Cleveland Clinic

R.J. Fasenmyer Center for Clinical Immunology

Primary Vasculitides: Best Practices and Future Advances

Giant Cell Arteritis: How do I Take Care of my Patients?

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Objectives

- Review current treatment
- Recognize disease chronicity
- Identify treatment-related morbidity
- Assess for vascular complications

MAYO CLINIC

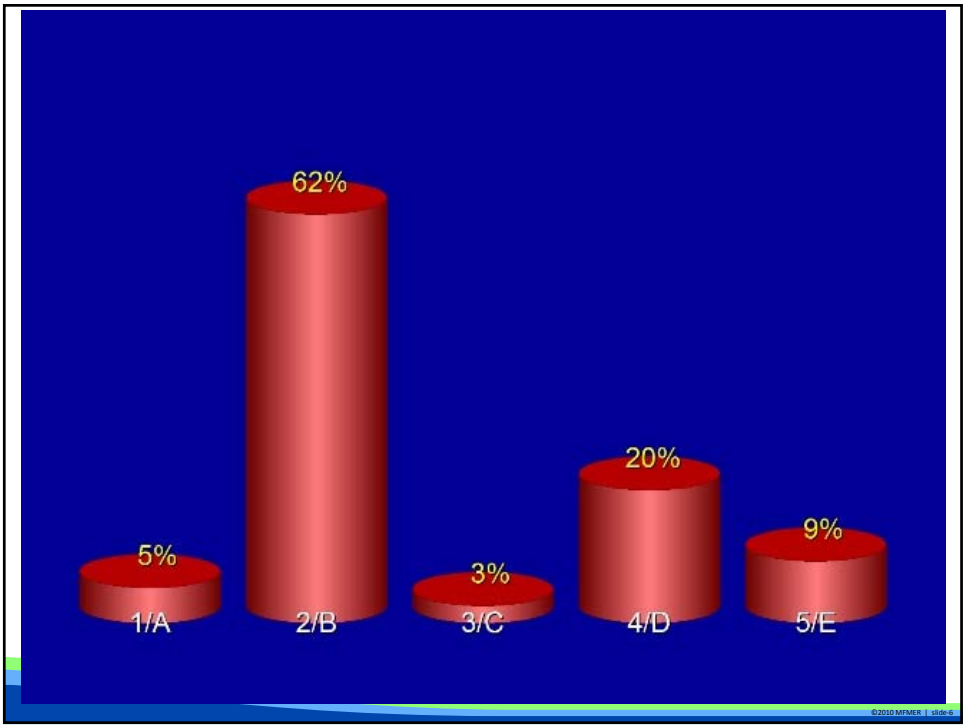
Question 1

- Mrs. Smith is a 73-year old white female
- Malaise and proximal myalgias
- Constant bitemporal headache for 3 weeks
  - Scalp tender; new skin sores
- Painless vision loss right eye
- Initial labs: ESR 36 mm/hr; CRP 23 mg/L
- Temporal artery biopsy is recommended

Question 1

What is the initial recommended treatment for this patient?

A. Prednisone 40 mg
B. Methylprednisolone intravenous 1000 mg
C. Prednisone 20 mg
D. Prednisone 60 mg
E. Methylprednisolone intravenous 100 mg



6-6-54 I think we must now regard this as a case of temporal arteritis, and is the first case observed at the Clinic, with loss of vision. We live, and learn. To date, 99 cases of temporal arteritis have been observed at the Clinic. Of this 99 cases, 12 cases showed unilateral loss of vision, and 23 cases showed bilateral loss of vision

Bayard T. Horton

Bayard T. Horton

The most serious complication I have encountered in this disease is sudden loss of vision and thus far I have seen no procedure which will prevent this from occurring. The use of dicumarol and heparin will not prevent it. Will Cortisone prevent such complications???

1949 - Horton's chart comments about the first patient ever treated with cortisone

MAYO CLINIC

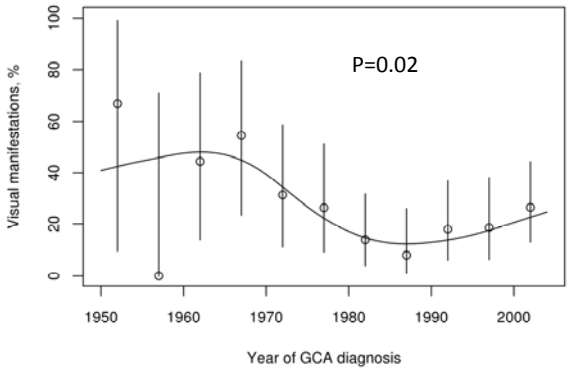
Glucocorticoids

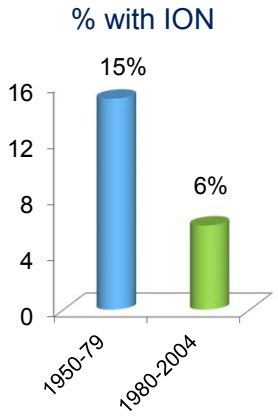
- Efficacy
  - Symptoms
  - Systemic inflammation
- Vision loss pre-GC: up to 60%
  - More recent data: 15-20%
- Predictors of vision loss
  - Jaw claudication
  - High inflammatory response is protective

Cid, M.C., et al. Circulation. 106, 1664-1671 (2002)
Nesher, G., et al. Medicine (Baltimore) 83, 114-22 (2004)

MAYO CLINIC

Prevalence of vision manifestations over 5 decades





Singh AG et al. J. Rheumatol. 42, 309-315 (2015)

MAYO CLINIC

Glucocorticoids

- High dose IV methylprednisolone
  - 1 gr daily x 3 days
  - Visual loss

Chan CC, et al. Br J Ophthalmol 2001;85(9):1061-4

- Prednisone
  - 40 - 60 mg daily for 4 weeks
  - Taper by ~10% of the dose every 2-4 weeks
  - Alternate day steroids not recommended

Birkhead NC, et al. J Am Med Assoc 1957;163(10):821-7
Hunder GG, et al. Ann Intern Med 1975;82(5):6
Mukhtyar, C. et al. Ann. Rheum. Dis. 68, 318-323 (2009)

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Glucocorticoids

- Do not reverse ION
- Prevent progression if partial visual loss
  - Protect contralateral eye
- Timing is critical
  - Fast track clinics
- On treatment
  - Beyond the 1st 2 weeks, risk is very low
  - 5 year probability of new loss of vision: 1%
    - progression of preexisting vision loss: 13%

Aiello PD et al Ophthalmology. 1993 Apr;100(4):550-5
Mukhtyar, C. et al. Ann. Rheum. Dis. 68, 318-323 (2009)

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Question 2

- Mrs. Smith returns
  - 3 month follow-up visit
- Reports: insomnia, weight gain, hyperglycemia
  - No symptoms of GCA or PMR
- Labs: ESR 8 mm/hr; CRP < 3.0 mg/L
- Prednisone dose is 20 mg daily
- While reviewing her treatment plan, she asks how long she will likely need to be on GC

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Question 2

- Following a diagnosis of GCA, how many patients are likely to be off of glucocorticoids at 2 years?

A. 0 – 20%
B. 20 – 40%
C. 40 – 60%
D. 60 – 80 %
E. 80 – 100%

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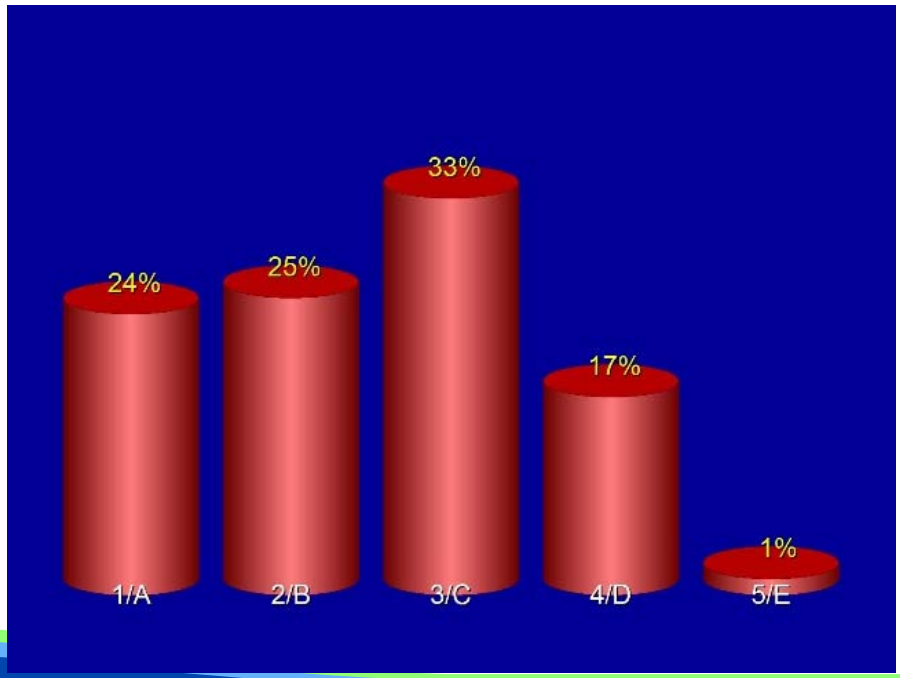
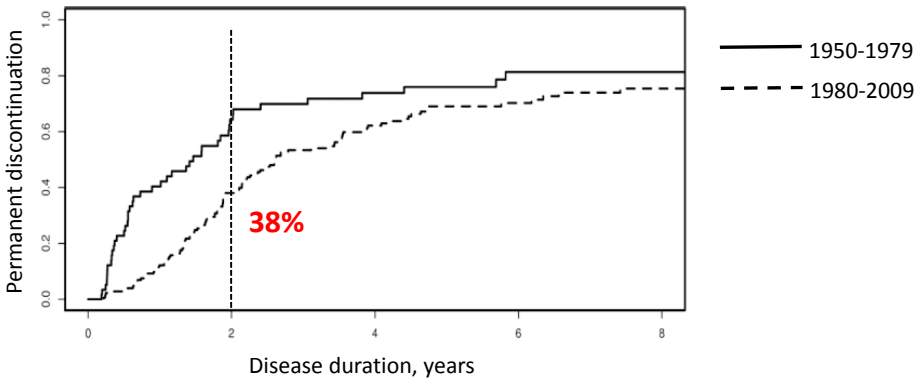


GCA – Olmsted Cohort

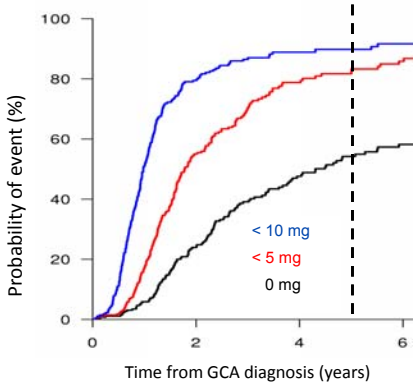
Median time to discontinuation (1980-2009) was 2.6 years



Chandran A et al. Clin Exp Rheumatol 2015

Treatment course

- Referral Cohort:
  - Discontinuation of GC
    - 24% by 2 years
    - 54% by 5 years



Labarca C, Koster MJ, et al. Rheumatology (Oxford). 2016 Feb;55(2):347-56

Retrospective Biopsy(+) Mayo Referral Cohort

	> 40 mg (N = 155)	≤ 40 mg (N = 109)	p-value
Age, years*	74.9 (±7.9)	75.0 (±7.5)	0.81
Female	110 (71%)	86 (79%)	0.15
Weight, kg*	68.8 (14.9)	65.0 (15.5)	0.01
Prednisone dose, mg/kg*	0.9 (0.2)	0.6 (0.2)	< 0.001
Headache	110 (72%)	67 (63%)	0.10
Jaw Claudication	86 (56%)	52 (48%)	0.21
Polymyalgia rheumatica	65 (43%)	56 (52%)	0.15
CRP, mg/L †	63.0 (21.0, 111.0)	49.0 (23.0, 81.0)	0.27

*mean (±SD), †median (IQR)

Labarca, Koster et al. Rheumatology (Oxford) 2015

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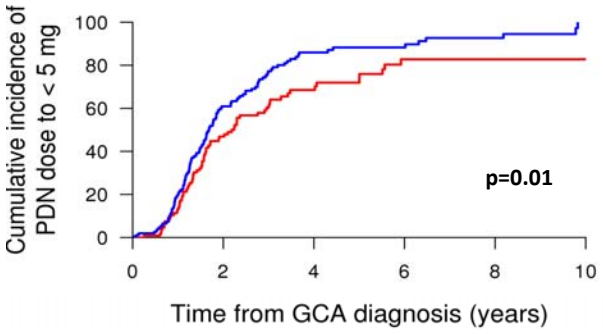

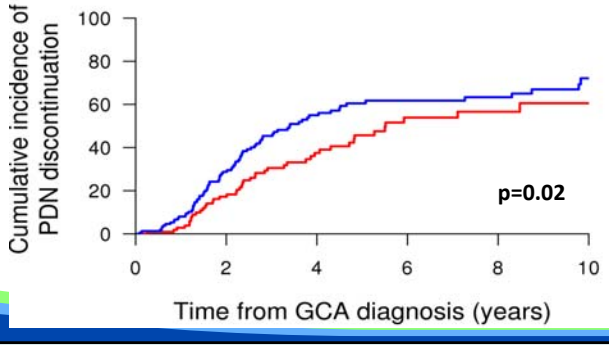

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Glucocorticoids - Limitations

- Chronic vasculopathy
- Relapses
- Treatment-related morbidity
- Vascular complications

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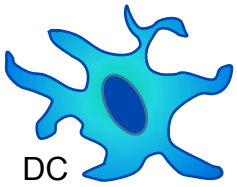
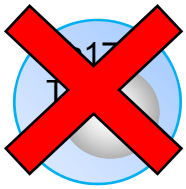
IL-17 Axis



DC

Glucocorticoids

IL-23



IL-17

Deng J et al. Circulation. 2010;121:906-915.

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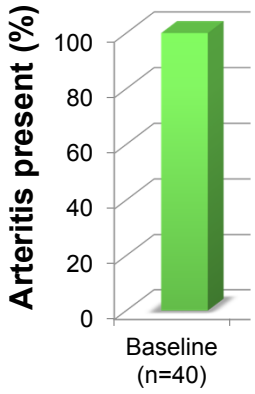
Prospective 2nd Biopsy study



Time from initial diagnosis to second TABx

Maleszewski J et al. Mod Pathol. 2017 Mar 3

Question 3

- Mrs. Smith returns
  - 12 month follow-up visit
- Relapse 2 months prior on 10 mg/day
  - Prednisone dose increased to 20 mg/day
- Current visit:
  - Prednisone dose 12.5 mg/day
  - Malaise and PMR symptoms
  - No cranial symptoms
  - CRP 53 mg/L

Question 3

- What percentage of patients with GCA experience a relapse?

A. 0%
B. 10-20%
C. 30-40%
D. 80-90%
E. It depends

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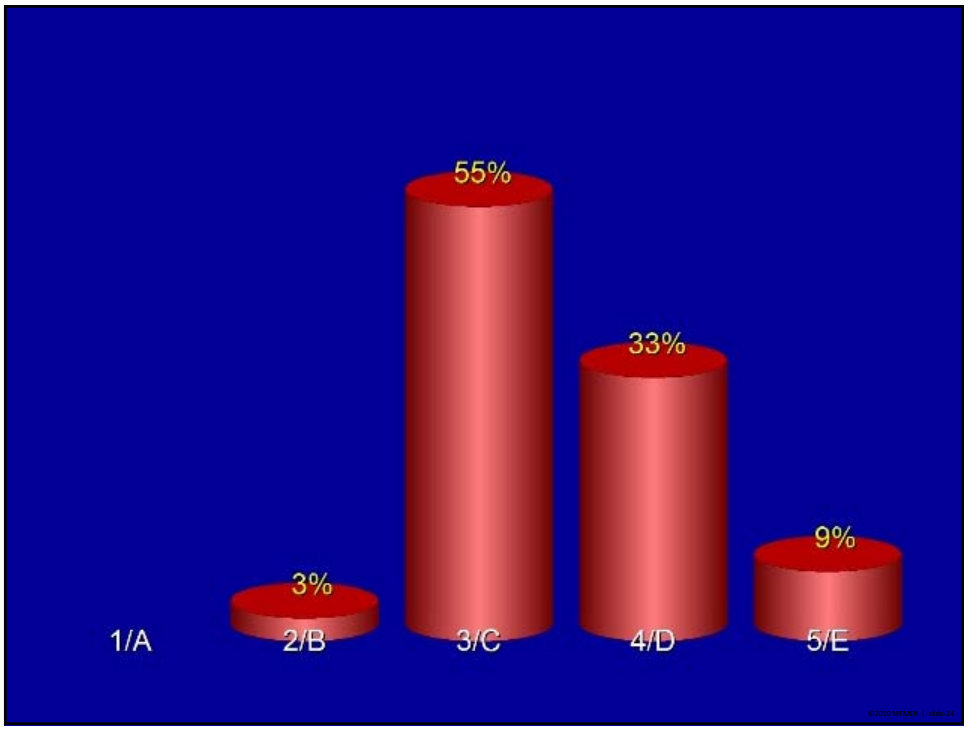
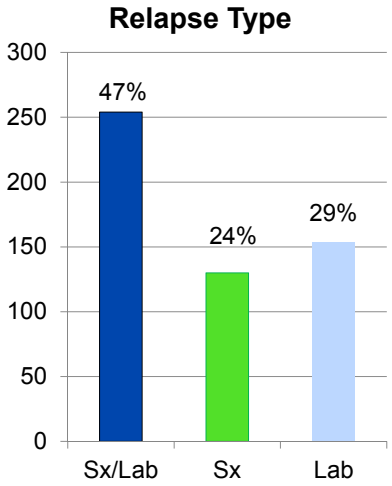


Mayo Biopsy (+) Cohort - Relapse

Relapse	Patients, N (%)
0	73
1	80
2	51
≥3	82

74% of patients relapsed

30% had ≥ 3 relapses



Labarca C, Koster MJ, et al. Rheumatology (Oxford). 2016 Feb;55(2):347-56

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Relapses – other studies

- Spanish cohort
  - Relapses seen in ~41%
- Reggio Emilia cohort
  - Relapses seen in ~37%
- Relapse symptoms
  - PMR
  - Headache
  - Constitutional symptoms
  - No vision loss

Martinez-Lado et al. Medicine 2011;90: 186-193

Restuccia G et al Medicine (Baltimore). 2016 May;95(19):e3524

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Relapses – other studies

- Prospective, multicenter, longitudinal study
- Relapse: 34%
  - Relapsers tend to relapse
  - Headache, PMR
  - 2% had new vision symptoms
- Lab: Normal ESR & CRP in 21% of relapses
- Median prednisone dose at time of relapse: 7.5 mg

Kermani T et al. J. Rheumatol. 2015 Jul;42(7):1213-7.

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Relapse - Predictors

Characteristic	No Relapse	Low relapse	High relapse	p-value
Female	46 (63%)	102 (79%)	65 (78%)	0.03
Hypertension	25 (35%)	58 (45%)	50 (60%)	0.01
Diabetes	2 (3%)	11 (9%)	12 (15%)	0.04

- Other predictors of relapse
  - Fever >38^{0}C
  - Severe inflammation on biopsy
  - Anemia (Hb <12 g/dL)

Labarca C, Koster MJ, et al. Rheumatology (Oxford). 2016 Feb;55(2):347-56
Restuccia G et al Medicine (Baltimore). 2016 May;95(19):e3524
Martinez-Lado et al. Medicine 2011;90: 186-193

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Relapses - management

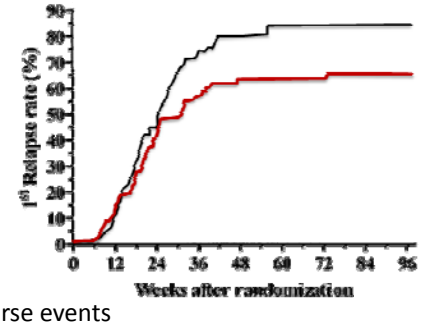
- Exclude mimics
- Increase GC's
  - Depends on relapse
  - High dose if ischemic complications
  - 5-10 mg increase may be sufficient
- Imaging
  - Only if new vascular signs/symptoms

Mukhtyar, C. et al. Ann. Rheum. Dis. 68, 318-323 (2009)
Dasgupta, B. et al. Rheumatology (Oxford). 49, 1594-1597 (2010)

MAYO CLINIC

Methotrexate

- Metaanalysis of 3 randomized trials
  - 84 on MTX - 77 on placebo
  - Mean dose about 11mg/wk
- MTX reduced:
  - Risk of 1st relapse by 35%
  - Risk of 2nd relapse by 51%
  - Exposure to GC's
  - No reduction in GC-associated adverse events



Mahr A et al Arthritis Rheum. 2007 Aug;56(8):2789-97.

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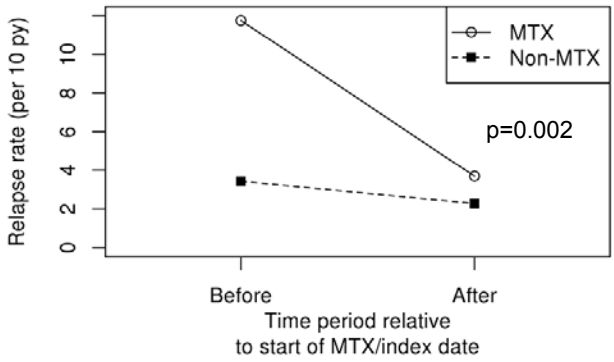
Mayo GCA referral cohort

- 84 GCA patients on MTX, 84 GCA controls



Koster et al. Arthritis Rheumatol 2016

Adjunctive therapy

- GCA associated with increased risk of coronary and cerebrovascular events
- Low-dose Aspirin
  - Retrospective data; controversial
  - Decreased risk of ischemic events
- Statins
  - No GC-sparing effect

Amiri N et al Rheumatology (Oxford). 2016 Jan;55(1):33-40
Mukhtyar, C. et al. Ann. Rheum. Dis. 68, 318-323 (2009)
Bienvenu B. Rev Med Interne. 2016 Mar;37(3):154-65.

GC-related morbidity

- Adverse effects in up to 86%
- Recent retrospective cohort study (>5000 pts)
- Increased risk (RR 1.2-2.4) of
  - Osteoporosis
  - Glaucoma
  - Hospitalization
  - Serious infections
  - Diabetes
  - Fracture

Proven A et al. 2003 Oct 15;49(5):703-8
Wilson JC et al. Semin Arthritis Rheum. 2016 Oct 13

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GC-related morbidity

- Infection risk increased 50%
  - First 6 months
  - 48% of patients with at least 1 infection
  - LRTI, UTI, Sepsis
- Pneumocystis pneumonia
  - Mean hospital stay – 21 days
  - Mortality 30 %

Durand M et al. Arthritis Care Res (Hoboken). 2012 Apr;64(4):581-8
Kermani TA et al. Arthritis Care Res (Hoboken). 2011 Jan 14

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Vascular Complications

- Large-vessel vasculitis under-recognized
- Careful history and examination
  - Vascular system: pulses, bruit
  - BP measurement
  - Vascular Laboratory studies
- Vascular Imaging

Grayson PC, et al, VCRC. J Rheumatol. 2012 Feb;39(2):303-9

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Non-invasive Vascular Lab - Doppler studies

Referral Diagnosis: Giant Cell Arteritis

Laboratory Interpretations:

RIGHT LOWER EXTREMITY: Normal Doppler signals. Segmental pressures are slightly greater than 200 mmHg.

LEFT LOWER EXTREMITY' Normal Doppler signals. Segmental pressures are slightly greater than 200 mmHg.

FINAL IMPRESSION: Upper extremity pressures are low, but symmetric. Normal lower extremity Doppler signals and elevated pressures. The lower extremity pressure are likely accurate given the normal Doppler signals.

No prior studies available for comparison.

Paul W. Wennberg, M.D. 5-3649

Doppler Signal

	Right	Left
Common femoral	Triphasic	Triphasic
Superficial femoral	Triphasic	Biphasic
Popliteal	Biphasic	Biphasic
Posterior tibial	Biphasic	Biphasic
Dorsalis pedis	Biphasic	Biphasic

Systolic Blood Pressure

	Right	Index	Left	Index
Arm	84[1]		78[1]	
Thigh	205[2]		210[2]	
Calf	228[2]		217[2]	
Ankle PT	208[2]		204[2]	
Ankle DP	214[2]		200[2]	

Exercise Performed: MPH 10% grade:
Resting Heart Rate: bpm
Max. Heart Rate: bpm
Onset of Symptoms '"/ yards

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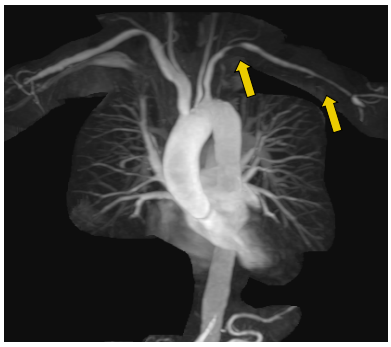
GCA
Upper Extremity Arterial Involvement

- Frequency by imaging:
  - PET - 74%
  - CT angio - 42%
  - Ultrasound - 30%
- Symptoms < 10%

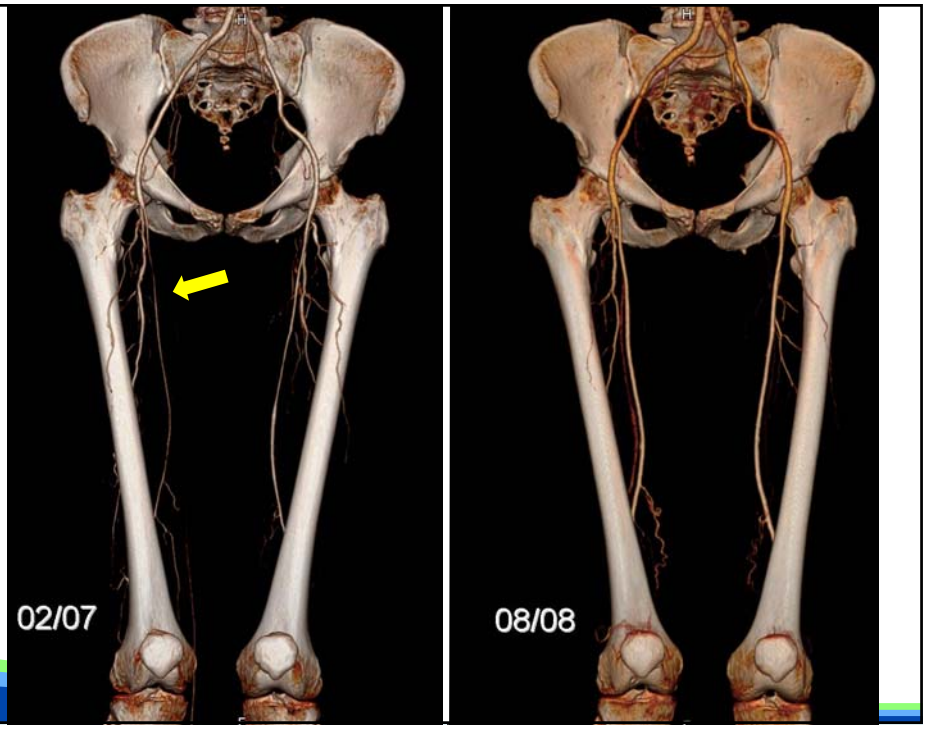


Schmidt WA et al. Rheumatology (Oxford). 2008 Jan;47(1):96-101

Ghinoi A et al. Rheumatology (Oxford). 2012 Apr;51(4):730-4

Prieto-Gonzalez S, et al. Ann Rheum Dis 2012;71:1170–6

MAYO CLINIC



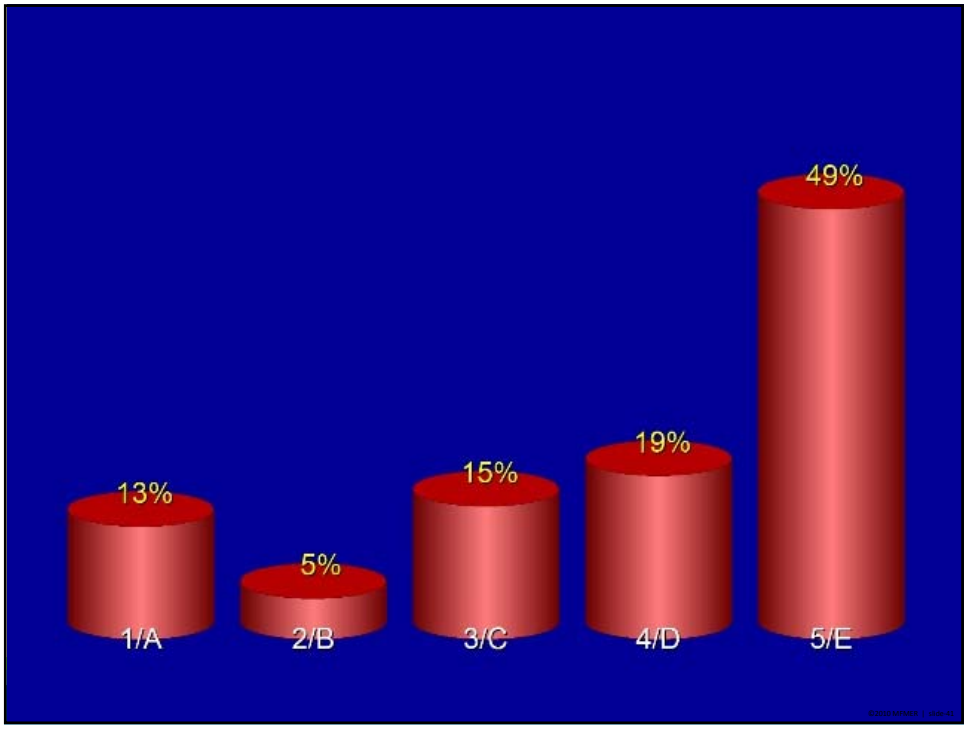
Question 4

- Mrs. Smith returns
  - 6 year follow-up visit
  - Clinical & lab remission
  - Exam is normal
- Co-morbidities: HTN, osteoporosis
- Has been off treatment for 2 years
- Active, enjoys travelling & golfing

Question 4

- Which of the following would you recommend?

A. Transthoracic echocardiogram
B. Chest CT scan
C. Chest X-ray
D. Chest MR angiogram
E. No further testing



Aortic aneurysm

- Thoracic Aortic Aneurysms
  - 17.3 – fold increased risk
  - 6.6 – fold increased risk
  - 12% - 33% incidence (10 yr F/U)
- No consistent clinical predictors
  - Aortic Regurgitation

Evans JM et al. Ann Intern Med 1995;122(7):502-7
Robson JC. Ann Rheum Dis. 2013 Oct 4
Kermani TA, Warrington KJ, et al. Ann Rheum Dis. 2012 Dec 19.
García-Martínez A, et al Ann Rheum Dis. 2013 Jul 19

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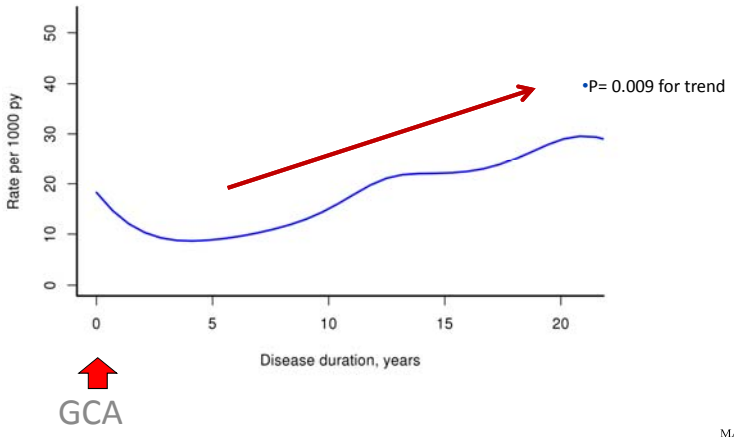
Aortic Aneurysm - Mainly a late complication when the disease is clinically in remission



Kermani TA, Warrington KJ, et al. Ann Rheum Dis. 2012 Dec 19.

Aneurysm screening

- Expert recommendations:
  - Yearly Chest X-ray
  - Echocardiogram
  - CT or MR
- Baseline CT scan or MRI (ACC/SVM)
  - Frequency ?
- To detect one previously unknown TAA/TAD
  - 5 to 10 patients with GCA would need aortic imaging

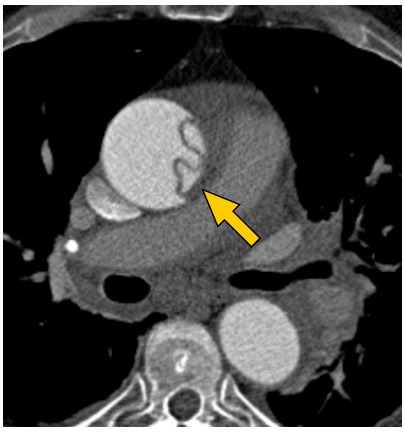
Salvarani C et al Lancet. 2008 Jul 19;372(9634):234-45

Mackie SL et al. Ann Rheum Dis. 2012 Dec 22

Hiratzka LF, et al. J Am Coll Cardiol 2010;55:e27–129

Bienvenu B. Rev Med Interne. 2016 Mar;37(3):154-65

GCA: Aneurysm/Dissection - increased mortality



Unknown:

- Rate of progression
- Optimal timing of repair

Conclusions

- GCA is a chronic, systemic vasculopathy
- Glucocorticoids
  - Reduce vision loss
  - Significant limitations & morbidity
- Great unmet need in LVV
  - Targeted, effective therapy
  - Less toxicity

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Questions and Discussion

Division of
RHEUMATOLOGY