 

# RESIDENT ROUNDS: PART I

## Program Spotlight: Florida State University College of Medicine Division of Dermatology at Dermatology Associates of Tallahassee

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The Florida State University College of Medicine (FSUCOM) Division of Dermatology is a vibrant, thriving, and unique learning environment. The program was initially accredited in January 2015 and is currently accredited until 2027. There are currently six residents and one Mohs surgery fellow. The mission of FSUCOM and the Division of dermatology is nobly stated as follows: "The Florida State University College of Medicine will educate and develop exemplary physicians who practice patient-centered health care, discover and advance knowledge, and are responsive to community needs, especially through service to elder, rural, minority, and underserved populations."

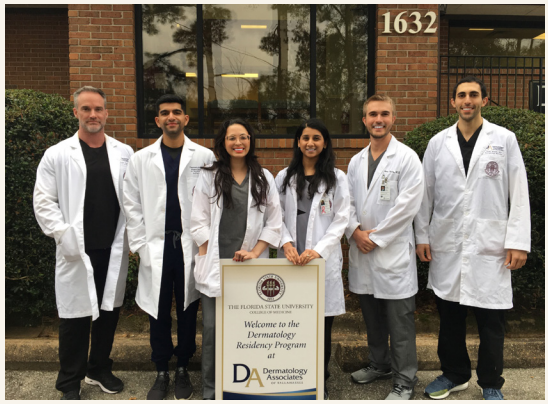
### Division Highlights

The division has diverse and talented faculty members to provide residency and fellowship training. A robust clinical and didactic program, an extensive array of treatment modalities and technologies, and rotations at numerous training venues all provide the residents and fellows with the much-needed skills to address the dermatologic needs of today's diverse patient populations.

The full-time faculty includes eight general dermatologists, five Mohs surgeons, three dermatopathologists, and one fellowship-trained pediatric dermatologist. There is also a part-time plastic surgeon on staff who supervises the residents during complex closures.

The residents' clinical training occurs primarily at the offices of Dermatology Associates of Tallahassee. There are six additional satellite clinics where the residents provide dermatologic care to elderly and rural patients who have difficulty traveling and are geographically separated. The residents also rotate through the Tallahassee Veterans Affairs Health Care Center and Southeast Plastic Surgery Center. They provide inpatient consultations at Tallahassee Memorial Healthcare Hospital.

In addition to rotating on our robust Mohs surgery rotation, the residents receive hands on experience with a variety of lasers including fractional CO2, pulse dye, xenon-chloride excimer, and Nd:YAG lasers. The Division of Dermatology also provides superficial radiation therapy (SRT) on site and the residents gain experience using SRT to treat non-melanoma skin cancers and keloids. Additionally, residents receive hands-on training in cosmetic dermatology to include hair transplantation, liposuction and fat transfer, as well as neuro-modulators and fillers.




From Left to Right: Christopher Wolfe DO (PGY-4), Amit Om MD (PGY-3), Samantha Marrone,MD (PGY-3), Shalini Thareja MD (PGY-2), Alex Davis MD (PGY-2), Tarek Shaath MD (PGY-4)

The structured didactic training includes journal club, textbook sessions, kodachrome review, dermatopathology lecture, and read-outs with the dermatopathologists, dermatologic pharmacology, and dermato-ethics. The entire FSUCOM is invited to our yearly live patient grand rounds each spring. The residents are required to prepare scholarly papers, present at regional and national conferences, participate in clinical research projects, and complete one international rotation or mission trip. The pace is vigorous, but the academic rewards and training benefits are commensurate.

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# RESIDENT ROUNDS: PART II

This table is derived from the 3rd edition of the "Dermatology Pocket Guide" from DermEducate.com. The table highlights many of the complex systemic medications used in dermatology along with dosing protocols, indications, lab monitoring, side effects, contraindications, and mechanisms of these drugs. The residents at our program frequently reference this guide during clinic which assists with prescribing medications while also reducing medical errors. The full contents of the pocket guide can be found at DermEducate.com.

**TABLE 1.**

## Dosing and Management of Complex Systemic Medications

| Drug | Dosing / Indications | Lab Monitoring (B/L = baseline, F/U = follow up) | Side Effects (green=common, blue=occasional, red=rare) | Avoid Use With | Mechanism | P |
|---|---|---|---|---|---|---|
| **Isotretinoin** (Accutane®) 10/20/30/40 mg Escalate QD, BID, TID Cost: **$750-1200** / 30 caps | 0.5–1 mg/kg/d ÷ BID w/ **fatty food** – improves absorption & bioavailability 120–150 mg/kg cumulative dose 220 mg/kg for high dose (↓ relapse) | B/L: **hCG**, LFT, FLP (routine CBC not indicated) F/U: hCG, LFT, FLP **x1 after 2 mo of therapy** (unless abnormalities detected) Half-life: 20 h, No pregnancy for 30 days | **Cheilitis, xerosis, dry eyes/mucosa, retinoid dermatitis,** palmoplantar **peeling, photosensitivity, hypertriglyceridemia,** alopecia (**telogen effluvium**), **HA,** myalgia, arthralgia, staph infxns, paronychias, excess granulation tissue/**PGs,** sticky skin, poor wound healing, **pseudotumor cerebri,** ↓ night vision, eruptive xanthomas, pancreatitis, hyperostosis (long term). **(Does NOT cause or ↑ risk of IBD)** | **Tetracyclines** (risk of pseudotumor cerebri), **vitamin A** (hypervitaminosis A) **MTX** (hepatotoxicity), **alcohol,** macrolides, azoles, rifampicin, phenytoin, carbamazepine, mini-pill OCP, photosensitizers *Controversial association with depression (studies show improvement of depression)* | *All Retinoids:* **Normalize keratinization (↑ filaggrin/KHGs**, downregulates proliferative **K6** & **K16**), **↓ follicular occlusion**, inhibits **ornithine decarboxylase, collagenase, TLR-2, IL-6, AP-1, NF-kβ**; ↑ dermal collagen I, ↑ hyaluronic acid, ↑ elastic fibers, ↑ fibronectin, transglutaminase and Th1 skewing, **↓ MMPs** | X |
| **Bexarotene** (Targretin®) 75 mg Cost: **$8,000** / 30 capsules Cutaneous T-Cell Lymphoma | Start at 150 mg/m²/day Increase to 300 mg/m²/day based on tolerability & response. **Start levothyroxine** 0.05 mg QD **Rosuvastatin** 10–20 mg QD | B/L: hCG, **CBC, CMP, FLP, T4/TSH ± TRH** F/U: **FLP** & **free T4** Q1-2 wks till stable Q1-2mo hCG, CBC, CMP, **FLP, T4/TSH ± TRH ± CK** (rhabdomyolysis with statin + fibrate combo) Half-life: 7h, No pregnancy for 30 days | **Acitretin**: SAME + alcohol converts it to **etretinate** (fat sol.) **Transaminitis** in 20%, ↑ **alopecia** & **palmoplantar peeling** **Bexarotene**: SAME + **hypertrig** (80%), **central hypoTH** (40%), **leukopenia** (30%), cataracts, hypoglycemia | **Acitretin**: same, **especially alcohol** **Bexarotene**: same + **gemfibrozil** & **simvastatin** (CYP3A4 interaction) (can use **fenofibrate & omega 3's**) | Isotretinoin (13-cis): **No nuclear receptor binding profile** Acitretin (9-cis): Binds **weakly** to all **RAR** subtypes Bexarotene: Binds all **RXR** subtypes | X |
| **Prednisone** 1, 2.5, 5, 10, 20, 50 mg Autoimmune & inflammatory dermatoses **(Rapid onset in 2-3 days)** Switch therapy ASAP | Basal hydrocortisone: 20-30 mg daily Prednisone equivalents: 5-7.5 mg Maximal stress hydrocort: 300 mg Prednisone equivalent: 75 mg **Have pt take dose upon awakening (more physiologic)** | If treating for 3 months of > 5 mg/day: B/L: **BP**, Q.Gold, Fasting **BMP/A1c**, **DEXA-scan**; **Ca (1000 mg)/ Vit D (1000 IU)** & bisphosphonate (Alendronate 10 mg QD) Consider teriparatide 20 mcg SC QD **Ophtho exam Q 6-12 mo** | **HTN, hyperglycemia,** weight gain, N/V, **acneiform** eruption, **$H_2$0 retention, hyperNa, hypoK, poor wound healing, infections,** mood changes, insomnia, myopathy, neutrophil leukocytosis, **osteoporosis, cataracts,** cushingoid, glaucoma, osteonecrosis of hip, adrenal insufficiency, peptic ulcer disease (prevent most AEs w/ alternate day therapy | **Avoid long-term use, elderly women**, smokers, drinkers, liver disease, **NSAIDs** (↑GI bleed risk), **active TB**, systemic fungal infxn, **CYP3A4** metabolism — except osteoporosis & cataracts) | Inhibits **NF-kβ/AP-1 (↓IL-1, TNF-α)**, Inhibits **phospholipase-A2, COX2 >> COX1, GM-CSF**, proinflammatory cytokines (esp. **IL-2**) Inhibits cell trafficking > cell function, Inhibits cellular immunity > humoral immunity | C |
| **MTX** (Rheumatrex®) 2.5 mg Generic Cost: **$107** / 30 tabs | Start at 5 mg Qwk Up to 25 mg Qwk Prednisone equivalent: 75 mg **Have pt take dose upon awakening (more physiologic)** | B/L: **CBC, CMP**, Hep panel (**A, B, & C**), Tb, ± HIV F/U: CBC/CMP Qwk x 4 → Qmo x 4 → Q3-4mo Avoid MTX in pts with **fatty liver & poor CrCl** hCG in young women consider liver bx Q 1.5 g or at 3.5-4.0 g | **Pancytopenia, photosensitivity/UV burn recall, alopecia, oral ulcers, N/V** (Ø w/folate), **hepatotoxic, necrosis of psor plaques, rheumatoid nodulosis, pulmonary fibrosis/pneumonitis,** ↑ **homocysteine** (↑ CV risk), anaphylactoid rxn reported (**test dose at 5 mg** → Leucovorin rescue) | **Metabolic syndrome, alcohol use, NSAIDs/ASA, TMP/SMX, retinoids, TCNs, CsA, dapsone,** prednisone, dexamethasone, ampicillin, vaccines, phenytoin | Folate analog that inhibits **DHFR**; cell-cycle specific (**S phase**); inhibits **TS** (thymidylate synthetase), methionine synthetase, and AICAR; increases local adenosine (anti-inflammatory effects related to adenosine) | X |
| **Azathioprine** (Imuran®) 50 mg Generic Cost: **$63** / 30 tabs (**last resort** for a life-threatening dz unresponsive to other agents) | 0.5 – 3 mg/kg/day, (ideally 2 mg/kg) 50 – 150 mg Qday, ↑ Q1-2 mo **Chronic Actinic Dermatitis, AD,** PV, BP, MMP, LE, DM, **oral LP** | B/L: **CBC** w/plt, CMP, UA, **TPMT** Ask about **allopurinol / warfarin** use F/U: CBC, LFT Q2wk x 2mo → Q2-3mo if stable Consider **Q. Gold & hCG** | **NMSC, pancytopenia,** opportunistic infections, N/V, **agranulocytosis (with low TPMT) hepatotoxicity, pancreatitis, lymphoma, GYN SCC,** oral ulcers, curly hair, **hypersensitivity syndrome** (morbilliform) at 14 days (fever/shock) | **Allopurinol** (↓ AZA dose by 75%), **warfarin** (↓ war. efficacy), **ACE-I, MTX, TMP/SMX, CsA, mycophenolate,** vaccines, sulfasalazine, IUDs | AZA → 6-MP → 6-TG – active metabolite (via **HGPRT**) **incorporates into DNA during S phase**; inhibits de novo purine synthesis (**lymphocytes**) Inactivated by **TPMT** & **Xanthine Oxidase** | D |
| **Cyclosporine** (Neoral®) 25/100 mg Generic Cost: **$165** / 30 caps **(Rapid onset; to induce remission of severe Dz)** | 2-5 mg/kg/day ÷ BID Start max dose then taper (take without food) **Severe Psor** (pustular) **& AD, SJS, TEN, PG,** DM, Acute GVHD, **Urticaria** | B/L: **✓ BP** (2 readings), **gingiva, hair,** CBC, **CMP** (w/ **Mg & Uric Acid**), UA, **FLP** (TG,Chol,HDL), Q. Gold F/U: BP, CMP, FLP at 2 weeks, then transition to BP, CBC, CMP, UA, FLP Qmo x 2 mo → Q3mo **Lower dose by 25-50% for Cr ↑ >25%, D/C if Cr ↑ ≥50%** | **HTN** (tx w/ CCB, not ACE-I/diuretic), **hyperlipidemia,** HA, **nephrotoxic,** cancer progression (↑**NMSC** risk, >2 yr) **hyperK** (w/ ACE-I)/**uricemia, hypoMg, gingival hyperplasia, hypertrichosis,** acne, sebaceous hyperplasia (10-15%, long term), paresthesias, myalgias, hepatotoxicity, lymphoma | **CYP3A4** metabolism (liver), **azoles, ACE-I, grapefruit** juice, macrolides, SSRIs, ticlopidine, **MTX, TMP/SMX**: ↑ toxicity with **nephrotoxic drugs** | Binds **cyclophilin → inhibits calcineurin** & inhibits dephosphorylation/activation of **NFAT-1**; inhibits **IL-2, IFN-γ** synthesis (**↓ Th1, CD4, CD8 response**) | C |
| **Mycophenolate Mofetil** (CellCept® 500 mg (Myfortic® 180/360 mg Generic Cost: **$238** / 30 tabs | 0.5 – 3 g / day, QD to BID (Cellcept 1000mg=Myfortic 720mg) **PV, BP,** LE, DM, **SSc,** Psor, AD, **GVHD, oral LP,** may combine w/ other drugs | B/L: **CBC,** CMP, hCG, ± HBV/HCV, ± Q.gold F/U: CBC Q2wk x 2-3 mo → Qmo x 1 yr → Q3mo CMP after 1st month → Q3-4 mo **Discontinue or ↓ dose if WBC < 3500-4000** | **Diarrhea/cramps/N/V** (Myfortic® enteric coated, ↓ GI side effects, ↑ absorption), pancytopenia (reversible, dose-related), opportunistic infections, BM suppression, hepatotoxicity, dysuria, sterile pyuria, insomnia, dizziness, tinnitus | **Dapsone**, Iron/Antacids chelate & ↓ absorption, cholestyramine ↓ levels, **acyclovir ↑ levels, echinacea** may ↓ efficacy | Inhibits **IMPDH (inosine monophosphate dehydrogenase)** → inhibition of **de novo purine** synthesis. **Lymphocyte specific** mechanism, so minimal side effects. | D |
| **Hydroxychloroquine** (Plaquenil®) 200 mg Generic Cost: **$122** / 30 tabs | 200-400 mg/day (6.5 mg/kg/day) **DLE, SCLE, LE, PMLE, PCT,** DM, LP, Morphea, Sarcoid, Chronic GVHD | B/L: CBC, CMP, visual acuity, **G6PD (primaquine)** F/U: CBC/CMP Qmo or none if normal @ B/L Eye exam Q 1-5 years **(Chloroquine highest risk)** | **Blue/grey/black** hyperpig (face/palate/shins), **lichenoid drug rxn,** N/V (↓ w/ brand name), irritability/nervousness, **retinopathy, hemolysis, psoriasis exacerbation,** cardiomyopathy | **Smoking ↓ efficacy**, cimetidine, digoxin, **porphyria (use low dose) DON'T combine w/ chloroquine.** | **DNA Intercalators** Ø transcription; disrupt UV $O^2$ radical formation; inhibits **IL-2** synthesis; inhibits chemotaxis; reduces platelet aggregation; inhibits endosome acidification | C |
| **Thalidomide** (Thalidomid®) 100 mg\|Cost: **$9,320** / 28 cap **Lenalidomide** (Revlimid®) | 50 – 300 mg Qhs, start at 100 mg Severe **pruritus, PN, DLE, SCLE, ENL,** aphthous stomatitis, GVHD, sarcoidosis | B/L: hCG, CBC, CMP, neuro exam F/U: hCG Qwk x 4 then Q2-4wk, CBC/CMP Q2-3 mo, neuro exam Qmo x 3 → Q1-6 mo | **Sedation, constipation, sensory neuropathy,** xerosis, peripheral edema, thromboses, HA, mood Δ, leukopenia, erythroderma & TEN (↑ risk in HIV+), **phocomelia. (does not Immunosuppress)** | Neuropathy, sedatives, histamine, serotonin, prostaglandin | Decreases **TNF-α** & **IFN-γ**; **immunomodulatory/anti-inflammatory**, inhibits **PMN** phagocytosis; inhibits **monocyte** chemotaxis; inhibits **angiogenesis** | X |
| Diaminodiphenyl sulfone (**Dapsone**®) 25/100 mg Cost: **$90** / 30 tabs (100mg) (Aczone for acne) | 25 mg/day then ↑ to 100-200 mg/d take w/ food, prescribe w/ vit. E **NØ dermatoses** (**DH, Sweets, PG, LCV, EED, LABD, bullous LE**) MMP, Leprosy | B/L: **CBC,** CMP, UA, **G6PD,** neuro exam (reflexes) F/U: CBC Q2wk x 2mo → Q3-4 mo → Q6mo CMP & UA Q3-4mo, neuro exam Q3-4mo Order **reticulocyte count** if anemia develops | **Hemolysis** (dose-related), **methemoglobinemia** (dose related, ↓ **with Vit.E / cimetidine**, **✓ MetHb levels**), dispepsia, **agranulocytosis** (idiosyncratic), **severe DRESS-like** syndrome – (F, rash, hepatitis, eosinophilia, w/in 2-12 wks), **motor** neuropathy | **MTX, TMP/SMX, antimalarials,** rifampin, probenecid | ***Antimicrobial*** (antagonist of dihydropteroate synthetase → prevention of folic acid formation) ***Anti-inflammatory*** (inhibits **PMN chemotaxis & MPO,** inhibits Ig binding) | C |
| **Colchicine** (Colcrys®) Generic Cost: **$202** / 30 tabs | 0.5 or 0.6 mg BID - TID **NØ dermatoses, Vasculitides** (LCV, UV Erythema Induratum), **EBA**/LABD, AI-CTD | B/L: **CBC**, CMP, UA F/U: CBC, CMP, UA Qmo x 3-4mo → Q3-6mo | **Diarrhea, cramping, N/V** (dose-related, ↓ w/ aluminum antacids), **alopecia,** neuropathy, myopathy, aplastic anemia, overdose can lead to cholera-like syndrome or multiorgan failure | Severe hepatic, renal, GI, or cardiac disease, blood dyscrasias | Inhibits **microtubule** assembly by binding tubulin → inhibition of neutrophil chemotaxis/adhesion/degranulation (like griseofulvin, podophyllin) | C |
| **Cyclophosphamide** (Cytoxan®), 25, 50 mg tabs Cost: **$9.00** / tab | 1-3 mg/kg/day Advanced **CTCL**, PV, BP, **MMP**, SSc **ANCA vasculitides, PAN, SLE** | B/L: CBC, CMP, **UA**, hCG F/U: CBC & UA weekly 2-3 mo → biweekly → monthly → Q3mo. CMP monthly → Q3mo | N/V, anagen effluvium (5-30%), **sterility, hyperpigmentation** (skin/teeth/nails), **hemorrhagic cystitis** (dose-related; give w/ MESNA), bladder fibrosis & **carcinoma,** leukemia, NHL, **SJS** | **Fluconazole, allopurinol,** ciprofloxacin, cimetidine, **azathioprine, cyclosporine** | **Alkylating agent**, cell-cycle non-specific. Alkylation leads to DNA cross-linking & strand breaks. Greater effect on B lymphocytes > T cells, T suppressors > T helper cells. | D |
| **IVIg (does not Immunosuppress)** | 1 g/kg/day x 3-4 days GVHD, DM, blistering dz, **Kawasaki, TEN** | B/L: CBC, CMP, HBV, HCV, cryoglobulins, **IgA level** (use **Gammagard** in IgA def.) | Fluid overload, **headache, anaphylactic shock** (in IgA def), **aseptic meningitis,** hemolytic anemia, **ARF, dyshidrotic eczema** | **CHF & renal failure** contraindicated | Immunomodulatory; In TEN blocks **Fas-FasL** interactions | C |
| **Rituximab** (RITUXAN®) Cost: **$10,400** for 1g infusion | RA dose: 1g on days 1 & 15; Q24 wks prn Chemo dose: 375 mg/m² x 4 Qwk | **PV/PF/PNP, BP/MMP,** Vasculitis, AI-CTD **(DM, MCTD), cGVHD, Wegener's (GPA)** | B/L: CBC, **HBV**/HCV F/U: CBC, ± **CD19** Q6-12 mo | Infusion rxns, **cardiac arrhythmias, severe mucocutaneous rxns,** **HBV reactivation, JC virus** reactivation-**PML,** bowel perforation, **SJS/TEN** | Chimeric IgG binds **CD-20** (surface Ag on **B cells**), B cells depleted in 2-3 weeks, response sustained for ~6 months. | C |
| **Apremilast** (OTEZLA®) Cost: **$42,600** / year | d1: 10mg AM, d2: 10mg BID, d3: 10/20mg, d4: 20mg BID, d5: 20/30mg, d6 30mg BID, continue | No labs necessary – Best for scalp, palmoplantar, & pustular psoriasis | Nausea, diarrhea, nasopharyngitis, 10% pts have 10% weight loss; HA, rarely worsens depression or alters mood (<1%) | Rifampin, carbamazepine, phenobarbital, phenytoin ↓ effect | Inhibits **PDE4** → decreases cAMP conversion to AMP (**↑cAMP**) **↓NF-kβ** (↓inflam. cytokines), **↑CREB** (↑anti-inflam cytokines) | C |
| **Etanercept** (ENBREL®) Cost: **$69,000+** / year | 50 mg SQ 2x/wk x 3 mo → 50 mg Qwk Psor, PsorA, RA, JRA, AS | B/L: CBC, CMP, **HBV**/HCV, ± HIV **Quant Gold** and/or CXR **ANA** when supported by history (**High ANA (≥1:160)** is contraindication to starting anti-TNF biologics) F/U: CBC Q3-12 mo, **Quant Gold Qyear** | **TB & HBV reactivation, opportunistic infxns,** injection site rxn, **CHF** exacerbation, **paradoxical pustular psoriasis** (when used for RA/CD/GVHD), lupus-like syndrome (ANA+, dsDNA+, Histone−), lichenoid drug rxn & DI-LP, interstitial granulomatous dermatitis (IGD), **autoimmune hepatitis,** demyelinating dz **↑ risk of lymphomas, NMSC, & MM** in select patients Infliximab: **Infusion** rxns, + **psoriasiform scalp alopecia** | 14% injection site reaction. **History of heart failure (CHF)** | Fusion protein of two **p75 TNF** receptors, binds **soluble TNF-α & β** **PASI 75: 42-57%** \| **PASI 90: 19-26%** \| **PASI 100: 4-7%** | B |
| **Infliximab** (REMICADE®) 25% mouse Ab 50% human Ab | 3, 5, or 10 mg/kg IV Week 0, 2, 6, then Q8wks PsorA, CD, UC, AS | | | 20% minor infusion rxn. 10% of RA pts develop anti-drug Abs – Low dose **MTX** helps reduce this | Chimeric IgG1, binds **soluble & membrane-bound TNF-α** **PASI 75: 76-88%** \| **PASI 90: 60%** | B |
| **Adalimumab** (HUMIRA®) Cost: **$69,000+** / year | 80 mg SQ wk 0; wk1 - 40 mg Q2wk Psor, PsorA, RA, CD, AS | | | **History of heart failure (CHF), active TB, HBV, positive ANA** | Fully Human IgG1, binds **soluble & membrane-bound TNF-α** **PASI 75: 71-78%** \| **PASI 90: 40-44%** \| **PASI 100: 14-15%** | B |
| **Ustekinumab** (STELARA®) **$69,000**/yr ($114k for >100kg) | ≤ 100 kg: 45 mg wk 0, 4 → Q12 wk > 100 kg: 90 mg wk 0, 4 → Q12 wk | B/L: **Quant Gold** ± CBC, CMP F/U: **Quant Gold Qyear**, observe for salmonella | Nasopharyngitis (8%), URI (5%), headache (3%), fatigue (2%), **TB** & **salmonella**, Reversible Posterior Leukoencephalopathy Syndrome (**RPLS** – 1 case) | **Active TB, IL-12/23 deficiency** → (mycobacterial & salmonella infections) | Fully Human IgG1κ, binds **p40** subunit of **IL-12 & 23 (Th17)** **PASI 75: 73-79%** \| **PASI 90: 42-53%** \| **PASI 100: 19-26%** | B |
| **Secukinumab** (COSENTYX®) Cost: **$77,500** / year | 300mg wks 0, 1, 2, 3, 4 → 300mg Q4wk (or 150 mg Q4wk) | B/L: **Quant Gold** ± CBC, CMP F/U: **Quant Gold Qyear,** observe for IBD signs | Nasopharyngitis (11%), diarrhea (4%), URI (2.5%), **chronic mucocutaneous candidiasis** (1%), tinea (<1%) | **Use with caution in IBD.** May exacerbate or result in new onset IBD. | Fully Human IgG1, binds **IL-17A**, preventing interaction w/ its rec. **PASI 75: 75-87%** \| **PASI 90: 54-69%** \| **PASI 100: 24-39%** | B |
| **Ixekizumab** (TALTZ®) Cost: **$97,500** / year | 160 mg wk 0 → 80 mg on wks 2, 4, 6, 8, 10, 12 → 80 mg Q4wk | B/L: **Quant Gold** ± CBC, CMP F/U: **Quant Gold Qyear,** observe for IBD signs | Injection site rxn (17%), neutropenia (11%), URI (14% vs 13% placebo), **tinea** (2%), **chronic mucocutaneous candidiasis** (1.4%) | **Use with caution in IBD.** May exacerbate or result in new onset IBD. | Humanized IgG4 binds **IL-17A**, preventing interaction w/ its rec. **PASI 75: 87-90%** \| **PASI 90: 68-71%** \| **PASI 100: 35-40%** | |
| **Brodalumab** (SILIQ®) Most Cost Effective | 210 mg wks 0, 1, 2 → 210 mg Q2wk Prescribe through **REMS** program | B/L: **Quant Gold** ± CBC, CMP F/U: **Quant Gold Qyear** | Arthralgia (5%), headache (4%), fatigue (3%), diarrhea (2%), injection site rxn (1.5%), neutropenia (1%), **tinea** (1%), **candidiasis** | **Contraindicated in Crohn's Dz**, Suicidal ideation (suicide in 4 at-risk pts) | Fully Human IgG**2**, binds to **IL-17Rec A** (blocks **IL-17A,F,C** & **IL-25**) **PASI 75: 83-86%** \| **PASI 90: 69-70%** \| **PASI 100: 37-44%** | |
| **Guselkumab** (TREMFYA®) Cost: **$88,377** / year | 100 mg wk 0, wk 4 → Q8 wk | B/L: **Quant Gold** ± CBC, CMP F/U: **Quant Gold Qyear** | URI (14% vs 13% placebo), headache (5%), injection site rxn (5%), arthralgia (3%), **tinea** (1%), **HSV** (1%) | No contraindications. Monitor for TB | Fully Human IgG1λ, binds **p19** subunit of **IL-23** (↓ **IL-17A,F** & **IL-22**) **PASI 75: 83-91%** \| **PASI 90: 64-73%** \| **PASI 100: 34-37%** | |
| **Omalizumab** (XOLAIR®) Cost: **$1,200** per 150 mg | 150-300 mg SC Q4wk For **CIU**, off label (**Atopic Derm**) | B/L: CBC, IgE F/U IgE levels are unreliable once complexed to drug | Injection site rxn (45%), URI (20%), serum sickness, **anaphylaxis (0.2%)** (must observe pt for 20 mins) | Caution in hx of anaphylaxis | Humanized IgG1κ binds & complexes with free **IgE** (Fc region), prevents binding to **FcεRI** on mast cells & basophils. FcεRI down-regulated | |
| **Dupilumab** (DUPIXENT®) Cost: **$1,700** per 300 mg | 600 mg x 1 → 300 mg Q2 wk **Atopic Dermatitis** | No necessary baseline labs, counsel on **conjunctivitis & keratitis**, don't stop asthma meds | **Conjunctivitis** (10%), injection site rxn (10%), **HSV** (6%) | Caution in hx of anaphylaxis | **IL-4Rα antagonist**, inhibits IL-4 & IL-13 responses, **↓ IgE** | |

# RESIDENT ROUNDS: PART III

# Case Report: Triple Combination Therapy for Recalcitrant Perineal Pyoderma Gangrenosum

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## ABSTRACT

Pyoderma gangrenosum (PG) is a destructive ulcerative process, which is usually idiopathic or associated with underlying systemic disease. Its pathogenesis remains unknown. A 30-year-old male with a history of Crohn's disease presented with an advanced perineal and inguinal ulcer consistent with pyoderma gangrenosum, which only partially responded to oral and intralesional corticosteroids and adalimumab 80mg biweekly. The patient was started on adjunct combination cyclosporine and thalidomide, which resulted in prompt relief and profound healing. Treatment of pyoderma gangrenosum is often challenging with no standardized treatment protocols. Combination therapy should be considered in patients with refractory disease, especially with failure of monotherapy.

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## INTRODUCTION

Pyoderma gangrenosum (PG) is a rare, chronic condition of complex etiology first described in 1930 by Brusting, Goeckerman, and O'Leary.[1] The term PG describes a painful disfiguring ulcerative process, which more commonly affects women between 20 and 50 years old, but can affect either sex and can occur at any age including childhood (4% of cases).[2] Roughly 50 percent of cases are idiopathic, while the other half of cases is associated with underlying systemic illness, of three main categories: inflammatory bowel disease (IBD), systemic arthritis including rheumatoid arthritis (RA), and bone marrow dyscrasias (paraproteinemia, acute myelogenous leukemia, myelodysplasia).[2] Given the association of PG with autoimmune illnesses, an immune dysregulation pathogenesis is implicated, though the exact pathogenesis remains to be elucidated.

PG belongs to the family of neutrophilic dermatoses. It represents an inflammatory process that initially manifests as an enlarging papule or pustule on a violaceous base that rapidly involutes into superficial to deep necrotic ulcers with overlying exudates. PG is classically well-circumscribed by an undermined border outlined by a gray to violaceous rim. Erythematous rims may indicate active areas of inflammation. Sites of involvement most commonly include the pretibial region of the lower extremities and sites of cutaneous injury. Pathergy, a phenomenon in which trivial cutaneous injury or trauma instigates new PG lesions and exacerbates existing ulcers, is seen in 20 to 30 % of PG cases.[2] Pathergy in PG characteristically occurs around surgical sites such as planned ostia formations in IBD patients and breast reconstructions. Subtle trauma may induce pathergy classically in sites of IV insertions and sites of intralesional corticosteroid therapy.

Idiopathic PG is a diagnosis of exclusion. When PG is suspected by physical exam, it is imperative to obtain a detailed history to identify or otherwise rule out comorbidities. Standard laboratory evaluation includes a complete blood count, complete metabolic panel with liver function tests, serum, and urine protein electrophoresis, free light chain assay, rheumatoid factor, anti-nuclear antibodies, anti-phospholipid antibodies, HIV serology studies, mycobacterial studies, and a gastrointestinal workup for IBD. A wedge biopsy at the periphery of the ulcer should be performed to sample the ulcer, its margin, and nearby uninvolved skin. Careful planning of the biopsy site with diligence to minimize biopsy size is essential to mitigate the chances of pathergy. However, enough tissue should be obtained for special dermatopathology stains to rule out infectious processes.

Treatment of PG has been difficult for several reasons including the lack of gold standard treatments and universal therapeutic protocols. There are currently no FDA approved therapies for PG. Only two randomized controlled trials have evaluated treatments for PG. Anti-tumor-necrosis-factor-α (TNF- α) therapy in the form of infliximab infusion and cyclosporine have both been deemed effective in the treatment of PG. Other TNF-antagonist studies

**FIGURE 1. (A)** Perineal ulcer with undermined borders. **(B)** Expansion of ulcer after aggressive debridement in the operating room; violaceous border becomes apparent.

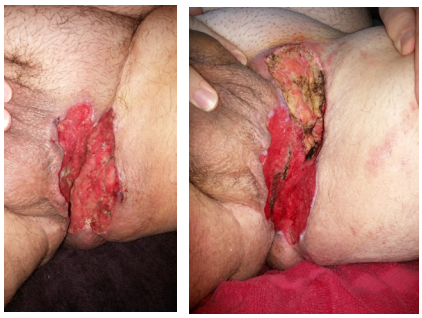
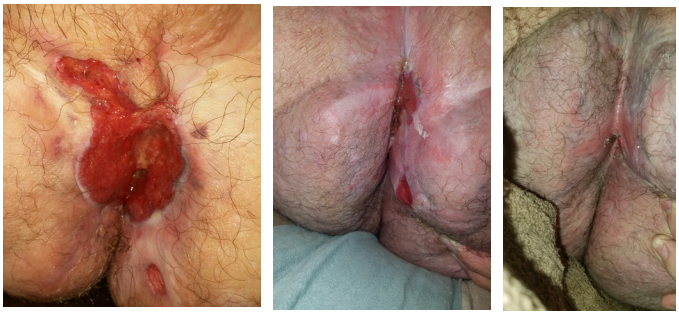


**FIGURE 2. (A)** Treatment-resistant perineal pyoderma gangrenosum after 18 months of treatment with prednisone 40 mg every other day and adalimumab 80 mg every other week. **(B)** One year after adjunct therapy with cyclosporine 500 mg daily (3.5 mg/kg/day) and thalidomide 200 mg daily added to adalimumab therapy. (c) Nearly complete healing of perineal and inguinal pyoderma gangrenosum over a two-year timeframe.



are limited to anecdotal data in case reports, the first of which dates back to 2005.[3] We herein describe our experience of clinical success using triple combination therapy of cyclosporine, thalidomide, and adalimumab for recalcitrant Crohn's-related perineal and inguinal pyoderma gangrenosum.

## CASE REPORT

A 30-year-old male with Crohn's disease (CD) developed an ulcer in the perineum and inguinal crease nearly five years after a total colectomy with ileostomy and rectal closure. The ulcer was initially treated with multiple surgical debridements, which led to ulcer expansion (Figure 1). An outside dermatologist was consulted and performed a biopsy that demonstrated perifollicular neutrophilic microabscesses with neutrophilic infiltrates undermining the epidermis. There was no granulomatous inflammation to suggest cutaneous Crohn's disease. Special stains including Gram, PAS, and Fite stains failed to reveal an infectious etiology. The patient was diagnosed with PG based on the history of pathergy with debridement, classic histological findings, and exclusion of other causes of ulceration, all in the setting of Crohn's disease. He was appropriately started on oral prednisone with intralesional corticosteroids and adalimumab which, led to moderate improvement. He was referred to our clinic after 18 months of treatment with prednisone 40 mg every other day and adalimumab 80 mg every other week (Figure 2a) after this regimen was no longer achieving progress.

For the remaining treatment-resistant ulcer, we initiated adjunct therapy with cyclosporine 500 mg daily (3.5 mg/kg/day) and thalidomide 200 mg daily. Neoadjuvant thalidomide was selected as treatment for this gentleman since the drug specifically inhibits TNF-α release and activity,[4] along with a myriad of other anti-inflammatory effects including suppression of IL-12 production[5] and inhibition of IFN-γ.[6] With combination cyclosporine, thalidomide, and adalimumab, the prednisone was tapered and discontinued. The patient noticed his ulcer contracting in size within eight weeks. After several months of consistent improvement, the patient was weaned off of cyclosporine and thalidomide. He was followed up periodically and his progress was measured by photo documentation. Over the next two years, the patient's disease waxed and waned, and each flare was controlled adequately by reintroducing varying doses of cyclosporine and thalidomide while remaining on adalimumab continuously.

## DISCUSSION

Treatment of PG is often challenging for multiple reasons. Many treatments have been attempted with limited success. The ongoing hunt for therapies suggests no one treatment has been particularly efficacious. Nearly all current therapeutic options are empiric and anecdotally based, lacking data to provide sound recommendations. Most therapeutic regimens have been described in case reports and small series. While no standardized treatment regimens have been proposed, two well-designed randomized controlled trials are documented for the treatment of PG. In 2005, Brooklyn et al conducted a blinded, placebo-controlled study describing the successful use of infliximab infusion at 5 mg/kg.[7] In 2015, results from Craig et al[8] in a head-to-head trial comparing prednisolone 0.75 mg/kg/day and cyclosporine 4 mg/kg/day demonstrated equal efficacy between both regimens.[9] Both randomized controlled trials were designed and implemented in the United Kingdom, which further highlights the need for trials in the United States, as demographics and environmental exposures differ between the two nations.

Therapeutic goals when treating PG include reducing local inflammation within the chronic ulcer to reduce pain and promote healing, while correcting any corresponding underlying systemic illness. Attempted treatments have included corticosteroids, either locally or in combination with systemic corticosteroids, paired with adjunctive corticosteroid sparing agents.[10] For mild or early lesions, local therapy is typically initially attempted.

Local therapy includes effective wound care with moisture-retentive dressings,[11] topical corticosteroids, 5-aminosalicylic acid, sodium cromoglycate, and nitrogen mustard, with or without intralesional corticosteroids, or a short course of systemic cyclosporine. For more advanced disease, systemic therapy is necessary and includes systemic corticosteroids, azathioprine, alkylating agents (cyclophosphamide, chlorambucil, melphalan), daunorubicin, cyclosporine, tacrolimus, thalidomide, sulfa drugs, and minocycline. Non-pharmacologic therapies for advanced disease include intravenous immunoglobulin (IVIG), plasmapharesis, and hyperbaric oxygen therapy. In recalcitrant or severe cases, systemic steroids are the initial mainstay treatment with consideration for combination cyclosporine.[12] Surgical treatment has been proposed with split and full-thickness skin grafting and negative pressure wound therapy with favorable results.[13] However, many would argue surgery in a PG patient is ill-advised given the known risk of pathergy. If skin grafting is proposed, one must understand the risks of new ulcer formation at the donor site and enlargement of ulcers at the recipient site.

Given the wide variety of aforementioned treatments, selecting a treatment regimen with confidence can certainly be challenging. Additionally, PG often portends an unpredictable course and delayed response to therapy which, heralds difficulty in assessing treatment successes and failures. Miller and colleagues have delineated a practical ranking of medication efficacies in a 2010 review.[12] Prednisone, infliximab, cyclosporine, mycophenolate mofetil, and adalimumab were ranked among the top five pharmacotherapies with regard to efficacy. In our opinion, the soundest recommendation is infliximab infusion at 5 mg/kg as the corresponding study was blinded and placebo-controlled.

Over the past few decades, anti-TNF therapy has obtained FDA approval for autoimmune diseases such as IBD, RA, and psoriasis. While infliximab has been proven to be effective in a well-designed study, no such study exists for adalimumab or etanercept in the treatment of PG. Etanercept has been used with success in a small case series,[14] while only case reports have documented the efficacy of adalimumab.

In our patient, the TNF-antagonist was also beneficial for his underlying systemic disease. This is expected since adalimumab is FDA approved for CD. In cases of PG with underlying systemic illness, it is imperative to manage such patients in conjunction with gastroenterologists, rheumatologists, hematologists, and oncologists, as necessary. Tailoring therapy to target the underlying illness will often improve the cutaneous manifestation of PG. In the common case of idiopathic PG, the dermatologist carries sole responsibility in providing care, perhaps in conjunction with wound care clinics.

Although there exists a dire need for clinical trials in such a refractory illness like PG, designing trials harbors difficulty, mainly due to the rarity of the PG. Additionally, it is difficult to define outcomes in a PG study since ulcers require extensive time spans to heal, even after inflammation has subsided, as demonstrated in some of our photos (Figure 2). Cessation of the primary inflammation of PG and healing of ulcerated wounds are two distinct processes that should be evaluated separately. Wound healing is further hindered by location on the lower extremities, venous insufficiency, diabetic circulation compromise, and old age.

In summary, the treatment of PG is difficult due to lack of treatment recommendations. Infliximab, prednisone, and cyclosporine are all well-known to induce rapid remission. However, given the chronicity of PG, a maintenance regimen is necessary, as up to 50% of patients require maintenance therapy to ensure remission.[15] Biological therapy is an excellent therapeutic modality for PG, boasting a favorable side effect profile compared to other immunosuppressive therapies. Adalimumab is inarguably more convenient for patient preference compared to receiving infliximab infusions. In our experience, many patients will benefit from adjuvant cyclosporine to induce rapid remission and for flare ups when a patient is controlled on adalimumab. In extremely resistant cases, like the one presented in this case report, multicombination therapy may be necessary to achieve desired outcomes.

## DISCLOSURE

The authors have no conflict of interest to declare.

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