Wound/Skin Care: Impact of Autoimmune Disorders & Associated Pharmacologic Agents

Niveditha Mohan, MBBS

Associate Professor, University of Pittsburgh

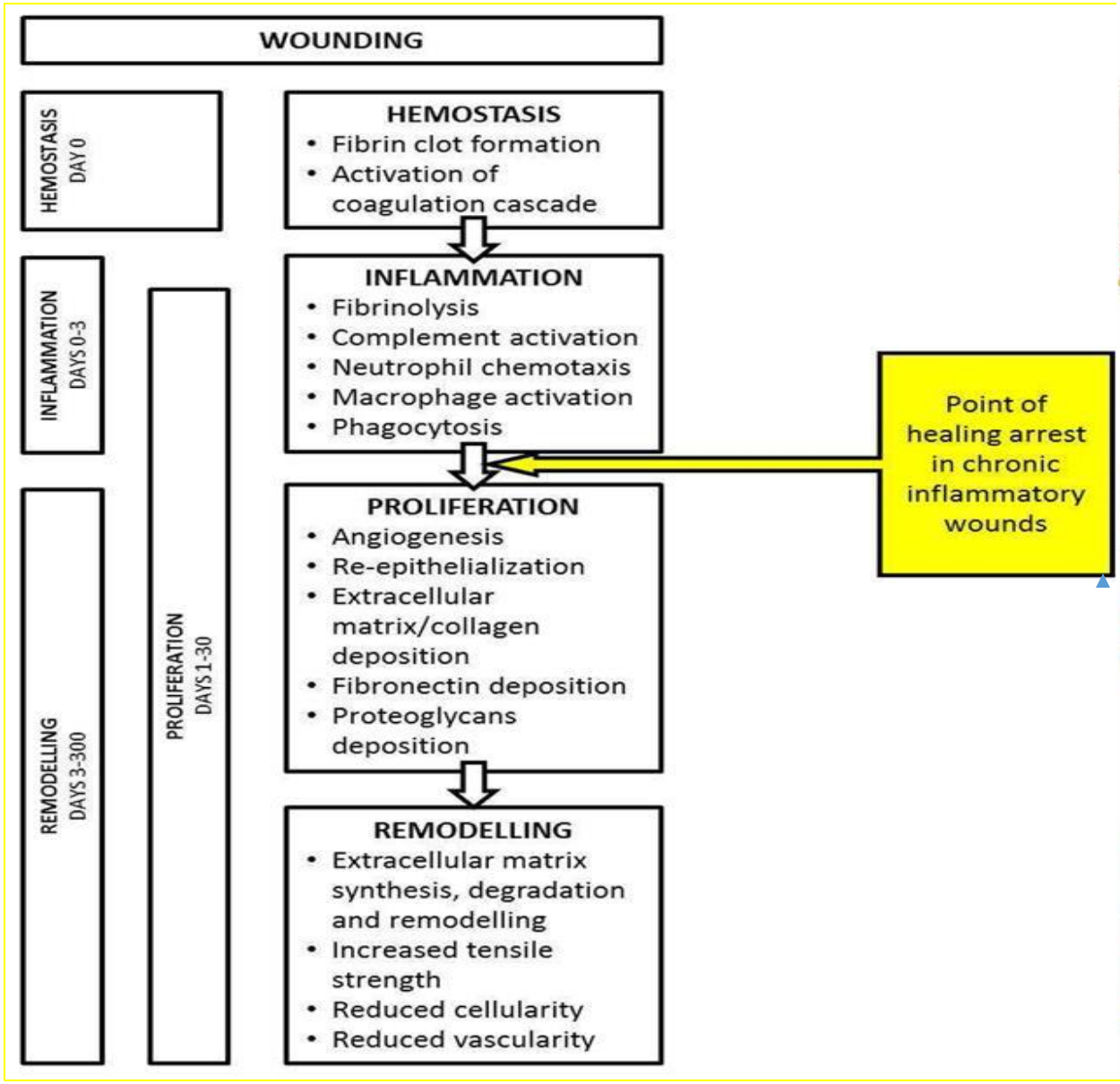
Objectives

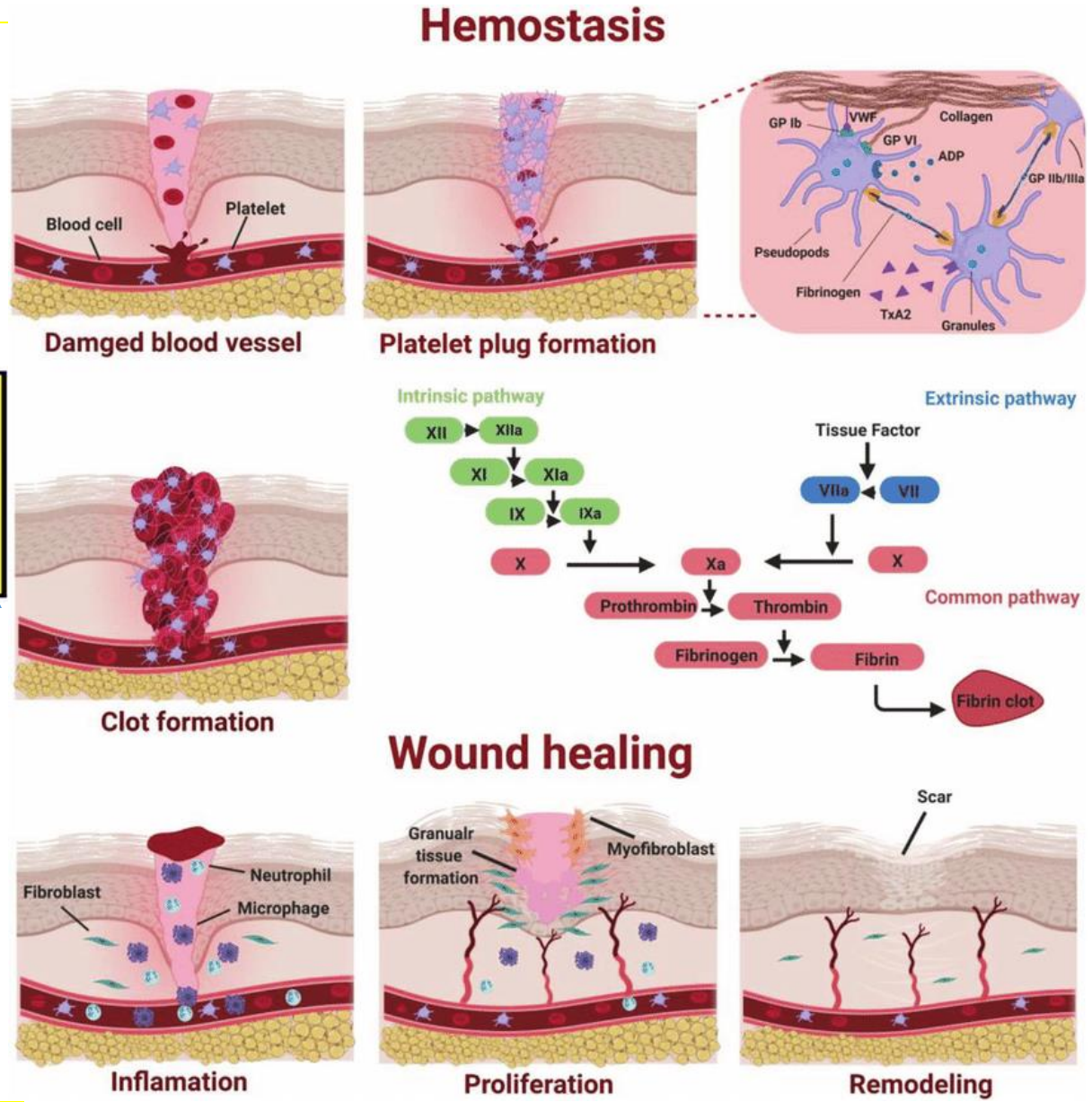
- Physiology of normal wound healing
- Epidemiology of chronic ulcers in autoimmune disorders
- Specific autoimmune disorders and wound healing
- Effects of medications used in autoimmune disorders on wound healing
- Diagnosis of underlying autoimmune disorders in chronic ulcers
- Co-management of autoimmunity and chronic wounds

Introduction

- An ulcer/wound that is nonresponsive to 3 months of appropriate wound care is defined as a chronic.
- Affects approximately 6.5 million people in the US with a prevalence of 1%
- Estimated costs per year - $25 billion
- Associated with increased mortality and pain
- Associated with decreased psychosocial well being and quality of life

Normal wound healing – 4 phases

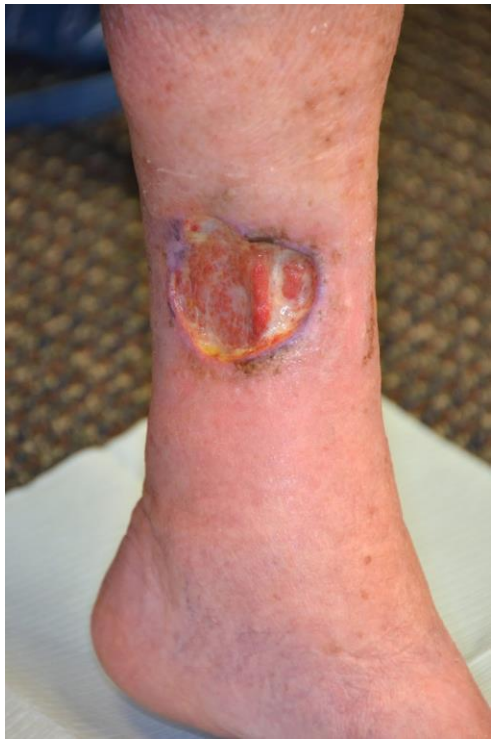




Epidemiology of autoimmune chronic ulcers

- Leg ulcers - vascular etiology in 79.7% (venous, peripheral arterial disease or mixed)
- 20-23% - complex causes (vasculitis, pyoderma gangrenosum, other autoimmune diseases)
- 6-7% of pts found to have leg ulcerations in association with a systemic autoimmune disease
- Significantly larger mean surface area (33.4cm² vs 22.5cm²; P=0.2)
- Higher rate of split-thickness skin graft failure (50% compared to 97%; P=0.0002)
- These may be predictors of immune-related diseases that warrant further evaluation

Specific autoimmune disorders and wound healing

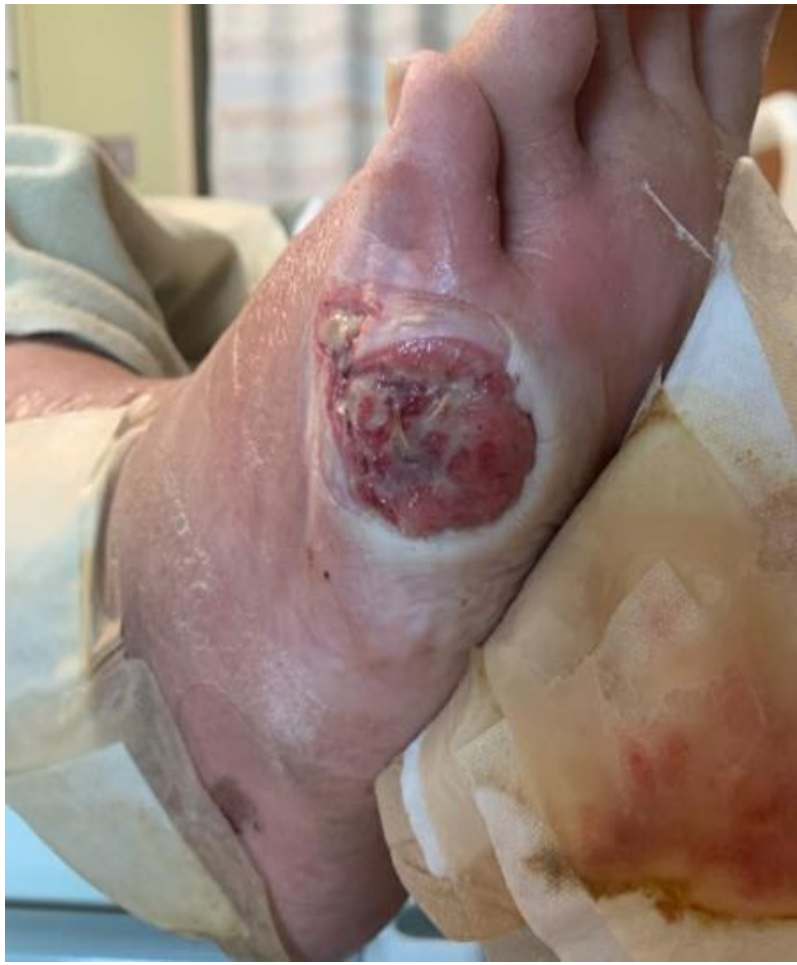


Etiologies of leg ulcers

Common	
Venous	
Arterial	
Neuropathic	
Uncommon	
Physical	Thermal burns, cold injury, radiation, trauma, factitial
Bites	Spider
Infection	Bacterial, fungal, spirochete, protozoal
Vasculopathies	Livedoid vasculopathy, Buerger's disease
Hypercoagulable states (inherited and acquired)	Factor V Leiden, antiphospholipid antibody syndrome, protein C and S deficiency, anti-thrombin III deficiency, prothrombin G20210A mutation, hyperhomocysteinemia and methylenetetrahydrofolate reductase (MTHFR) polymorphism
Vaso-occlusive disorders	Calciphylaxis, cholesterol emboli, type I cryoglobulinemia, cryofibrinogenemia, oxalosis
Vasculitis (small and medium-sized vessel)	Henoch-Schönlein purpura, rheumatoid vasculitis, mixed cryoglobulinemia, polyarteritis nodosa, granulomatosis with polyangiitis, lupus erythematosus
Pyoderma gangrenosum	
Necrobiosis lipoidica	
Panniculitis	Alpha-1-antitrypsin deficiency, pancreatic fat necrosis, erythema induratum (nodular vasculitis)
Neoplastic conditions	Squamous cell carcinoma, basal cell carcinoma, cutaneous T and B cell lymphoma, Kaposi's sarcoma
Systemic sclerosis	
Hematologic disease	Hemoglobinopathies, thrombocytosis
Drugs	Hydroxyurea, warfarin, heparin
Metabolic	Calcinosis cutis, gout, prolidase deficiency, leukocyte adhesion deficiency, Werner syndrome

Rheumatoid arthritis

- Most common autoimmune disease associated with leg ulceration
- Risk factors – older age (HR1.73 per 10 year increase), positive rheumatoid factor (HR 1.63), rheumatoid nodules (HR 2.14), venous thromboembolism (HR 2.16)
- Gravitational/venous ulcers are most common; arteritic ulcers are rare and seen in advanced disease
- Evaluate for underlying Felty's syndrome
- Use of TNF blockers associated with significantly higher likelihood of healing
- Bx - exclude malignancy and infection– vasculitis in 50%, non-specific findings in rest (fibrosis, scar tissue)



Treatment of RA associated ulcers

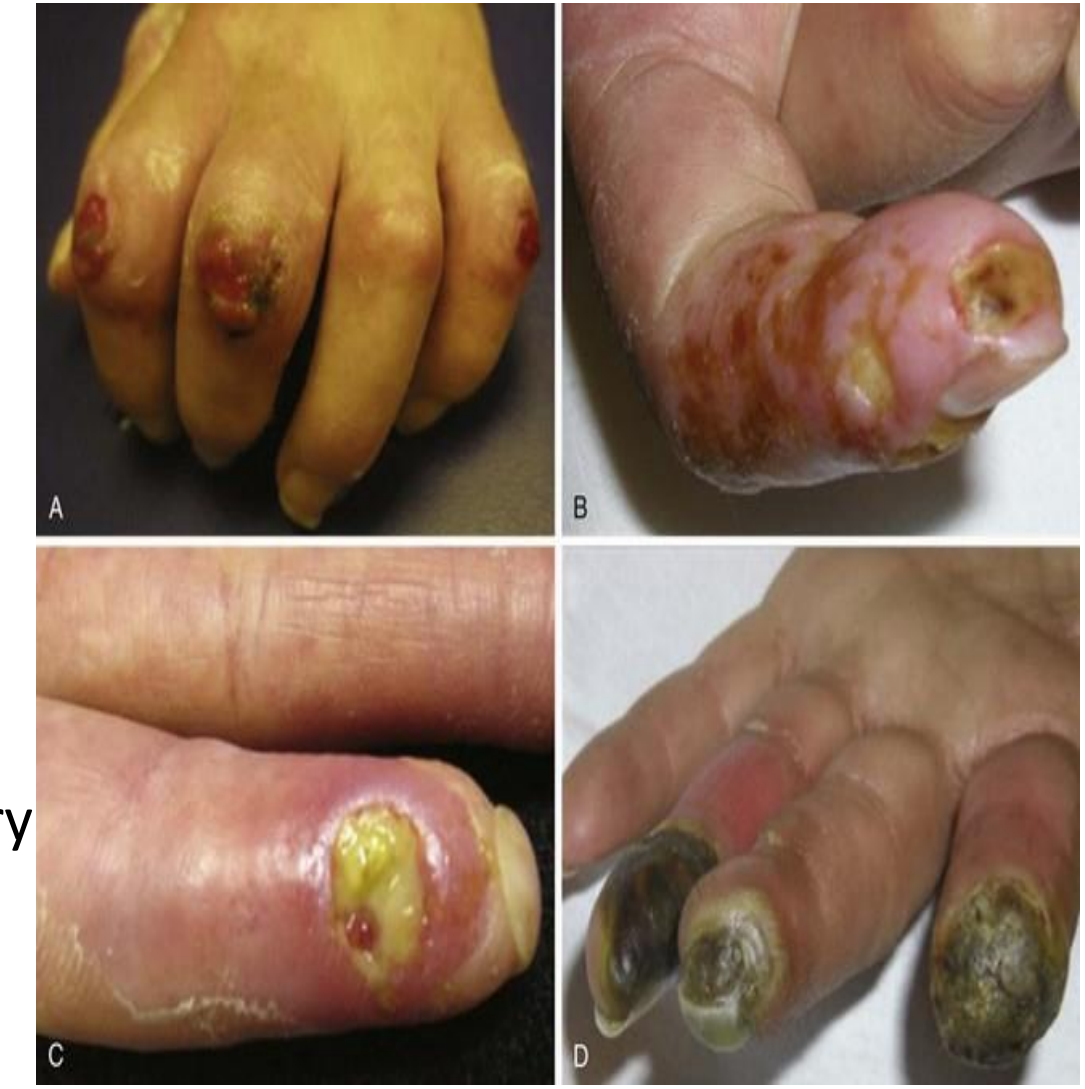
- Rx – Decrease glucocorticoid use; more aggressive immunosuppression to treat underlying disease
- Relieve pain
- Treat locally
- Treat coexisting infection
- Surgical intervention – endovascular intervention for critical limb ischemia- related ulcers – 1 year amputation free survival and freedom from reintervention was 89% and 91%

SLE

- Rarely seen in lupus
- Secondary to immune complex-mediated vasculopathy
- Coexistant procoagulant states may contribute
- Bx – leukocytoclastic vasculitis with fibrinoid necrosis and prominent PMN cell infiltration; thrombo-occlusive findings should raise suspicion for antiphospholipid antibodies
- Rx – Treat underlying disease; anticoagulation if needed; belimumab (Benlysta) have shown efficacy in treating cutaneous manifestations of lupus

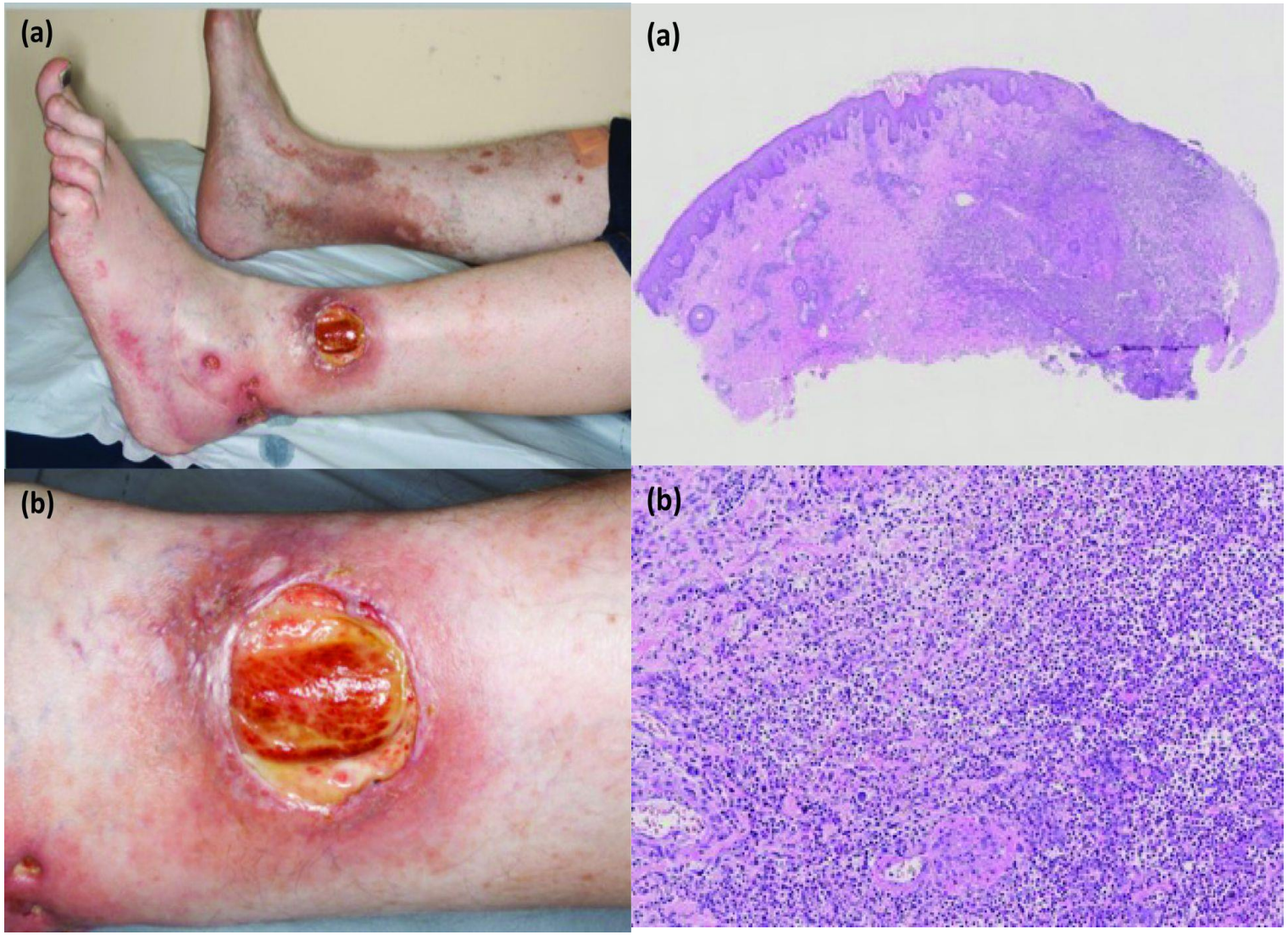
Scleroderma and MCTD

- LE ulcers seen in 4% of long standing scleroderma
- Etiology is multifactorial
- Arterial and venous disease can contribute to delayed healing in 50% of Scl patients
- Vascular evaluation and procoagulant workup recommended in all patients
- Bx – fibrin occlusive vasculopathy with intimal thickening and mild inflammation
- Rx – multidisciplinary approach; bypass surgery may be less effective due to associated distal vasculopathy. Endovascular treatment may be more successful. Medical interventions to address vasculopathy are critical.

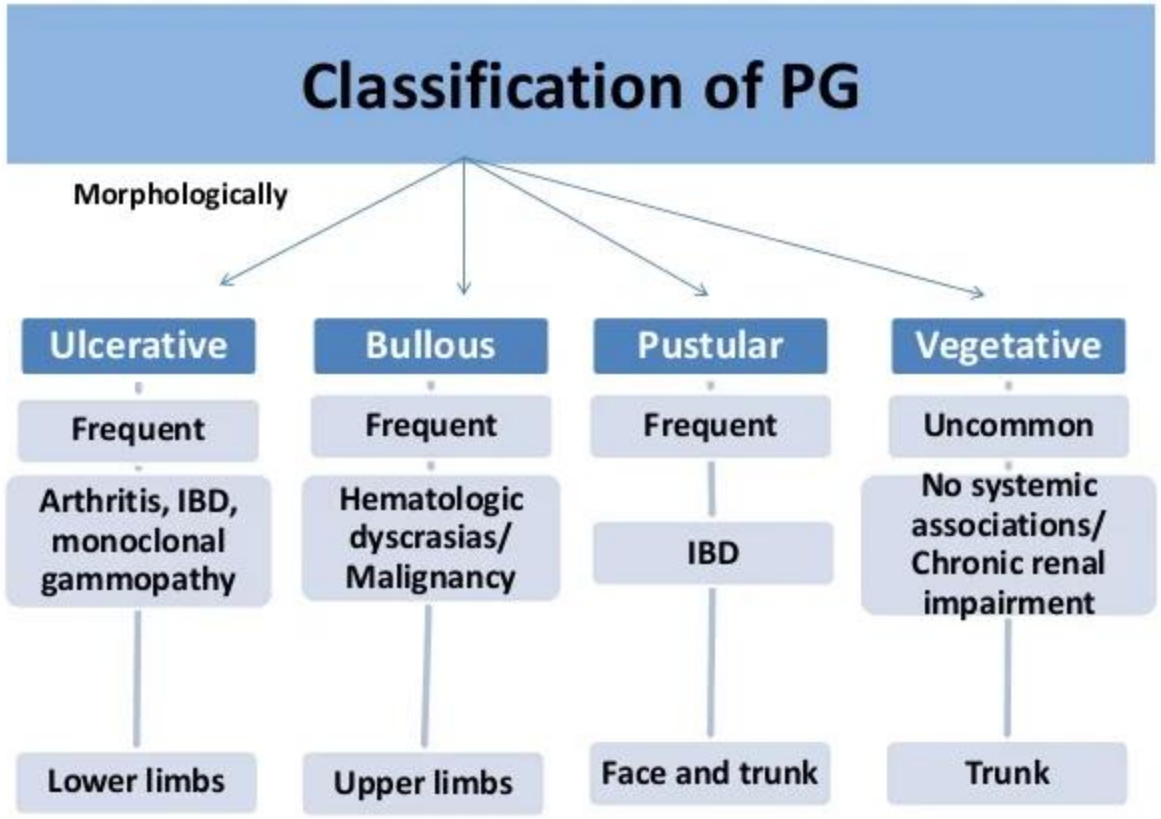


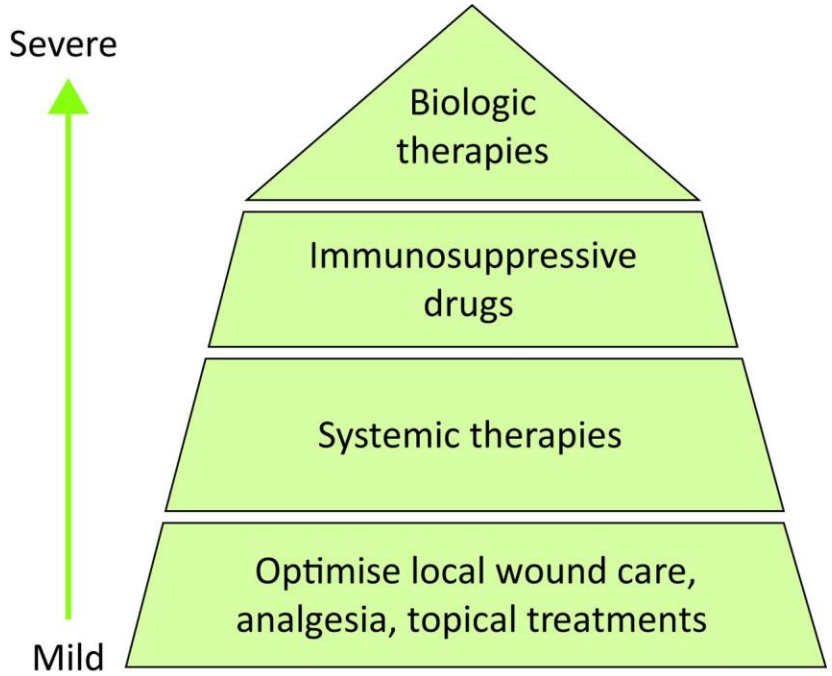
Pyoderma gangrenosum

- Neutrophilic dermatosis resulting in cutaneous ulceration, non-infectious, usually associated with an underlying condition
- Pustule→Bullae→Ulceration with purulent drainage
- Associated with pathergy (worsening in response to surgical debridement or bx)



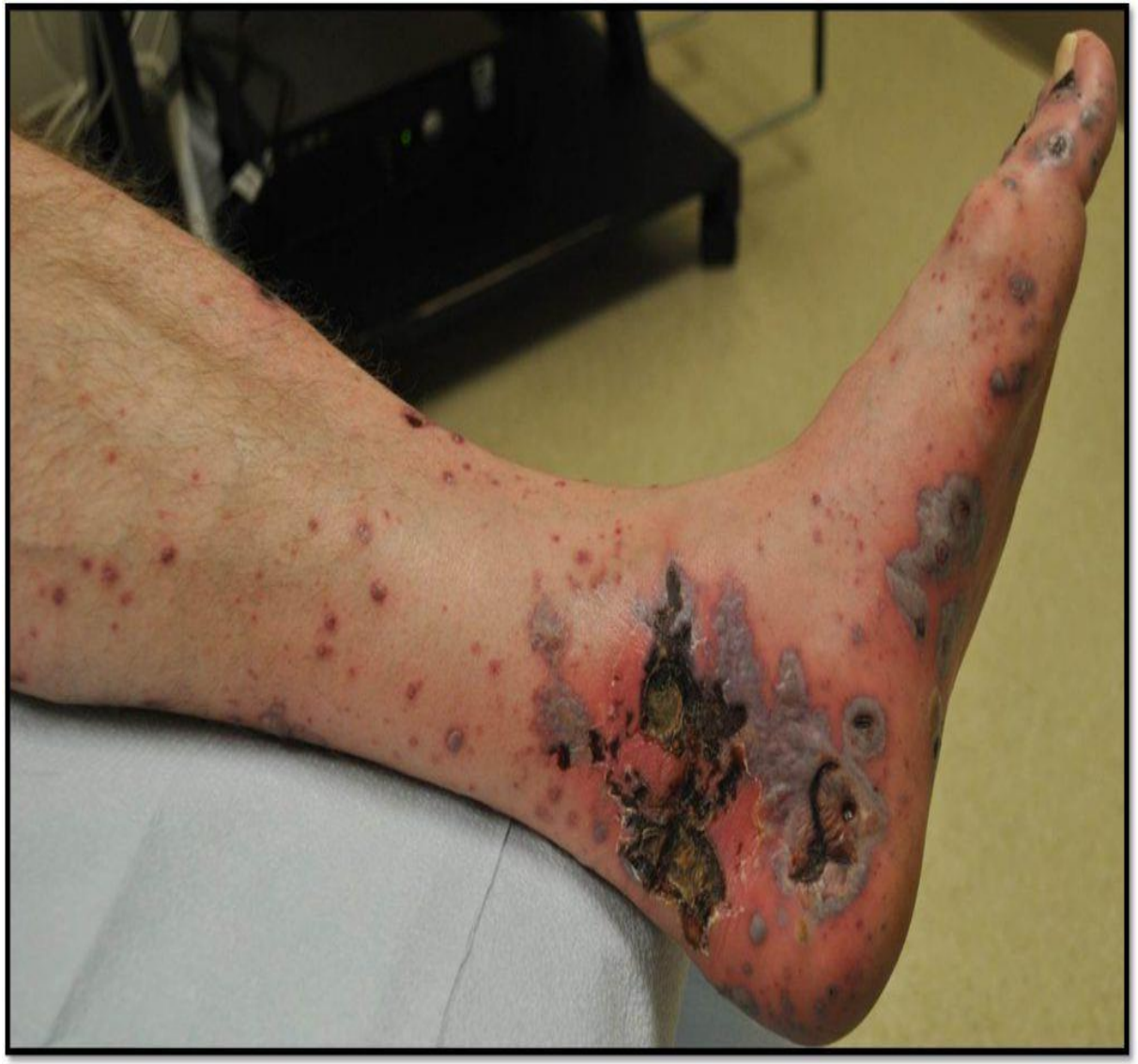
Pyoderma gangrenosum





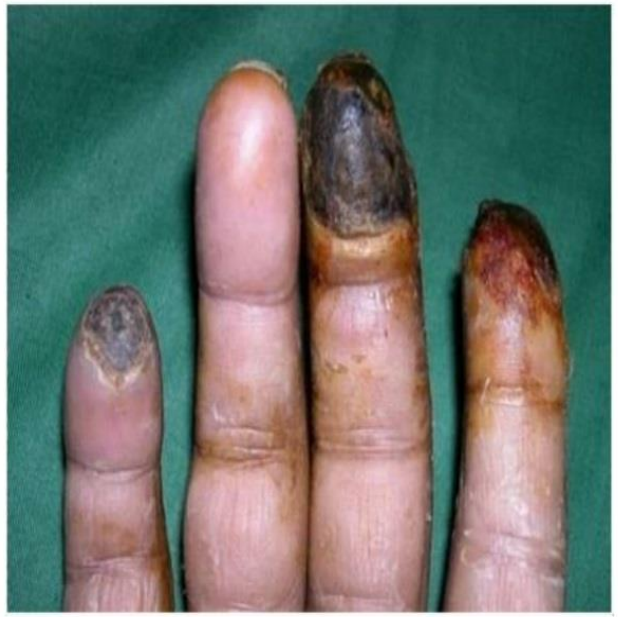
ANCA associated vasculitis

- GPA, MPA and EGPA
- Biopsy should include subcuticular tissues; yield is better when done early
- Bx – leukocytoclastic vasculitis, fibrinoid necrosis; vasculitis can be seen in medium and small arteries of the reticular dermis and fat; direct immunofluorescence for immunoglobulin and complement deposits
- Rx – treat the cause



TAO – thromboangiitis obliterans (Buerger's disease)

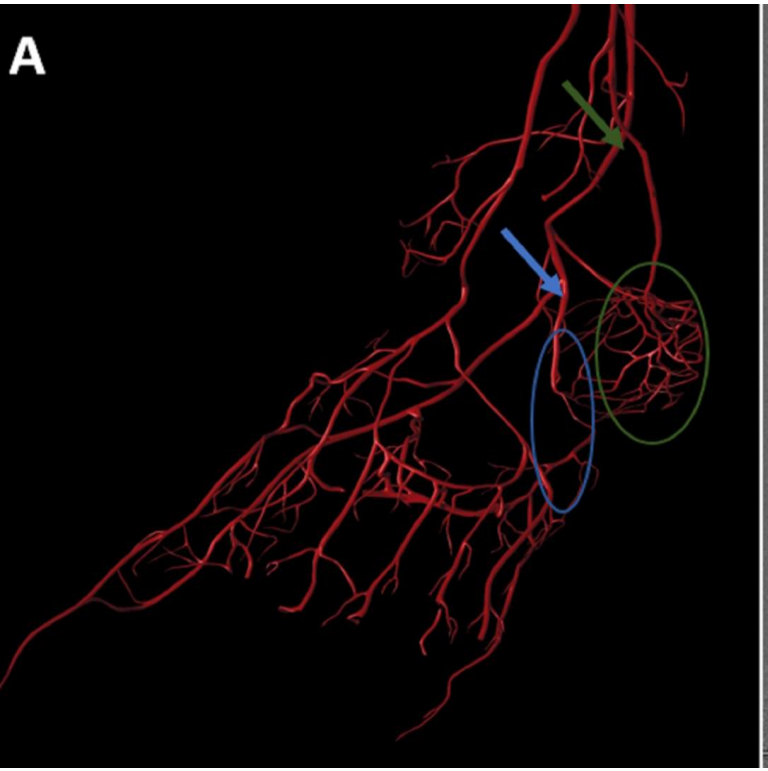
- Nonatherosclerotic segmental inflammatory occulusion of small to medium-sized arteries an veins, affecting peripheries
- Presenting complaint - claudication→rest pain→ischemic ulceration
- Low in Europe (0.5-5.6%)<India (45-63%)<Ashkenazi Jews in Israel (80%)
- Consider when critical limb ischemia is seen in p <50years
- Strong association with smoking unfiltered cigarettes

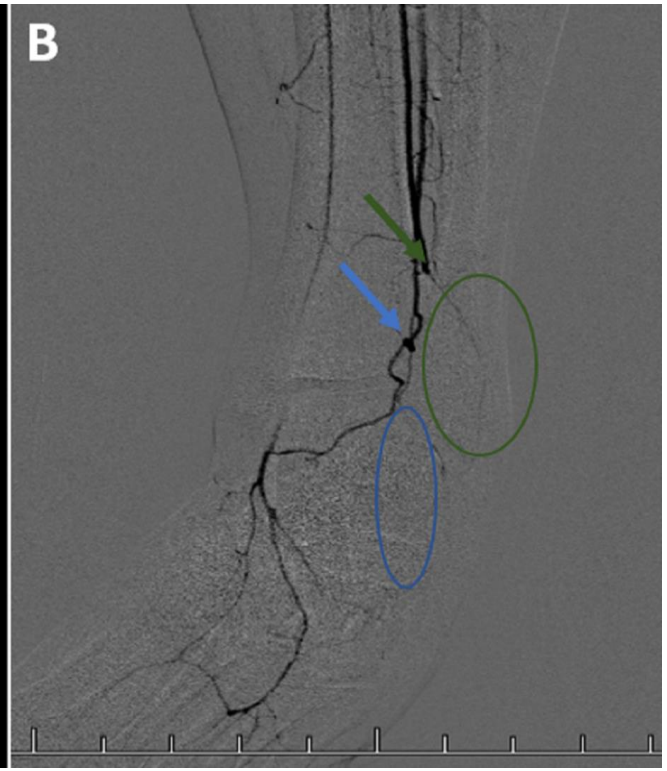


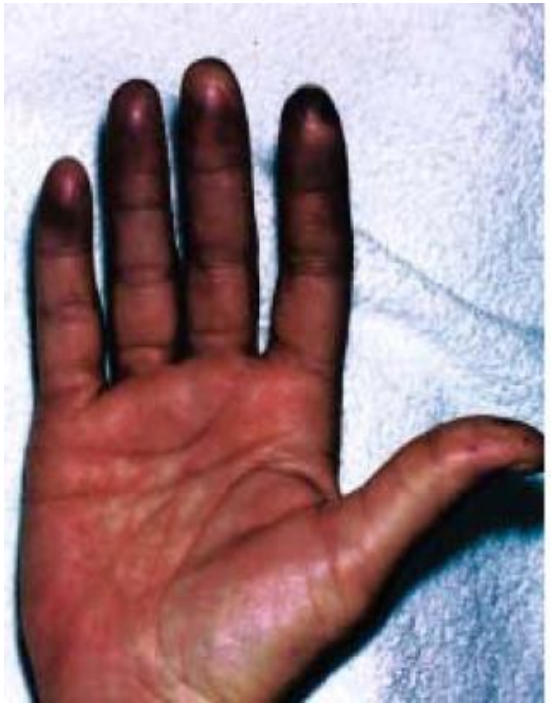
BUERGER'S DISEASE

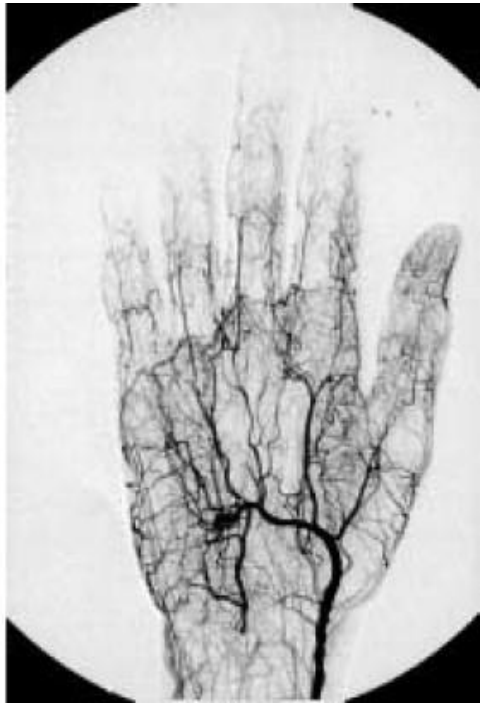
TAO

- Imaging – distal segmental occlusive lesions interspersed with normal appearing arteries with areas of collateralization (corkscrew collaterals); typically infra popliteal and distal to brachial arteries.



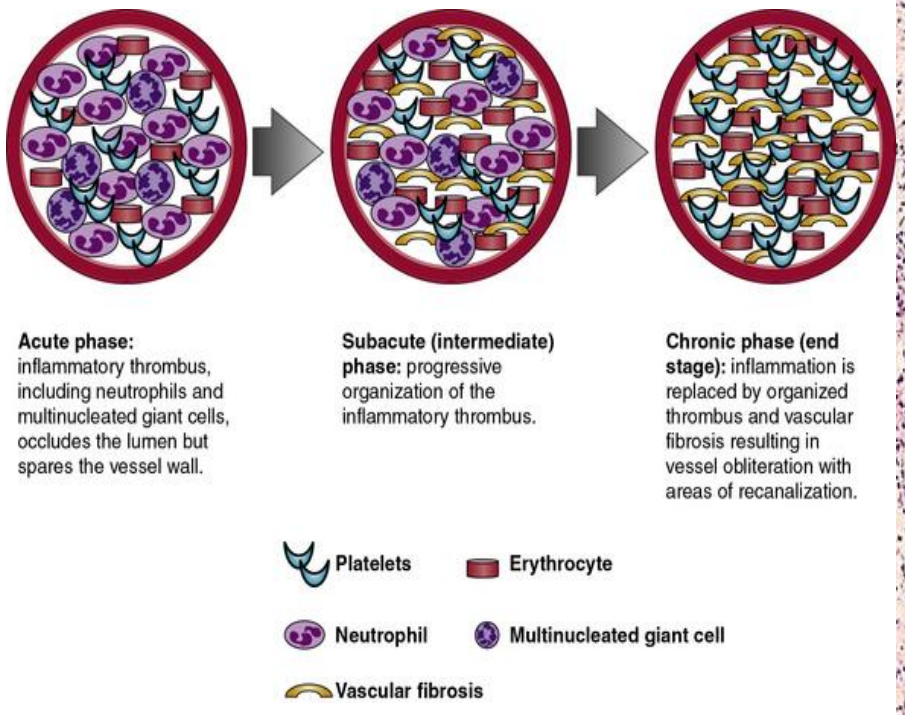


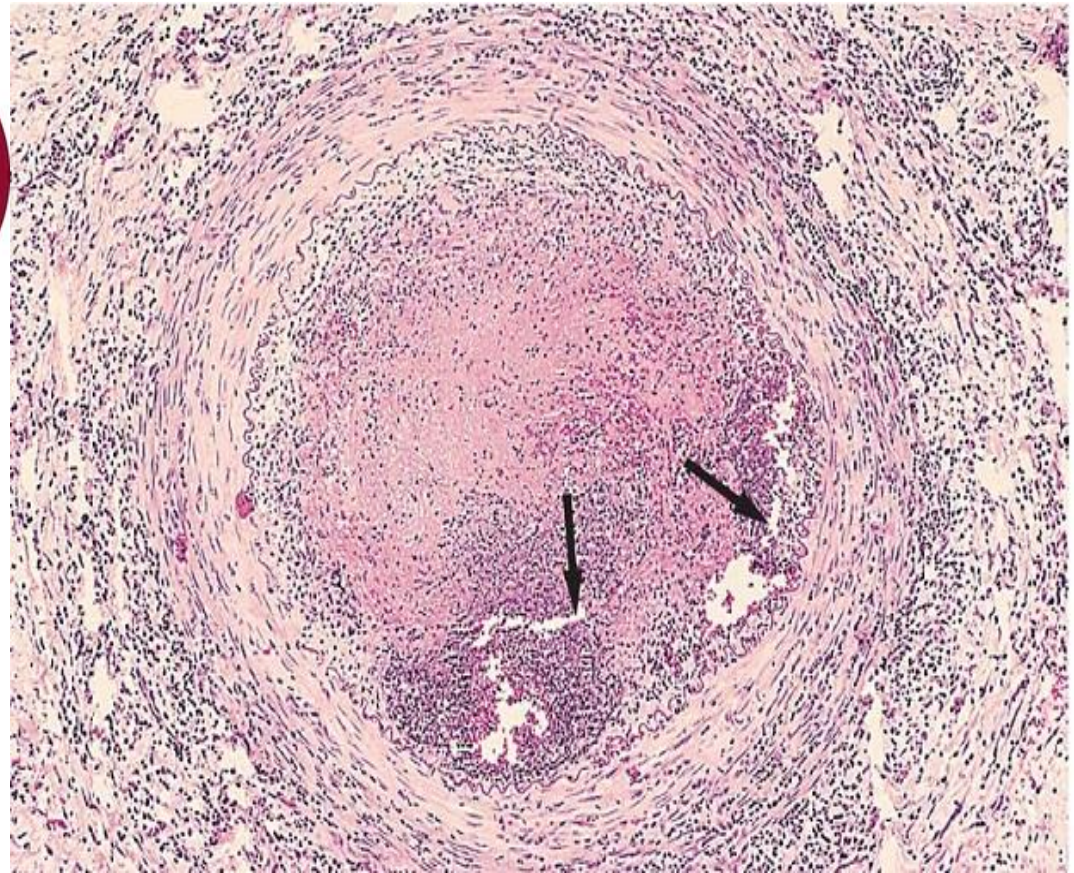




TAO

- Bx – Highly cellular inflammatory occlusive thrombosis with relative sparing of vessel wall and internal elastic lamina





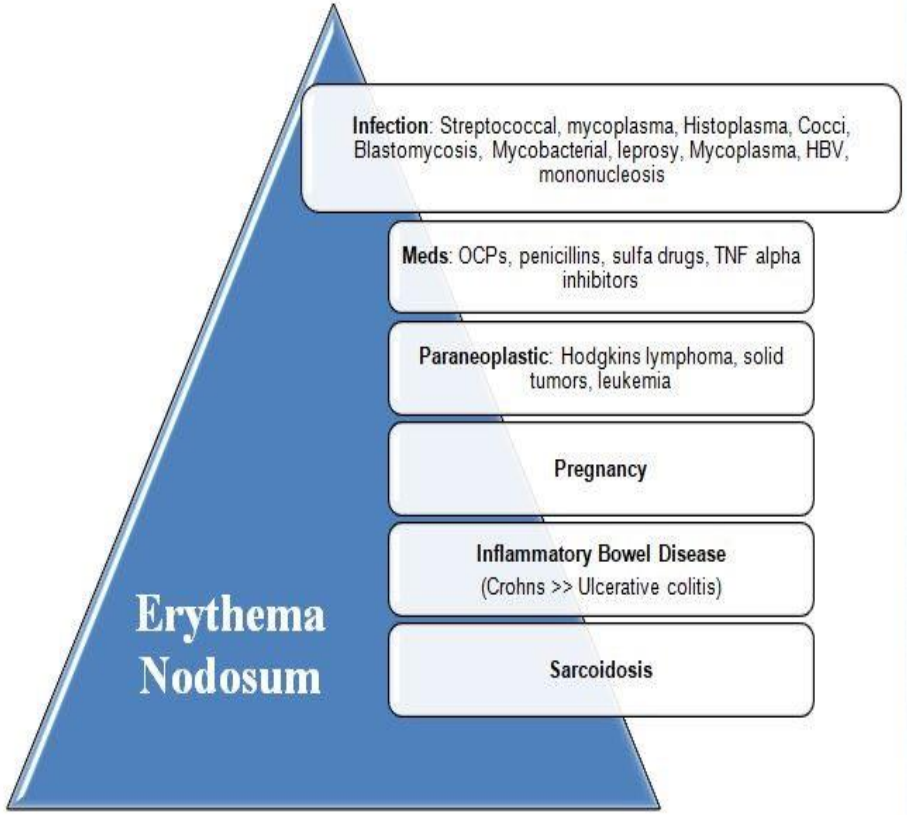
Demonstrates a vessel completely occluded by an inflammatory thrombus. Arrows indicate the presence of microabscesses.

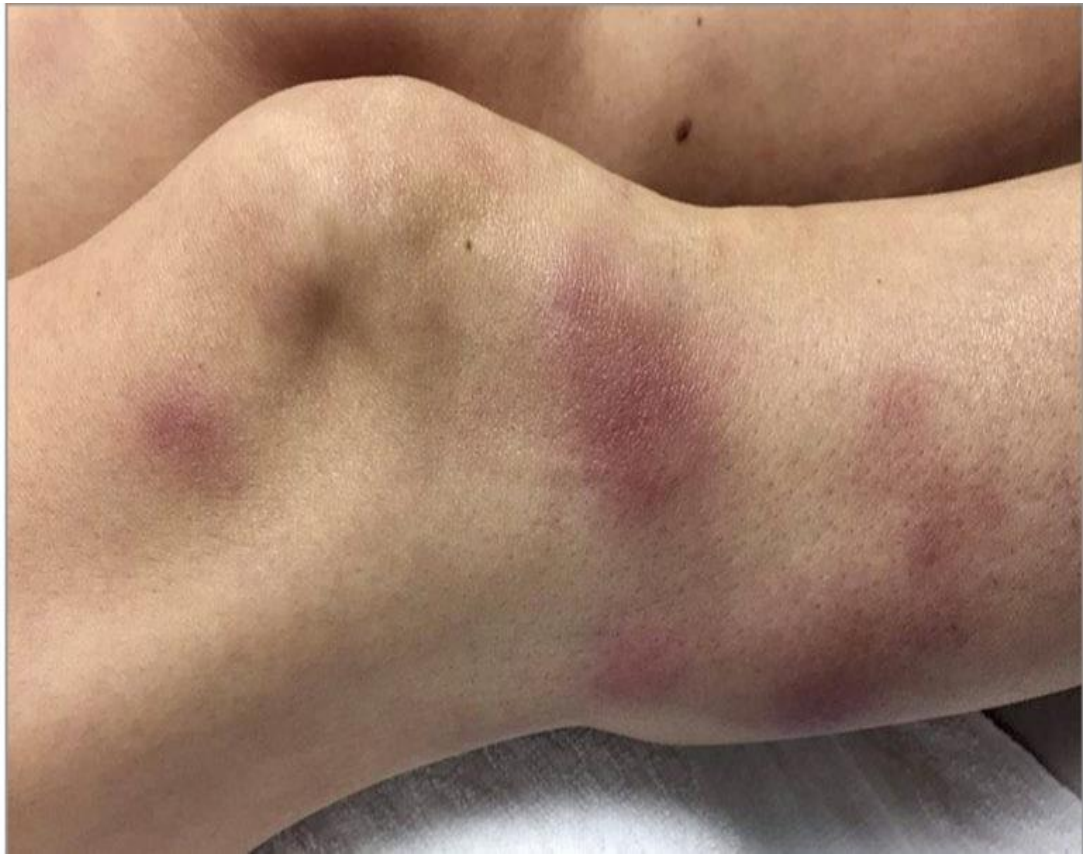
TAO - management

- STOP SMOKING
- Nicotine replacement therapy is not recommended
- Vasodilators, prostacycline analogues, antiplatelet drugs, autologous whole bone marrow stem cell transplantation
- Endovascular treatment
- Graduated exercise to improve collateral circulation

Erythema nodosum and panniculitis

- Inflammation, induration and ulceration of subcutaneous tissues
- Ulceration can be seen in nodular vasculitis, pancreatic disease, α1antitrypsin deficiency





Hematological disorders

- Sickle cell disease – 2.5% of patients
- Hydroxyurea-associated leg ulcers – 9% of pts with myeloproliferative syndrome, 29% with sickle cell anemia, dose dependent
- Atrophie blanche (livedoid vasculopathy) – chronic small vessel vasculopathy, recurrent leg ulcers, stellate porcelain white scars, presence of hyaline thrombi in the mid nad upper dermal vessels with fibrinoid changes
- Cholesterol emboli – post procedure, elongated cholesterol-clefts in the deep dermal arterioles
- Calciphylaxis – calcific uremic arteriopathy in CKD, progressive occlusion of dermal vessels, painful indurated plaques that develop necrosis and ulceration, poor prognosis (,50% 1 year survival), bx shows calcium deposition in the media of adipose vasculature
- Cryoglobulinemia
- Antiphospholipid antibody syndrome
- Genetic prothrombotic states

Infections

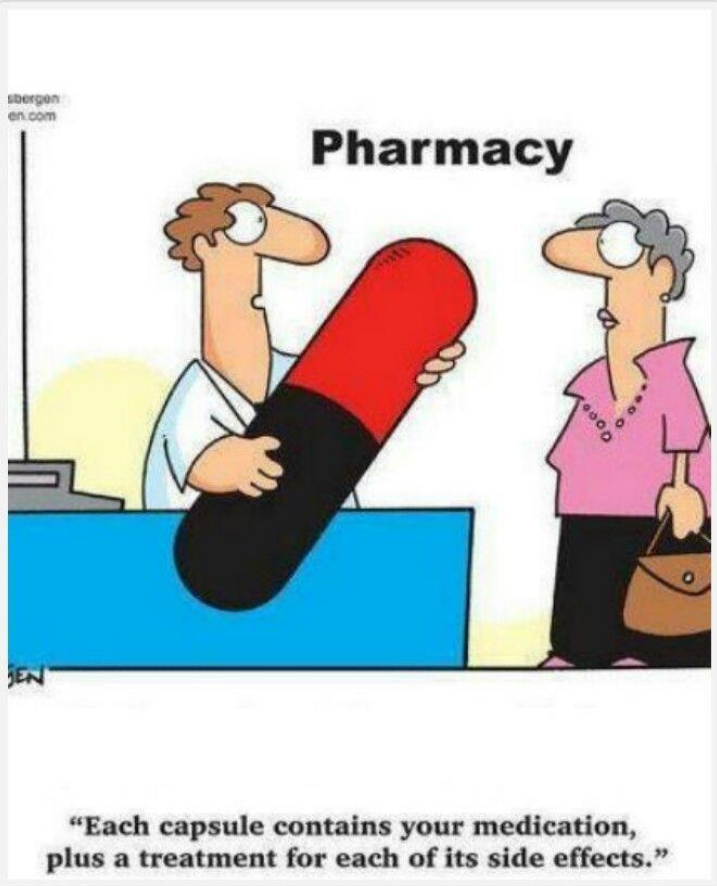
- Hepatitis C with cryoglobulinemia causing small and medium vessel vasculitis
- Hepatitis B causing polyarteritis nodosa
- Non-tuberculous bacteria

➢ Buruli ulcer – Mycobacterium ulcerans – sub-Saharan Africa, Australia

➢ Leprosy – Mycobacterium leprae – India, Brazil, Indonesia

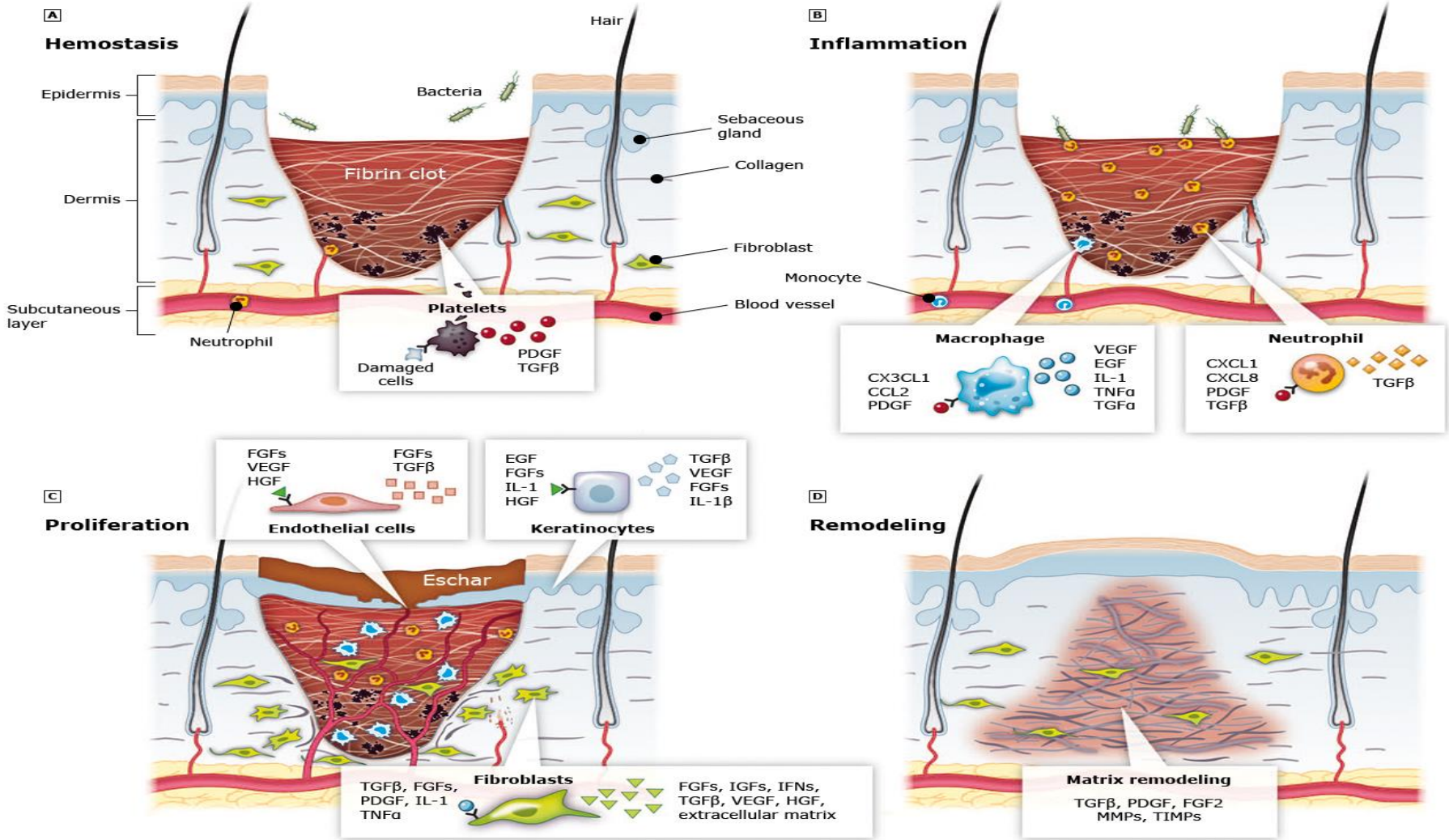
Effect of medications used on autoimmune disorders on wound healing

- Caused by medication directly



- Caused by delayed wound healing

Stages of wound healing



Wound healing is classically divided into 4 stages: (A) hemostasis, (B) inflammation, (C) proliferation, and (D) remodeling. Each stage is characterized by key molecular and cellular events and is coordinated by a host of secreted factors that are recognized and released by the cells of the wounding response. A representative subset of major factors are depicted.

PDGF: platelet-derived growth factor; TGF: transforming growth factor; FGFs: fibroblast growth factors; IL-1: interleukin-1; TNF: tumor necrosis factor; KGF: keratinocyte growth factor; IGF: insulin-like growth factor; IFN: interferon; VEGF: vascular endothelial growth factor; HGF: hepatocyte growth factor; MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinase.

Reproduced from: Sun BK, Siprashvili Z, Khavari PA. Advances in skin grafting and treatment of cutaneous wounds. Science 2014; 346:941.

Direct medication toxicity

- TNFα blockers
- IL-17, IL-23 blockers
- Methotrexate
- Glucocorticoids

Table 1. Classification of traditional chemotherapy agents and new molecular target therapies inducing skin ulcers.

TYPE	FUNCTION	DRUG	MOLECULAR TARGET
EGFR inhibitors	Tyrosine kinase inhibitors Monoclonal antibodies	Gefitinib Cetuximab	EGFR
Angiogenesis Inhibitors	Multikinase multitarget inhibitors Recombinant human mono-clonal antibody	Sorafenib Sunitinib Bevacizumab	VEGFR1, 2 , 3; Flt3; c-KIT; PDGFR; RAF VEGF
BCR-ABL, c-KIT, PDGFR inhibitors	Tyrosine kinase inhibitors	Imatinib	BCR-ABL;c-KIT;PDGFR
m-TOR inhibitors	Serine-threoninne kinases	Sirolimus	VEGF; HIF
Antimetabolites	Folic acid antagonists Pyrimidines antagonists	Methotrexate Gemcitabine	DHFR Ribonucleotide Reductase
Antiproliferative	DNA synthesis inhibitor	Hydroxyurea	Ribonucleotide reductase

Medications affecting wound healing

- Chemotherapy – direct and indirect effects on VGEF

- Anti-rheumatic meds – evidence of mixed, low to moderate quality, conditional recommendations, low to moderate quality evidence, supported by the American College of Rheumatology and the American Association of Hip and Knee Surgeons.
- Glucocorticoids

2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty

DMARDs: CONTINUE these medications through surgery.	**Dosing Interval**	**Continue/Withhold**
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	Daily	Continue
Doxycycline	Daily	Continue
BIOLOGIC AGENTS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection, or systemic infection.	**Dosing Interval**	**Schedule Surgery (relative to last biologic agent dose administered) during**
Adalimumab (Humira)	Weekly or every 2 weeks	Week 2 or 3
Etanercept (Enbrel)	Weekly or twice weekly	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra)	Every week (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra (Kineret)	Daily	Day 2
Secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Belimumab (Benlysta)	Every 4 weeks	Week 5
Tofacitinib (Xeljanz): STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**
Mycophenolate mofetil	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue
Tacrolimus	Twice daily (IV and PO)	Continue
NOT-SEVERE SLE: DISCONTINUE these medications 1 week prior to surgery	**Dosing Interval**	**Continue/Withhold**
Mycophenolate mofetil	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Withhold

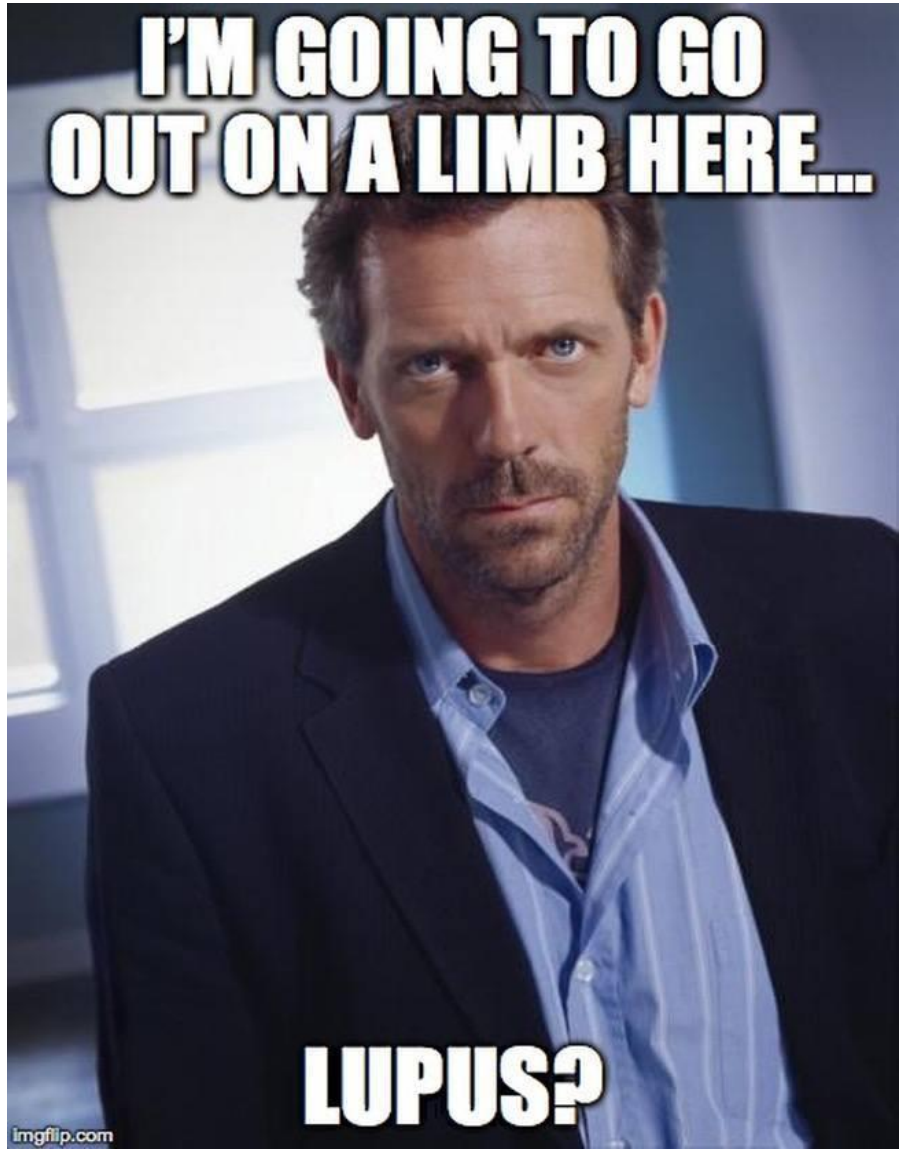
Arthritis Care & Research, Volume: 69, Issue: 8, Pages: 1111-1124, First published: 16 June 2017, DOI: (10.1002/acr.23274)

Medications affecting wound healing

- Glucocorticoids – dose dependent effect; anti-inflammatory effect in lower doses can prevent wounds from being arrested in the inflammatory stage vs significant suppression of inflammation can prevent wounds from progressing into next stages of wound healing
- Keratinocytes -epidermal atrophy, delayed reepithelialization
- Fibroblasts - reduced collagen and ground substance, resulting in dermal atrophy and striae
- Vascular connective tissue support -telangiectasia, purpura, easy bruising
- Impaired angiogenesis - delayed granulation tissue formation.

Diagnosis of underlying autoimmune disorders

- History and physical exam
- Directed labs based on exam
- Labs should be viewed in the context of the clinical presentation
- Biopsy
- Rheumatology and/or hematology consultation



Laboratory testing to investigate autoimmune and prothrombotic states in patients with chronic non-healing wounds.

Test	Disease detected
Anti-nuclear antibody	Systemic Lupus Erythematosus and other autoimmune diseases
Anti-Smith antibody	Systemic Lupus Erythematosus
Anti-dsDNA antibody	Systemic Lupus Erythematosus
Complement C3 **Complement C4**	Systemic Lupus Erythematosus (low in active disease)
Anti-Centromere antibody	Scleroderma
Anti-Scl70 antibody	Scleroderma
Anti-ribonuclear protein (RNP)	Mixed connective tissue disease
SSA and SSB antibodies	Sjogrens Syndrome
Rheumatoid Factor	Rheumatoid Arthritis
Anti-Cyclic Citrullinated Peptide	Rheumatoid Arthritis
Anti-neutrophil cytoplasmic antibodies	Granulomatosis with polyangiitis, Microscopic Polyangiitis, Eosinophilic granulomatosis with polyangiitis, Cocaine and Levamisole associated vasculitis
Anti-β2-glycoprotein I antibodies	Antiphospholipid syndrome
Anti-cardiolipin antibodies	Antiphospholipid syndrome
Lupus Anticoagulant	Antiphospholipid syndrome
Prothrombin gene mutation	Genetic prothrombotic state
Factor-V Leiden mutation	Genetic prothrombotic state
Plasminogen Activator Inhibitor	Genetic prothrombotic state
MTHFR mutation	Genetic prothrombotic state
Quantiferon gold	Tuberculosis exposure
HIV test	HIV
Hepatitis B and C	Hepatitis B and C

Co-management of autoimmune ulcers

- Multidisciplinary approach
- Treatment of underlying cause
- Concomitant wound care
- Surgical interventions when underlying disease process is well controlled to have best outcomes

"OK, but if we work *together*... Whammo! Depth perception!"

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