

Raynaud's Phenomenon and Digital Ischemia

Laura K. Hummers, MD, ScM
Associate Professor of Medicine
Co-Director, Johns Hopkins Scleroderma Center
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- All of the medications in this presentation are discussed for use for non FDA-approved indications

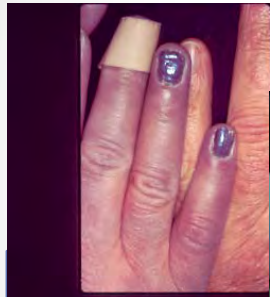
Goals

- Review the factors that increase risk for CTD among those with RP
- Briefly discuss the relevant pathophysiology of Raynaud phenomenon and digital ischemia in scleroderma
- Review unique situations in scleroderma
- Discuss established therapies and those currently in trial
- Review possible treatment algorithms

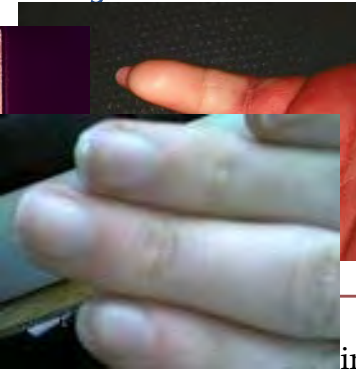
Raynaud's Phenomenon



What is and is not Raynaud's

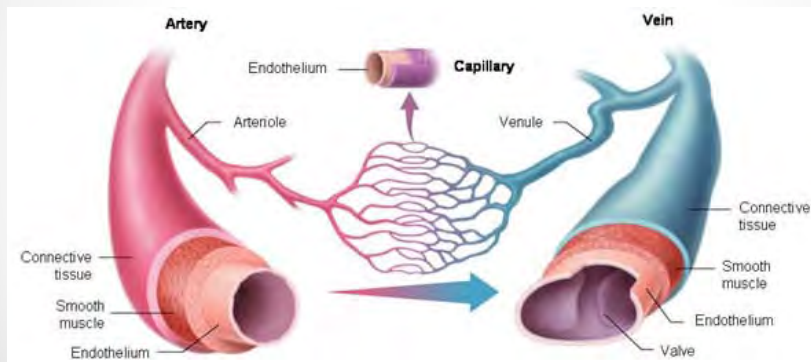


- Palmar
- Symmetric
- Sharp Demarcation

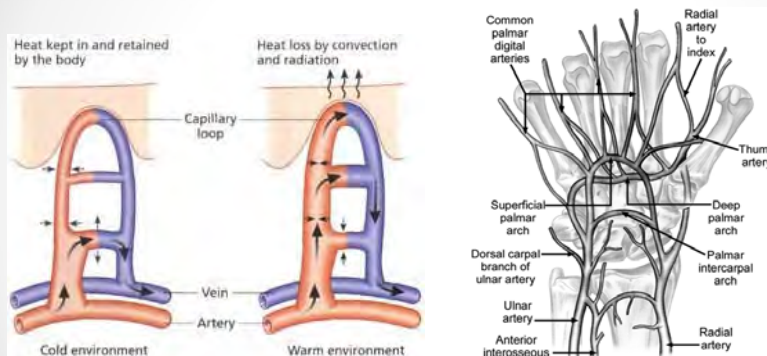


- Fingernails only
- Unilateral

Blood Vessel Structure



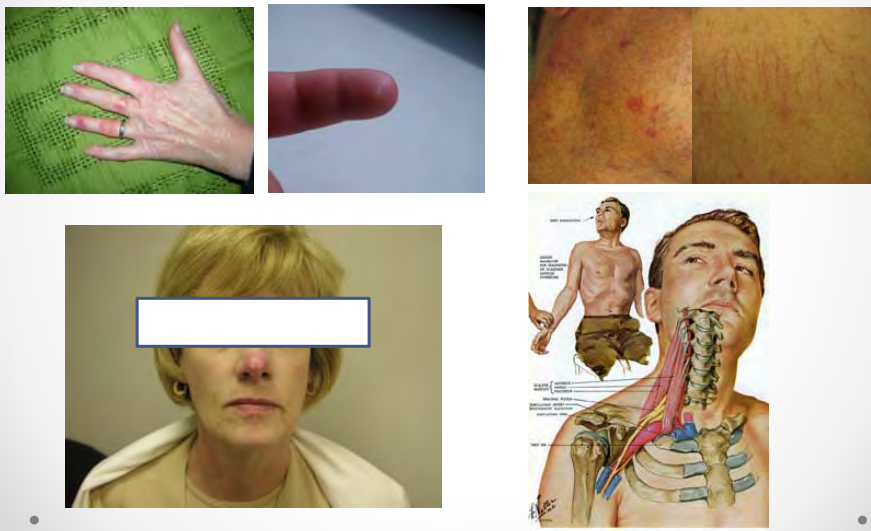
Peripheral Vascular Disease



Secondary Raynaud's Phenomenon/Mimics-Differential Diagnosis

- Immune: Autoimmune Disease (Scleroderma, Lupus, Myositis, UCTD)
- Trauma: Hand-Arm Vibration Syndrome
- Mechanical: Thoracic Outlet Syndrome
- Proteins: Cryoglobulins; Cryofibrinogens
- Neurogenic: Carpal Tunnel Syndrome
- Hormones: Estrogens
- Toxins/Drugs/Vasoconstrictors: Smoking (TAO), sympathomimetics, chemotherapy, polyvinyl chloride, cocaine (levamisole)
- Vascular disease: Diabetes, Vasculitis, etc.

Physical Exam Findings



Predictors of Development of CTD/Scleroderma

- Abnormal nailfold capillaries
 - Nailfold dilatation/Dropout (avascular areas)
 - **HR 14-18** for development of SSc
- Autoantibodies
 - 30% risk of CTD if just ANA positive
 - **HR 10-23** for SSc with just ANA positivity
- Both abnormal NFC and SSc antibody
 - **HR 60**
- Negative ANA, normal nailfold capillaries have high NPV (>95%)

Moizadeh P et al. *Clinic Rev Allerg Immunol* (2012) 43:249-55
 Zeigler S. *Scand J Rheumatol* (2003) 32(6): 343-47
 Ingegnoli F et al. (2010) *Rheumatol (Oxford)* 49(4):797-805
 Koenig et al. (2008) *Arthritis Rheum* 58 (12):3902-3912

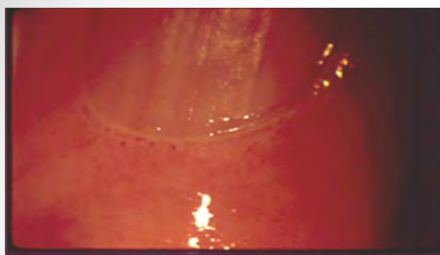
Classification of Systemic Sclerosis

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (<i>sufficient criterion</i>)	–	9
Skin thickening of the fingers (<i>only count the higher score</i>)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions (<i>only count the higher score</i>)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease (<i>maximum score is 2</i>)	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) (<i>maximum score is 3</i>)	Anticentromere	3
	Anti-topoisomerase I	
	Anti-RNA polymerase III	

van den Hoogen et al. Arthritis Rheum. 2013 Oct 3.

Nailfold Capillary changes



Method:

Drop of Immersion Oil on Nailfold

Ophthalmoscope at +40 diopters (10x magnification)

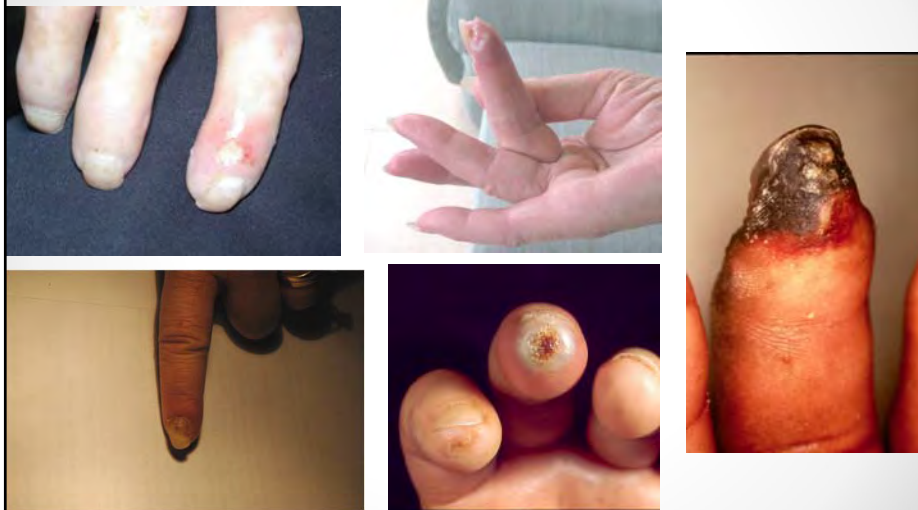
OR

Dermatoscope



Complications

Digital Ischemic Ulcers



Risk Factors of Digital Ulcerations

- Digital loss (10%)
 - Anti-centromere antibody
 - Multiple prior digital ulcerations
 - Large vessel involvement (ulnar artery)
 - Older age, long disease duration, PAD, HLD
- Ulcers (50%)
 - Centromere and topo (not Pol III)
 - Smoking?

Caramaschi P et al. J Rheumatol. 2012 Aug; 39(8): 1648-53
 Steen V et al. Rheumatology 2009; 48:iii19-24=

Acute digital ischemia



- Ischemic?
 - Severe pain
 - Location
 - Surrounding hyperemia
- Therefore:
 - At risk for further tissue loss and continued pain
 - Pain triggers sympathetic response
 - At risk for further ischemia

- ❖ 58% of scleroderma patients with digital ulcerations
- ❖ 11% with severe disease (gangrene, amputation)

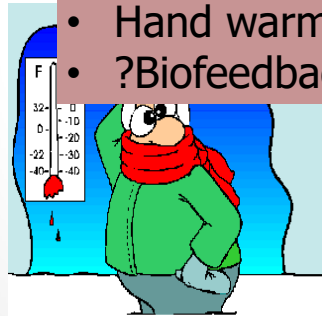
Non (or less) Ischemic Ulcers



Management

Behavior Modification

- Avoid
- Stress
- Layers
- Ambient temperature
- Hand warmers
- ?Biofeedback



Local Care

Cleansing

- Warm soapy water soaks a few times per day

Protection

- Covering with bandage, wrap if going to be using hands

Infection

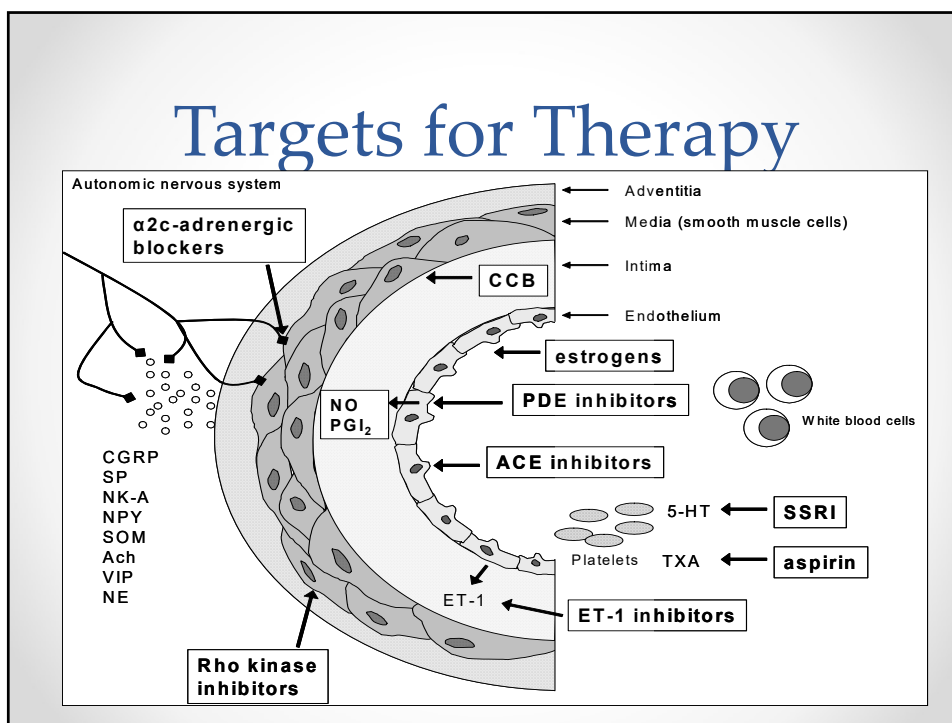
- Antibacterial ointment (mupirocin)

Pain

- Topical Anesthetics (lidocaine)



Targets for Therapy

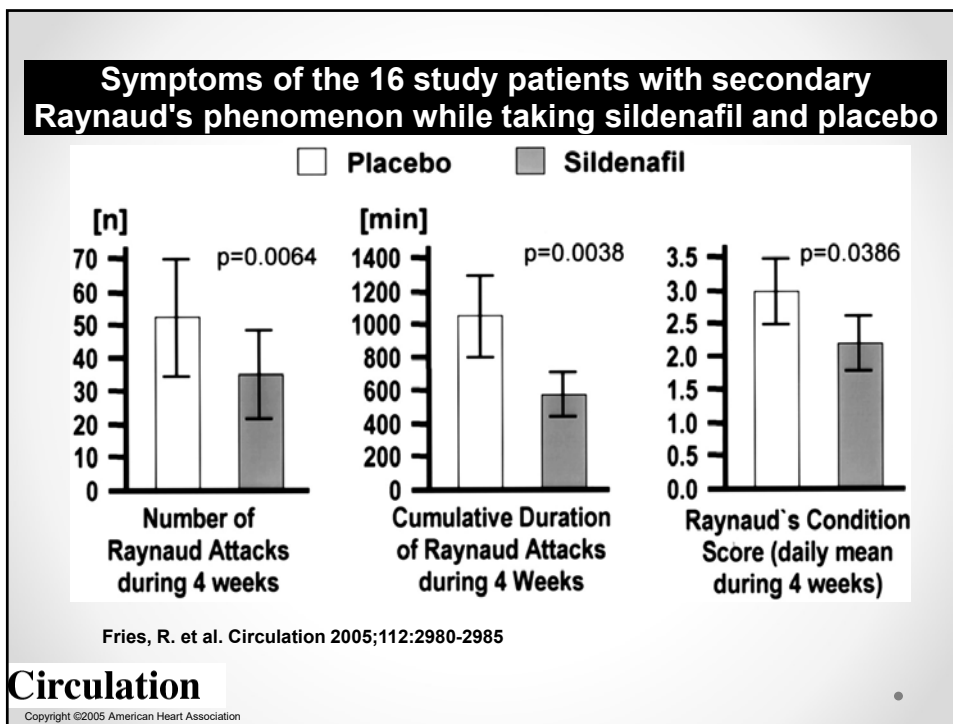


Calcium Channel Blockers

All calcium channel blockers vs. placebo

- (6 trials): Reduction of frequency of attacks in a 2-week period of **-8.31** (95% CI: -15.71, -0.91)
- (3 trials): Reduction in severity of ischemic attacks of **-0.69** (95% CI: -1.21, -0.17)

Thompson et al., 2001



Oral Tadalafil

- Scleroderma patients off all treatment for Raynauds (N=39)
- 20 mg of tadalafil daily for 4 weeks compared with placebo
- Medication was found to be well tolerated

	Baseline	Tadalafil	Placebo	Difference
RCS	3.76	2.43	2.53	NS
Raynauds Frequency	2.93	2.08	2.1	NS
Raynauds Duration	53.4	40.6	47	NS

Schiopu E et al. *J Rheum.* 2009

Tadalafil – ACR 2010

- Randomized controlled trial, tadalafil vs. placebo
- 53 scleroderma patients treated for 8 weeks
- Baseline treatments remained the same
- Improvements seen in duration and frequency of Raynaud and in RCS
- 14/18 had healing of digital ulcers compared with 5/13 in placebo arm
- Fewer new ulcers in tadalafil group than placebo (1 vs. 9)

• Agarwal et al. Plenary session III, ACR national meeting October, 2010

Bosentan

- Dual endothelin receptor antagonist, FDA approved to treat pulmonary hypertension
- 2 Large, Phase III studies in patients with digital ulcers secondary to scleroderma (RAPIDS1, RAPIDS2, open label extension)
- 312 patients total
- Fixed dose titration 62.5 BID to 125 BID
- Primary outcome: # new digital ulcers; time to healing (RAPIDS2)
- RAPIDS 1: 2.7 vs. 1.4 new ulcers at 16 weeks ($p=0.178$); 2 post hoc analyses ($p<0.01$)
- RAPIDS2: 2.7 vs. 1.9 new ulcers at 24 weeks ($p=0.04$)

Seibold JR, Matucci-Cerinic M, Denton CP et al. Ann Rheum Dis 2006;65(Suppl II):9

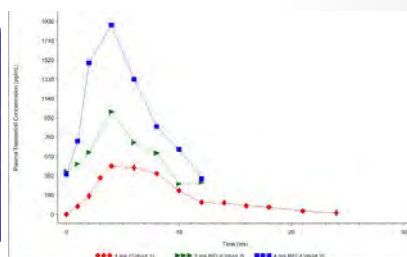
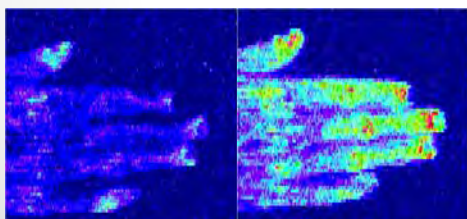
Korn JH, Mayes M, Matucci-Cerinic M et al. Arthritis Rheum 2004;50:3985–93.

Digital Ulcers prevention with mAcitentan in systemic scLerosis

- 285 patients, 75 centers, 30 countries
- 2 active doses vs. placebo (1:1:1); parallel
- Macintentan is a dual, tissue targeting ERA
- Inclusion:
 - Baseline ulcer + history of ulcers in past 6-12 months
- Outcomes:
 - # of new digital ulcers at 16 weeks
- Trial ended early due to lack of efficacy
- No adverse safety signals

Oral Treprostenil

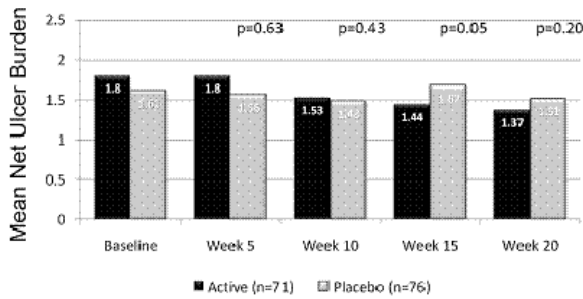
- Long acting, chemically stable, prostacyclin analogue
- Phase I/IIb study



A. Shah; poster presentation at EULAR 2010; Rome, Italy

Oral Treprostenil

- 148 scleroderma patients at 27 centers
- Randomized, double-blind, placebo-controlled, multicenter study
- At 20 weeks, mean net ulcer burden was significantly lower in the active group compared with the placebo group (p=0.05)
- Other clinical outcomes were similar between groups



Seibold J et al; Digital Ischemic Ulcers in Scleroderma Treated with Oral Treprostinil Diethanolamine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. [abstract]. Arthritis Rheum 2011;63 Suppl 10 :2483

Why the discrepancies?

- How to evaluate an ulcer?

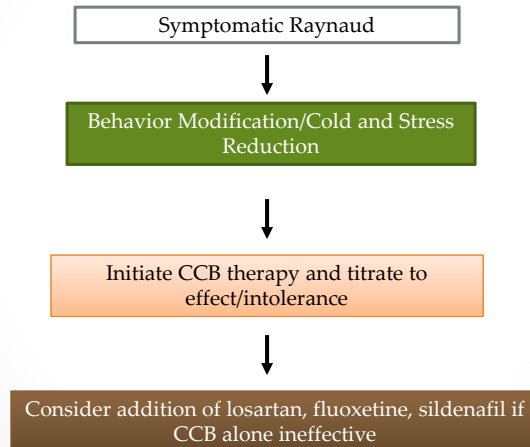


- Is this an ulcer?
- Is it "active"?
- Is it healing?

Summary of Agents

- Calcium Channel blockers: Nifedipine, amlodipine, felodipine
- Nitric oxide: Nitrates (?topical)
- Phosphodiesterase inhibitors:
 - Sildenafil, Tadalafil, Udenafil, Vardenafil
- Selective Serotonin Reuptake inhibitors: Fluoxetine
- Angiotensin receptor inhibitor: Losartan
- Endothelin-1 inhibitor: Bosentan, Ambrisentan, Macintentan
- Prostacyclins: epoprostenol, treprostinil, iloprost
- sGC stimulators: Riociguat
- Other: Statins, ASA, pentoxifyline, Botulium toxin A

Treatment Algorithm- RP



Management for Raynaud/Digital Ischemia: Evidence

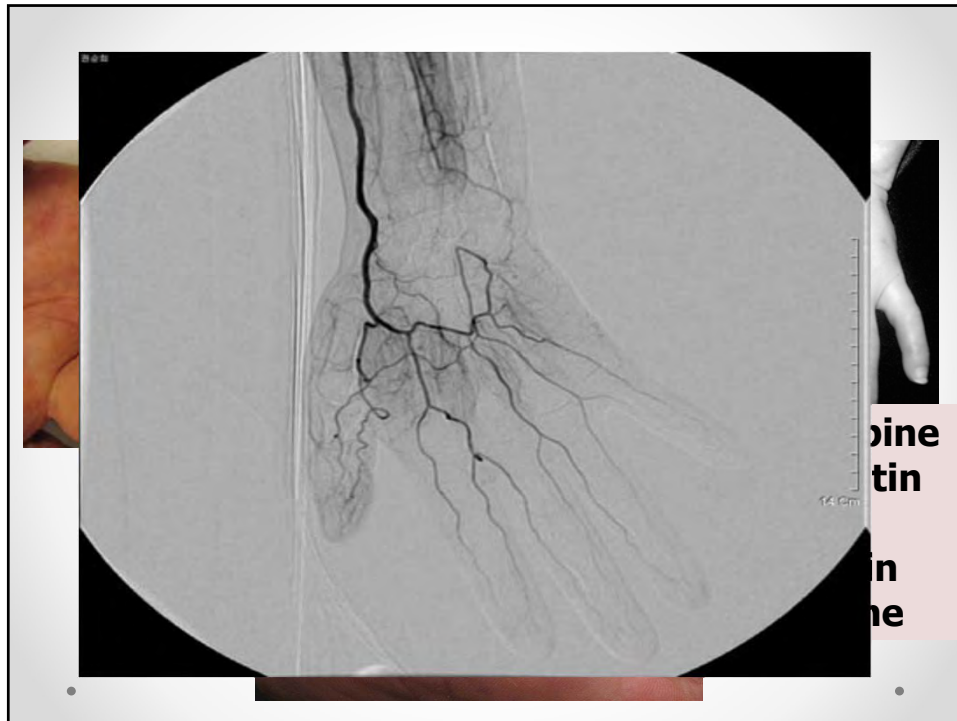
Agent Class	Type of Evidence	Positive outcomes
Calcium channel blockers	RCT	Raynaud frequency and duration
Endothelin receptor antagonists	RCT	Reduction in new digital ulcerations
IV prostaglandins	RCT	Raynaud frequency, duration, severity; healing of ulcers
Phosphodiesterase inhibitors	RCT/conflicting	Raynaud frequency, duration, Raynaud condition score, ulcer healing
Surgical sympathectomy	Case reports/series	Ulcer healing

Huisstede BM, et al. Arch Phys Med Rehabil. 2011 Jul;92(7):1166-80.
Galluccio F, Matucci-Cerinic. Autoimmunity Reviews. 10 (2011) 241-3.
Thompson et al. Rheumatology. 2005; 44:145-50.

Shenoy PD et al. Rheumatology 2010; 49; 2420-8
Schiopu E et al. J Rheumatol 2009; 36:2264-8
Wigley FM et al. Ann Int Med 1994; 120:199-206

Digital Ischemia/Ulcers

- **Acute Management**
 - Pain control (narcotics)
 - Aspirin
 - Epoprostenol
 - Peripheral IV
 - 0.5-2 ng/kg/min
 - 6 hours daily
 - 3-5 days
 - Inpatient/outpatient
 - Consider digital sympathectomy
- **Chronic Management**
 - Topical antibiotics
 - With lidocaine
 - Soaking
 - Pain control
 - Adjust chronic meds
 - Titrate CCB
 - Add second line agent
 - ERA
 - PDE5
 - Watch for additive side effects



Conclusions

- Raynaud is a common phenomenon
- History/exam can help distinguish primary vs. secondary and can identify those at risk for early scleroderma and Raynaud mimics
- Patients with CTD have more severe phenotype due to combination of vasospasm and intrinsic vessel disease
- Numerous potential targets for therapy

