH. How to Address the Rheumatology Workforce Gap. The Rheumatologist. May 17, 2019.

Challenges to APC Recruitment

- Hindrances of Recruitment of APCs
  - Low exposure of APCs in their education both didactic and clinical
  - Rheumatology's obscurity, though improving
  - Rheumatologists' reluctance to embrace
    - Time investment
    - Financial risk
- Optimal operational construct
  - Working under direct supervision of rheumatologist*
  - Separate panel of patients
  - Working independently? (e.g. Arizona allows NPs)

E.6.2.6 Non-Physician Provider (Nurse Practitioners (NP) and Physician Assistants (PA). The ACR/ARHP should strongly consider optimal strategies for increasing the numbers of NPs and PAs to augment the workforce and access-to-care. Several authors have suggested that employing NPs and/or
PAs for patients in need of laboratory monitoring, those with chronic conditions, and those requiring a greater focus on education and coping skills, can lead to better patient outcomes and more efficiently utilization of rheumatologists' time. Data from the survey indicate that only about one-quarter of rheumatologists are in a practice with an NP or PA. In addition, best estimates indicate that less than 1% of the existing rheumatology NPs/PAs work in pediatric rheumatology. Thus, there appears to be substantial room for increasing the role of non-physician providers in both adult and pediatric rheumatology. In addition, the ACR/ARHP should investigate strategies for providing appropriate rheumatology training for NPs/PAs. Currently, limited rheumatology-based resources are available to aid in the readiness of an NP or PA to join a rheumatology practice. The ARHP Working Group is vested in the development of a standardized curriculum for NPs and PAs. Additional consideration could be given to a more formal training program that parallels rheumatology fellowship training for physicians. This recommendation carries with it a greater commitment in terms of time and financial resources. Better training could serve to increase interest in our specialty among health professionals and increase exposure of students in NP and PA schools to our specialty.

Advanced Practice Clinicians

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- Training starts as RN
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- Nursing Model
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  - Separate panel of patients
  - Working independently e.g. Arizona allows NPs

How do we attract more APCs to Rheumatology?

- Guest lecturers at Universities on rheumatologic topics
- Access to rheumatology clinical sites as students
- Access to educational dinners as a student
- Standardized beginner courses in rheumatology for new graduate and experienced NPs, applicable grants where needed.

Training of APCs

- Experienced APCs
  - Positives
    - Possess clinical patient skill set
    - Familiarity of patient working environment
    - Efficiency of working habits
  - Negatives
    - Skills in other discipline/s - hard to adapt
    - If previous experience non-cognitive intense

Training of APCs

- Newly graduated APCs
  - Positives
    - Newly “minted” – eager to learn and work hard
    - Molded to your clinical experience and knowledge
  - Negatives: well, inexperienced
    - Raw history/examination techniques
    - Lack of seasoned patient interactions
    - Lack of clinical acumen

APC Training Models

Table 1.	Structural Ideas for APC training
Formal Academic Fellowship	Currently, Duke University has the only program, with 2 positions
Externship	Having substantive elective rotation in interested practice to provide training, orientation, and relationship-building before hiring.
Private "Fellowship"	Begins with organizing a national network of experienced rheumatology APCs. These APCs train new candidates for 3-6 months within the context of their practices and assist in placement after the period of training. Support is solicited from the ACR's grant program and/or from industry. Grants of $50K are split between economic support of the trainee and the training practice and its APC.
Organic Growth	Practice rheumatologist(s) makes the investment of time and risk to train first APC. Established practice APC(s) train new APCs on the job and receive incentivizing training compensation.

PRA/AARA APC Symposium May 2018 outcome potential models. P. Caldron

APC Educational Conferences

- The Training Rheum (https://www.aapa.org/events/training-rheum)
  - 2.5 day course designed to give a firm foundation for PAs and NPs entering rheumatology
  - The Association of Rheumatology Professionals (ARP) and the American Academy of Physician Assistants (AAPA)
- Phoenix Rheumatology Association Strategic Training for Advanced Practice Clinicians (https://meetings.association-service.org/pra/strapc/info)
  - 1.5 day course for potential, new and experienced APCs in rheumatology
- Rheumatology Nurses Society (RNS) Annual Conference
  - https://rnsnurse.org/events/2020-13th-annual-rns-conference/

Arizona Arthritis & Rheumatology Associates (AARA): Model for Rheumatologist/APC Teams in Rheumatology Practice

Arizona Arthritis & Rheumatology Associates

- Private single-specialty rheumatology practice
- 8 office locations throughout Arizona
  - 6 Phoenix, 1 Tucson, 1 Flagstaff
- Clinicians
  - 15 Rheumatologists
  - 26 APCs
    - 9 PAs and 10 NPs
  - One Podiatrist
  - One Electrophysiologist

Arizona Arthritis & Rheumatology Associates

- Team Approach
  - Rheumatologist
  - APC(s)
  - Administrative Medical Assistant

AARA Clinical Team Organization

- Rheumatologist is lead
- APCs: 1-2
- Administrative medical assistant (Admin MA) who fields all messages and documents
- Admin MA: answers those messages and documents of which they are trained in their scope
- Forwards the others to the APCs - the majority of which they can field
- Only the remaining are fielded to the rheumatologist
- Everyone works at the top of their license

AARA Training of APCs: A Methodology

- Introduction to Rheumatology Course
  - Personalized review one-on-one with APC
  - AARA practice generated online curriculum
    - Disease specific and topic specific slide sets generated from our STRAP conferences
    - Reading curriculum
    - ACR High Impact Rheumatology
    - ACR Rheum2Learn
- Shadowing the rheumatologist and other APCs
  - eight to twelve weeks – new and returning patients
  - demonstrating rheumatology history and physical exam
  - teaching rheumatology data assimilation and problem organization
  - one-on-one teaching of EHR utilization

Training of APCs: A Methodology

- Honing the history and physical exam processes
- Initiating the rheumatologic work-up process
  - laboratory, imaging
- Solidifying treatment paradigms
  - medical and physical
- Procedures
  - injections
  - interventional ultrasound

Rheumatology APC Education

- Education is Vital
  - Maintain Certification and Licensing
  - Stay up-to-date
- Foundation is Integral to Retention
  - Confidence = mini-rheum
- AARA APC curriculum
  - Presentations, Articles, Websites, Textbooks
  - Diagnostic Criteria and Management
  - Beginner to Advanced
  - ACR’s Certification Course for APCs

Online Course

Advanced Rheumatology Course

Date:
01/01/2019

Location:
Online

Program Information

The Advanced Rheumatology Course is a comprehensive, innovative online course designed to expand the knowledge and practical skills of providers in rheumatology practice, academic training, and primary care.

Includes the following:

- Pre-assignment challenge questions
- Audio presentation, PowerPoint slides, and clinical pearls
- Post-test assessment* and activity evaluation

**CME credits are not offered at this time, but you can request a certificate of completion.*

Target Audience

The course was created for rheumatology fellows-in-training, primary care providers, nurse practitioners, physician assistants, primary care physicians/internists, residents, or providers new to rheumatology.

APCs: Oversight and Supervision

- State regulatory driven
  - Number of PAs set by state (AZ - ≤ 4: NPs are independent)
  - AARA physicians utilize 1-3: some full, some part-time
- Staffing patient encounters: new and return
- Co-signing of notes reviewed
- Documentation is critical
- Real supervision is essential
  - Atmosphere of encouragement for APCs to bring questions and patient issues for review

APCs: Delegation of Responsibilities

- Seeing new patients
  - new patient encounters: history and physical exams
  - staffing new patients to rheumatologist for review
  - work-up and treatment plan developed
  - completing note
- Seeing return patients
  - return patient encounters without staffing
  - reviewing case with rheumatologist: may elect to see patient or not
  - follow-up lab, imaging, treatment plans
  - completing note

APCs: Delegation of Responsibilities

- Screen messages
- Review labs, images
- Review incoming records, from outside physicians:
  - Labs, imaging, consult notes
- Patient teaching
- Completing miscellaneous tasks
  - Ordering meds, labs, imaging outside of regular visits for cause
  - Prescribing meds
  - FMLA, disability, and insurance forms: assist with Admin MA
  - Telephone contacts with other professionals, lab, imaging centers
- Research: serve as sub-PIs to do assessments e.g. joint counts (independent assessor)

Billing by APCs

- Incident to Billing
  - Per Medicare guidelines, can bill under physician NPI number if physician present in office for maintenance treatment
    - New problems/treatments, direct physician involvement required
    - Each APC has their own NPI number for billing if CMS requirements can not be met
- In a state of flux per CMS

APCs: Compensation and Benefits

- Annual Salary – negotiated with respective physician
- Base and bonus Model:
  - 25% over threshold of revenue
- Relative Value Unit Model
  - Base RVU of 4400 units
  - $$ per RVU over base
- Costs for maintaining certificate/licensure
- Malpractice insurance (e.g. on doctor's policy vs independent)

APCs: Compensation and Benefits

- Health, 401k, life, disability
- CME
  - CME allowance and paid days
  - Essential to maintain environment of ongoing education in daily practice; requirement for licensure maintenance

APCs: Financial Benefit for the Practice

- Augment amount of revenue for practice
  - Via E&M and ancillary derived income
  - Increase corporate revenue for enhanced cost-sharing of overhead (after APC earnings covered)
  - Increase in overall corporate income after all expenses
- Increased revenue for rheumatologist
  - After all expenses met, monies fall to bottom line of rheumatologist

APCs: Potential Downsides

- Potential adverse patient decisions
  - Poor care decisions
  - Improper documentation issues
  - Potential negative patient interactions
  - Medical-legal ramifications
- Poor acceptance by patients
- Poor acceptance by referring physicians
  - Regional differences: west vs east (less accepting)

APCs: Potential Downsides

- Increased effort and attention to the supervision required
- Retention paramount
  - Losing an APC equates virtually as to losing a rheumatologist from the practice
- Balance of benefit to risk
- Potential replacement of rheumatologists in healthcare systems by APCs for financial benefit
- Not all rheumatologists are able to assume the role and responsibilities of to bring on an APC and train and supervise appropriately

JT: Personal Experience With APCs

- Trained now 10 APCs in two different practices
- Previously all PAs: two new DNPs
- Sustainability of 3 PAs in my history
- Bringing 3 from previous to new practice (AARA) 2004
- All 3 tried sharing with other rheumatologists in AARA but over time migrated to returning to me
- AAPA: 2014 Paragon Partnership Award

AARA APC Workforce Study 2018

- Positives include rheumatology complexity affords continuous diversity for puzzle solving
- Seeing often dramatic results of therapeutic successes
- Long term patient relationships

APCs concerns:
AARA Workforce Study 2018

- Competency and confidence
  - Complexity of diseases: presentation and physical findings
  - Ambiguity of laboratory findings and treatments
  - Requires ongoing education by hands-on identification of physical findings and highly developed skills of taking a history
  - On the fly patient specific disease and treatment discussions
  - Didactic discussions: 5-15 minutes to elucidate key concepts
- Respect as clinician: work at the top of their license
- Financial security and reward
- Need to be listened to

APCs Concerns: AARA Workforce Study 2018

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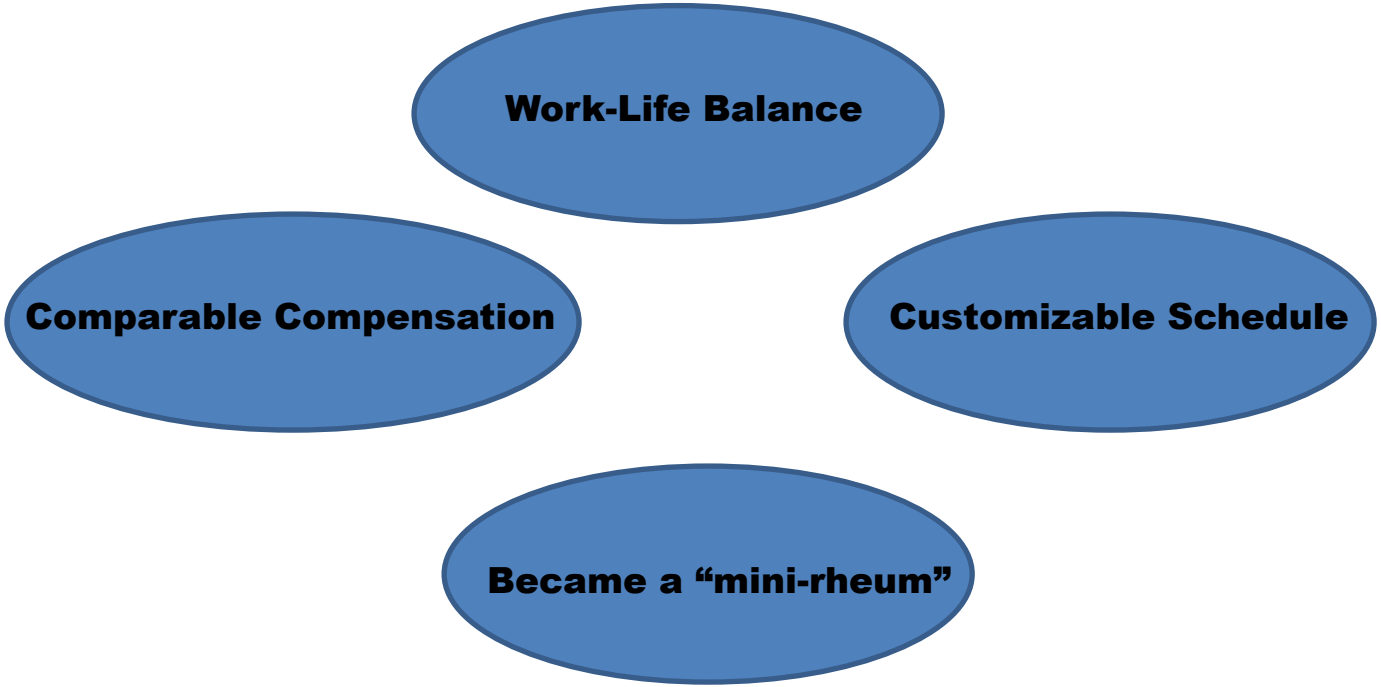
  - Didactic discussions: 5-15 minutes to elucidate key concepts
- Respect as clinician: work at the top of their license
- Financial security and reward
- Need to be listened to

Organizations With Interest in Furthering APC Development

- Phoenix Rheumatology Association
- Association of Women in Rheumatology
- Rheumatology Nurses Society
- Duke University Physician Assistant Rheumatology Fellowship Program
- American College of Rheumatology
  - Advanced Rheumatology Course
  - eBytes
  - ACR, ARP, AAPA: summer meeting for foundational instruction 2019
- Great Healthcare Value: The RAPP project

Arizona Arthritis & Rheumatology Associates



Summary: APCs in Rheumatologic Practice

Risk/benefit reward is absolutely worth it

"A strong, experienced APC is like having an excellent senior fellow that never leaves.": Paul Caldron DO, PhD, FACP, FACR, MBA

Behçet Syndrome: A 2020 Update

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Disclosures

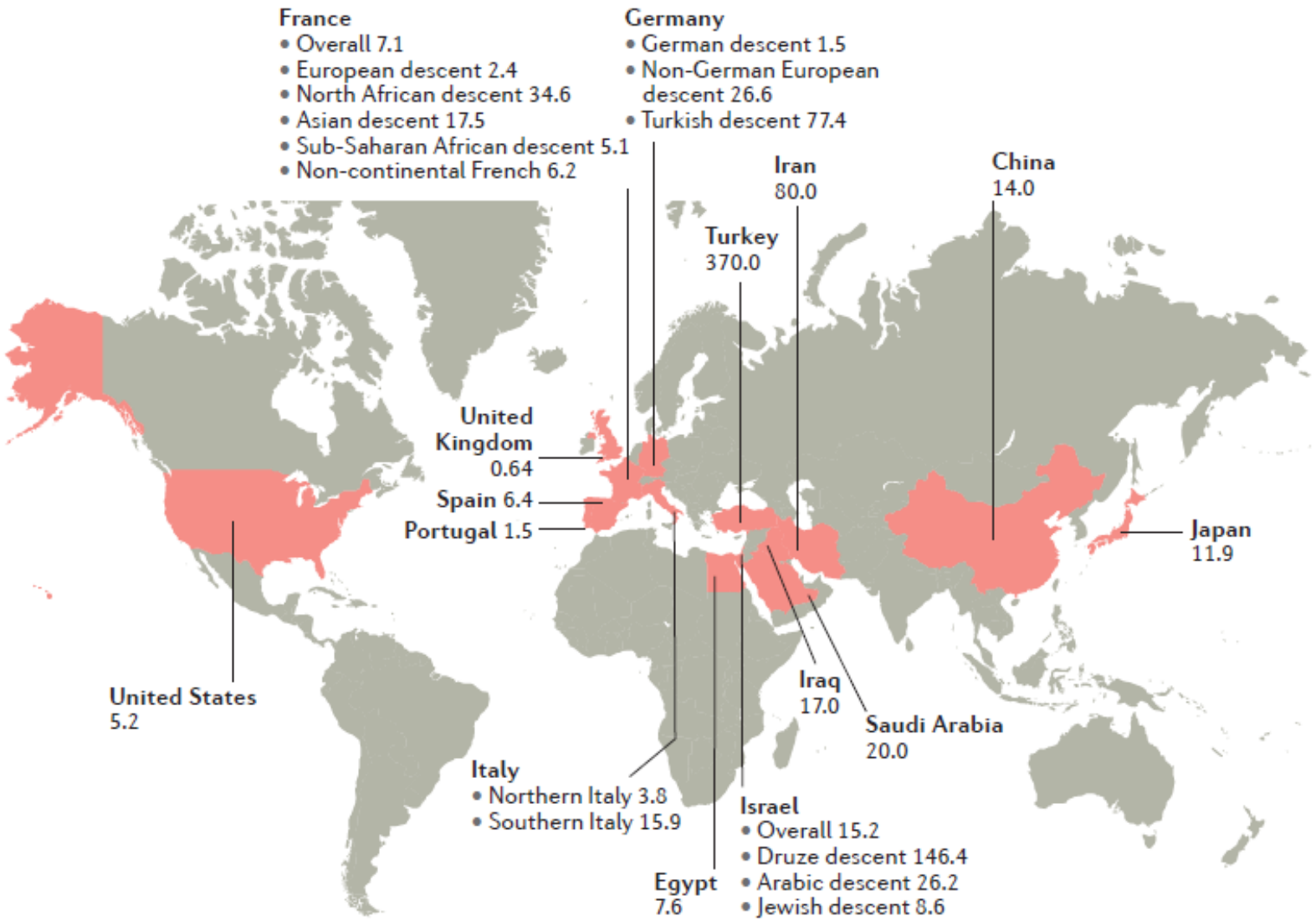
- Celgene/Amgen – Consultant, research support
- Sanofi – Consultant
- BMS – Research support
- Genentech – Research support
- Samumed – Chief medical officer

History

- Dr Hulusi Behcet (1889-1948)
- 3 patients, over 17 years
  - aphthous mouth ulcers
  - genital ulceration
  - hypopyon uveitis
- “triple symptom complex”
- 1937-Dermatologische Wochenschrift
- Prof. Mischner first proposed “Morbus Behcet” at a congress in Geneva (1947)

Demographics

- Mediterranean basin, Korea, Japan
  - Silk road?
- Rare < puberty, > 50 yr
- Usual onset 20s
- Male=female
  - Worse disease in males



Yazici H, et al. Nature Rev Rheum 2018

Diagnosis

ISG Criteria for the Diagnosis of Behçet Syndrome

Oral ulcers (100%)

+

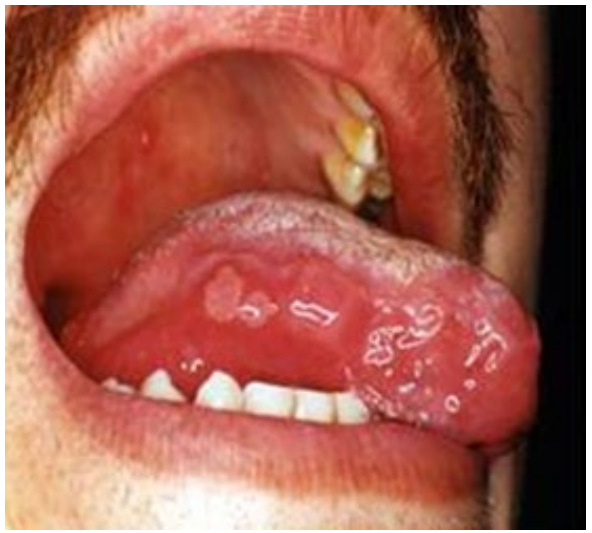
2/4 of the following:

Genital ulcers (80%)

Skin lesions (80%)

Eye lesions (50%)

Pathergy (50%)



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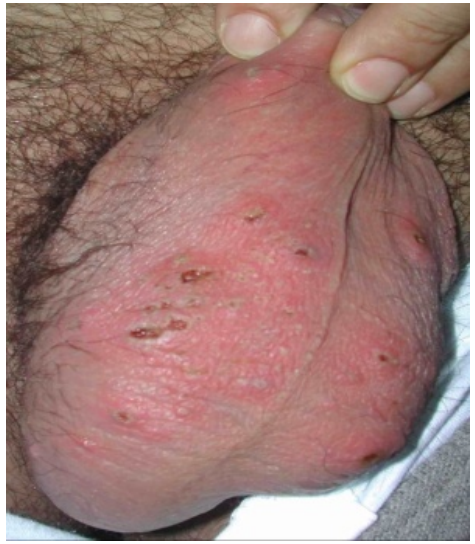
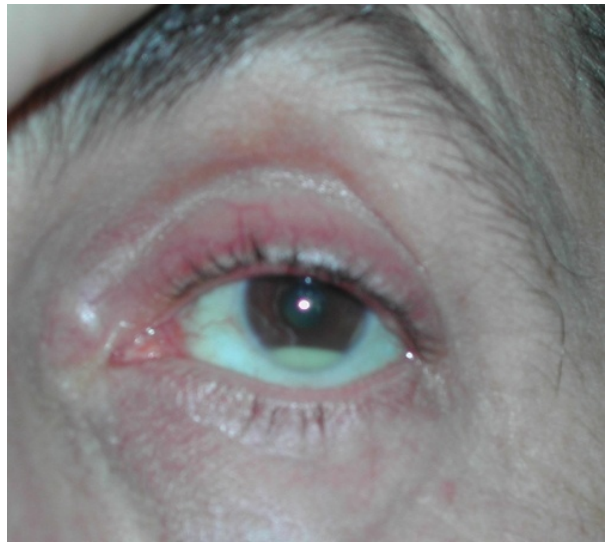
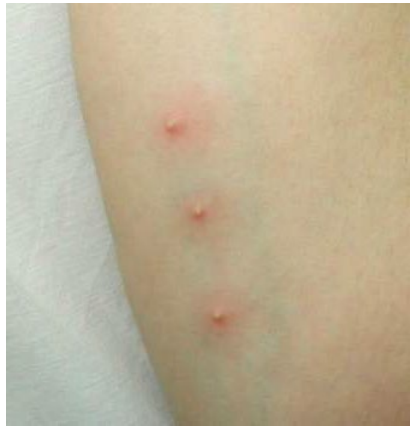
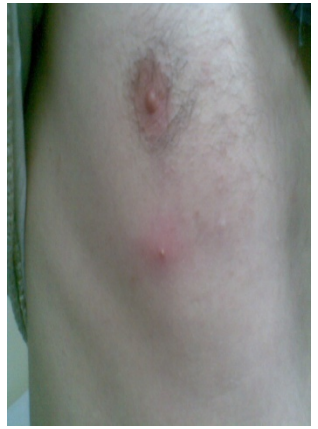
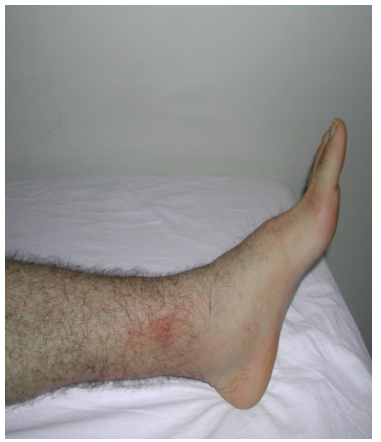










Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 1990

ISG criteria 1990		Japanese criteria 2003	
Mandatory component	Oral ulcer	Major symptoms	Oral ulcer
Plus 2 of following	Genital ulcer		Genital ulcer
	Skin lesion		Skin lesion
	Ocular lesion		Ocular lesion
	Positive pathergy test		
		Minor Symptoms	Arthritis
			Epididymitis
			GI lesion
			Vascular lesion
			CNS lesion
		Complete type:	4 major symptoms
		Incomplete type:	- 3 major - 2major + 2 minor - Ocular + 1major - Ocular + 2 minor

Kobayashi T, et al. Mod Rheumatol. 2013

International Criteria for Behcet's Disease (ICBD)

Table 5. International Criteria for Behçet's Disease – point score system: scoring ≥4 indicates Behçet's diagnosis

Sign/symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test [a]	1 [a]

a Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result.

Davatchi F, et al. J Eur A Derm Ven 2013

International Criteria for Behcet's Disease (ICBD)

Table 4 Sensitivity and specificity of various criteria in training and validation sets

Criteria*	Training				Validation			
	Sensitivity (*N* = 1278)		Specificity (*N* = 582)		Sensitivity (*N* = 1278)		Specificity (*N* = 581)	
	n	95% CI †	*n*	95% CI	*n*	95% CI	*n*	95% CI
Curth[10]	1255	98% (97–99)	486	84% (80–86)	1265	99% (98–99)	475	82% (78–85)
Mason/Barnes[11]	1046	82% (80–84)	554	95% (93–97)	1046	82% (80–84)	554	95% (93–97)
Hewitt revised[12]	755	59% (56–62)	558	96% (94–97)	731	57% (54–60)	555	96% (94–97)
Japan (original)[13]	1089	85% (83–87)	539	93% (90–95)	1125	88% (86–90)	536	92% (90–94)
Hubault and Hamza[14]	701	55% (52–58)	566	97% (96–98)	741	58% (55–61)	562	97% (95–98)
O'Duffy[15]	1115	87% (85–89)	534	92% (89–94)	1123	88% (86–90)	523	90% (87–92)
Cheng and Zhang[16]	1232	97% (95–97)	505	87% (84–89)	1249	98% (97–98)	484	83% (80–86)
Dilsen (original)[17]	1094	86% (84–87)	527	91% (88–93)	1130	88% (87–90)	527	91% (88–93)
Japan (revised)[18]	1125	88% (86–90)	533	92% (89–93)	1160	91% (89–92)	527	91% (88–93)
ISG[8]	1038	81% (79–83)	558	96% (94–97)	1086	85% (83–87)	558	96% (94–97)
Iran traditional[19]	1119	88% (86–89)	537	92% (90–94)	1149	90% (88–92)	536	92% (90–94)
Iran Classification Tree[20]	1199	94% (92–95)	528	91% (88–93)	1223	96% (94–97)	522	90% (87–92)
Dilsen (revised)[21]	1057	83% (81–85)	556	96% (94–97)	1106	87% (85–88)	557	96% (94–97)
Korea[22]	1139	89% (87–91)	542	93% (91–95)	1179	92% (91–94)	536	92% (90–94)
ICBD‡	1200	94%	536	92%	1211	95% (93–96)	526	91 (88–93)

*For those criteria that use the pathergy test result this was assumed negative for the patients who did not have the test for the purposes of creating this table.

†CI: confidence interval.

‡ICBD: International Criteria for Behçet's Disease.

Davatchi F, et al. J Eur A Derm Ven 2013

Sensitivity vs Specificity

- UK, 281 BS in Birmingham Centre of Excellence for Behçet's disease
- 281 pt between 2012-2015
  - 190 were diagnosed as BS
  - 7 as incomplete BS
  - 84 as not having BS
- Sensitivity
  - ICBD criteria (97.9%, 95%CI: 94.7–99.4) vs ISG criteria (77.9%, 95%CI: 71.3–83.6)
- Specificity
  - ICBD (19.1%, 95%CI: 11.3–29.1) vs ISG criteria (69.1%, 95%CI: 58.0–78.7)
- Use of ICBD criteria may result in overdiagnosis of BS in the UK population.

Blake T et al. BMC Musculoskelet Disord 2017; 18: 101

Utility of the new rheumatoid arthritis 2010 ACR/EULAR classification criteria in routine clinical care

Lauren Kennish,[1] Monalyn Labitigan,[2] Sam Budoff,[3] Maria T Filopoulos,[1]
W Andrew McCracken,[4] Christopher J Swearingen,[4] Yusuf Yazici[1]

Figure 1: % Patients Fulfilling 2010 ACR/EULAR RA Criteria By Diagnosis. OA: Osteoarthritis, SS: Sjogren's Syndrome, SpA: Spondyloarthritis

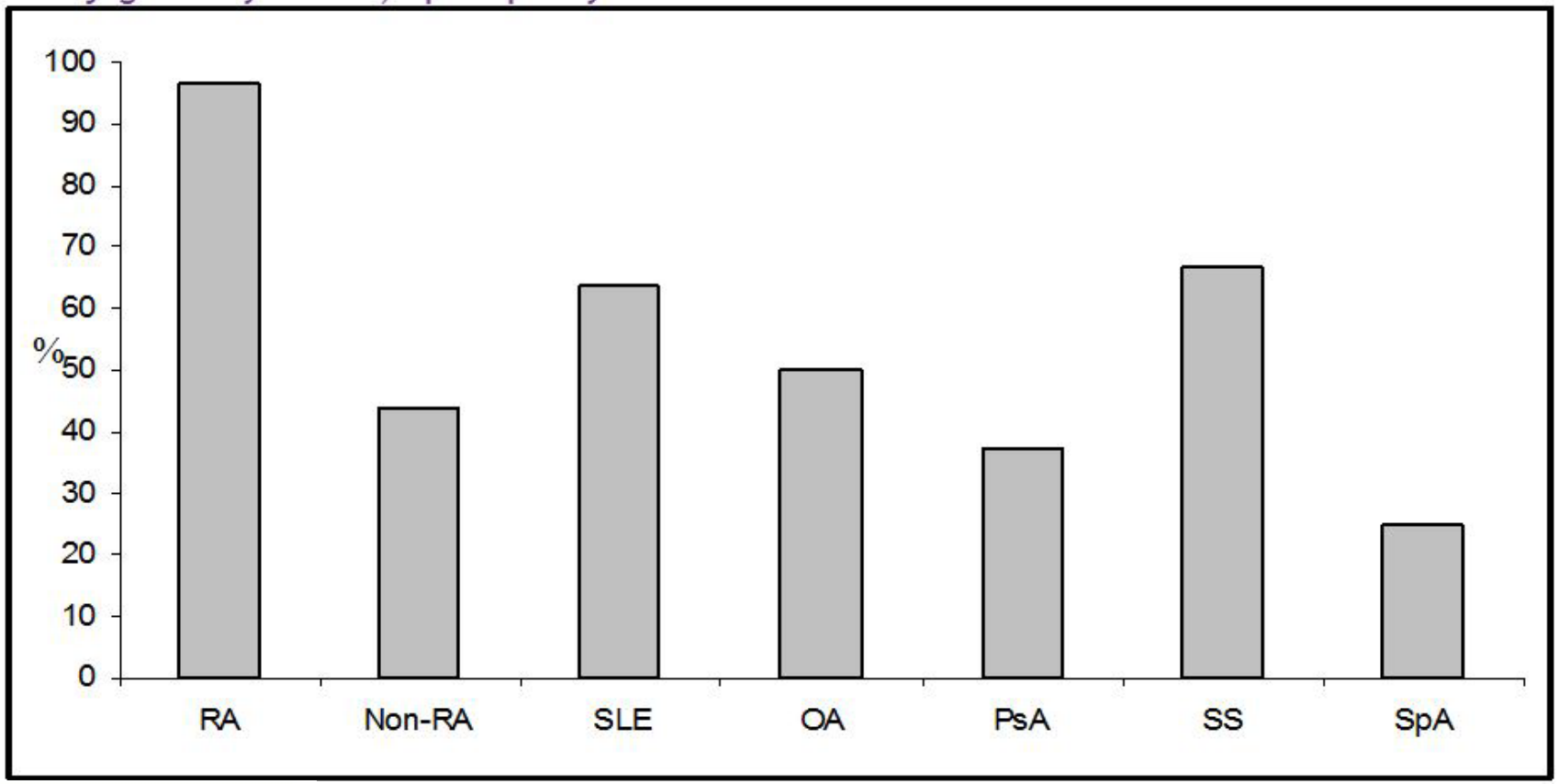


Table 2 Comparison of sensitivity and specificity of 2010 vs 1987 rheumatoid arthritis criteria

	2010 Criteria	1987 Criteria
Sensitivity (%)	97	93
Specificity (%)	55	76
Positive predictive value (%)	44	61
Negative predictive value (%)	98	97

Kennish L, et al. BMJ Open 2012

2010 ACR/EULAR criteria

Table 2 Results of studies testing the performance of the 2010 ACR/EULAR criteria for RA

	van der Linden *et al*[9]		**Cader** *et al*[10]		**Britsemer** *et al*[21]		**Alves** *et al*[12]		**De Hair** *et al*[11]		**Kaneko** *et al*[22]		**Varache** *et al*[23]	
N	2258		265		455		231		301		82		270	
Outcome	DMARD use year 1; MTX use year 1; persistency of arthritis 5 years		DMARD use; MTX use 1.5 year		MTX use year 1; expert opinion; erosiveness		MTX use year 1; persistency of arthritis year 1		1987 ACR positive year 2		Diagnosis rheumatologist		Diagnosis rheumatologist after 2 years	
Mean or median symptom duration at study entry	25.9 Weeks		42 Days		5.5 Months		np		3 Months		18 Weeks		np	
	2010	1987	2010	1987	2010	1987	2010	1987	2010	1987	2010	1987	2010	1987
Sensitivity	74	54	62	38	85	76	74	np	83	np	74	47	58	64
Specificity	74	87	78	93	50	59	66	np	76	np	71	93	86	80
PPV	84	89	75	85	86	87	76	np	77	np	93	97	71	65
NPV	60	50	66	59	49	41	63	np	91	np	36	27	78	79
AUC	0.74	0.71	np	np	0.78	0.71	0.79	np	np	np	np	np	0.83	0.81

Van der Helm-van Mil AHM, Huizinga TWJ. Ann Rheum Dis 2012

Differential Diagnosis

Evidence for autoimmunity in Behcet Syndrome?

Uncommon/not seen in Behcet:

- Sjögren's syndrome
- Association with other autoimmune diseases
- Raynaud's phenomenon
- Polyserositis
- Hemolytic anemia
- Sun sensitivity
- No autoantibodies

Unique to Behcet:

- Pathergy
- Genital ulcers – *scrotal*
- Pulmonary artery aneurysms
- Clinical course

Differential diagnosis

- Sacroiliitis and spinal joint involvement are not features of BS
- Skin lesions do not include psoriasis
- Urethral discharge is not a feature of BS
- GI involvement with ileocaecal ulceration and sometimes colonic perforation is distinct from typical IBD

Disease course in Behcet Syndrome

- Disease burden decreases with the passage of time
- Occurrence of all manifestations decrease in frequency, except:
  - CNS disease
  - Major vascular pathology.
- Disease course unlike RA and SLE
- Biological meaning unclear

Autoinflammatory?
(FMF as the prototype)

- Epidemiology
  - Mediterranean vs. Japan
  - Rare and almost all defined from the West
  - Children vs adults
- Clinical findings
- Genetic aspects
  - HLA-B51
  - Pyrin
- Response to treatment (colchicine)
- Well defined mutations (TNF-receptor, pyrin or CARD/NOD) and transmission
- Usually a non - abating course

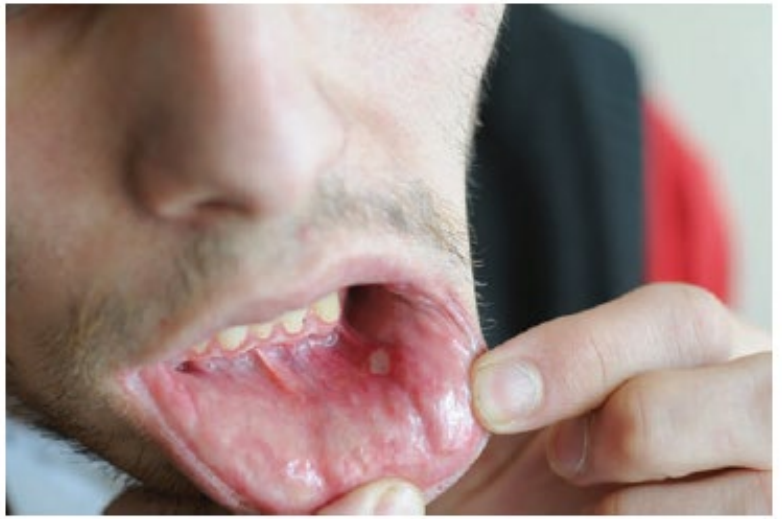
Genetic vs Environmental

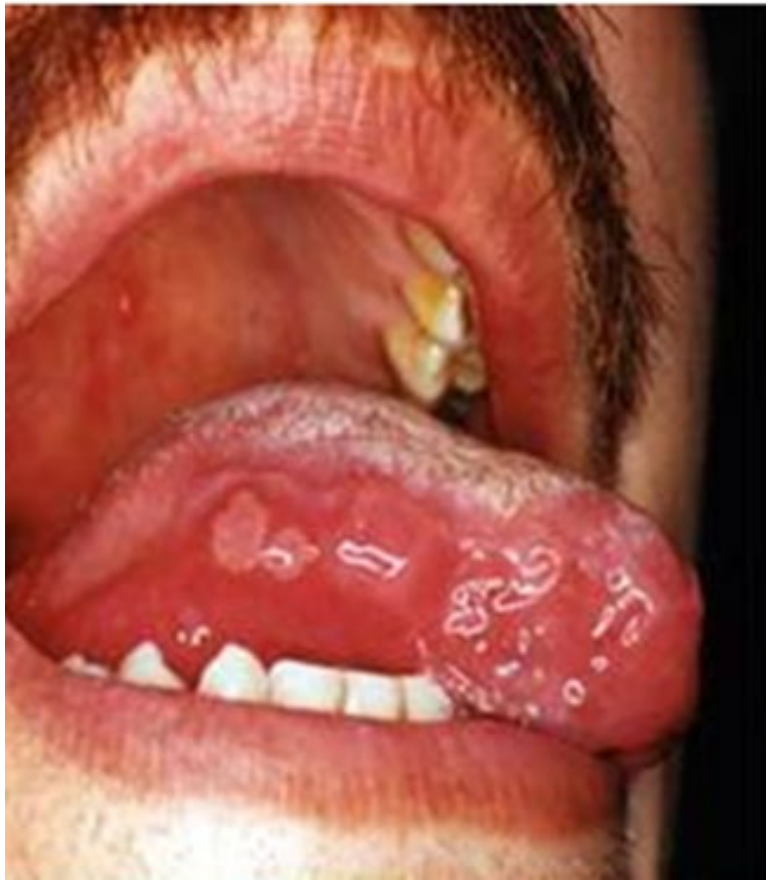
- Japanese living in Hawaii
  - Hirohata et al. Hawaii Med J , 1975
- Turkish immigrants vs Germans in Berlin
  - Papoutsiset NG, et al. Clin Exp Rheumatol 2006
- Arabs/Druzes vs Jews in Israel
  - Krause I, et al. Clin Rheumatol 2007
- North African immigrants vs Europeans in Paris
  - Mahr A, et al. Arthritis Rheum, 2008
- NYU Behcet Center
  - Yazici Y, et al. 2012

Clinical Manifestations

Oral Ulcers

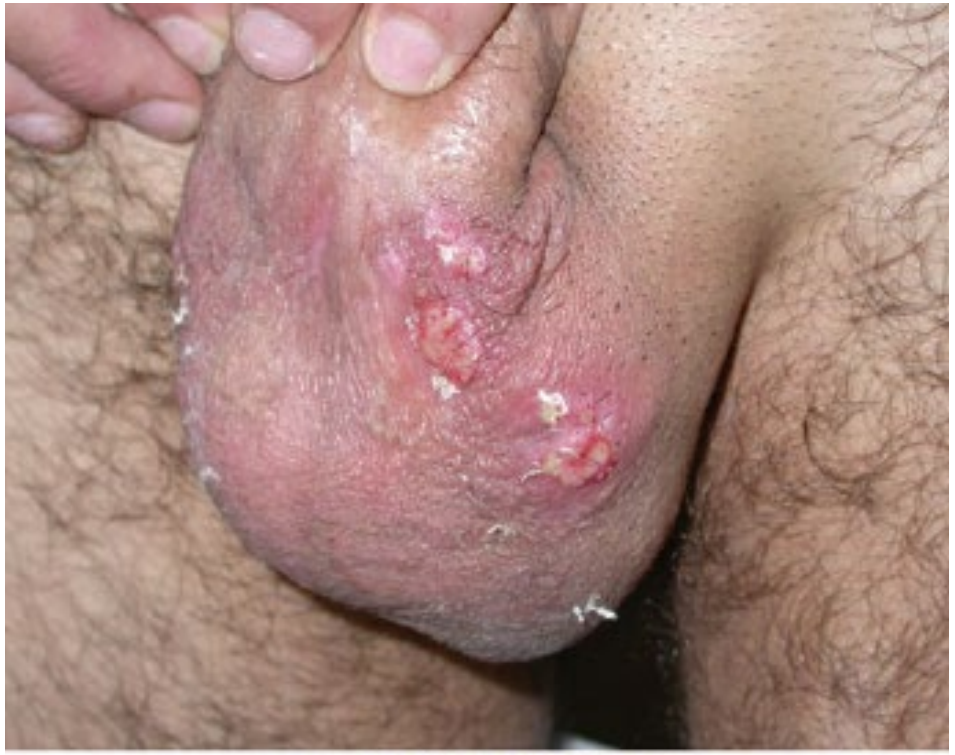
- Virtually all patients, frequently first lesion
- Minor aphthous ulcers are most common
  - Lips, gingiva, cheeks and tongue
  - Unlike herpes, skin covered part of lips not involved
  - Usually heal in 15 days without scarring
  - Some complain of premenstrual activation
- Major ulcers
  - Larger, may scar, lasts longer, less common
- Recurrent aphthous stomatitis (RAS)
  - 20% in population
  - Very rare for RAS to have another clinical finding
  - No HLA B51 association
  - There are no differences among the two ulcers histologically

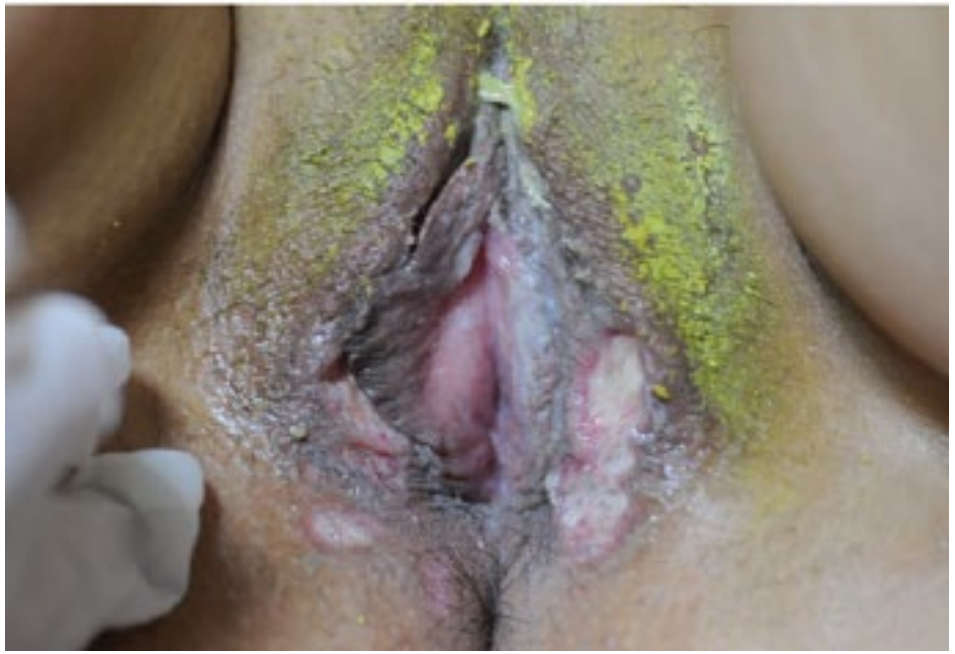




Genital Ulcers

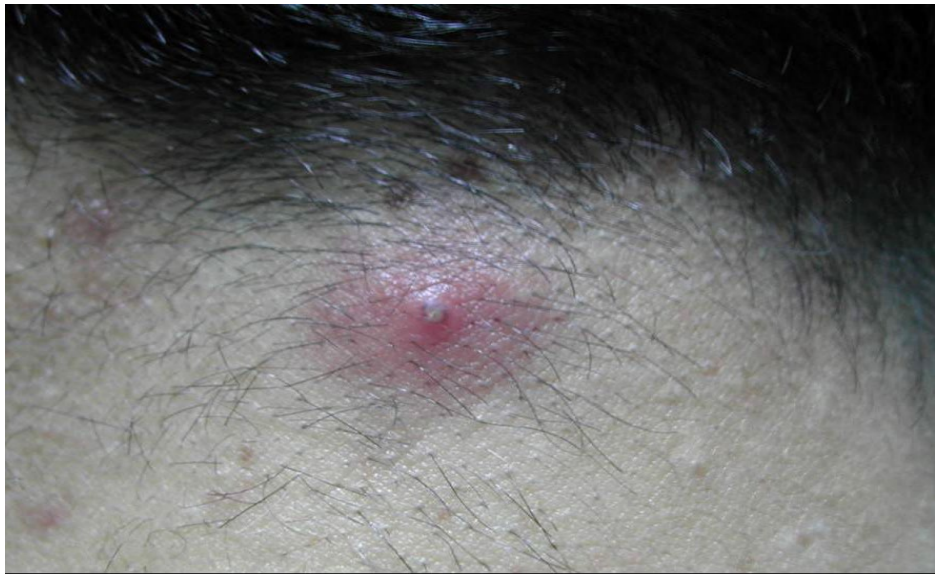
- Papules or pustules that ulcerate quickly
- Punched out appearance
- Aseptic ones heal in 3 weeks, very likely to get secondary infections
- In males usually scrotum is involved, scars, and absence of lesions on glans penis is typical
- All females should have a gynecologic examination, scarring in the right clinical picture is good evidence

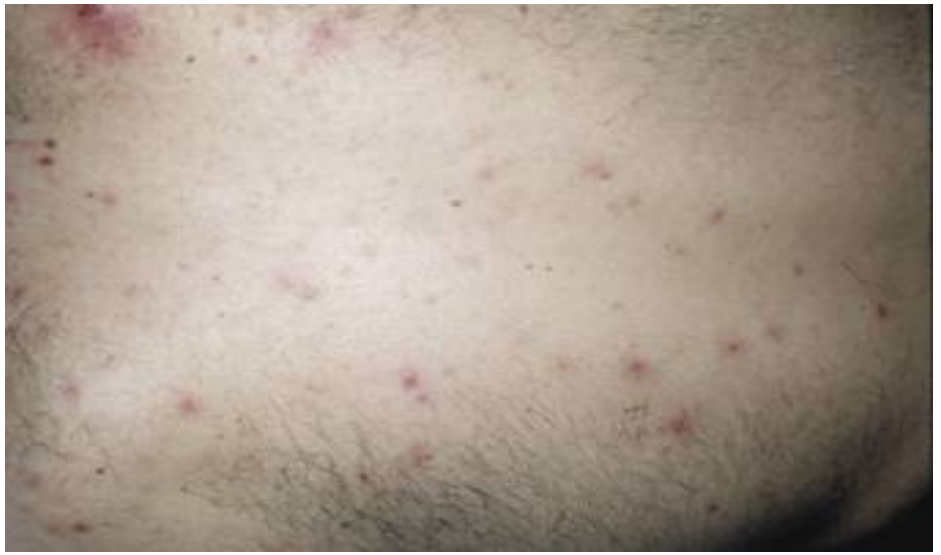




Skin Manifestations

- Papulopustular 85%
  - Acne vulgaris
  - Not teenagers
  - Atypical places
  - Acne is androgen dependent, however, androgen levels are normal
- Increased severity in males?





Acne, Arthritis and Enthesopathy

- Acne scores and arthritis: 44 BS + arthritis, 42 BS - arthritis, 21 RA, 33 HC
  - Acne scores higher in BS + arthritis [1]

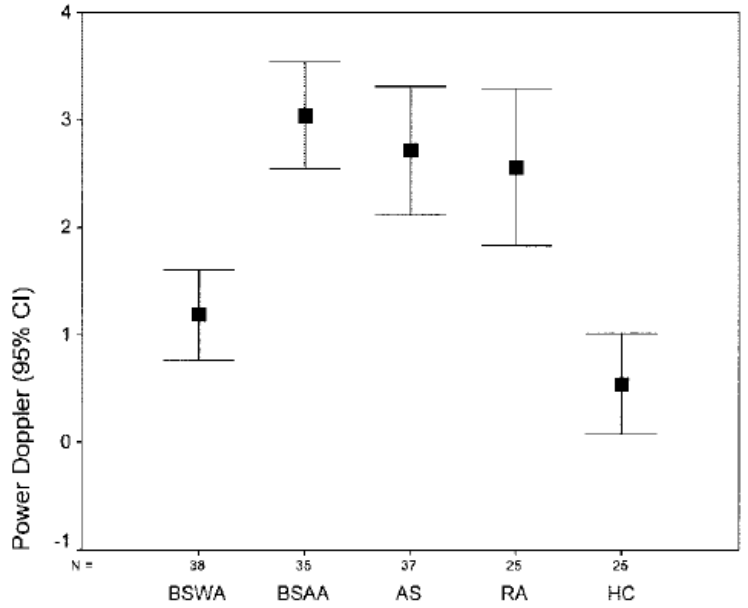
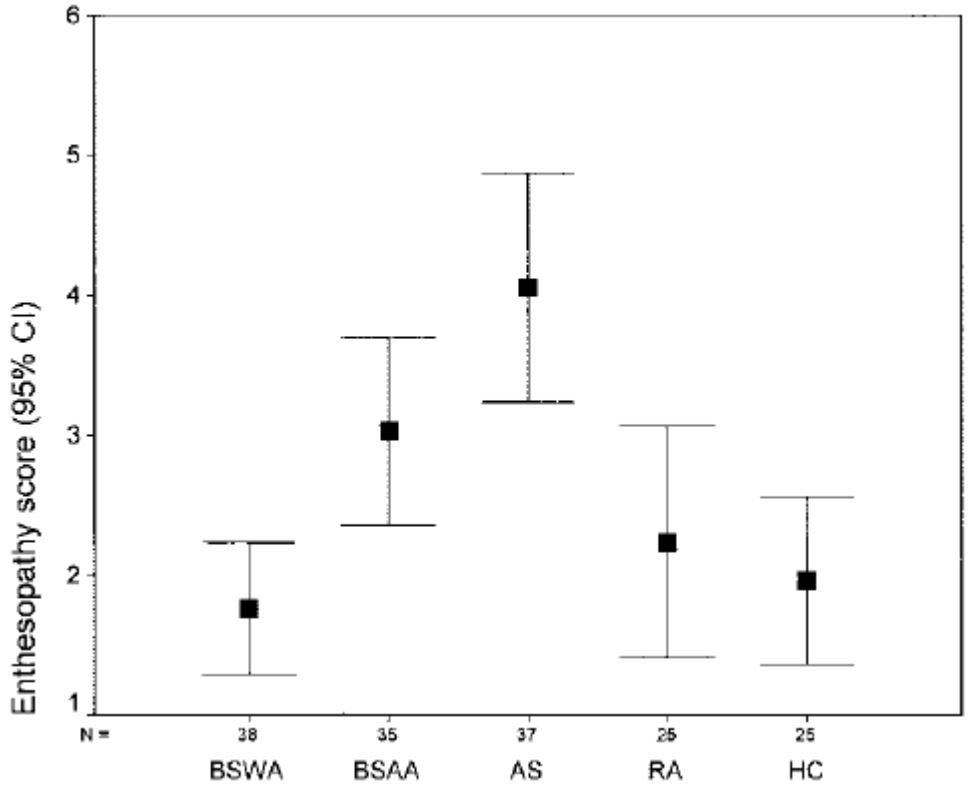


Figure 2. Mean (95% confidence interval [95% CI]) enthesopathy scores and power Doppler scores for each group. BSWA = Behçet's syndrome without arthritis; BSAA = Behçet's syndrome with acne and arthritis; AS = ankylosing spondylitis; RA = rheumatoid arthritis; HC = healthy control.

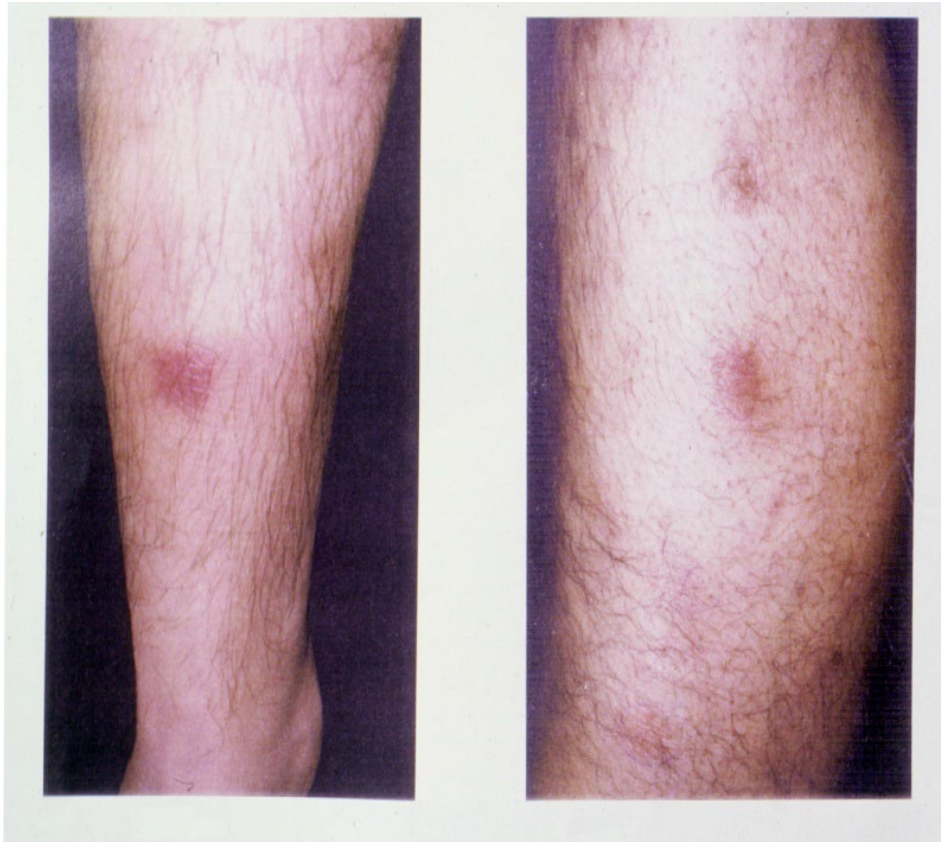
2

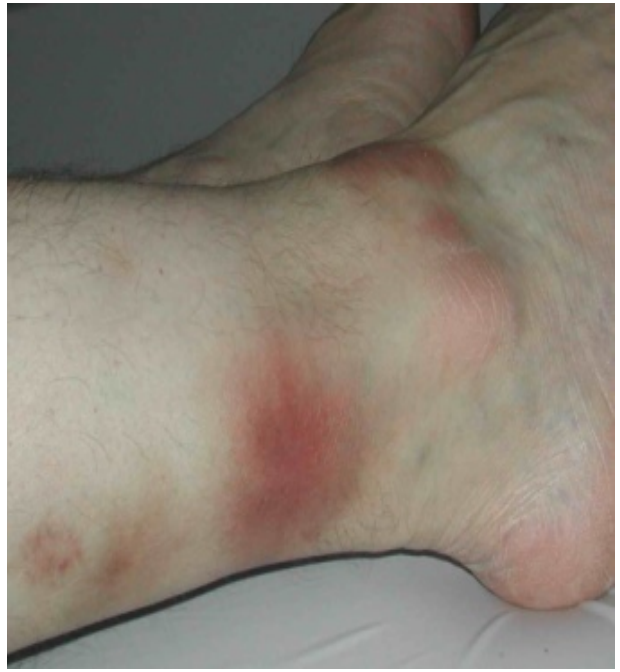


1- Diri, E, et al, Ann Rheum Dis 2001 2- Hatemi G, et al, Arthritis Rheum 2008

Skin Manifestations

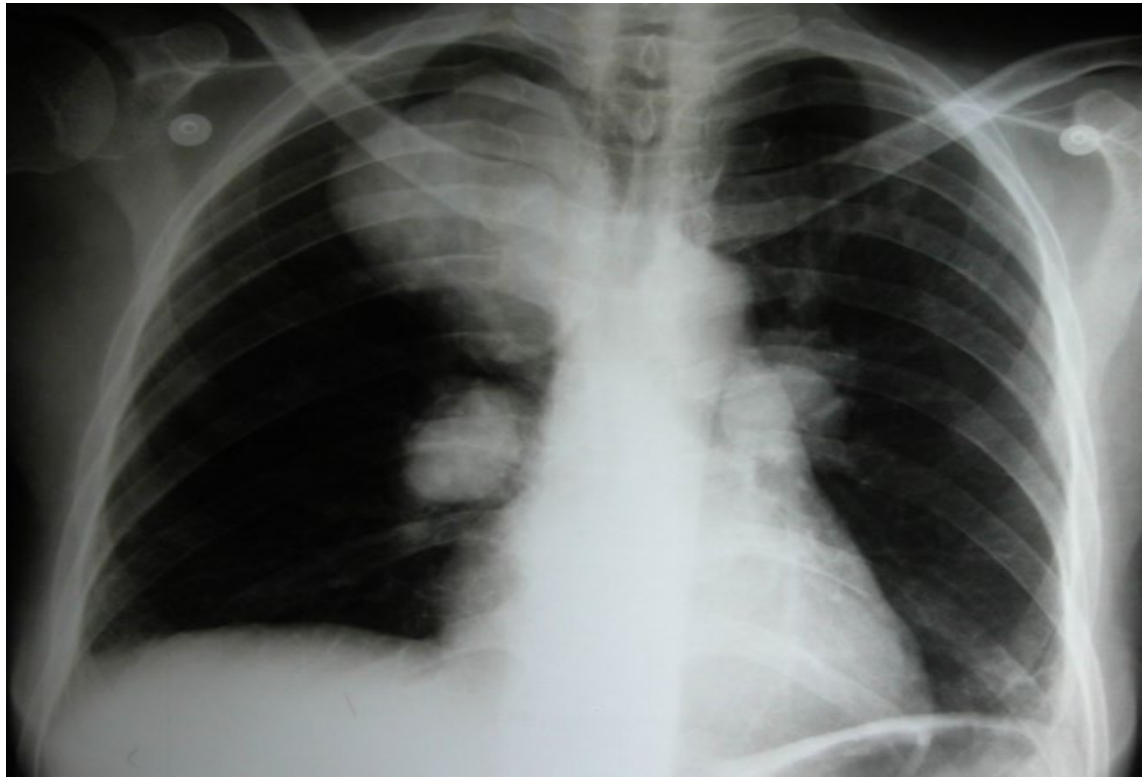
- Nodular lesions 60%
  - 50% EN-like lesions
  - 50% superficial thrombophlebitis
    - associated with major vessel involvement

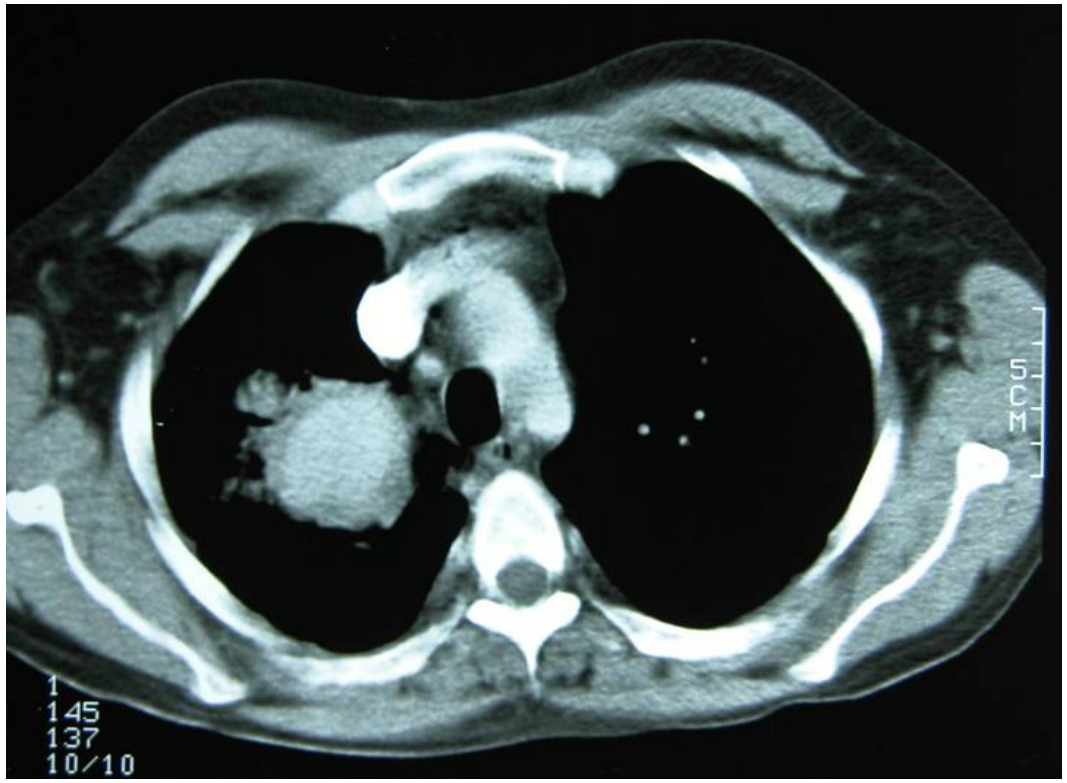




- Difficult to tell one from the other

Pulmonary Artery Aneurysms

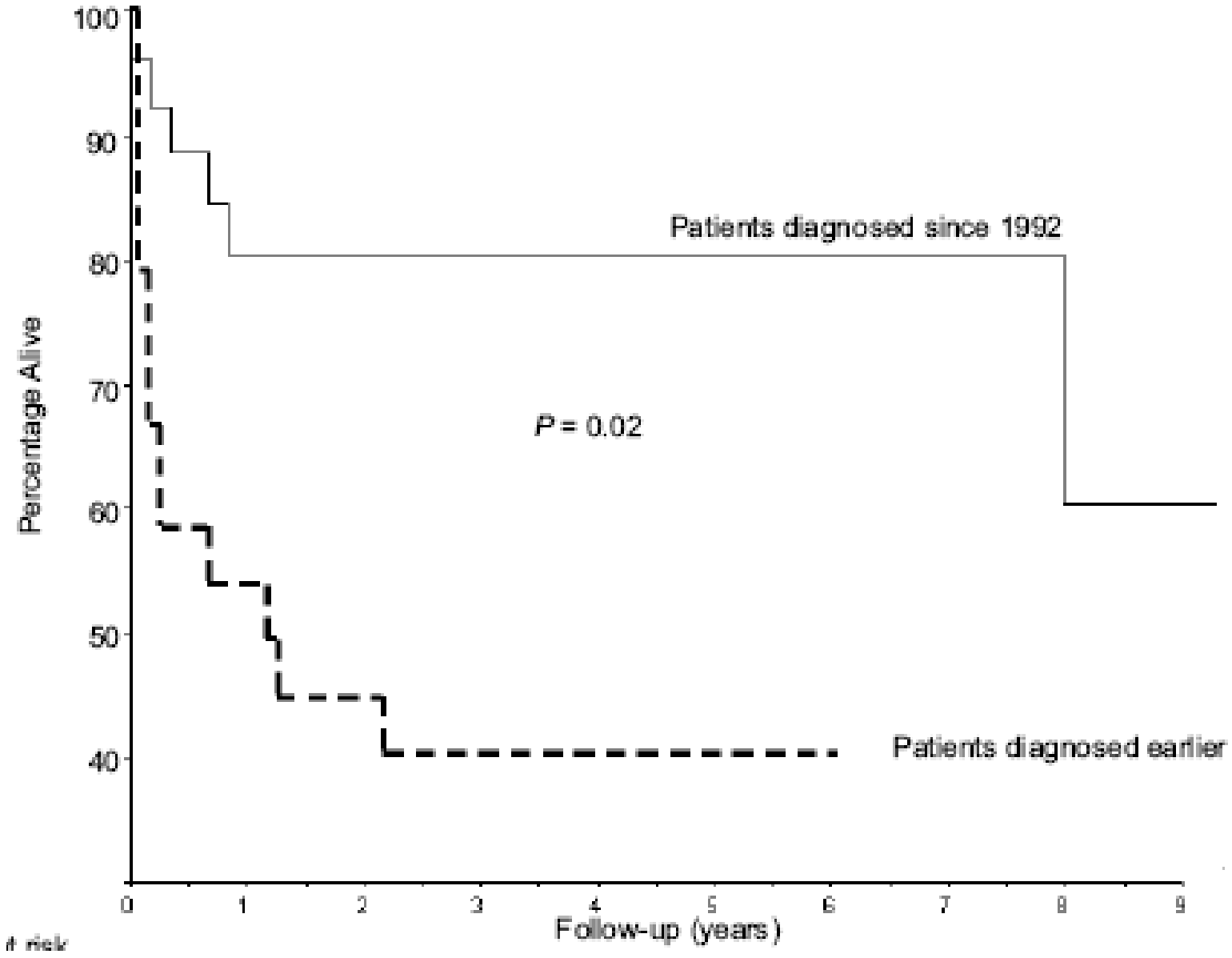




- Unique to BS
- Dx postmortem until 1980s
  - Most common arterial complication today
- Strongly associated with venous thrombosis
- Large proximal branches of PA

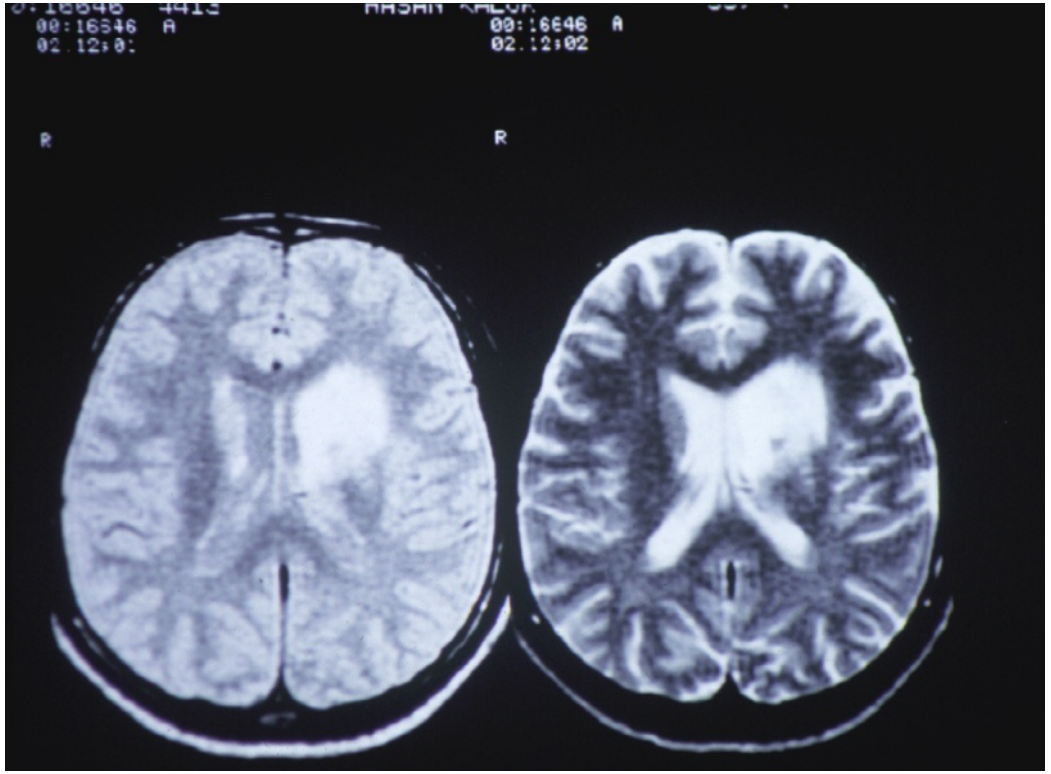
Mortality in PAA

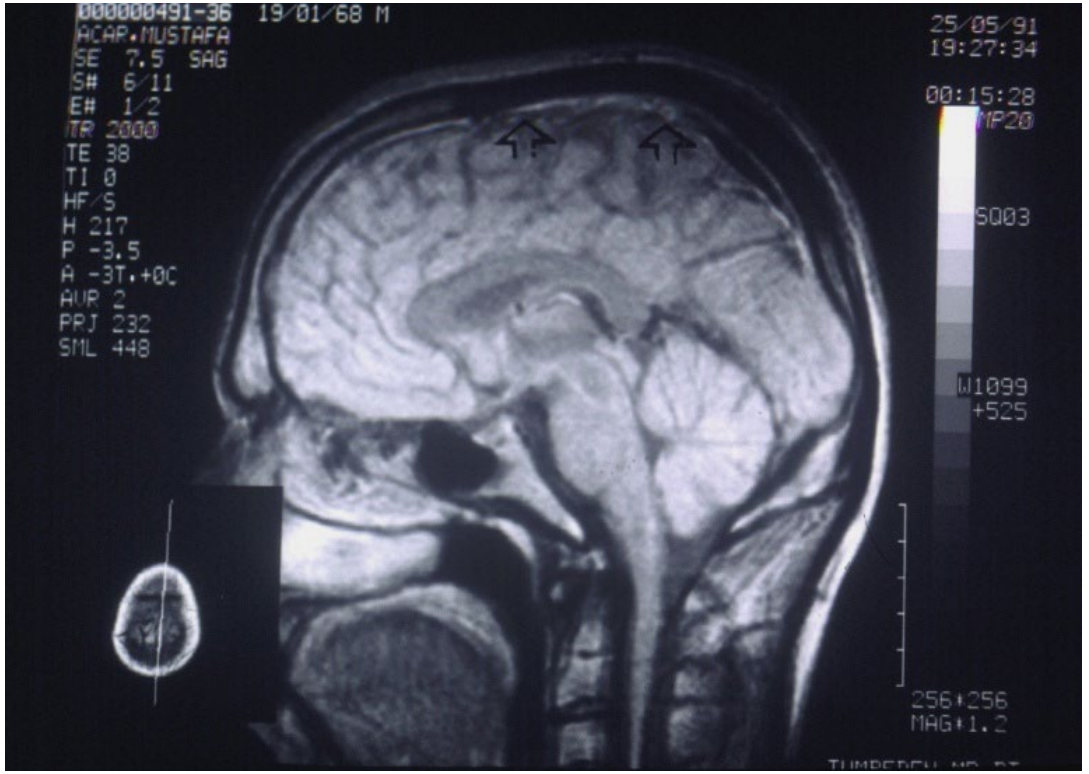
- Survival rate 62% at 5 yr
- 70% deaths 1 yr after PAA



Hamuryudan V, et al Am J Med 2004

CNS Involvement



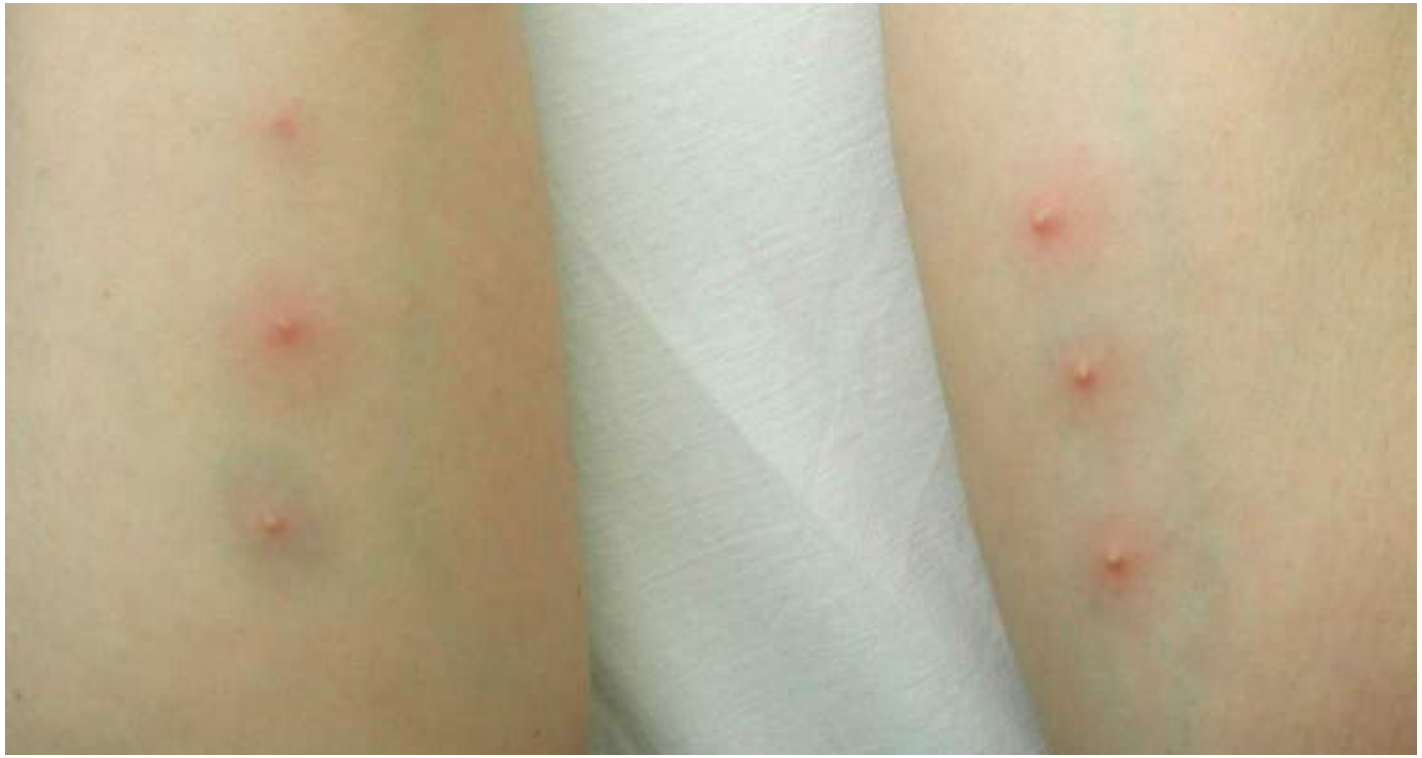


- ~ 4 % in prospective, cross-sectional studies, ~ 10 % in longer follow-up.
- Peripheral neuropathy is distinctly rare.
- CNS involvement has two distinct forms:
    - A. Parenchymal disease (80%, bad prognosis)
    - B. Dural sinus thrombi (20%, favourable prognosis)

  - A and B rarely co-exist

Pathergy Reaction

- Non-specific hyperreactivity to minor trauma
- Pyoderma gangrenosum
- Standard technique
  - 20 gauge needle
  - Papule or pustule in 48 hours
  - Induration required
  - More common in Middle East
- PPD is not augmented in BS



Hatemi G et al. Rheumatology 2008

BS or Crohn's ?

	BS (%)	Crohn's (%)
Oral ulcers	100	10
Nodular lesions	50	2-10
Pyoderma gangrenosum	<1	1-10
Rectal, anal disease	<1	10-15
Perforation	25-50	2
Fistula	5-10	20-30
Stricture	8	17
Granulomas	<1	10-15
ASCA	28-49	62-41

Cheon JH, et al. Behcet's Syndrome, Ed: Yazici Y, Yazici H, Springer 2010

Eye Disease

- Most serious when considering frequency and morbidity

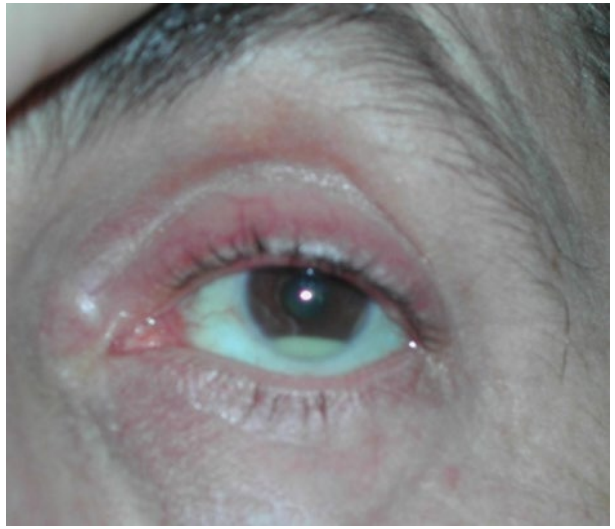
- Leading cause of non-traumatic blindness after DM in Japan, Israel

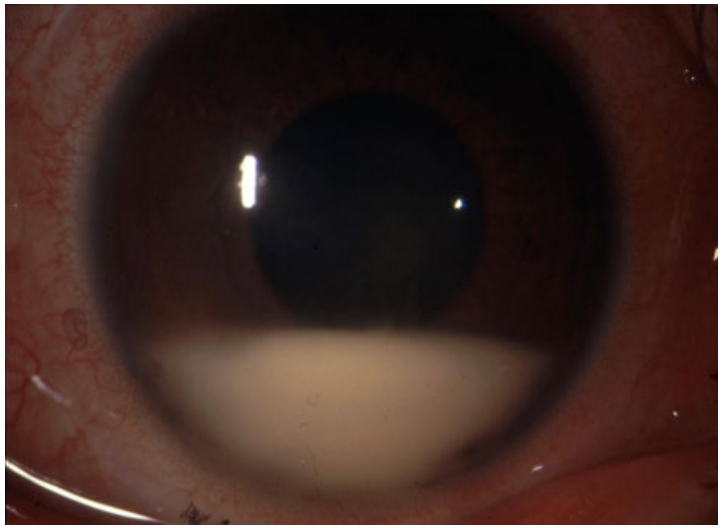
- Non-granulomatous panuveitis
- Retinal vasculitis

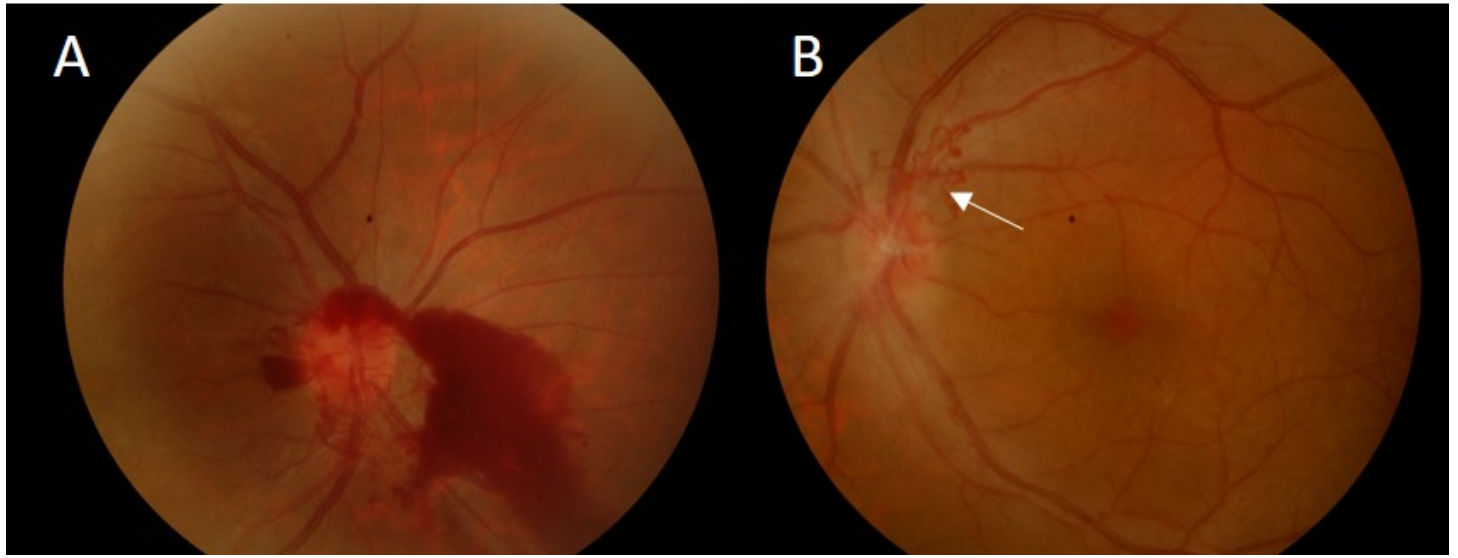
- Over all 50%
  - 70% of males <25 yr

- Frequently present at onset or first 2-3 yr
  - Rare after 5 yr
  - Bilateral in 90%

- Hypopyon (20%)
  - Almost always severe retinal vasculitis







Natural History

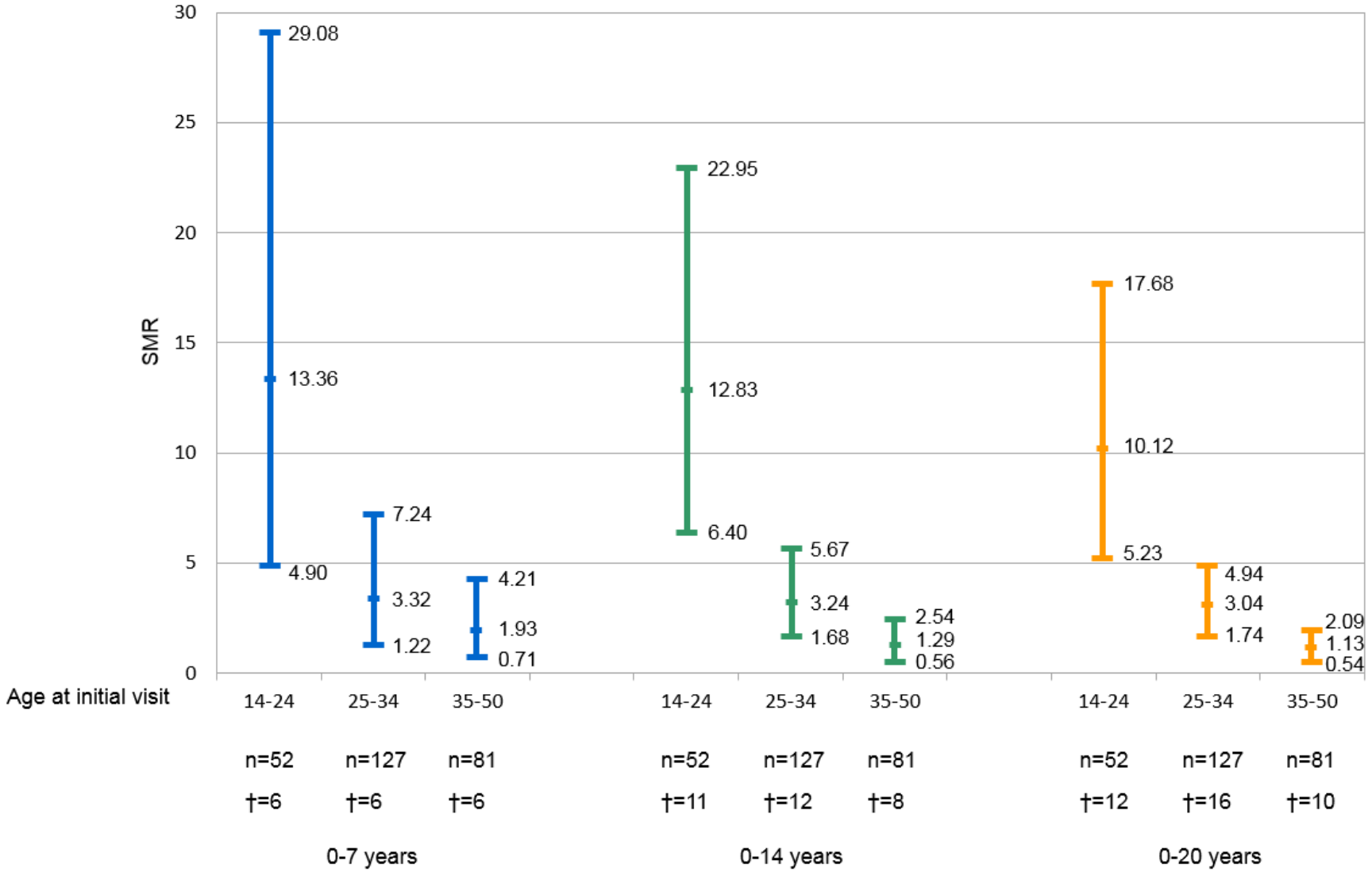
Long-term mortality and morbidity of Behcet Syndrome: Two decade outcome study

- 428 (286 M/142 F) BS patients registered at Cerrahpaşa Behcet Syndrome Multidisciplinary Outpatient Clinic between 1977-1983
  - Evaluated 1999-2000
  - Could not be reached: 41 (9.6 %)-24 M/17 F

- Found to have died: 42 (9.8 %)-39 M/3 F

Kural-Seyahi E, et al. Medicine (Baltimore) 2003

Mortality

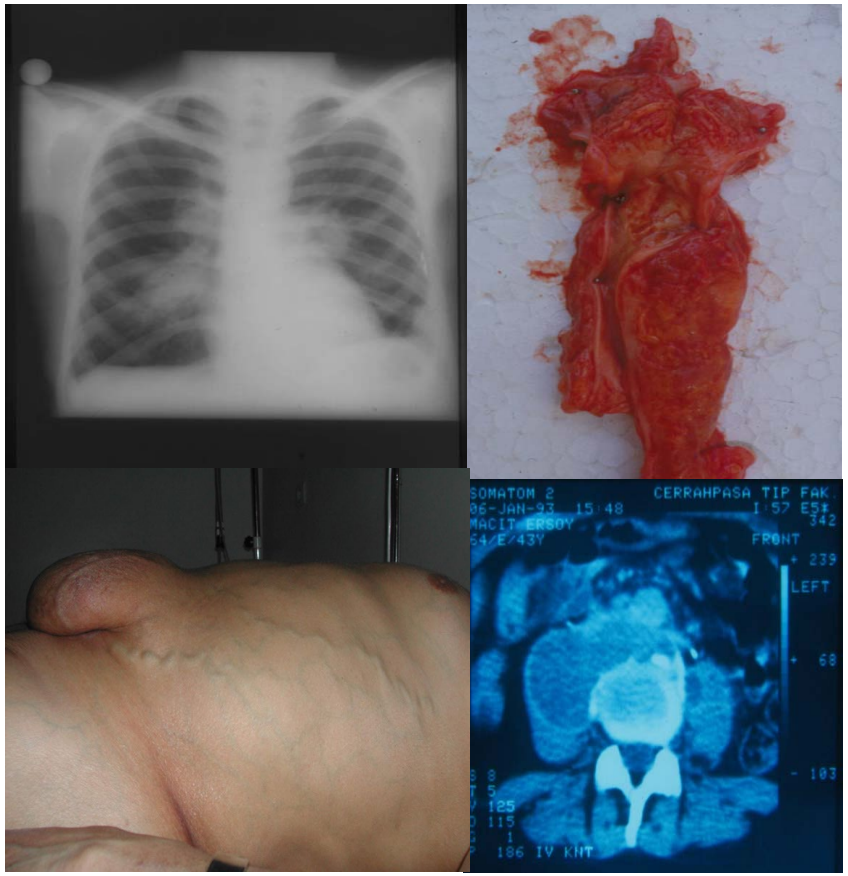


Kural-Seyahi E, et al. Medicine (Baltimore) 2003

Main causes of death among 42 patients

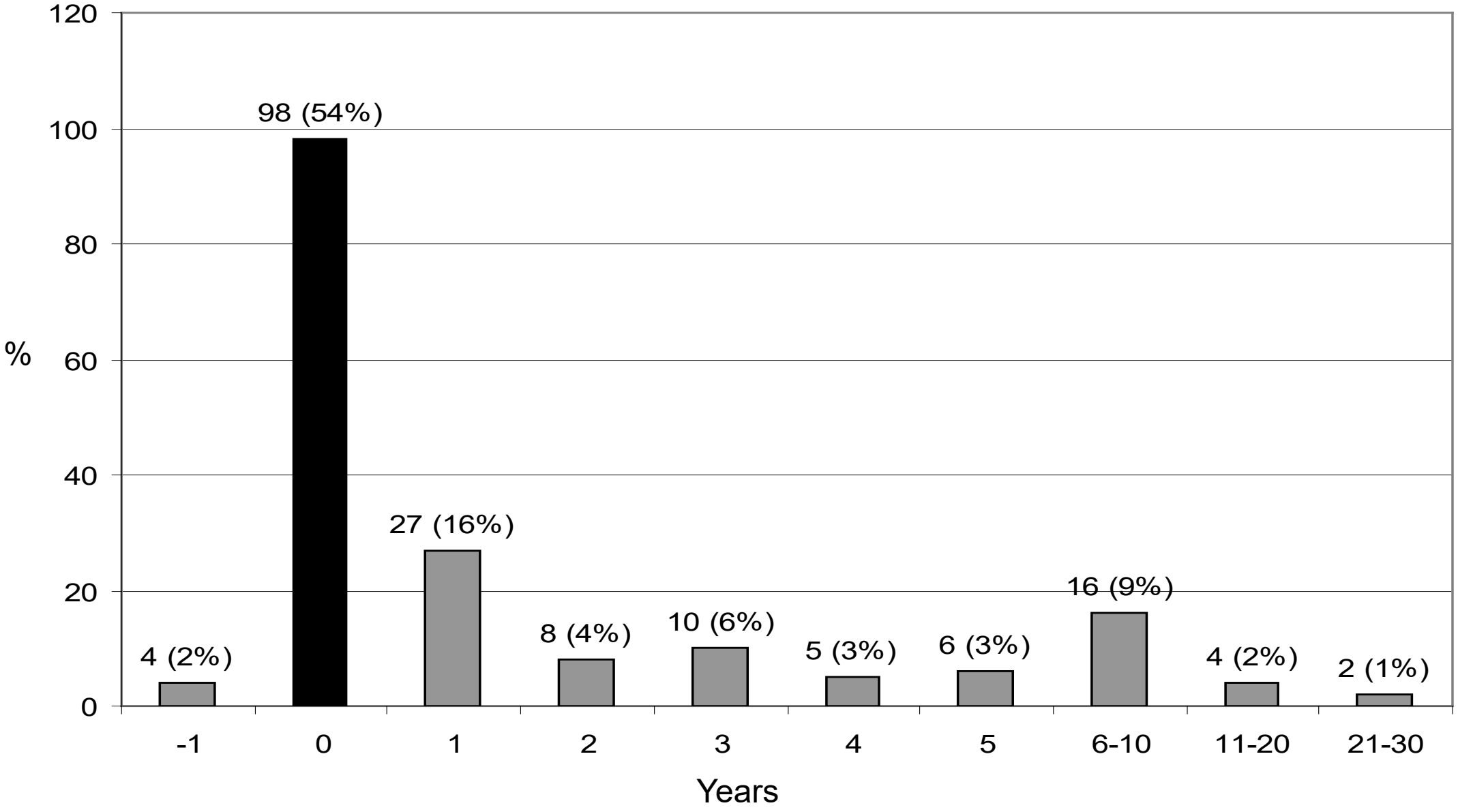
- Vascular disease: 17 (venous 5)
- CNS disease: 5
- Amyloidosis: 3
- Malignancy: 4
- Suicide: 2
- Misc: 11

- PAA
  - Main reason for mortality
  - Frequently associated with thrombi in inferior vena cava and iliac-femoral system
  - Presents with hemoptysis, may look similar to PE
  - Anticoagulation contraindicated



Seyahi E, et al. Medicine (Baltimore) 2003

Onset of eye disease in males



Kural-Seyahi E, et al. Medicine (Baltimore) 2003

Mucocutaneous Manifestations and Arthritis

	Beginning	End
Oral ulcers	345 (100%)	220 (64%)
Genital ulcers	310 (90%)	90 (26%)
Erythema nodosum	223 (64%)	88 (26%)
Papulopustular lesions	291 (84%)	123 (36%)
Arthritis	140 (41%)	34 (10%)

P=0.001

Kural-Seyahi E, et al. Medicine (Baltimore) 2003

Reanalysis of being disease free

- 428 total patients
  - 42 died
  - 41 lost to follow up
- 345 could be evaluated at 20 years
- 94/345 would have fulfilled BS criteria
  - 94 still active +
  - 41 (lost to follow up) +
  - 42 (died) = 177 (had disease or died at 20 years)
- 428 – 177 = 251 (59%) free of disease at 20 years
  - worst case scenario

Seyahi E, Yazici H. *Behçet's Syndrome, Springer, 2010*

Treatment

Colchicine

	Results	Study
Case reports (n≥5)	Some improvement in lesions caused by BD	Hazen et al, 1979; Raynor et al, 1980; Miyachi et al, 1981; Moreno et al, 1981; Harper et al, 1982; Sander et al, 1986
Double-blind RCT (n=35)	Ineffective except for erythema nodosum and arthralgia	Aktulga et al, 1980
Double-blind RCT (n=116)	Ineffective except for genital aphthosis and erythema (women), and arthritis (both genders)	Yurdakul et al, 2001
Open trial (n=54)	Effective overall for patients with oral aphthosis	Fontes et al, 2002
Reviews	Confirmed value of colchicine treatment in BD based on personal experiences	Vidaller et al, 2002; Wechsler et al, 2002; Lange et al, 2001
Double-blind cross-over RCT (n=169)	Significantly improved overall disease	Davatchi et al, 2009

Colchicine summary by gender

	Females	Males
Oral ulcers	?	X
Genital ulcers	✓ (*P*=0.001)	X
Erythema nodosum	✓ (*P*=0.002)	?
Follicular lesions	X	X
Arthritis	✓ (*P*=0.014)	✓ (*P*=0.026)

- In a long-term survey of patients from this trial, continuous use of colchicine did not decrease the use of immunosuppressives in the long-term[2]

1. Yurdakul S, et al. *Arthritis Rheum*. 2001;44(11):2286-2692; 2. Hamuryudan V, et al. *J Rheumatol.* 2014;41:735-738.

Azathioprine

- 2 yr, DBRCT, AZA 2.5 mg/kg
  - Group 1=no eye disease, AZA=12, Plc=13
  - Group 2= eye disease, AZA=25, Plc=23
- Prevents emergence of eye disease in the unaffected ($p < 0.01$)
- Prevents eye disease becoming bilateral ($p < 0.001$)
- Less frequent attacks of hypopyon ($p < 0.001$)

Table 2. Effects of Azathioprine on Eye Disease.

Effect	Group 1		Group 2	
	Azathioprine	Placebo	Azathioprine	Placebo*
	no. of patients (no. of episodes)			
Necessitating withdrawal	0	0	0	6
New eye disease	1†	8†	—	—
Involvement of previously unaffected eye	—	—	0†‡	5†‡
Hypopyon uveitis	0	0	1 (1)§	7 (15)§
Pulsed intravenous corticosteroid treatment	0	1 (1)	6 (9)	10 (16)
Oral corticosteroid treatment	0	0	1	4

*Five of the six patients withdrawn at months 11, 15, 16, 19, 21, and 22 received nine episodes of intravenous treatment with pulsed corticosteroids before withdrawal and are included in both figures.

†P<0.01. ‡Of seven patients. §P<0.001.

Yazici H, et al New Engl J Med 1990

Azathioprine

Table 3. Extraocular Manifestations.

Manifestation	Ever Present		Present at Initial Visit		New during Trial*		Present at 24 Months	
	Azathioprine (N = 37)	Placebo (N = 36)	Azathioprine (N = 37)	Placebo (N = 36)	Azathioprine	Placebo	Azathioprine (N = 34)	Placebo (N = 23)
	number of patients (percent)							
Oral ulceration†	37 (100)	36 (100)	16 (43)	21 (58)	11 (52)	7 (47)	4 (12)	8 (35)
Genital ulceration‡	32 (86)	29 (80)	6 (16)	4 (11)	3 (10)	12 (38)	1 (3)	8 (13)
Erythema nodosum	20 (54)	11 (31)	5 (14)	3 (8)	6 (19)	7 (21)	0 (0)	0 (0)
Papulopustular lesions	28 (76)	29 (81)	23 (62)	23 (64)	11 (79)	11 (85)	27 (79)	17 (74)
Arthritis§	8 (22)	10 (28)	3 (8)	5 (14)	1 (3)	7 (23)	1 (3)	2 (9)
Thrombophlebitis	10 (27)	8 (22)	9 (24)	5 (14)	3 (11)	8 (26)	10 (29)	8 (35)
Neurologic involvement	1 (3)	0 (0)	1 (3)	0 (0)	2 (6)	3 (8)	1 (3)	1 (4)

*Percentages were obtained by dividing the number of new patients with each manifestation by the number of patients free of the manifestation at the initial visit.

†$P<0.005$ for the comparison between the first and 24-month visits in patients receiving azathioprine.

‡$P<0.001$ by life-table analysis for the emergence of new patients with the manifestation.

§$P<0.02$ by life-table analysis for the emergence of new patients with the manifestation.

- Less frequent oral ulcers ($p<0.005$), genital ulcers ($p<0.001$), arthritis ($p<0.02$) and thrombophlebitis ($p<0.10$)

Yazici H, et al New Engl J Med 1990

TNF-alpha antagonists

Table 3 Anti-TNF Therapy-Induced Improvement of Various Clinical Manifestations in Patients with Behçet's Disease, Published through March 2010

	Improving Patients/Treated Patients[a]		
	Infliximab	Etanercept[b]	Adalimumab
Oral ulcers	110/122 (91%)	8/10 (82%)	8/11 (73%)
Genital ulcers	76/80 (96%)	5/7 (71%)	6/7 (86%)
Skin involvement	51/67 (77%)	2/3 (67%)	4/5 (80%)
Erythema nodosum	13/16 (81%)	1/1 (100%)	1/1 (100%)
Ocular involvement	233/262 (89%)	6/10 (60%)	16/16 (100%)
Gastrointestinal involvement	29/32 (91%)	—	3/3 (100%)
Central nervous system involvement	27/30 (90%)	2/2 (100%)	3/3 (100%)
Joint involvement	50/53 (94%)	6/6 (100%)	3/5 (60%)
Thrombophlevitis	7/10 (70%)	—	1/1 (100%)

[a]Patients with variable degree of improvement according to treating physicians are shown.
[b]Patients treated in the course of the RCT were excluded since they were not refractory to conventional immunosuppressants.

Arida et al, Semin Arth Rheum 2011

IFN-α

- Retrospective study, France
- Interferon-alpha (IFN-α2a or IFN-α2b) severe uveitis of BS
- Number of relapses before, under, and after IFN-α.
  - 3 million units 3 times a week
  - Mean tx duration 54 m
  - Median follow up 8.2 yr
- 81% (31/36) patient responded
- Frequency of uveitis relapses
  - 1.39 p/yr to 0.05 p/yr
- 21 patients (58%) discontinued IFN
  - 81% did not relapsed during 5 years f/u
  - 19% relapses responded to reintroduction of IFN
- 89% of the eyes improved or remained stable re: visual acuity

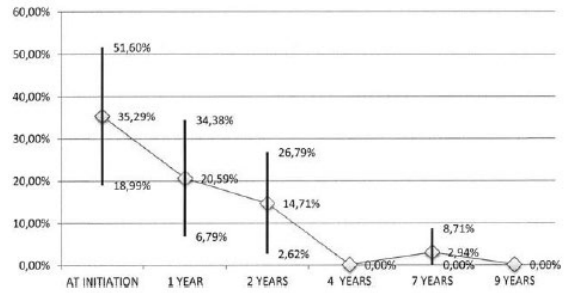


FIGURE 2. Prevalence of macular edema for the 9 y group with 95% CI (n=18).

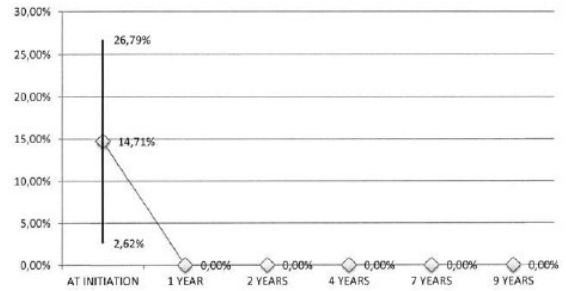


FIGURE 3. Prevalence of papilledema for the 9 y group with 95% CI (n=18).

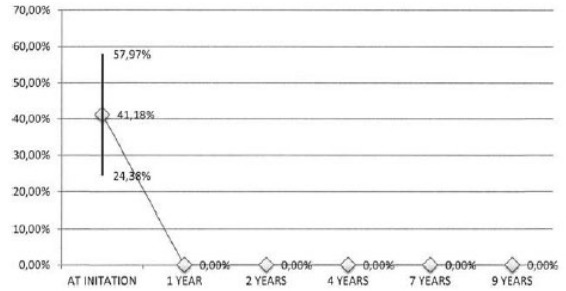


FIGURE 4. Prevalence of vasculitis for the 9 y group with 95% CI (n=18).

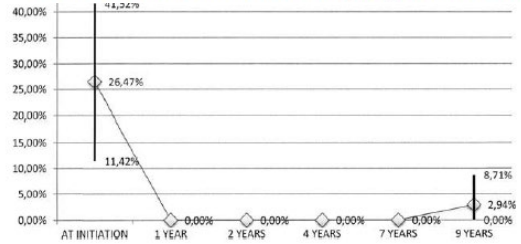


FIGURE 5. Prevalence of retinitis for the 9 y group with 95% CI (n=18).

Diwo E, et al. Ocul Immunol Inflamm 2017

Uveitis

TABLE 3 Comparisons of observational studies of IFN-α and IFX in BS uveitis

Outcome	IFN (%)	IFX (%)
Onset of action	2–4 weeks	Within first 24 h
Visual acuity improvement	133/291 (46) (eyes)	71/94 (76) (patients)
Complete remission	149/233 (64)	123/216 (57)
Complete + partial remission	280/310 (90)	120/126 (95)
Sustained remission	90/127 (71)	24/54 (44)
CS cessation	95/144 (66)	28/84 (33)
Withdrawal due to side effect	17/310 (5.5)	18/332 (5)

Ozguler Y, et al. Rheumatology 2018

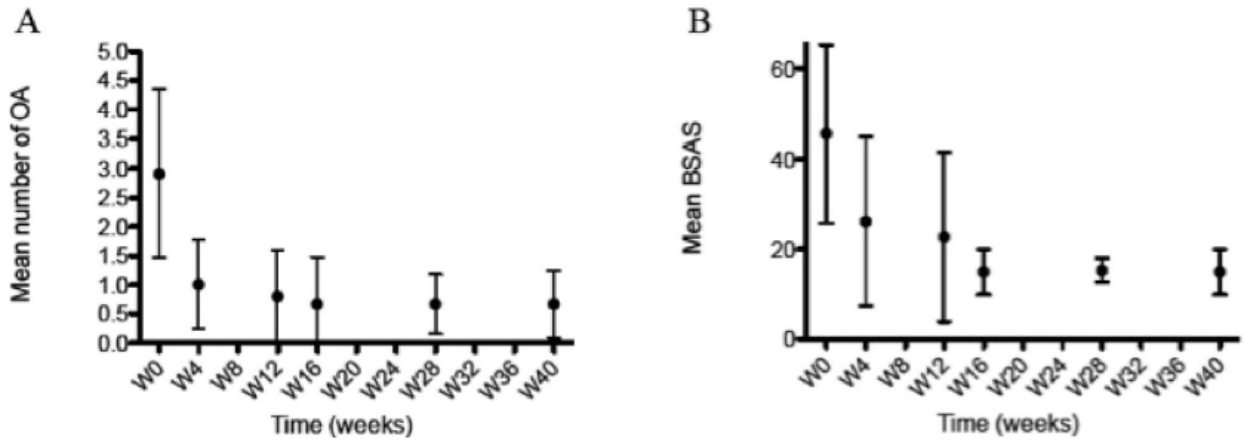
Ustekinumab

- Open pilot study, France
- 14 patients, failed colchicine
- SQ ustekinumab 90 mg at weeks 0, 4, q12wk
- Median number of oral ulcers
  - 2 at baseline
  - 1 at week 12
- 9 (69%) were free from ulcers at week 12 (complete response, primary outcome)
- Genital ulcers
  - 4 patients at baseline
  - 1 patient at week 12
- Median follow-up 7 m
  - 10 patients (71%) still on ustekinumab.
- 4 DC'd
  - 1 headache
  - 3 partial response or relapse

Table 3
Outcomes at week 12 for 14 BD patients treated with ustekinumab.

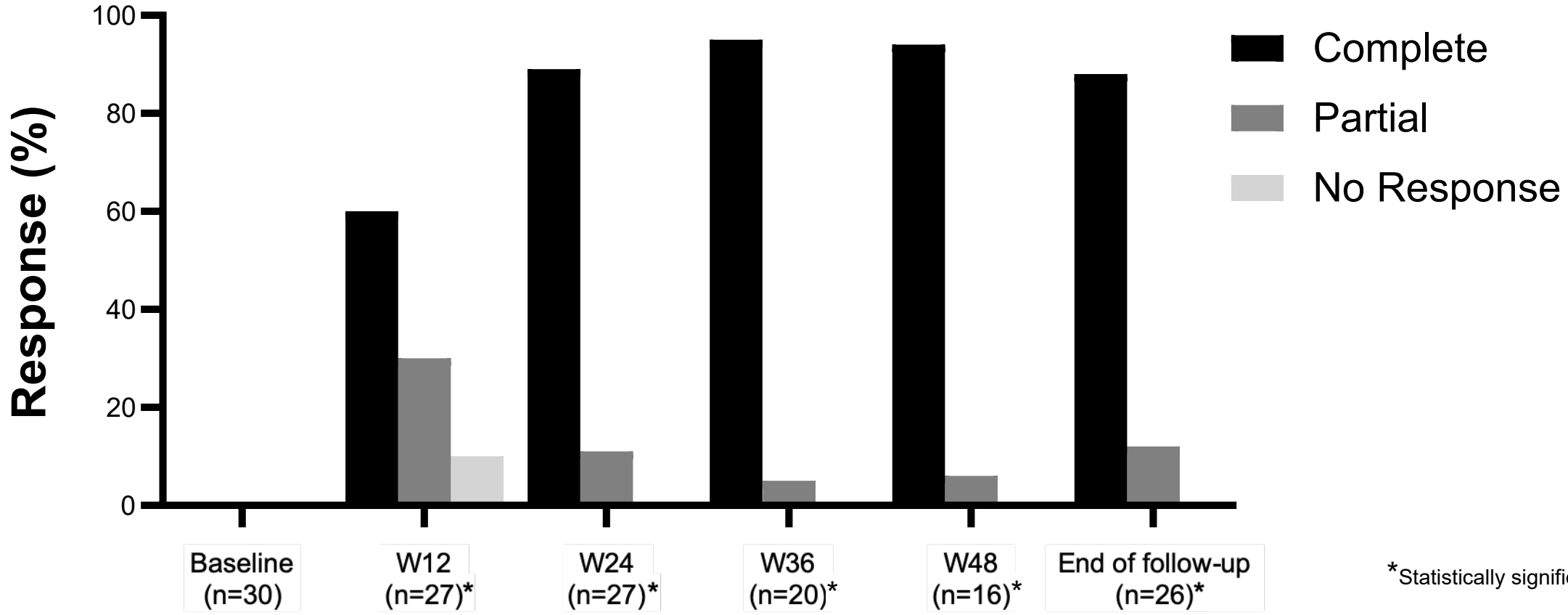
Measure	At inclusion (n = 14)	At week 12 (n = 14)	p value
Oral ulcerations, median [IQR]	2 [2; 4]	1 [0; 1.25]	0.0005
Steroids dose mg/day, median [IQR]	12.5 [10; 16.3]	5 [5; 10]	0.02
BSAS score, median [IQR]	39 [30; 65]	15 [10; 35]	0.01
Outcomes at week 12, n (%)			
Complete remission		9 (64.3%)	
Partial remission		3 (21.4%)	
Non remission		2 (14.3%)	
Other BD manifestations, n (%)			
Scleritis	1 (7%)	0 (0%)	–
Articular	2 (14%)	0 (0%)	–
Pyoderma gangrenosum	2 (14%)	1 (7%)	–
Pseudo-folliculitis	2 (14%)	1 (7%)	–
Gastro-intestinal tract	1 (7%)	1 (7%)	–

Abbreviations: BD: Behçet's disease.



Mirouse A, et al. J Autoimmun 2017

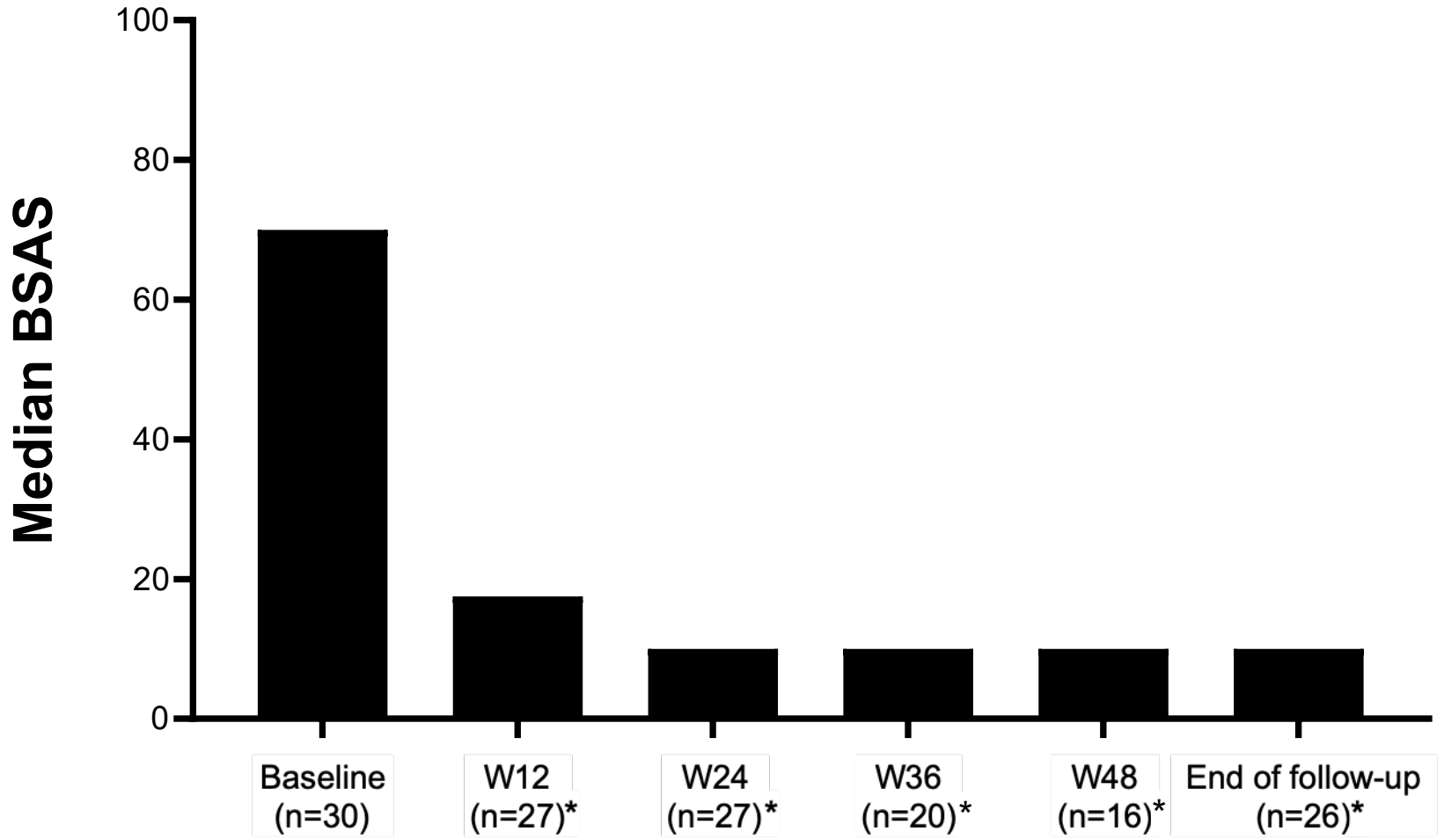
Ustekinumab - oral ulcers



*Statistically significant

Mirouse A, et al. Arthritis Rheum 2019

Ustekinumab - BSAS



*Statistically significant

Mirouse A, et al. Arthritis Rheum 2019

Thrombosis

- Retrospective analysis of 807 patients
- 296 / 807 (37%) had venous thrombosis.
  - 99% patients had received anticoagulants,
  - 47% received additional immunosuppressives
  - 63% received corticosteroids.
- 100 / 296 (34%) experienced at least 1 venous relapse
- Factors that prevented relapse of venous thrombosis:
  - use of immunosuppressives (HR 0.27; 95%CI: 0.14 – 0.52)
  - corticosteroids (HR 0.62; 95%CI: 0. 40 – 0.97)
- Bleeding complications occurred in 7 (2.4%) patients.

Desbois AC, et al. Arthritis Rheum 2012

Immunosuppression vs anticoagulation

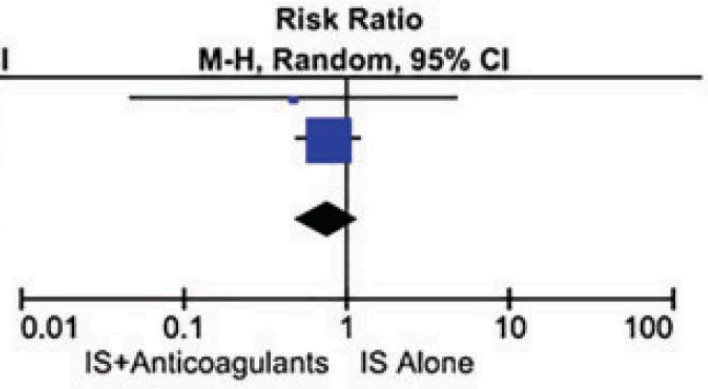
FIG. 2 Relapse risk of deep vein thrombosis

A

Study or Subgroup	IS+Anticoagulants Events	Total	IS Alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahn et al. 2008 [69]	1	17	2	16	3.7%	0.47 [0.05, 4.70]
Alibaz-Oner et al. 2015 [71]	28	125	28	96	96.3%	0.77 [0.49, 1.21]
Total (95% CI)		**142**		**112**	**100.0%**	**0.75 [0.48, 1.17]**
Total events	29		30			

Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (*P* = 0.68); I^2 = 0%

Test for overall effect: *Z* = 1.25 (*P* = 0.21)

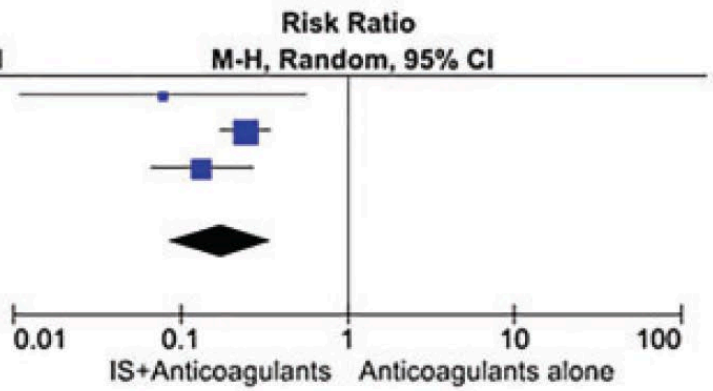


B

Study or Subgroup	IS+Anticoagulants Events	Total	Anticoagulants alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahn et al. 2008 [69]	1	17	3	4	10.6%	0.08 [0.01, 0.57]
Alibaz-Oner et al. 2015 [71]	28	125	22	24	51.7%	0.24 [0.17, 0.35]
Desbois et al. 2012 [70]	8	137	68	156	37.7%	0.13 [0.07, 0.27]
Total (95% CI)		**279**		**184**	**100.0%**	**0.17 [0.08, 0.35]**
Total events	37		93			

Heterogeneity: Tau² = 0.22; Chi² = 5.21, df = 2 (*P* = 0.07); I^2 = 62%

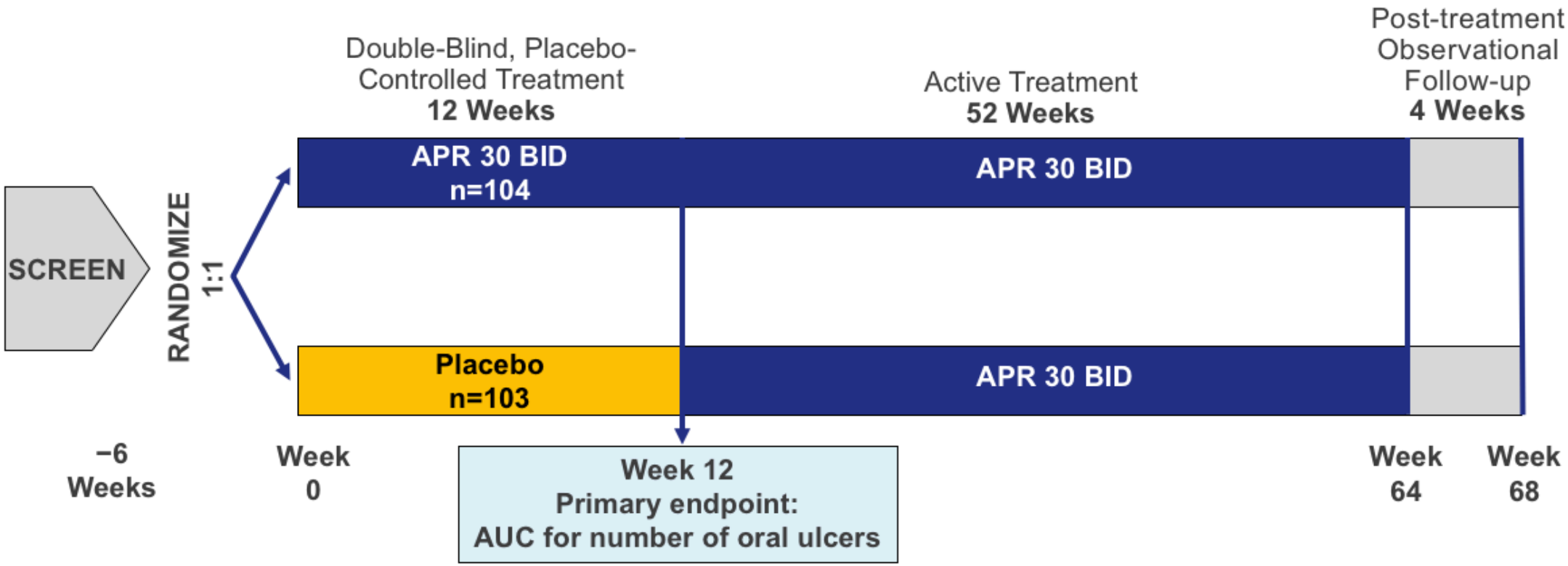
Test for overall effect: *Z* = 4.83 (*P* < 0.00001)



(**A**) Relapse risk of deep vein thrombosis with immunosuppressives and anticoagulants compared to anticoagulants alone (**B**) Relapse risk of deep vein thrombosis with immunosuppressives and anticoagulants compared to immunosuppressives alone.

Ozguler Y, et al. Rheumatology 2018

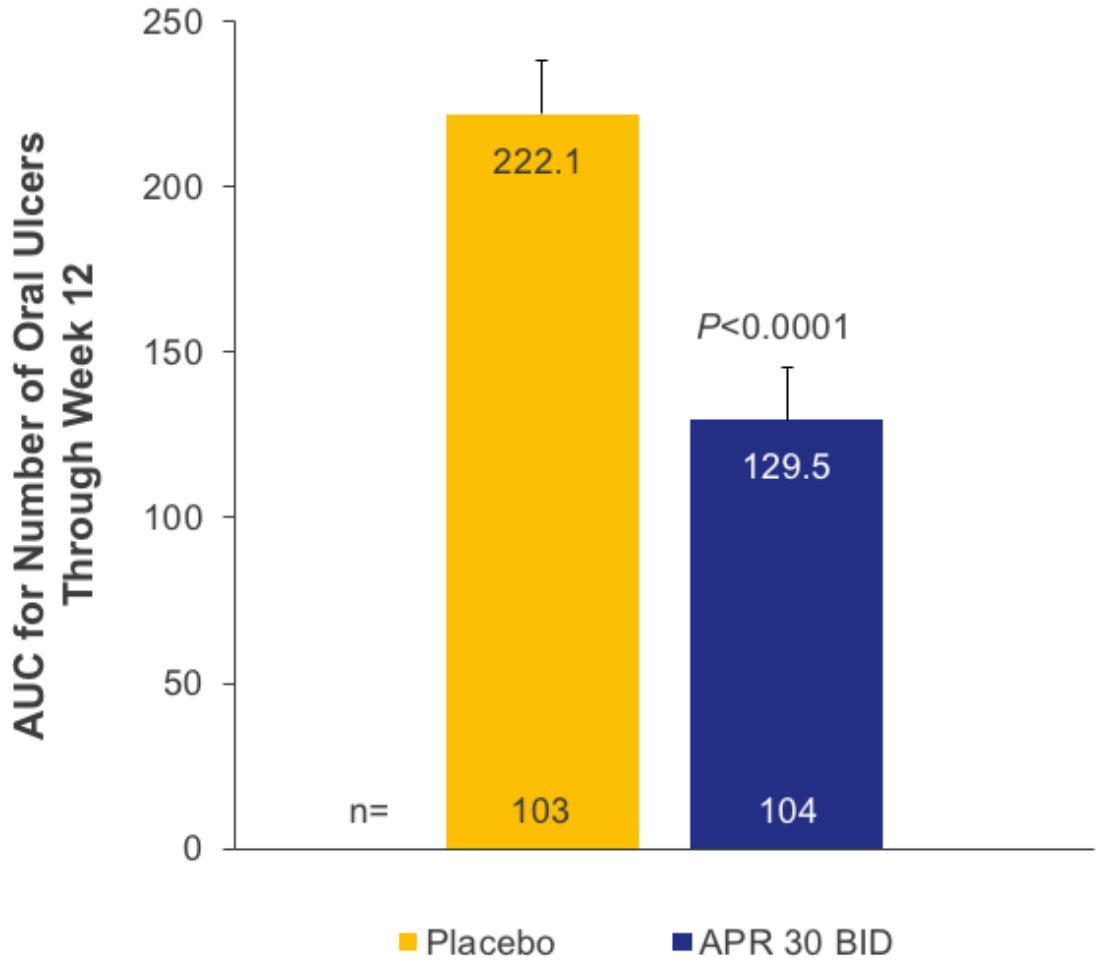
Apremilast

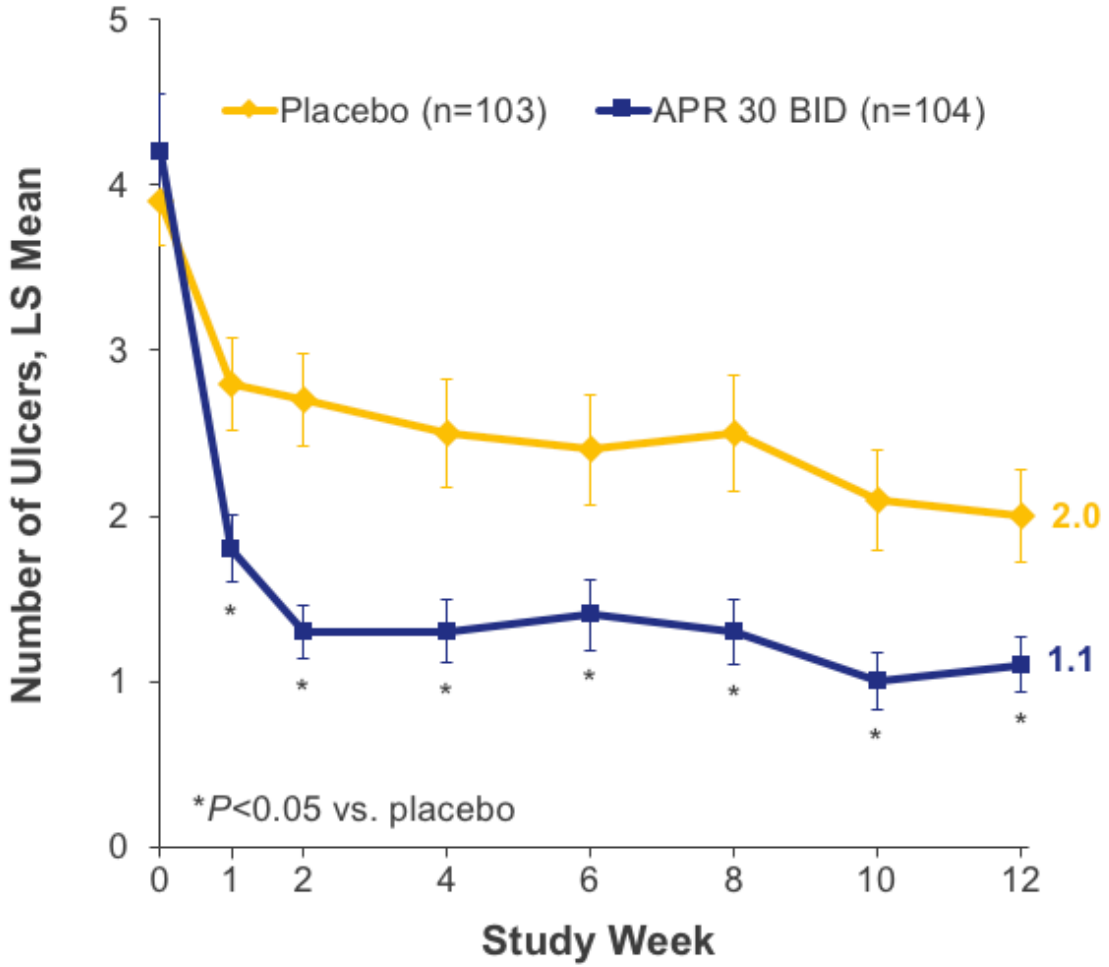


- Stratified by gender, history of uveitis, and region (Japan and other)
- Dose titration occurred over first week
- Secondary endpoints: Change from baseline in pain of oral ulcers, BSAS, BDCAI, and BD QOL score at Week 12

Hatemi G, et al. ACR Chicago 2018

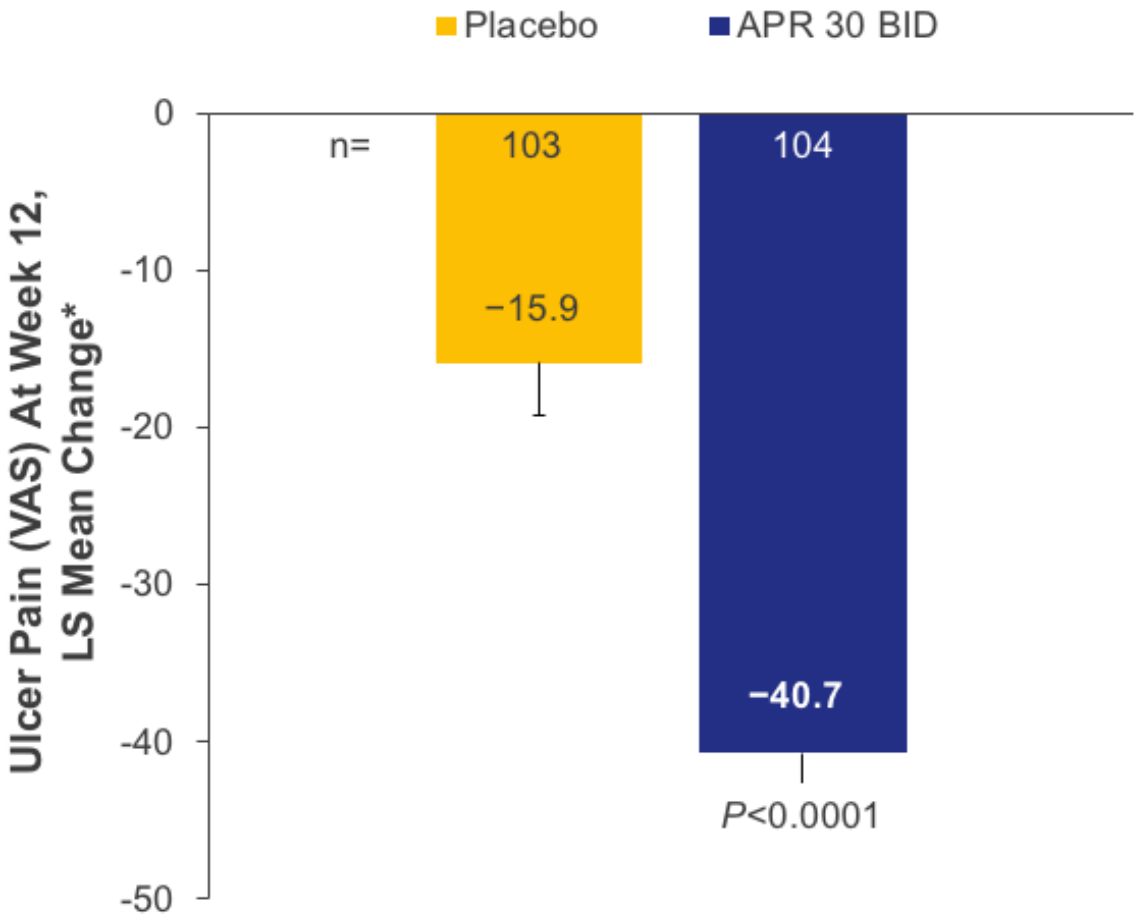
Oral ulcers

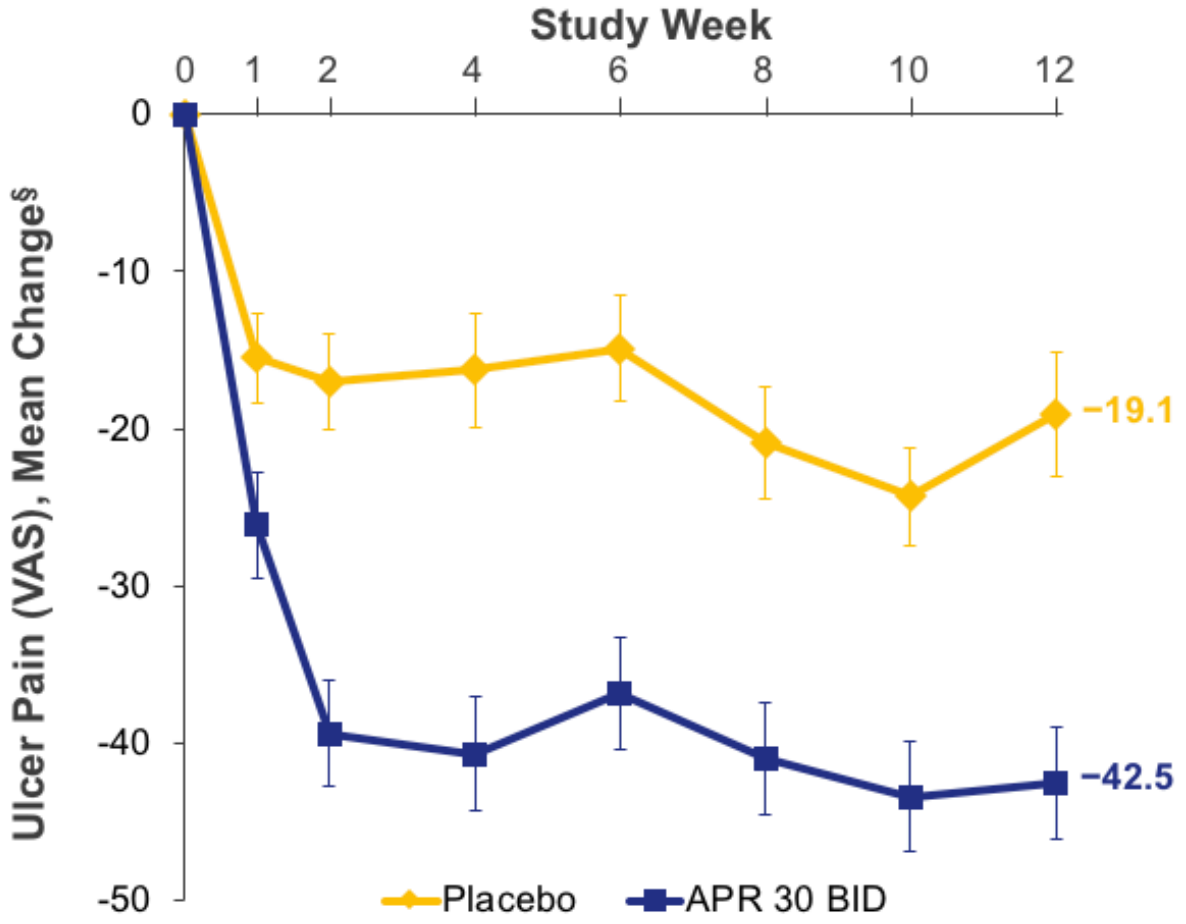




Hatemi G, et al. ACR Chicago, 2018

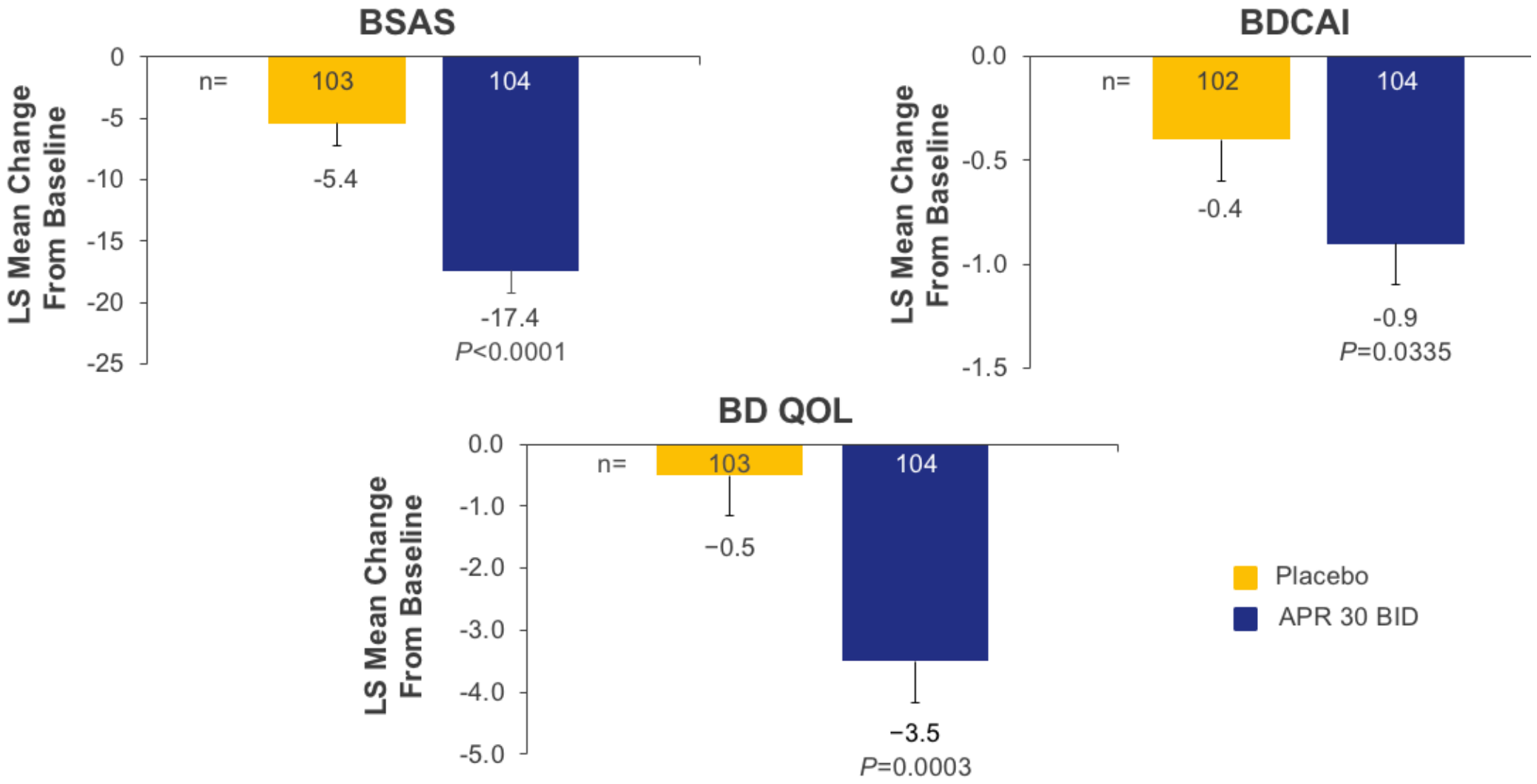
Oral ulcer pain



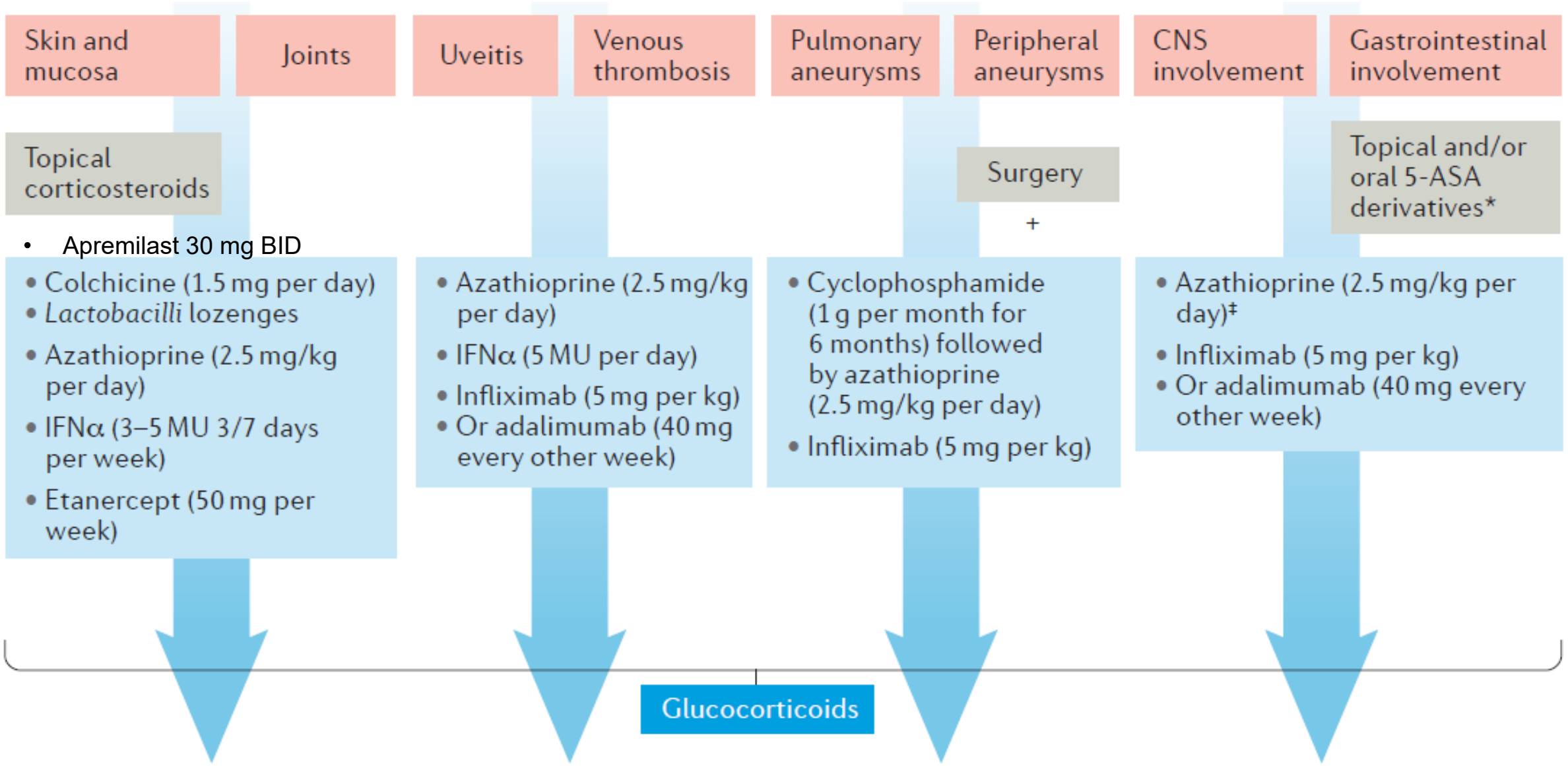


Hatemi G, et al. ACR Chicago, 2018

Disease activity and QoL



Hatemi G, et al. ACR Chicago, 2018



Yazici H, et al. Nature Rev Rheum 2018

Considerations for Treatment Approach

- Criteria (+) vs (-)
- Overlaps
- Male vs female
- Young vs old
- Mucocutaneous involvement only
- Eye disease

Conclusions

- Distinct features that differentiate from autoimmune and autoinflammatory diseases
- Various factors need to be considered when making treatment choices
- Most patients do well over time with treatment, remission likely for 2/3 of patients
- New treatments

Thank you

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- Yasmin Bata, MD
- Gabrielle Turyan
- Johannes Nowatzky, MD
- Hui Zhan
- Ranit Shriky

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Slam Dunk Diagnosis – Or is Something Else Hiding in the Trenches?

29 year old male presents to the ED with acute onset, right-sided chest pain and SOB while playing basketball…

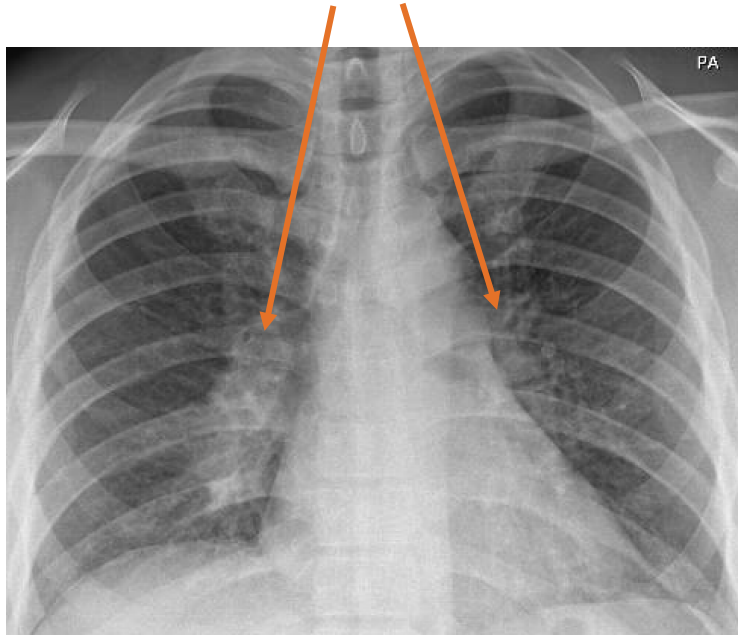
History

- One episode of hemoptysis on the way to the ED
- ROS negative for fevers, weight loss, night sweats, syncope, LE swelling, cough
- No significant PMH or medications
- Previously incarcerated for 2 years. Smokes 1 PPD cigarettes and occasional marijuana. Drinks 5-10 alcoholic drinks per week. Denies IVDA.

Exam

T 38.3 | **HR** 110 | **BP** 164/97 | **RR** 22 | **SpO2** 96% RA
Gen: Uncomfortable appearing male
HEENT: No scleral icterus, clear conjunctiva. MMM with no oral ulcers.
Neck: Bilateral, non-tender, cervical lymphadenopathy
Cardio: Tachycardic rate, regular rhythm, nl S1/S2, 2/6 systolic murmur at RUSB
Pulm: Lungs clear bilaterally.
GI: Normoactive BS, soft, non-tender, non-distended. No hepatosplenomegaly.
MSK: No LE edema. No joint swelling or tenderness.
Skin: No rashes
Neuro: A&Ox3, CN II-XII grossly intact.

Prominent bilateral hila



10	15	263	135	99	9	99	
			3.4	21	1.1		

Tbili: 0.7
Alk phos: 81
AST: 29
ALT: 25

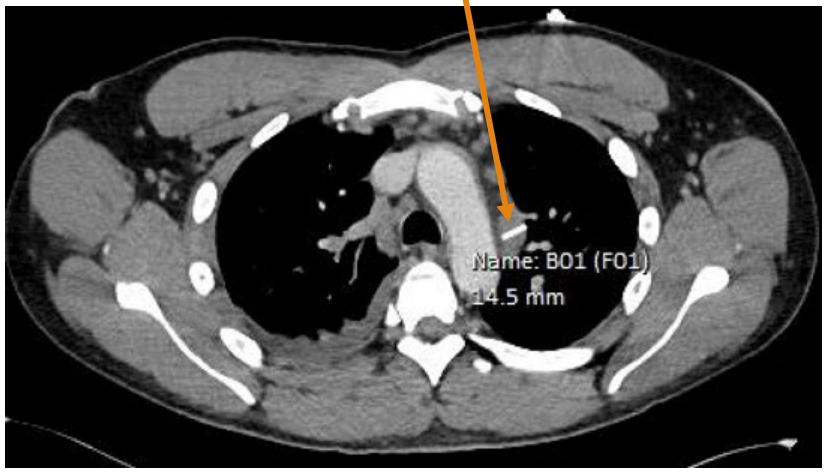
Troponin: < 0.02

D-dimer: 636

ESR: 29
CRP: 3.5

CTPA: Acute PE in all RLL segmental and subsegmental branches

Mediastinal and bilateral hilar lymphadenopathy



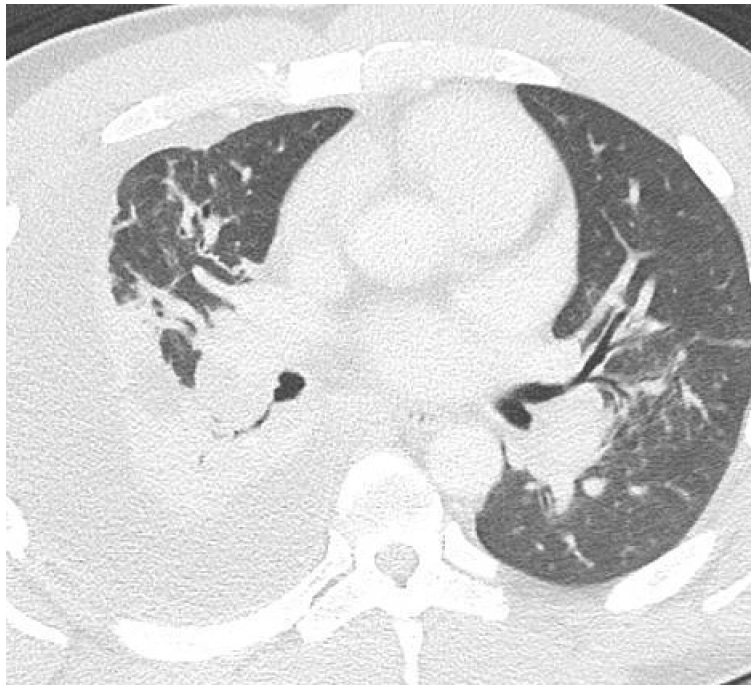
CT neck/soft tissue showed bilateral supraclavicular, multistation cervical, and mediastinal LAD.

CT abdomen/pelvis showed mild bilateral iliac chain and inguinal LAD.

Labs and Imaging

Patient had persistent daily fevers and developed RLL consolidation with pleural effusion…

What is the differential diagnosis for patients with fever and generalized lymphadenopathy??



Pleural fluid studies showed exudative effusion.

Before committing to treatment, we wanted to…

1. Rule out infection, malignancy, and autoimmune ds
2. Confirm the presence of granulomatous disease, since sarcoidosis was high on the differential

Patient was started on antibiotics and excisional LN biopsy was performed

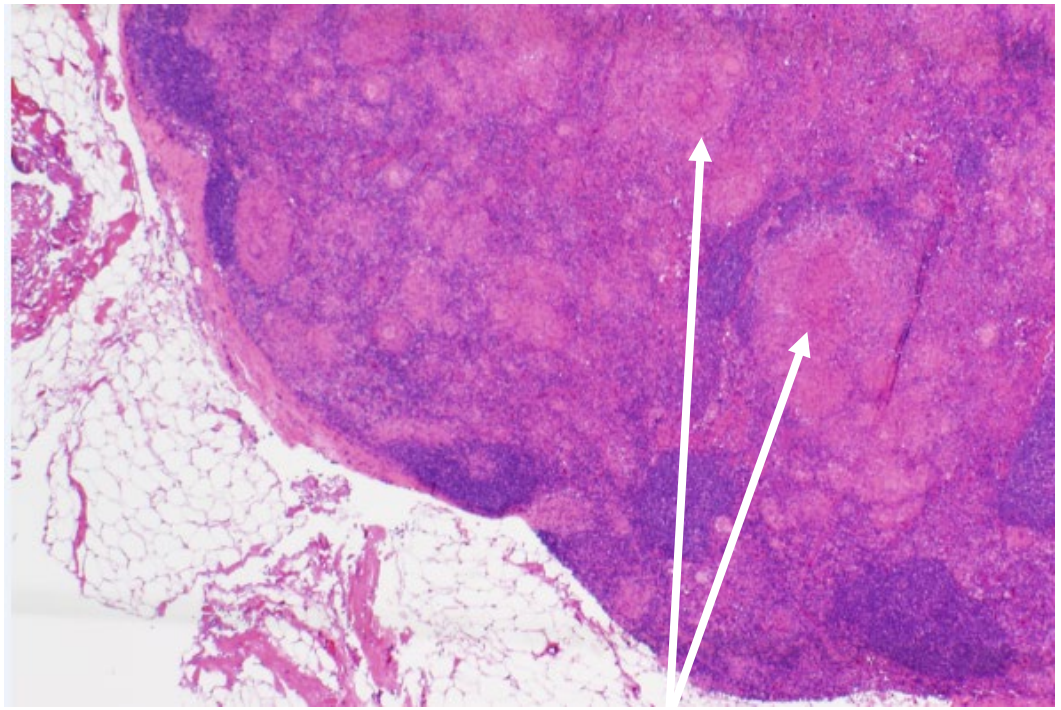
FINAL DIAGNOSIS AND ATTENDING SIGNATURE

A. LYMPH NODE, RIGHT INGUINAL, BIOPSY:
-GRANULOMATOUS LYMPHADENITIS WITH FOCAL NECROSIS. (SEE NOTE.)

FINAL DIAGNOSIS COMMENT

The lymph node is completely replaced by numerous granulomas with associated giant cells. A minority of the granulomas exhibit central necrosis. In a patient of this age and in this location, the differential diagnosis is primarily among infectious diseases of bacterial, mycobacterial, fungal or spirochetal etiologies. A panel of special stains is performed. A Warthin-Starry stain demonstrates the presence of small bacterial forms within the giant cells. This finding, along with the location of the lymph node, raises the differential consideration of chancroid (H. ducreyi). Cat-scratch disease/B. henselae infection should also be considered, although the lack of infiltrating neutrophils is unusual for that disorder. A silver stain is negative for fungal organisms. Fites and Truant stains are negative for acid fast bacilli. An immunohistochemical stain for spirochetes is negative.

In summary, the presence of necrotizing granulomatous inflammation in this lymph node suggests and infectious etiology which is further supported by the presence of organisms on Warthin-Starry stain. The tissue blocks will be sent to the University of Washington for molecular studies in attempt to identify the causative organism.



Granulomas with central necrosis

More Data

Cultures are negative… no surprise here. What other infectious studies do we need to perform?

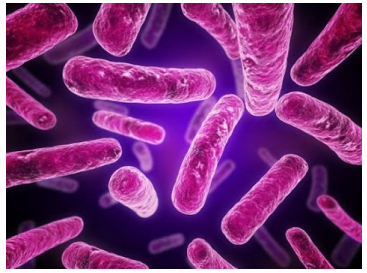
Cultures:

Blood cultures: No growth

Lymph node biopsy culture: No fungal or acid fast bacilli seen.

Pleural fluid culture: No growth

Fluid culture/AFB/fungal from BAL: No growth

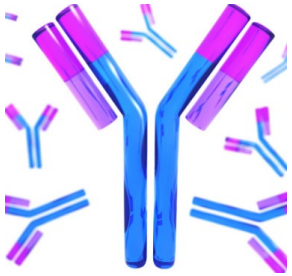


Autoimmune workup:

ANA: Negative

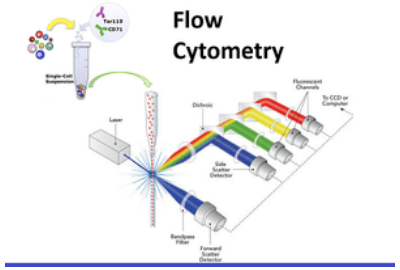
ANCA: Negative

ACE: **55**



Flow Cytometry:

Peripheral blood and LN: No abnormal population of B-cells or T-cells



Targeted infectious workup

EBV: Negative

HIV: Negative

Quantiferon gold: Negative

Urine histoplasma antigen: Negative

Fungal immunodiffusion (coccidiodes, blastomyces, histoplasma): Negative

Syphilis: Negative

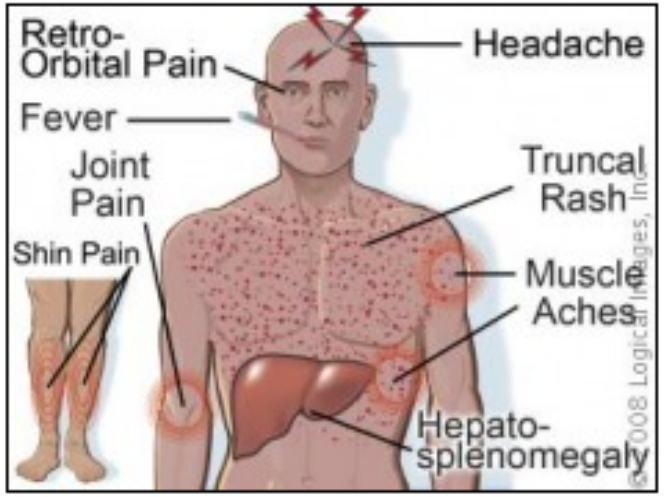
Tularemia antibody: Negative

Bartonella Quintana: **IgM Positive. IgG negative.** **Trench Fever??**

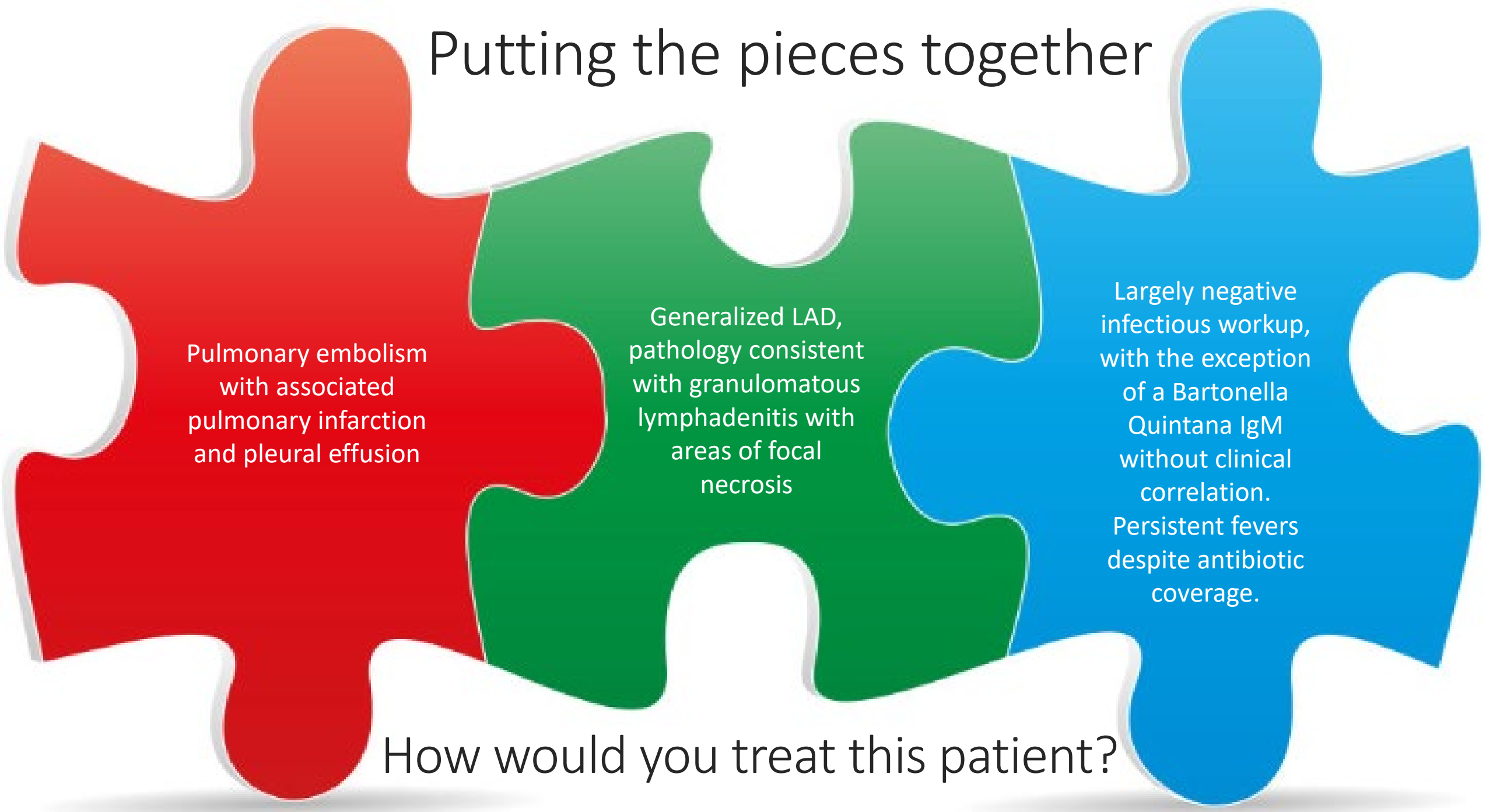
Bartonella henselae IgM/IgG: Negative

UWashington PCR for bacterial 16S rRNA: **Negative**

Uses next generation sequencing to identify bacteria without culture



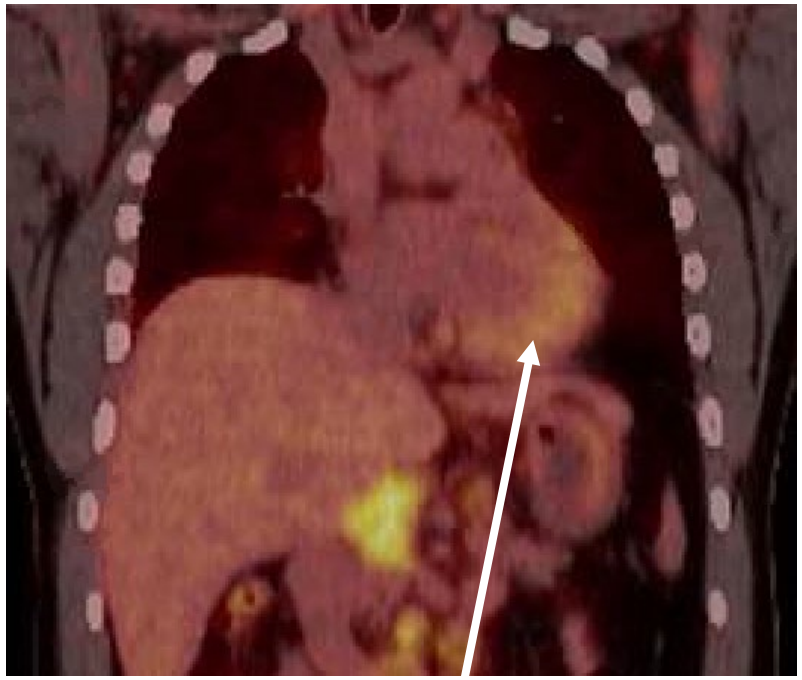
Putting the pieces together



How would you treat this patient?

Patient Course

- Patient was started on prednisone 40 mg daily. Fevers subsided within days.
- Steroids were gradually tapered. Over months of follow-up, he developed other features consistent with sarcoidosis:
  - Skin lesions
  - Infiltrative cardiomyopathy
  - Perilymphatic pulmonary inflammation (seen on PET)
- Steroids were increased and patient was started Cellcept at time of cardiac sarcoid diagnosis.
  - LFTs increased to 3x ULN on Cellcept, so he was transitioned to azathioprine.
- Most recent follow-up PET showed improvement in infiltrative disease. Steroids have been tapered off.
- Final diagnosis: sarcoidosis with necrotizing features complicated by stage II pulmonary disease and infiltrative cardiomyopathy



FDG uptake in basal inferolateral and anterolateral walls on cardiac PET.

Teaching Points

- There is an increased risk of PE and DVT in patients with sarcoidosis.[1]
  - Hazard ratio of 3.04 compared to non-sarcoidosis cohort

- Small amounts of central fibrinoid necrosis can be seen in sarcoidosis.
  - Large amounts of necrosis should prompt investigation for an alternate diagnosis – most common cause is infectious.[2]

- Necrotizing sarcoid granulomatosis is a rare disease entity that more closely resembles GPA. Characterized by extensive necrosis and vasculitis.[3]
  - Our patient did not meet this based on lack of clinical or pathologic vasculitis.

References:

1. *Chest. 2017;151(2):425-430*
2. *Chest. 2013;144(3):813-824*
3. *Clin resp J. 2018;12(4):1313-1319*

MORE THAN MEETS THE EYE

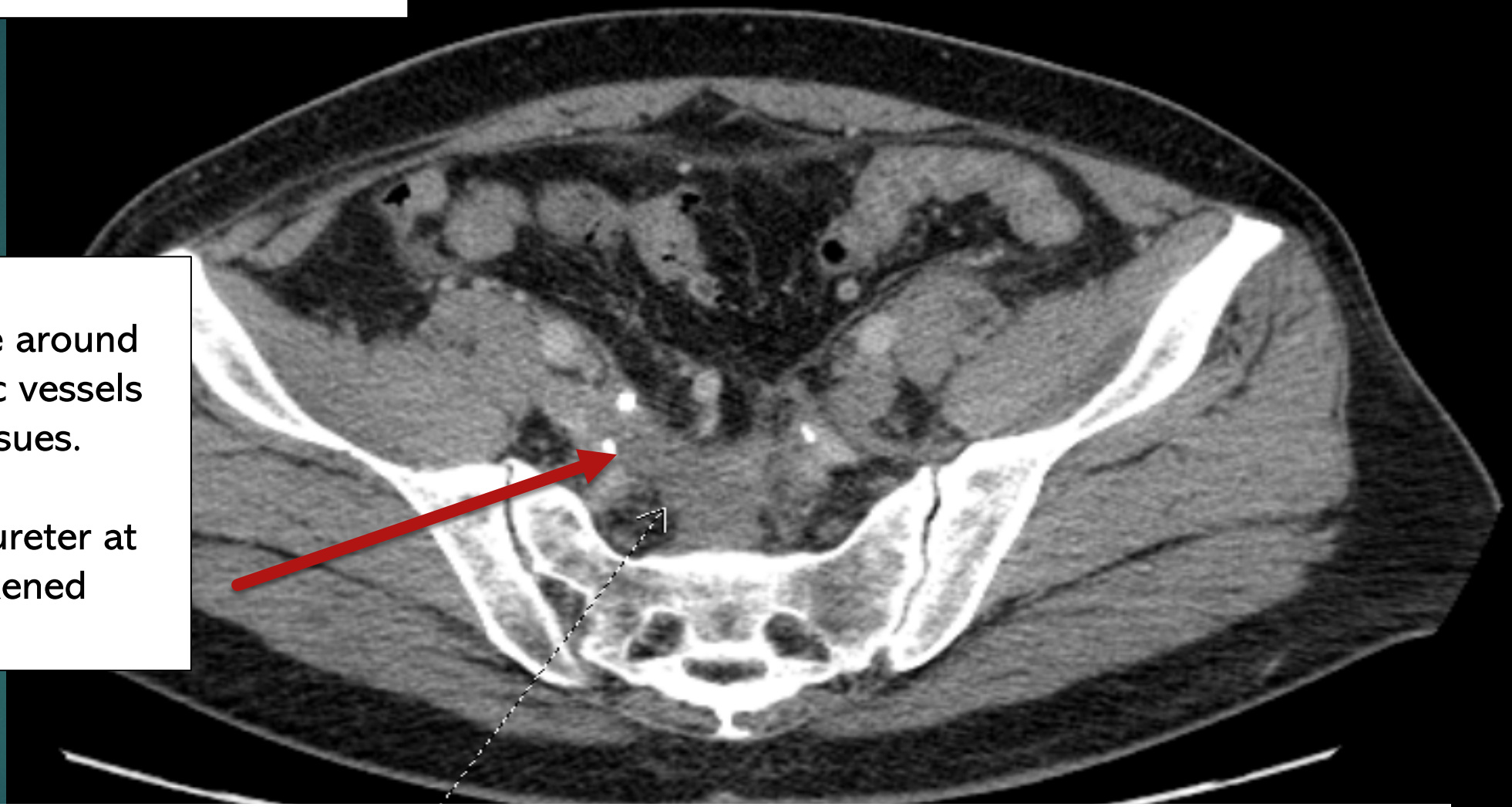
74 year old male in the ED with unilateral right eye redness, pressure, and headache

(NOT ACTUAL PATIENT. HTTPS://HEALTHJADE.COM/WP-CONTENT/UPLOADS/2019/01/SCLERITIS.JPG)

Past Medical History

Feb 2015:
*Abnormal soft tissue around distal aorta, both iliac vessels and presacral soft tissues.

* Envelops the right ureter at the sacrum with thickened ureter



BIOPSY: Benign Fibrous tissue with chronic inflammation

Past Medical History

November 2019: Abdomen Pain due to Pancreatitis
MRI: Pancreas is bulbous with heterogeneous signal with diminutive pancreatic duct. There is no peripancreatic inflammatory changes, collection or discrete mass. Overall, the findings suggest **autoimmune pancreatitis**.

Biopsy: Marked lobular and interlobular inflammatory infiltration with plasma cells and lymphocytes and fibrosis/atrophy. **Positive plasma cells with many IgG and IgG4(+) plasma cells (30 IgG4/ HPF). The IgG4+: IgG+ ratio is approximately 45%.**

Work Up

- MRI of orbit - bilateral eye proptosis of globe
- Fundoscopic exam - Anterior Scleritis of Right Eye.

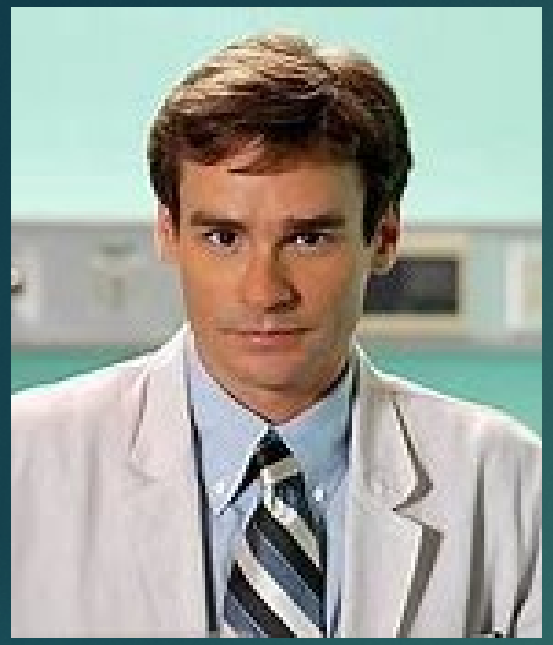
COMPLEMENT	
COMPLEMENT C3	38
COMPLEMENT C4	<2

SSA-SSB ANTIBODY	
SSA AB	41.3 *
SSB AB	2.6 *

Negative ANA/ANCA, RF cryoglobulin screen

WBC		2.22
RBC		2.66
HGB		8.5
HCT		27.5
PLATELET COUNT		130

IGG1	382 - 929 mg/dL	1,155
IGG2	241 - 700 mg/dL	637
IGG3	22 - 178 mg/dL	69
IGG4	4.0 - 86.0 mg/dL	453.0
IGG, SERUM	600 - 1,540 mg/dL	2,474



We have a 74 year old male with:

- Hx of Autoimmune pancreatitis
- Hx of Retroperitoneal fibrosis
- Orbital proptosis w/ anterior scleritis
- Positive SS-A Ab but no sicca, no parotid enlargement
- Hypocomplementemia
- Pancytopenia w/ neutropenia, no eosinophilia
- Elevated IgG4 -2x UL normal

Does this patient have IgG4 disease?

Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Serum IgG4 concentration	
Normal or not checked	0
> Normal but <2× upper limit of normal	+4
2–5× upper limit of normal	+6
>5× upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual, and submandibular glands	
No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest	
Not checked or neither of the items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
Not checked or none of the items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of above) and biliary tree involvement	+19
Kidney	
Not checked or none of the items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low-density areas	+10
Retroperitoneum	
Not checked or neither of the items listed is present	0
Diffuse thickening of the abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8

ACR/EULAR 2019 Classification Criteria

Maybe.
Pancytopenia does not fit the picture

We need a Bone Marrow Biopsy.

Peripheral Blood Smear, Bone Marrow Biopsy and Aspirate Smears, Left Hip:

1) **Acute leukemia in bone marrow, favor AML containing occasional Auer rods. Further subtyping awaits immunophenotypic analysis. Also pending are cytogenetics, FISH and next generation sequencing with rapid FLT3.**
2) **Peripheral blood smear shows a normal total WBC count with about 7% circulating blasts, anemia with anisopoikilocytosis, a few nucleated RBCs, and a normal platelet count with some giant and hypogranular platelet forms.**

Diagnosis: AML

Treatment started with induction chemotherapy: Cytarabine, Idarubicin

For suspected IgG4- related disease, prednisone 60 mg taper was started. Rituximab will be considered post AML therapy if work up remains suggestive of IgG4

Learning Points:

- IgG4 disease is a fibro-inflammatory disease characterized by IgG4 plasma infiltrates that can present in multiple organs
- Although IgG4 can involve bone marrow, it is atypical to present with pancytopenia. SS-A Ab and anterior scleritis are also atypical.
- Prior studies show that compared to matched controls, IgG4 has 3 fold higher frequency of associated malignancy. There is little data on association with AML

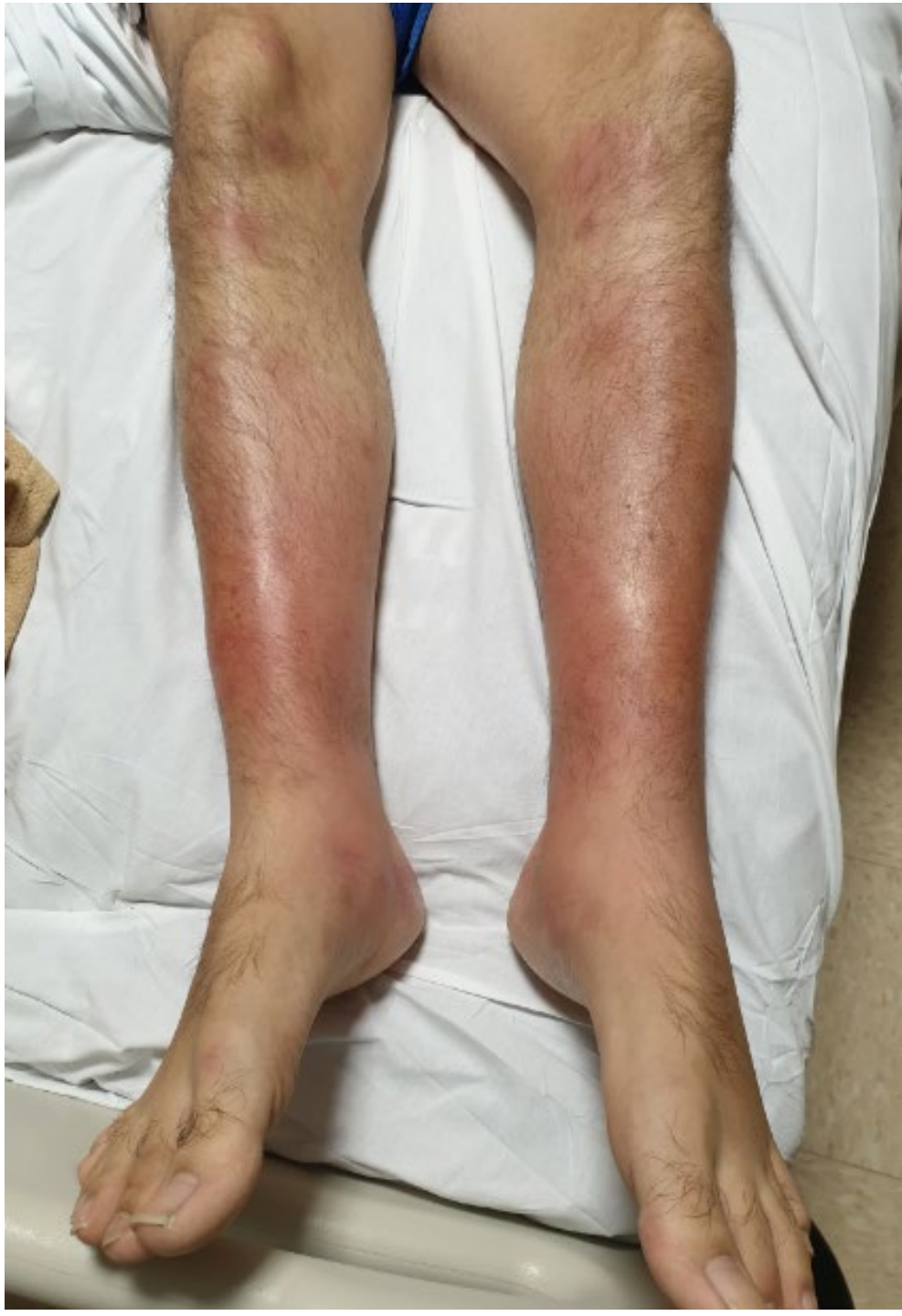
I FEEL HOT,
I CAN'T WALK AND
MY THROAT HURTS

Case Presentation

- 29 yo Caucasian male admitted for high fever, sore throat, poly-arthralgias and bilateral upper and lower extremity painful rash.
- Symptoms started 1 month ago after a trip to Guatemala.
- Treated by his PCP with Doxycycline and a Medrol dose pack with transitory improvement on his fever.
- No PMH, no medications, no known allergies.

Initial findings

- T-max 40 C, otherwise hemodynamically stable.
- Tender raised erythematous rash on bilateral lower extremities on ankle, knee, and right wrist.
- Synovitis and enthesitis in bilateral wrist and ankles.
- WBC 23, Hb and Plt Normal, CMP normal
- ESR 75, CRP 260.5, Ferritin 413, Triglyceride: 58



Preliminary differentials

Fever

Young man

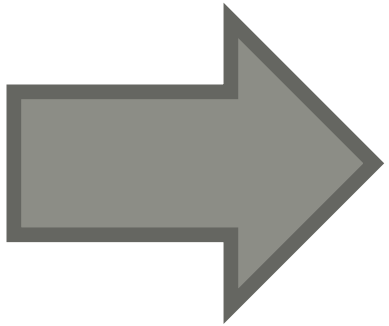
Odynophagia

Poly-arthritis

Elevated Inflammatory markers

Erythema nodosum

Leukocytosis



Rheumatic Fever

Post-Streptococcal Reactive Arthritis

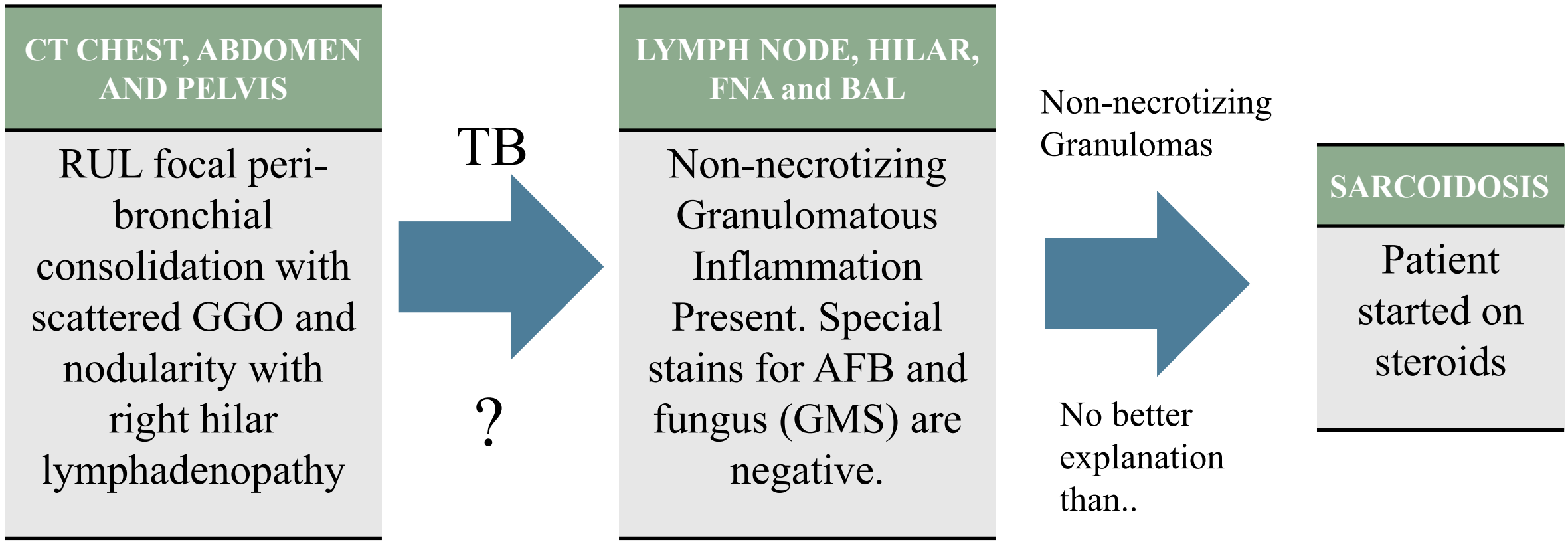
Further testing

- Blood cultures negative
- ASO <55 IU/mL
- Bartonella, Brucella ,aspergillus, Blastomyces, Coccidioides, Histoplasma, Strongyloides, Trichinella, Schistosoma, hepatitis B and C serologies negative.
- Neisseria and Chlamydia negative
- Mononucleosis screen negative
- HIV negative
- RPR negative
- QuantiFERON gold negative
- Malaria thick and thin smears negative

- ANA titer 1:320
- Normal C3 and C4
- dsDNA, ENA, ANCA, RF and CCP negative

- EKG and 2D echo normal
- CXR normal

Diagnostic Process



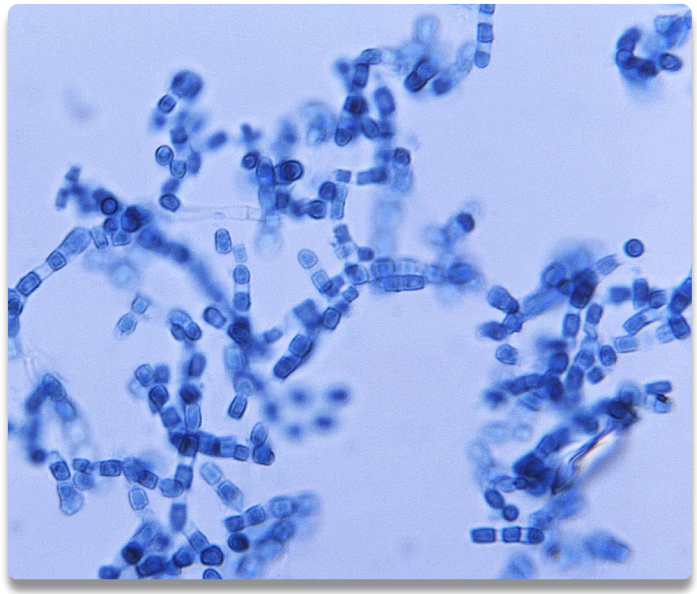
Audience response

- Regarding to Lofgren's syndrome, which of the following is TRUE:

a) It's the most common presentation of sarcoidosis
b) It's associated with a poor prognosis
c) It's more common in female
d) It's more common in people older than 40

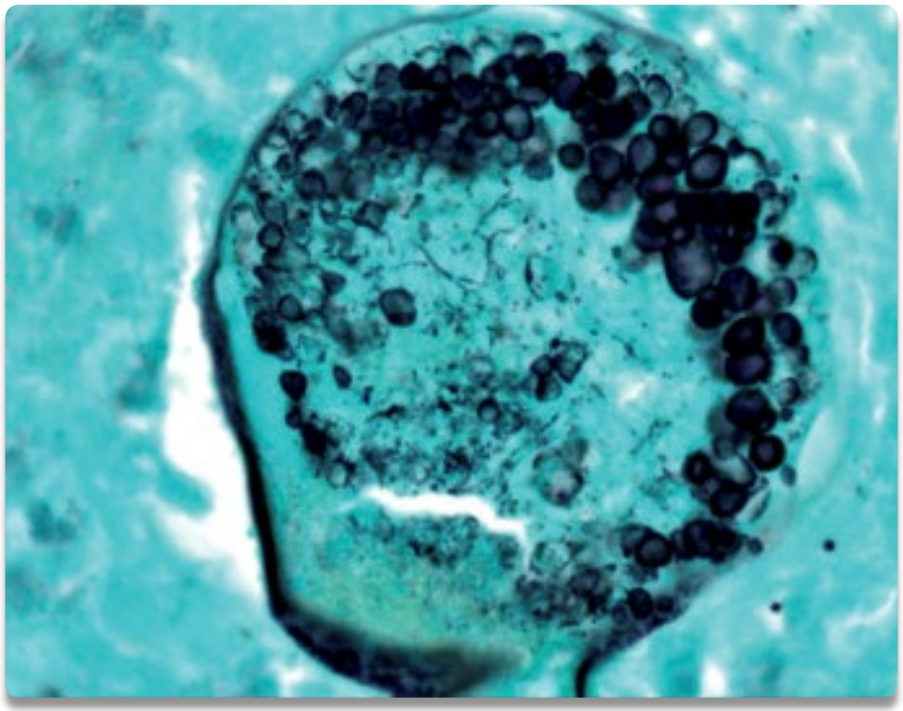
Final diagnosis

- 5 weeks later



- Respiratory Fungal Culture:
  - *Coccidioides immitis*

- **FINAL DIAGNOSIS:**
  - *Coccidioidomycosis*
    - Desert Rheumatism, San Joaquin Valley fever



- Patient started on Fluconazole for 8 months

Case Discussion: Sarcoidosis vs Infection

Causes of Erythema Nodosum

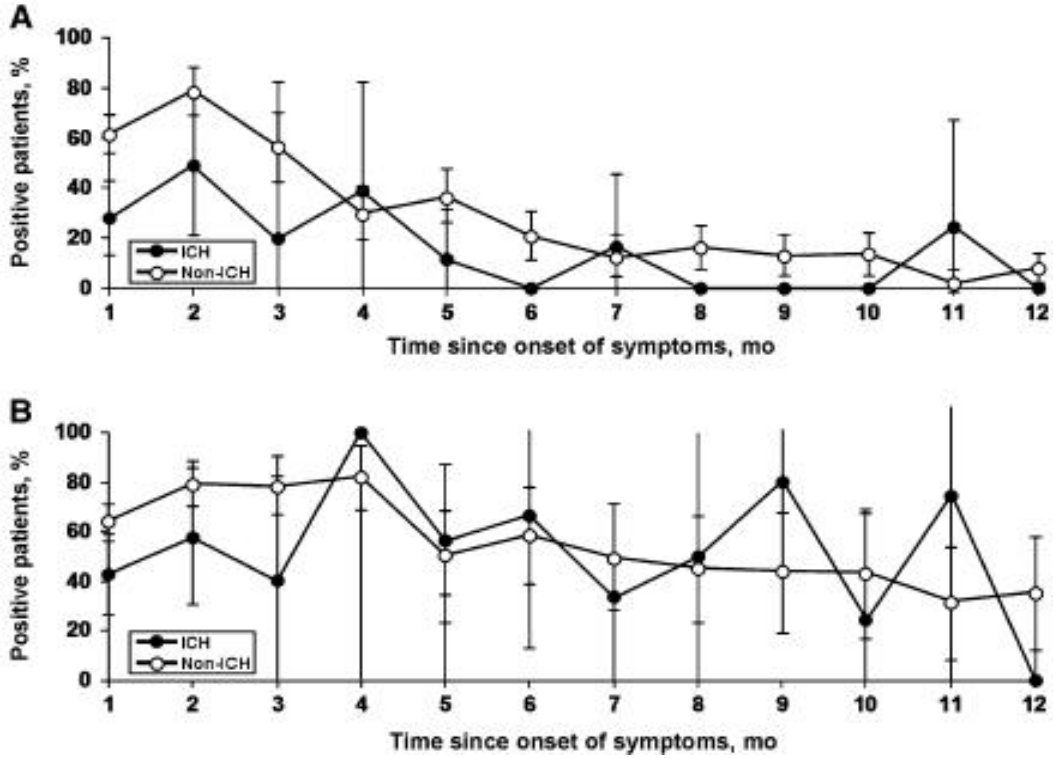
Common
- Idiopathic (up to 55%)
- Infections: GASP (28- 48%), Yersinia, mycoplasma, chlamydia, histoplasma, coccidioides, mycobacteria
- Sarcoidosis (11-25 %)
- Drugs (3-10 %): antibiotics, OCPs
- Pregnancy (2-5 %)
- Enteropathies (1-4%) regional enteritis, UC

Rare (less than 1 percent)
- Infections: HSV, EBV, HepB, HepC, HIV, rickettsiae, Salmonella, Syphillis, Bartonella, Giardia
- Miscellaneous: lymphoma

Coccidioidomycosis diagnosis

- Serological testing is the most common diagnostic method and includes EIA, IMDF and CF

Study method	Sensitivity
EIA IgG	79%
EIA IgM	63%
IMDF	71%
CF	64%



- Positive serologies are helpful, but negative ones cannot be relied on to rule out infection early in the course of the disease
- Recovery by culture from respiratory specimens (8.3%)

Case Discussion: Sarcoidosis vs Infection

Establishing Sarcoidosis diagnosis

- The pathological diagnosis of sarcoidosis generally halts clinical attempts to search for specific causes.

- To achieve a timely diagnosis, it is essential to :

(1) recognize both the typical and atypical radiologic manifestations of the disease

(2) Take note of features that may be suggestive of diseases other than sarcoidosis

- Lofgren syndrome (fever, bi-hilar lymphadenopathy, ankle swelling, and erythema nodosum) has 95% specificity for sarcoidosis and typically does not required a confirmatory biopsy.

- A bilateral hilar lymphadenopathy with a peri-lymphatic micro-nodular pattern is highly specific for sarcoidosis- so if unilateral- needs closer examination.

American College of Rheumatology 2020 Update

Angus Worthing MD
Board of Directors
September 26, 2020

Empowering rheumatology professionals
to excel in their specialty

American College of Rheumatology
Empowering Rheumatology Professionals

A Tale of Two Cities

CHARLES DICKENS

Pre-Coronavirus ACR Top Policy Priorities

- Cognitive care, E/M codes; protecting E/M win for rheumatology
- Prior Authorizations
- Step therapy
- Coverage for biologics in office
- Increase GME funding/rheum slots; loan repayment/forgiveness
- PBM transparency
- Reduce patient cost sharing
- Research funding
- MACRA/Quality Payment Program
- RISE registry
- Health care reform
- Biosimilars

The American College of Rheumatology (ACR), on behalf of its more than 7,700 members of the professional rheumatology community, wishes to express strong support for Dr. Anthony Fauci and his continued and close involvement in the work to address the nation's response to the COVID-19 pandemic.

During this national public health emergency, it is vital that we adhere to sound scientific and public health guidance from medical experts, including Dr. Fauci. The ACR urges that scientific evidence shape our decisions and actions as we battle the COVID-19 pandemic. Dr. Fauci has dedicated his life to public service, leading the National Institute of Allergy and Infectious Diseases (NIAID) since 1984. Trained in immunology, Dr. Fauci has been recognized as a Master of the ACR, one of the highest honors the College bestows. He has earned the respect of the medical and scientific community and has proven his commitment to relying on science and the best available data as we work collectively to preserve public health in these challenging times.

The government's financial commitment to vaccine development to address this pandemic is laudable. In addition, Dr. Fauci, as well as other long-term professional leaders from the CDC, FDA, and NIH, should guide and inform the response of the government and the American people as we all work to control the spread of the SARS-CoV-2 virus. By following their collective lead, we have the best chance for a speedier mitigation of this deadly virus.

July 28, 2020

An Important Message from the ACR on the Death of George Floyd

June 11, 2020 • By From the College

The American College of Rheumatology is deeply troubled by the recent events surrounding the death of George Floyd. This tragedy is the latest in a long history of senseless killings of people of color. We recognize that racial inequality is an invisible undercurrent impacting the lives of many of our members and patients, and we condemn all acts that cause marginalization, discrimination, harm or death to any person. From lupus mortality to arthritis disability, and most recently to COVID-19 deaths, our minority communities have suffered disproportionately. As physicians and healthcare professionals, we are bound to protect the health of all of humanity. The American College of Rheumatology pledges to be a leader for inclusion and change for our members, our trainees, our staff and our patients.

Practice and Advocacy Resources

The ACR's COVID-19 Practice and Advocacy Task Force continues to work rapidly to provide support to you during this unprecedented time. You'll find guidance documents that include approaches to drug shortages, support for telehealth, information about federal stimulus relief aid, and guidance for infusions. Working with experts in COVID-related topics, we are focused on developing meaningful information and resources to help guide you.

Practice and Advocacy Resources

COVID-19 Manufacturer Resources and Patient Assistance Programs - *New*

Clinical Guidance for Adult Patients with Rheumatic Diseases

The ACR has developed clinical guidance for the care of adult patients with rheumatic diseases during the COVID-19 pandemic. Populations considered include patients with a documented COVID-19 infection, those who are stable following exposure to SARS-CoV-2 (but without known infection), and patients who are stable with no infection or exposure. The recommendations address various treatment options and provide general guidance, as well as direction for when to start, stop, or reduce medications. All recommendations are based on current knowledge and will be revised as circumstances and evidence evolve.

Telehealth

ACR Telemedicine Provider Fact Sheet - *Updated May 7, 2020*

The ACR's Telemedicine Provider Fact Sheet provides coding and other practical guidance for ensuring proper reimbursement for telehealth services.

Telehealth Quick Reference Guide - *Updated May 6, 2020*

The ACR quick reference coding guide is designed to assist rheumatologists and rheumatology professionals to navigate coding and billing for telehealth services.

Telehealth Frequently Asked Questions - *Updated May 14, 2020*

The Frequently Asked Questions (FAQs) resource is a companion to the ACR Telemedicine Provider Fact Sheet to assist rheumatologists and their staff locate answers to key questions on practice flow and coding/billing telehealth services.

Commercial Payer Temporary Telehealth Policies - *Updated June 1, 2020*

The ACR has compiled a chart of the temporary changes that commercial payers have made to their telehealth policies.

States Waiving of Modifying Licensure Requirements for Telemedicine in Response to COVID-19 - *Updated April 24, 2020*

The ACR has compiled a chart of state modifications to licensure requirements enabling providers to conduct telehealth across state lines during the COVID-19 emergency.

Telehealth Vendor List

The ACR list of vendors is designed to help navigate an increasingly crowded space to choose the telehealth company that best meets rheumatology practices specific operational needs and unique patient population.

Patient Resource: How to Navigate Telehealth - *Updated April 11, 2020*

The ACR has developed guidance for rheumatologists and rheumatology professionals talking to patients who have questions about remote or telehealth visits with their rheumatology provider during the COVID-19 pandemic.

Template Letter to State Boards Regarding Malpractice Carriers

The ACR has created a template letter that providers can use to reach out to their state medical boards to advocate for clearer directives on practicing telehealth across state lines.

2021 Physician Fee Schedule changes

16% proposed increase for rheumatologists

- CMS revalued E/M codes according to the AMA RUC recommendations
- GPC1X complex care code

Telehealth

- CMS seeks comment on longer audio-only virtual check in visits
- May allow E/M visits and GPC1X codes over telehealth on a permanent basis

ACR Task Forces

- Global Strategy Task Force
  - position ACR as a global organization
  - projects to improve education, research, training, membership, volunteering starting 2021

- Governance Task Force
  - Reform ACR governance, to enhance ACR work, decisions, and communication (starting Fall 2020)

RRF MISSION:

To advance research and training to improve the health of people with rheumatic disease.

Since 1985, the Foundation has committed **$180M** directly to RESEARCH and TRAINING.

Rheumatology Research Foundation

What is RDAM?

Rheumatic Disease Awareness Month

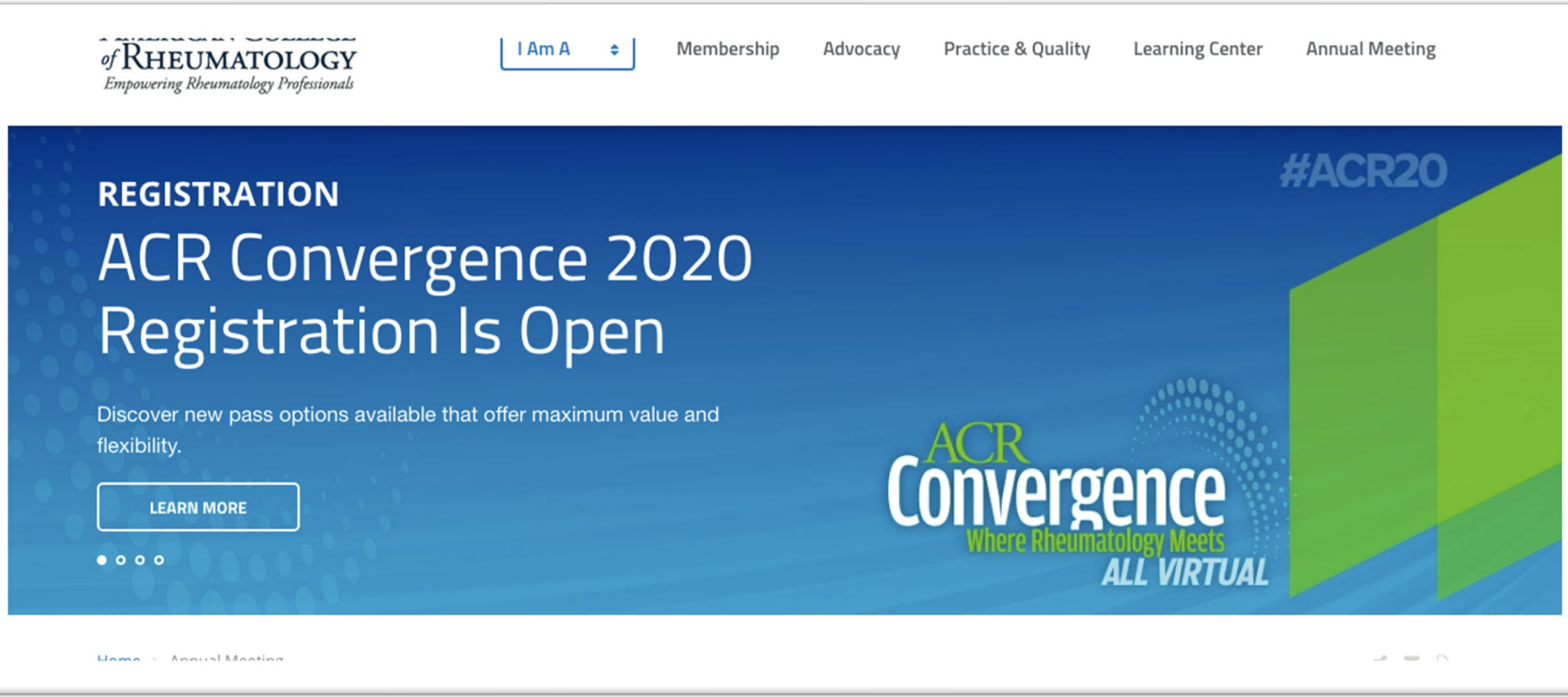
- Annual awareness event sponsored by ACR &its Simple Tasks™ campaign.
- Brings together the rheumatic disease provider and patient communities to raise awareness about rheumatic
- Inspire actions that improve the health and well-being of those living with rheumatic diseases.
- www.simpletasks.org

2020 theme: “My disease may be invisible, but I’m not.”

Featuring real patients and their stories.

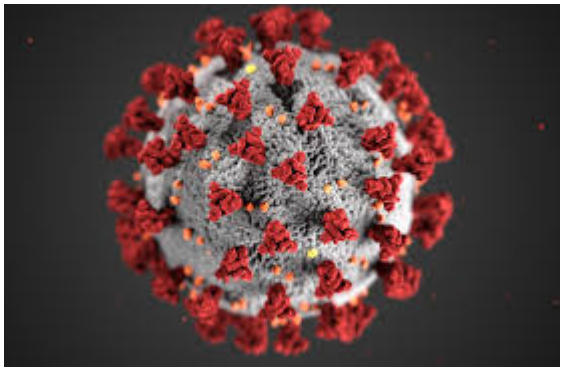
Empowering rheumatology professionals
to excel in their specialty

American College of Rheumatology
Empowering Rheumatology Professionals



Pennsylvania in Focus

- Lots of activity on our issues in 2019-2020
  - Not many wins
- Why?



- COVID-19 took up most of the energy in 2020

Pennsylvania: Bills introduced, 2019-2020

- Prior Auth/Step Therapy Reform
  - SB 920 and HB 1194
- PBM Reform
  - HB 941, HB 942, HB 943, and HB 944
- Copay Accumulator
  - SB 731
- Non-medical switching
  - HB 953
- Only HB 943 (gag clause ban) has passed

Why is RheumPAC Important for Rheumatology?

- Builds relationships new Members of Congress
- Educates legislators about our issues
- A seat at the table with other competing groups
- Support our legislative champions and ensure they remain in Congress

- Make a donation & learn more at www.rheumpac.org

Questions?

Email Advocacy@rheumatology.org about:

- advocacy
- insurance denials
- practice & COVID solutions

How I Diagnose and Treat IgG4-RD in 2020

Zachary S. Wallace, MD, MSc
Rheumatology Unit
Clinical Epidemiology Program
Division of Rheumatology, Allergy, and Immunology
Massachusetts General Hospital
Harvard Medical School

Disclosures

- No financial disclosures
- Will be discussing off-label use of FDA-approved medications

Objectives

- **Review** the diverse presenting features of IgG4-RD
- **Discuss** the diagnostic approach to IgG4-RD
- **Explore** approaches to the management of typical IgG4-RD

What is IgG4-RD and why should clinicians be aware of it?

- Immune-mediated condition
- Responsible for fibro-inflammatory lesions
- Often mistaken for malignancy
  - 2% to 3% of all Whipples for suspected pancreatic cancer actually show AIP
- Can lead to irreversible damage if untreated
  - Pancreatic insufficiency, ESRD, aortic dissection…
- Treatment can prevent damage
- Lessons learned may have applicability to other fibrosing conditions

Ann Surg. 2003;237:853–858

Four Cases: Who has IgG4-RD?

- 59 yo M w/ cough and LAD
- PET w/ FDG-avid
  - Pancreatic head
  - Prostate
  - LAD
  - LN biopsy benign
- Progresses
  - Loose stool, wt loss
  - Sinus congestion, anosmia
  - Submandibular gland enlargement
  - Worse BPH symptoms
- Gland resection and prostate biopsy

- 57 yo M w/ cough, wheezing, and LAD
  - Asthma-like symptoms in his 40s, worsening
  - Progressive Sx CT → hilar/med LAD
  - Elevated IgG4 and Eosinophilia
- LN biopsy

- 57 yo F w/ low back pain, weight loss and decreased urinary frequency
  - New renal failure
  - CT with RPF → stents
- RP biopsy

- 65 yo M w/
  - Scleral injection, light sensitivity
  - Hearing loss, sinusitis with bloody discharge
  - Severe headaches
  - Submandibular and parotid swelling
  - New IDDM
  - Elevated IgG4
- PET-CT
  - Mastoiditis
  - 4.5cm pancreatic tail mass w/ pancreatic enlargement
  - 3.2cm lung mass
- Lung biopsy

IgG4-Related Disease

WHO GETS IGG4-RD AND WHAT ARE COMMON MANIFESTATIONS?

Cohort Descriptions

- In 2001, initially recognized in a Japanese cohort with AIP
- By 2012, reported in cohorts around the world
- Affects patients of diverse racial and ethnic backgrounds
- Typically in the 5th - 7th decades of life
- Slight male predominance overall

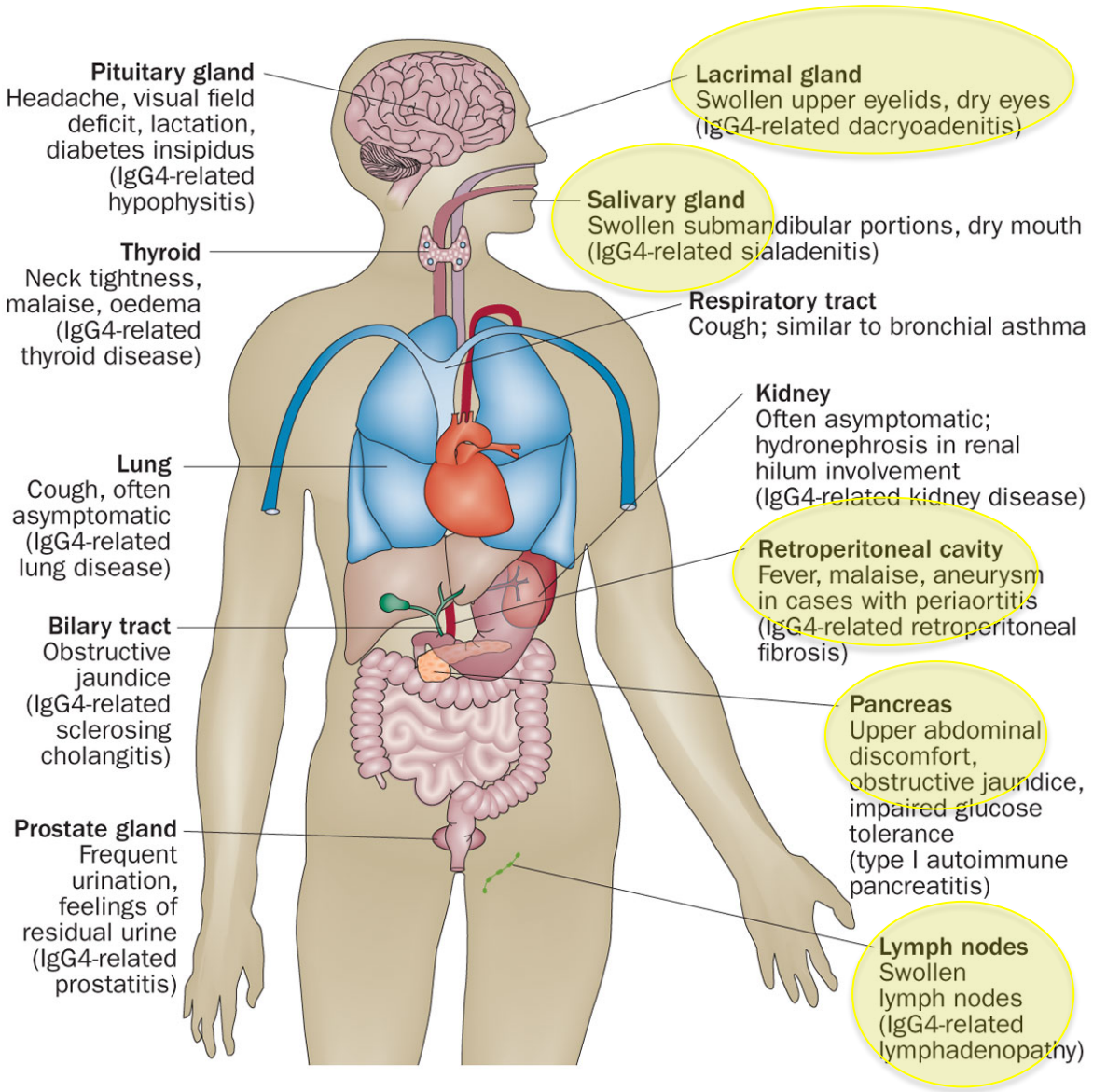
N Engl J Med 2001;344
Arthritis Rheum 2016;68:2290
Gut 2013;62:1771
Rheumatology 2015;54:1982
Medicine 2015;94:e680
Am J Gastroenterol 2014;109:1675
Arthritis Rheum 2015;67:2466

International Cohort

Demographic/Feature	Mean (SD) or N (%)
Age at Symptom Onset (yrs)	58 (15)
Age at Diagnosis	60 (14)
Time to Diagnosis	2 (3)
Male	322 (65%)
Race	
Caucasian	198 (40%)
Asian	208 (42%)
Latino/Hispanic	58 (12%)
South Asian	14 (3%)
Black	9 (2%)
Other	6 (1%)

Ann Rheum Dis 2019;78:406

IgG4-RD Manifestations



Single organ ~40%

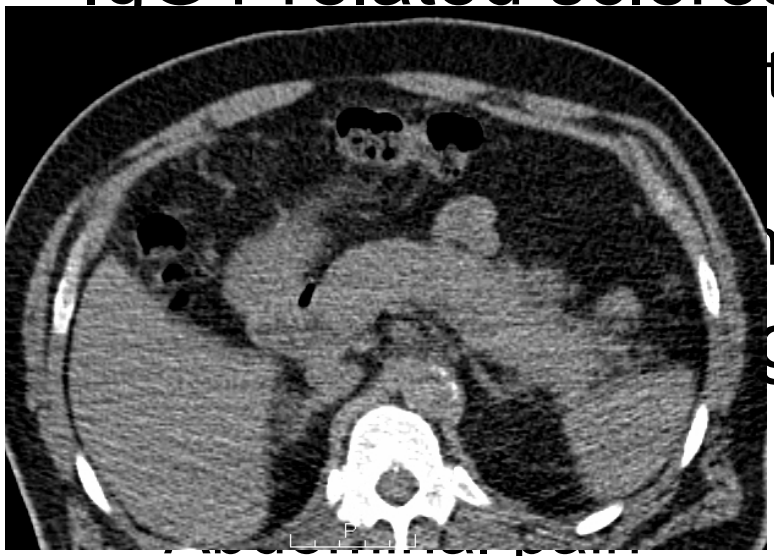
Multi-organ presentations common

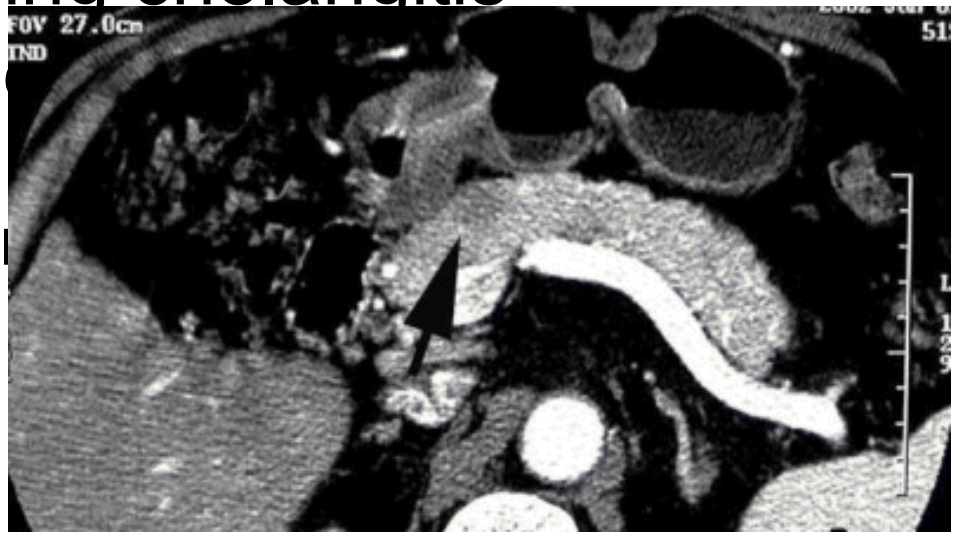
Synchronous vs metachronous

Nat Rev Rheumatol 2014;10:148

Pancreato-hepato-biliary Manifestations

- Type 1 autoimmune pancreatitis
  - Type 2 is a/w IBD, distinct process/pathology
  - Diffuse pancreatic enlargement, pancreas mass
- IgG4-related sclerosing cholangitis

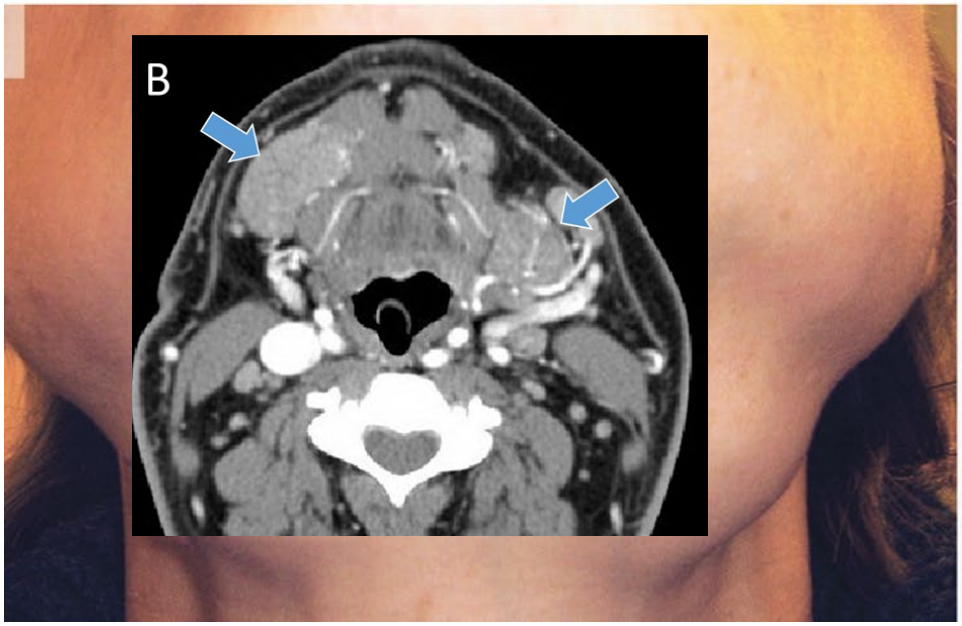


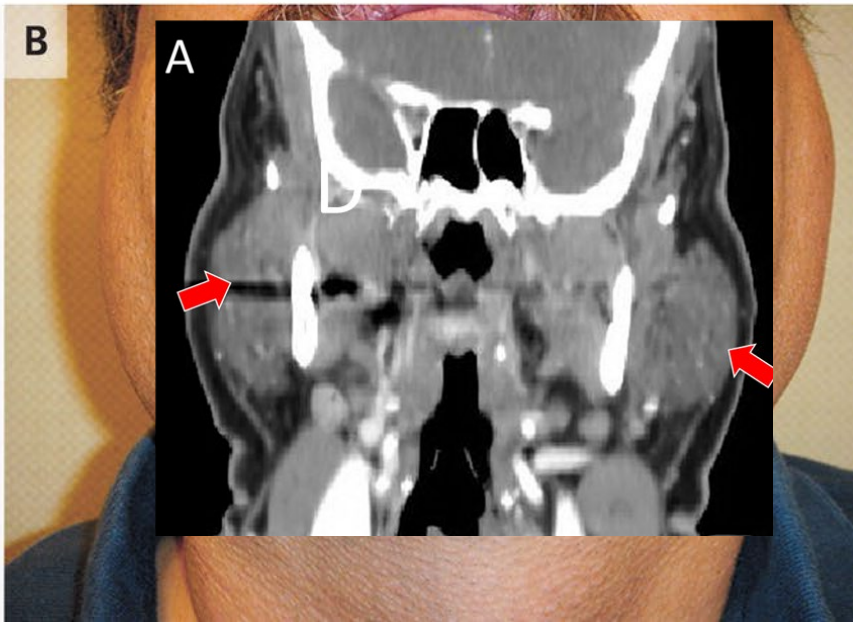


Am J Gastroenterol 2004;99:2038
Gut 2013;62:1771
Arthritis Rheum. 2020;72:7

Salivary Gland Manifestations

- Submandibular, parotid, sublingual glands may be enlarged
- Typically symmetric, often firm

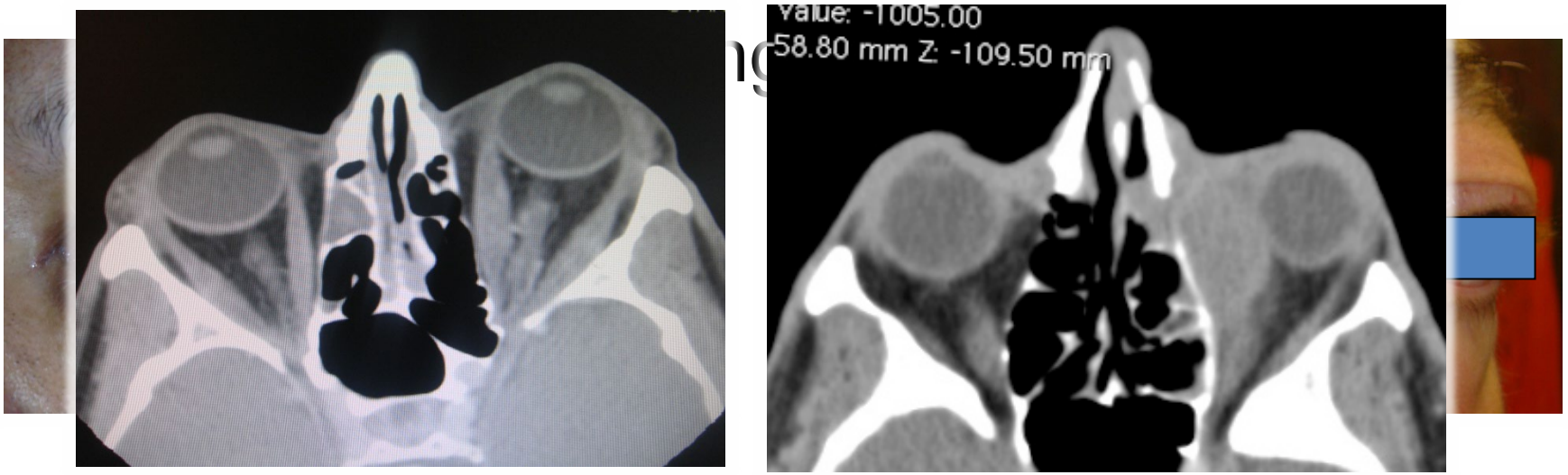




NEJM 2012;366:539

Orbital Manifestations

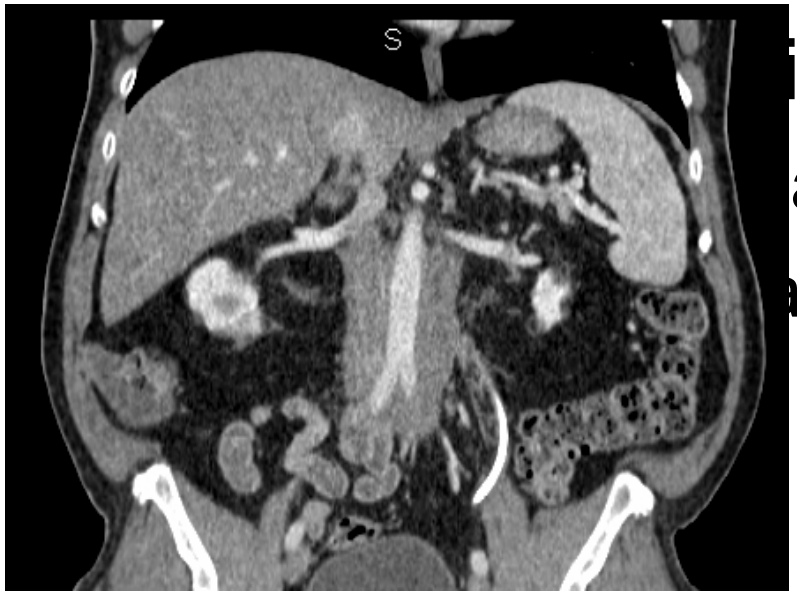
- Lacrimal glands, extra-ocular muscles, orbital soft tissue
- May be associated with trigeminal nerve enlargement

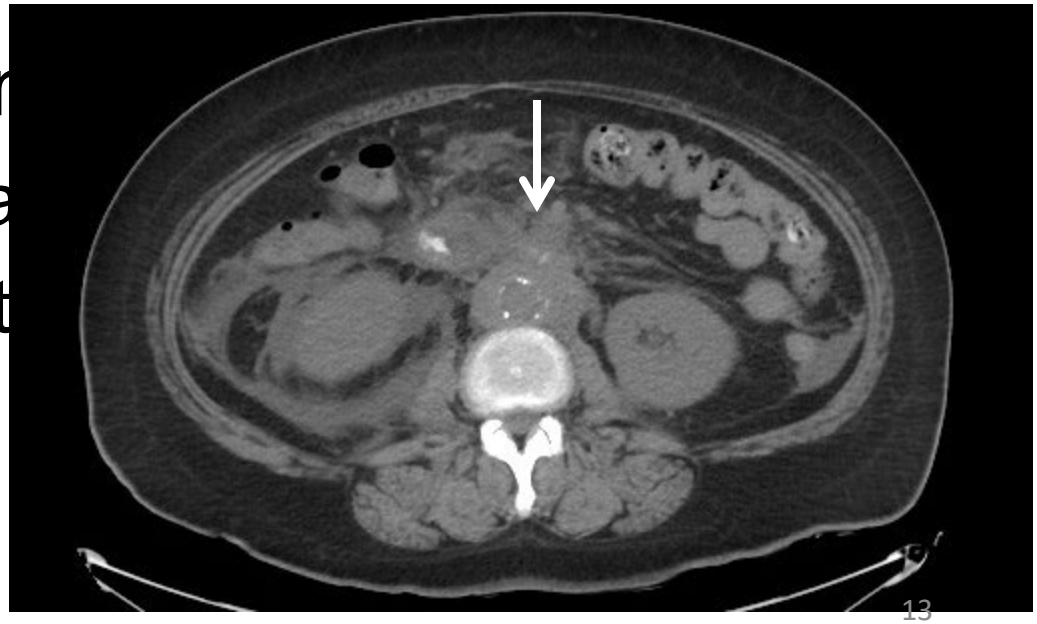


Semin Arthritis Rheum 2014;43:806

Retroperitoneal Manifestations

- Retroperitoneal fibrosis (RPF) extending anteriolaterally around the aorta/iliacs
- Often traps the ureters and pulls them medially

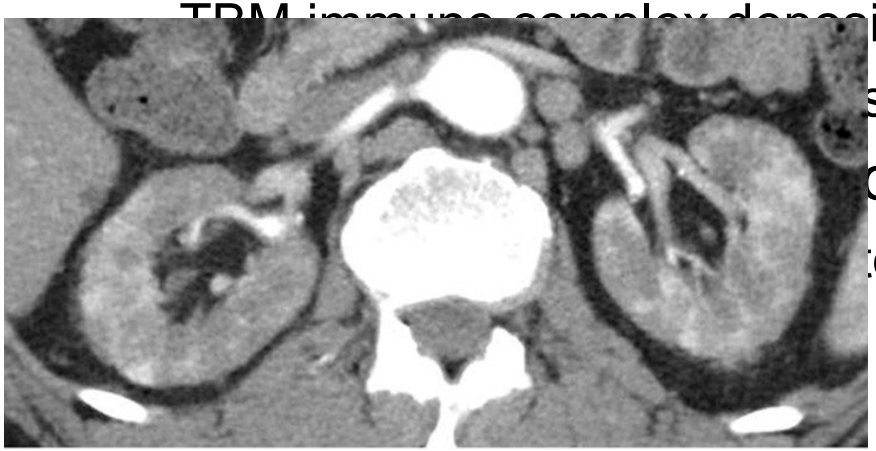


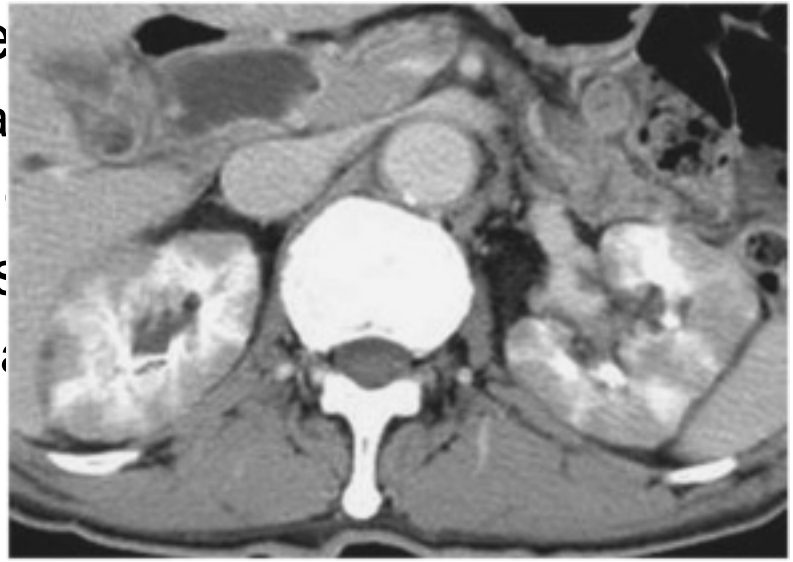


J Am Soc Nephrol 2016;27:1880

Renal Manifestations

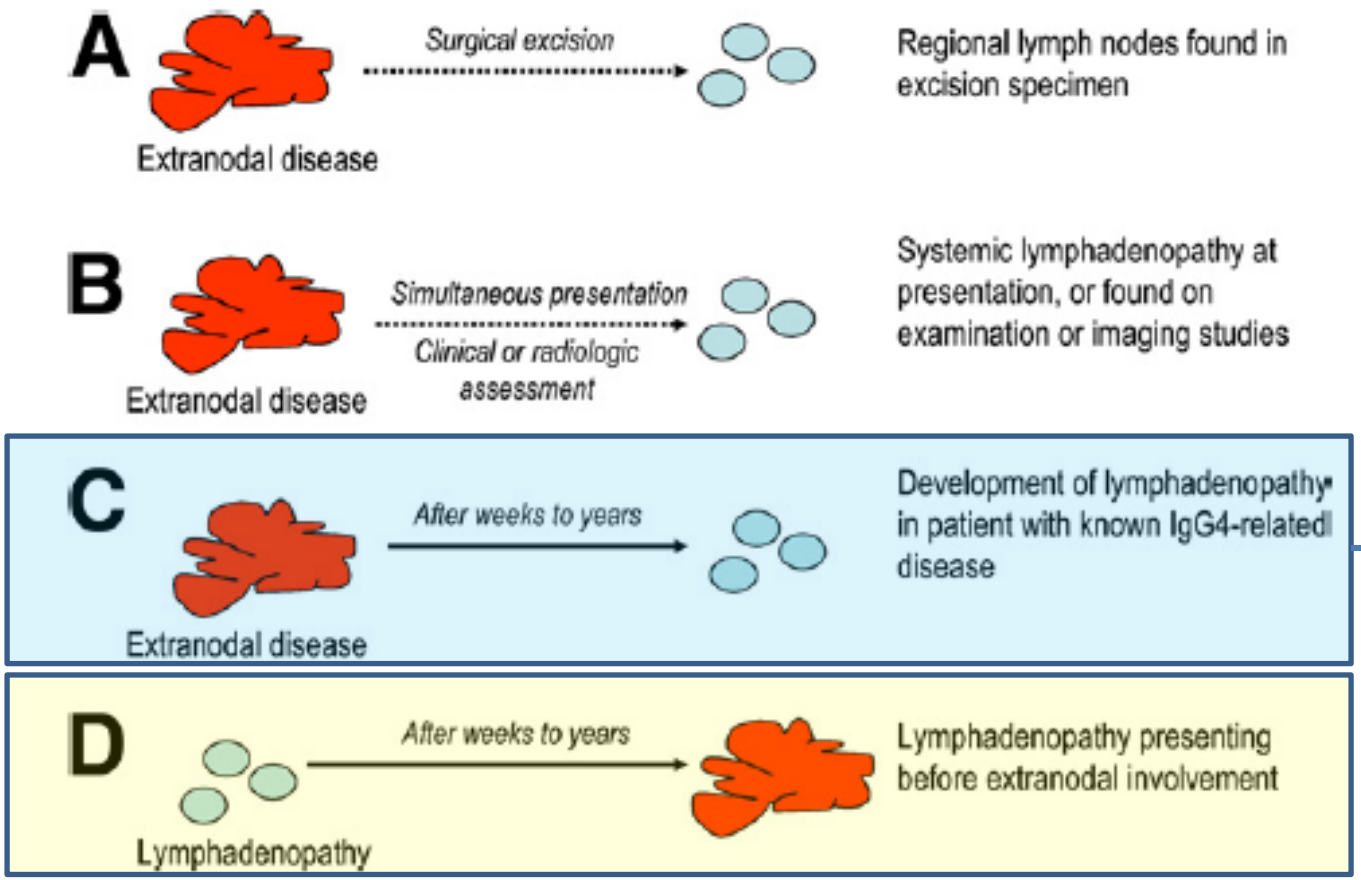
- Most commonly tubulointerstitial nephritis (TIN)
  - Non-PLA2R membranous nephropathy also reported
- Imaging w/ multiple, bilateral cortex lesions
  - May also find round or wedge-shaped parenchymal lesions
- Pathology with variable degree
  - TBM immune complex deposits a
  - s to
  - oms
  - temia





Kidney Intl 2014;85:251
Curr Opin Nephrol Hypertens 2015;24:193

Lymphadenopathy in IgG4-RD



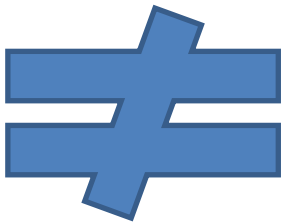
Lymphoma?

IgG4-RD?

Seminars in Diag Path 2012;29:226
Virchows Arch 2018;472:839

Lymph Node Biopsies in IgG4-RD

Lymph node biopsy with significant IgG4+ plasma cell infiltrate



IgG4-Related Disease

Other Manifestations

- Destructive Sinus Disease
- Thoracic
  - Bronchovascular and septal thickening
  - Pseudotumor
  - Paravertebral lesion
- Papular skin lesions
- Aortitis/Large Vessel Manifestations
- Pachymeningitis

Clustering of IgG4-RD Features

Pancreato-hepato-biliary group	Retroperitoneum and Aorta	Head and Neck Limited	Mikulicz and Systemic Disease

Ann Rheum Dis 2019;78:406

What do clusters tell us about IgG4-RD?

- Differences in pathogenesis?
- Differences in risk factors?
  - RP/Aorta → tobacco associations
- Differences in comorbidities?
  - Head/neck → allergic conditions
- Delays in diagnosis?
- Response to treatment?

Ann Intern Med. 2014;161(3):181
Mod Rheumatol. 2018;28(5):845-8.

General Clinical Features

- Prominent features in some patients:
  - Fatigue
  - Weight loss (esp with pancreatic insufficiency)
  - Arthralgias
- Atypical features:
  - Fevers without alternative explanation (in the absence of cholangitis, etc)
  - Severe pain

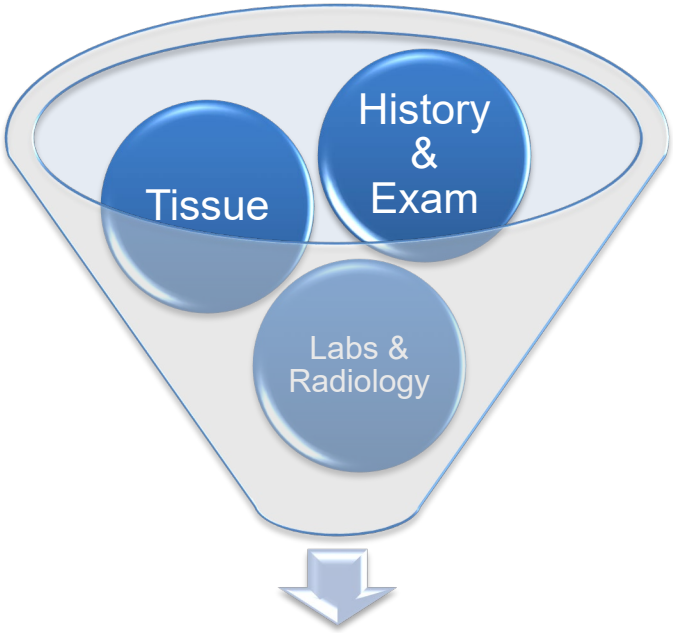
Laboratory Features

- Serum IgG4 elevation
  - Normal in 30% of IgG4-RD
  - Does not always normalize despite clinical remission
- Hypocomplementemia
  - Most often in the setting of renal disease
- Peripheral eosinophilia and ↑ IgE
  - With or without atopic disease
- Elevated ESR and/or CRP

IgG4-Related Disease

HOW DOES ONE DIAGNOSIS IGG4-RD?

Making the Diagnosis



IgG4-Related Disease

- Clinico-pathologic correlation
- No pathognomonic sign, symptom, or finding
- Biopsies are not always possible
- IgG4 concentration elevations and infiltrates are not specific
- Consider the differential

What could I be missing?

- Antineutrophil cytoplasmic antibody–associated vasculitides
  - Granulomatosis with polyangiitis (Wegener's)
  - Microscopic polyangiitis
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Adenocarcinoma and squamous cell carcinoma, peritumoral infiltrate
- Castleman's disease (multicentric or localized)
- Cutaneous plasmacytosis
- Erdheim-Chester disease
- Inflammatory myofibroblastic tumor
- Inflammatory bowel disease
- Lymphoproliferative diseases
  - Extranodal marginal zone lymphomas
  - Lymphoplasmacytic lymphomas
  - Follicular lymphomas
- Perforating collagenosis
- Primary sclerosing cholangitis
- Rhinosinusitis
- Rosai-Dorfman disease
- Sarcoidosis
- Sjögren's syndrome
- Splenic sclerosing angiomatoid nodular transformation
- Xanthogranuloma

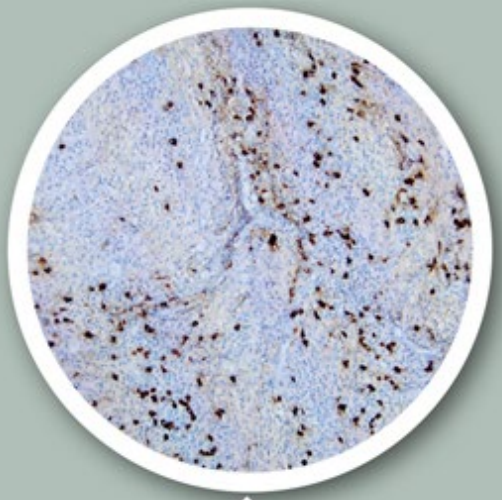
What other tests might you send?

How much to push for a biopsy?

Often site-specific or manifestation-specific

Arthritis Rheum 2015;67:1688

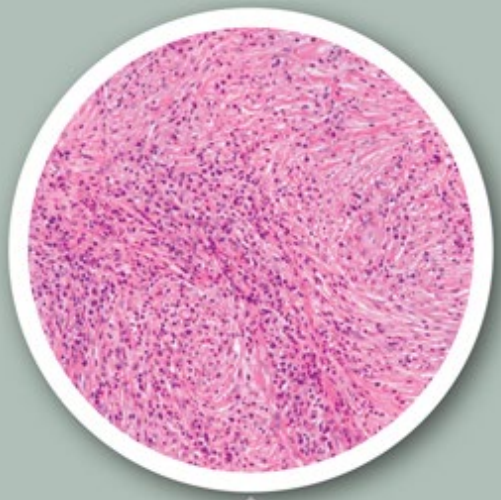
The Classic Pathology of IgG4-RD



Lymphoplasmacytic infiltrate

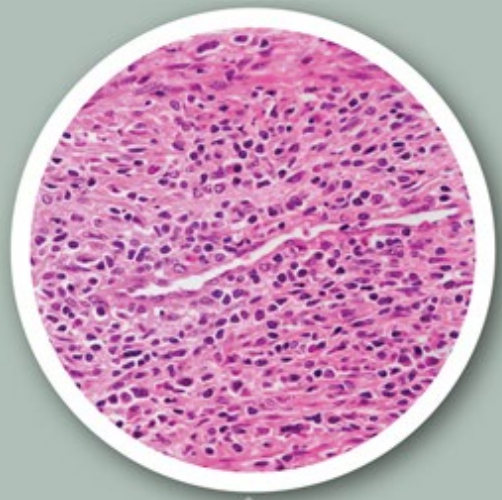
Both B- and T-lymphocytes are present. A monoclonal population rules out IgG4-RD.

T-lymphocytes often out-number B-lymphocytes.



Storiform fibrosis

Often described as resembling the spokes of a wheel

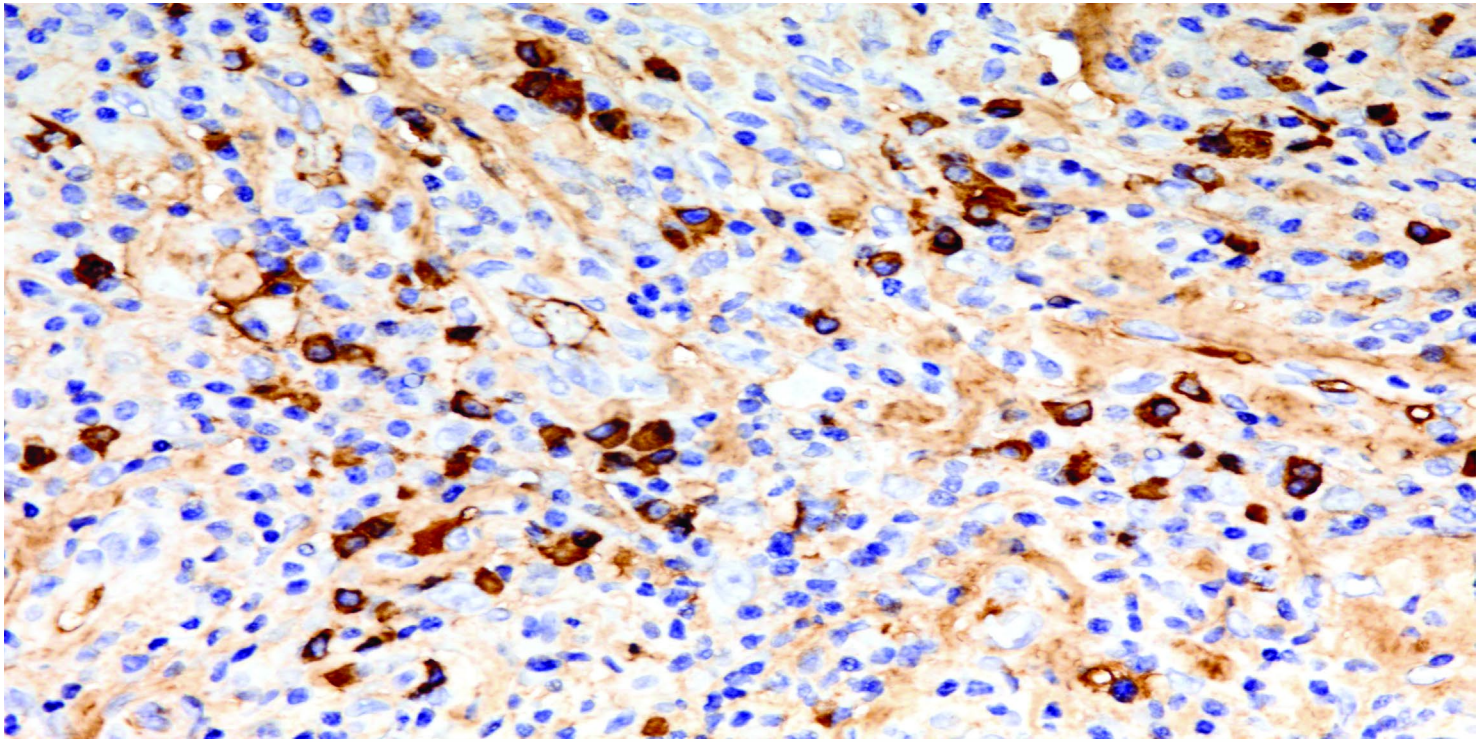


Obliterative phlebitis

Inflammation in the wall of a vein so extensive that the lumen is obstructed.

(This is distinct from the necrosis seen in vasculitis.)

Mod Pathol. 2012;25(9):1181-92



Antibodies to IgG4

Images Courtesy of V. Deshpande

Pitfalls in Diagnosing IgG4-RD

BRIEF REPORT

Spuriously Low Serum IgG4 Concentrations Caused by the Prozone Phenomenon in Patients With IgG4-Related Disease

Arezou Khosroshahi,[1] Lynn A. Cheryk,[2] Mollie N. Carruthers,[3] Judith A. Edwards,[2] Donald B. Bloch,[3] and John H. Stone[3]

Original contribution

IgG4-positive plasma cells in granulomatosis with polyangiitis (Wegener's): a clinicopathologic and immunohistochemical study on 43 granulomatosis with polyangiitis and 20 control cases ☆

Sing Yun Chang MD[a], Karina A. Keogh MD[b], Jean E. Lewis MD[a], Jay H. Ryu MD[b], Lynn D. Cornell MD[a], James A. Garrity MD[c], Eunhee S. Yi MD[a,*]

EXTENDED REPORT

The diagnostic utility of serum IgG4 concentrations in IgG4-related disease

Mollie N Carruthers,[1] Arezou Khosroshahi,[2] Tamara Augustin,[3] Vikram Deshpande,[4] John H Stone[1]

Arthritis Rheum. 2014;66:213
Ann Rheum Dis. 2015;74:14
Human Pathology 2013;44:2432

ACR/EULAR Classification Criteria (NOT diagnostic criteria)

Characteristic clinical or radiologic involvement of a typical organ* (OR lymphoplasmacytic involvement in a typical organ)

Absence of certain clinical, serological, radiology, and pathology features.

Weighted criteria typical of IgG4-RD

*Pancreas, salivary glands, bile ducts, orbit, kidney, lung, aorta, retroperitoneum, pachymeninges, thyroid

Arthritis Rheum. 2020;72:7
Ann Rheum Dis. 2020;79:77

Selected Exclusion Criteria

Clinical

- Fever
- No objective response to 4 weeks of GC

Serological

- Unexplained ↓ WBC & PLT
- Eos > 3,000 / mm^3
- + PR3- or MPO-ANCA
- Positive specific antibodies (e.g., Ro, La, dsDNA)
- + Cryo that could explain presentation

Radiological

- Unexplained findings concerning for malignancy or infection (necrosis, cavitation, etc)
- Rapid progression (4-6 wks)
- Osteosclerotic long bone abnormalities c/w Erdheim-Chester
- Unexplained splenomegaly

This is not a laundry list of tests to perform or steps to take in making the diagnosis.

Pathology Exclusion Criteria

- Findings concerning for malignancy
  - Monotypic inflammatory infiltrates
  - Cellular atypia
  - Light chain restriction
- + Myofibroblastic tumor marker (e.g., ALK)
- Neutrophilic abscess/prominent infiltrate
- Necrotizing vasculitis
- Prominent necrosis
- Primarily granulomatous inflammation
- S100+ macrophages c/w Rosai-Dorfman

Even in the setting of IgG4+ plasma cell infiltrates, storiform fibrosis, and other features

Arthritis Rheum. 2020;72:7
Ann Rheum Dis. 2020;79:77

ACR/EULAR Classification Criteria (NOT diagnostic criteria)

Arthritis Rheum. 2020;72:7
Ann Rheum Dis. 2020;79:77

Histopathology	
Uninformative biopsy	+ 0
Dense Lymphoplasmacytic Infiltrate	+ 4
Dense Lymphoplasmacytic Infiltrate and Obliterative Phlebitis	+ 6
Dense Lymphoplasmacytic Infiltrate and Storiform Fibrosis w/ or w/o Obliterative Phlebitis	+ 13

	IgG4+ Cells/HPF			
IgG4:IgG+ Ratio	0 to 9	Indeterminate	10 to 50	≥50
0 to 40%	0	7	7	7
Indeterminate	0	7	7	7
41-70%	7	7	14	14
≥70%	7	7	14	16

Serum IgG4 Concentration	
Normal or Not Checked	+ 0
> Normal but < 2x Upper Limit of Normal	+ 4
2x to 5x Upper Limit of Normal	+ 6
≥ 5x Upper Limit of Normal	+ 11

Bilateral Lacrimal, Parotid, Sublingual, and Submandibular Glands	
No set of glands is involved	+ 0
One set of glands is involved	+ 6
Two or more sets of glands are involved	+ 14

Chest and Thoracic Aorta	
Not checked or neither of the items listed is present	+ 0
Peribronchovascular and septal thickening	+ 4
Paravertebral Band-Like Soft Tissue in the Thorax	+ 10

Pancreas and Biliary Tree	
Not checked or none of the items listed is present	+ 0
Diffuse pancreas enlargement (loss of lobulations)	+ 8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+ 11
Pancreas (either of above) and biliary tree involvement	+ 19

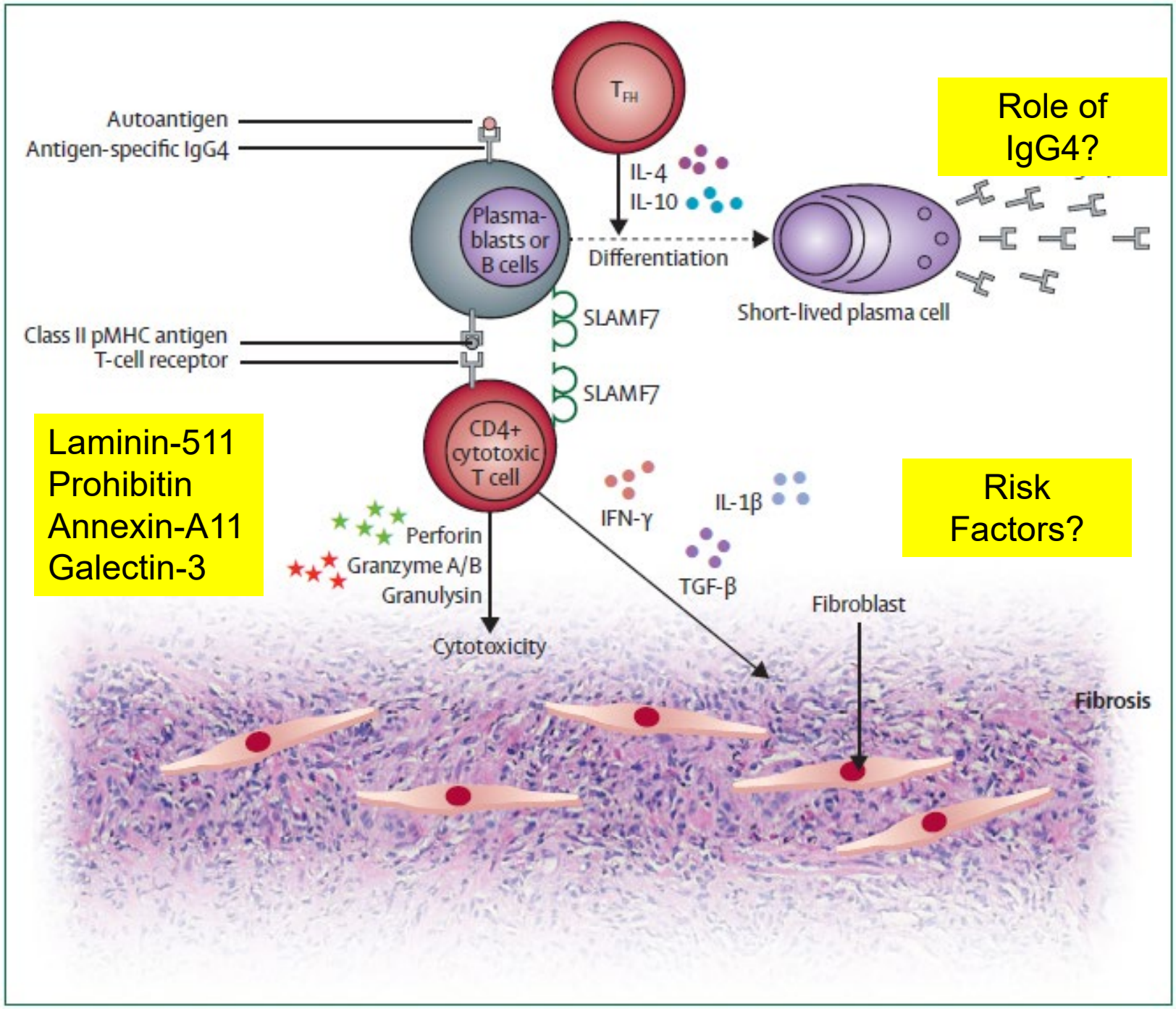
Kidney	
Not checked or none of the items listed is present	+ 0
Hypocomplementemia	+ 6
Renal pelvis thickening/soft tissue	+ 8
Bilateral renal cortex low density areas	+ 10

Retroperitoneum	
Not checked or neither of the items listed is present	+ 0
Diffuse thickening of the abdominal aortic wall	+ 4
Circumferential or antero-lateral soft tissue around the infra-renal aorta or iliac arteries	+ 8

Fulfills criteria if total points > 20

IgG4-Related Disease

WHAT CAUSES IGG4-RD?



Lancet Rheumatol 2019;1:e55

IgG4-Related Disease

HOW DO WE TREAT IGG4-RD?

Who gets treatment?

- All symptomatic patients with active IgG4-RD require treatment
  - It is important to distinguish active disease from symptoms due to damage
- Asymptomatic disease often requires treatment to minimize damage
  - Aortic aneurysms, renal disease, lung disease
- Some asymptomatic disease may be monitored after reviewing risks/benefits
  - e.g., salivary gland disease

Arthritis Rheumatol 2015;67:1688

Treatment Options

- Pharmacologic
  - Glucocorticoids
  - Steroid Sparing Agents
    - Conventional DMARDs (Azathioprine, 6-MP, methotrexate, Leflunomide, MMF)
    - Rituximab
  - Combination therapy (GC + Steroid-sparing agent)
- Interventional
  - Biliary and ureteral stents, nephrostomy tubes
  - Resection/debulking

Glucocorticoids

- Generally considered first-line treatment
- Dosing varies based on the manifestation
  - 40-60mg/day (or 0.6-1mg/day)
  - Lower dose in less severe forms
- Single-arm prospective trial
  - Highly effective: overall response rate of >90%
  - Complete remission rate of 66%
  - No patients were refractory to treatment
  - Most frequent adverse event was glucose intolerance

Mod Rheumatol 2016;15:1
Arthritis Rheumatol 2015;67:1688

Relapses on Glucocorticoids

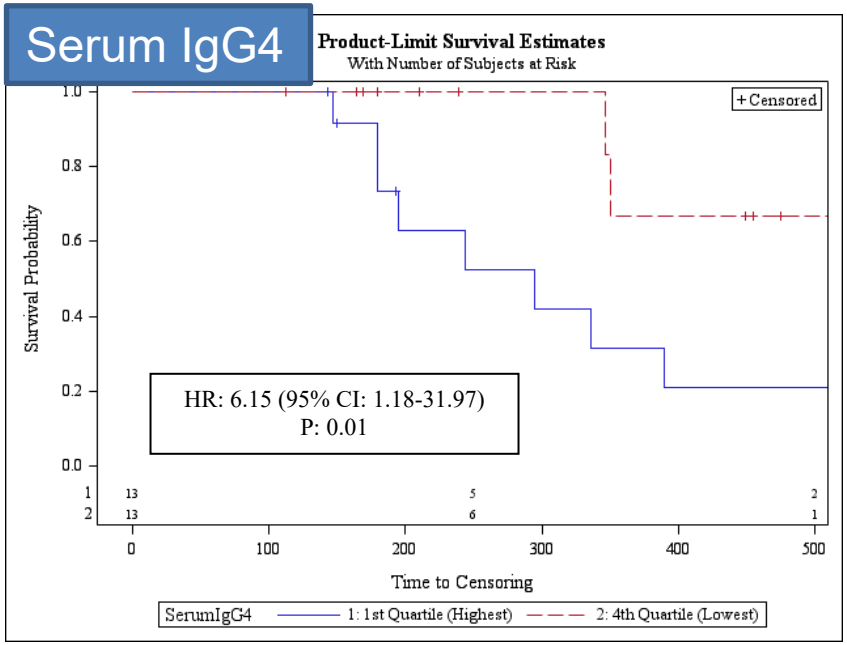
- Steroids are effective, but…
  - Relapses occur in 20-40% while on GC maintenance therapy
  - 26% of relapses occurred on prednisone doses > 10mg/day
  - In one study, only 30% of pts were able to discontinue GC
  - ~20% of patients developed diabetes on GC

This is often a relapsing condition, necessitating a steroid-sparing option for long-term remission

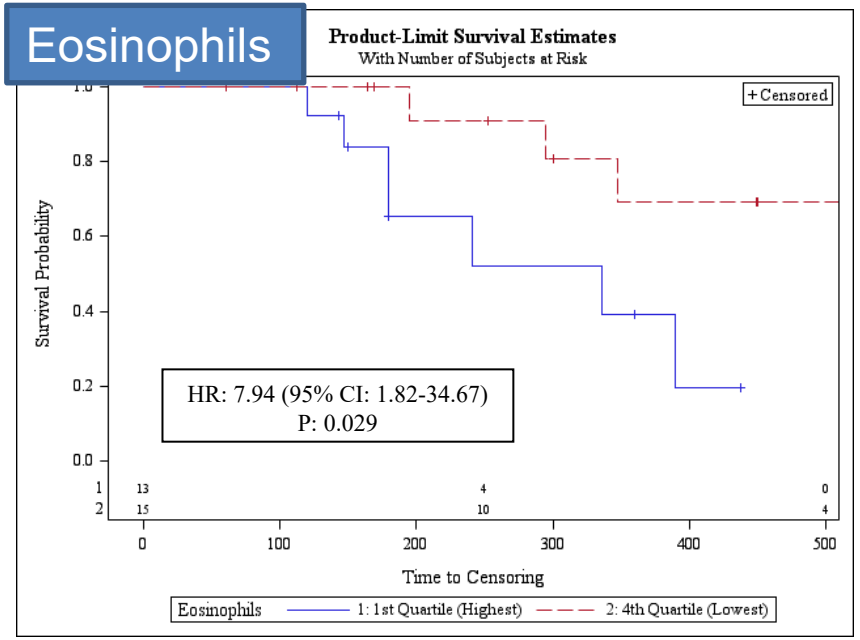
J Gastroenterol 2014;49:961
Arthritis Care Res 2014;66:86
Arthritis Rheum 2015;67:2466
Rheumatology 2019;58:52

Who relapses?

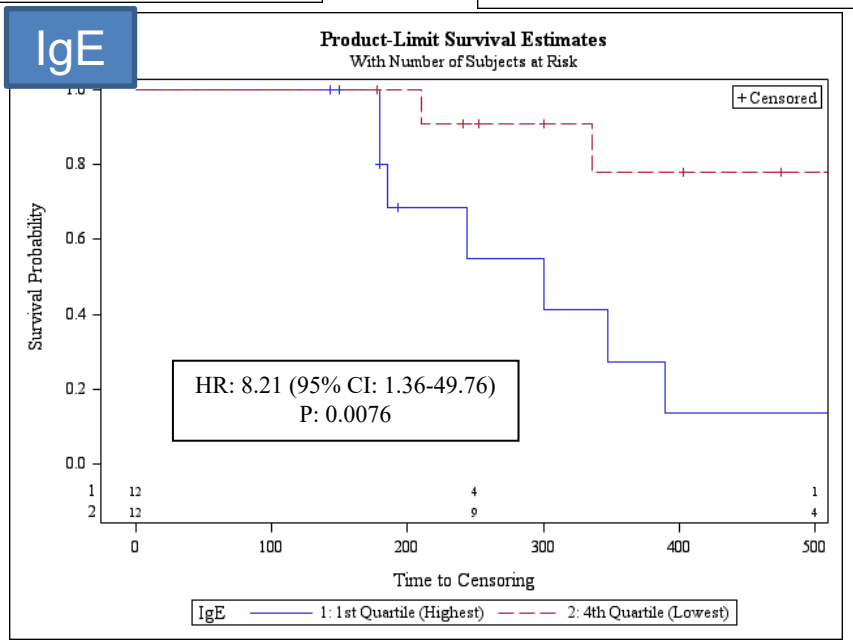
Serum IgG4



Eosinophils



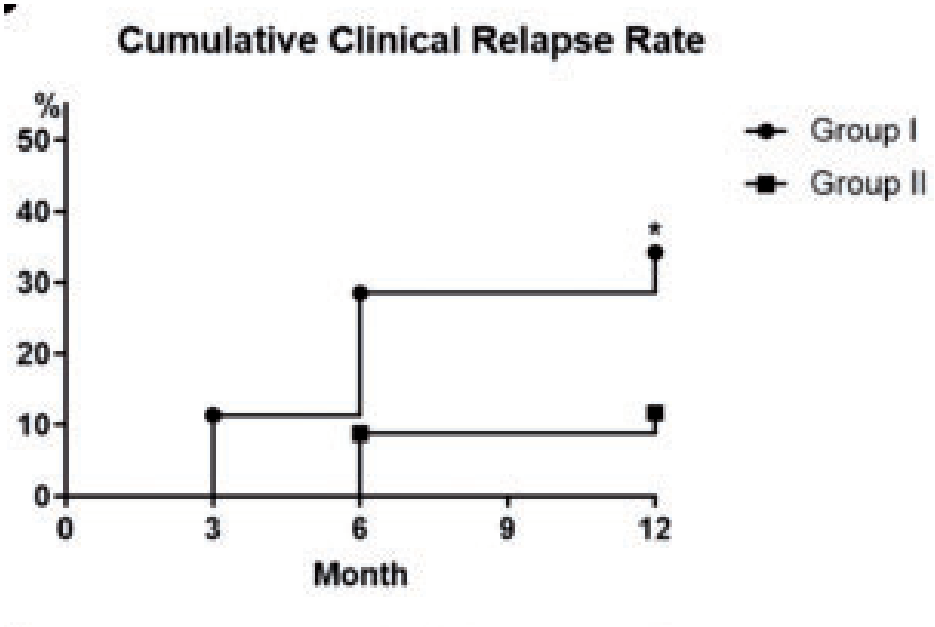
IgE



Rheumatology. 2016;55:1000

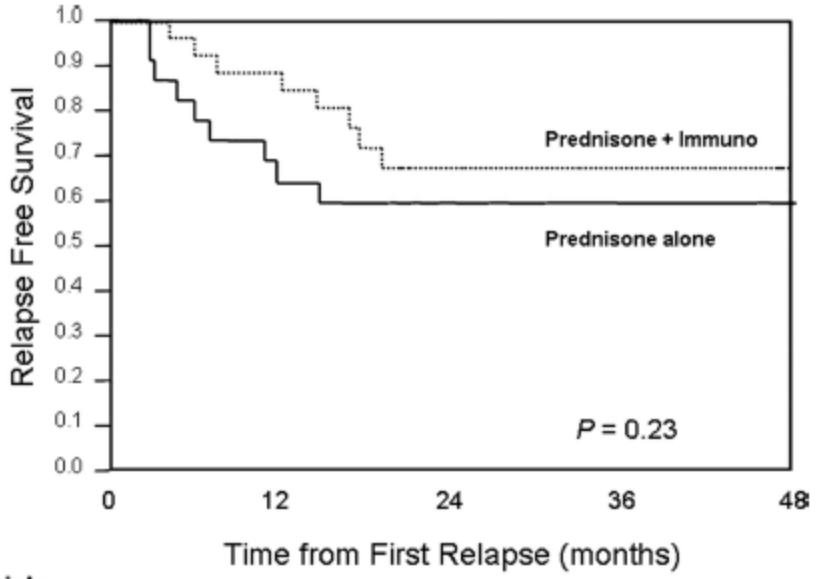
MMF in IgG4-RD

- Single-center, open-label RCT
- Newly-diagnosed
- GC (Group I) vs GC + MMF (Group II)
- 69 patients total
- GC continued for 12 months



Rheumatology 2019;58:52

Conventional steroid-sparing agents (e.g., azathioprine) are often ineffective



Number at risk					
Pred + Immuno	27	22	13	11	7
Pred alone	24	15	11	9	8

Caveats…

- Retrospective
- Patients with autoimmune pancreatitis (50% OOI)
- Patients experiencing 2nd relapse
- Similarities between two groups except that prednisone group had higher serum IgG4

Gut 2013, 62(11):1607

Rituximab in IgG4-RD: Pilot Trial (N=30)

Table 2 Primary and secondary outcomes

Outcome	Proportion of participants (%)
Primary outcome	23/30 (77%)
Disease response (6 months)	29/30 (97%)
Sustained disease response	22/30 (73%)
Complete remission (6 months)	14/30 (47%)
Complete remission (6 months), exclusive of serum IgG4	18/30 (60%)
Complete remission (any time point)	18/30 (60%)
Complete remission (any time point), exclusive of serum IgG4	20/30 (67%)
Relapses occurring before month 6	3
Relapses occurring between months 6 and 12	4
Time to endpoint	**Duration (days)**
Time to disease response (mean±SD)*	43±37
Time to complete remission (mean±SD)*	198±87
Time to relapse (mean±SD)	210±105
Treatment	
Total prednisone dose equivalent (mg) administered in the 28 days prior to the 6 month study visit (mean, range)	15 (0–280)
Retreatment with RTX for relapses during the 12 months after enrolment	4/30 (13%)

*The time to disease response and time to complete remission measures overestimate the speed required to achieve these measures because an in-person visit was required for these measures.
RTX, rituximab.

The primary outcome was defined by three criteria:
(1) Decline of the IgG4-RD RI ≥2 points compared with baseline;
(2) No disease flares before month 6; and
(3) No GC use between months 2 and 6

26/30 participants were **not** on GC during the trial.

Ann Rheum Dis 2015;74:1171

Therapeutic Options

- GC Monotherapy – High risk of relapse
- GC + DMARDs
  - MMF
  - Other oral DMARDs (MTX, leflunomide)
  - Rituximab
- Rituximab monotherapy
- Additional randomized trials are needed

Ann Rheum Dis 2015;74:1171
Rheumatology 2016;55:1000
Rheumatology 2019;58:52

Four Cases: Who has IgG4-RD?

- 59 yo M w/
  - Pancreatitis
  - Prostatitis
  - Sialoadenitis
  - Sinusitis
- Submandibular gland resection
  - Non-specific inflammation
- Prostate biopsy
  - "odd inflammation"
  - Second opinion, interpreted as IgG4-RD
- Reviewed submandibular gland, found c/w IgG4-RD
- ↑ IgG4 and new renal failure

- 57 yo M w/
  - cough, wheezing, LAD, eosinophilia, ↑ IgG4
- LN biopsy
  - Reactive lymphoid hyperplasia
  - Mild capsular fibrosis
  - > 50% IgG4+, > 50 IgG4+ cells/hpf

- 57 yo F w/ RPF
- RP biopsy
  - Lymphoplasmacytic infiltrate
  - Storiform fibrosis
  - IgG4+ plasma cell infiltrate
- ↑ IgG4

- 65 yo M w/
  - Pancreatitis c/b DM
  - Sialoadenitis
  - Scleritis
  - Hearing loss
  - Sinusitis / mastoiditis
  - Elevated IgG4
  - Lung mass
- Lung biopsy
  - PMNs, giant cells, few plasma cells
  - Microabscesses
- PR3-ANCA+

Conclusions

- IgG4-RD is often under-recognized but typically presents in characteristic patterns
- IgG4 concentrations and IgG4+ plasma cell infiltrates are neither sensitive nor specific for IgG4-RD
- Glucocorticoids are highly effective but flares and toxicities are frequent
- Additional clinical trials are necessary to define optimal treatment strategies

Thank You!

John Stone
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Ana Fernandes
Payal Patel
Tyler Harkness
Vikram Deshpande
Liam Harvey

Rheumatology Research Foundation
Advancing Treatment | Finding Cures

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Allergy and Infectious Diseases

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RHEUMATOLOGY
SOCIETY

Representing Pennsylvania Rheumatologists

Speaker Slides Sunday

7th ANNUAL SCIENTIFIC MEETING

SEPTEMBER 26-27, 2020 • VIRTUAL

Common Challenges in Image Interpretation of Arthritis

Donald J. Flemming, MD, FACR
Dept of Radiology
Penn State Hershey Medical Center

Disclosures

- Royalties – Author, Elsevier

Common Challenges

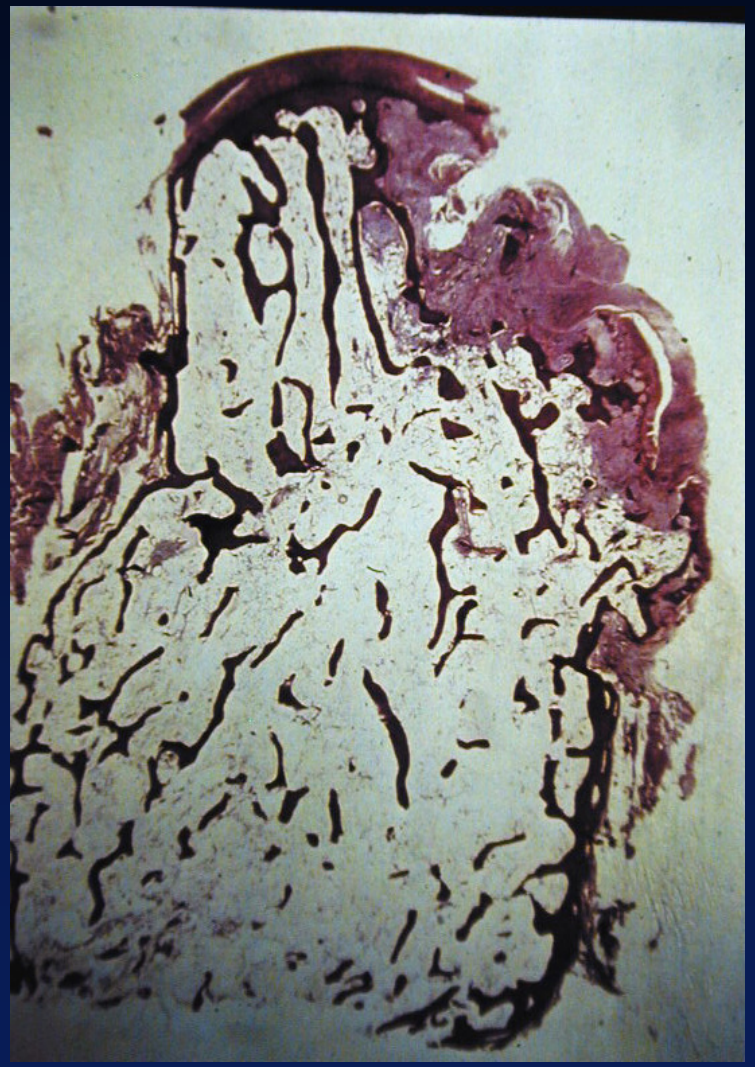
- Erosion vs Pseudoerosion
- SI joints
- Synovitis
- “Signs”
- Multiple arthropathies

Common Challenges

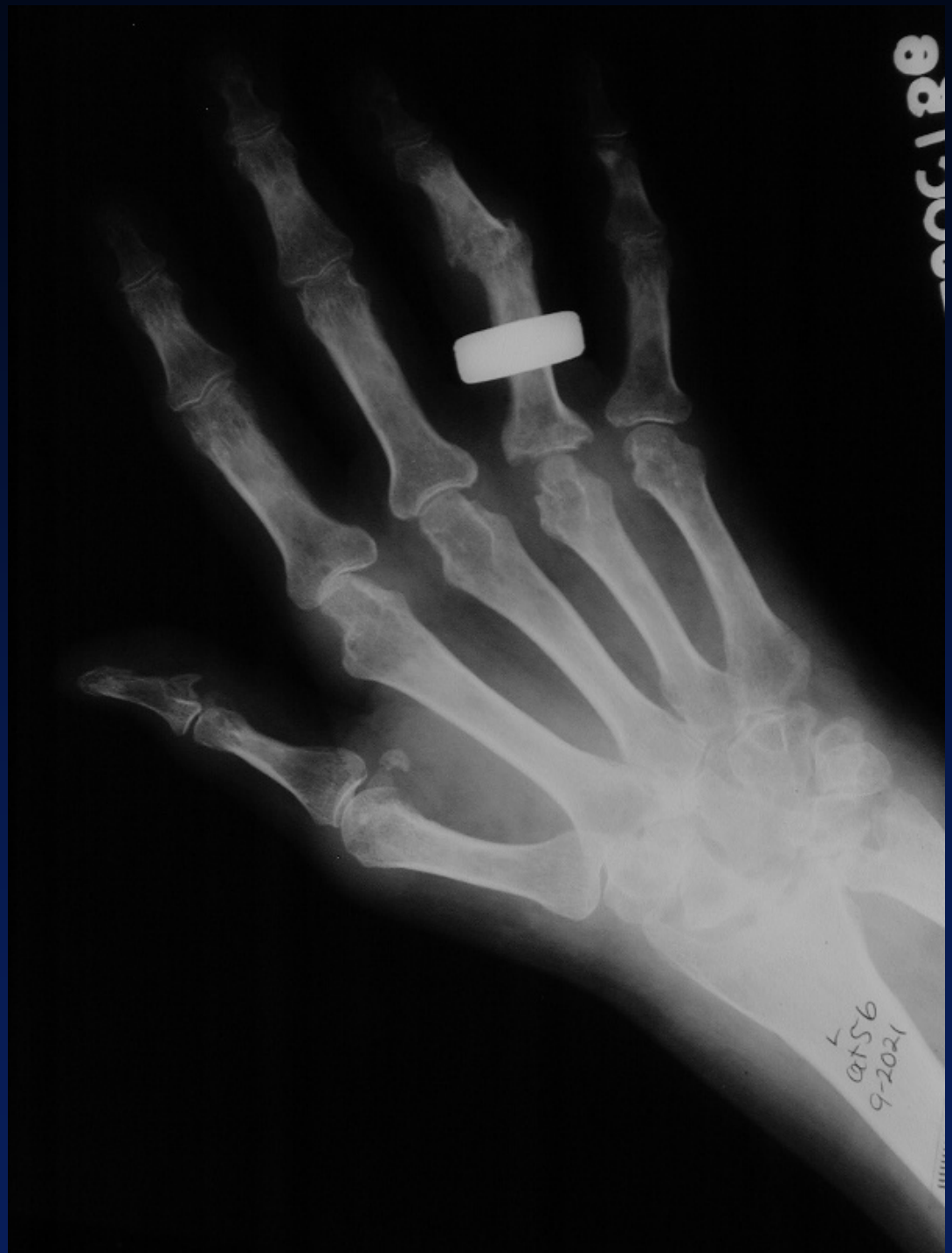
- Clinical syndromes
- Bone, entheses and synovium are dumb
- Sensitivity vs Specificity
- Harder to apply exams to individual patients than to study populations

Erosion

- Interruption of bone
  - PF sensitivity – 19%[1]
  - Needs to be tangential
  - MR/US more sensitive/ CT specific
  - PF complimentary
- Aggressive vs Nonaggressive
- Location-marginal vs central
  - Pencil in cup

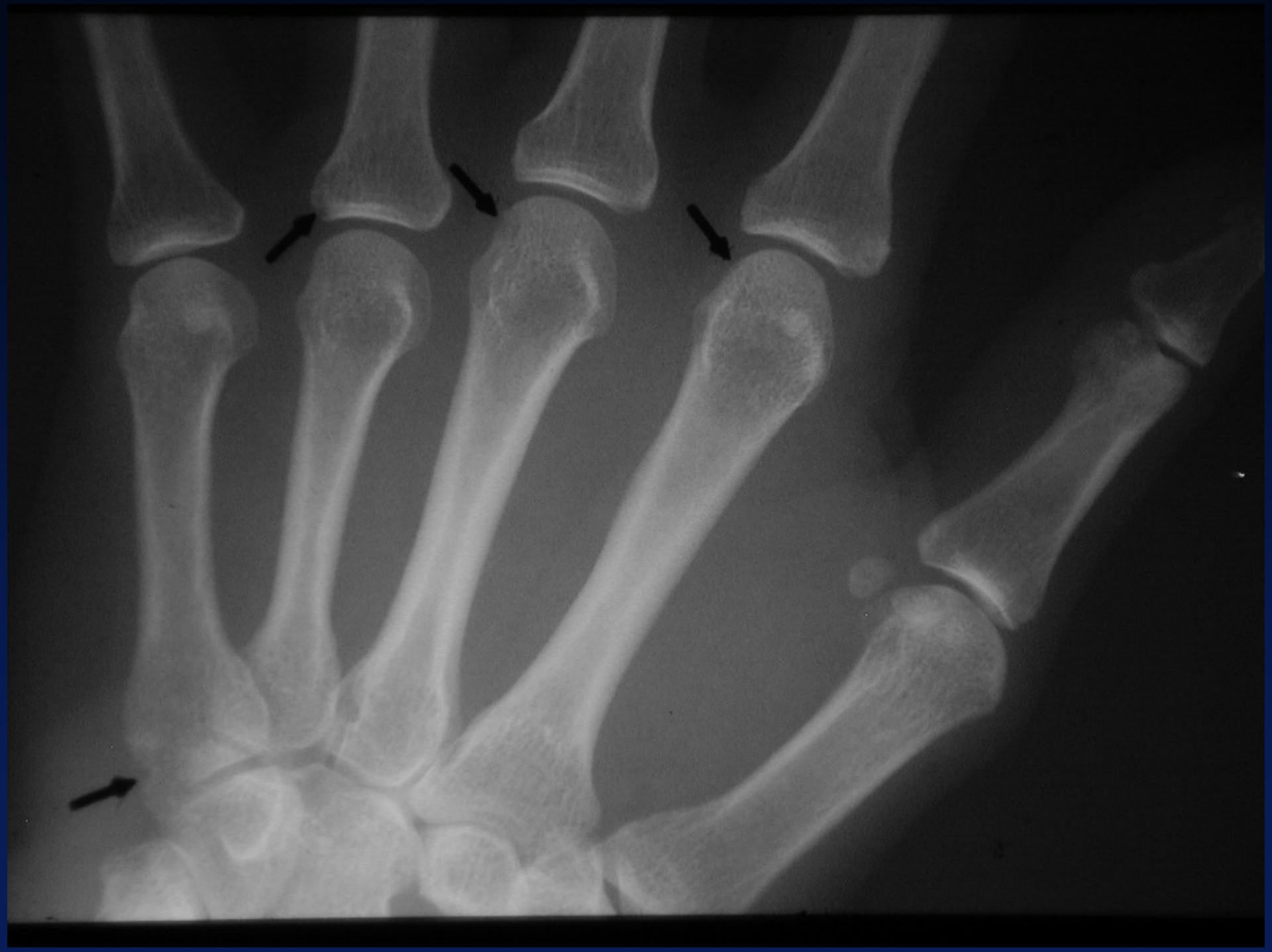


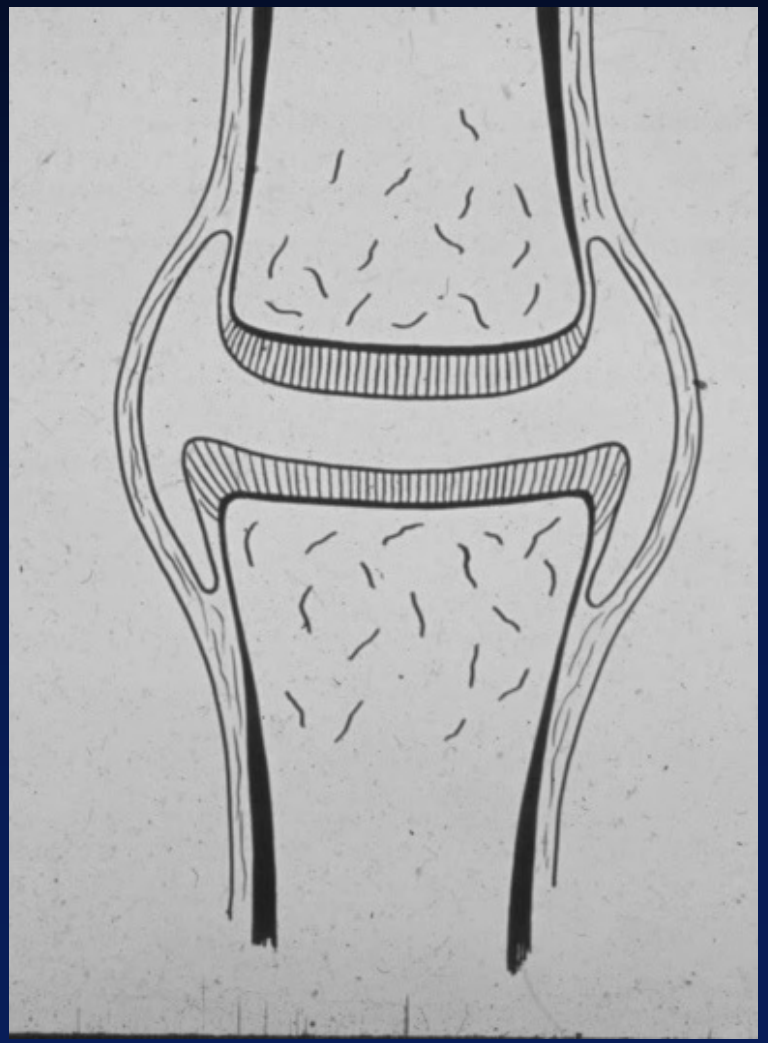
[1] *Arthritis Res Ther*. 2006;8(4):R110.

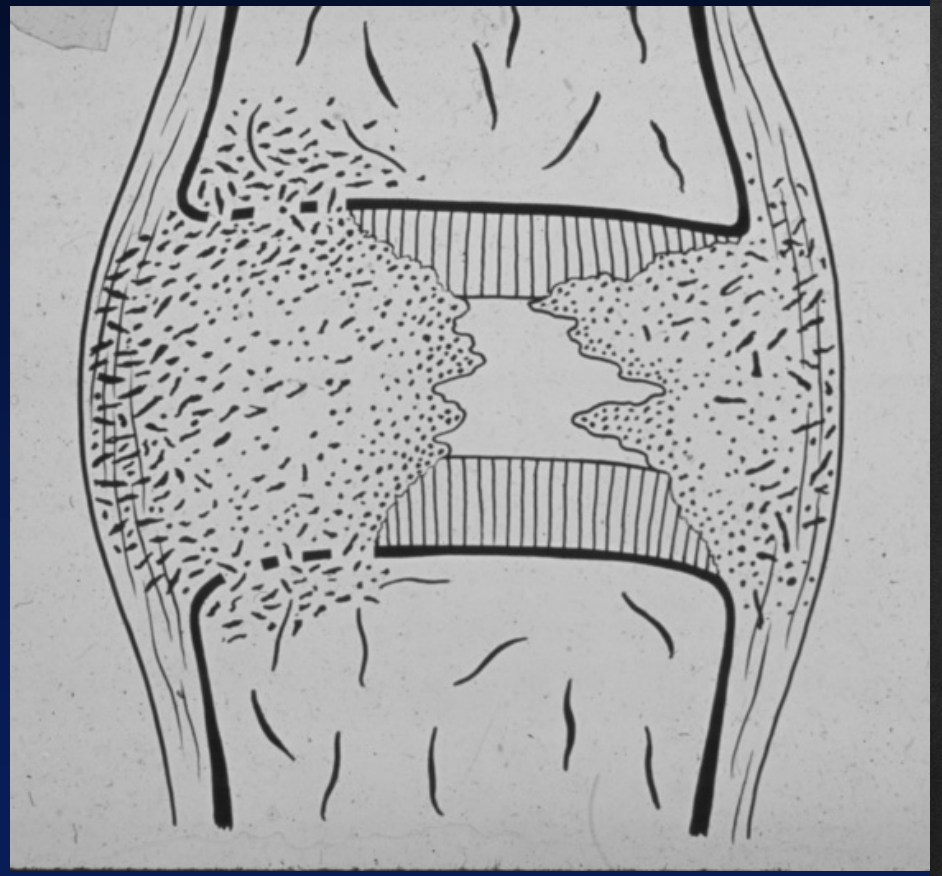


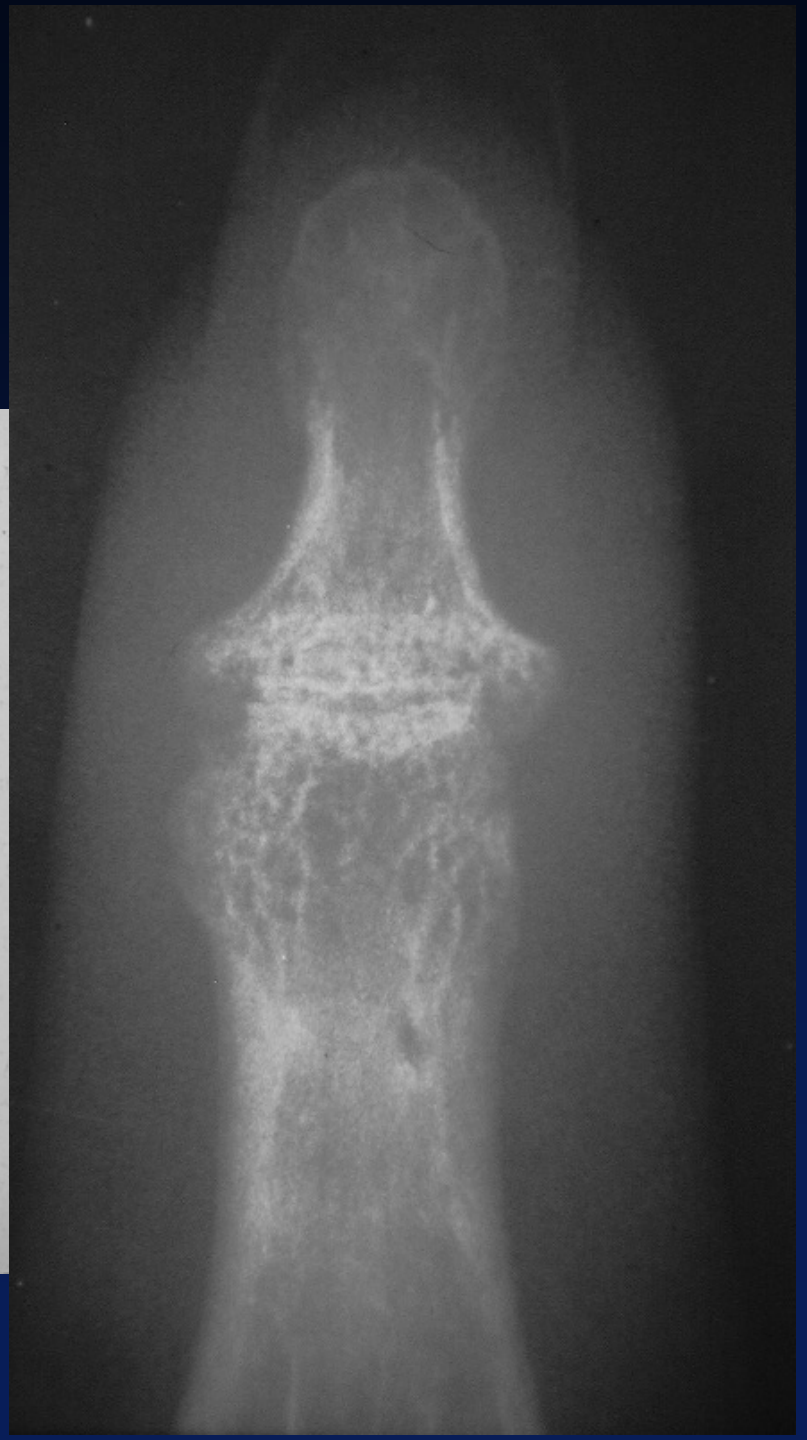
2010 ACR/EULAR Criteria for RA

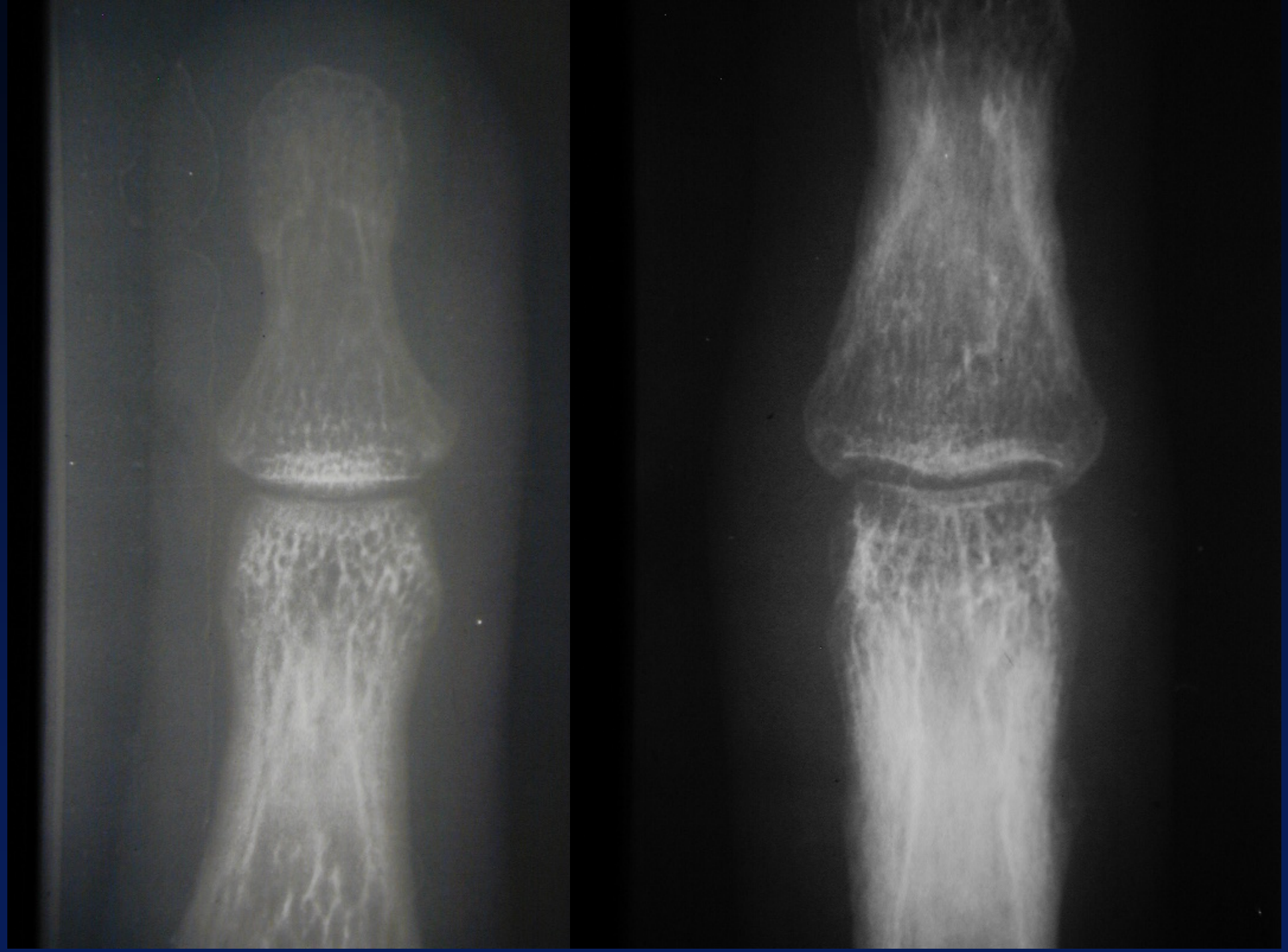
- Erosions in 3 separate joints
  - PIP, MCP, Wrist

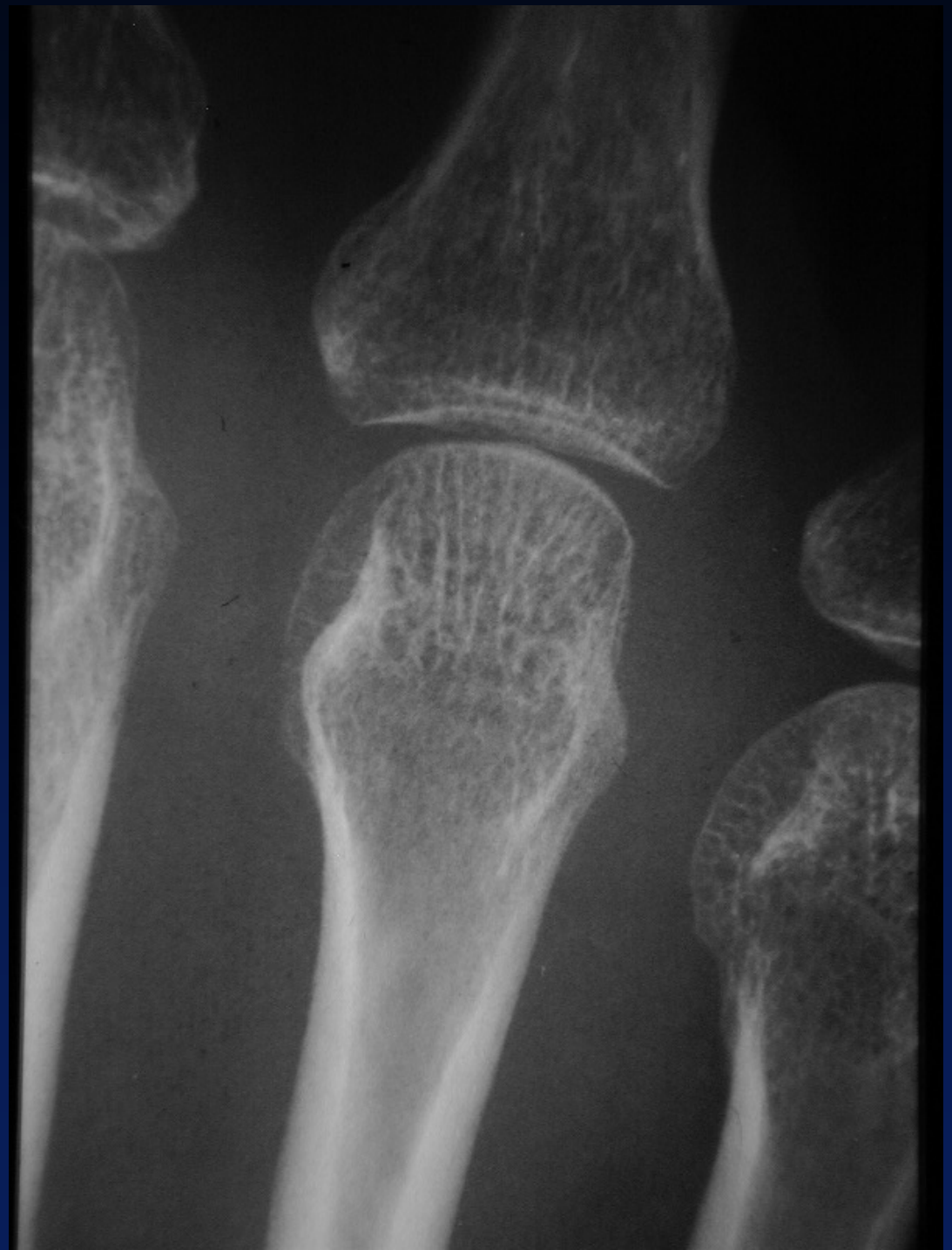


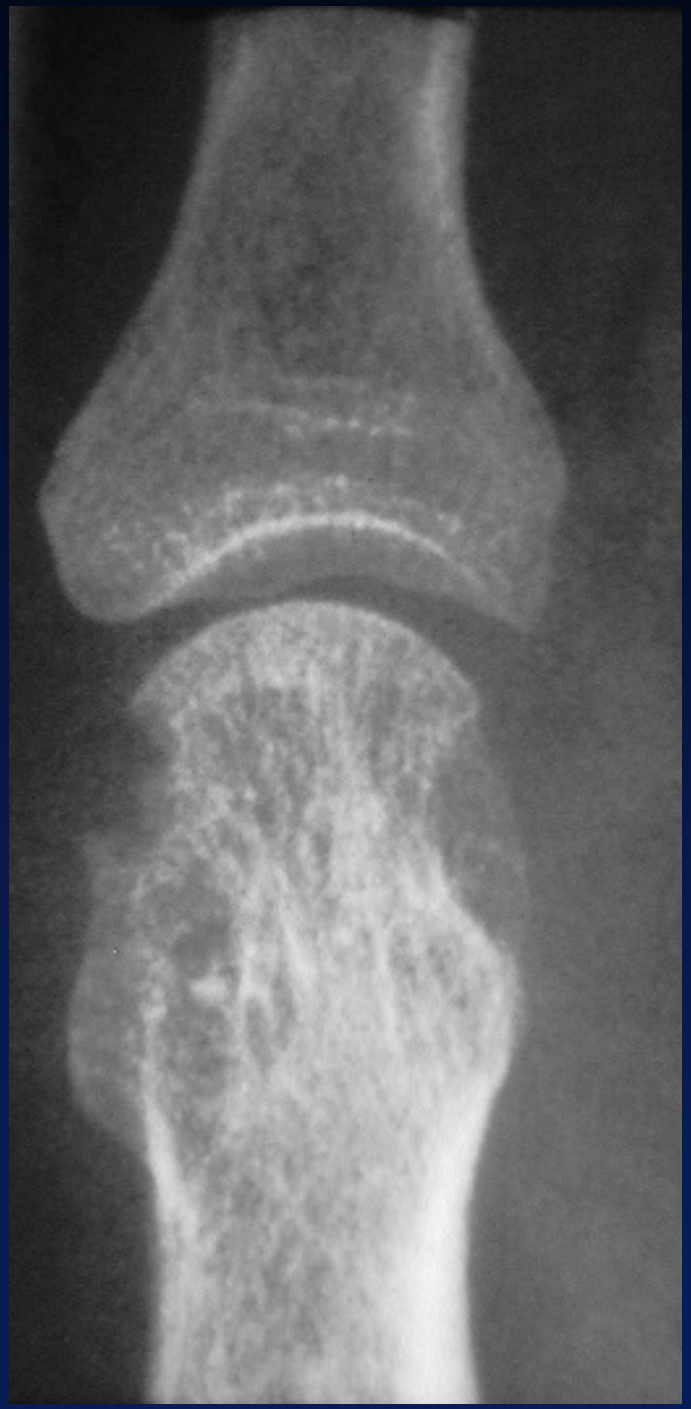


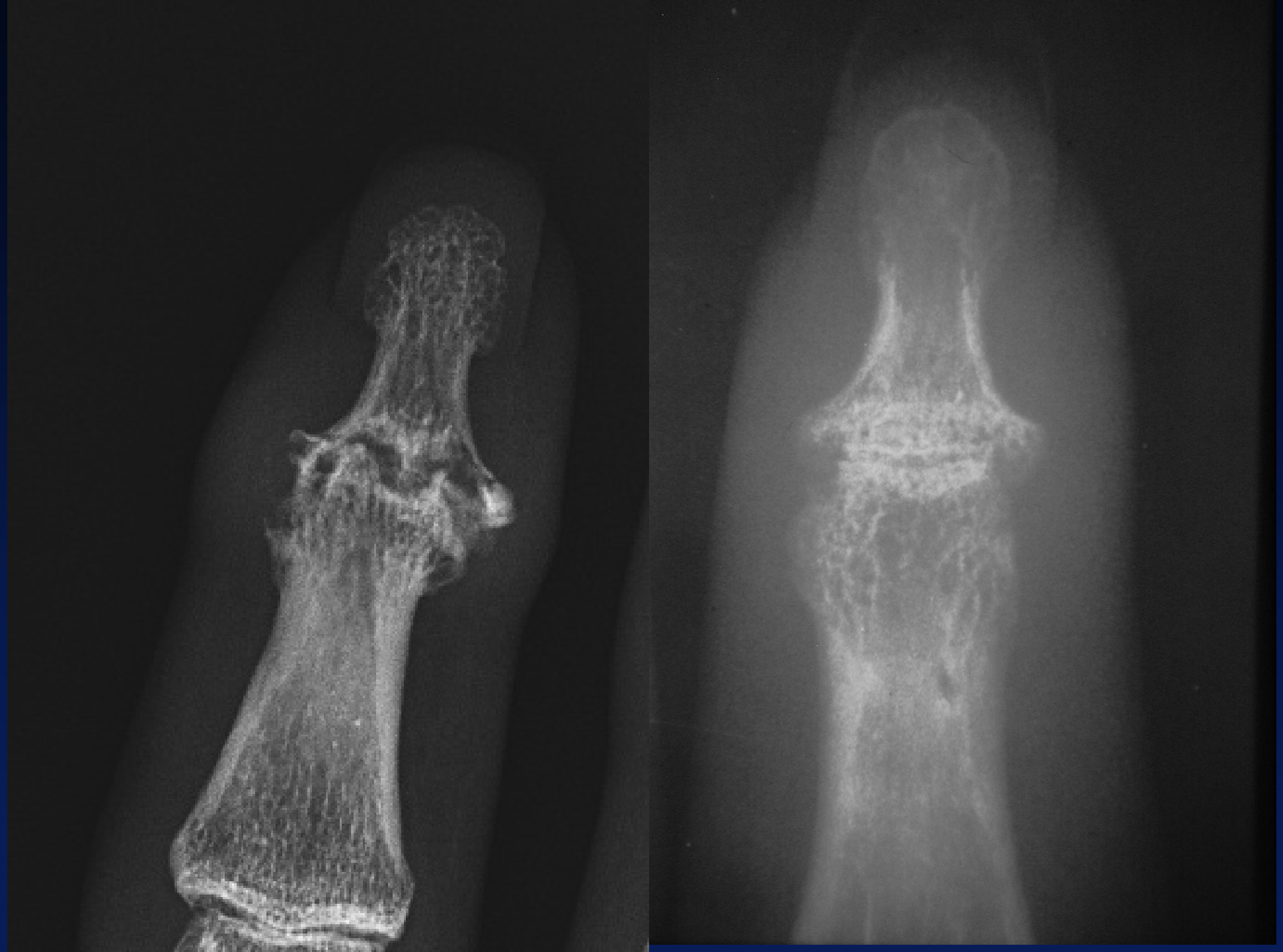


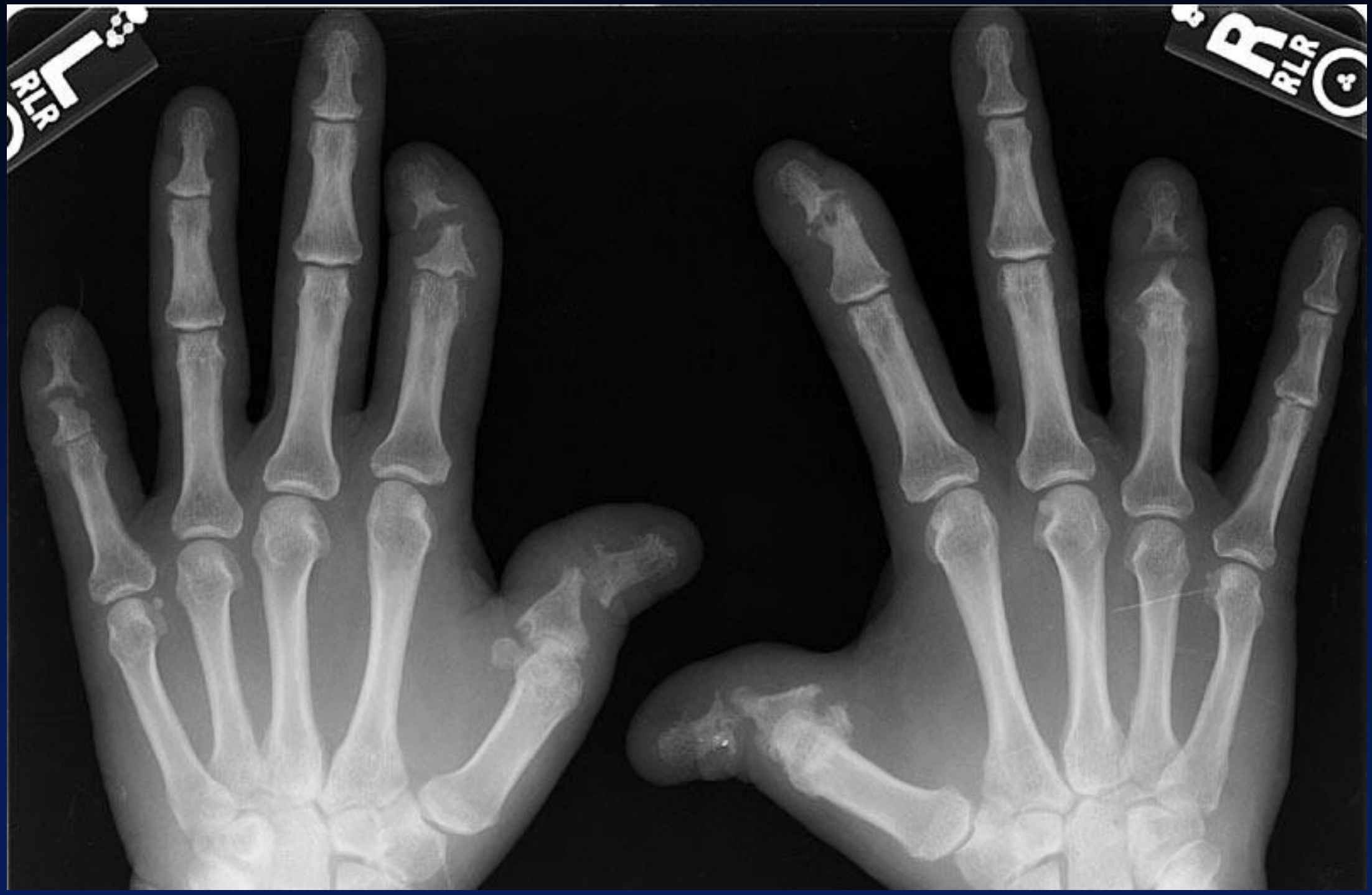








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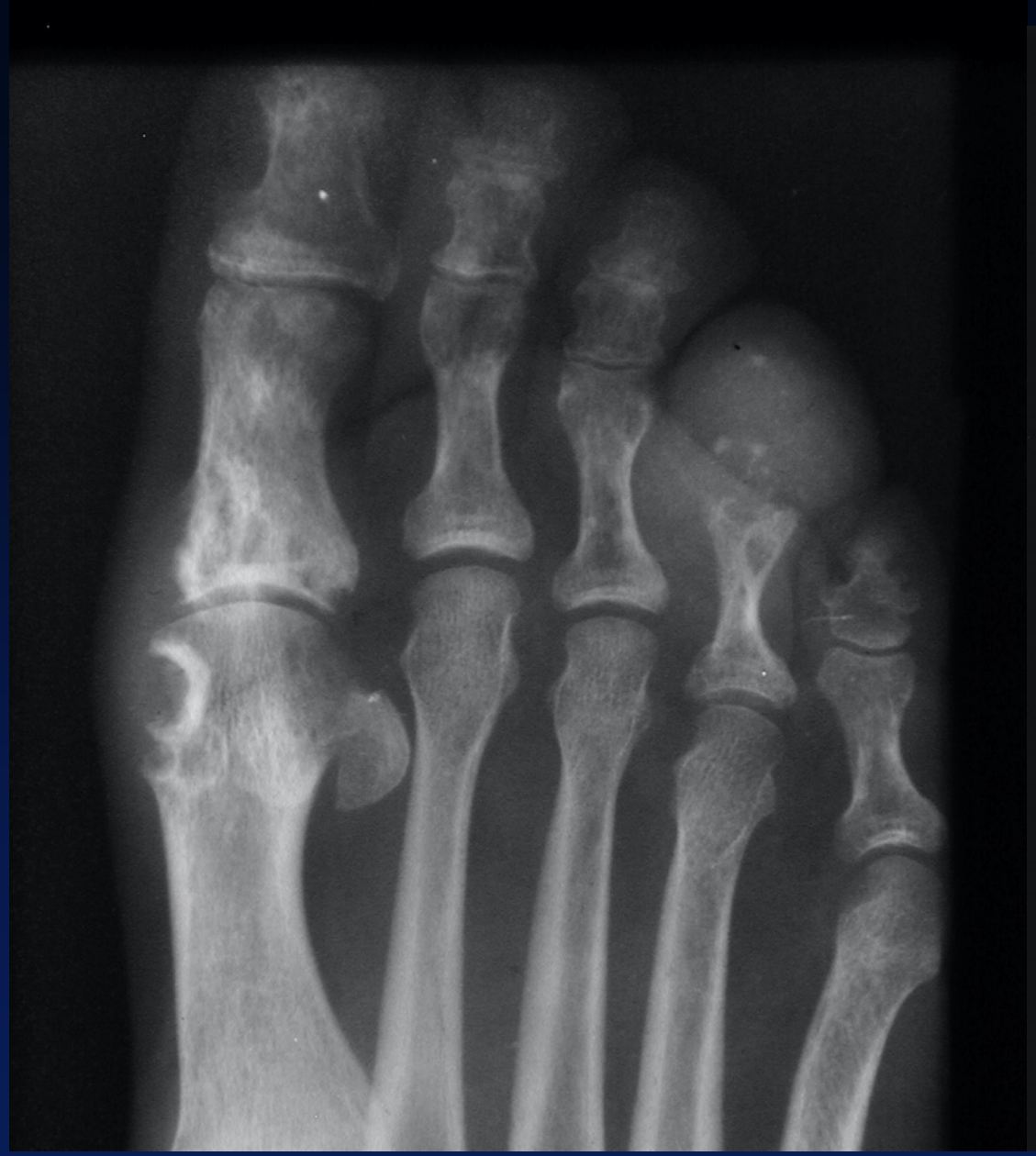
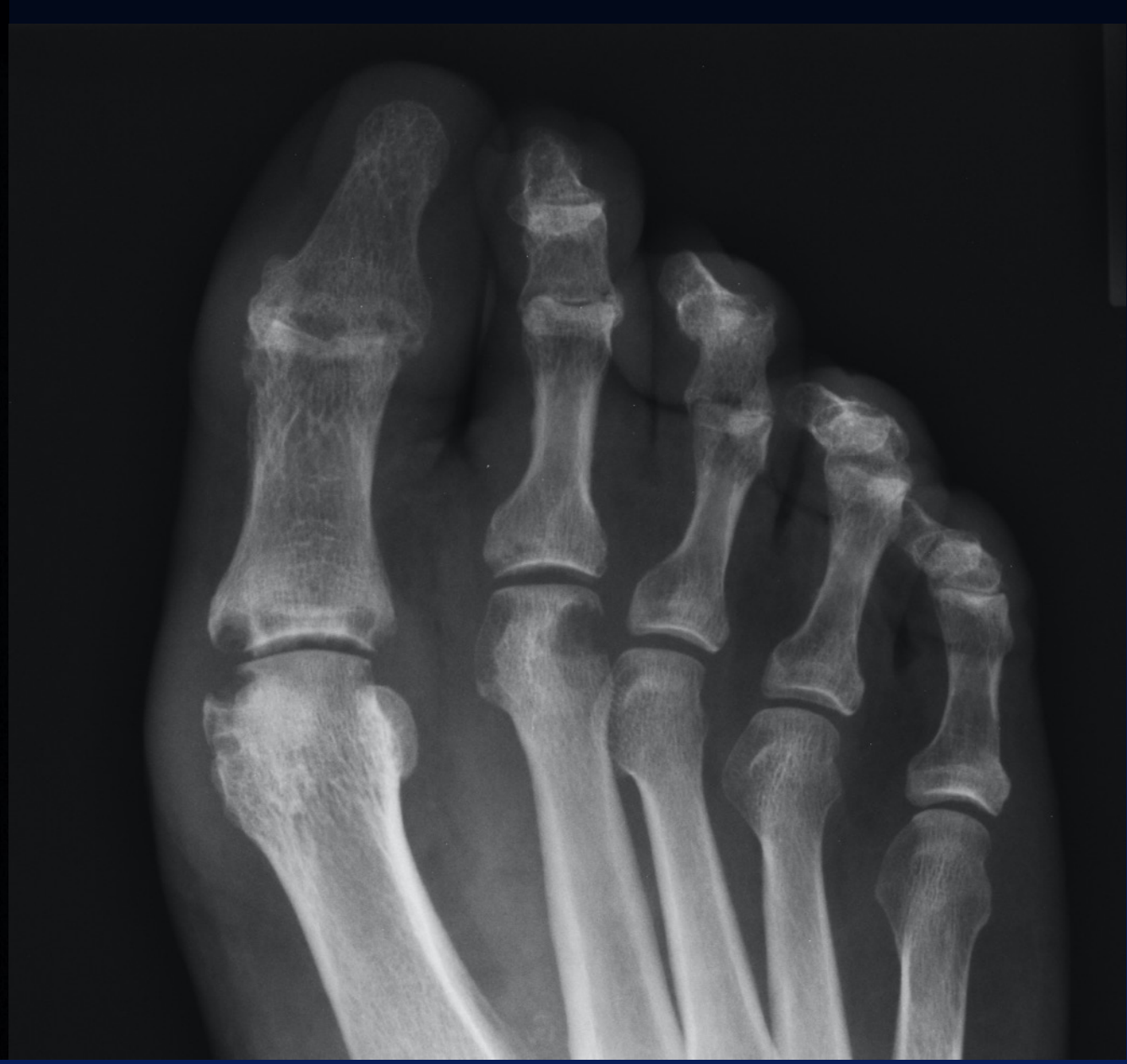
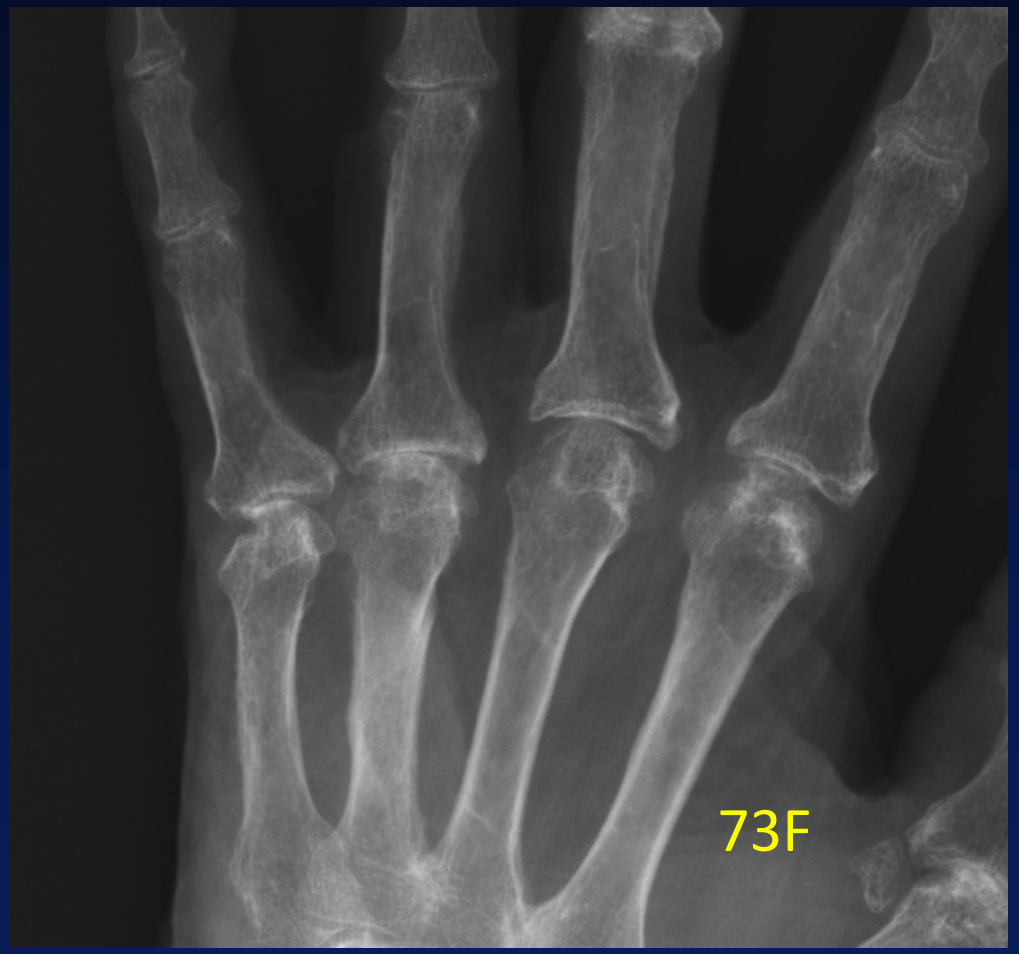


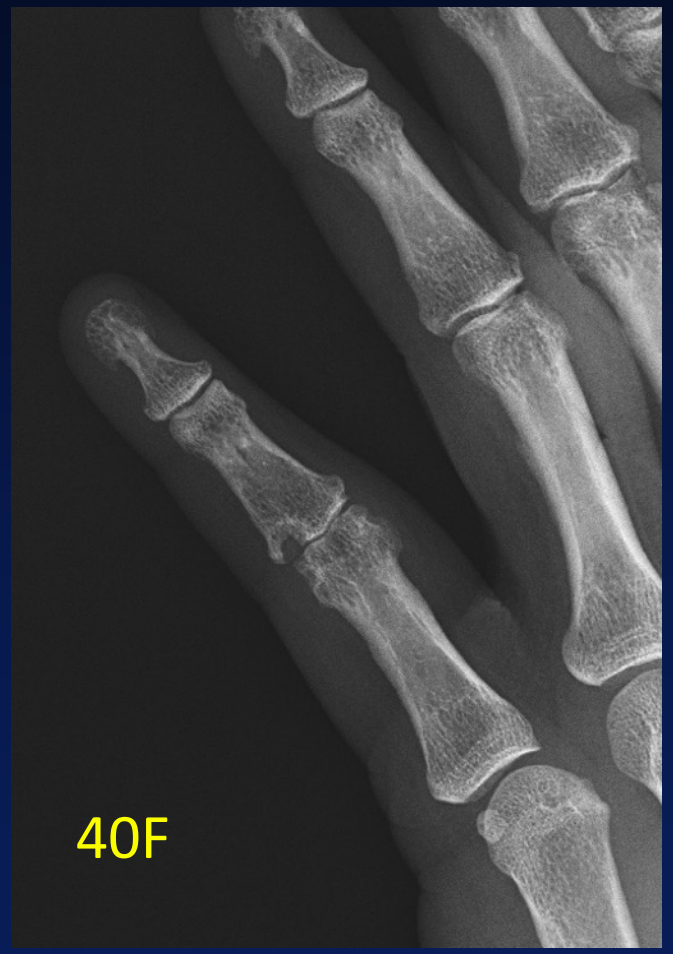
Gout



RA

RA - Corticated Erosions



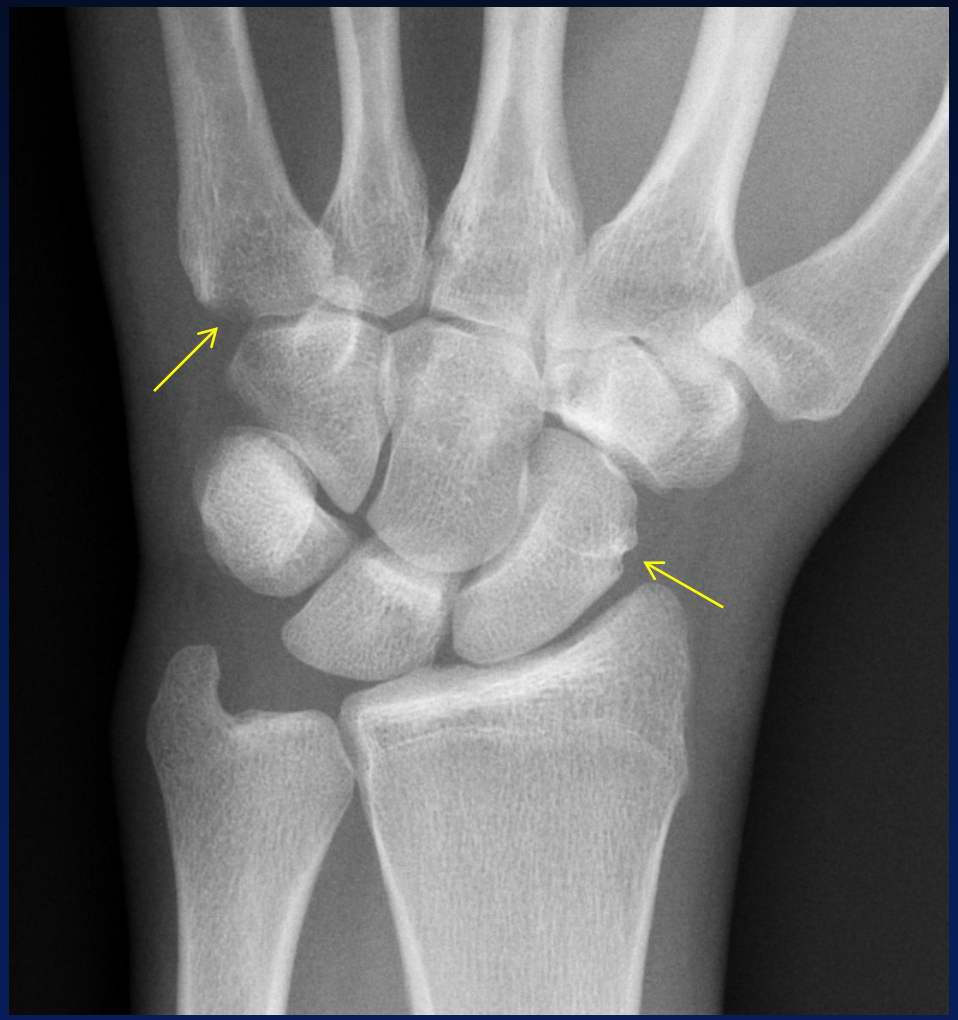


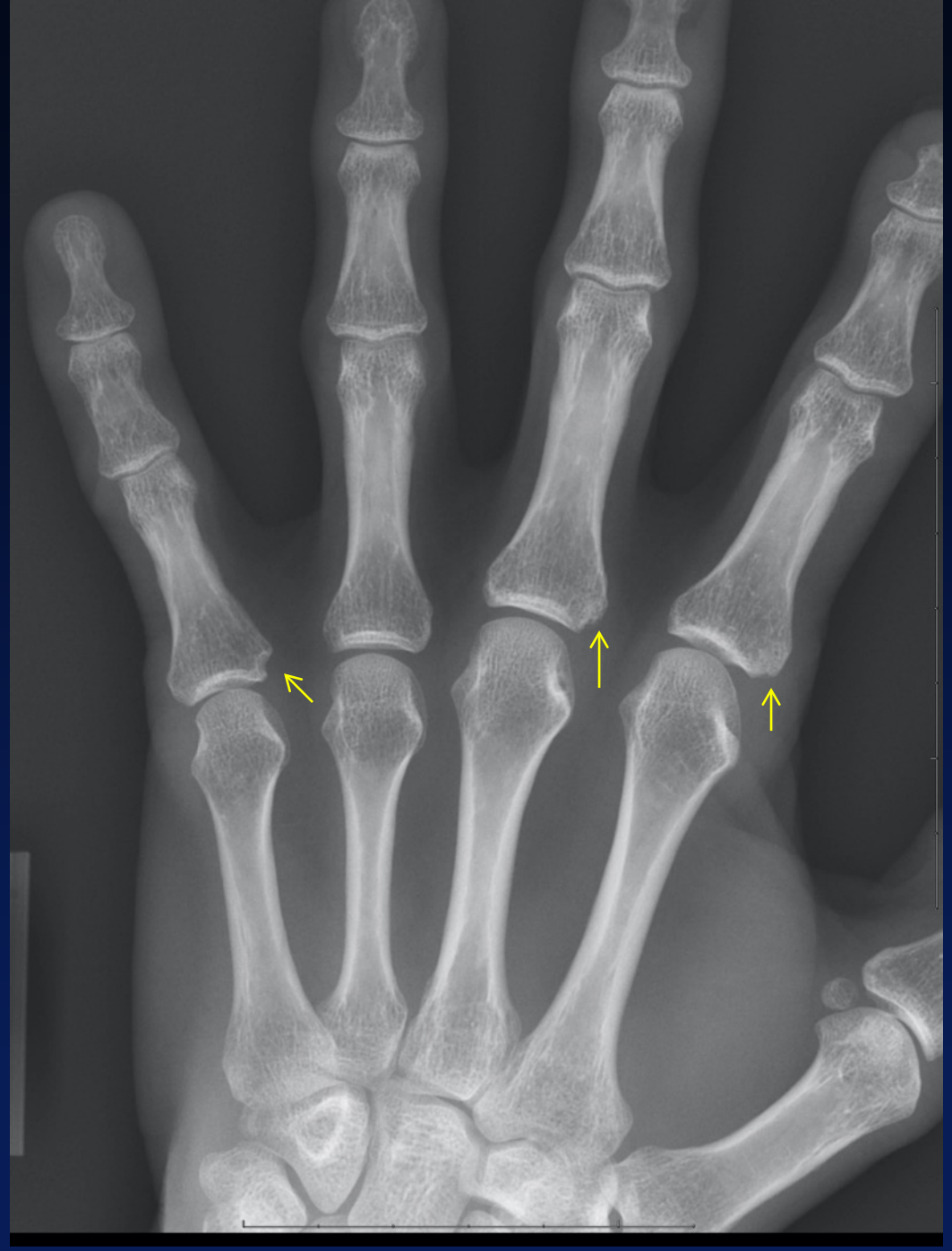
Uniform JSN
No tophus
No “spiky” bone
No sig osteophytes

Common Challenges

- Erosion vs Pseudoerosion
- SI joints
- Synovitis
- “Signs”
- Multiple arthopathies

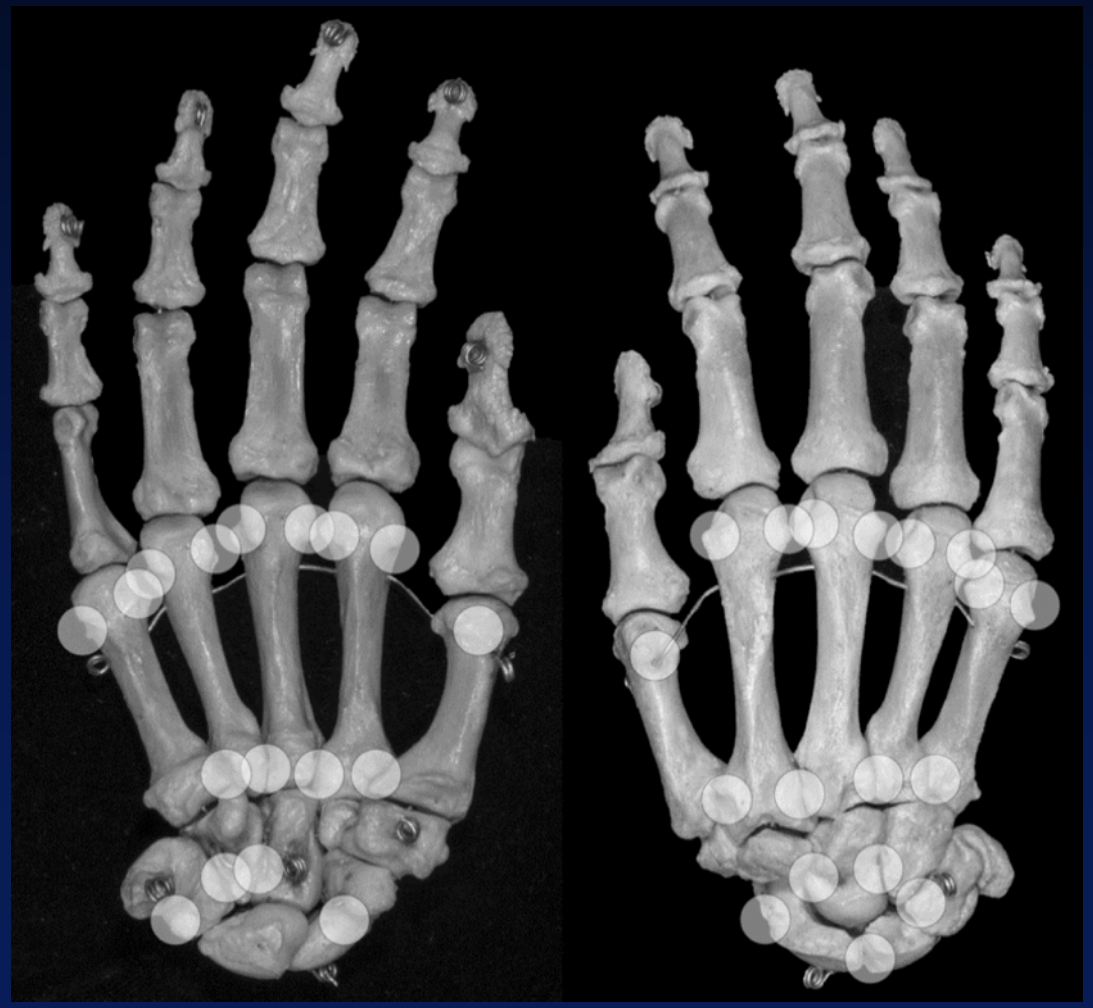
Pseudoerosion





Pseudoerosion

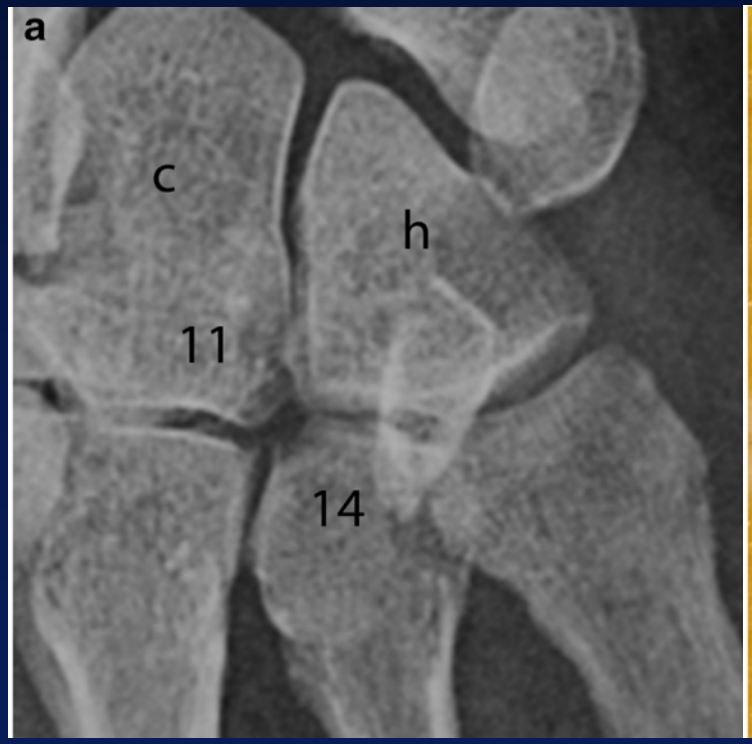
- Typical locations
  - Base of proximal phalanges
  - 3rd/4th CMC joint
  - 5th CMC joint
  - Scaphoid/triquetrum

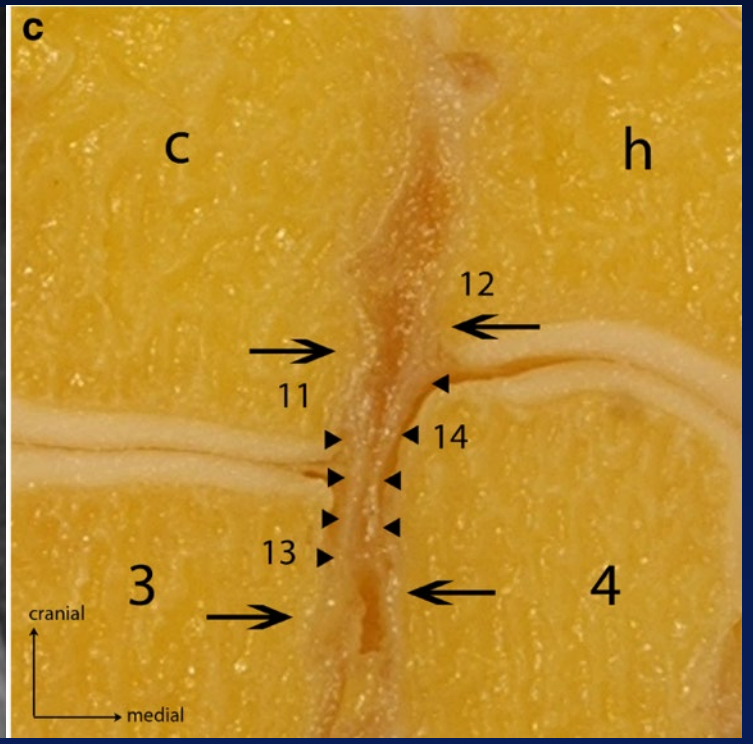


J Clin Med. 2019;8:2174
Skeletal Radiol 2014; **43:**377–1385

Pseudoerosion

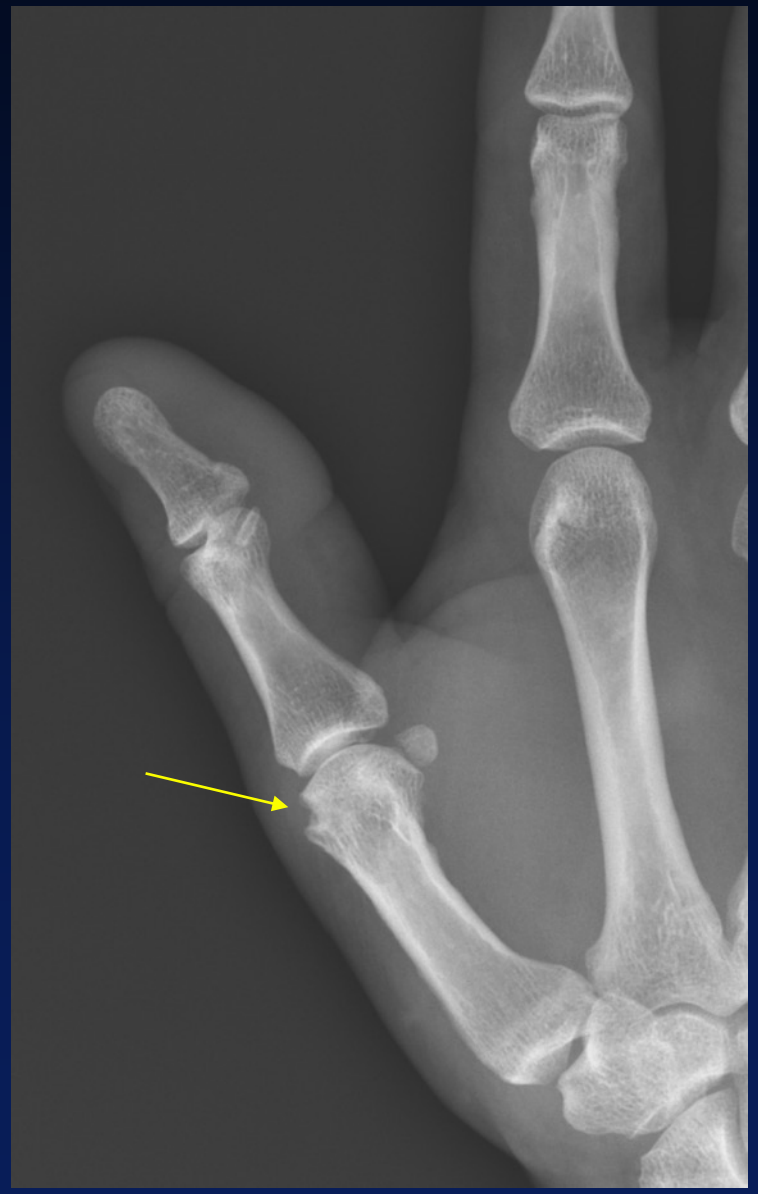
- Ligament or capsular insertion
- Feeding vessel
- Loss of bone volume
- Clues
  - Location important
  - Sclerotic margin
  - Normal soft tissues

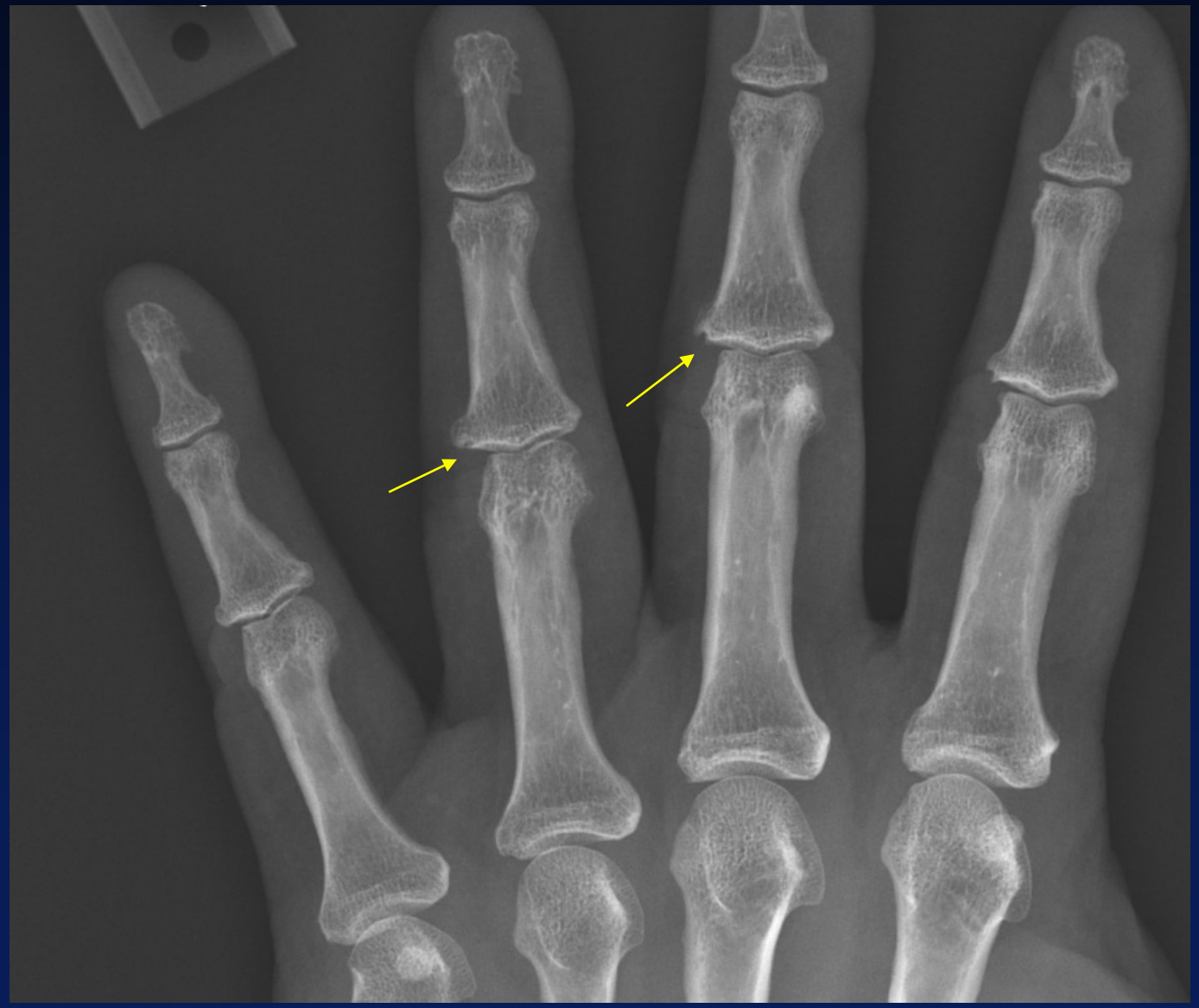




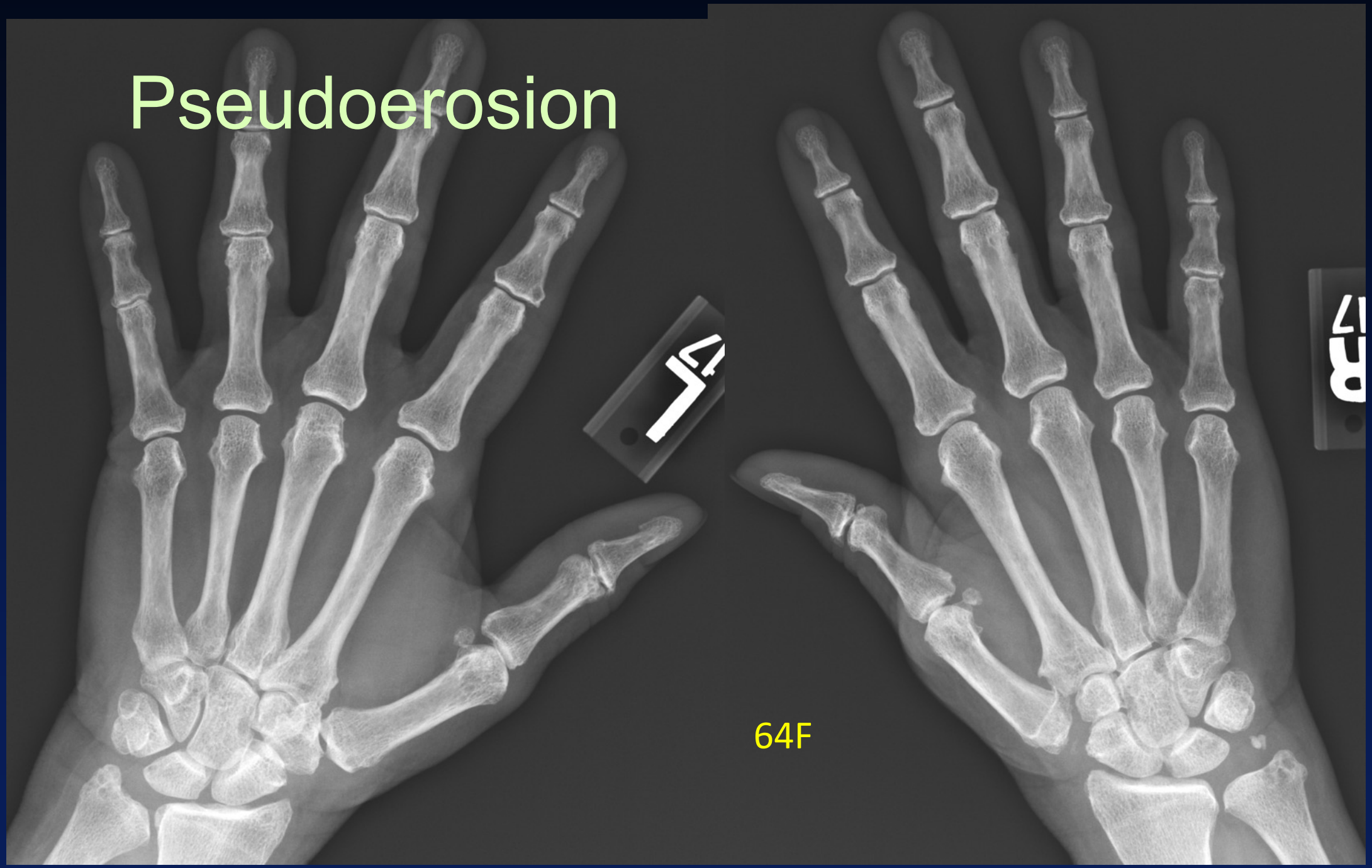
Skeletal Radiol 2014; **43:**377–1385

Pseudoerosion



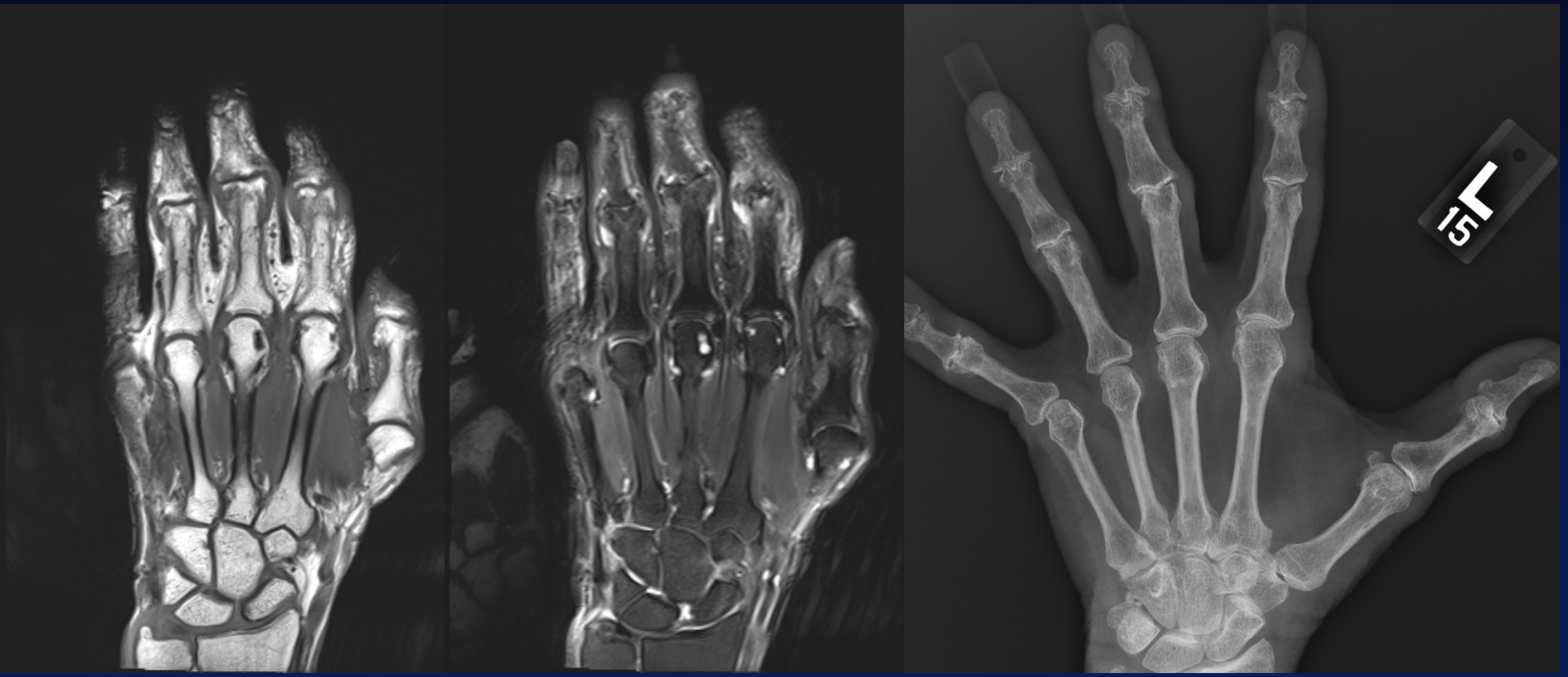


Pseudoerosion



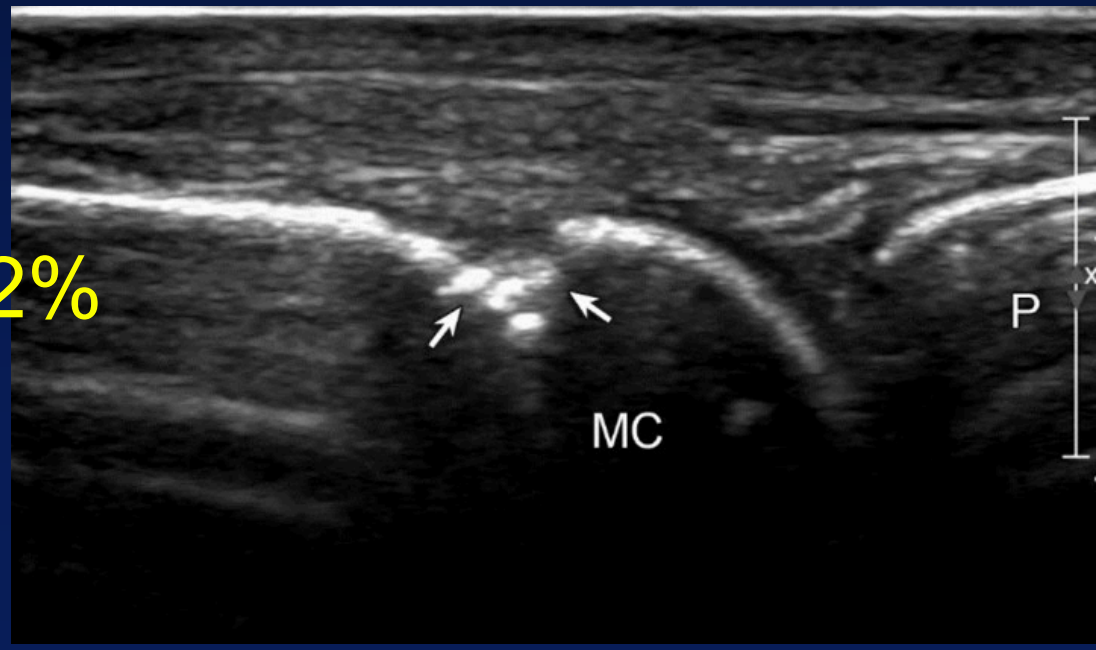
64F

Pseudoerosion - MR



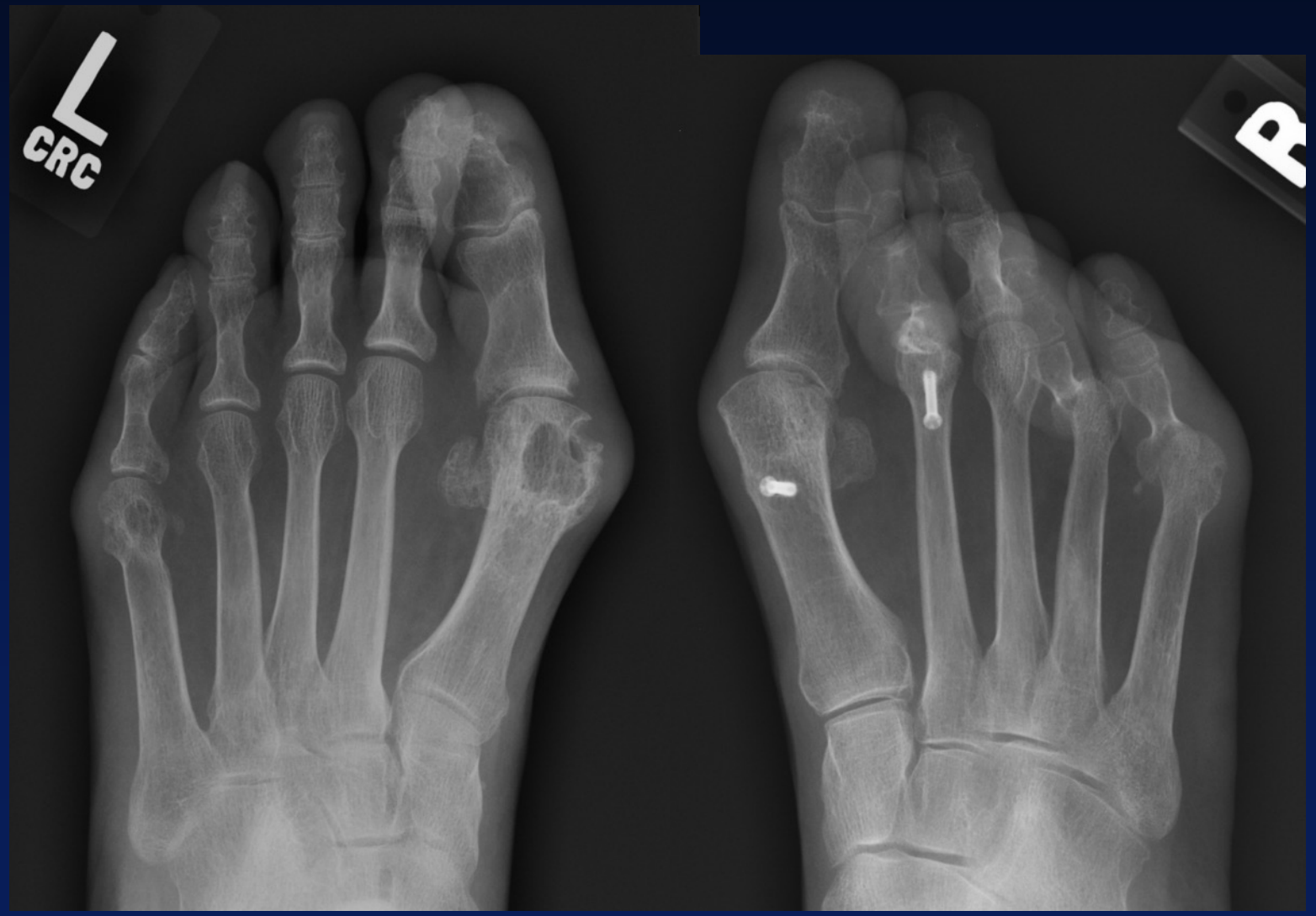
Pseudoerosion - US

- Bilateral asx hand in 100 subjects
  - Average age 47 (19-82) 52% male
- Metacarpal head – 100% of subjects
  - 1-3%, 2-16%, 3-28%, 4-45%, 5-8%
  - Central at dorsal MC head
- Lunate, triquetrum, ulnar styloid – 92%



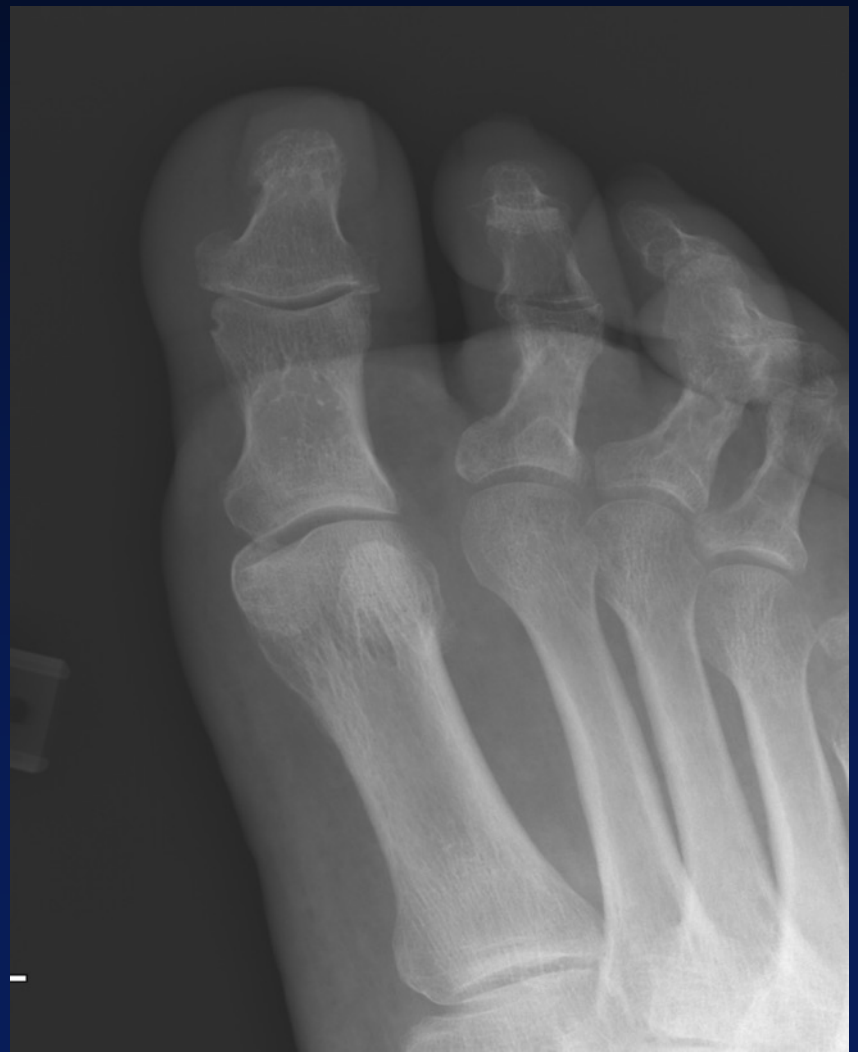
Eur J Radiol 2020 Mar;124:108842

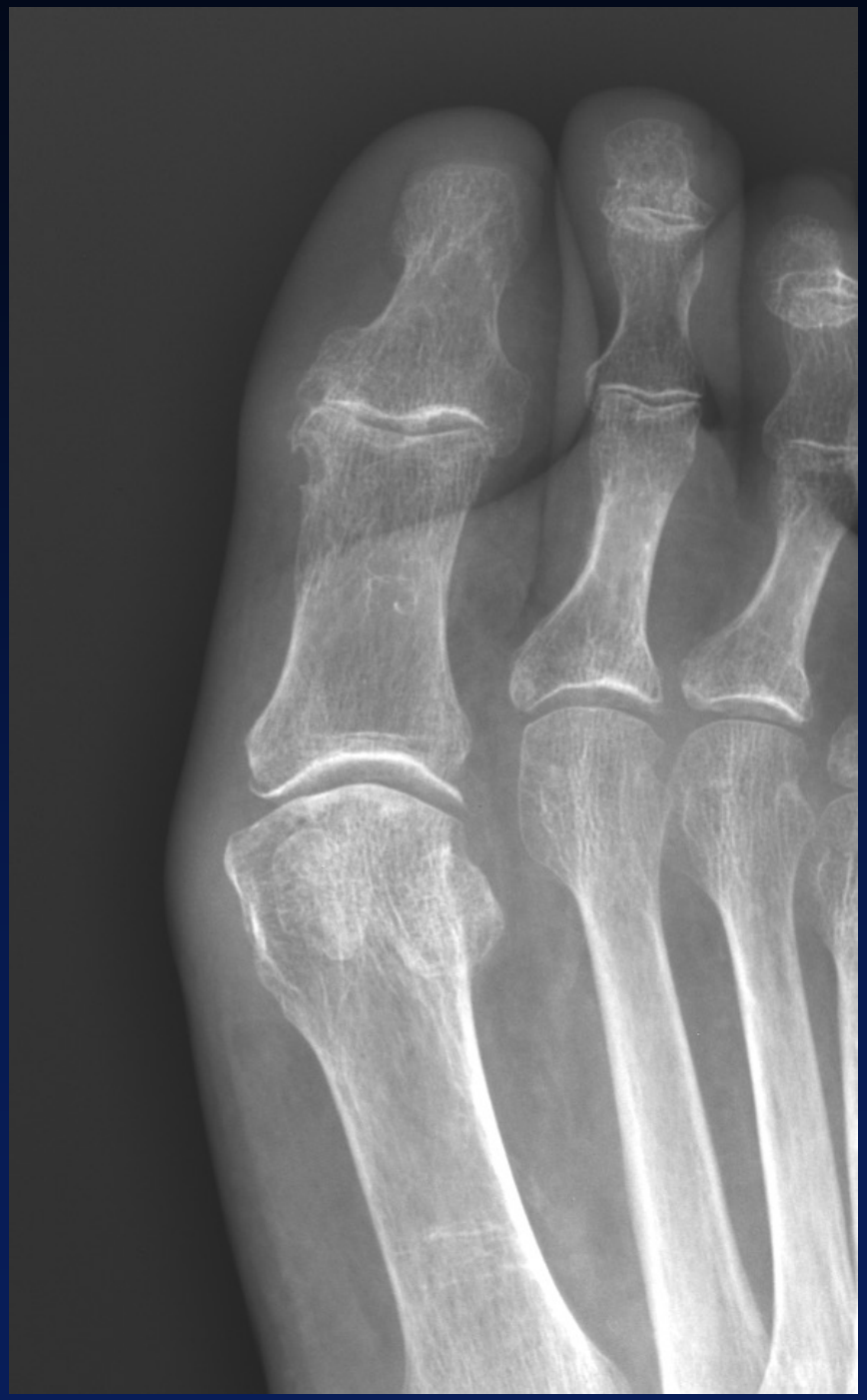
Pseudoerosion - Foot

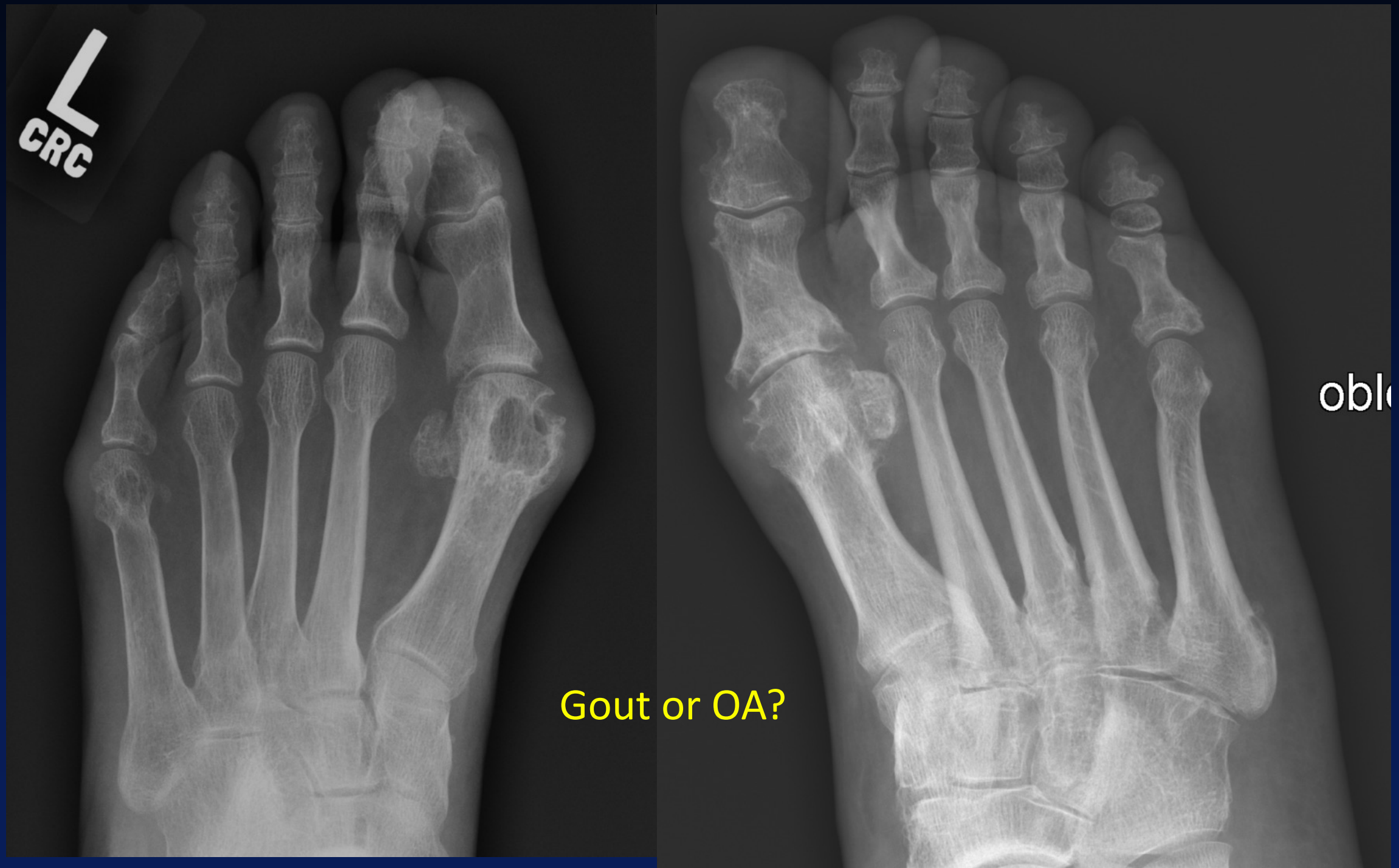


75F

Pseudoerosion - Foot





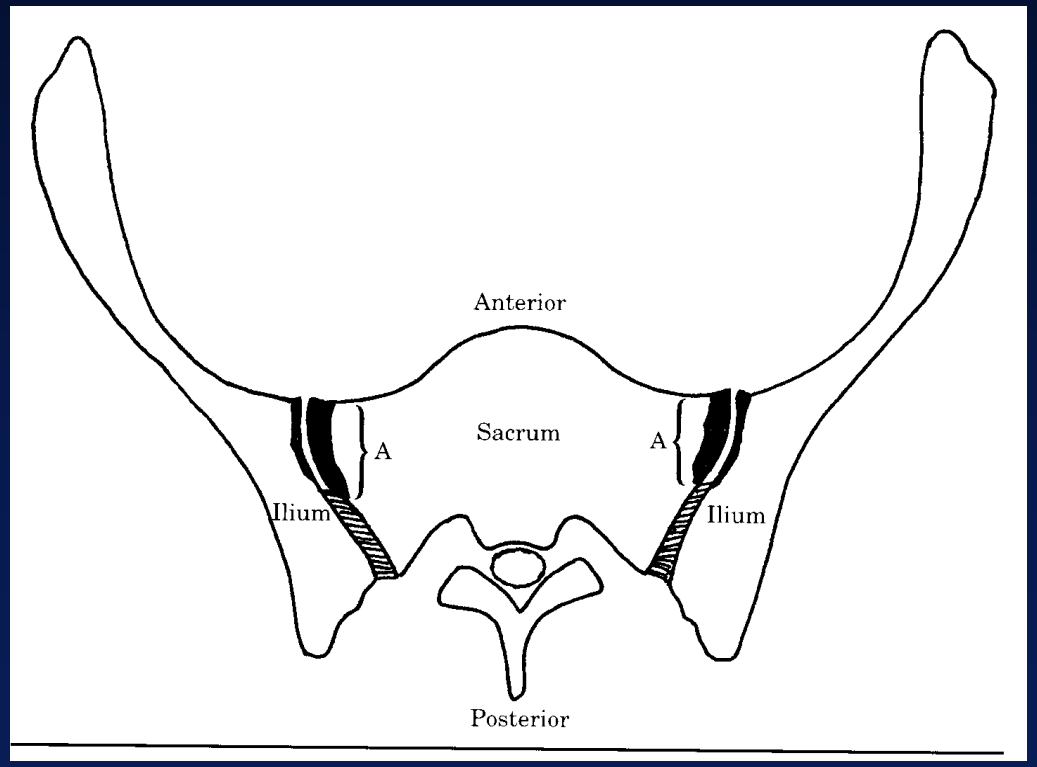

L
CRC
Gout or OA?

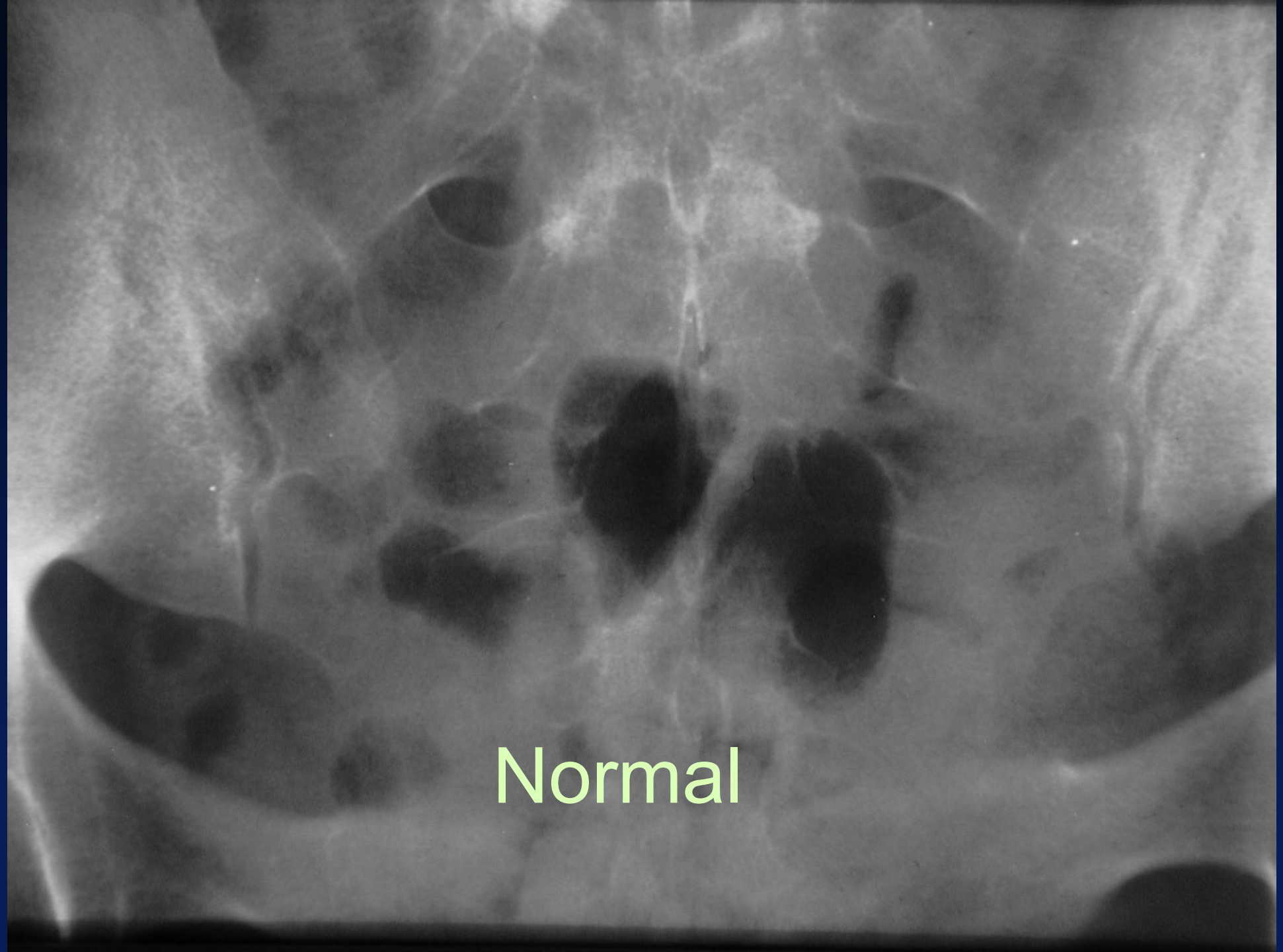
Common Challenges

- Erosion vs Pseudoerosion
- SI joints
- Synovitis
- “Signs”
- Multiple arthopathies

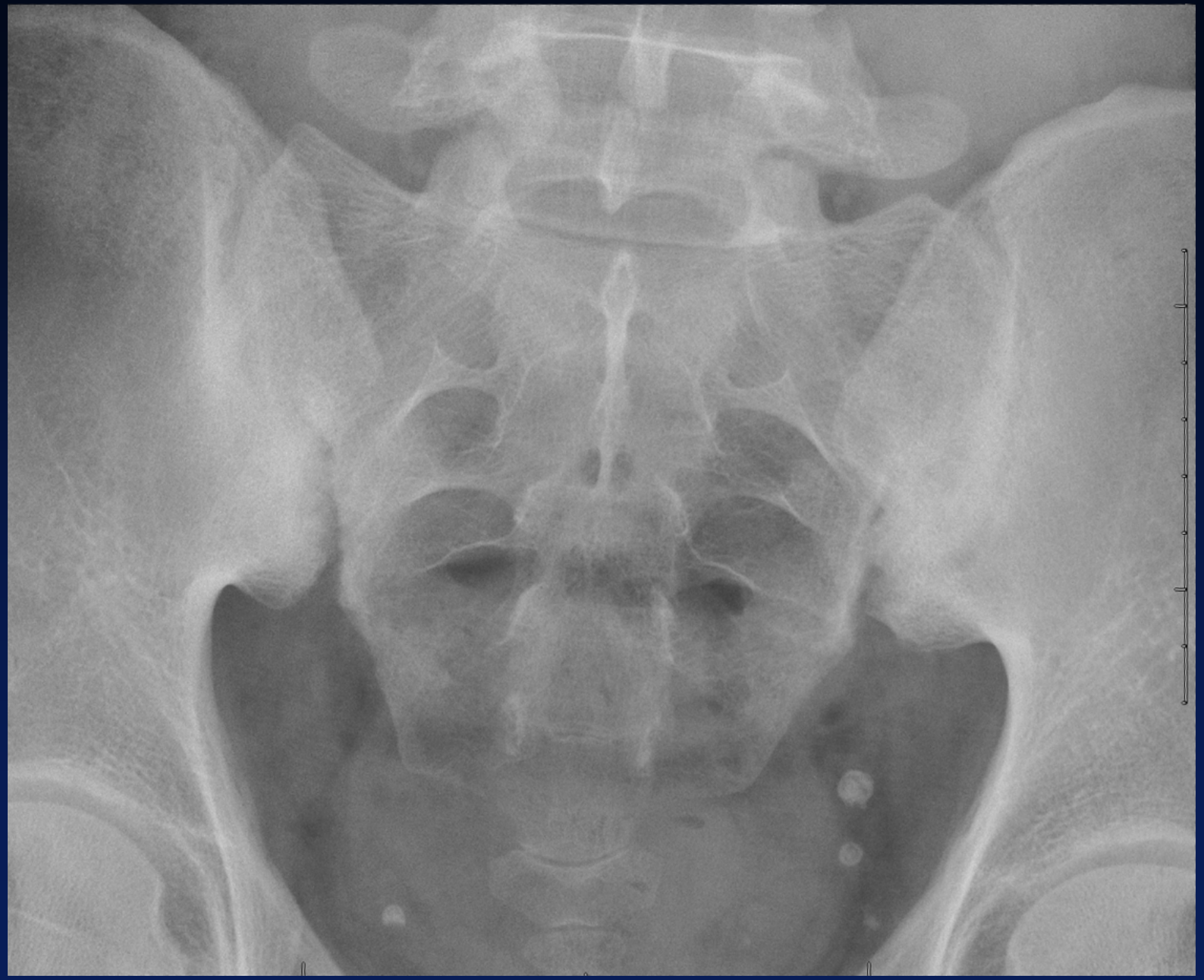
Imaging of SI Joints

- Challenging!!
- Erosion
  - Anterior inferior 2/3rd of joint
  - CT is most sensitive and specific
- Bone repair
  - Bone marrow edema
  - Sclerosis
  - Fat metaplasia



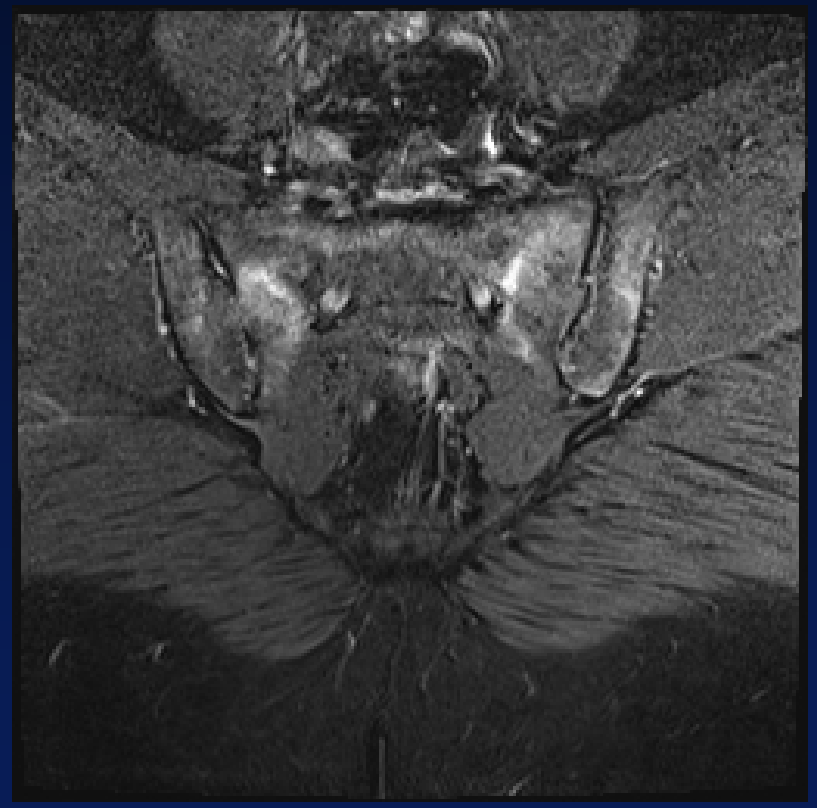

Normal

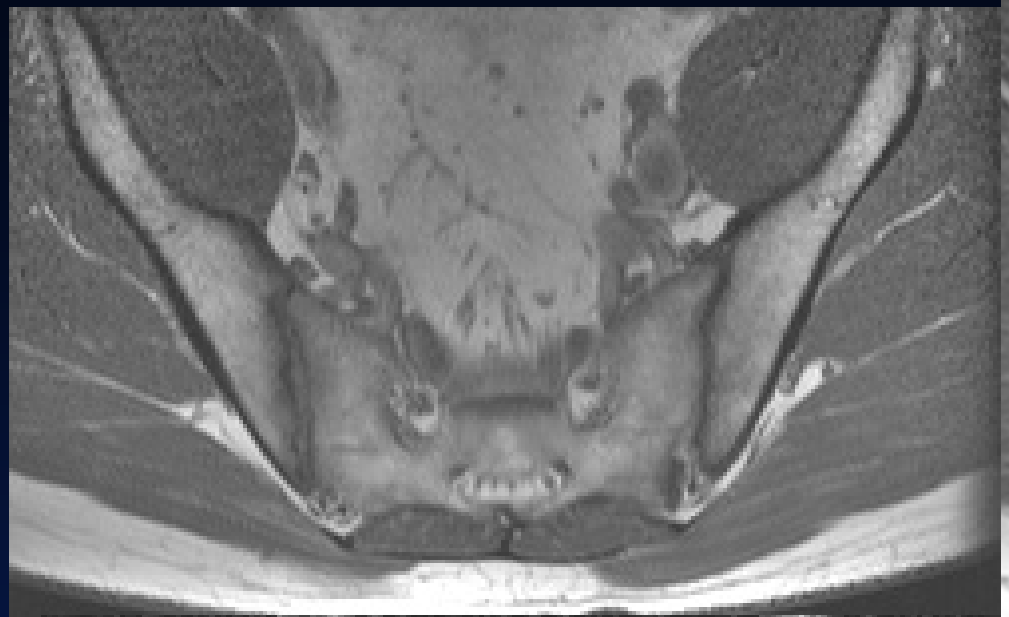
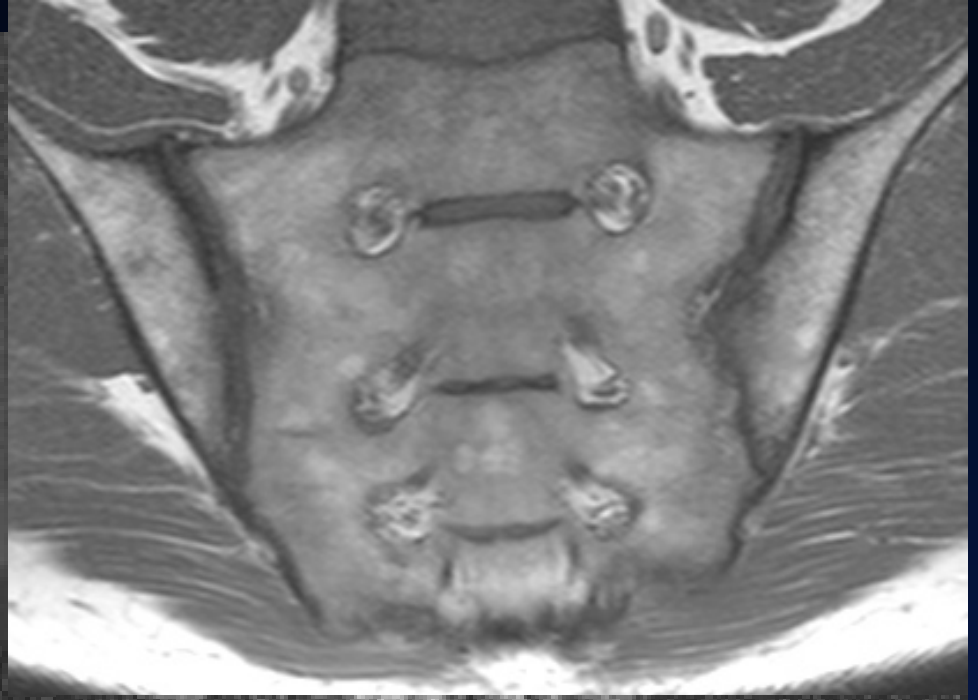
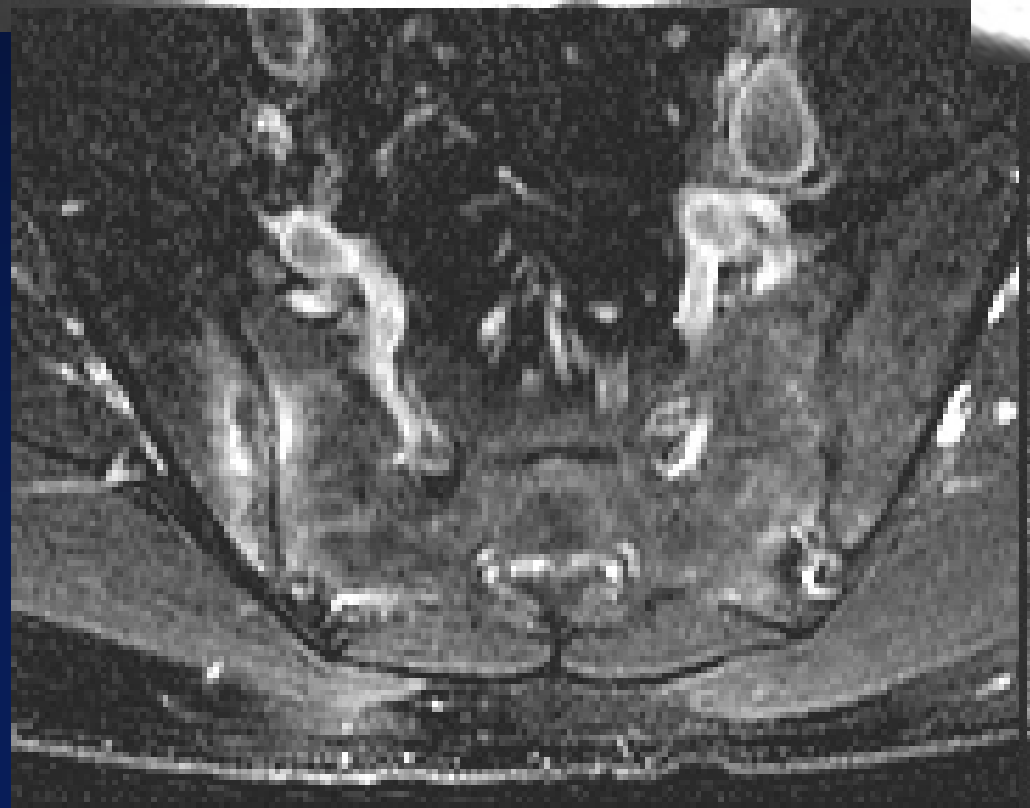
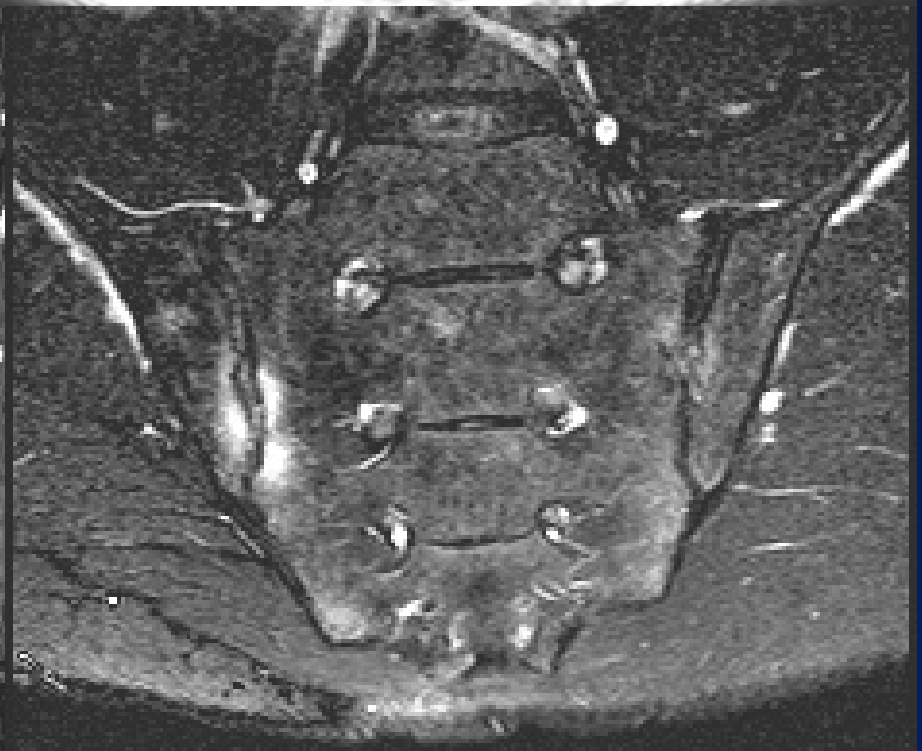
Ankylosing Spondylitis



MRI of Sacroiliitis

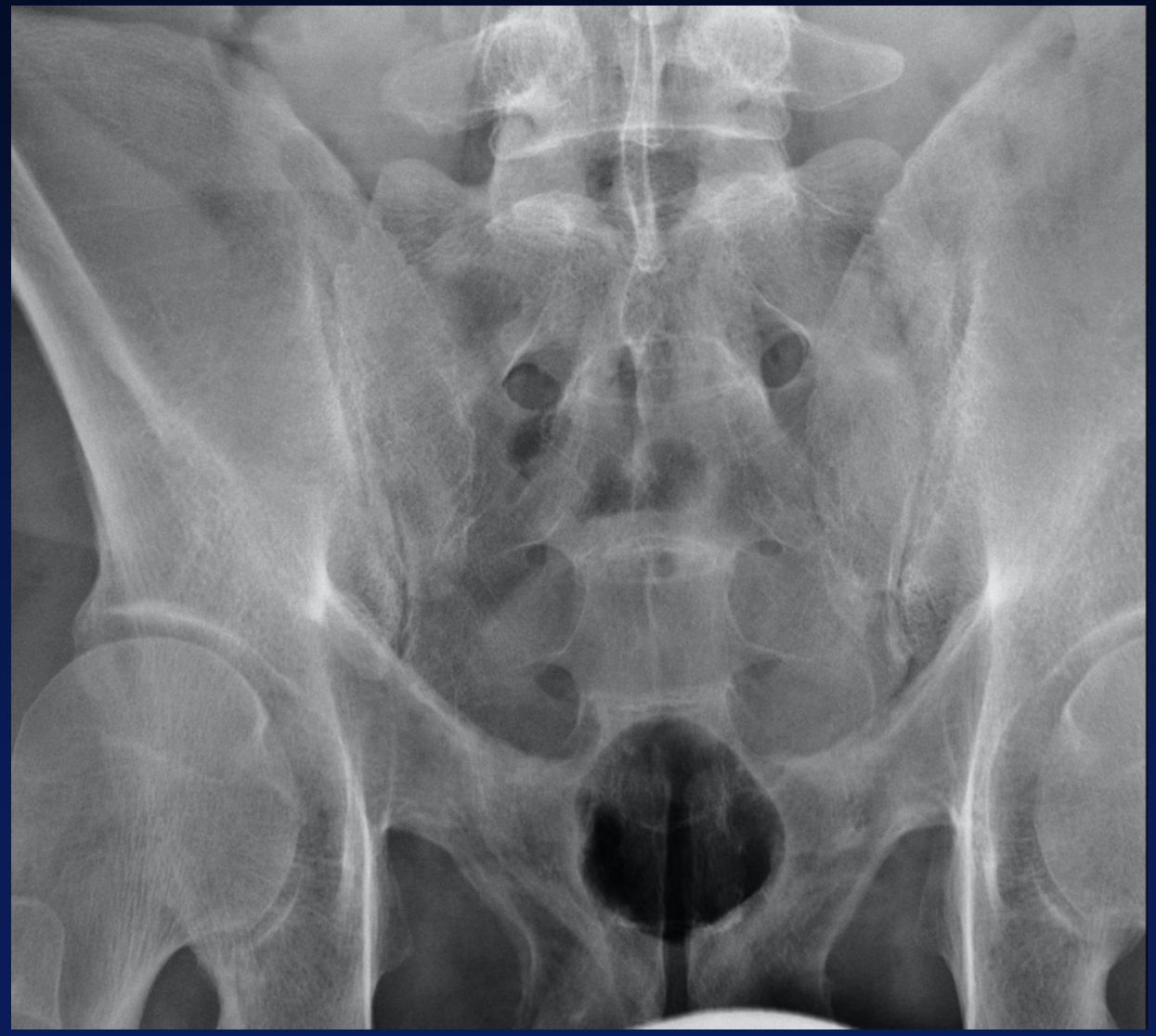
- Erosions – better seen on T1
- Active = BME or SC enhancement
  - Single lesion on two or more slices
  - Multiple lesions on single slice
  - Capsulitis or enthesitis not sufficient
- Sclerosis - >5mm deep to SC bone
- Periarticular fat deposition
- Ankylosis



SI Joints

- PF
  - Low sensitivity/ higher specificity[1]
    - Sens 55%, Spec 87%
    - Sens ~ 30% – BME only MR
  - Low interobserver reliability
    - κ 0.19-0.79
- MR
  - High sensitivity and specificity for structural damage
    - Sens 85%, Spec 92%
    - κ 0.73



SI Joints - MR

- Normal population
  - Fat metaplasia – 51% <45 up to 94%>75[1]
  - Erosion – 2.6% total but in 0.6% <45[1]
  - BME – 17% of pts less than 45[2]
- Military recruits [3]
  - BME - 41% before training / 50% after
  - ASAS+ MRI in 22.7% before/ 36.4% after
  - Erosion 14%

1-J Rheumatol 2018; 45:915–921.
2-Ann Rheum Dis 2020; 79:186–192.
3-Rheumatology (Oxford) 2018; 57:508–513.

SI Joints - MR

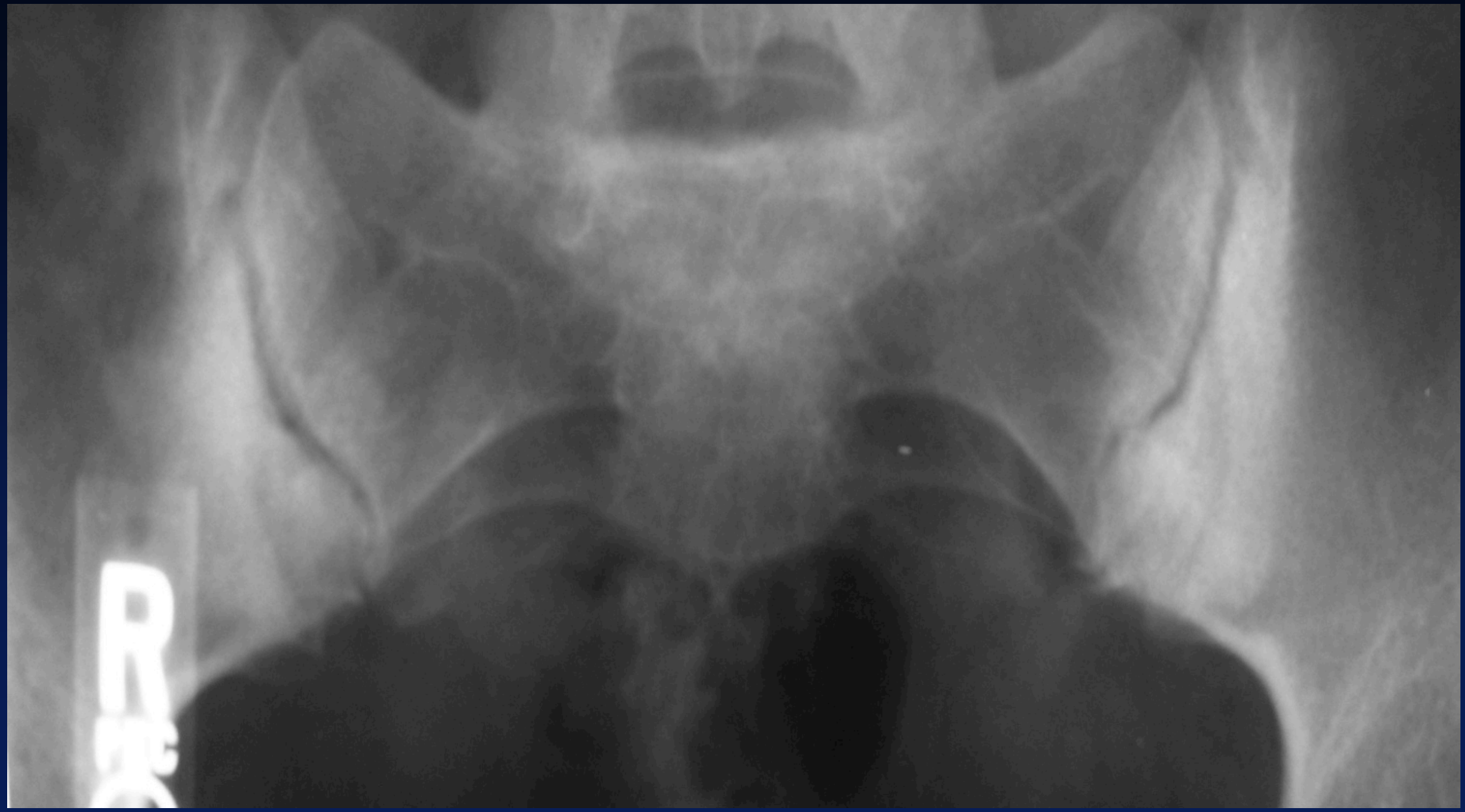
- Athletes[1]
  - ASAS + MRI in 30-35% of runners and 41% hockey
- Postpartum[2]
  - BME - 63% postpartum – 87% with axSpA
  - Erosion – 10% postpartum – 57% axSpA
  - SPARCC score not different

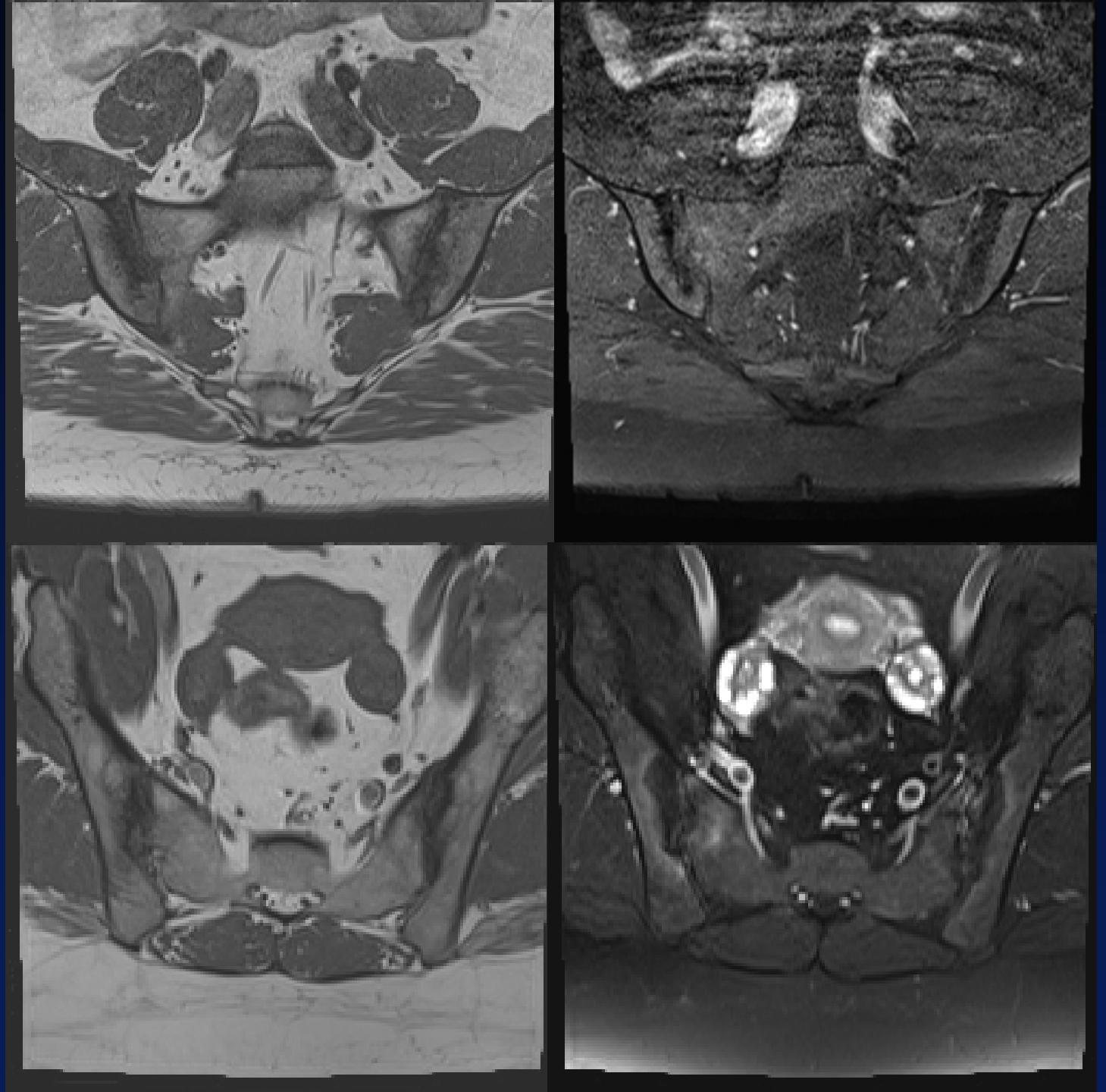
1- AJR Am J Roentgenol 2018; 211:1306–1312
2 -Arthritis Rheumatol 2018; 70:1042–1048

SI Joints - MR

- Postpartum[1,2]
  - BME, fat metaplasia and erosions can be seen in postpartum patients.
  - Erosions and ankylosis are more likely seen in axSpA

1- Arthritis Rheumatol 2019; 71:2034–2046.
2 - Clin Imaging 2019; 58:70–73.



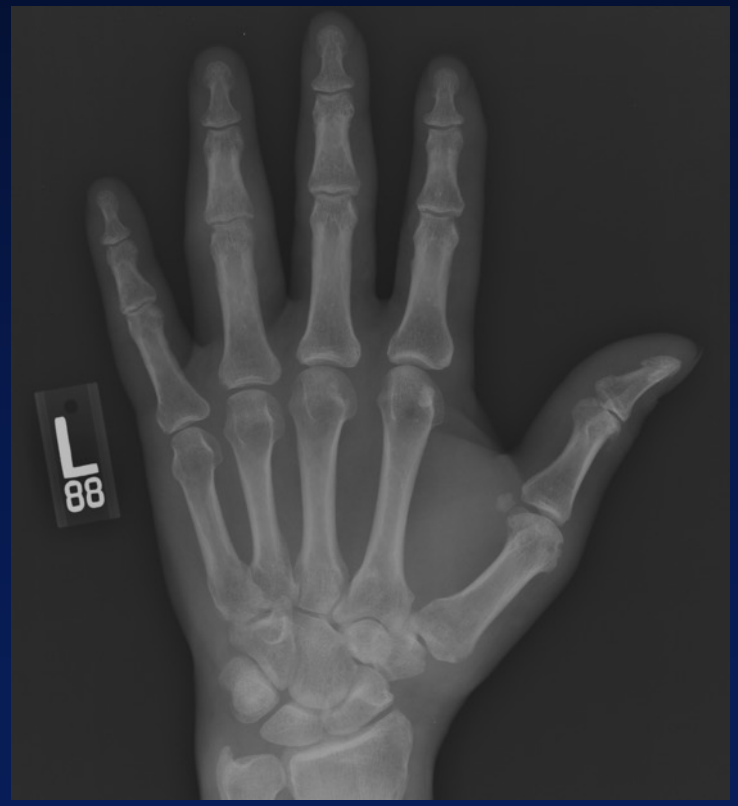


Common Challenges

- Erosion vs Pseudoerosion
- SI joints
- Synovitis
- “Signs”
- Multiple arthropathies

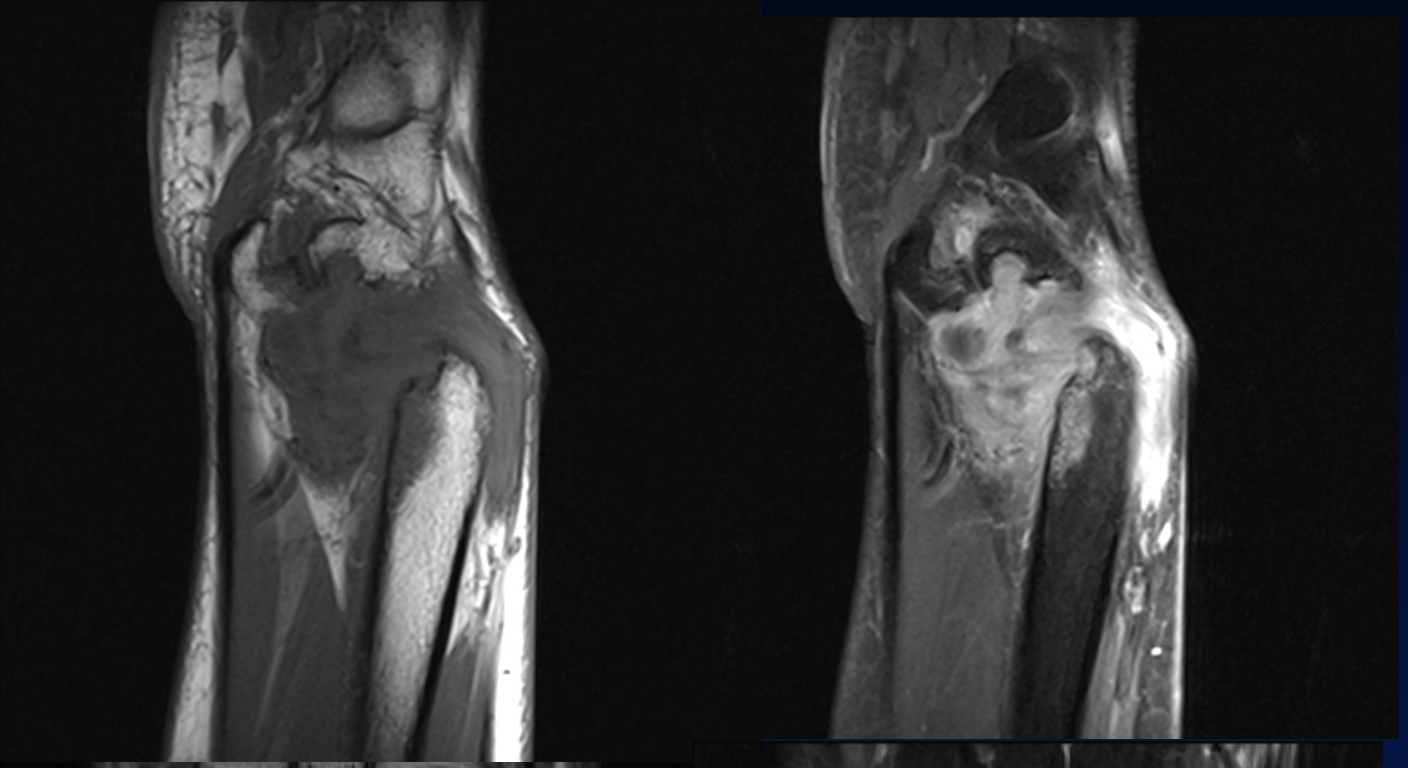
Synovitis

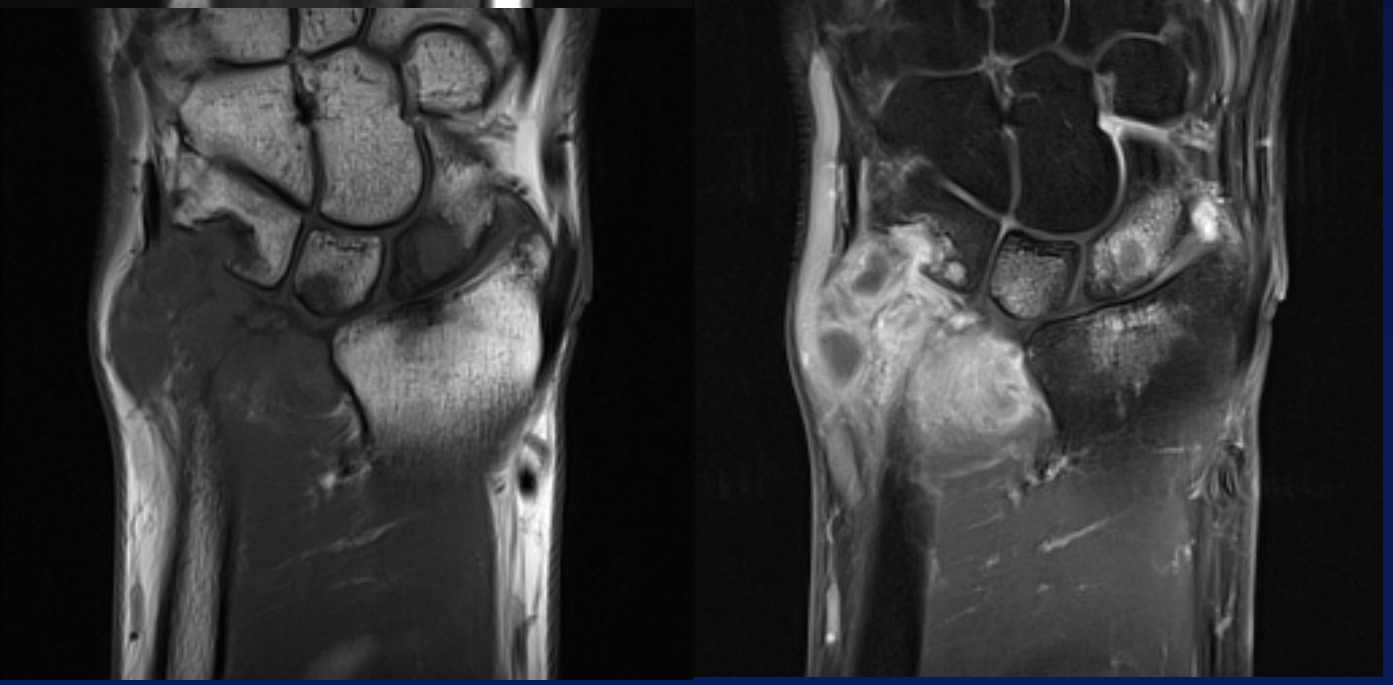
- US and MRI sensitive for detection of synovitis
  - Need contrast to assess synovitis on MR
- US power doppler
  - Hyperemia
- OA vs RA vs Secondary OA
  - OA may show ”erosions”
  - OA may show synovitis[1]
  - OA synovitis may be hyperemic[1]

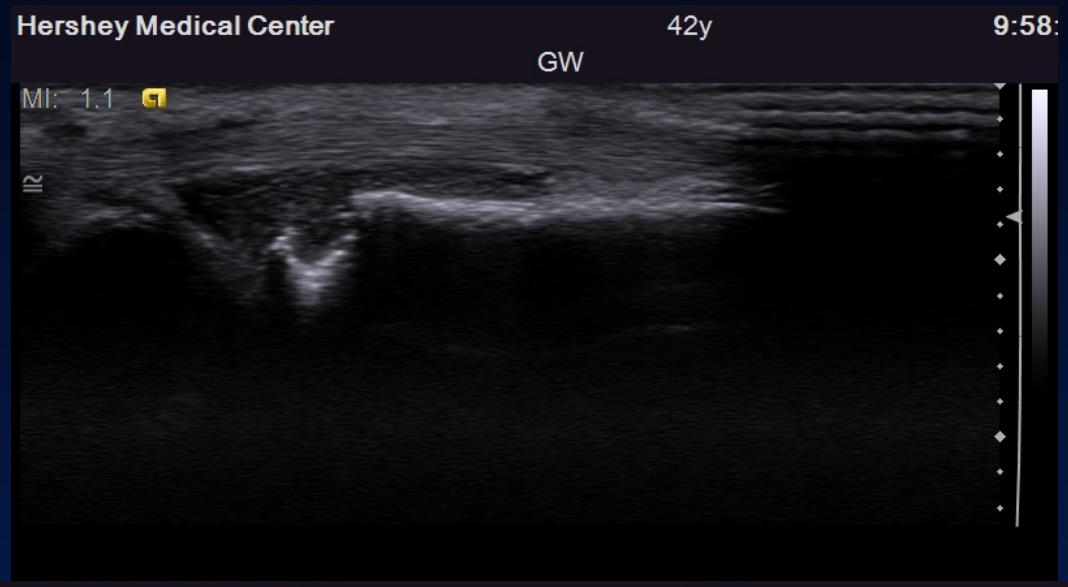


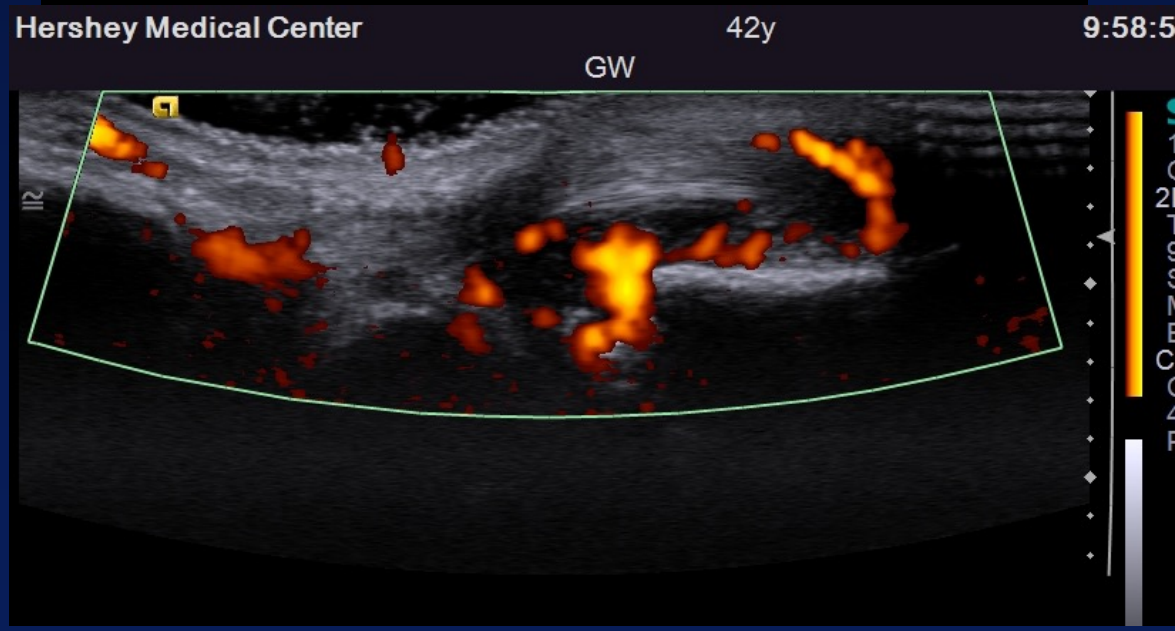
Ann Rheum Dis. 2010;69(7):1367-1369.

RA-42F

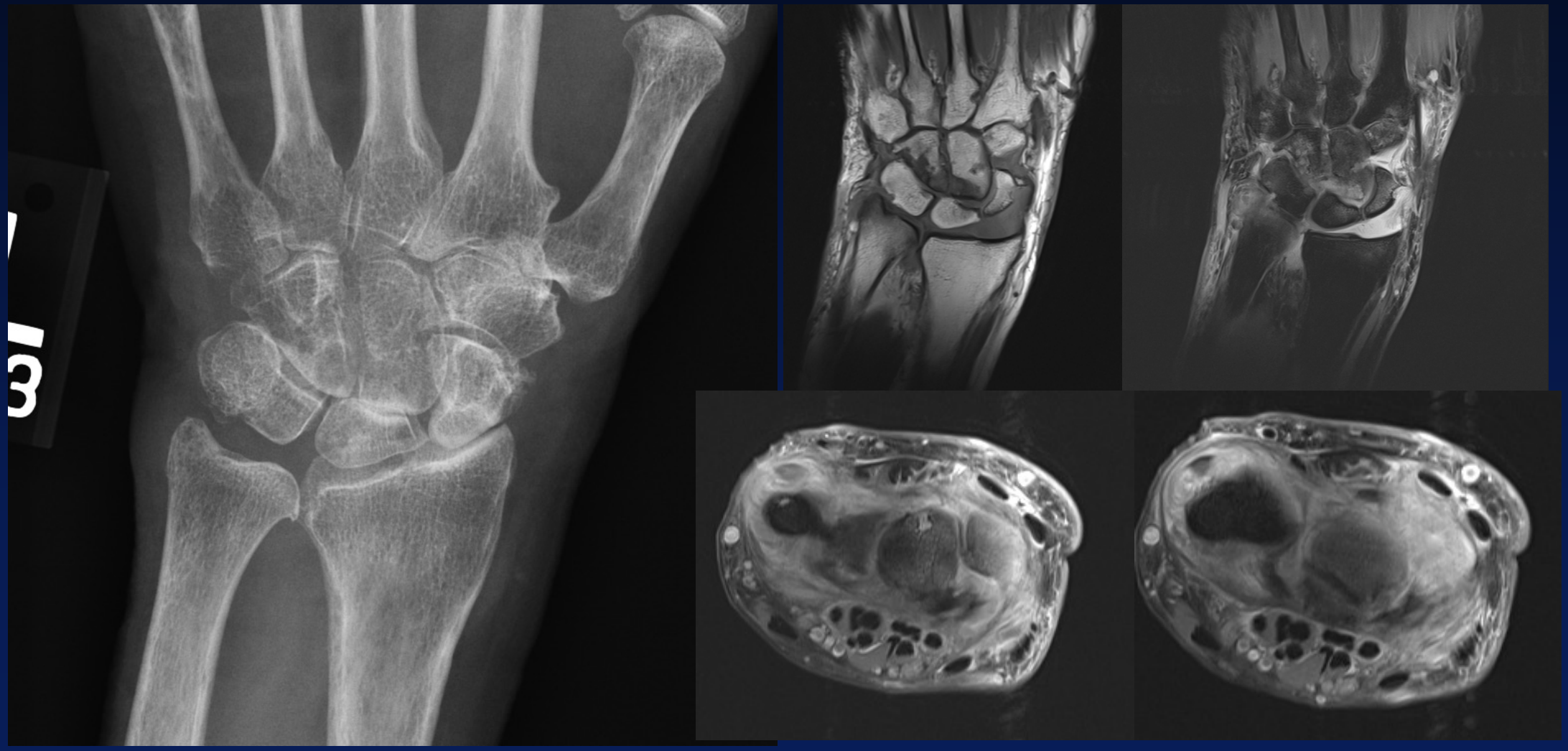





Hershey Medical Center
42y
9:58:
GW
MI: 1.1


Hershey Medical Center
42y
9:58:5
GW

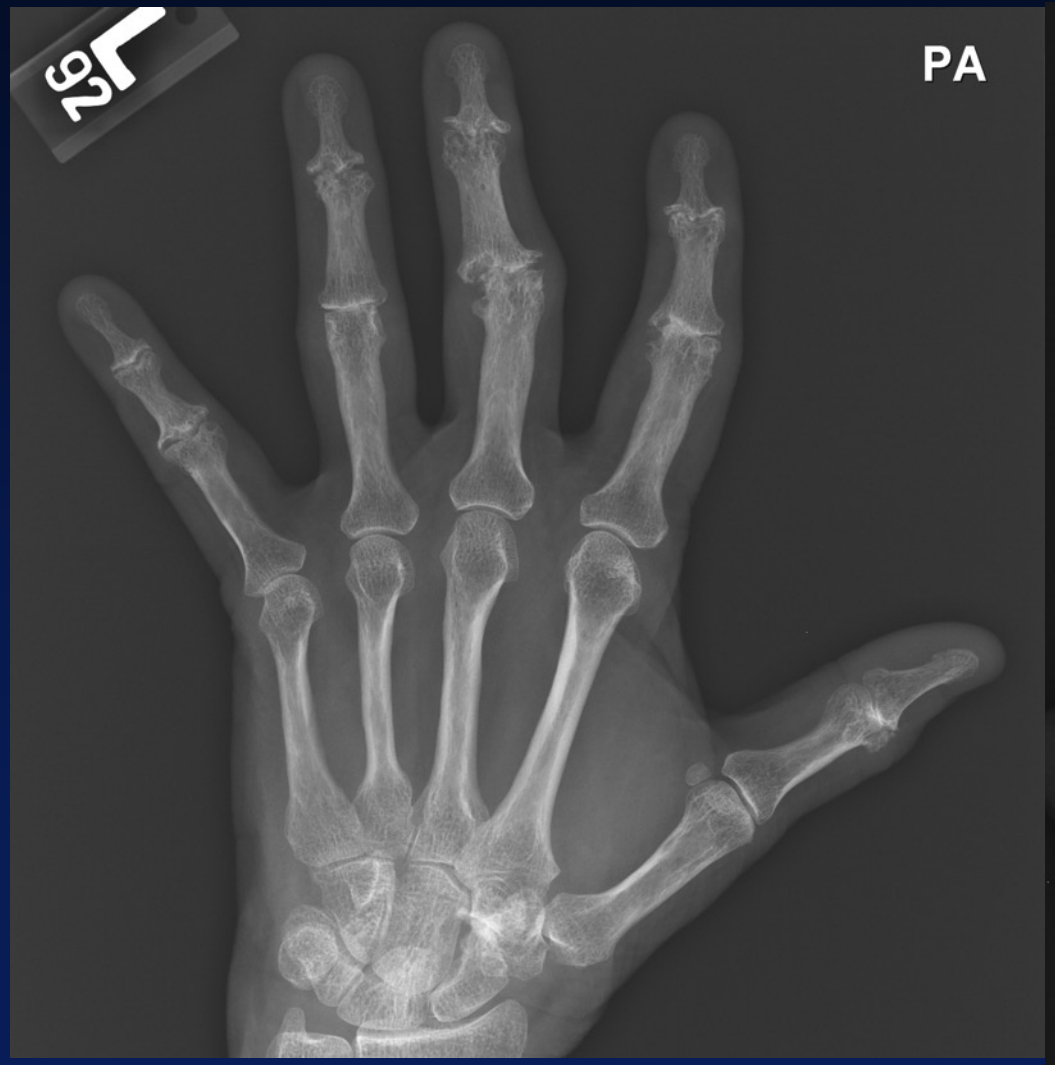
OA - SLAC Wrist

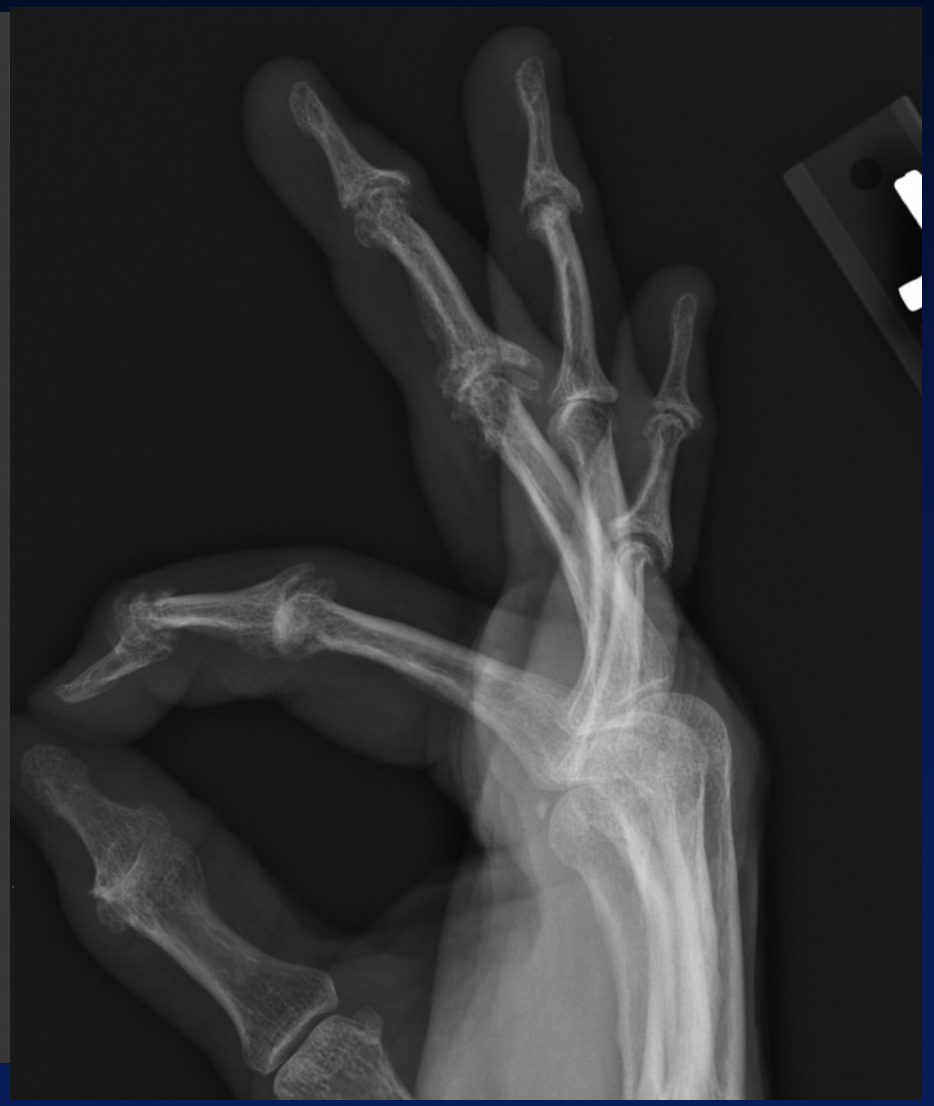


Common Challenges

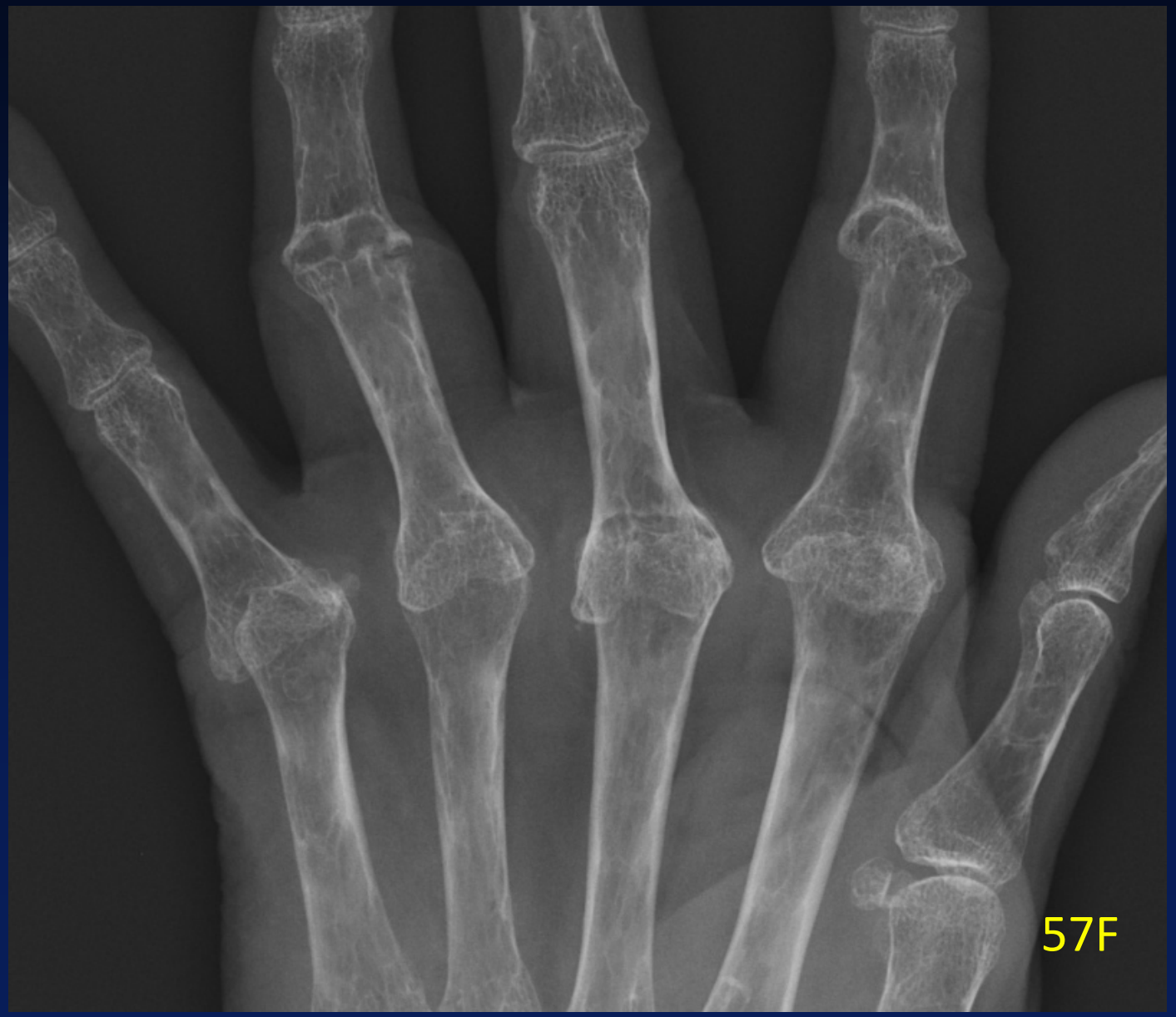
- Erosion vs Pseudoerosion
- SI joints
- Synovitis
- “Signs”
- Multiple arthropathies

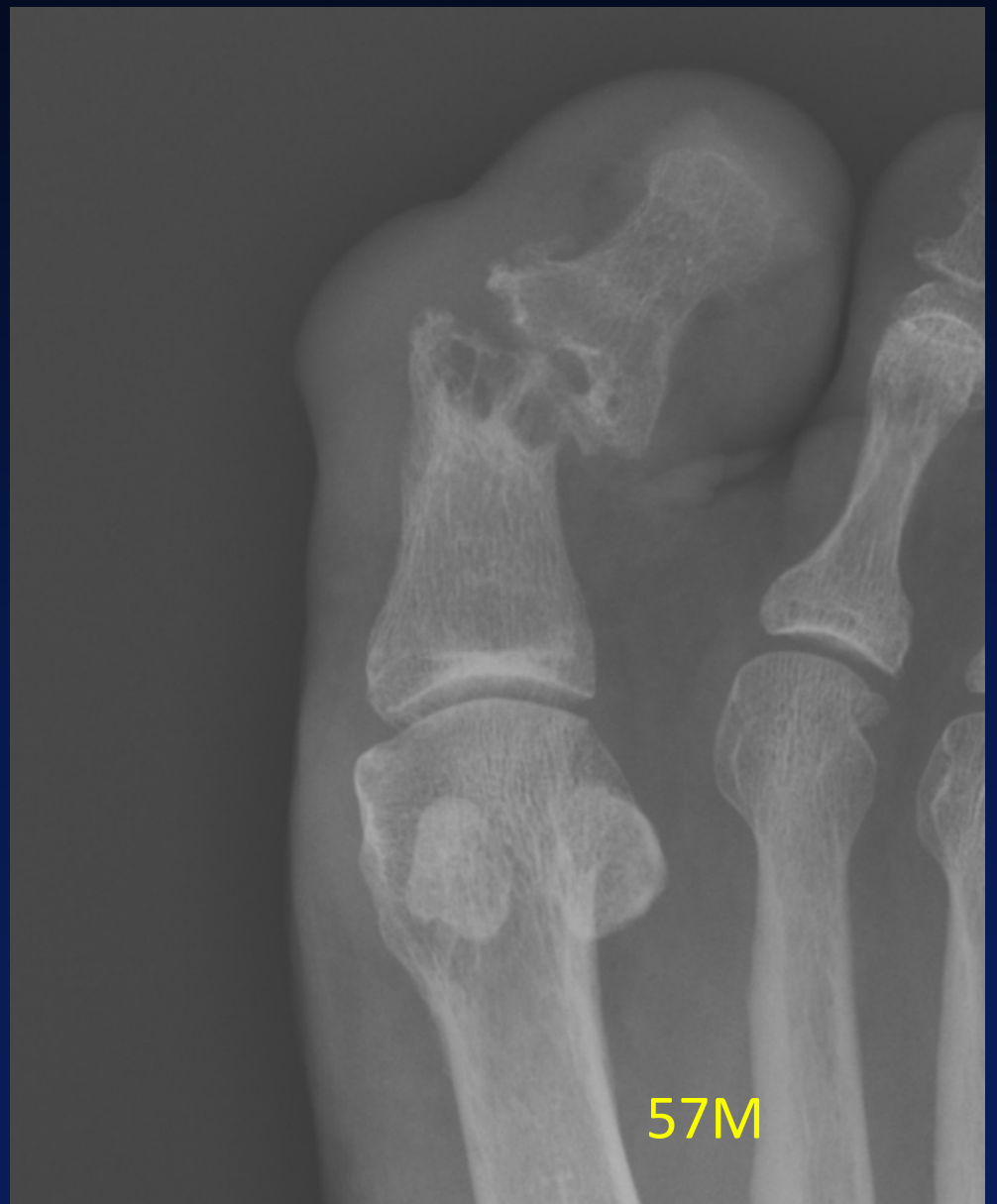
EOA - Central Erosions



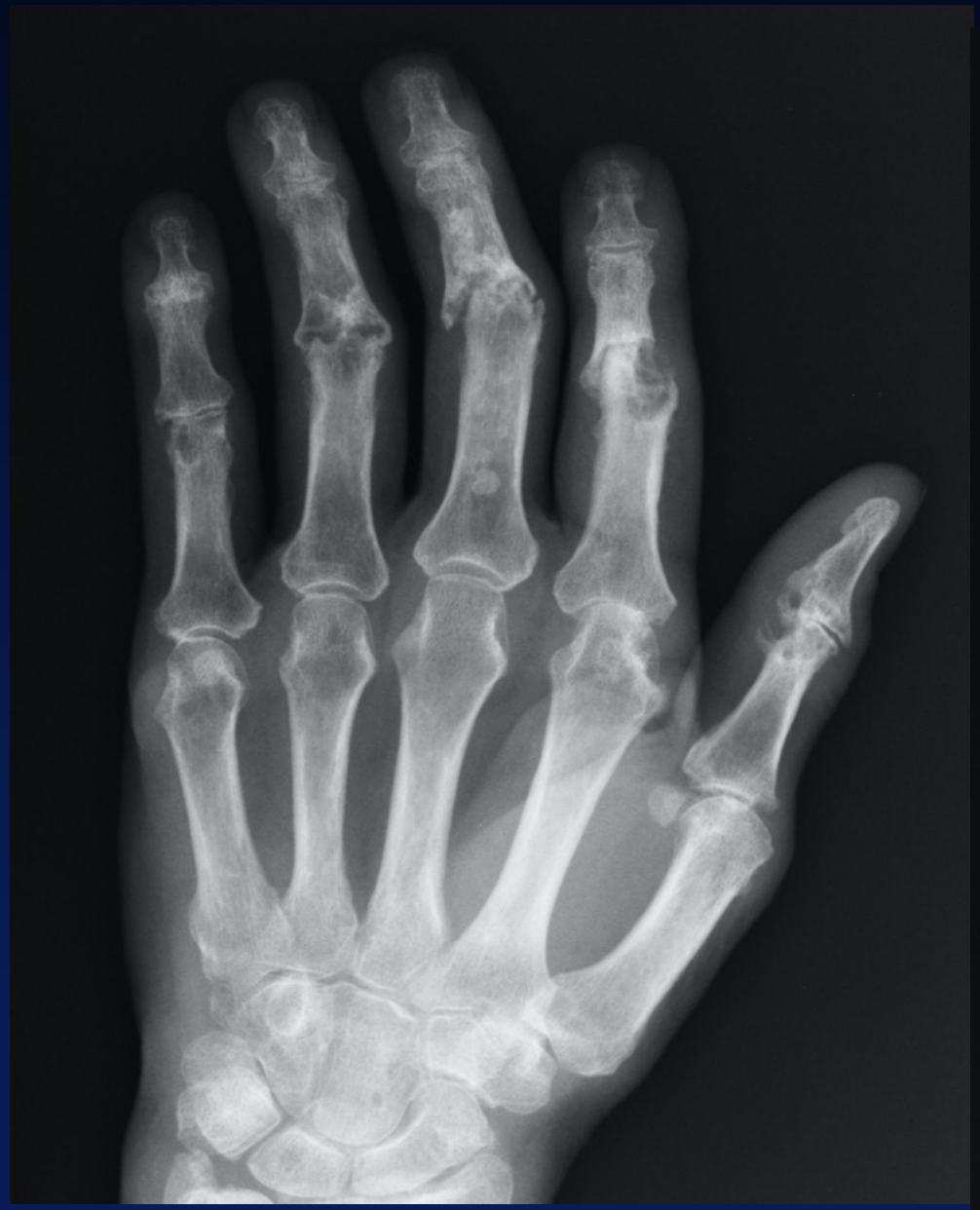


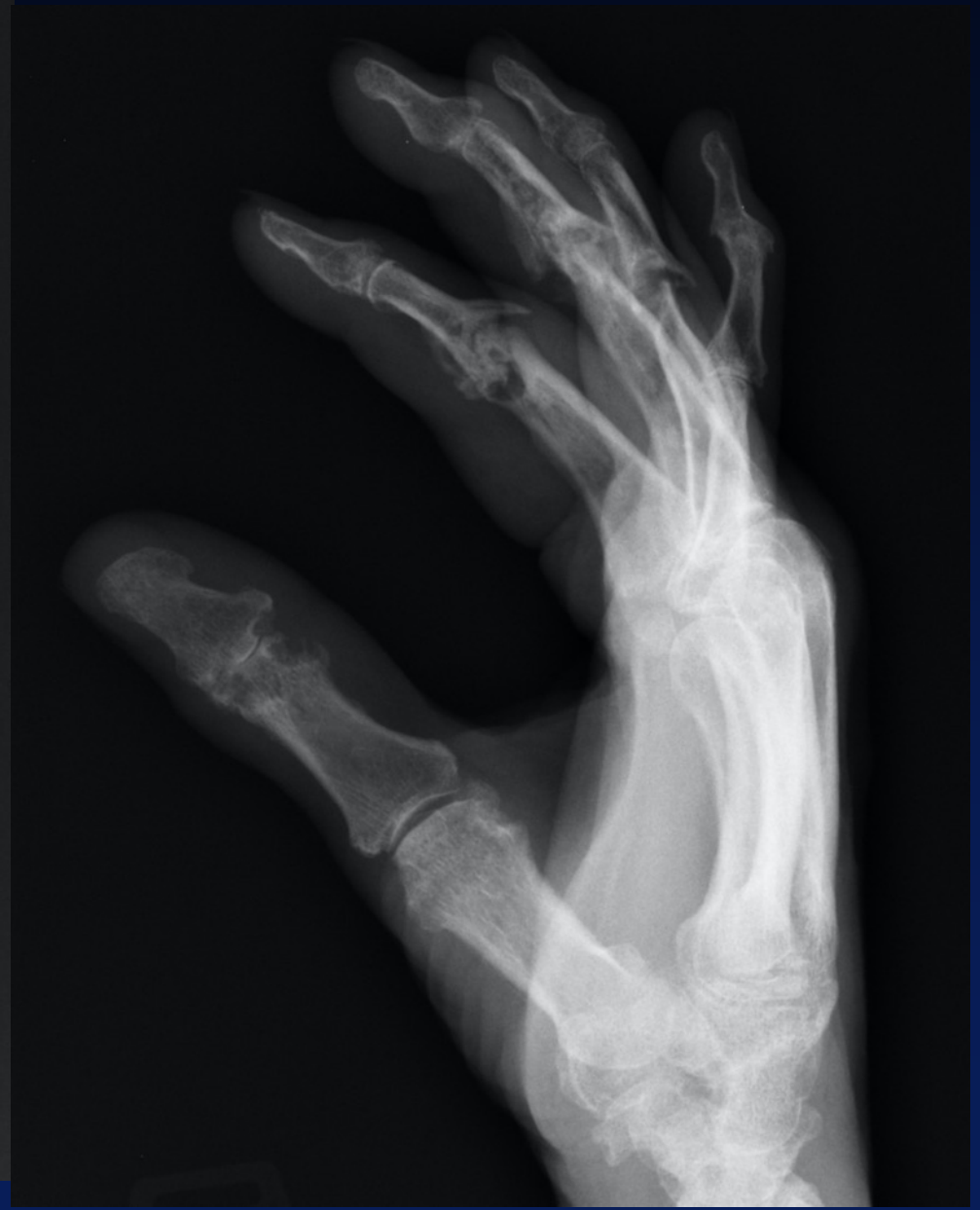
RA - Central Erosions



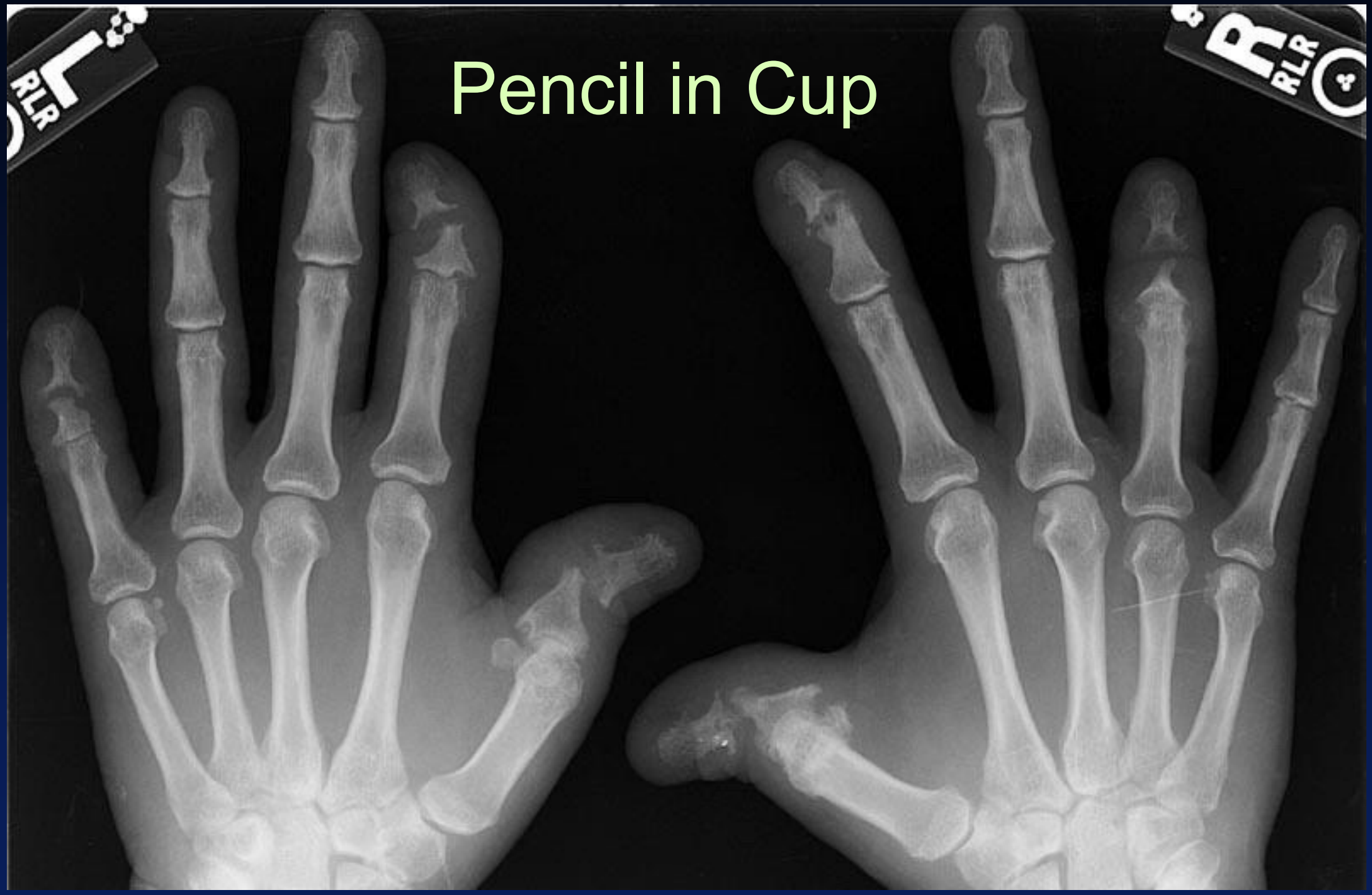


Gout - Central Erosions

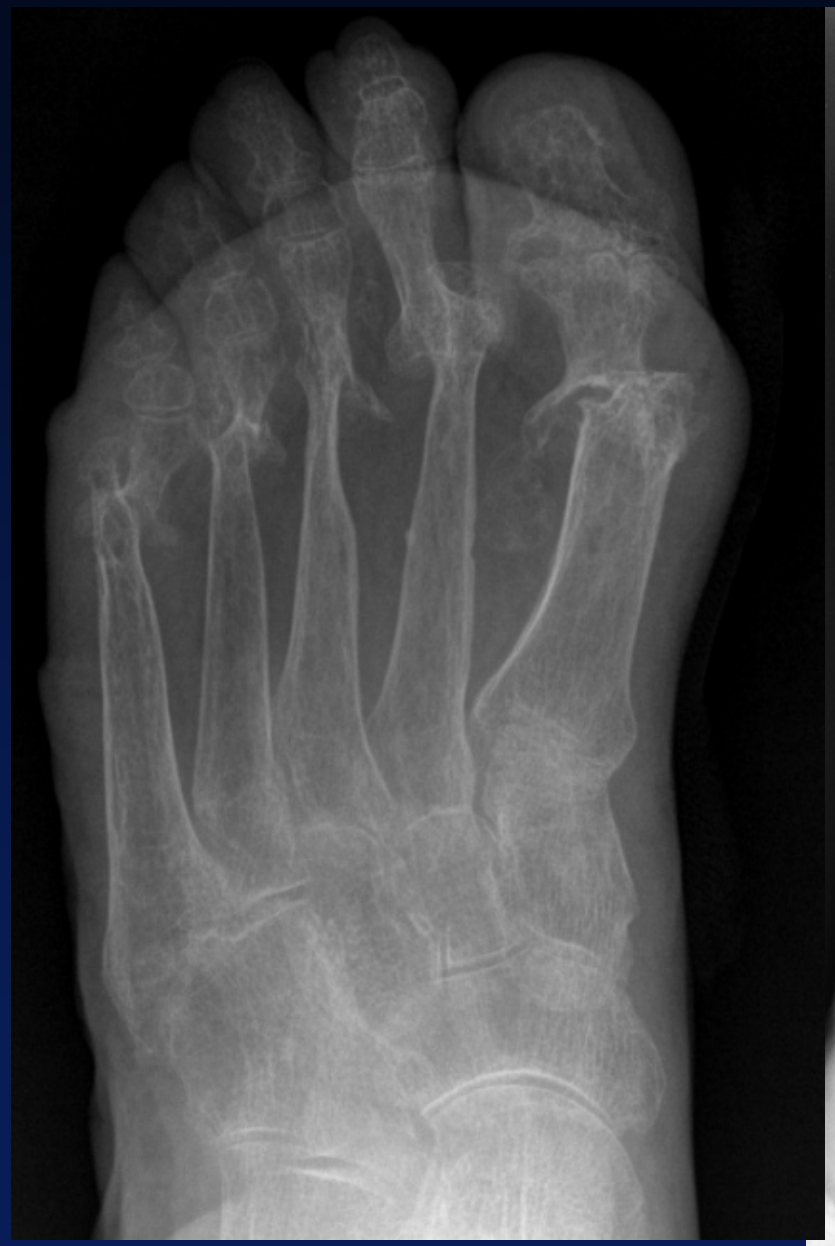


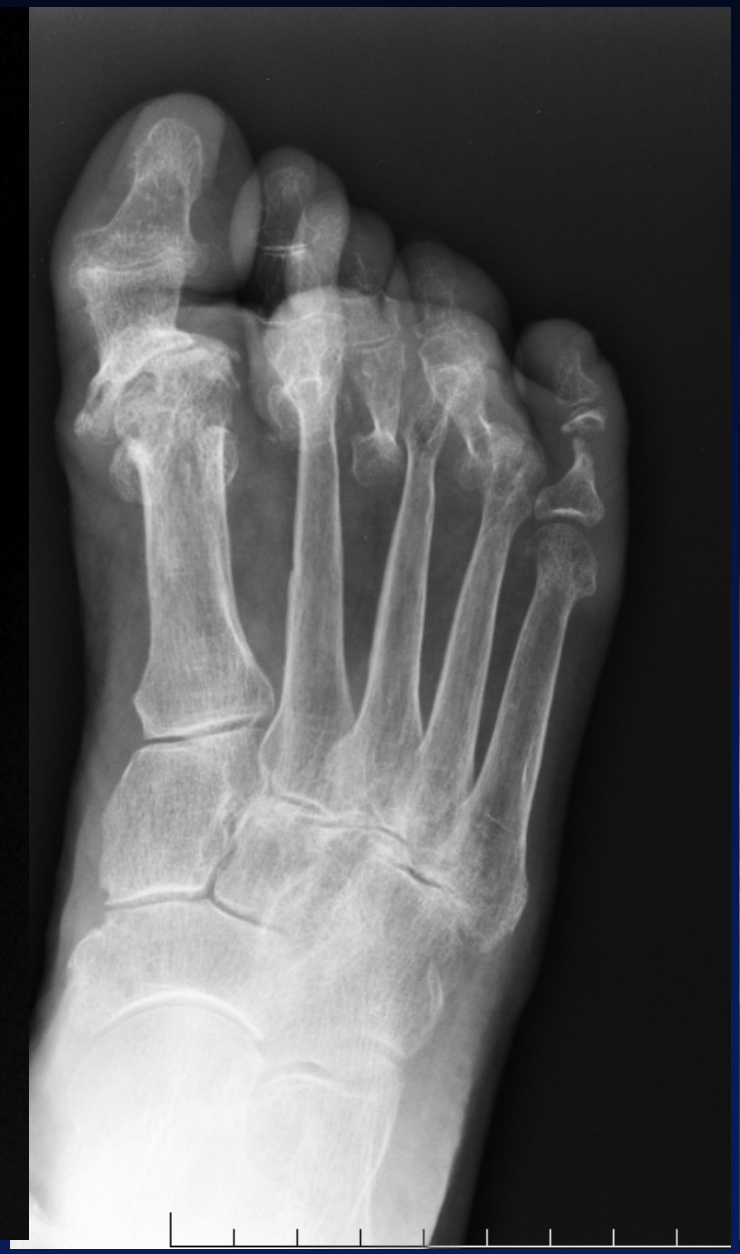


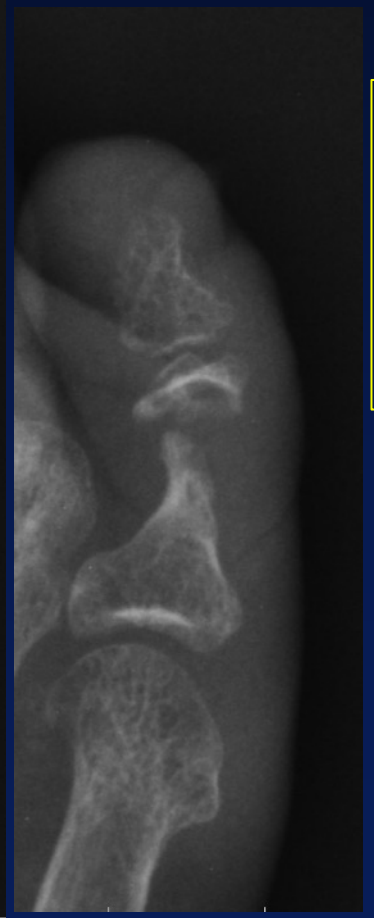
Pencil in Cup



RA -“Pencil in cup”

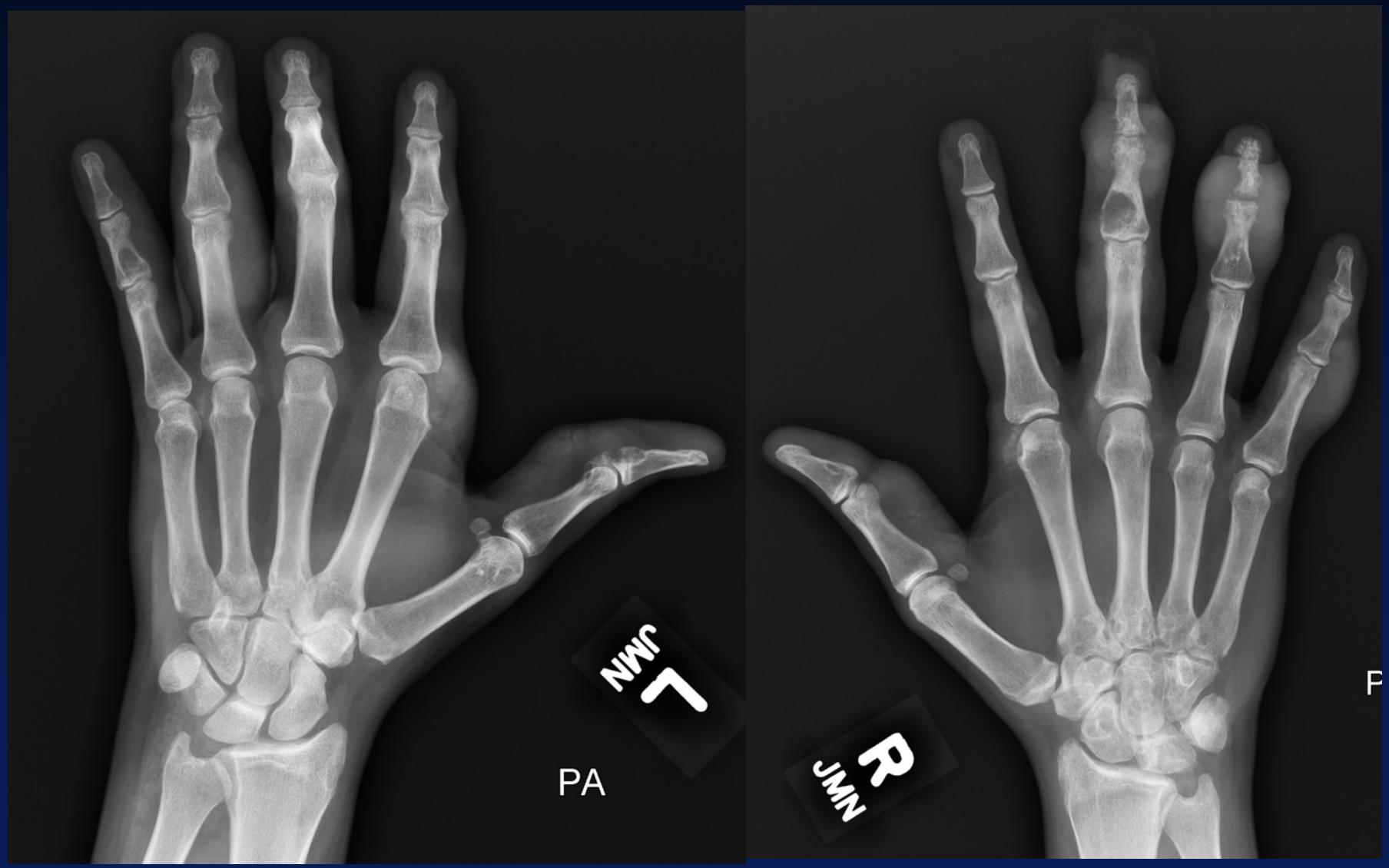






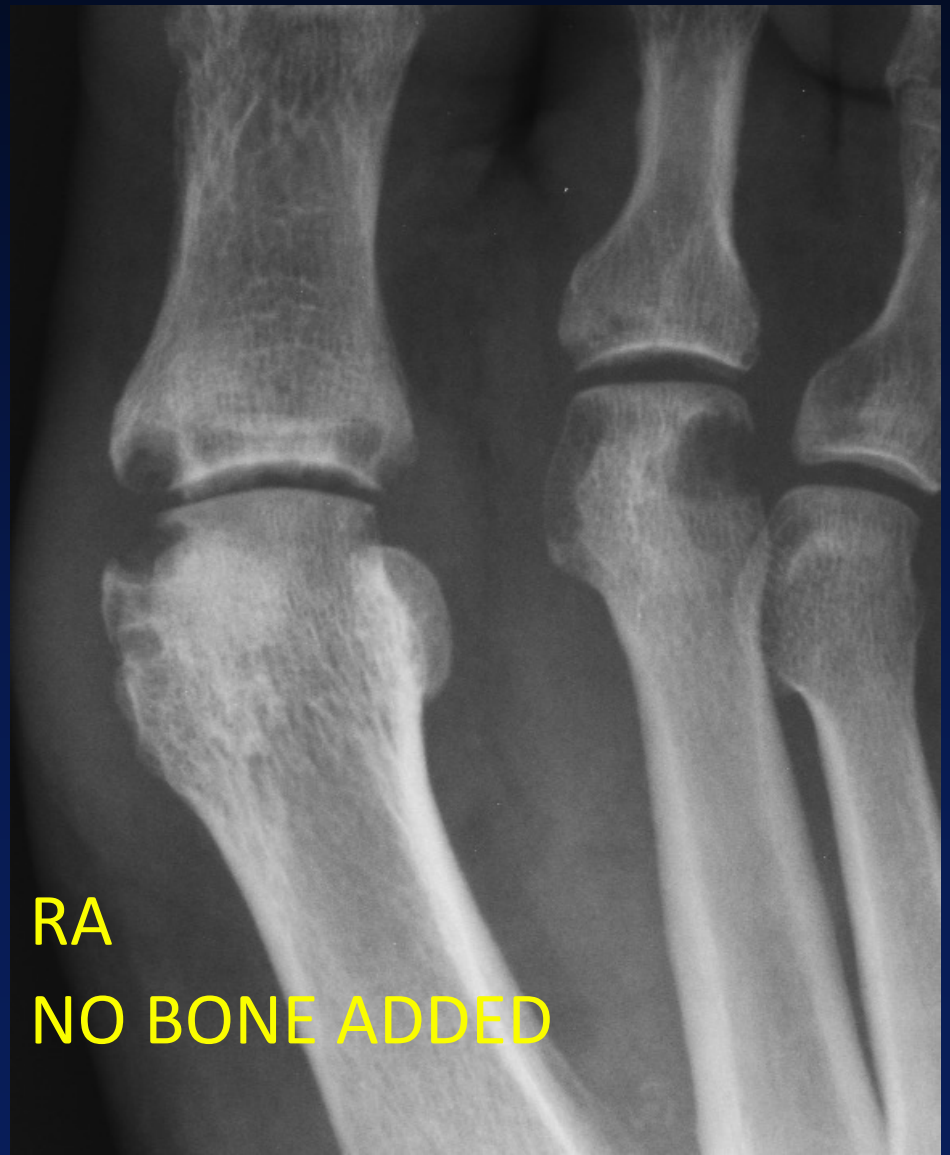
- More commonly seen with SpA
- Note lack of bone formation

Overhanging Edge of Cortex



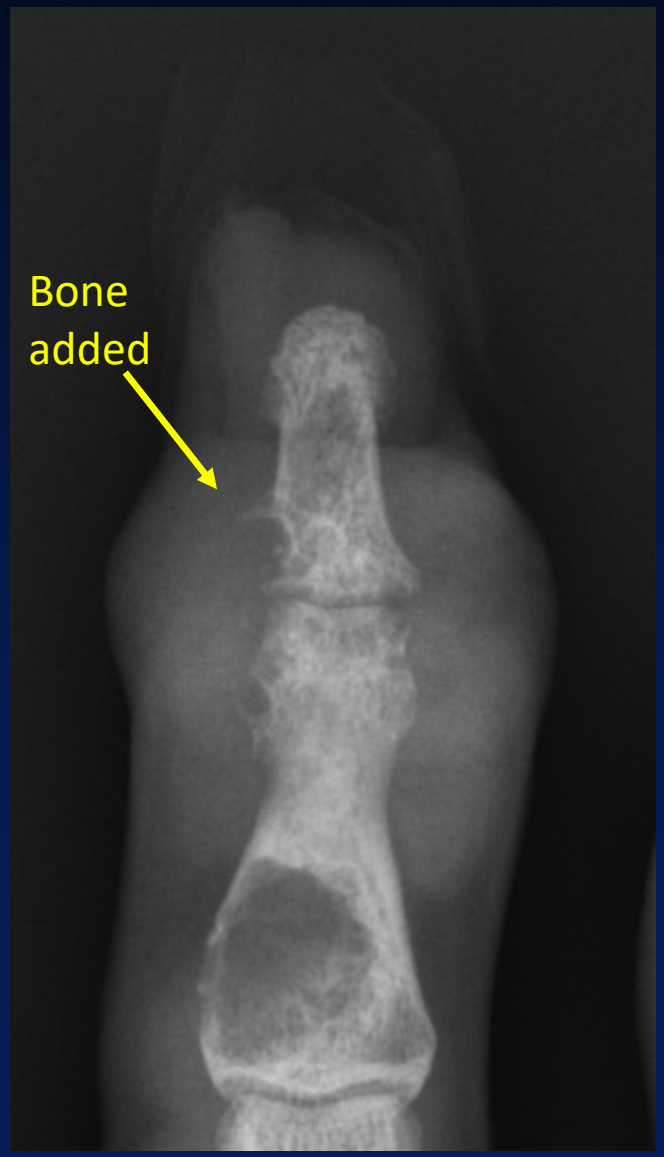
28M

Overhanging Edge of Cortex

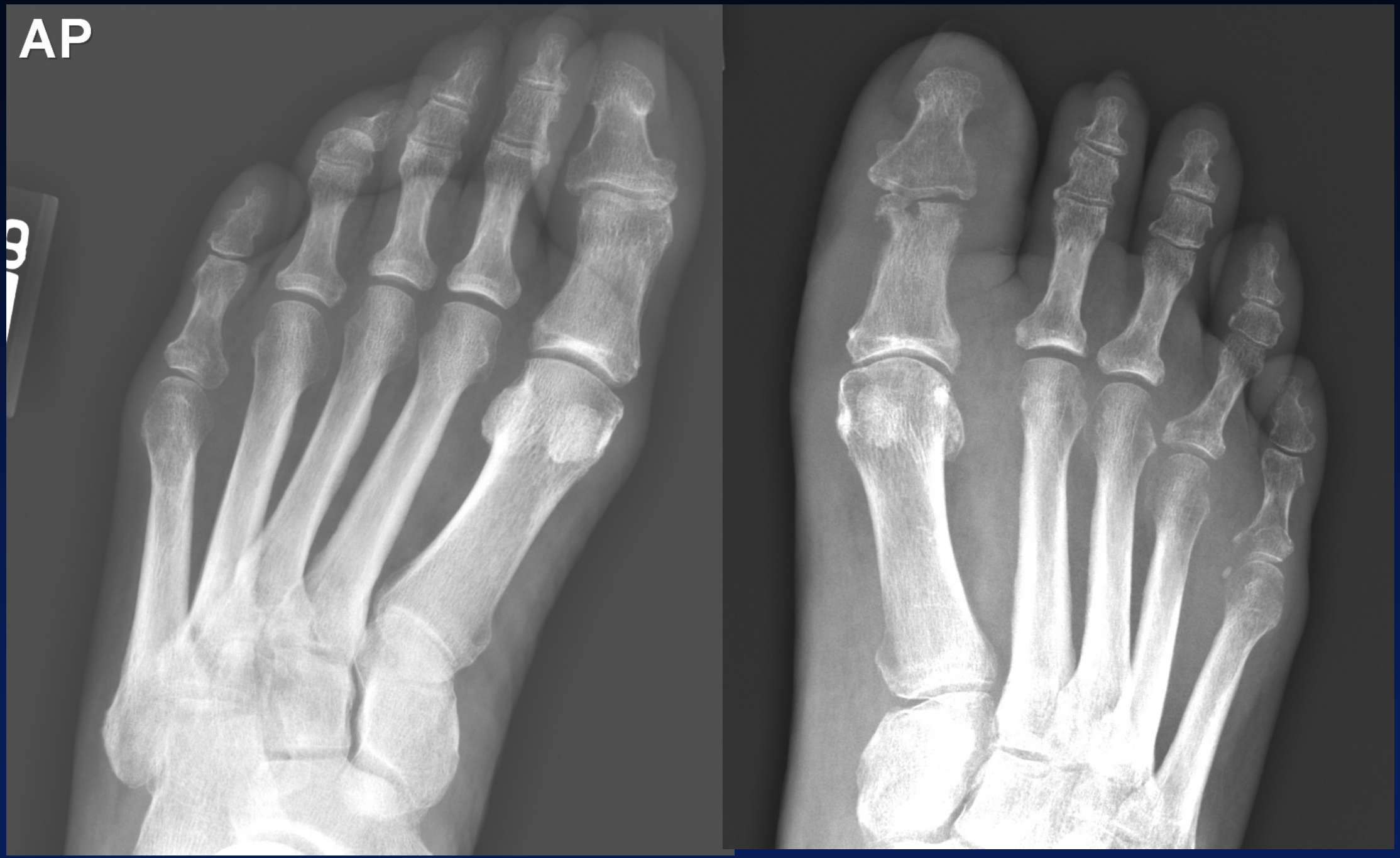


RA

NO BONE ADDED



Gout


AP

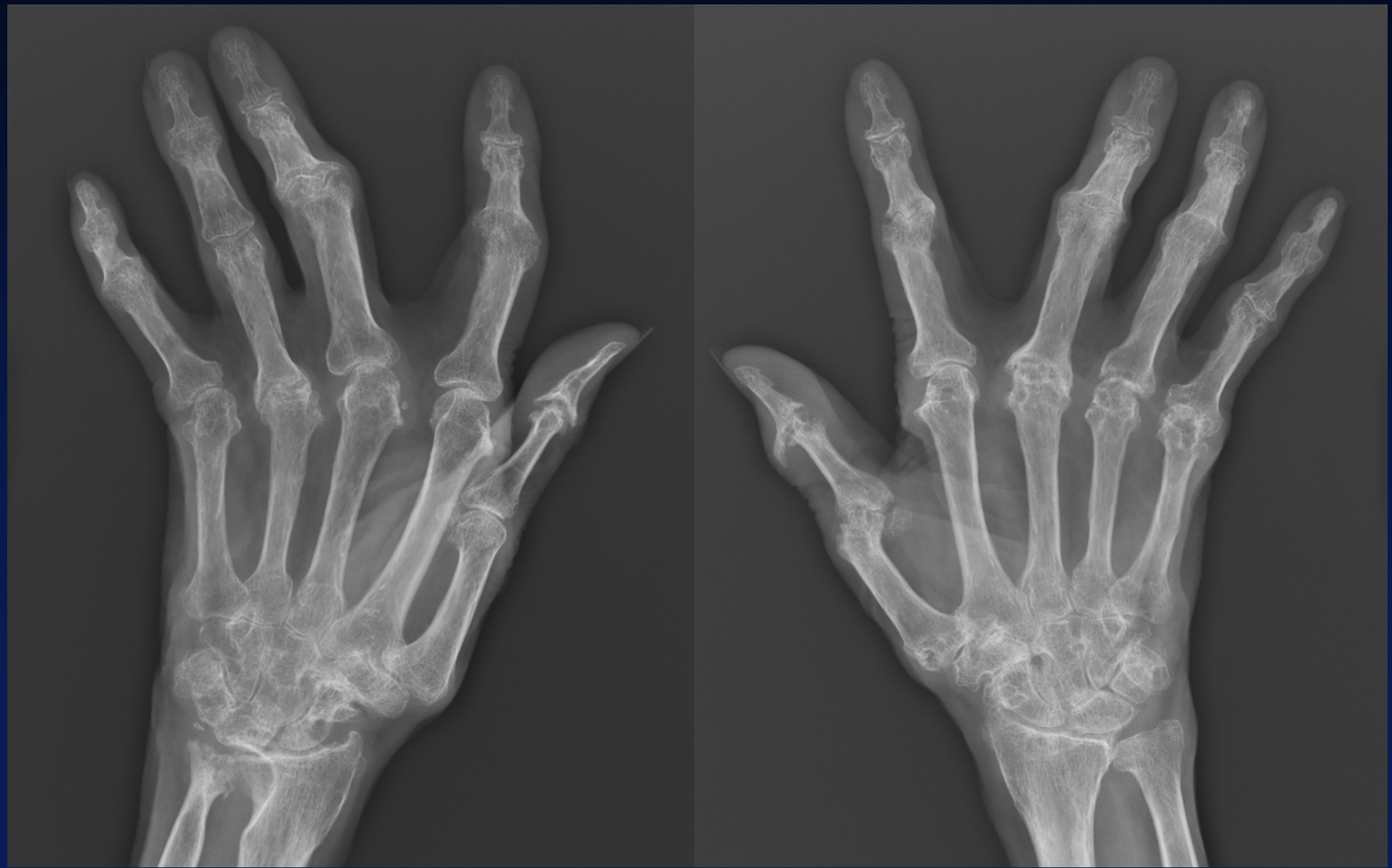
Common Challenges

- Erosion vs Pseudoerosion
- SI joints
- Synovitis
- “Signs”
- Multiple arthropathies

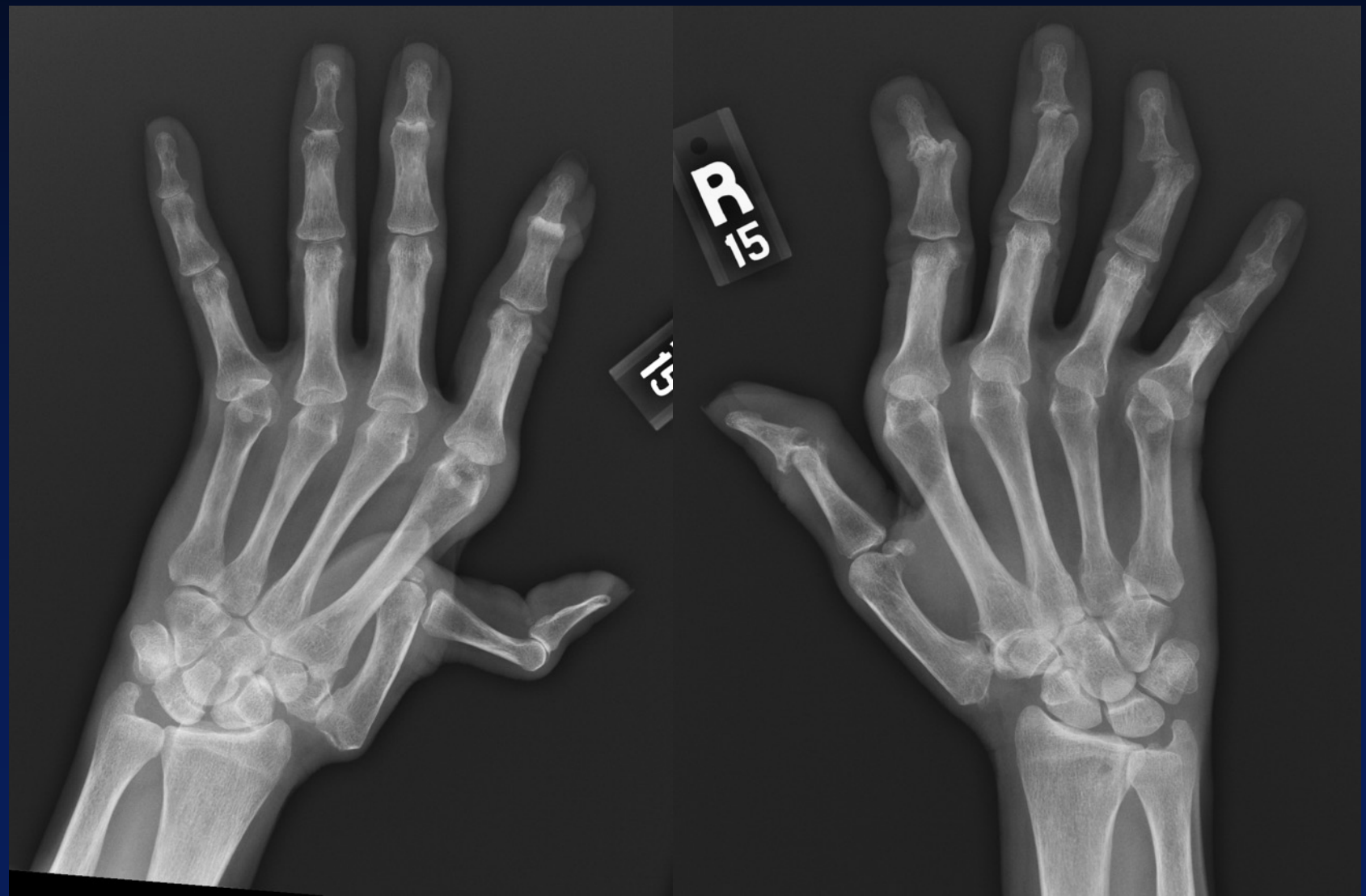
Multiple Arthropathies

- Common
  - RA – EOA
  - RA – OA
  - Gout – OA
  - Gout – CPPD
- Uncommon
  - Gout - RA

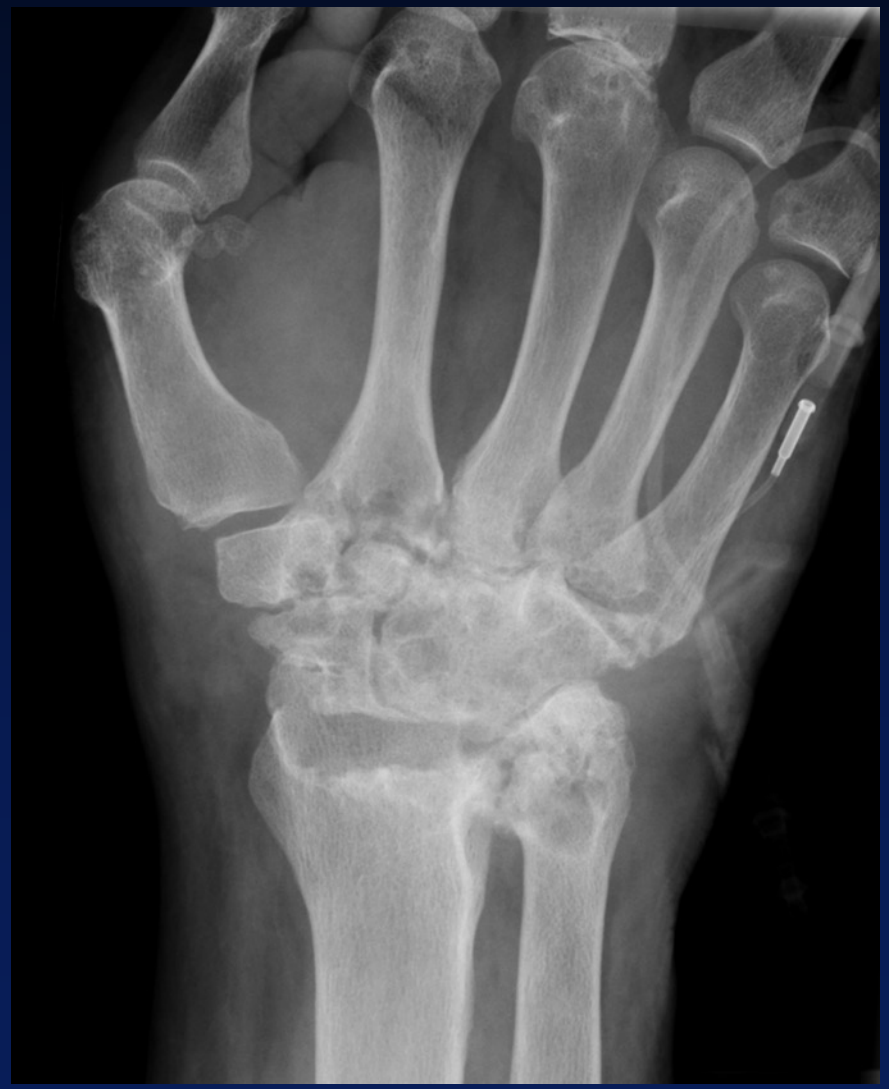
RA-EOA with IP ankylosis

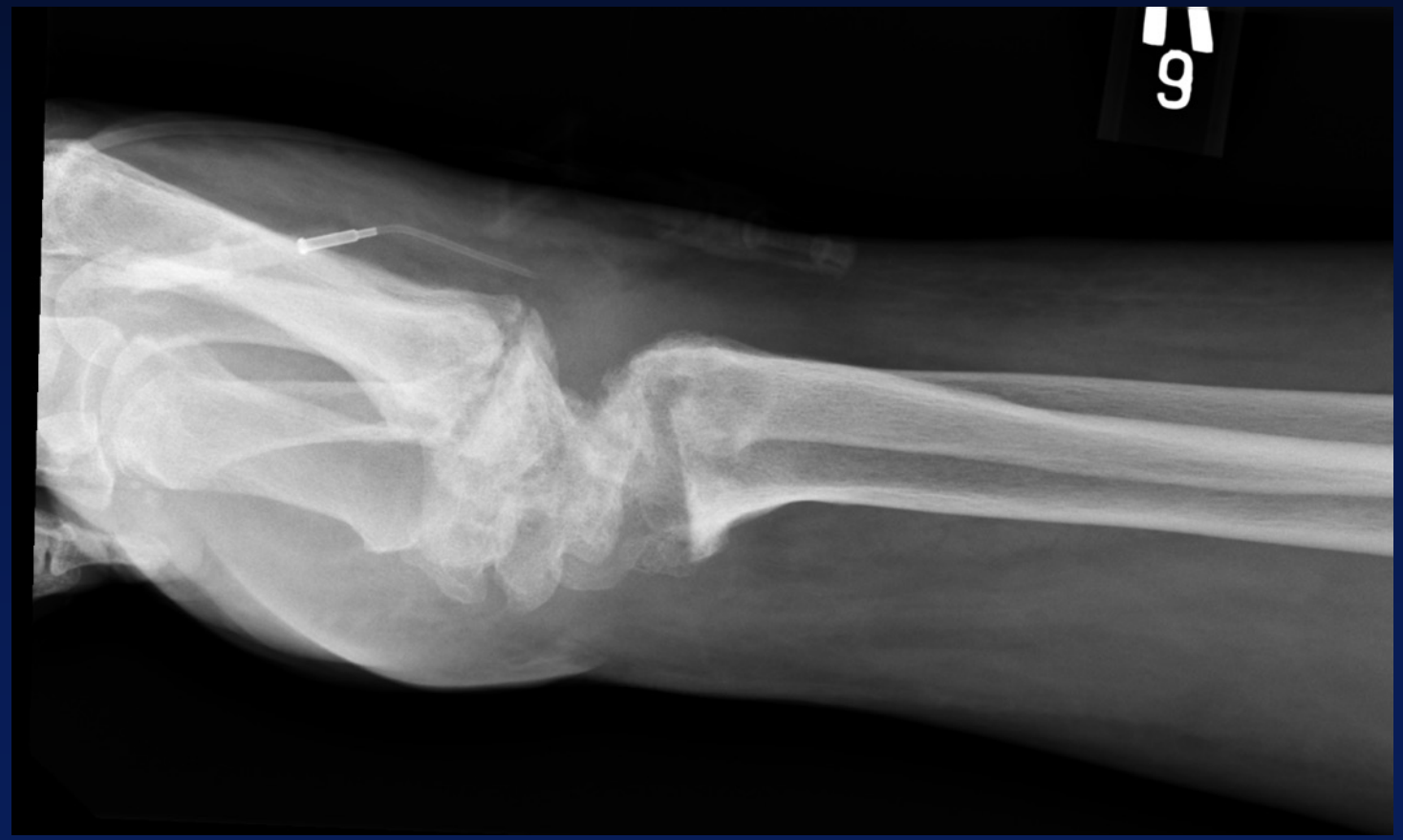


RA-DIP Erosions EOA?



Gout and RA – 61M





Summary

- Diagnosis in clinical syndromes is challenging
- Not every defect is an erosion
- MRI and US are sensitive at cost of specificity
- SI joint imaging is really challenging
- Synovitis and hyperemia may not be RA in older pts
- Do not over rely on “classic signs”
- Group think patients with discordant findings

Systemic Sclerosis: A new Decade

Chris T. Derk, MD, MS
Professor of Clinical Medicine
Fellowship Program Director
Division of Rheumatology
University of Pennsylvania School of Medicine

PRS Annual Scientific meeting
27 September 2020

Conflicts of Interest:

Research:

Celgene

Gilead

Cytori

Boehringer Ingelheim

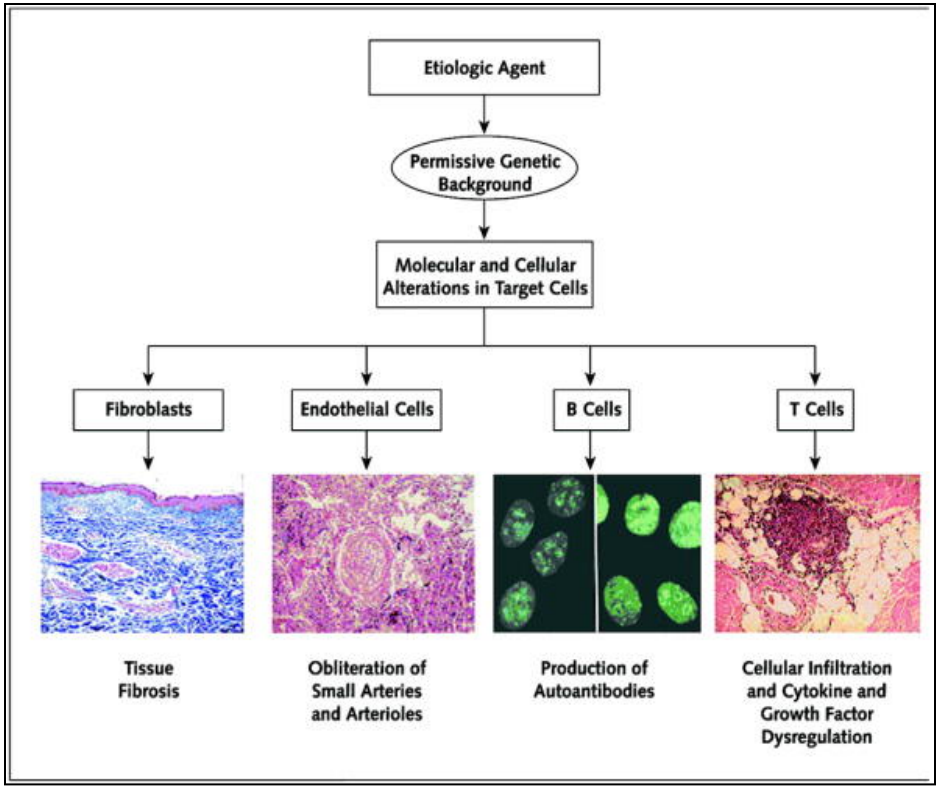
Goals

- General Review
- Review the 2013 ACR/ EULAR classification criteria
- Screening of SSc patients
- Current therapies based on expert recommendations
- Past high impact treatment studies
- New primary outcome measure CRISS
- Recent high impact studies
- Looking into the future

Review

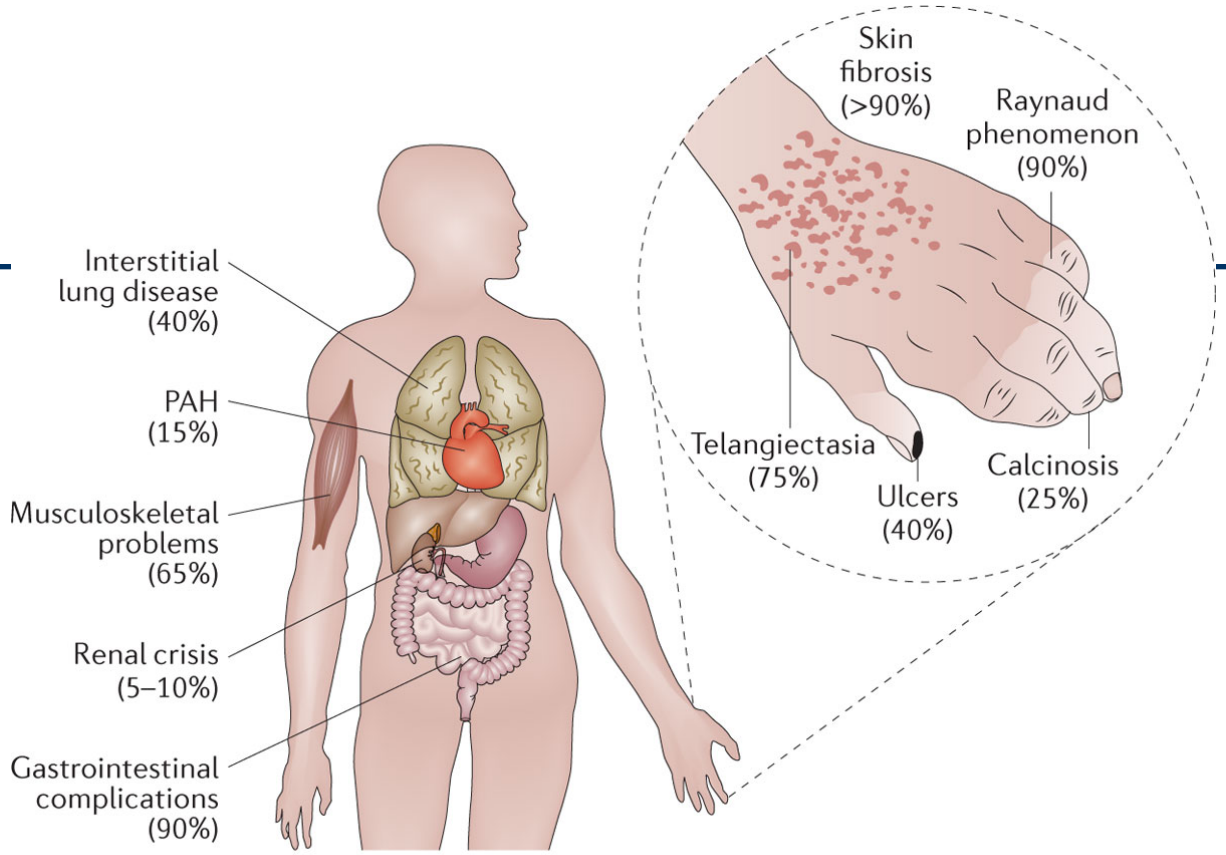
An autoimmune connective tissue disorder of unknown etiology characterized by the triad of

- **Fibrosis**
- **Vascular dysfunction**
- **Immune dysregulation**



Jimenez SA, DerkCT. Ann Intern Med 2004;140(1):37-50.

Figure 4 Organ complications associated with systemic sclerosis



Nature Reviews | Disease Primers

Perelman School of Medicine
University of Pennsylvania

Varga, J. *et al.* (2015) Systemic sclerosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.2

Classification

- **Diffuse cutaneous scleroderma**
  - Symmetric, widespread skin fibrosis
  - Advances from the distal aspect of the extremities to above the knees and elbows, trunk, face, neck
  - Rapid progression
  - Early visceral organ involvement
  - Absence of anticentromere antibodies
  - Poor prognosis (10 year survival 40-60%)

Classification

- **Limited cutaneous scleroderma**
  - **Symmetric skin fibrosis limited to the distal extremities and face.**
  - **Manifestation of Raynaud's almost a decade before the first skin findings.**
  - **Slow progression with late appearance of internal organ manifestations.**
  - **Anticentromere antibody positive**
  - **Good prognosis (>70% ten year survival)**

Clinical Manifestations

- New phenotype (lcSSc with high rate of visceral damage and anti-Scl-70 +).
- Predictors of disease worsening in dcSSc (digital ulcer, lung fibrosis, muscle weakness, elevated CRP).
- Increase in mRSS > 5 and >25% within 1 year predictor of long term decline in lung function and increase in all cause mortality.

- Arthr Rheumatol 2019;71: 1553-70
- Ann Rheum Dis 2019; 78:1242-8
- Ann Rheum Dis 2019; 78:648-56

- Lung US in patients without respiratory issues correlated with HRCT findings (sensitivity 91.2% and specificity 88.6%)
- FDG-PET/CT to differentiate inflammation to fibrosis in the lungs.
- New Lung patterns(typical NSIP and less commonly UIP)

1.Pleuroparenchymal fibroelastosis PPFE(fibrosis of the pleura and subadjacent parenchymal areas of the upper lobes)

2. Combined pulmonary fibrosis and emphysema CPFE (higher orbidity and mortality

- Rheumatol Clin 2019 Aug 7 (online)
- Ann Rheum Dis 2019; 78:577-8
- Medicine 2019;98:e16086
- BMD Open 2019;5: e000820

Clinical Manifestations

- Cardiac MRI can detect myocardial inflammation in 73% of patients who have symptoms . Young age and high starting mRSS risk factors. SSc subset, visceral organ involvement, inflammatory markers, cardiac or muscle enzymes did not correlate with MRI findings.
  - Int J Rheum Dis 2019; 22: 2125-33

- SRC patients had higher rate of anti-Ro and anti-RNA Poly II antibodies while control had more anticentromere positivity.
- HfpEF is common in SSc with increase in NT-pro-BNP and relates to worse prognosis, related to left atrial stiffness.
  - J Rheumatol 2019:46:85-92
  - Int J Cardiovasc Imaging 2019; 35:1795-802

Pathogenesis of SSc

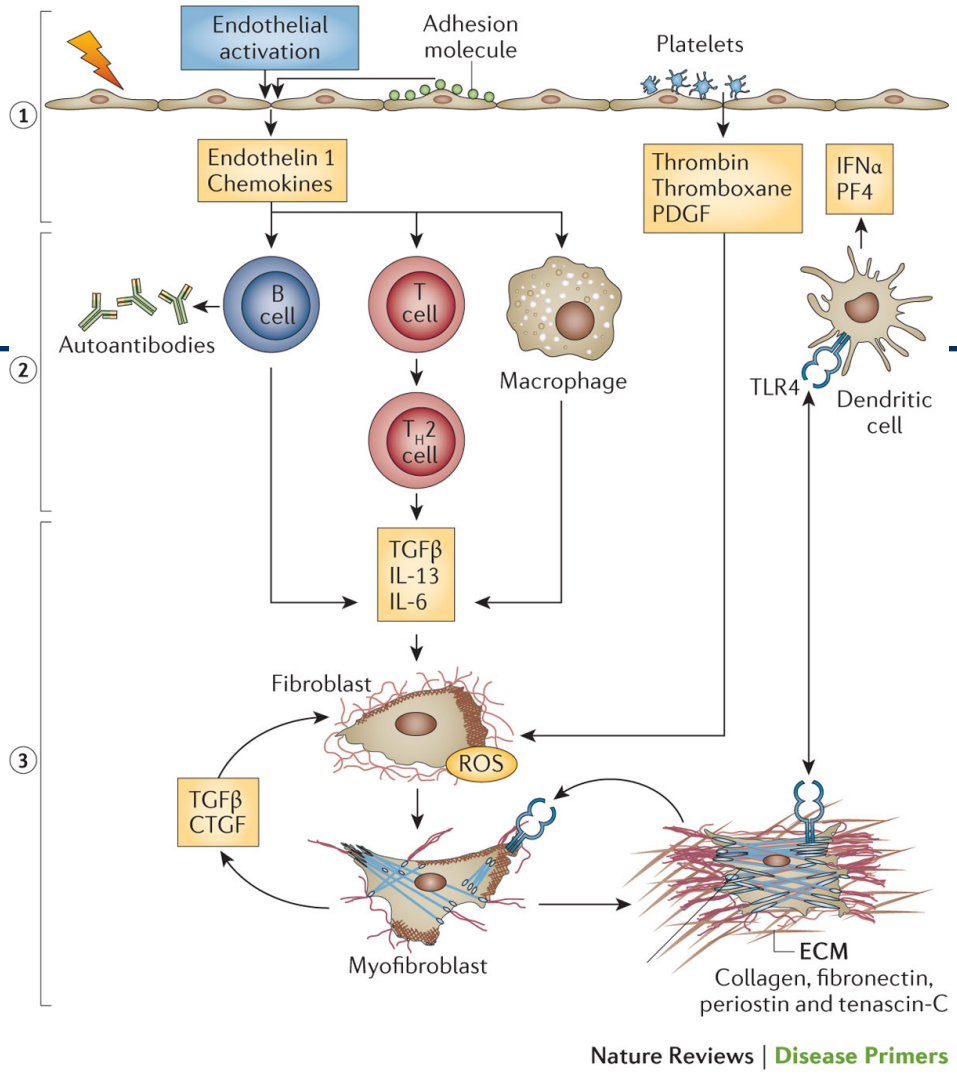
- Alleles as risk factors for SSc, HLA-DRB1, HPB1.
- 28 non-HLA loci identified as risk for SSc
- SNPs identified in Vit D receptor gene polymorphism
- In skin biopsies of early dcSSc the TNF signaling pathway was over expressed.

- Proc Natl Acad Sci 2020;117:552-62
- Nat Commun 2019;10;4955
- Arch Med Res 2019:50:368-76
- BMC Med Genomics 2019;12:199

- Long non coding RNAs (lnc-RNAs) were downregulated in SSc (typically regulate tumor proliferation, inflammation, vascular alteration and fibrosis). Possible link of malignancy and SSc.
- IL-18 higher in SSc inversely correlated with DLCO.
- IL-17 higher in SSc
- IL-6 levels correlated with severity of symptoms

- J Clin Med 2019;8:320
- Clin Transl Immunol 2019;8:e1045
- Arch Med Sci 2019; 15: 706-12
- Clin Exp Rheumatol 2019;37(Suppl 119)S15-22

Figure 2 The disease process in systemic sclerosis



Varga, J. *et al.* (2015) Systemic sclerosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.2

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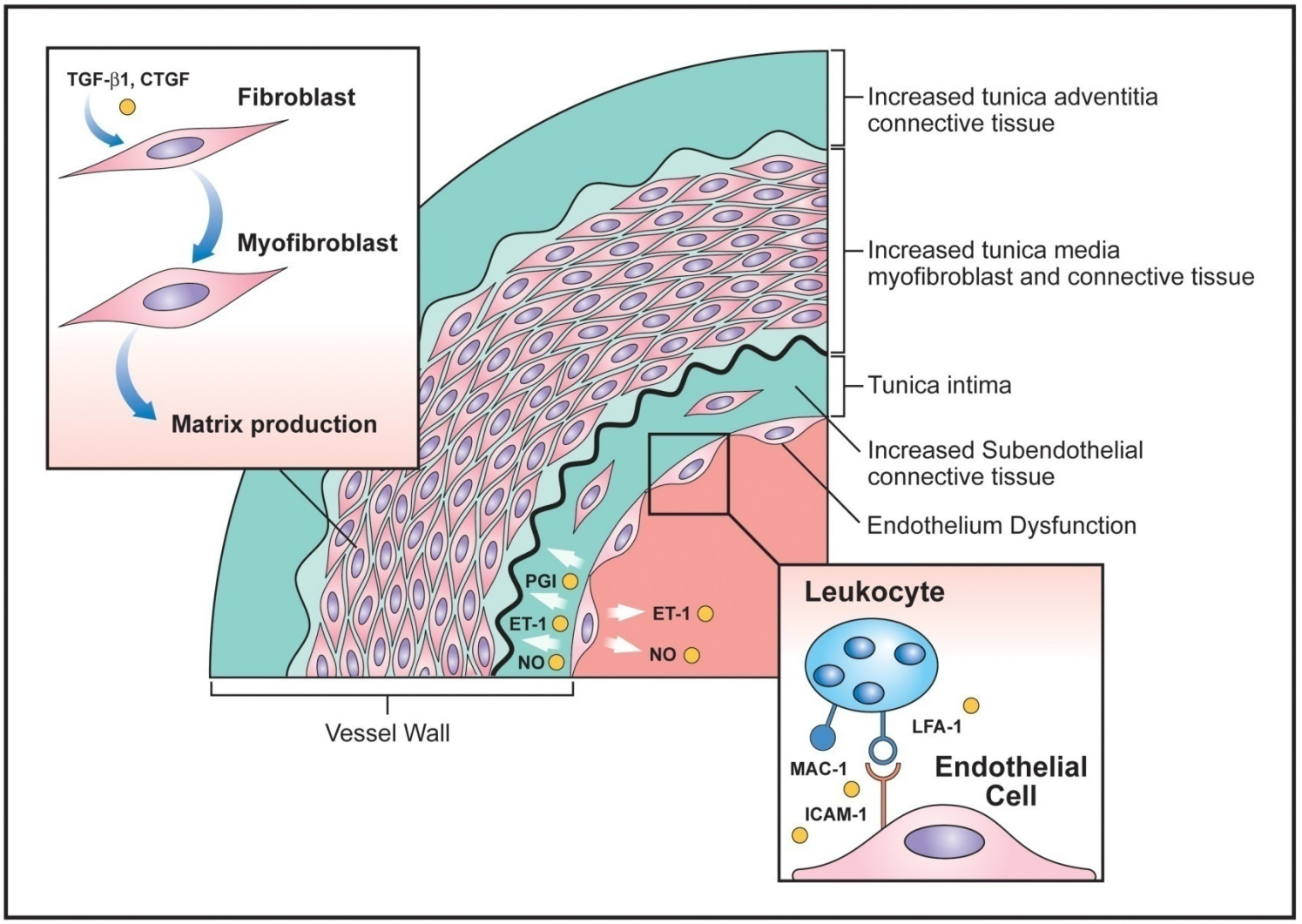
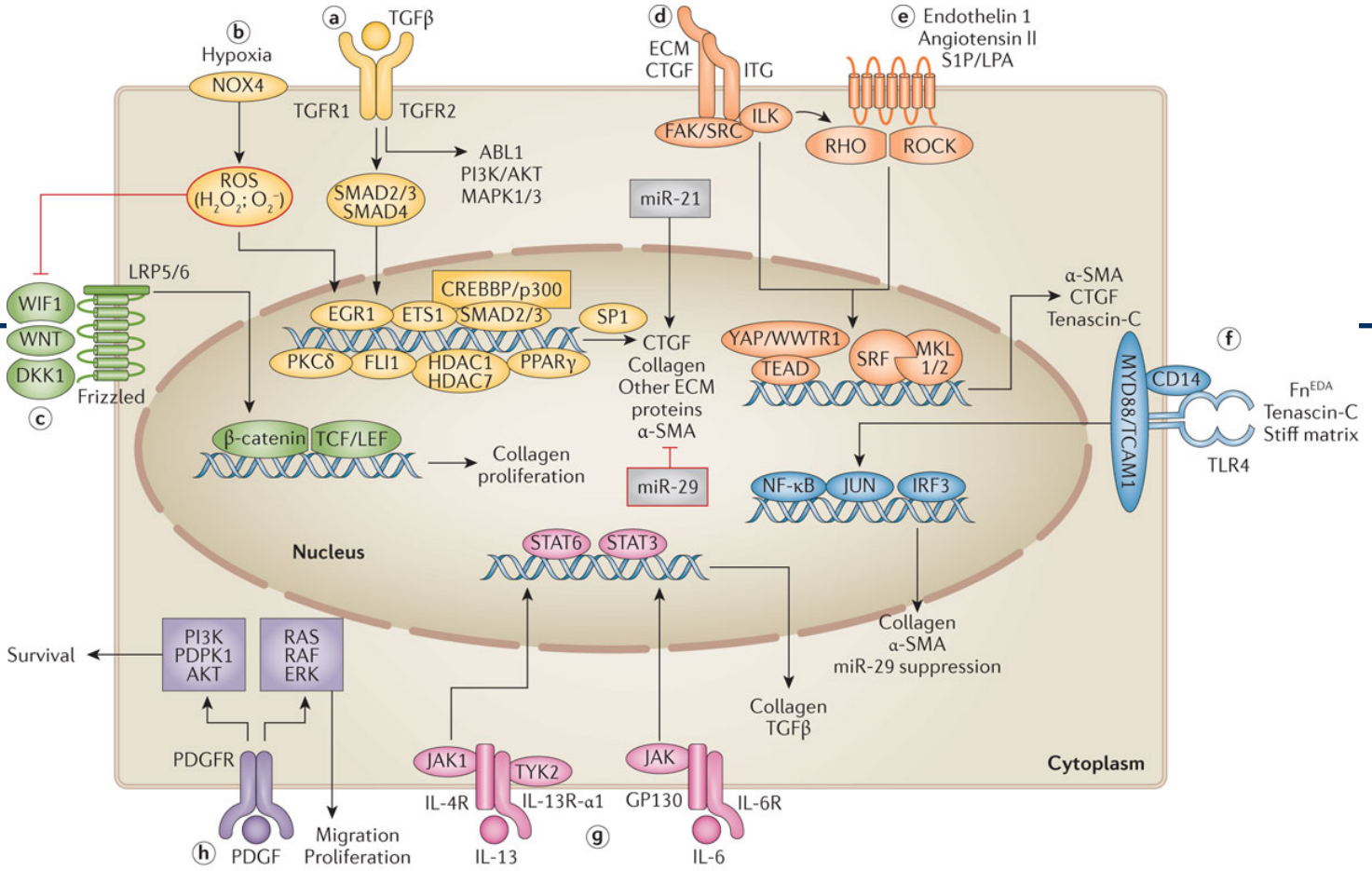
University of Pennsylvania



Derk CT, Jimenez SA. Autoimmun Rev. 2006 ;5(1):25-32.

Figure 3 Molecular mechanisms of fibroblast activation in systemic sclerosis



Nature Reviews | Disease Primers

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Varga, J. *et al.* (2015) Systemic sclerosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.2

1980 Systemic Sclerosis (Scleroderma) Classification Criteria

- **Requirements**
- **Either the sole major criterion or ≥2 of the minor criteria.**
  - Major Criterion
    - Proximal scleroderma: symmetrical thickening, tightening and induration of the skin of the fingers and the skin proximal to the metacarpophalangeal or metatarsophalangeal joints. These changes can involve the entire limb, face, neck and trunk.
  - Minor Criteria
    - Sclerodactyly: induration and tightening of the skin of the fingers
    - Digital ischemia: as manifested by digital pitting scars or atrophy of finger pads.
    - Bibasilar pulmonary fibrosis: reticular or reticulonodular densities most pronounced in the basilar areas of the lungs on CXR. This may produce the appearance of "honeycomb lung" and must not be due to a primary pulmonary disease.

Deficiencies

- **Fails to include some patients with limited scleroderma or CREST Syndrome**
- **Does not include subtle features of the disease**
- **Does not include serological markers**

2013 ACR / EULAR Criteria For The Classification Of Systemic Sclerosis (Scleroderma)*

Item	Sub-items(s)	Weight/score †
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal 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 *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere 3 Anti–topoisomerase I Anti–RNA polymerase III	3

* The criteria are not applicable to patients with skin thickening sparing the fingers or to 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).

† The total score is determined by adding the maximum weight (score) in each category.
Patients with a total score of ≥ 9 are classified as having definite scleroderma.

Sensitivity 91% Specificity 92%

Van den Hoogen et al. 2013 Classification Criteria for Systemic Sclerosis. Arthritis and Rheumatism. Vol. 65, No. 11, November 2013, pp 2737–2747

Screening

- **Definitive criteria for early diagnosis are still lacking. VEDOSS (Very Early Diagnosis of Systemic Sclerosis)**

  Raynaud's phenomenon in combination with *puffy hands*,

  and

  characteristic *nailfold cappilaries* or *SSc specific antibodies*

  or

  More than one of above items in absence of Raynaud's

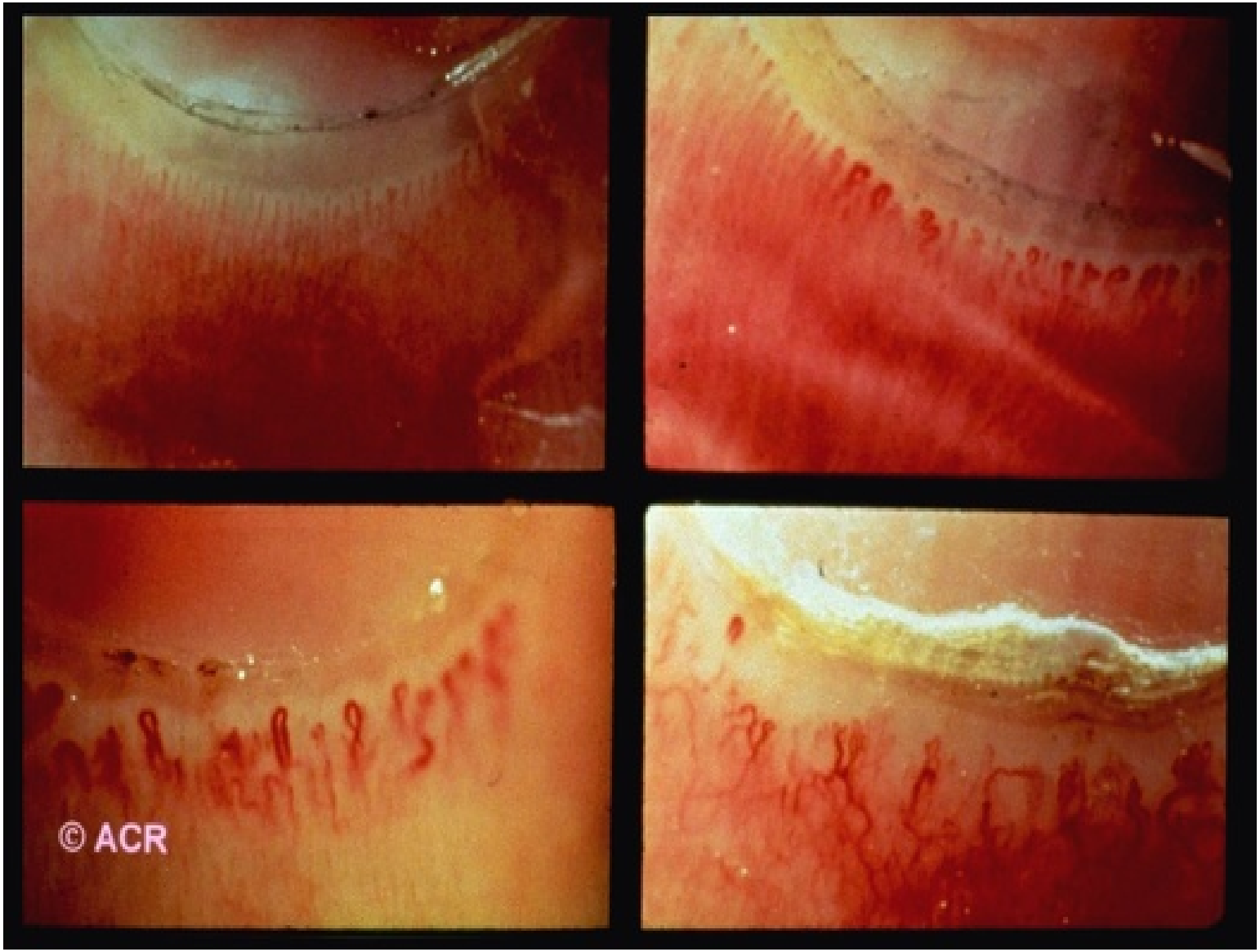
  Patients that meet above criteria should be referred to a Scleroderma center for evaluation

65% of patients with Raynaud's who have abnormal cappilaroscopy and/or specific antibodies developed definitive SSc in 5 years.

<1% of patients with only Raynaud's developed SSc in 5 years.

Avouac J et al. Ann Rheum Dis 2011; 70:476-81.
Minier T et al. Ann Rheum Dis 2013;73: 2087-93.
Koenig M et al. Arthritis Rheum 2008; 58:3902-12

Nailfold Cappilaroscopy



Screening

- **Routine screening for PAH (yearly Echos and every 3-4 months NT pro-BNP (amino terminal pro-brain natriuretic peptide) screens) identified patients earlier with milder PAH and** *led to improved survival of patients*.
- **Patients at high risk for Scleroderma renal crisis (early or progressive disease, and positive RNA polymerase III) regular BP screening is appropriate, though** has *not been shown yet to lead to improved patient outcomes.*
- **Pulmonary screening with PFTs on yearly basis is also thought to help** *diagnosing patients with ILD earlier though has not been related to improved patient outcomes.*

Humbert M et al. Arthritis Rheum 2011; 63:3522-30

Galie N, et al. Lancet 2008; 371:2093-2100

Pulmonary Arterial Hypertension

- **In 15 % of patients**
- **Risk factors**
  - Longer disease duration
  - Anti-centromere antibodies
  - High telangiectasia burden

  Screening by Echo yearly and NT pro-BNP every 4 months in the clinic.

- **When to proceed with Right heart cath:**
  - Unexplained and progressive dyspnea
  - Disproportionately low DLCO
  - Echo evidence of elevated PAP and/or RV volume overload (such as increase levels of NT-proBNP.

Shah A et al. J Rheumatol 2010;37:98-104
Avouac J, et al. Ann Rheum Dis 2014:191-97.
Khanna D et al. Arthritis Rheum 2013; 65:3194-3201

Pulmonary Arterial Hypertension

- **Most PAH trials have included patients with SSc**
- **Only one randomized trial of epoprostenol was exclusively done in SSc patients.**
- **Below agents have shown hemodynamic and symptomatic improvement in PAH**
  - Endothelin antagonists (bosentan, ambrisentan and macicentan) (macicentan has shown event free survival (hospitalization and death))
  - PDE 5 inhibitors (sildenafil and tadalafil)
  - Guanylate cyclase inhibitors (riociguat)
  - Prostacyclin analogues (epoprostenol, treprostinil)
- **NYHA class II (mild to moderate)**
  - Start with ET1 and PDE5 inhibitors
  - Combination may be more effective
- **NYHA class III-IV**
  - Prostacyclin analogues need to be considered

Badesch DB et al. Ann Intern Med 2000; 132:425-34

Chaisson NF et al. Chest 2013;144: 1346-56

Pulido T et al. N Engl J Med 2013;369:809-18

Buckley MS et al. Int J Clin Pract 2013; 67:13-23

Badesch DB et al. J Rheumatol 2009; 36: 2244-49

Interstitial Lung Disease

- **Seen in 40% of SSc patients**
- **With PAH currently accounts for 50% of SSc deaths**
- **PFT yearly screening in asymptomatic patients, though both spirometry and DLCO as well as 6 minute walk have low sensitivity in detecting SSc-ILD.**
- **>50% of SSc-ILD had normal lung functions**
- **Possibility of using limited CT cuts for screening and to avoid significant radiation exposure.**
- **HRCT of the chest detects ILD in most SSc with abnormal PFTs (typically nonspecific interstitial pneumonitis (NSIP))**
  - Early ground glass opacification (basilar in nature)
  - Later Honeycombing with traction bronchiectasis

Winstone TA et al. Chest 2014; 146: 422-36

Sullman YA et al. Ann Rheum Dis 2014; 72: A500-501

Goldin JG et al. Chest 2008; 134: 358-67

Herzog AL et al. Arthritis Rheumatol 2014;66: 1967-78

Frauenfeilder T et al. Ann Rheum Dis 2014; 73:2069-73

Interstitial Lung Disease

- **Bronchoalveolar lavage and lung biopsies not shown to be diagnostic or predictive of disease severity.**
- **Predictors of ILD progressions in SSc**
  - Early stage dcSSc (<3-4 years)
  - Extensive fibrosis on high resolutions CT (>20% lung volume)
  - Low lung function parameters
  - Presence of anti-topoisomerase I Ab (Scl-70)
- **Therapies**
  - Cyclophosphamide
  - Mycophenolate mofetil
  - Nintenadib

Moore OA et al. Rheumatol 2013; 52:155-60
Steen V et al. Arthritis Rheum 2012; 64: 2986-94.

Scleroderma Renal Crisis

- Occurs in 5-10% of patients most commonly in dcSSc, and early stage disease (<4 years)
- Risk factors
  - Steroid use
  - RNA polymerase III positivity
  - Rapidly progressive skin disease
  - Contractures

- **PRESENTATION**
  - Abrupt onset of severe hypertension: retinal changes of malignant hypertension, encephalopathy/seizure, flash pulmonary edema,
  - Rapid progressive renal failure, oliguria or anuria
  - Proteinuria is common in SRC, usually <2.5 g/24h
  - Microangiopathic hemolytic anemia
  - Consumptive thrombocytopenia (rarely <50,000)
  - Renal failure and death if left untreated
  - 10% SRC normotensive at presentation

Scleroderma Renal Crisis

- 15-20% scleroderma pts have HTN in the absence of SRC
- Nonmalignant hypertension alone, without azotemia, is not SRC. Likewise, mild azotemia and urine abnormalities, without other findings, is usually not SRC.

- **Even with early use of ACE inhibitors progression to end stage renal disease remains at 50%**
- **30% of patients who require dialysis are able to discontinue after a year of ACE inhibitor treatment.**

Penn H et al. Curr Opin Rheumatol 2008; 20:692-6

Mouthon L et al. J Rheumatol 2014; 41:1040-48

Raynaud's and Digital Ulcers

- Raynaud's 90% of SSc patients and Digital ulcers (DU) in 40% of SSc patients.
- Previous or current DUs strongest risk factor for recurrent DUs.
- First line therapy for Raynaud's calcium channel blockers.
- Resistant or severe Raynaud's can be treated with PDE5 inhibitors, which have also shown benefit in digital ischemic ulcers.
- Endothelin antagonists (ERAs) prevent digital ulcers but not in healing established ulcers. In Europe bosentan approved to prevent DUs.
- Other treatments : topical nitrates, ARBs, ACE inhibitors, SSRIs, antiplatelet therapy, PDE-5 inhibitors, intra digital injections of botulinum toxin, IV/inhaled/or oral prostanoids, sympathetic blocks, Niacin, Niacenamide, hot baths.

Sebastiani M et al. Arthritis Rheum 2009; 61: 688-94

Tingey T et al. Arthritis Care Res 2013; 65: 1460-71

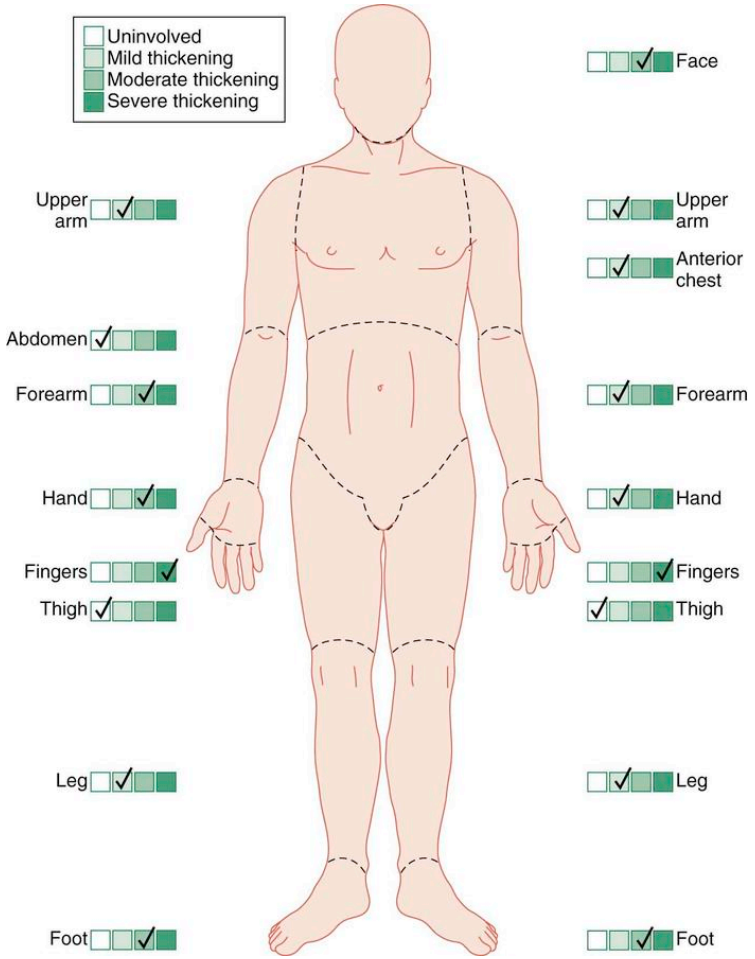
Korn JH et al. Arthritis Rheum 2004; 50:3985-93

Mattuci-Cerinic M et al. Ann Rheum Dis 2011; 70:32-38

Skin fibrosis

Extent of skin fibrosis is quantified using the modified Rodnan skin score (mRss) .

- **mRss**
  - Reliable, valid and responsive to change
  - Substantial inter-observer variability
  - Used as the primary outcome measure for therapeutic studies



Skin Fibrosis

- **Skin thickness progression rate (STPR) :** mRSS at first visit divided by years from skin onset to 1st visit
  - Slow STPR less than 25/year
  - Intermediate STPR 25-44/year
  - Rapid STPR more than 45/year
  - Rapid STPR is predictive of renal crisis and mortality at 2 years.

Maurer B et al. Ann Rheum Dis 2015;74(6): 1124-31
Domsic RT et al. Ann Rheum Dis 2011;70(1): 104-9

Gastrointestinal

- **Upper GI Tract (90% of patients)**
  - Small oral aperture, sicca
  - Dysphagia, heartburn
  - Loss of peristalsis in the distal esophagus
  - Persitent esophagitis: stricture, Barrett's, CA
  - Aspiration, delayed gastric emptying
  - Watermelon stomach (GAVE)

GERD

- A significant proportion of asymptomatic SSc patients have esophagitis on EGD (revealed reflux-esophagitis in 77%, dysmotility of the distal esophagus in 85%, gastritis in 92% [31% erosive gastritis])
- Management includes lifestyle modification; avoidance of medications that can cause irritation;
- Proton pump inhibitors in higher than typical doses appear to control symptoms.
- Starting PPIs even in asymptomatic SSc patient needs to be considered and may need be a lifelong therapy.

Thonhofer R et al Rheumatol Int 2012; 32(1):165-68
Aliment Pharmacol Ther 1992; 6(5); 565-577.
Cln Exp Rheumatol 2009 27(3 suppl 54), 5-8

GAVE

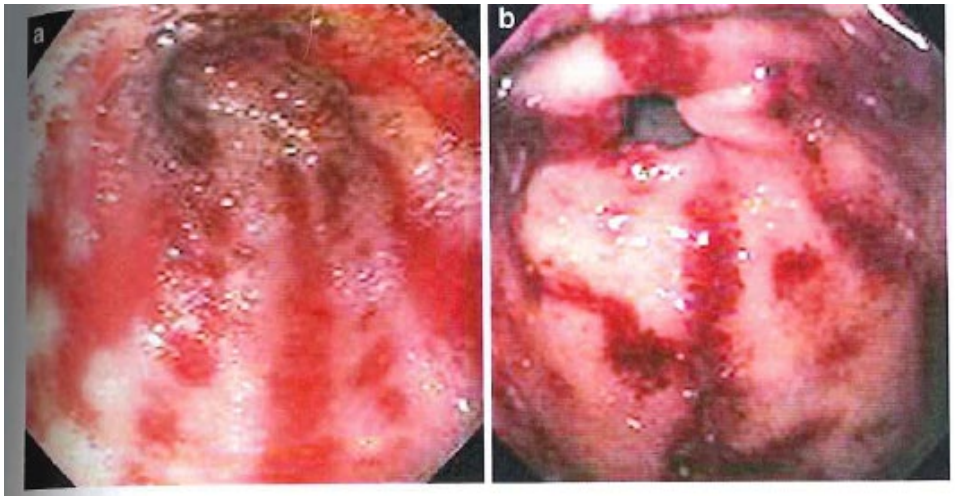


Fig. 17.1 Esophagogastroduodenoscopy (EGD) appearance of gastric antral vascular ectasia (GAVE) showing (**a**) parallel longitudinal rows of tortuous red vessels that traverse the gastric antrum and radiate in a spoke-like fashion to the pylorus and (**b**) stripes of ectatic vessels in the antrum

Littlejohn J, Derk CT. in Silver RM, Denton CP. Case studies in Systemic Sclerosis. Springer New York 2011. page165-172

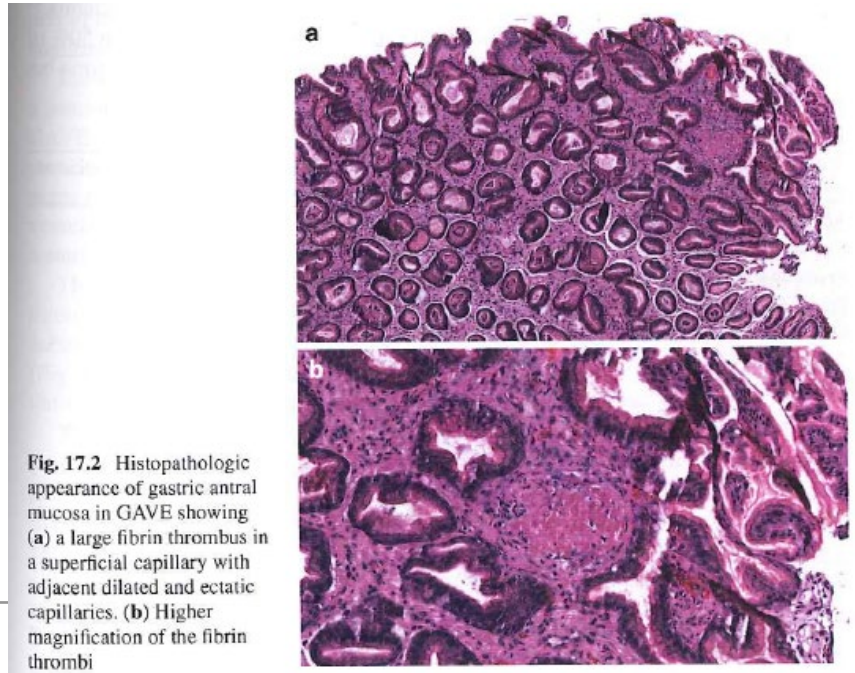


Fig. 17.2 Histopathologic appearance of gastric antral mucosa in GAVE showing (**a**) a large fibrin thrombus in a superficial capillary with adjacent dilated and ectatic capillaries. (**b**) Higher magnification of the fibrin thrombi

Bacterial overgrowth (SIBO)

- **Responds to antibiotics and prokinetic agents.**
  - Norfloxacin 400 mg bid
  - Amoxicillin-Clavulanic acid 500 mg tid
  - Rifamixin 1200mg/day
  - Metronidazole 250 mg tid
  - Ciprofloxacin 250 mg bid
  - Neomycin 500 mg qid
  - Trimethoprim-sulfamethoxazole DS bid
- **If SIBO suspected even with lack of breath test can use a 10 day or 21 day course of initial antibiotics and if good response then do prn**
- **If patient has quick relapse then use for the first 10 days of 4 consecutive months.**
- **If patient still relapses do alternating every 10 days antibiotics continuously.**

Cardiac

- Subtle, variable, late in the course
- SOB, palpitations
- Myocardium (patchy infiltrate, fibrotic cardiomyopathy)
- Myocardial vessels (contraction band necrosis)
- Conduction abnormality (due to infiltration)
- Pericardium (pericardial effusion 30-40%)

Cardiac MRI can reveal cardiac involvement (myocardial fibrosis) in up to 43% of asymptomatic patients.

Di Cesare E et al. Eur J Radiol 2013; 82:e268-73

Thuny F, et al. Radiology 2014; 271:373-80

Pingitore A, et al. Rheumatology 2013: 52:1920-1

Consensus Threrapies for SSc

- **Skin Scleroderma**
  - Methotrexate
  - Mycophenolic mofetil
  - Low dose corticosteroids
  - HSCT
- **Renal Scleroderma**
  - ACE inhibitors
- **Interstitial Lung Disease (ILD)**
  - Nintenatib (First FDA approved agent for SSc-ILD, 2019)
  - Mycophenolic Mofetil
  - Cytoxan
- **Pulmonary arterial HTN**
  - PDE- 5 inhibitors
  - ERAs
  - Prostacyclin analogs
- **Gastrointestinal manifestations**
  - PPIs, H2 blockers
  - Motility agents
  - SIBO therapy
- **Raynauds**
  - Long acting Dihydropiridine type CCB
  - PDE-5 inhibitors
  - Iloprost
  - Fluoxetine
- **Digital Ulcers**
  - PDE-5 inhibitors (healing)
  - Bosentan (preventing)
  - Iloprost (healing)

- **Ann Rheum Dis 2017; 76:1327-39**

Past high impact studies (Skin fibrosis)

- Multicenter trial of methotrexate vs placebo in 71 randomized dcSSc patients showed a trend of improvement at 12 months.
- In the Scleroderma Lung Study I a modest but significant skin improvement was observed in the cyclophosphamide 2mg/kg arm in dcSSc+ILD compared to placebo over 12 months in 158 randomized patients.
- In the Scleroderma Lung Study II a modest but significant improvement in skin score was observed in both the cyclophosphamide 2mg/kg/d x1 year and mycophenolate mofetil arm 3 gr/d x2 years in 142 dcSSc+ILD patients randomized to the two treatment groups, with the trend favoring CYC.

Pope JE et al. Arthritis Rheum 2001;44:1351-58

Tashkin DP et al. N Engl J Med 2006;354:2655-66

Tashkin DP et al Lancet Respir Med 2016; 4(9):708-19

Past high impact studies (Interstitial Lung Disease)

- **Scleroderma Lung Study I**: showed significant benefit in lung function parameters (FVC) . Follow-up study showed that benefit decreased in 2 years. Post hoc analysis showed greater improvement in patients with more lung fibrosis at baseline
- **Scleroderma Lung Study II**
  - FVC=45-80%, ground glass opacification on HRCT, moderate dyspnea in SSc-ILD patients
  - 142 patients randomized to CYC 2mg/kg/day for 1 years and then 1 year of placebo vs MMF at 1.5 gr po bid x 2years. 106 patients completed.
  - Results:
    - At 24 months %FVC improvement comparable in both arms
    - mRSS improvement in both arms with trend towards CYC.
    - Fewer premature withdrawals with MMF
    - Leukopenia/thrombocytopenia less frequent with MMF

Past high Impact studies (Raynaud's)

- **RAPIDS-2 study (Bosentan treatment of digital ulcers related to systemic sclerosis)**
  - 188 SSc patients with at least 1 active DU were randomized to bosentan 125 mg bid vs placebo for 24 weeks.
  - There was a 30% reduction in the number of new DUs in the treatment group but no effect in healing.
  - This allowed for the approval of bosentan in the European Union for prevention of new DUs in SSc patients but not in the US

- **SEDUCE study(efficacy of sildenafil on digital ischemic ulcer healing in SSc)**
  - Randomized placebo controlled study sildefanil 20 mg po tid vs placebo for 12 weeks on ischemic DU healing.
  - 83 patients with 192 DUs (89 in sildenafil, 103 in placebo)
  - Primary end point for intention to treat not reached though decrease in number of DUs in favor of sildenafil at week 8 and 12.

Ann Rheum Dis 2011; 70(1):32-8

Ann Rheum Dis 2016; 75(6): 1009-15

Past high Impact studies (Raynaud's)

- **DUAL-1 and 2: (Effect of macitentan on the development of new DUs in patients with SSc)**
  - 289 SSc patients with active DUs were randomized to macitentan 3mg/d, 10 mg/d or placebo at 1:1:1 over 16 weeks
  - At 16 weeks there was no reduction of the development of new DUs in the active arms vs the placebo

JAMA 2016; 315(18): 1975-88

Past high Impact studies (Using biomarker genes)

- **Fresolimumab (high-affinity neutralizing antibody, targets all 3 TGF-beta isoforms)**
  - 7 patients got 1mg/kg x2
  - 8 patients got 5mg/kg x1
  - Serial mid-forearm skin biopsies performed before and after treatment were analyzed for expression of TGF-beta regulated biomarker genes. Both groups showed significant declines in the biomarkers that paralleled mRSS improvement.
- **Nilotinib (tyrosine kinase inhibitor)**
  - 10 patients were treated with nilotinib, 7 patients completed 12 months of treatment. Skin biopsies at baseline, 6 and 12 months, and mRSS primary endpoint.
  - mRSS improved by 6.3 points (23%). Improvers had higher baseline TGF-Beta receptor and PDGF receptor signaling genes than non-improvers

J Clin Invest 2015; 125(7): 2795-807

Arthritis Res Ther 2015;17(1):213

CRISS: Combined Response Index in Systemic Sclerosis

CRISS is a composite outcome measure that incorporates change in clinical and patient reported outcomes to generate a probability that a patient with diffuse SSc has improved over the observed period.

STEP 1: Patients are evaluated for the following

(If any present CRISS= 0, if all absent proceed to STEP2)

New scleroderma renal crisis

Decline in FVC of > 15% predicted

New decline of LV EF <45%

New pulmonary hypertension that requires treatment

STEP2: 52 week change in 5 outcome variables are measured

mRss

% predicted FVC

Physician Global Assessment

Patient Global Assessment

Health Assessment Questionnaire Disability Index (HAQ-DI)

Likelihood true improvement (>0.6 improved)

Arthritis Rheumatol 2016; 68(2); 299-311

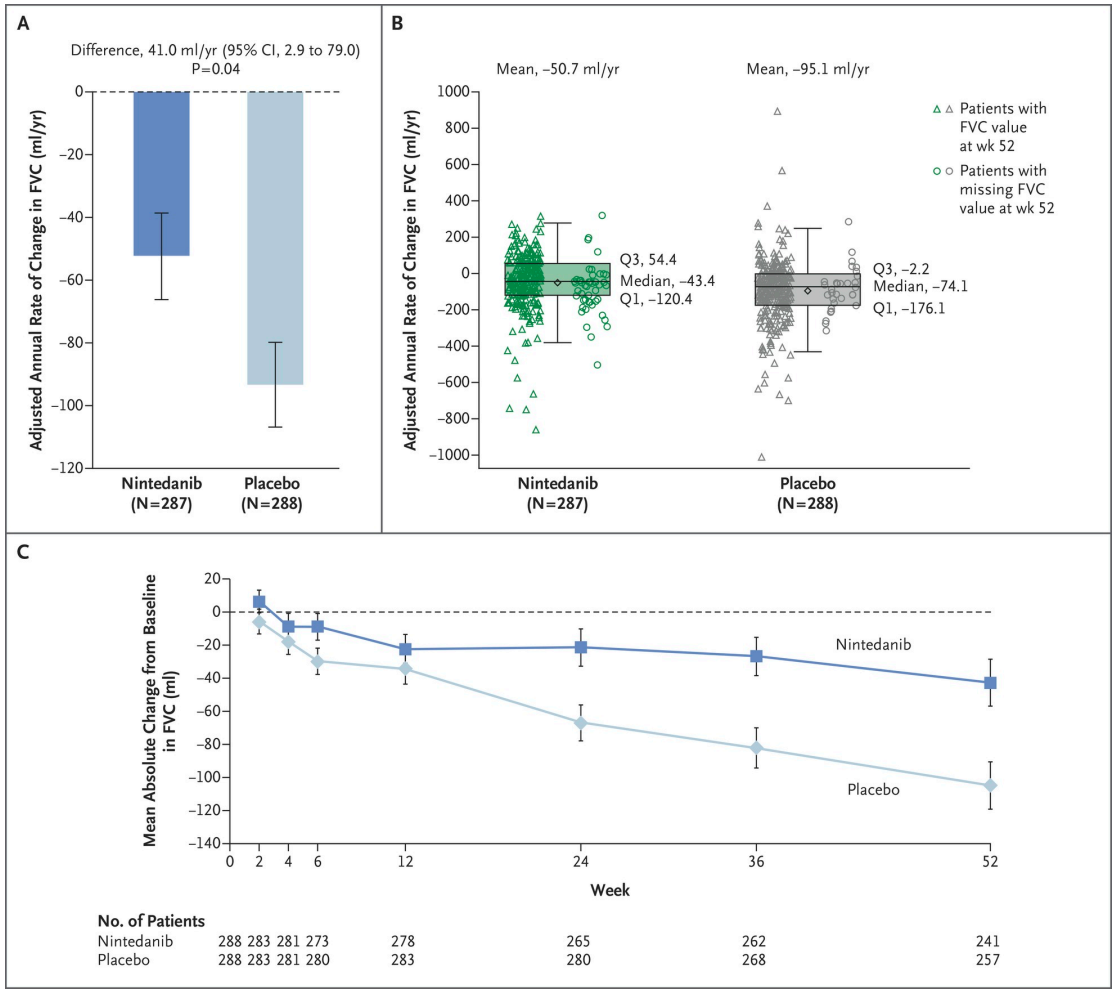
New high Impact studies

- **SENSCIS: S**afety and **E**fficacy of **N**intedanib in Systemic **Scl**erosi**s**
- **Nintendanib- tyrosine kinase inhibitor, antifibrotic effects:**
  - platelet-derived growth factor (PDGF)
  - fibroblast growth factor receptor (FGFR)
  - vascular endothelial growth factor (VEGF)
  - Fms-like tyrosine kinase-3 (FLT3)
  - proliferation, migration, and transformation of fibroblasts
- **52 week study, 576 patients with SSc+ILD in 32 countries**
- **Patients up to prednisone 10mg/d and/ or MMF and/or MTX at a stable dose for at least 6 months were allowed to participate (48.4% were on MMF)**
- **Randomization 1:1 , nintendanib 150 mg po bid vs placebo**
- **First non-Raynaud symptom < 7 years, >10% lung scarred**
- **Primary outcome: Rate of decline of FVC over 52 weeks**
- **Secondary outcomes: mRSS, St. George's Respiratory Questionnaire (SGRQ) at 52 weeks.**

N Engl J Med 2019; 380:2518-2528

SENSCIS

- **Adjusted annual rate of change in FVC:**
  - **−52.4 ml per year in the nintedanib group**
  - **−93.3 ml per year in the placebo group**
  - **difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P = 0.04)**
- **mRSS:**
  - **−0.21 (95% CI, −0.94 to 0.53; P = 0.58)**
- **SGRQ:**
  - **1.69 (95% CI, −0.73 to 4.12)**



SENSCIS

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Nintedanib	Placebo	Difference (95% CI)
Primary end point			
Annual rate of decline in FVC assessed over 52 weeks — ml/yr	−52.4±13.8	−93.3±13.5	41.0 (2.9 to 79.0)†
Key secondary end points			
Absolute change from baseline in modified Rodnan skin score at week 52	−2.17±0.27	−1.96±0.26	−0.21 (−0.94 to 0.53)‡
Absolute change from baseline in total score on the SGRQ at week 52	0.81±0.88	−0.88±0.87	1.69 (−0.73 to 4.12)§
Other secondary end points			
Absolute change from baseline in FVC at week 52 — ml	−54.6±13.9	−101.0±13.6	46.4 (8.1 to 84.7)§
Annual rate of decline in FVC — % of predicted value	−1.4±0.4	−2.6±0.4	1.2 (0.1 to 2.2)§
Absolute change from baseline in DL_{CO} at week 52 — % of predicted value	−3.21±0.54	−2.77±0.54	−0.44 (−1.94 to 1.06)§
Absolute change from baseline in net digital ulcer burden at week 52	0.03±0.05	0.06±0.04	−0.03 (−0.16 to 0.09)§
Patients with an absolute decline from baseline in FVC of >5 percentage points of the predicted value at week 52 — no./total no. (%)	59/287 (20.6)	82/288 (28.5)	0.65 (0.44 to 0.96)§¶
Patients with an absolute decline from baseline in FVC of >10 percentage points of the predicted value at week 52 — no./total no. (%)	20/287 (7.0)	24/288 (8.3)	0.82 (0.44 to 1.52)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >5% at week 52 — no./total no. (%)	95/287 (33.1)	125/288 (43.4)	0.65 (0.46 to 0.91)§¶
Patients with a relative decline from baseline in FVC, measured in milliliters, of >10% at week 52 — no./total no. (%)	48/287 (16.7)	52/288 (18.1)	0.91 (0.59 to 1.41)§¶

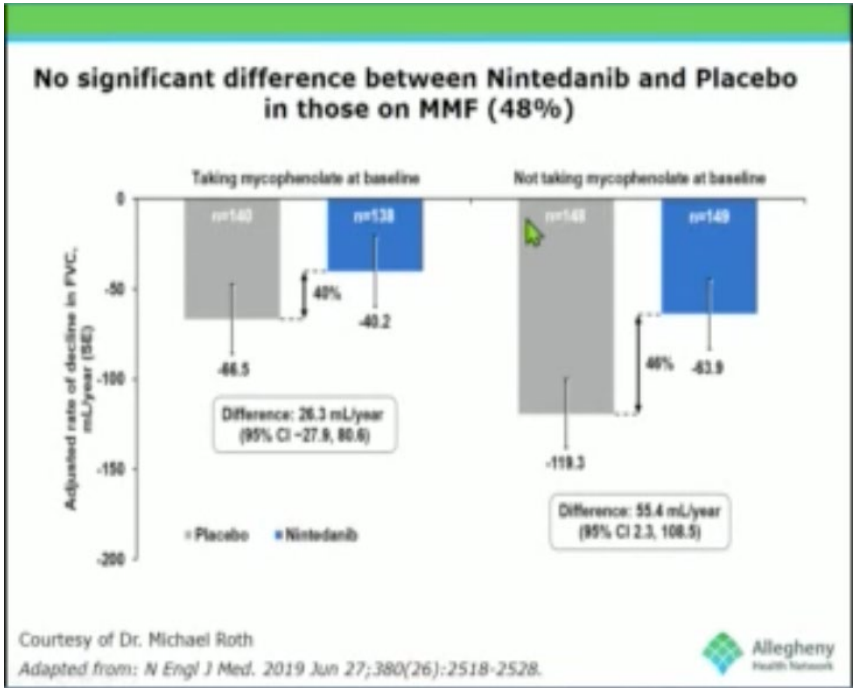
* Changes from baseline are adjusted means ±SE based on the statistical models. Data on some variables were not available for all patients. FVC end points were analyzed in 287 patients in the nintedanib group and 288 patients in the placebo group, except for the absolute change from baseline in FVC in milliliters, which was analyzed in 288 patients in both groups. Modified Rodnan skin score was analyzed in 288 patients in the nintedanib group and 286 patients in the placebo group, total score on the SGRQ in 282 and 283 patients, DL_{CO} in 285 and 284 patients, and net digital ulcer burden (the number of fingers with ulcers of vascular origin distal to the proximal interphalangeal joints) in 288 patients in both groups.
† P=0.04.
‡ P=0.58.
§ The 95% confidence interval was not adjusted for multiple comparisons.
¶ The difference was assessed as an odds ratio.

Table 3. Adverse Events.*

Event	Nintedanib (N=288)	Placebo (N=288)
	no. of patients (%)	
Any adverse event	283 (98.3)	276 (95.8)
Most common adverse events†		
Diarrhea	218 (75.7)	91 (31.6)
Nausea	91 (31.6)	39 (13.5)
Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)

* Adverse events, as reported over 52 weeks plus a 28-day post-treatment period, were coded according to the preferred terms in the *Medical Dictionary of Regulatory Activities*. Data are shown for the patients who had at least one such adverse event.
† The most common adverse events were those that were reported in more than 10% of the patients in either trial group.
‡ A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities.
§ A serious adverse event was defined as an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

SENSCIS



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Skin ulcer	53 (18.4)	50 (17.4)
Vomiting	71 (24.7)	30 (10.4)
Cough	34 (11.8)	52 (18.1)
Nasopharyngitis	36 (12.5)	49 (17.0)
Upper respiratory tract infection	33 (11.5)	35 (12.2)
Abdominal pain	33 (11.5)	21 (7.3)
Fatigue	31 (10.8)	20 (6.9)
Weight decrease	34 (11.8)	12 (4.2)
Severe adverse event‡	52 (18.1)	36 (12.5)
Serious adverse event§	69 (24.0)	62 (21.5)
Fatal adverse event	5 (1.7)	4 (1.4)
Adverse event leading to discontinuation of the intervention	46 (16.0)	25 (8.7)

* Adverse events, as reported over 52 weeks plus a 28-day post-treatment period, were coded according to the preferred terms in the *Medical Dictionary of Regulatory Activities*. Data are shown for the patients who had at least one such adverse event.

† The most common adverse events were those that were reported in more than 10% of the patients in either trial group.

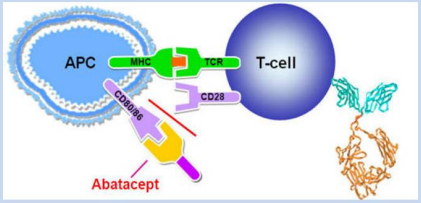
‡ A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities.

§ A serious adverse event was defined as an event that resulted in death, was life-threatening, resulted in hospitalization or prolongation of hospitalization, resulted in persistent or clinically significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed to be serious for any other reason.

ASSET: Abatacept Systemic SclErosis Trial

- **Abatacept: T cell costimulatory blocker**
- **Phase 2, 12 months, 1:1 abatacept 125 mg sq/week : placebo**
- **22 centers in the US, Canada, and UK**
- **All 88 patients:**
  - <36 months from 1st non-Raynaud symptom
  - Diffuse cutaneous disease
  - No immunomodulators (stable prednisone up to 10 mg/d for > 2 weeks)
- **Primary outcome: Safety, change in mRSS at 12 months**
- **Secondary outcomes: Quality of life scores, joint count, FVC, CRISS, Skin bx at 0, 3 and 6 months**

Abatacept Mechanism of Action

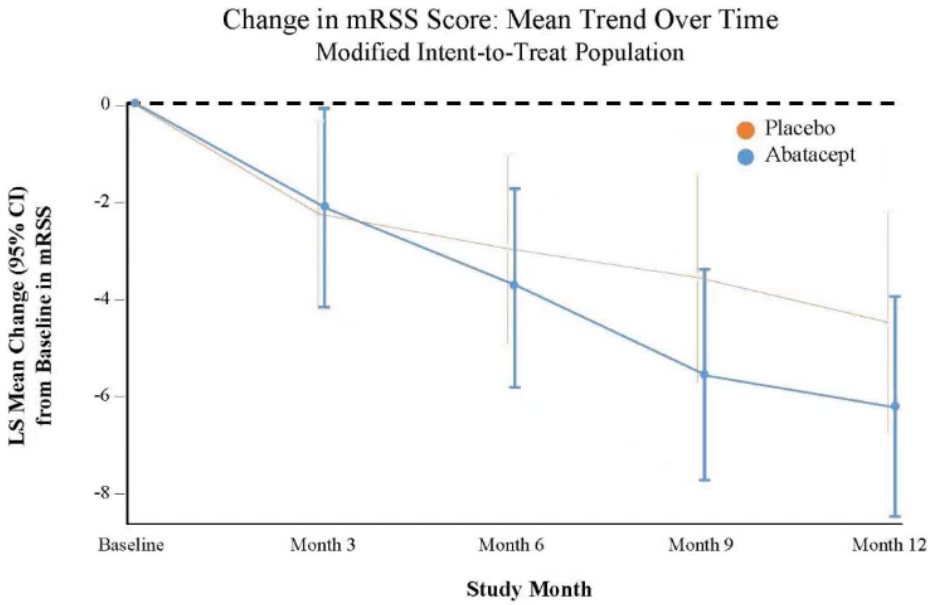


Abatacept modulates the immune response by bonding to CD80/CD86 on an antigen-presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding of CD28 on naïve T cells and attenuating T-cell activation.

Arthritis Rheumatol. 2020; 72(1): 125-36.

ASSET: Abatacept Systemic SclErosis Trial

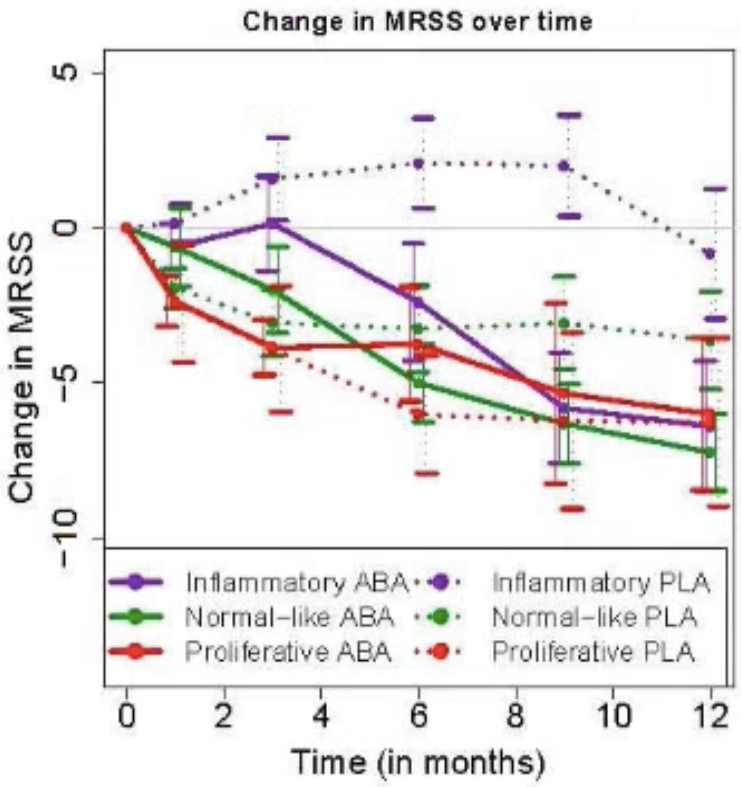
- **Primary Outcome: Nonsignificant skin change vs placebo**
  - -1.75 (-4.93, 1.43), p=0.28
- **Secondary Outcomes: Mixed**
- **ACR-CRISS: Likelihood true improvement (>0.6 improved)**
  - Median (IQR) 0.02 (0.75) placebo, vs 0.72 (0.99) abatacept (p=0.03)
  - change in mRSS, Patient Global Assessment (PtGA), HAQ-DI, Physician Global Assessment (MDGA), and FVC% predicted



ASSET: Abatacept Systemic SclErosis Trial

- **Gene Expresion on skin biopsy**
  - Inflammatory
  - Normal like
  - Fibroproliferative

mRSS statistically significant improvement in inflammatory ($p<0.001$), and normal like ($p=0.03$)



SCOT Trial: Stem Cell Transplantation

- **Scleroderma: Cyclophosphamide Or Transplantation**
- **Phase 2, 72 month study**
- **Autologous Stem cell transplant vs IV cyclophosphamide**
- **Transplant: Total-body irradiation (pulmonary and renal shields), CYC 120 mg/kg, anti thymocyte globulin followed by reconstitution with a CD34+ selected autograft which was mobilized before the above procedure with G-CSF.**
- **Inclusion:**
  - <5 years since first non-Raynaud symptom
  - Active ILD (FVC <70% or DLCO <70%) or Renal crisis
- **Exclusion**
  - GAVE
  - DLCO <40%, FVC <45%
  - EF <50% or pulmonary hypertension
  - >6 months previous cyclophosphamide
- **Primary end point: Global rank outcome score (death, event free survival (without respiratory, renal or cardiac failure), FVC, HAQ-DI and mRss.)**
- **75 Patients randomized: 36 to SCT, 39 to cyclophosphamide**

N Engl J Med 2018;378:35-47

SCOT Trial: Stem Cell Transplantation

Table 1. Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Transplantation (N=36)	Cyclophosphamide (N=39)	Total (N=75)
Mean age — yr	44.9±10.9	46.9±10.4	45.9±10.6
Female sex — no. (%)	19 (53)	29 (74)	48 (64)
Race — no. (%)†			
White	29 (81)	31 (79)	60 (80)
Black	2 (6)	4 (10)	6 (8)
Other	5 (14)	4 (10)	9 (12)
Smoking status — no. (%)			
Current or former smoker	14 (39)	10 (26)	24 (32)
Never smoked	22 (61)	29 (74)	51 (68)
Mean duration of scleroderma before randomization — mo	25.1±12.9	29.0±16.0	27.1±14.6
DMARD use in previous 6 mo — no. (%)	26 (72)	25 (64)	51 (68)
Previous use of cyclophosphamide — no. (%)	8 (22)	17 (44)	25 (33)
Lung involvement — no. (%)	36 (100)	37 (95)	73 (97)
Mean modified Rodnan skin score‡	28.5±8.7	30.8±10.5	29.7±9.7
Mean FVC — % of predicted value	74.5±14.8	73.8±17.0	74.1±15.9
Mean DL_{CO} — % of predicted value	53.9±7.6	52.7±8.2	53.3±7.9
Mean left ventricular ejection fraction — %§	61.0±6.1	59.9±4.3	60.4±5.2
Mean creatinine clearance — ml/min	122.8±41.7	124.9±54.3	123.9±48.3
Mean ESR — mm/hr¶	29.8±26.5	32.2±24.9	31.1±25.4
Mean SF-36 physical component score‖	29.5±9.2	28.9±9.5	29.2±9.3
Mean SF-36 mental component score‖	44.7±10.7	44.6±9.9	44.6±10.2
Mean HAQ-DI score**	1.2±0.6	1.4±0.9	1.3±0.8

* Plus–minus values are means ±SD. Although the between-group differences for sex, smoking status, and previous use of cyclophosphamide appear potentially clinically relevant, no P values for comparisons between the two groups were less than 0.05, on the basis of t-tests for numerical variables and Fisher's exact test for categorical variables. P=0.06 for sex, 0.39 for smoking status, and 0.06 for previous use of cyclophosphamide. Additional data on participant characteristics are provided in Table S3 in the Supplementary Appendix. DL_{CO} denotes diffusing capacity of the lung for carbon monoxide, DMARD disease-modifying antirheumatic drug, ESR erythrocyte sedimentation rate, and FVC forced vital capacity.

† Race was reported by the participant.

‡ Modified Rodnan skin scores range from 0 (normal) to 51 (severe skin thickening).

§ Data were available for 36 participants in the transplantation group and 37 in the cyclophosphamide group.

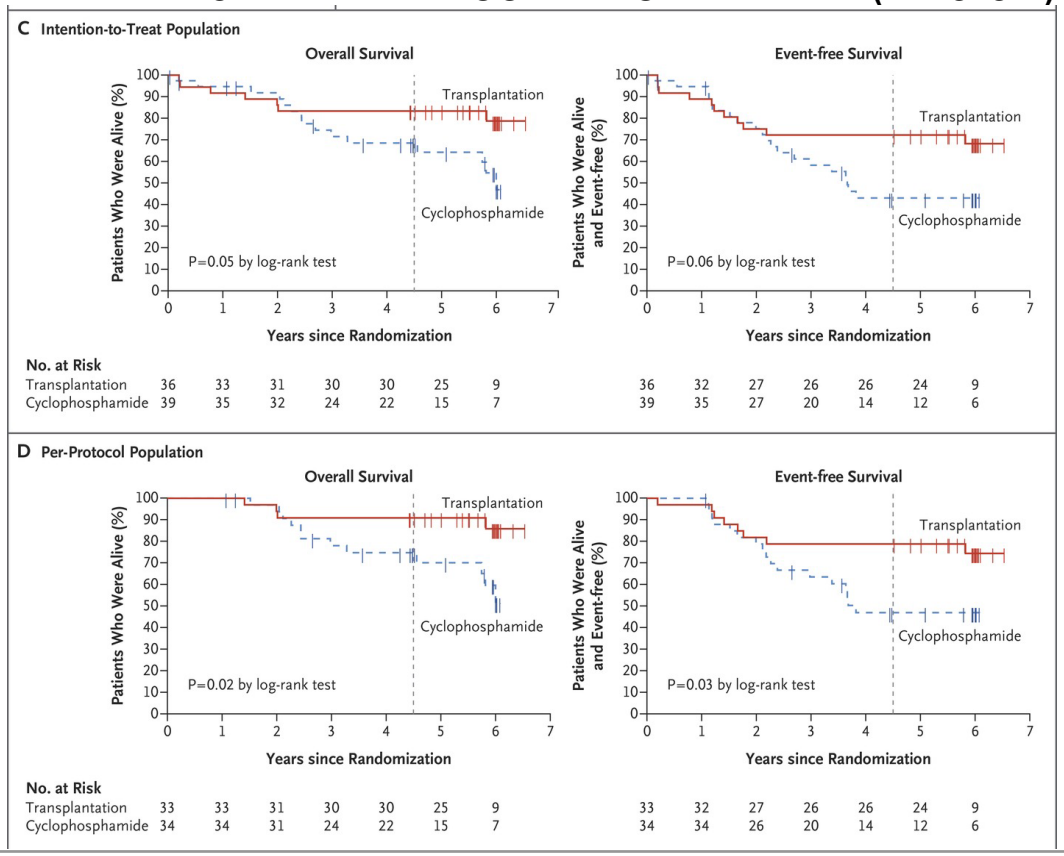
¶ Data were available for 29 participants in the transplantation group and 34 in the cyclophosphamide group.

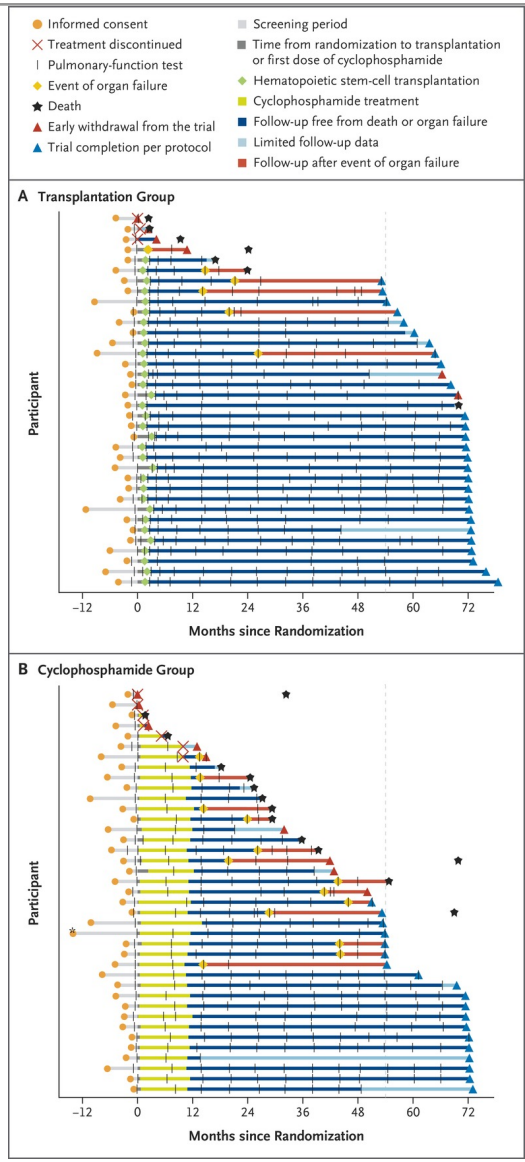
‖ Scores on the physical and mental components of the 36-Item Short Form General Health Survey (SF-36) range from 0 to 100, with higher scores indicating better quality of life. Data were available for 35 participants in the transplantation group and 35 in the cyclophosphamide group.

** Scores on the Disability Index of the Health Assessment Questionnaire (HAQ-DI) range from 0 to 3, with higher scores indicating more disability. Data were available for 35 participants in the transplantation group and 38 in the cyclophosphamide group.

SCOT Trial: Stem Cell Transplantation

- **Transplant group (N=34): 3 died, 27 completed**
- **CYT group (N=39): 11 died, 19 completed**
- **Comparisons favor transplant vs CYT:**
  - 67% versus 33% at 54 months (P=0.01)





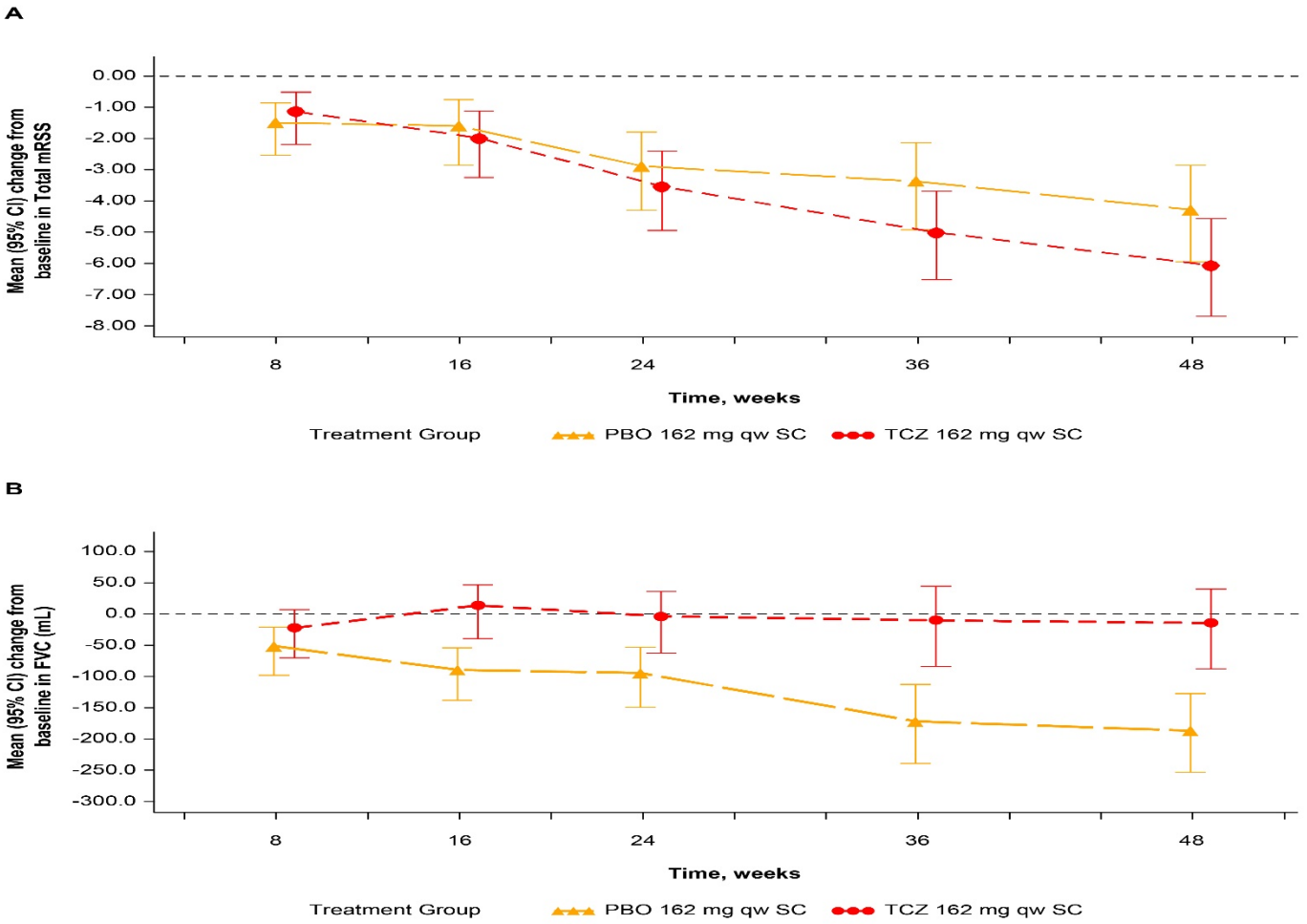
Tocilizumab efficacy and safety in Systemic sclerosis : Phase III randomized controlled trial.

- Double blind randomized controlled Phase 3 trial
- 1:1 assignment of TCZ 162 mg sq weekly or PBO for 48 weeks
- Inclusion mRSS=10-35; >18 y/o; ACR/EULAR SSc classification, active disease, <60 months duration
- Escape therapy could be given at 16 weeks for worse FVC, and at 24 weeks if worse mRSS
- Primary outcome change in mRSS from baseline to 48 weeks
- Secondary endpoints: FVC change , time to treatment failure
  (death, decline in FVC>10%, mRSS increase >20% and mRSS>5 points, or SSc related complication)
- 212 patients randomized at 106 study sites

Arthritis and Rheumatol 2018; 70(Suppl10)

Tocilizumab efficacy and safety in Systemic sclerosis : Phase III randomized controlled trial.

Figure. Change from baseline in mRSS (A) and FVC (B)



A mixed model for repeated measures analysis was implemented.
The analysis included the fixed, categorical effects of treatment, visit, the stratification factor IL-6 level (<10; ≥10 pg/mL) at screening, IL-6 level at screening-by-visit interaction, and treatment-by-visit interaction, as well as the continuous covariates of baseline score and baseline score-by-visit interaction.

Safety and efficacy of B-cell depletion with Rituximab in SSc-PAH

- **Phase II , randomized, double blind, placebo multicenter NIH sponsored, 2010-18**
- **SSc-PAH patients with no ILD, or renal disease on stable PAH therapy.**
- **Rituxan 1 gr at o and 14 days vs PBO.**
- **Primary endpoint 6MW distance change from baseline to 24 weeks.**
- **Secondary endpoints: 6MW distance at different time points, PVR, time to change or addition of PAH meds**
- **57 patients randomized, (29 Rx/ 28PBO)**
  - 91%Female/ mean age =58/ 90%LcSSc/ mean duration PAH 1.8 years.

Arthritis Rheumatol 2019; 71 (Suppl 10)

Safety and efficacy of B-cell depletion with Rituximab in SSc-PAH

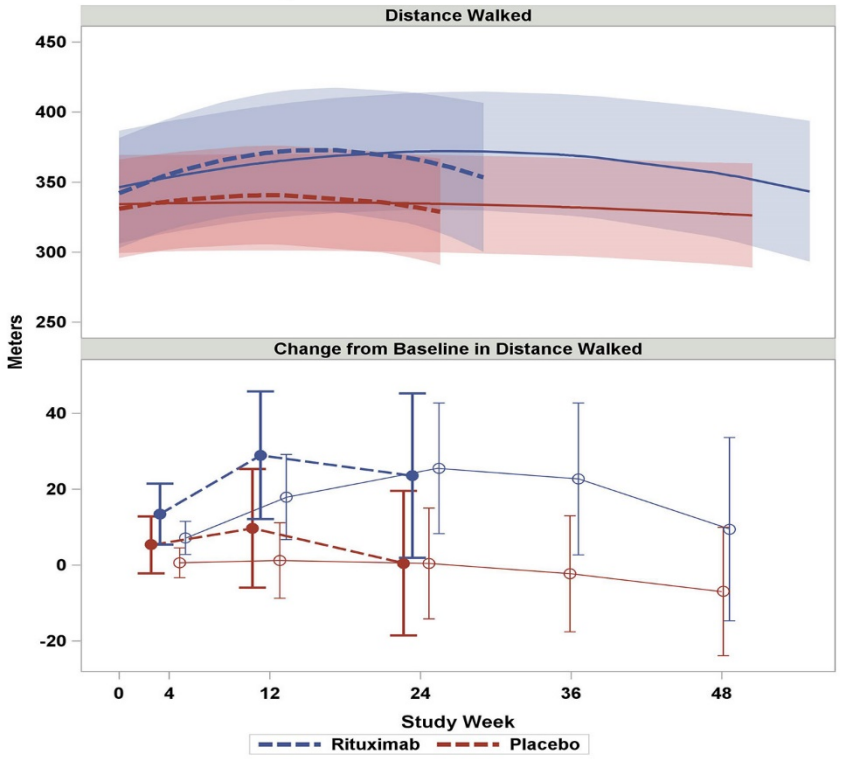
Table 1: Primary and Secondary Endpoints
Population: Modified Intention-to-Treat[1]

	Rituximab (n=27)	Placebo (n=27)	p-value
Primary Endpoint			
Change from Baseline in SMWT (meters)[2], mean (SE)			
Week 24	23.6 (11.05)	0.5 (9.71)	0.12
Secondary Endpoints:			
Change from Baseline in SMWT (meters)[3], mean (SE)			
Week 24	25.5 (8.79)	0.4 (7.43)	*
Week 48	9.5 (12.35)	-7.0 (8.63)	
Change from Baseline in PVR at Week 24 (dyes/sec/cm^5), mean (SD)	-39.0 (28.85)	7.2 (48.51)	
Change or Addition of PAH Medications, % Probability[4]			
By Week 12	11%	0%	
By Week 24	11%	15%	
By Week 36	28%	41%	
By Week 48	28%	41%	

* The p-value = 0.03 for this treatment group comparison. For all other secondary endpoints, the p-values for treatment group comparisons were >0.05.

1. The modified intention-to-treat population includes all eligible subjects who initiated treatment.
2. Model uses all data through Week 24 for estimates.
3. Model uses all data through Week 48 for estimates.
4. The probabilities are estimated from Kaplan-Meier curves for time-to-change or addition of PAH medications.

Figure 1: Six Minute Walk Distance



Dashed lines represent the primary endpoint model using data out to Week 24. Solid lines represent secondary analyses including all data out to Week 48. A repeated measures random effect model was fit to distance walked as a function of treatment, visit week, a treatment by visit week interaction, and a quadratic term for visit week. A random slope and intercept were fit for each subject using a separate unstructured covariance matrix for each treatment group. Shaded bands and whiskers represent 95% confidence intervals.

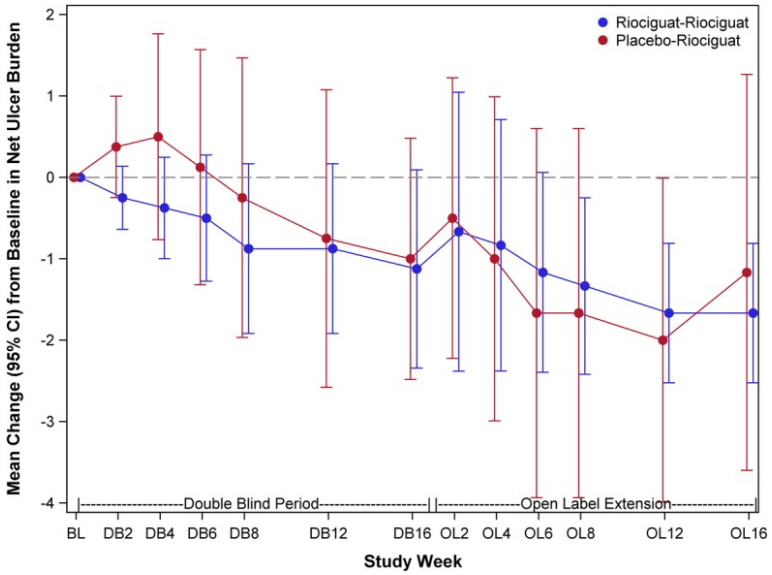
Riociguat in early dcSSc, Randomised double blind, placebo Phase IIb (RISE-SSc)

- **Riociguat (guanylate cyclase stimulator) approved for PAH**
- **Antifibrotic effects in animal models**
- **Inclusion**
  - dcSSc
  - Disease duration <18 mo
  - mRSS >10 and <22
  - FVC>45%, DLCO.40%
- **Riociguat adjusted from 0.5 mg up to 2.5 mg tid**
- **Primary endpoint mRSS difference from 0 to 52 weeks**
- **Secondary endpoints**
  - CRISS
  - HAQ-DI
  - Change in FVC %
- **121 patients randomized**
- **The primary as well as the secondary endpoints did not reach significance**

Arthritis Rheumatol 2018; 70 (Suppl 10).

Riociguat for digital ulcers

- 17 patients, 1:1 riociguat or placebo
- 8 week induction, 8 week maintenance
- Outcome: Change from baseline to week 16 in net ulcer burden (NUB)
- Result: Adjusted mean treatment difference − 0.24, 95% CI (− 1.46, 0.99), $p = 0.70$)
- But safe (no drug-related complications)



Arthritis Res Ther. 2019 Sep 3;21(1):202.

Saccharomyces + Metronidazole for SIBO

- **Saccharomyces + Metronidazole**
  - 40 patients with SSc and SIBO
  - Metronidazole (M),
    Metronidazole + Saccharomyces (M+S),
    Saccharomyces alone
  - SIBO was eradicated in 55% of M + SB,
    33% of SB, and 25% of M
  - Reductions in expired hydrogen at 45 to 60 min at 1 and 2 months:
    M + SB 48% and 44%, M 18% and 20%, and SB 53% and 60%

Dig Dis Sci. 2019 Sep 23.

Tofacitinib in early dcSSc Phase I/II

- 6 month, 2 center double blind randomized study
- dcSSc< 60 mo
- mRss >10 and <45
- Background stable immunosuppression allowed
- 15 patients 2:1 TOFA 5mg bid vs PBO
- 13 patients on MMF and MTX
- Trends towards improved mRss

Outcome at Month 6	Tofacitinib N=10	Placebo N=5	P-value
*ΔmRSS, 0-51, mean/median**	-5.8, -6.0	-2.3, -3.0	0.42
*ΔPatient Global Assessment, 0-10, mean/median **	0.0, 0.0	-2.8, -1.5	0.06
*ΔPhysician Global Assessment, 0-10, mean/median **	-1.6, -1.5	0.5, 0.5	0.04
*ΔHAQ-DI, mean/median **	-0.11, -0.06	0.06, 0.13	0.35
*ACR CRISS index, median**	0.30	0.10	0.68

*Two-sample t-tests (Kruskal-Wallis Test), Δ= *change*

Arthritis and Rheumatol 2019 : 71: (Suppl 10)

The Future

- **Lenabasum** (synthetic, non-immunosuppressive, selective cannabinoid receptor type 2 agonist)
  - RESOLVE-1 has enrolled 365 individuals with SSc in an international, multicenter, randomized, double-blind, placebo-controlled study that is being conducted in North America, Europe, Israel, Japan, South Korea, and Australia. Patients in the study are randomized 1:1:1 to either receive lenabasum 5 mg twice per day, lenabasum 20 mg twice per day, or placebo twice per day for 52 weeks. Results summer 2020.

- **Primary endpoint ACR CRISS**
- **Secondary endpoints HAQ-DI, mRSS, FVC %**

The Future

- **Scleroderma Lung Study III**
  - A Phase II multi-center, double-blind, parallel group, randomized and placebo-controlled clinical trial addressing the treatment of patients with active and symptomatic SSc-ILD.
  - Patients who are either treatment naive or only recently started treatment (</= 6 months of prior treatment) will be randomized in a 1:1 assignment to receive either oral mycophenolate mofetil (MMF) and a placebo or a combination of oral MMF and oral **pirfenidone** (PFD), with both regimens administered for 18 months.
  - 16 sites recruiting for total 150 patients . Estimated study end 12/2021
    - Pirfenidone may inhibit TGF-beta, TNF-alpha and IL-1b production

New targeted therapies for SSc Fibrosis

Drug	Target	Outcome of trial
Privigen	IVIg	Phase 2 improvement in CRISS, not recruiting yet
Abituzumab	Ab αν integrin	Phase 2 SSc-ILD, fail to recruit
Rilonacept	IL-1-TRAP	Phase 2 , mRSS, neg study
Iloprost	Prostacyclin analog	Phase 2, Raynaud's in SSc , recruiting
AVID200	Inhibitor of TGF-beta ligands	Phase 1, recruiting
Lanifibranor	PPAR agonist	Phase 2, mRSS neg study
Brentuximab	CD30	Phase 1/2 recruiting

New targeted therapies for SSc Fibrosis

Drug	Target	Outcome of trial
Bermekimab	Monoclonal Ab that targets and neutralizes IL-1a	Phase 2, recruiting
Belimumab/ Rituxan comb	Belimumab/ Rituxan /MMF vs Placebo/ placebo/MMF	Randomized placebo control
Allogeneic BMT		
KDO25	Selective inhibitor of ROCK2 with antifibrotic properties	Phase 2, CRISS at 24 weeks , recruiting

Questions??

Myositis 2020: Moving on from Dermatomyositis and “Polymyositis”

Pennsylvania Rheumatology Society Annual Meeting

September 27, 2020

Lisa Christopher-Stine,. MD, MPH
Director, Johns Hopkins Myositis Center
Associate Professor of Medicine and Neurology

JOHNS HOPKINS
MEDICINE

Disclosures

- I have intellectual property interest in a novel autoantibody assay detection for anti- HMGCR (ELISA and IP). [Inova Diagnostics]
- I was the Safety Officer for the JBT-101 Trial sponsored by Corbus funded by the NIH
- I have been a consultant for AbbVie
- I will reference unlabeled or unapproved use of drugs in my presentation.

Lisa Christopher-Stine, MD, MPH

JOHNS HOPKINS MEDICINE

Objectives

To review the Bohan and Peter classification criteria and how the updated classification criteria for polymyositis and dermatomyositis compare

To examine the concept that true ‘polymyositis’ is a rare disease

To review how myositis autoantibodies help diagnose and risk stratify patients

To outline current treatment options for all myositis subtypes

INFLAMMATORY MYOPATHY SUBTYPES AND CLASSIFICATION CRITERIA

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Idiopathic Inflammatory Myopathies (IIM)

- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- IMNM
- Giant cell myositis
- Eosinophilic myositis
- Granulomatous myositis
- Macrophagic myofasciitis
- Pipestem capillary disease
- Myositis related to other connective tissue diseases

Bohan and Peter Diagnostic Criteria for Polymyositis/Dermatomyositis

- Symmetric Proximal Muscle Weakness
- Elevated Muscle Enzymes (CPK, Aldolase, Transaminases, LDH)
- Myopathic EMG Abnormalities
- Typical Changes on Muscle Biopsy
- Typical Rash of Dermatomyositis

*PM diagnosed as Definite with 4/5 criteria; probable with 3/5 criteria

*DM Diagnosed as Definite with Rash + 3/ 4 Criteria; probable with Rash + 2/4 criteria

Bohan A, Peter JB, Bowman BS, et al.. Medicine (Baltimore). 1977;65:255-286.

In the beginning…
Bohan and Peter Criteria for PM and DM

- Symmetric Proximal Muscle Weakness
- Elevated Muscle Enzymes (CK, Aldolase, Transaminases, LDH)
- Myopathic EMG Abnormalities
- Typical Changes on Muscle Biopsy
- Typical Rash of Dermatomyositis

*__PM__ diagnosed as Definite with 4/5 criteria; probable with 3/5 criteria

*__DM__ Diagnosed as Definite with Rash + 3/ 4 Criteria; probable with Rash + 2/4 criteria

Bohan A, Peter JB. NEJM. 1975; 292:344–347. Bohan A, Peter JB. NEJM1975; 292:403–407

JOHNS HOPKINS MEDICINE

Updated Myositis Classification Criteria

- After over forty years…
  - Progress!

  - Maybe…

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EDITORIAL REVIEW

Neurologists are from Mars. Rheumatologists are from Venus: differences in approach to classifying the idiopathic inflammatory myopathies

Lisa Christopher-Stine

Curr Opin Rheumatol 22:623–626

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From Venus:
EULAR/ACR Classification Criteria for IIM

Online web calculator available at:

www.imm.ki.se/biostatistics/calculators/iim

Score range	0 – 20.7
Probability (min – max)	0 – 100%
Classification	
Subgroup	

		Yes	No
Age of onset of first symptom	0 – 17	☐	
	18 – 39	☐	
	40+	☐	
Objective symmetric weakness, usually progressive, of the proximal upper extremities		☐	☐
Objective symmetric weakness, usually progressive, of the proximal lower extremities		☐	☐
Neck flexors are relatively weaker than neck extensors		☐	☐
In the legs proximal muscles are relatively weaker than distal muscles		☐	☐
Heliotrope rash		☐	☐
Gottron's papules		☐	☐
Gottron's sign		☐	☐
Dysphagia or esophageal dysmotility		☐	☐
Anti-Jo-1 (anti-Histidyl-tRNA synthetase) autoantibody positivity		☐	☐
Elevated serum levels of creatine kinase (CK) or lactate dehydrogenase (LDH) or aspartate aminotransferase (ASAT/AST/SGOT) or alanine aminotransferase (ALAT/ALT/SGPT)		☐	☐
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		☐	☐
Perimysial and/or perivascular infiltration of mononuclear cells		☐	☐
Perifascicular atrophy		☐	☐
Rimmed vacuoles		☐	☐

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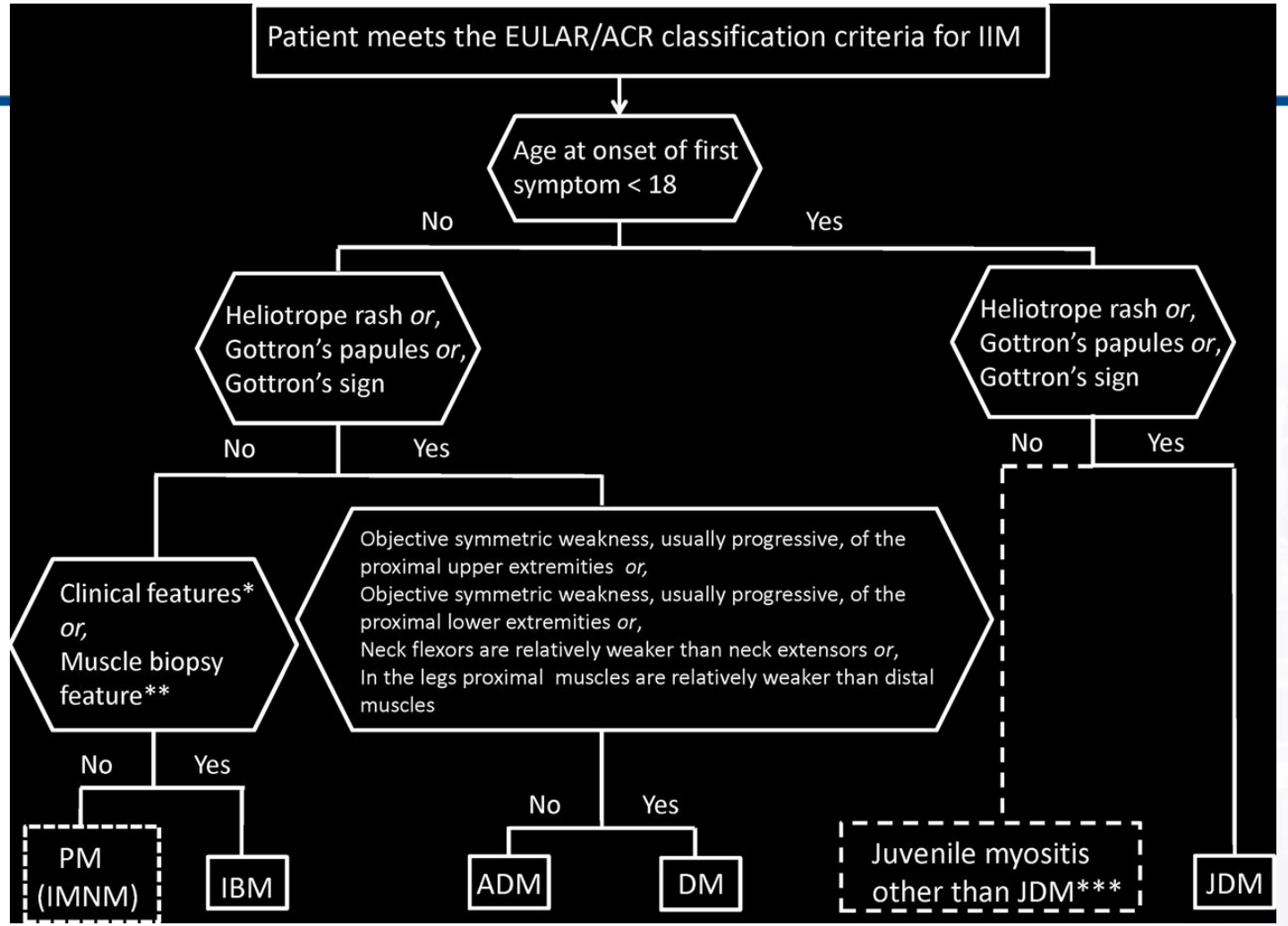
Classification tree for subgroups of IIM. A patient must first meet the EULAR/ACR classification criteria for IIM (probability of IIM ≥55%).



*Finger flexor weakness and response to treatment: not improved, or **muscle biopsy: rimmed vacuoles, is required for classification.

***Juvenile myositis other than JDM was developed based on expert opinion.

IMNM and hypomyopathic DM were too few to allow subclassification.

Ingrid E Lundberg et al. Ann Rheum Dis 2017;76:1955-1964

From Mars…

- Observational Retrospective Cohort Study
- Jan1, 2003-Feb 1, 2016
- 260/445 patients with complete data
- Unsupervised multiple correspondence analysis and hierarchical clustering analysis for subgroups

- Four Group Clusters:
  - DM (Tif1;Mi-2;MDA5)
  - IBM
  - IMNM (HMGCR; SRP)
  - ASynS (Jo-1; PL7)

Mariampillai K. JAMA Neurology Published online September 10,2018

JOHNS HOPKINS MEDICINE

Features pointing away from diagnosis of myositis

- Family history of similar illness
- Weakness related to eating or fasting
- Sensory, reflex, or other neurologic signs
- Cranial nerve involvement
- Fasciculations
- Severe muscle cramping
- Early atrophy
- CPK<2X or >100X ULN

Features pointing toward the diagnosis of myositis

- Characteristic rashes
- Gradual onset
- Proximal limb and truncal weakness
- Other CTD features – Raynaud's , arthritis
- Lung disease-ILD, unexplained infiltrates

Christopher-Stine L and Plotz, PH. Adult Inflammatory Myopathies. Best Pract Res Clin Rheumatol. 2004 Jun;18(3):331-34.

Features pointing toward the diagnosis of myositis

- Characteristic rashes
- Gradual onset
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- Other CTD features – Raynaud's , arthritis
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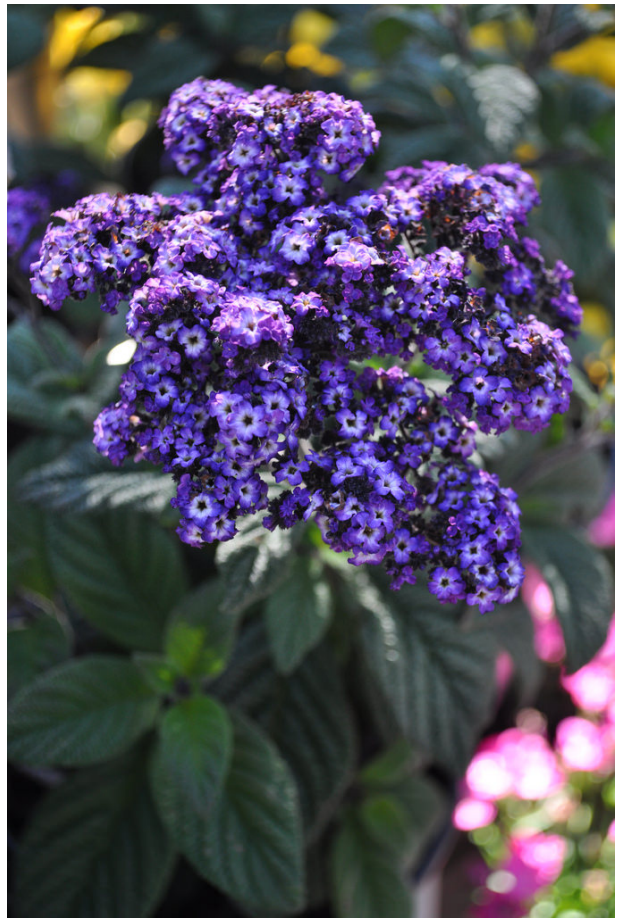
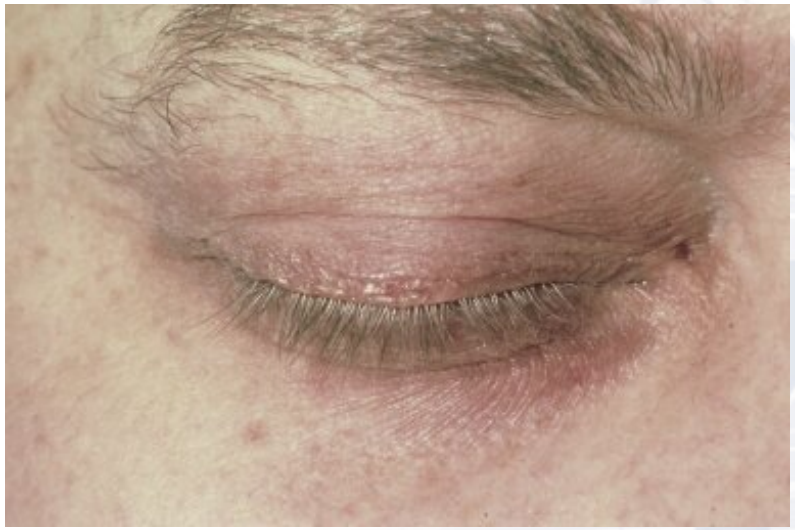
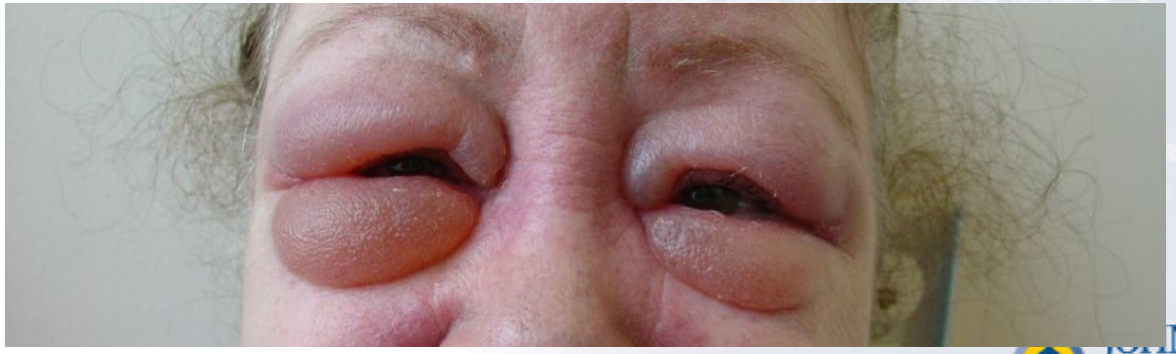
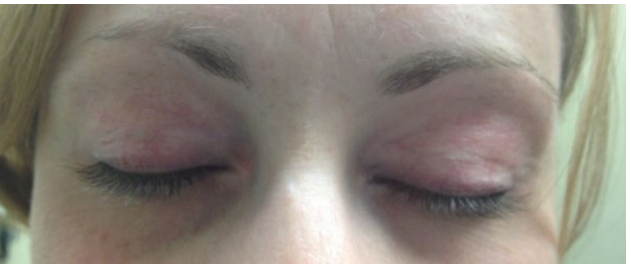
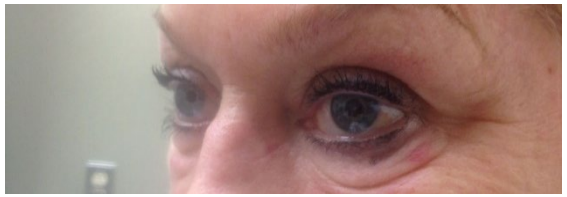
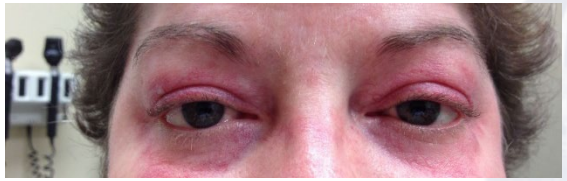
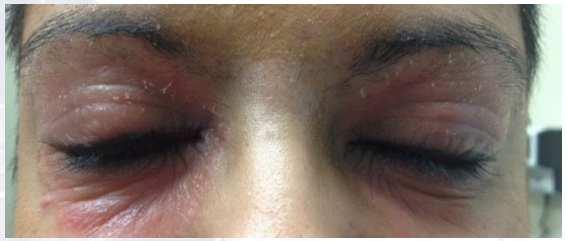
Christopher-Stine L and Plotz, PH. Adult Inflammatory Myopathies. Best Pract Res Clin Rheumatol. 2004 Jun;18(3):331-34.

Heliotrope







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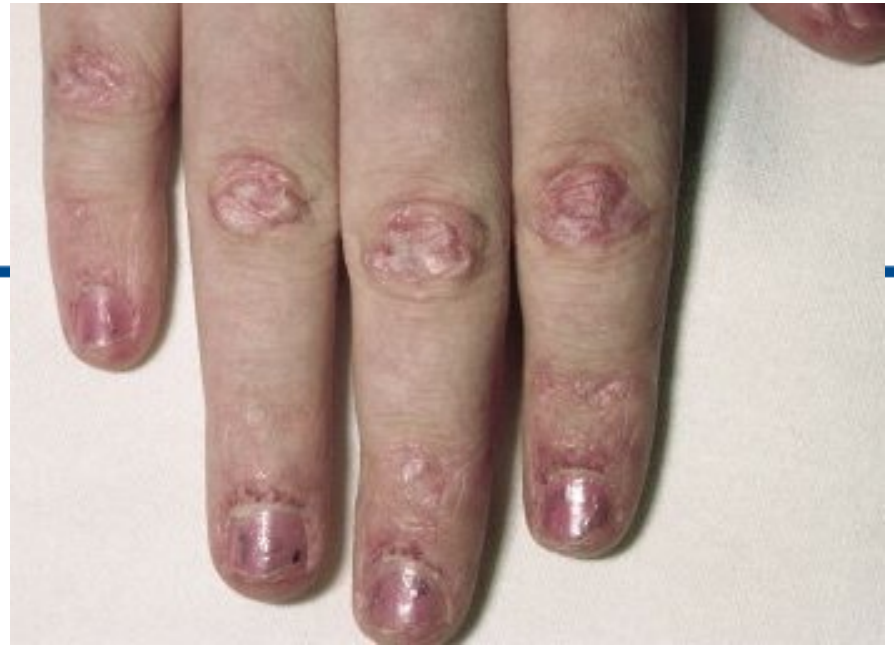
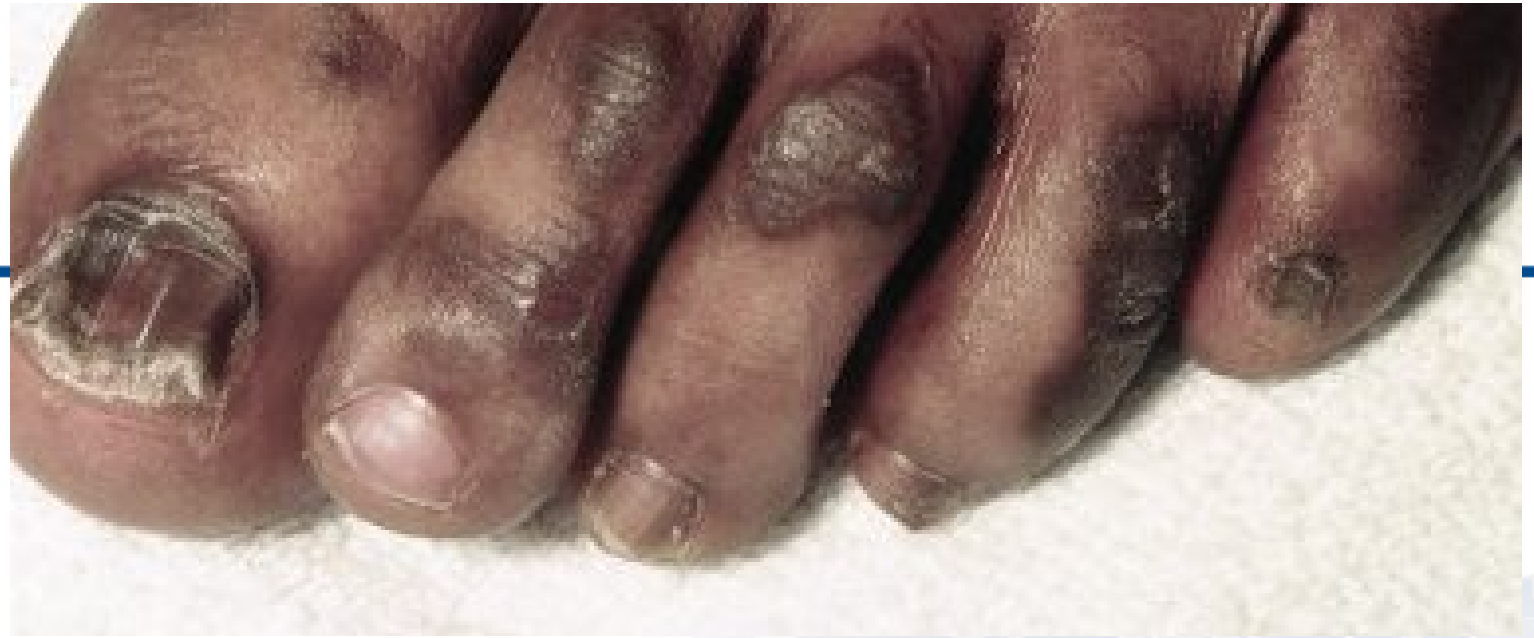
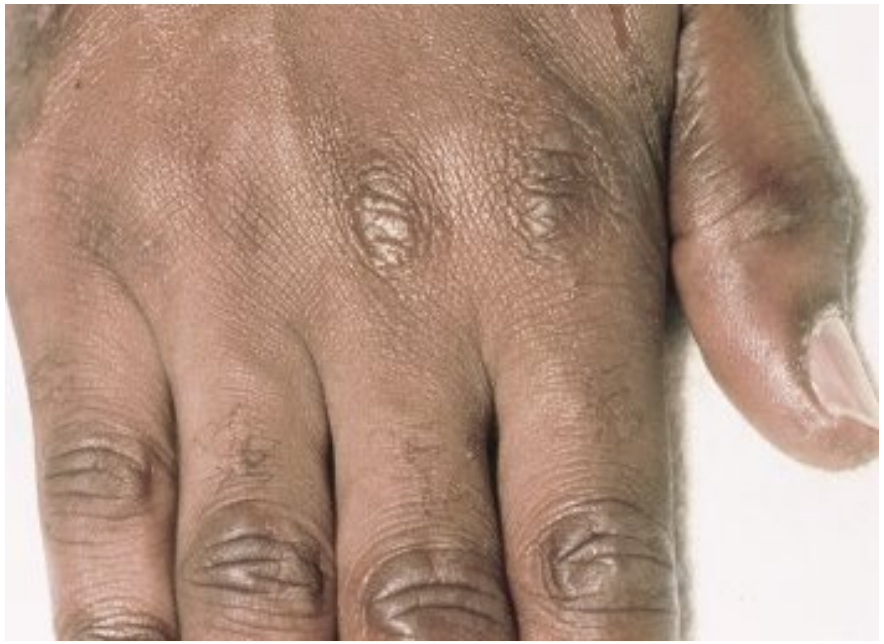
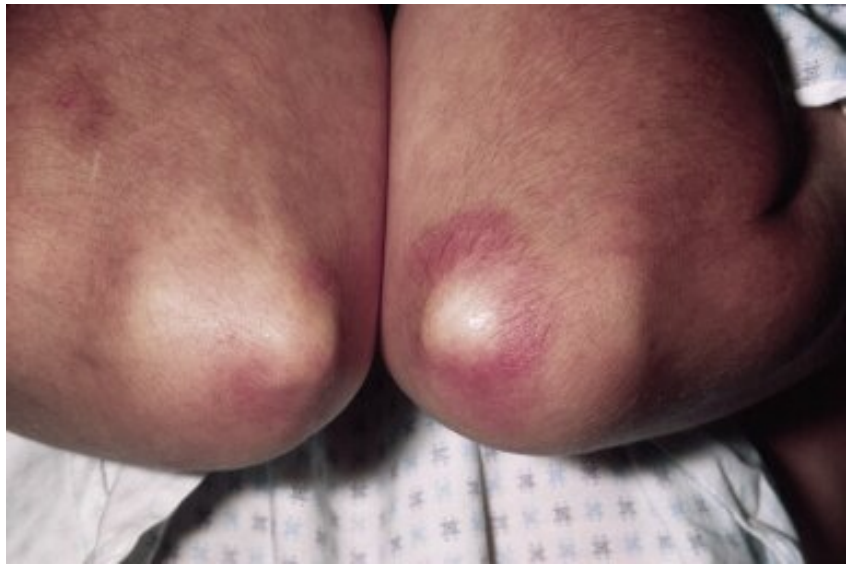




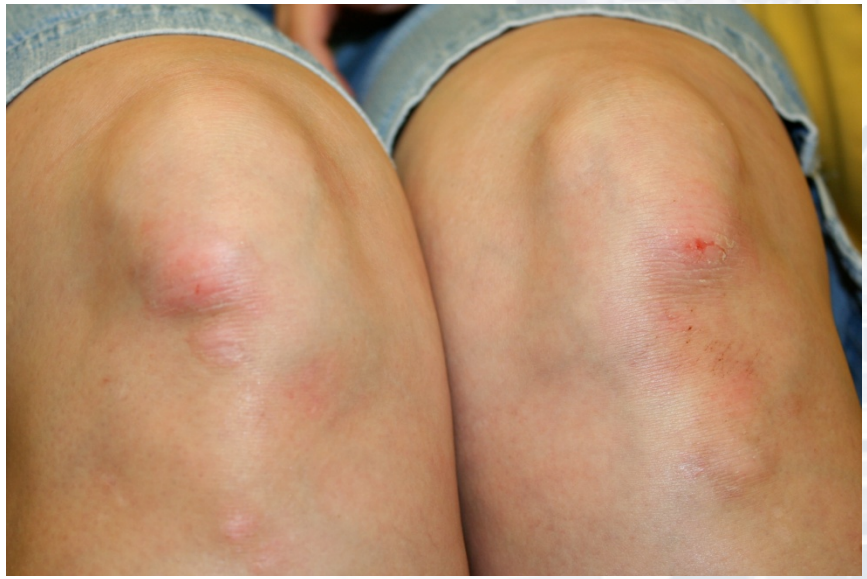


Gottron’s Papules

Gottron's Sign

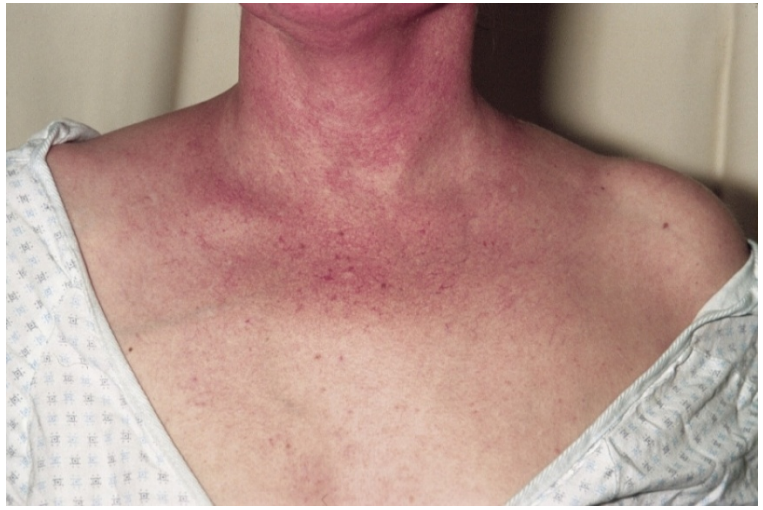


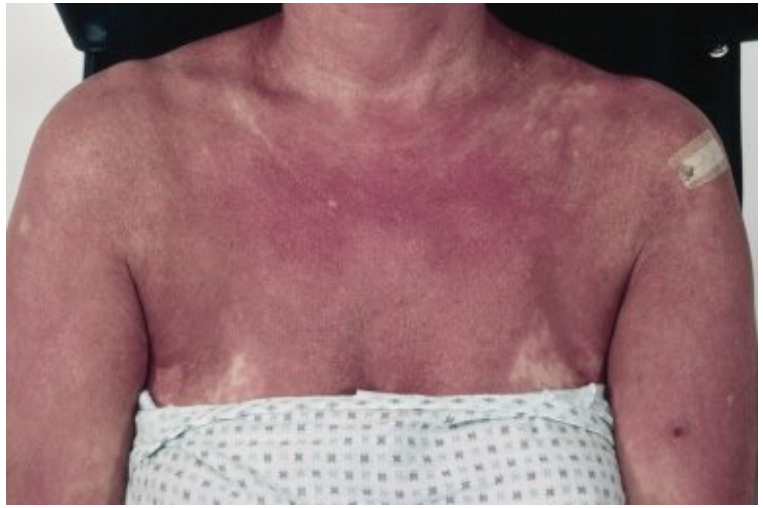
Elbows

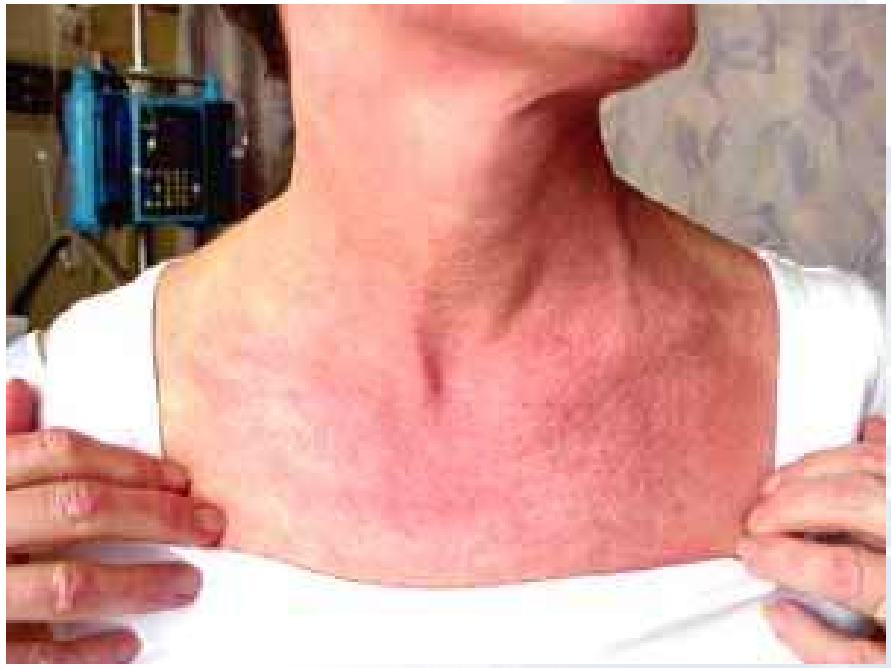


Knees

V-Sign







http://neuromuscular.wustl.edu/pics/people/patients/myoossif/dmchest.jpg

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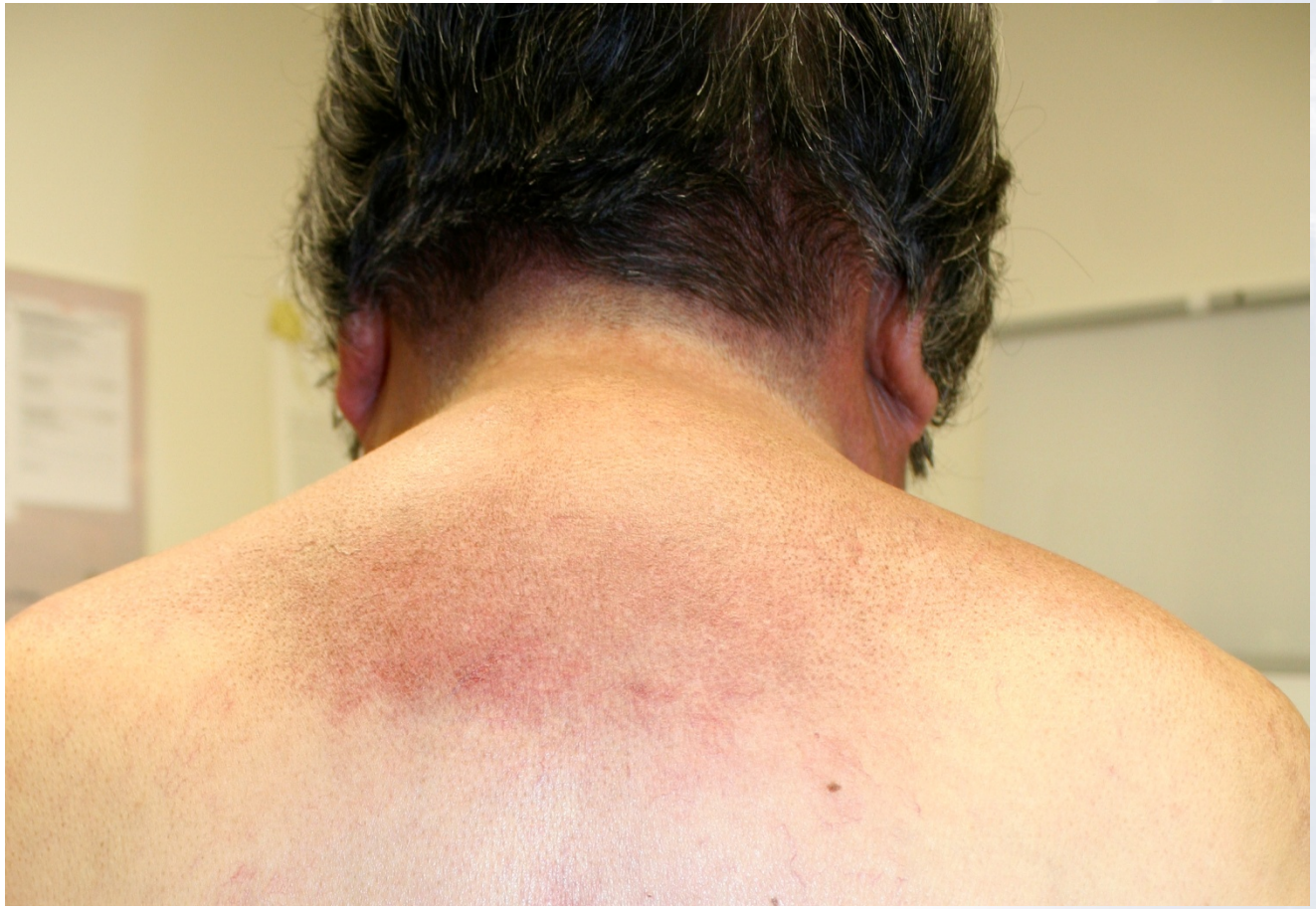
Shawl Sign



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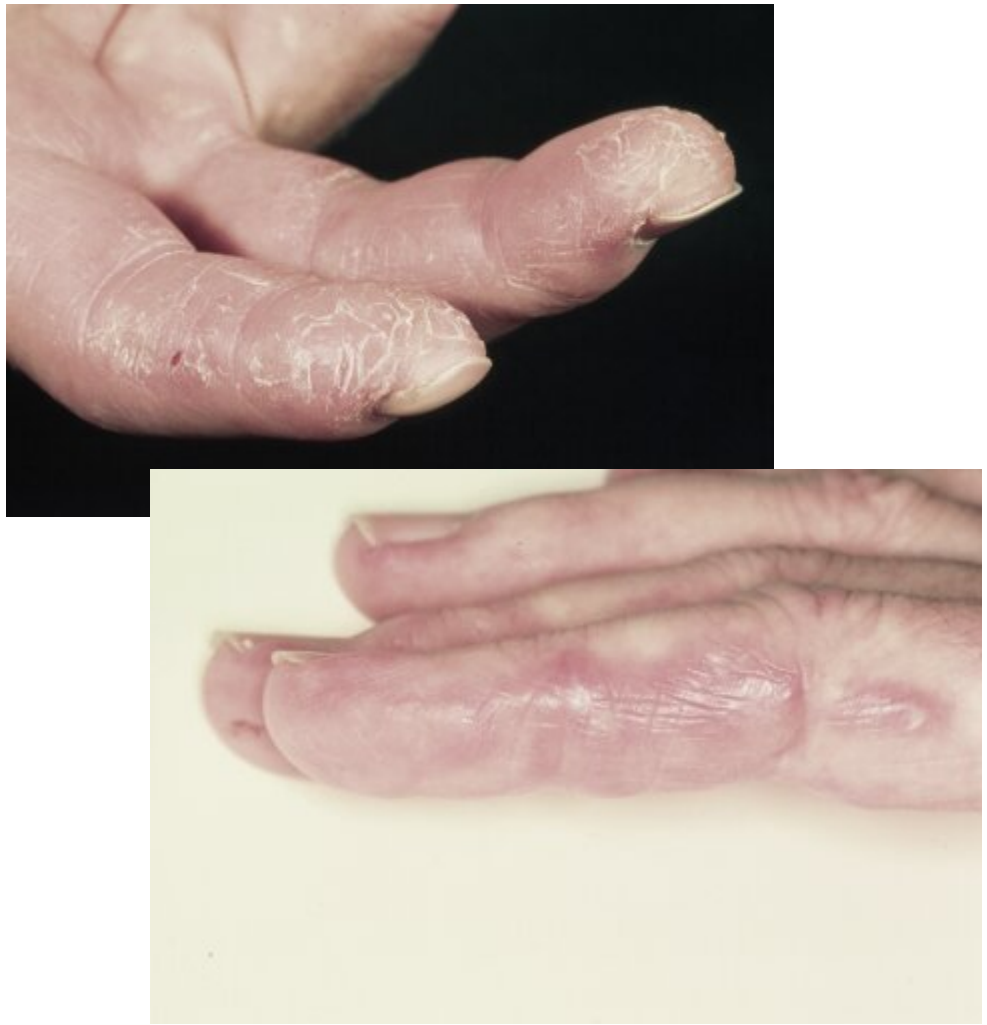
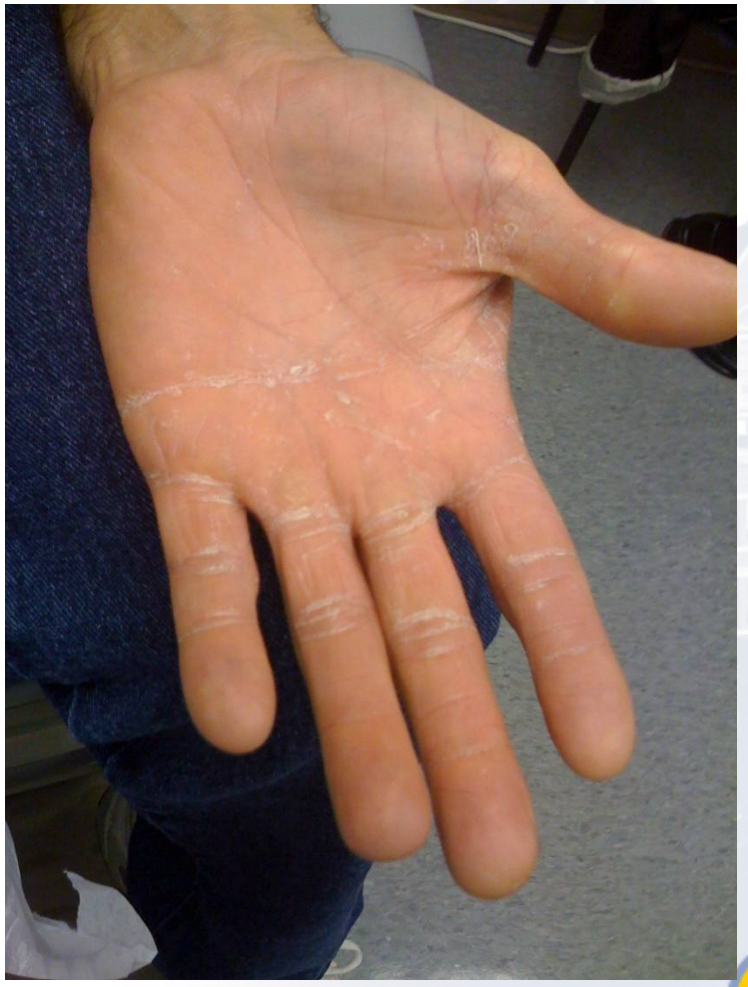
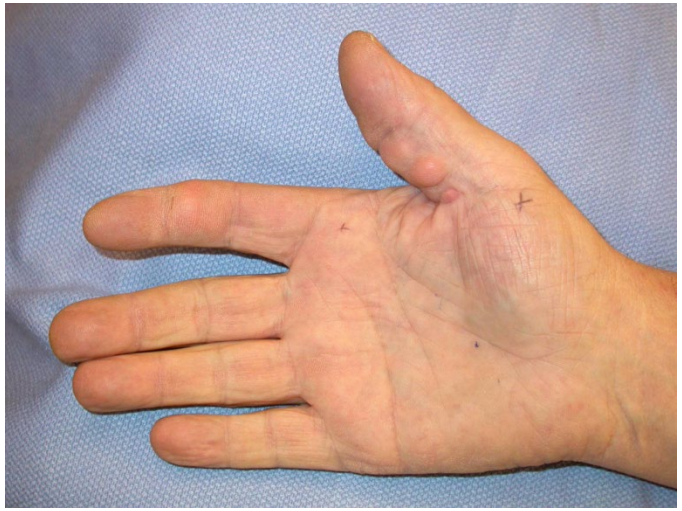
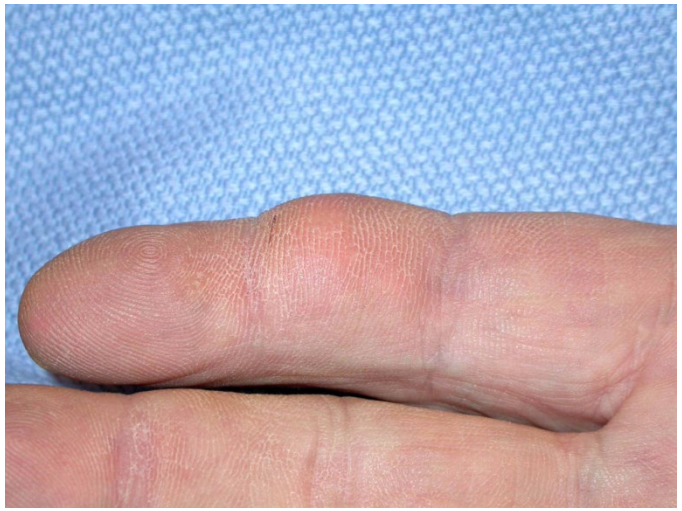
Mechanic's Hands

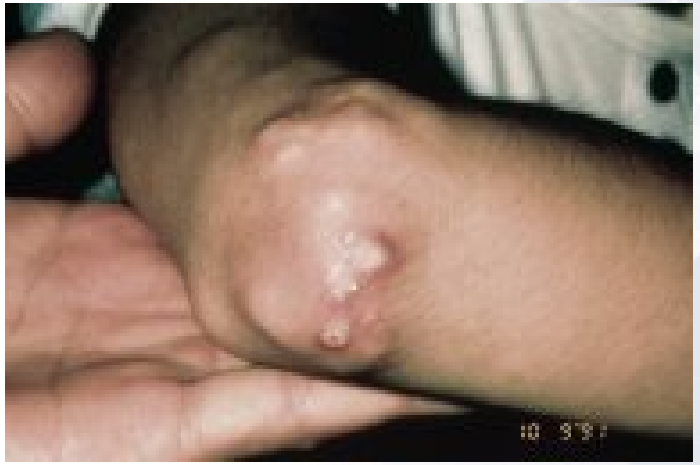


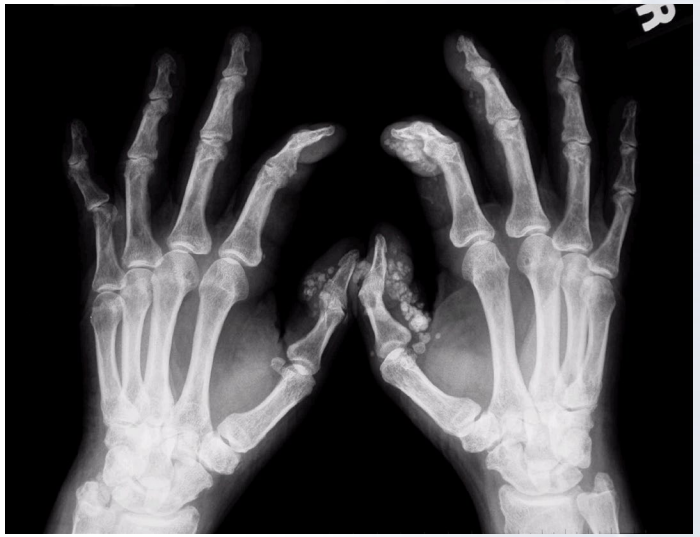


Calcinosis









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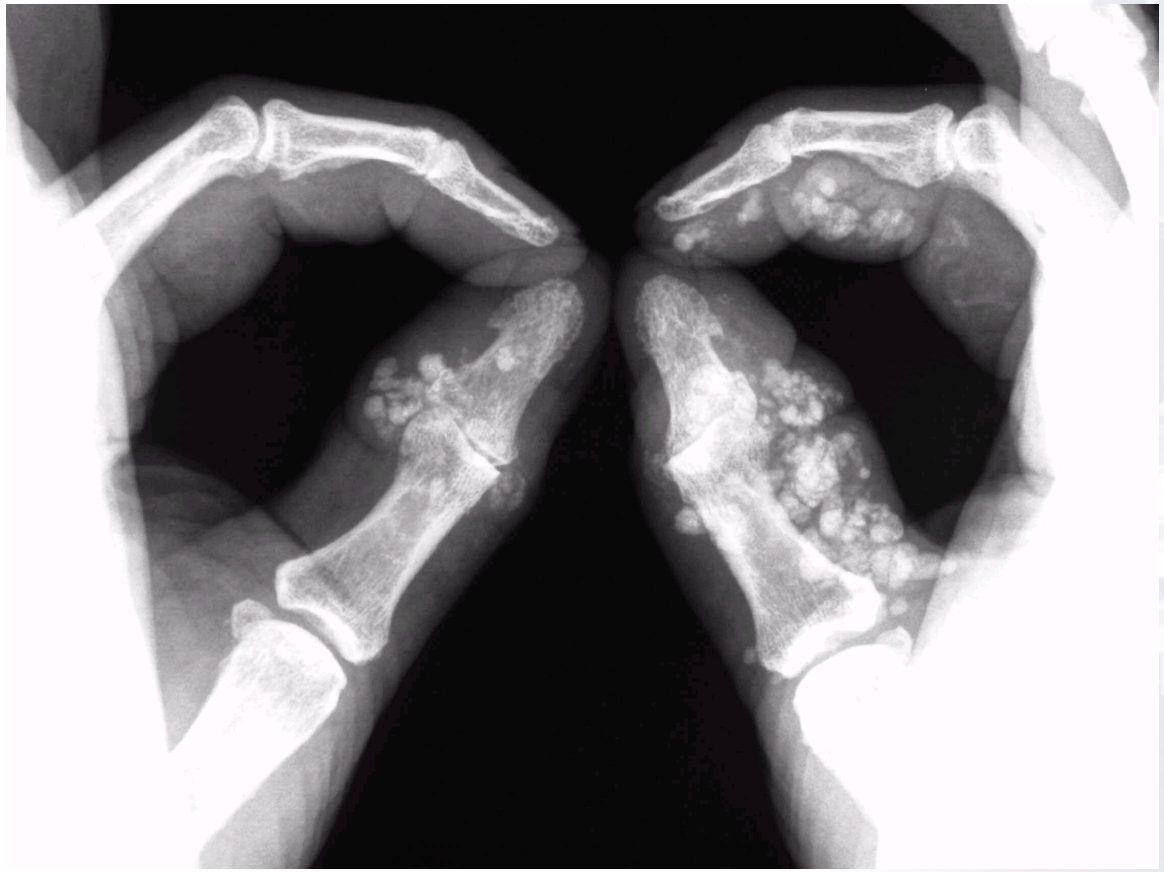
Calcinosis: radiograph



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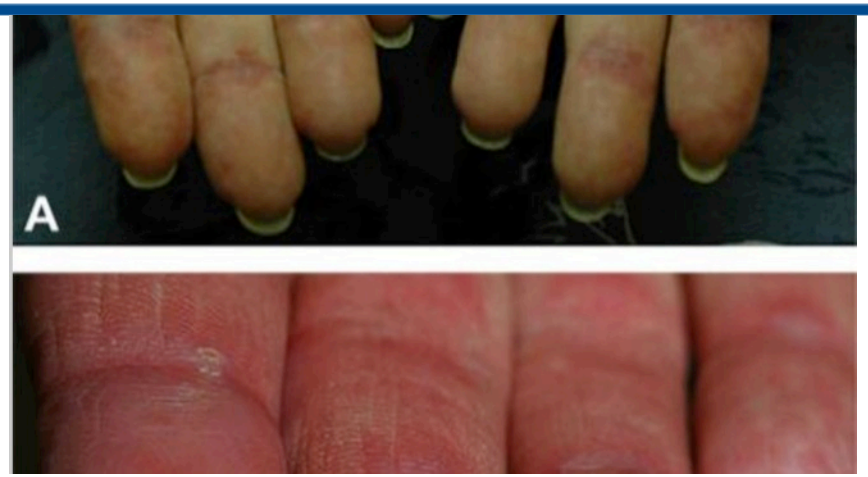
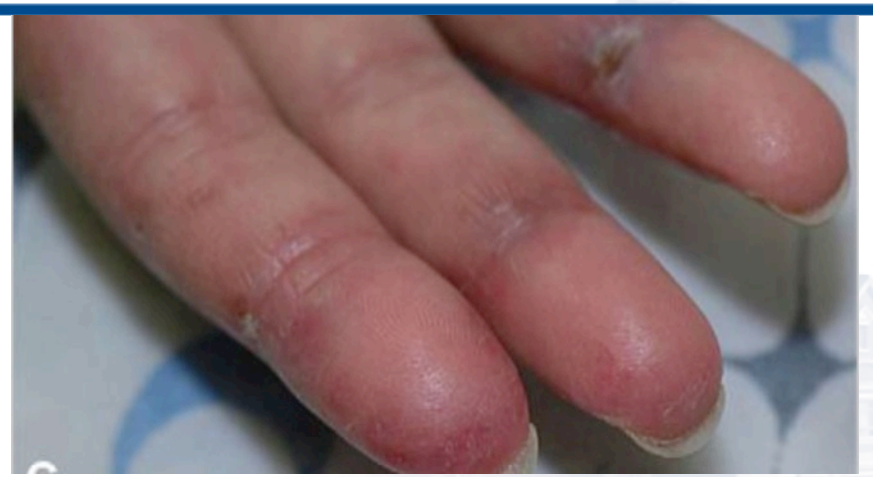
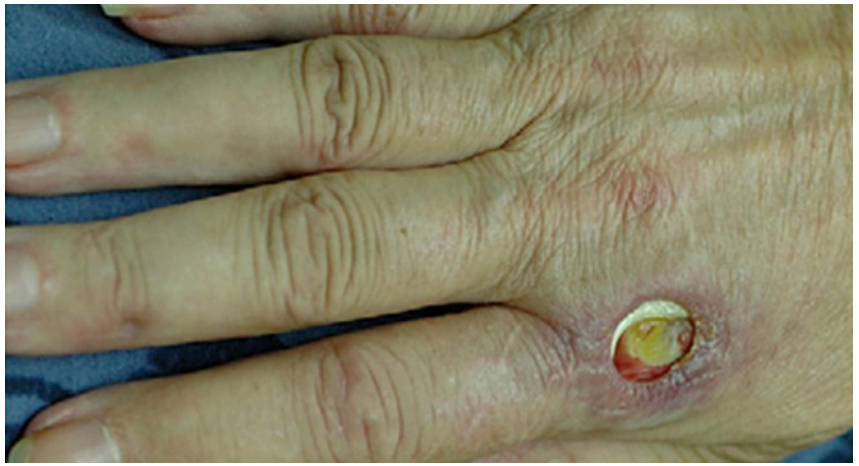
SPECIAL RASHES IN DERMATOMYOSITIS AND WHAT THEY MEAN…

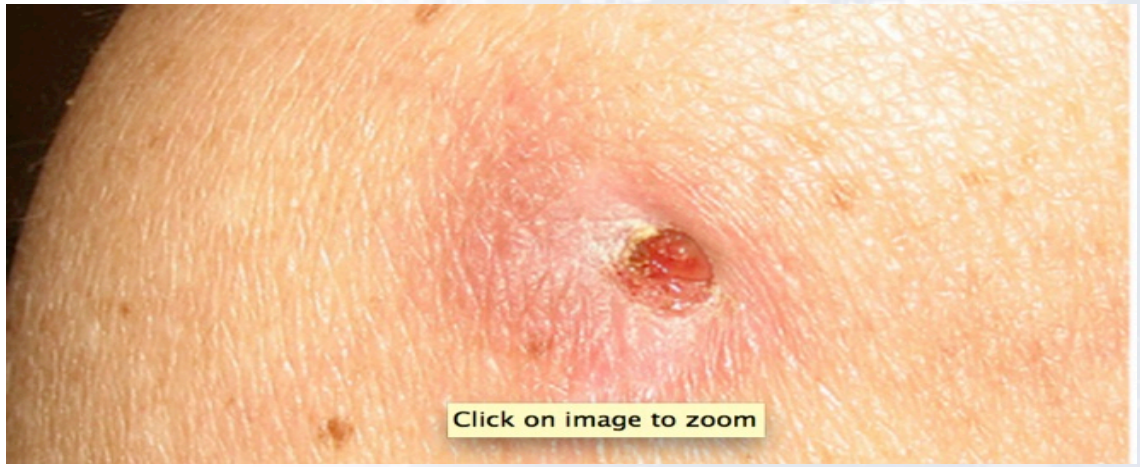
JOHNS HOPKINS MEDICINE

Anti-MDA5 : Unique cutaneous features









JOHNS HOPKINS MEDICINE

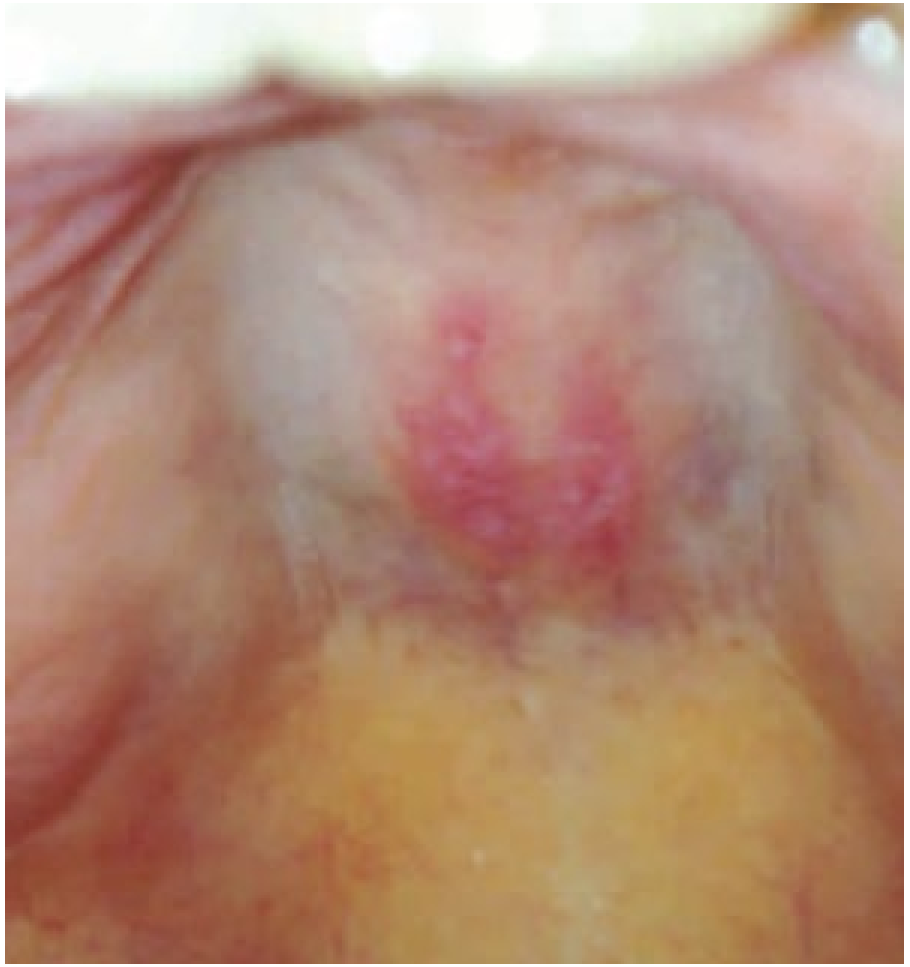
Fiorentino et al 2011

Ulcerated palmar papules and necrotic fingertips occurring on a purple and livedoid background

Kurtzman J and Vleugels Am Acad Derm 2018

Ovoid Palatal Patch in Dermatomyositis

- Data were recorded for 52 consecutive DM patients; 45 included
- 18 (40%) of the 45 patients had a well-demarcated, erythematous patch on the posterior hard palate
- Non-ulcerating, white arcuate markings, midline, and asymptomatic
- Biopsy may show interface dermatitis with a thickened basement membrane and increased dermal mucin
- The patch was significantly associated with the presence of an anti-TIF1γ antibody ($P < .001$)
- None of the 16 patients with any of the other defined antibodies had this oral lesion.
- The oral lesion was associated with female sex ($P = .01$) and clinically amyopathic disease ($P = .03$).
- Also highly associated with cancer-associated DM ($P = .004$); of the 6 anti-TIF1γ antibody–positive patients with cancer, all 6 had this oral lesion.

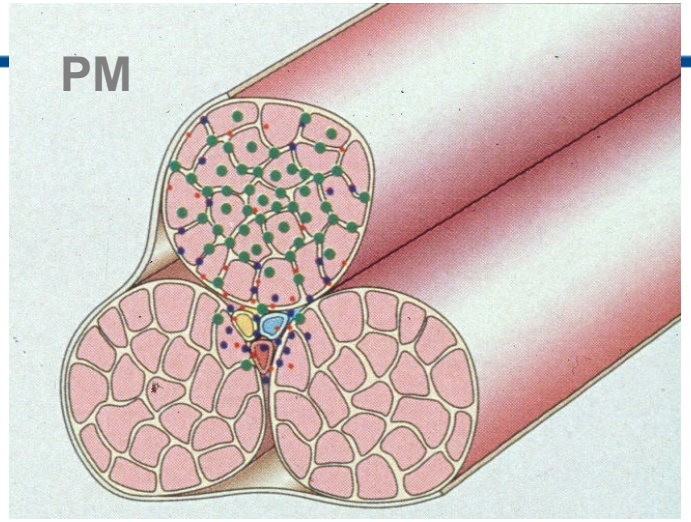


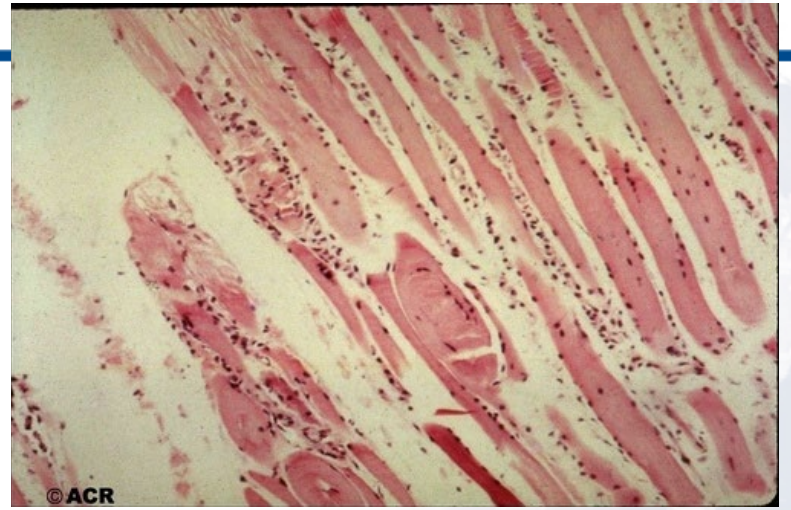
Bernet LL JAMA Dermatol. 2016;152(9):1049-1051

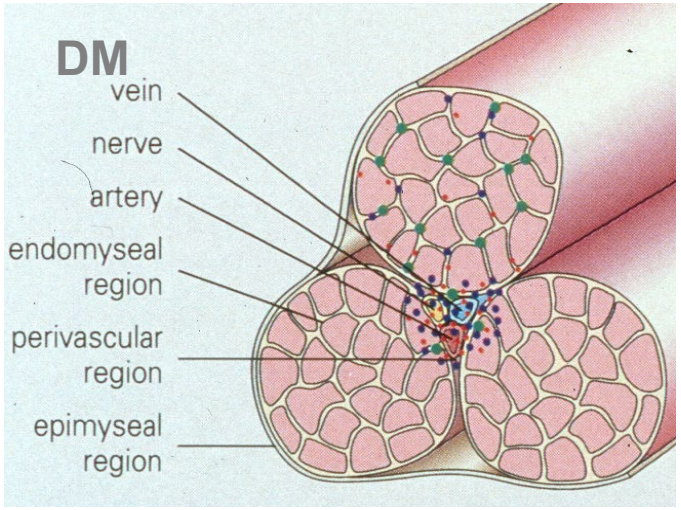
Amyopathic Dermatomyositis

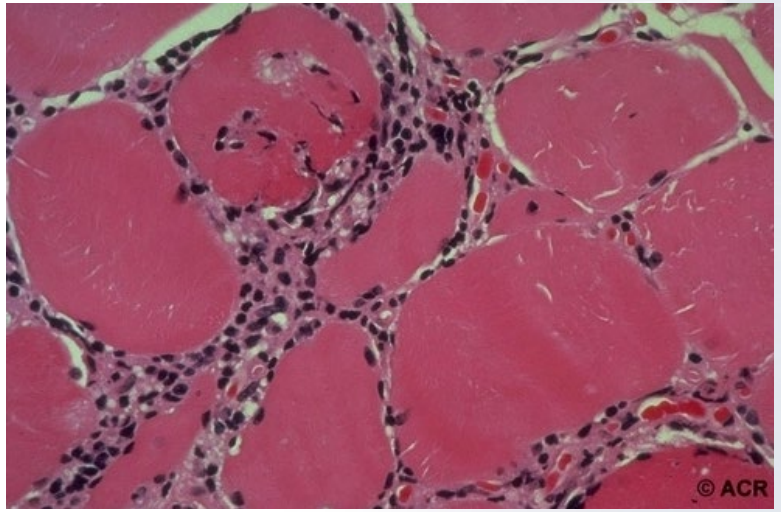
- “DM sine myositis”
- Typical cutaneous disease with no evidence of muscle weakness and normal serum muscle enzymes on repeated testing
- Potentially fatal interstitial lung disease can occur in clinically amyopathic dermatomyositis.
- Malignancy may occur as well
- Pulmonary and Malignancy work-up same

Muscle Pathology in Myositis







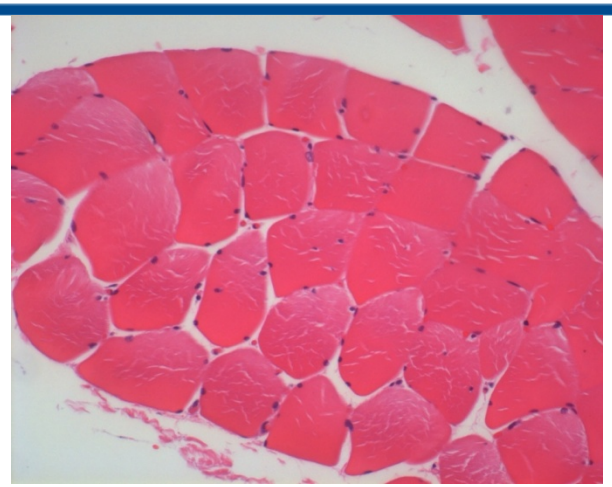


Klippel JH, 2nd ed. *Rheumatology.* 1998. Klippel and Dieppe. *Rheumatology*. 2nd ed. ((year)); (7)14.8.((fix pages))

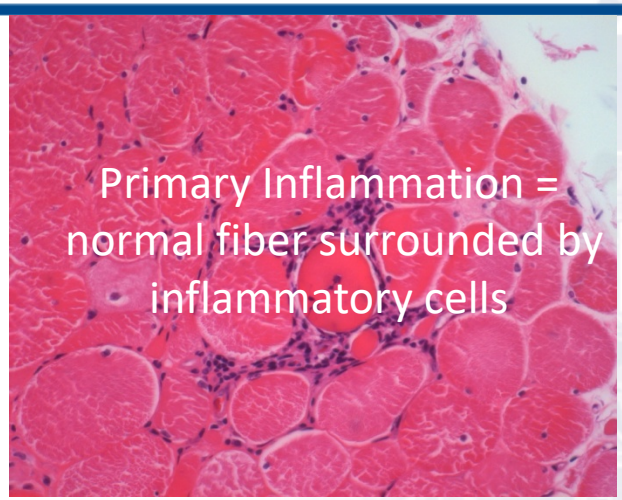
JOHNS HOPKINS MEDICINE

Muscle review: Under the microscope

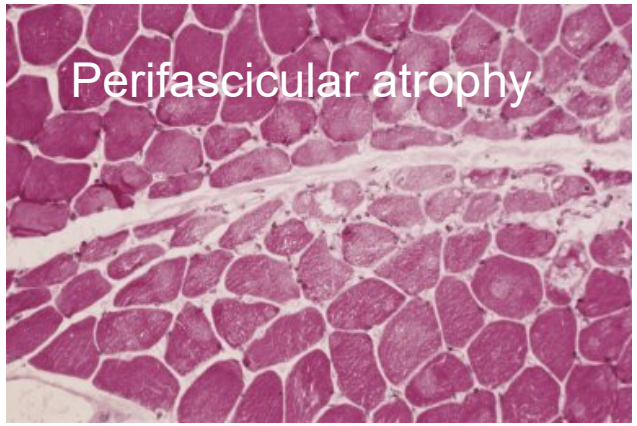
Normal muscle

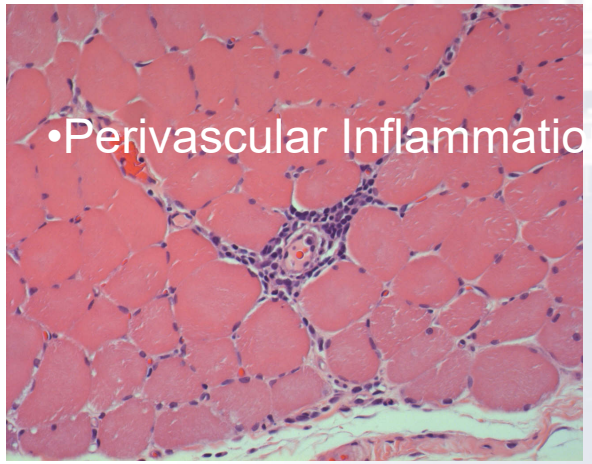


Polymyositis



Dermatomyositis





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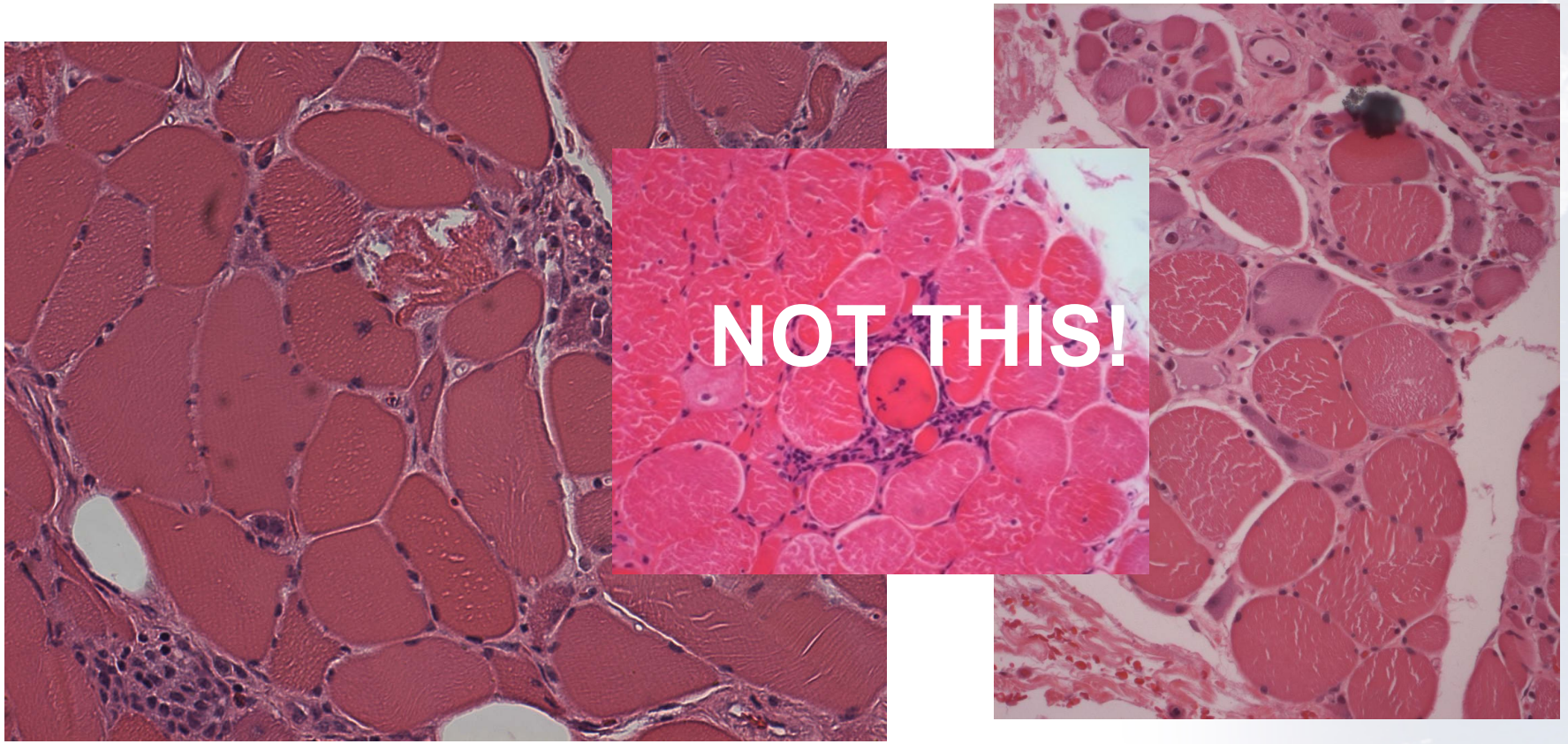
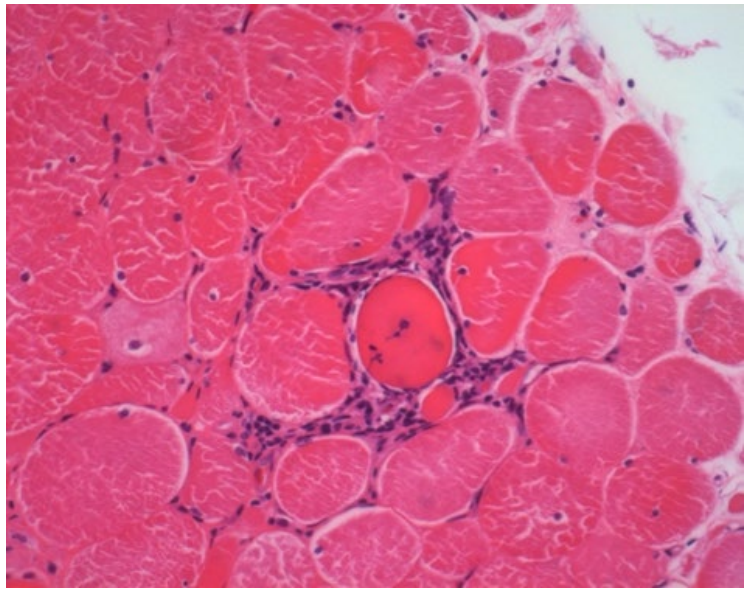
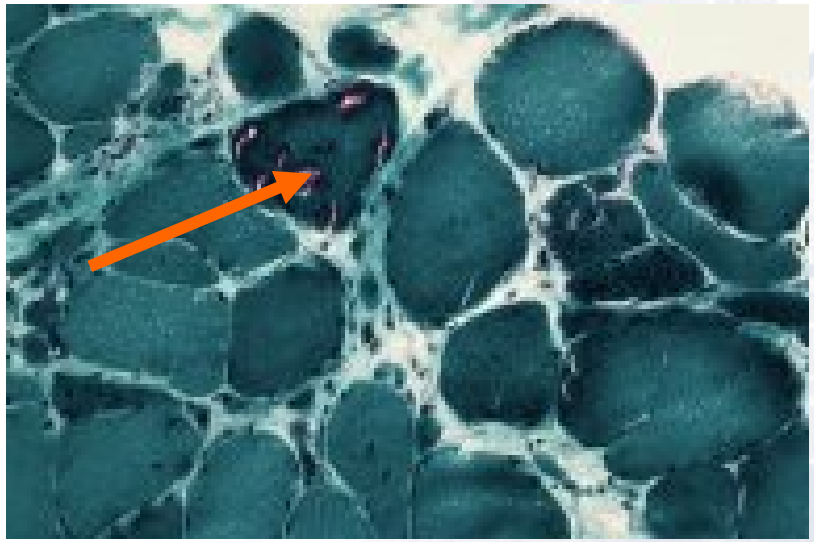
Immune Mediated Necrotizing Myopathy



Inclusion Body Myositis

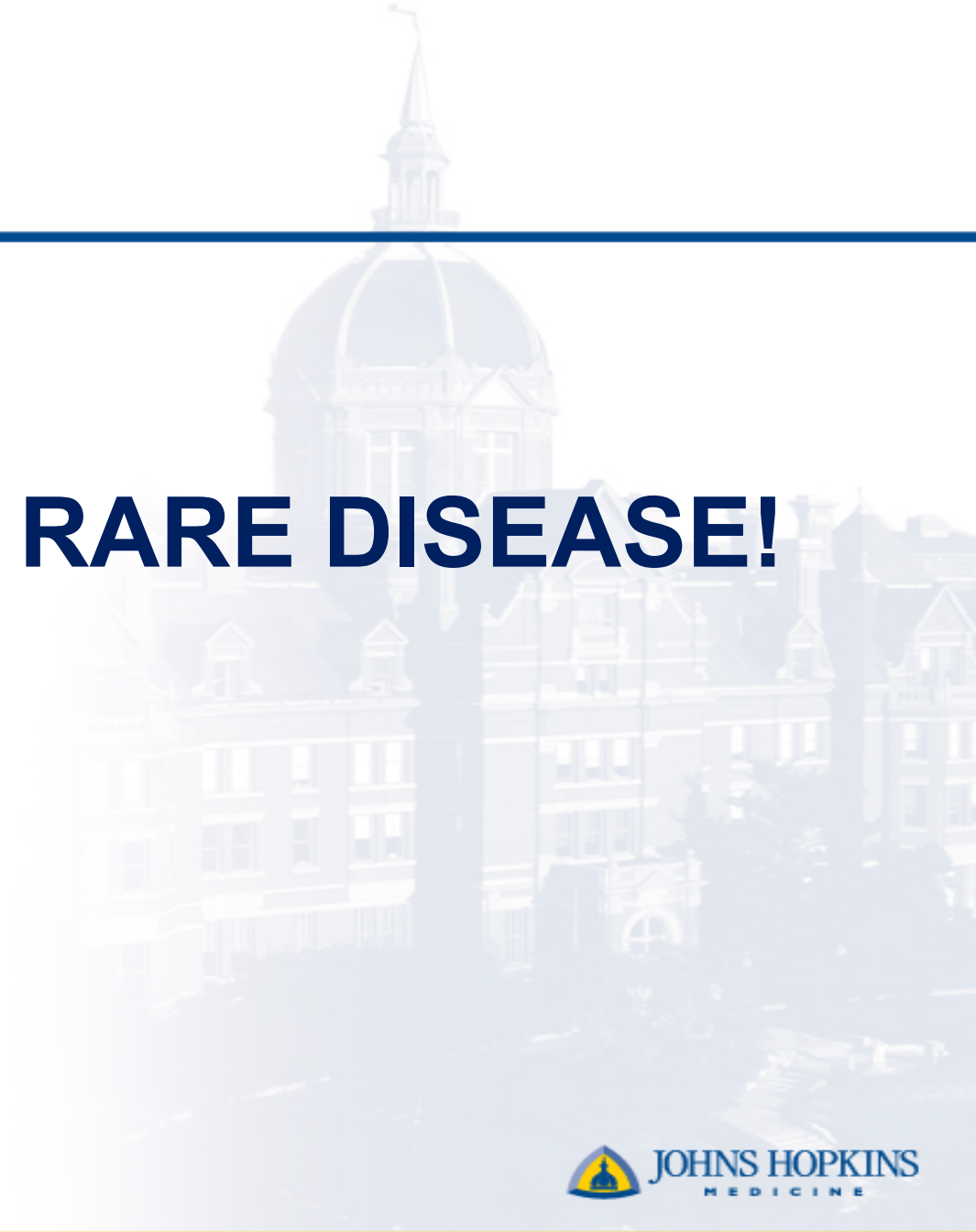


Primary inflammation



Red rimmed vacuoles on GT Stain

“POLYMYOSITIS” IS A RARE DISEASE!



JOHNS HOPKINS MEDICINE

Most common diagnoses for "Polymyositis"

- Immune mediated necrotizing myopathy
- Overlap : with scleroderma (often anti-PMScl or anti-RNP +), lupus(rare), or RA
- Antisynthetase syndrome (without a rash typical of DM)
- Inclusion body myositis
- Muscular dystrophy

Most common diagnoses for "Polymyositis"

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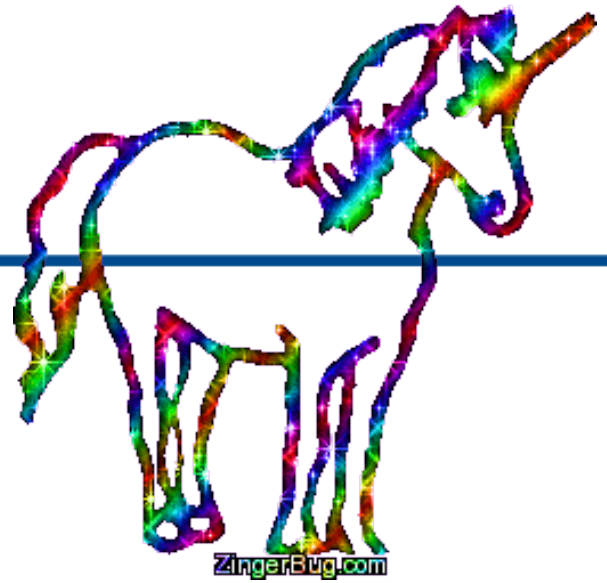

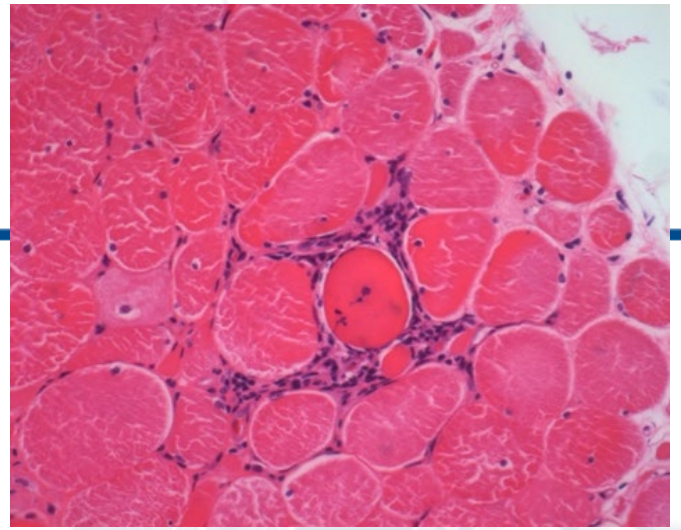

NEUROLOGY 2003;61:288–290

Editorial

Unicorns, dragons, polymyositis, and other mythological beasts

Anthony A. Amato, MD; and Robert C. Griggs, MD

[redacted]

Polymyositis

An overdiagnosed entity

M.F.G. van der Meulen, MD; I.M. Bronner, MD; J.E. Hoogendijk, MD, PhD; H. Burger, MD, PhD; W.J. van Venrooij, PhD; A.E. Voskuyl, MD, PhD; H.J. Dinant, MD, PhD; W.H.J.P. Linssen, MD, PhD; J.H.J. Wokke, MD, PhD; and M. de Visser, MD, PhD

Retrospective follow-up study of 165 patients (1977 and 1998)

-Previous diagnosis of myositis

-Subacute onset of symmetric, proximal weakness

-Excluding other neuromuscular disorders

Results:

Thirty-two patients (**19%**; 95% CI, 14 to 26%) assigned to “possible myositis” category.

The biopsy specimens of these patients showed a **necrotizing myopathy** containing no or only minimal inflammatory cells in the vicinity of necrotic fibers

Conclusion: PM is overdiagnosed and rare

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Immune Mediated Necrotizing Myopathy Diagnostic Criteria (October 2003 at the 119th ENMC workshop

DIAGNOSTIC CATEGORIES	CRITERIA
Clinical criteria	Inclusion Criteria: • Age > 18 years • Subacute or insidious onset • Symmetric proximal muscle and neck flexor weakness > distal and neck extensor weakness Exclusion Criteria: • Clinical features of IBM • Ocular weakness, isolated dysarthria, neck extensor>flexor weakness • Toxic myopathy, active endocrinopathy, amyloidosis, family history of muscle dystrophy or proximal motor neuropathies (SMA)
Elevated CK	
Laboratory Criteria (1 of 3)	• Positive EMG: Fibrillation potentials, positive sharp waves, or complex repetitive discharges. Short-duration, small amplitude, polyphasic MUAPs • Muscle MRI: Increased signal (edema) within muscle on STIR images • Myositis-specific antibodies detected in serum
Muscle biopsy	• Prominent muscle fiber necrosis • Sparse inflammatory infiltrate, no perimysial infiltrate • MAC deposition on small vessels or pipestem capillaries • Rare tubuloreticular inclusions in endothelial cells

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IMNM Clinical Pearls

- Patients with IMNM present with similar clinical symptoms as polymyositis and dermatomyositis, mainly **proximal muscle weakness**.
- Compared to the other idiopathic inflammatory myopathies, patients with IMNM tend to have **higher CK levels**, more prominent **myalgias** and more extensive **muscle atrophy** and functional **disability**.
- Because the clinical presentation in IMNM can be clinically indistinguishable from other inflammatory myopathies, **the muscle biopsy in IMNM is often important** in making the diagnosis.
- Histologically, patients with IMNM have **prominent myocyte necrosis** and muscle fiber regeneration, and a **relative paucity of lymphocytes**
- The extensive muscle necrosis may explain why CK levels are higher in IMNM compared to the other myopathies.

Most common diagnoses for "Polymyositis”

- Immune mediated necrotizing myopathy
- Overlap : with scleroderma (often anti-PMScl or anti-RNP +), lupus(rare), or RA
- Antisynthetase syndrome (without a rash typical of DM)
- Inclusion body myositis
- Muscular dystrophy

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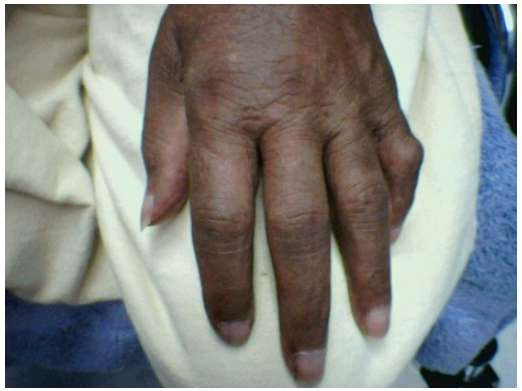
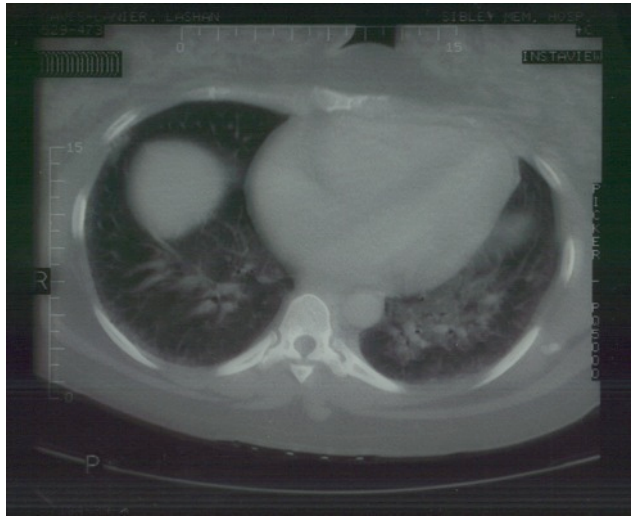
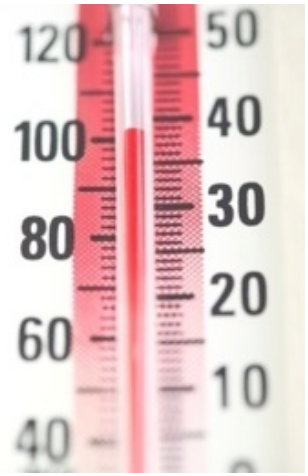
Antisynthetase Syndrome (with or without rash): Extramuscular Phenotype



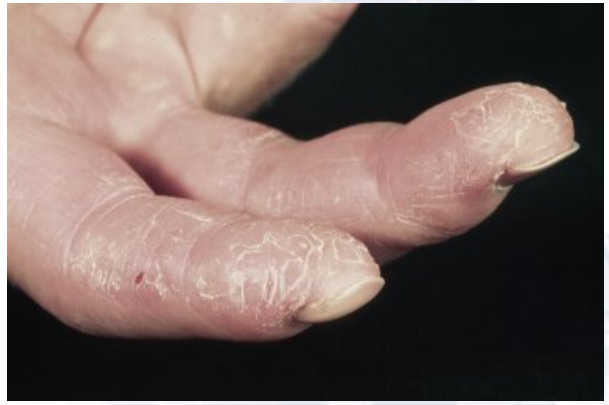
Arthritis



Interstitial Lung Disease



Fever



Mechanic's Hands

Raynaud's Phenomenon

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Most common diagnoses for “Polymyositis”

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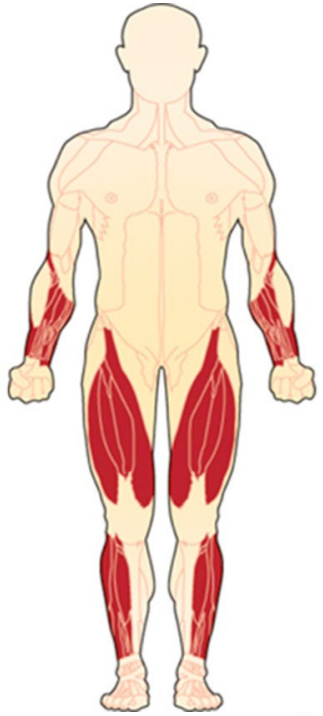
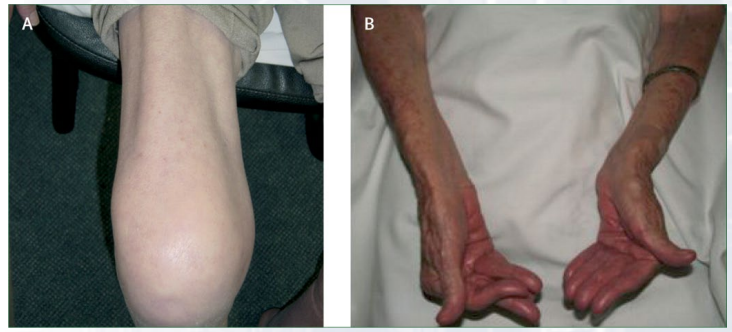
- Overlap : with scleroderma (often anti-PMScl or anti-RNP +), lupus(rare), or RA
- Antisynthetase syndrome (without a rash typical of DM)
- **Inclusion body myositis**
- Muscular dystrophy (dyferlinopathy (limb girdle 2B), FSHD

Inclusion Body Myositis (IBM)

- Age> 30 (most often>50)
- Middle-aged/Elderly (M/F 2:1)
- Proximal strength loss
- Asymmetry
- Muscle atrophy
- Distal strength loss (forearm/finger flexors)
- Mixed Myopathic and Neuropathic EMG
- Muscle biopsy: characteristic inclusions on GT stain
- May be labeled as “treatment-resistant polymyositis”



Examples of sporadic inclusion body myositis-related muscle wasting



Needham M. The Lancet Neurology; (6) 7, 620-631

Tawil R and Griggs RC. Curr Opin Rheumatol. 2002 Nov;14(6):653-7
Muscular Dystrophy Association

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IBM data-derived criteria with 90% sensitivity and 96% specificity among 371 patients

- (1) CLINICAL: finger flexor or quadriceps (knee extensor) weakness
- (2) BIOPSY: endomysial inflammation
- (3) BIOPSY: either invasion of nonnecrotic muscle fibers or rimmed vacuoles

Lloyd TE. Neurology July 29, 2014; 83 (5)

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Most common diagnoses for “Polymyositis”

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*Myositis Mimics: Muscular Dystrophy Summary

- Duchenne's Manifesting Carrier
- Limb Girdle Type 2 B (Dysferlinopathy)
- Myotonic Dystrophy (DM 2> DM 1)
- FSHD

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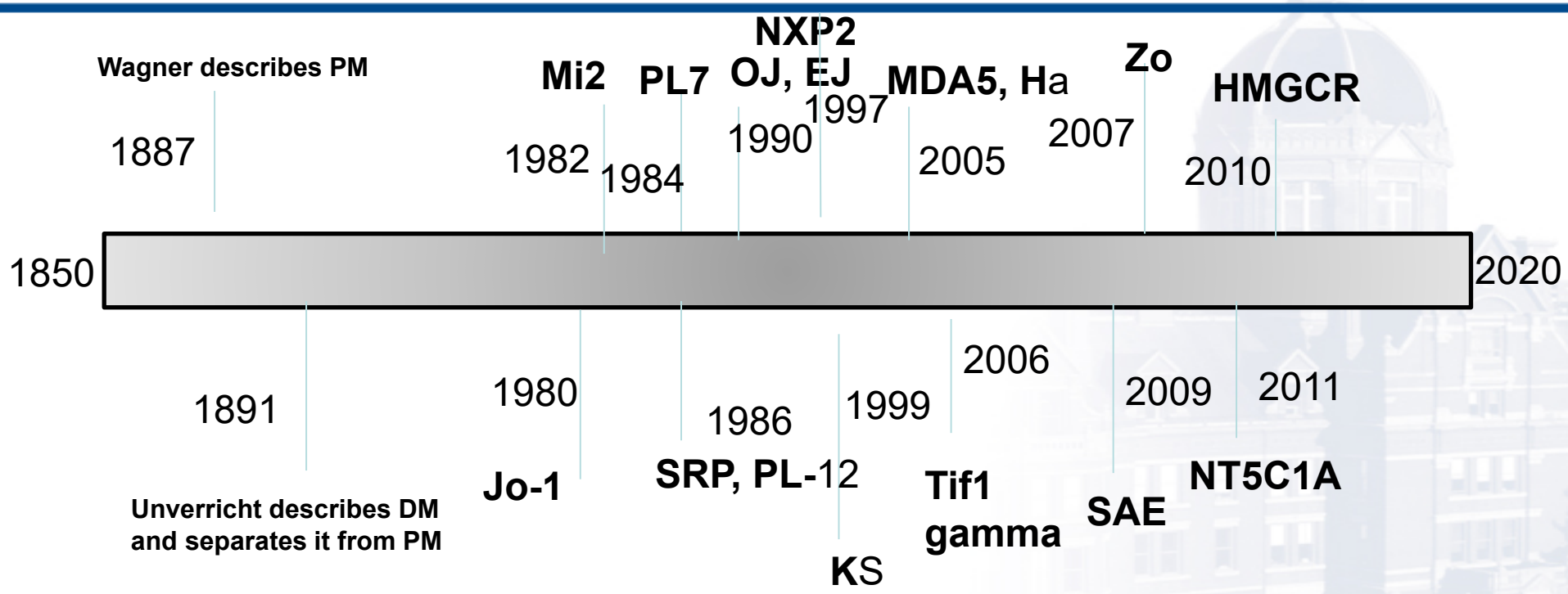
Myositis Autoantibodies

A brief timeline of IIM and Autoantibody Discovery



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AsynS

OM

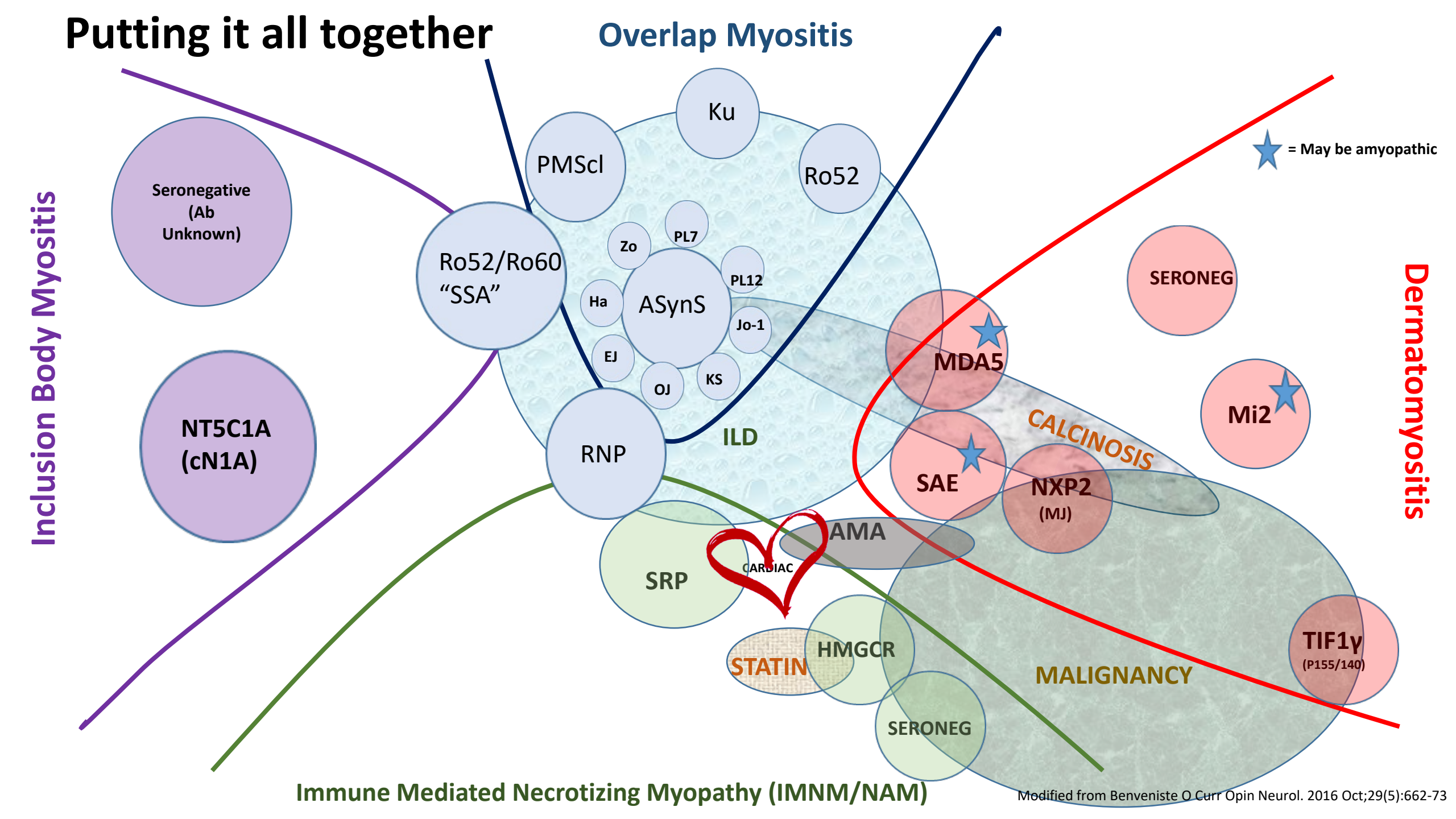
DM

NM

IBM

Auto-antibody	Frequency	Typical clinical features
Anti-tRNA: Jo-1, PL-7, PL-12, HA (YRS/Tyr), OJ, KS, ZO, EJ	anti-tRNA: 30% in myositis Jo-1: 15-20% in myositis PL-7 and PL-12: each 3 -4% All others <2%.	Higher rate of ILD and mortality in PL-7/PL-12 than Jo-1
Anti-SS-A/Ro52/Ro60 SS-B/La	SS-A: up to 19% in myositis, 25% in OM, SS-B: 7% in myositis, 12% in OM Ro52 often together with anti -synthetase, e.g. 56-72% of Jo-1.	Association with Sjögren's syndr., SLE and systemic sclerosis. Ro52 more common in myositis than Ro60; both occur in CTD. Ro52 and Jo-1-double positive: high rate of malignancies, poorer prognosis.
U-snRNP	up to 10% of myositis	Associated with CTD, SLE and systemic sclerosis. Often good prognosis.
PM/Scl	~8-10% of myositis	Associated with systemic sclerosis. Often severe disease course and insufficient treatment response.
Ku	up to 20-30% in OM	Associated with systemic sclerosis, SLE and CTD. High rate of ILD, which does not respond well to glucocorticosteroids.
Mi-2	5-10% in DM	Classical DM
MDA5	15-30% in DM	Often amyopathic DM, often ILD.
TIF-1α/β/γ	~20% in DM	Malignancy common (75%). Most common in JDM–without tumor.
NXP-2	10-15% in DM	Malignancy frequent (37.5%). Second most common antibody in JDM–without malignancy, but often calcinosis.
SAE	2-8% in DM	Often amyopathic and with ILD.
SRP	5% in myositis	Often severe with muscle atrophy, ILD and dysphagia. Often basic immunosuppressive treatment regimen not sufficient.
HMGCR	5-8% in myositis	High frequency of malignancy.
cN1A	~30% in IBM	Sjögren or SLE positive by 20-30%, even without muscle symptoms. In IBM: more severe disease course, dysphagia and higher mortality.

Schmidt, Jens. 'Current Classification and Management of Inflammatory Myopathies'. 1 Jan. 2018 : 109 – 129



Modified from Benveniste O Curr Opin Neurol. 2016 Oct;29(5):662-73

TREATMENT

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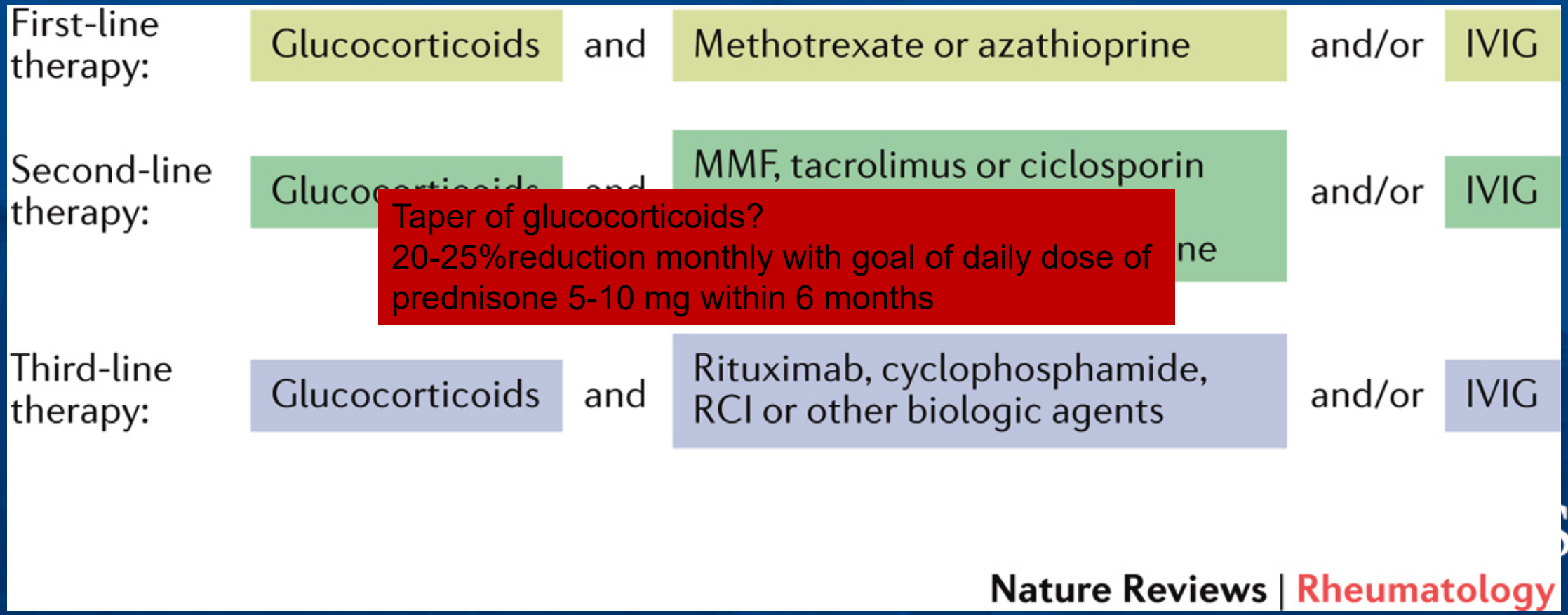
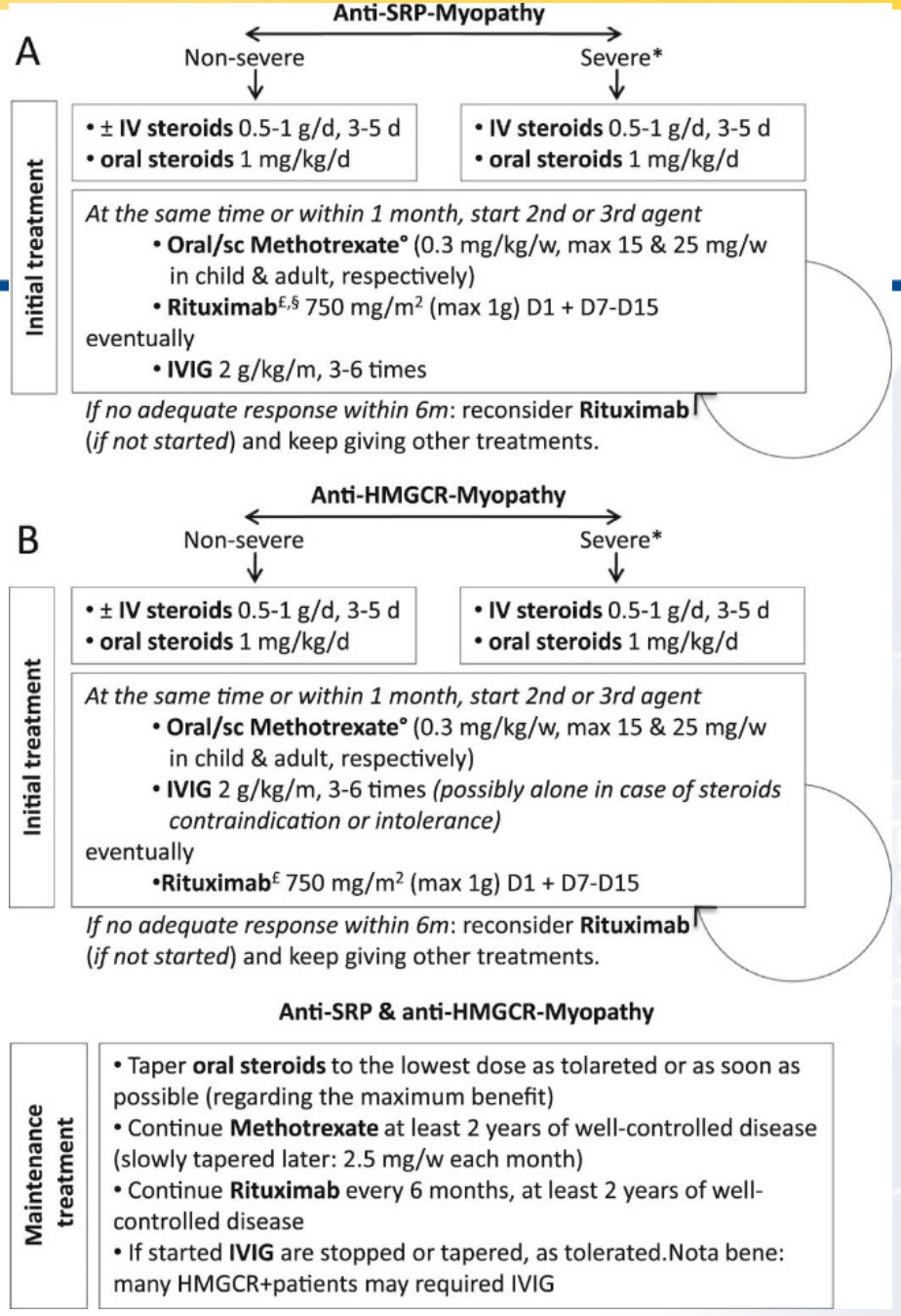
MEDICINE

Overview of pharmacological therapy in idiopathic inflammatory myopathies



Oddis, C. V. & Aggarwal, R. (2018) Treatment in myositis
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2018.42

Autoimmune Necrotizing Myopathy Treatment



Neuromuscul Disord. 2018 Jan;28(1):87-99

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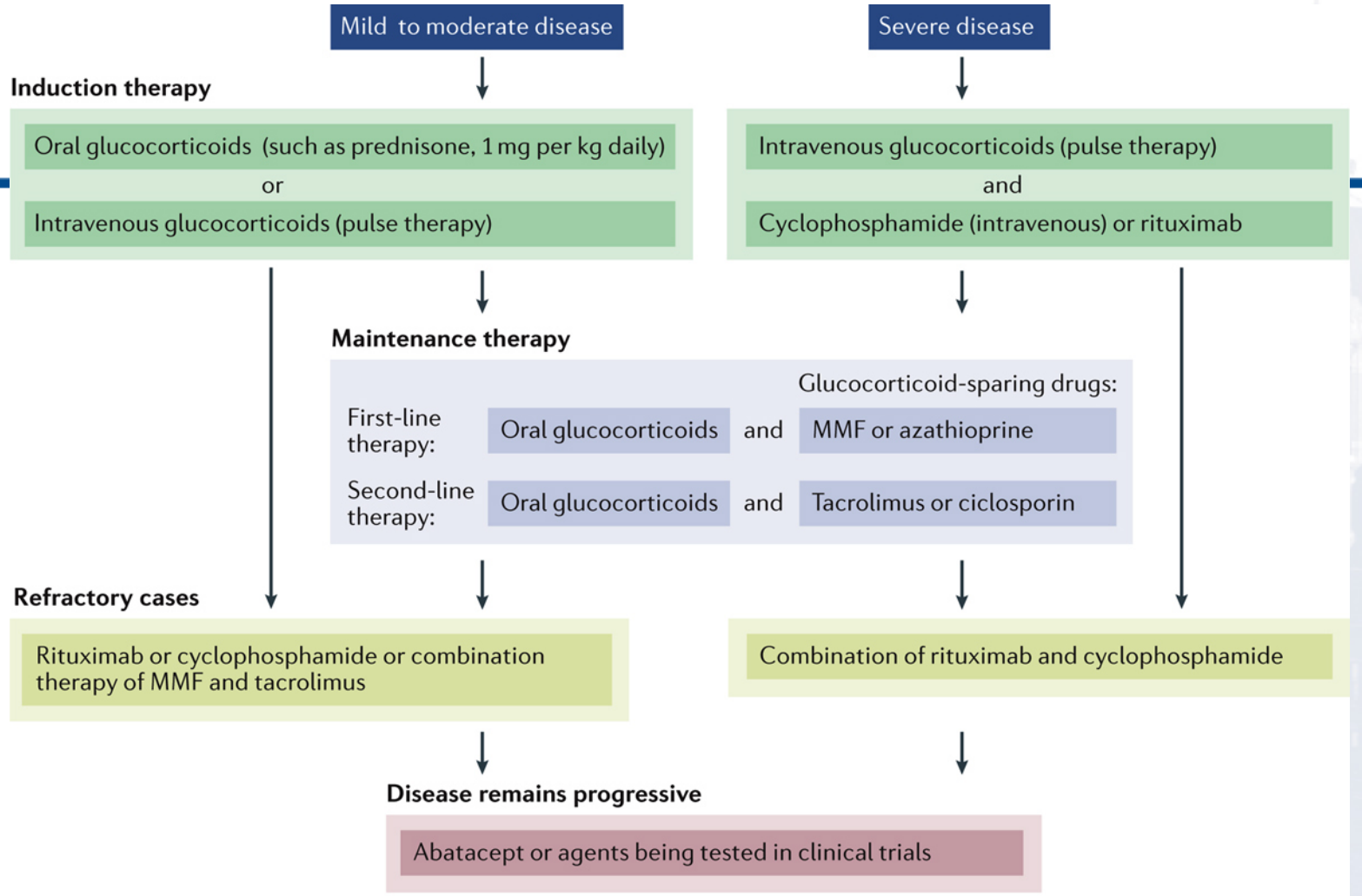
Proposed approach to treating myositis-associated interstitial lung disease



Adapted from Moghadam-Kia, S., Oddis, C. V. & Aggarwal, R. Update on the treatment of myositis. *Int. J. Clin. Rheumatol.* **9**, 505–518 (2014).
Oddis, C. V. & Aggarwal, R. (2018) Treatment in myositis
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2018.42

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WHAT ABOUT IBM CLINICAL TRIALS?

Arimoclomol :induces HSP-1 and helps with protein misfolding)

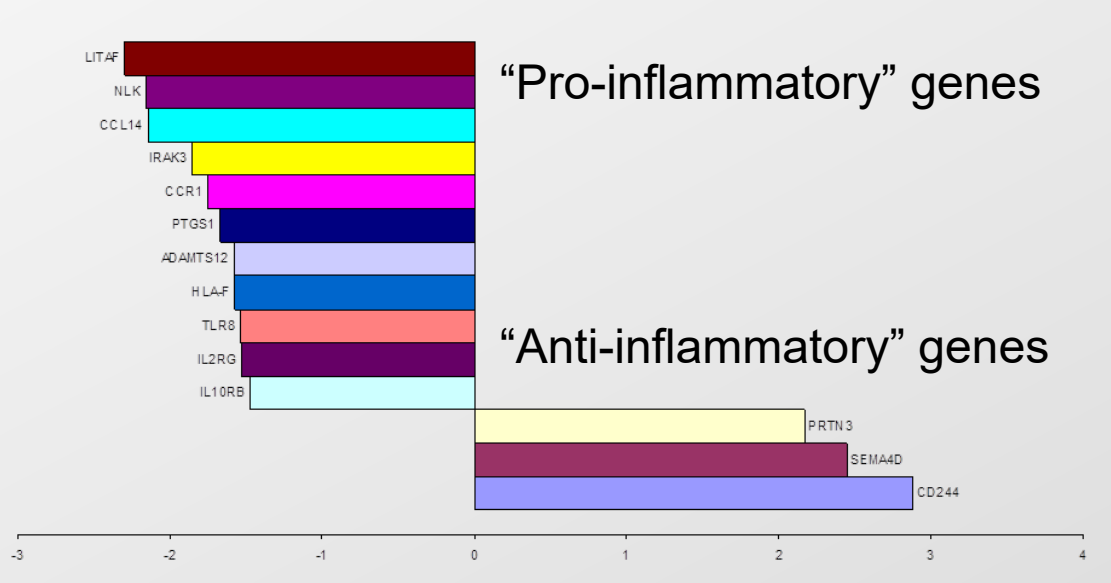
Rapamycin : restores aberrant autophagic (protein degradation) pathways by inhibiting mTOR (nutrient/energy/redox sensor that controls protein synthesis)

Pioglitazone: increases expression of AMPK and PGC-1α, resulting in increased mitochondrial biogenesis in muscle and improved exercise capacity and mitochondrial function

RESISTANCE EXERCISE

- Once thought to be harmful in myositis , exercise now should be part of a therapeutic regimen plan
- Anti-inflammatory; combats atrophy

Change in gene expression after 7 weeks of intensive exercise



- A total of 8 myositis patients underwent a 7-wk resistance exercise training program (3x/week) that resulted in improved muscle strength and increased maximal oxygen uptake (VO2max).
- Training also resulted in marked reductions in gene expression, reflecting reductions in proinflammatory and profibrotic gene networks, changes that were also accompanied by a reduction in tissue fibrosis.

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Nader GA et al 2010 Mol Med. 2010 Nov-Dec;16(11-12):455-64

Take home points

- New classification criteria provide a needed update to the 40 year old existing criteria; yet further updates are anticipated.
- True polymyositis is a rare disease. Be skeptical , exhaustive and thorough in your work-up if patients are referred to you for this diagnosis.
- Autoantibodies can help narrow down the myositis subtype and help with risk stratification
- Several pharmaceutical therapies are available (with novel agents currently being tested in clinical trials) and there are eminence based algorithms though no approved drugs outside of Repository Corticotropin Injection (adrenocorticotropic hormone gel) and prednisone.
- Exercise plays an integral part of recovery in myositis (shown on histologic, molecular and genetic levels) and its benefit should not be underestimated.

The Johns Hopkins Myositis Center Physician Team

www.hopkinsmyositis.org

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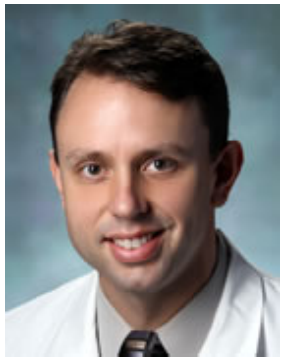

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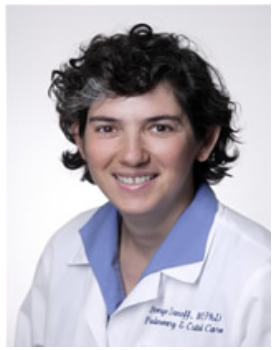

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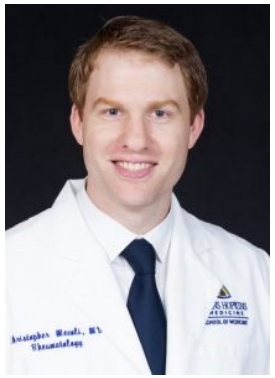

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CME EVALUATION & CREDIT INFORMATION

There will be no paper evaluation forms distributed at the course. Instead, you will receive an email with a link to an online evaluation on **Monday, September 28th, 2020**. In order to receive CME credit, you must complete the online evaluation and submit an electronic attestation form. The online evaluation will be available for **two weeks** following the course. This evaluation is necessary in order to meet CME requirements established by the Pennsylvania Medical Society. This information will not be shared with outside parties or companies and is for the sole use of CME evaluation purposes.

THE EVALUATION WILL BE OPEN FROM:

MONDAY, SEPTEMBER 28th – MONDAY, OCTOBER 12th, 2020.

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