Dilemmas in Rheumatology

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Management of Acute Monoarticular Arthritis What procedure is critical to the diagnosis?

A 52-year-old man is admitted with community–acquired pneumonia (CAP). On hospital day 3, the patient was awakened at 4:00 am by an aching pain in his right knee. Within a few hours, the joint was dusky red, hot, and exquisitely tender to the point that the patient was unable to actively move the joint or ambulate. There is no history of trauma to the joint.

1. **Blood cultures**
2. **CBC with differential**
3. **Weight-bearing knee x-ray**
4. **Arthrocentesis**
5. **Serum uric acid level**

Approach to the Patient with Acute Inflammatory Monoarthritis

- **Three most common etiologies:**
  - **Infection: assume present until proven otherwise**
  - **Crystal-induced**
  - **Chronic inflammatory arthropathy**
- **Diagnostic studies:**
  - **Synovial fluid analysis**
  - **Radiograph of the joint**
  - **CBC**
  - **In selected patients:**
    - **ESR; pan-cultures; PT, PTT; uric acid - not diagnostic as the level can be normal in up to 30% of patients experiencing an acute gouty attack**

Ma L et al. CMAJ 2009;180:59

Synovial Fluid Analysis
The Big Three

1. Cell count with differential
2. Crystal analysis by polarized microscopy
3. Gram's stain and culture

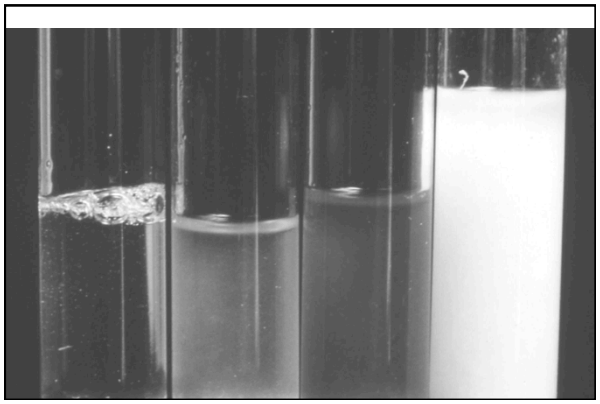
Synovial Effusions: Classification

Type of Fluid	*Special Features*	*Leukocytes/mm^3*
Normal	Clear, Colorless, Viscous	<200 (<25% PMNs)
Noninflammatory (Type I)	Clear, Yellow, Viscous	200-2,000 (<25% PMNs)
Inflammatory (Type II)	Cloudy, Yellow, Low viscosity	2,000 or greater (>50% PMNs)
Septic (Type III)	Purulent	>50,000 (>75% PMNs)

Synovial Fluid Characteristics

- Cell count:
  - WBCs > 50,000: increase suspicion of infection;
    - WBCs < 25, 000 (LR 0.32)
    - WBCs > 25,000 (LR 2.9)
    - WBCs > 50,000 (LR 7.7)
    - WBCs > 100,000 (LR 28)
  - Not all counts > 50,000 are septic!
  - WBCs > 100,000:
    - Infection
    - Reactive arthritis (Reiter's): neg GS and culture
    - Crystal-induced (pseudosepsis): neg GS and culture
    - RA pseudosepsis syndrome: neg GS and culture

Margaretten ME et al. JAMA 2007;297:1478



Synovial Fluid Characteristics

- Gram's stain (sens 50-75%; spec 100%):
  - 60-75% positive in gram positive septic arthritis
  - 50% positive in nongonococcal gram negative septic arthritis
- Culture:
  - Bacterial: nearly 95% positive with exception of gonococcus (25%)
  - AFB: 50-80% positive; may need synovial biopsy for culture, histology
  - Fungal: < 50% positive, candida higher yield; may need synovial biopsy for culture, histology

Brannan SR et al. J Emerg Med 2006;30:331

Septic Arthritis

- A true rheumatologic emergency!
- "If you don't aspirate, prepare to litigate"
- A missed septic joint = irreversible cartilage loss within a few days particularly with gram-positive organisms
- Rule of thumb: assume that the joint is infected until proven otherwise
- If infection cannot be ruled out by initial diagnostic studies, treat presumptively for a septic joint until synovial culture results become available

Septic Arthritis: Common Organisms

AGE	ORGANISM
< 6 months	Staph, Strep, gram neg
6 months – 2 years	H. influenzae, S. aureus
2-15 years	Staph, Strep pyogenes and pneumoniae
16-50 years	Neisseria gonorrhoeae, S. aureus
> 50 years	Staph, Strep, gram neg

*S. aureus: most common due to a collagen adhesion factor (**agr** gene) and fibronectin binding proteins*

Points to Remember

- Most common etiologies of acute monoarticular arthritis are: infection, crystal-induced, and chronic inflammatory arthritis
- Synovial fluid analysis is key to diagnosis:
  - Cell count with differential
  - Crystal analysis
  - Gram's stain and culture
- Not all synovial WBC cell counts > 50,000 are septic
- Synovial fluid WBCs > 100,000 with a negative gram stain could be septic but also consider *pseudoseptic* syndromes

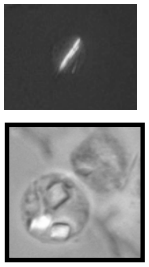
Acute Crystalline Arthropathy
What is the safest treatment option?

Back to the case: right knee arthrocentesis: 48K WBC with 90% PMNs, Gram's stain negative, + intracellular needle-shaped negatively birefringent crystals; Cr 2.0.

1. NSAIDs
2. Colchicine
3. Corticosteroids
4. Analgesics with observation

Synovial Fluid Examination: Crystals

- Monosodium urate (MSU): needle-shaped; yellow-parallel; negative birefringence
- Calcium pyrophosphate dihydrate (CPPD): rhomboid-shaped; blue-parallel; positive birefringence; *ABC*: *A*lign, *B*lue, *C*alcium



Treatment of Acute Gouty Arthritis

- Comorbid medical illnesses, status of GI, hepatobiliary, cardiac, hematopoietic, and renal function guide the safest options:
  - NSAIDs
  - Colchicine
  - Corticosteroids
  - Analgesics with observation
- "Pill-in-the-pocket" strategy should be considered

Neogi T. N Engl J Med 2011;364:443

Nonsteroidal Anti-inflammatory Drugs

- Indomethacin: 50 mg qid x 1d, 50 mg tid x 1-2d, 25 mg qid x 1-2d, 25 mg tid x 2-3 d, taper
- Most NSAIDs effective: use maximum dose as soon as the attack occurs
- Contraindications: bronchospasm, PUD, CRI, hepatic insufficiency, severe CHF, warfarin therapy
- Use with caution: mild renal insufficiency, h/o PUD, IBD, unstable CAD or HTN

Oral Colchicine (Colcrys®) ≈$5.00/tab

- Most effective within 24 hr of an attack
- Dosing (normal renal and hepatic function): 0.6 mg orally every hour until: joint symptoms ease; GI toxicity occurs (N/V/D); maximum dose of 4.8 mg (8 tabs) : 80% of patients develop increased peristalsis, abdominal pain, or N/V/D before pain relief occurs!
- Low-dose colchicine regimen may be as effective:
  - Colchicine 1.2 mg followed by 0.6 mg in 1 hour
  - Incidence of N/V/D less with the low-dose regimen versus the above high-dose regimen

Terkeltaub RA et al. Arthritis Rheum 2010;62:1060

Oral Colchicine: Toxicity

- Gastrointestinal
- Alopecia
- Neuropathy
- Myopathy: often confused with polymyositis
- Bone marrow depression: ↓ wbc / plts
- Toxicity is more common in the elderly, in the setting of renal or hepatic insufficiency, and in patients already on daily low-dose colchicine prophylaxis for recurrent gouty attacks

Oral Colchicine: Toxicity

- Fatal and non-fatal cases of colchicine toxicity have been reported with concomitant use of CYP3A4 and P-glycoprotein inhibitors:
  - Clarithromycin; erythromycin
  - Calcium channel blockers: verapamil and diltiazem
  - Keto- and itraconazole
  - HIV protease inhibitors
  - Grapefruit juice
  - Cyclosporine: avoid colchicine as a *severe* neuromyopathy can occur (Simpkin PA et al. J Rheumatol 2000;27:1334)

www.fda.gov/Drugs/DrugSafety 2009

Prophylactic Colchicine

- **Prophylactic colchicine is used to prevent recurrent attacks of gout or when starting urate-lowering therapy (24% risk of precipitating an acute gouty attack)**
- **Dosage:**
  - **Normal renal and hepatic function: 0.6 mg po bid**
  - **Elderly or CrCl 30-50: 0.6 mg po qd or qod**
  - **CrCl < 30: avoid acute or prophylactic therapy**
  - **Avoid in hemodialysis and in severe hepatic dysfunction**

Terkeltaub RA. Semin Arthritis Rheum 2009;38:411

Intra-articular Corticosteroids

- **Useful if the acute gouty arthritis is limited to 1 or 2 aseptic joints or bursae**
- **Large joints: 40 mg triamcinolone acetonide or methylprednisolone acetate diluted with several mls of 1% lidocaine**
- **Smaller joints or bursae: 10 to 20 mg of the above preparations diluted with a few mls of lidocaine**
- **90% effective within the first 24 hours**

Systemic Corticosteroids

- **Indications: contraindications to other acute therapies, acute gout refractory to other rxs**
- **Widely used: PO, IM, IV routes**
- **Prednisone: 30-50 mg daily with taper over 7-10 days (rare CNS effects; cautious use in diabetics, concurrent infection)**
- **Triamcinolone acetonide (Kenalog®-40):**
  - **60 mg IM (gluteal) - can repeat x 1 the next day if necessary**
- **Rebound arthropathy: rare**

Janssens HJ et al. Lancet 2008;371:1854
Janssens HJ et al. Cochrane Database Syst Rev 2008;16:CD005521

Pseudogout

- Acute or subacute arthritis attacks which last several days if untreated; clusters of attacks may last several weeks to months
- Typically involves a large joint: knee, wrist, ankles, shoulders; successive polyarticular involvement with a migratory pattern can occur
- In the elderly, attacks may be associated with high and prolonged fever, confusional state

Pseudogout: Management

- Acute attacks (pseudogout):
  - NSAIDs
  - Aspiration and injection of steroids
  - Prednisone 30-50 mg daily with taper over 7-10 days
  - Triamcinolone acetonide 60 mg IM, can repeat x 1
- Recurrent attacks:
  - Prophylactic oral colchicine (requires renal dosing, do not use if CrCl < 30)

Points to Remember

- The treatment options for acute crystalline arthropathy include NSAIDs, colchicine, corticosteroids, or analgesics with observation
- Assess the patient's comorbid medical illnesses including renal, hepatic, and hematopoietic function to guide the safest treatment option
- Corticosteroids (PO, IM, IV, Intraarticular) can be used to treat acute crystalline arthropathy in patients with renal insufficiency or on anticoagulation therapy

Urate-lowering Therapy (ULT)
What are the indications and options?

Back to the case: no history of previous attacks, renal stones, or tophi; consumes 1-2 drinks/day. BMI 30. sUA 10 (<7). Cr 2.0. LFTs nl.

1. **Lifestyle modification**
2. **Allopurinol 100 mg/day**
3. **Allopurinol 300 mg/day**
4. **Febuxostat 40 mg/day**

Reversible Secondary Causes of Hyperuricemia

- **Alcohol consumption**
- **Diets containing purine-rich foods**
  - **Meats, organ meats, shellfish**
  - **Purine content of diet only contributes 1.0 mg/dl to the sUA concentration!**
- **Medications that decrease the renal excretion of uric acid: CSA, nicotinic acid, diuretics, ethambutol, low-dose ASA, PZA.**
- **Obesity: 10% weight loss can improve hyperuricemia**

Symptomatic Hyperuricemia Lifestyle Modification

- **Weight loss advised**
- **Consume meat, seafood, and alcohol in moderation**
- **Limit fructose intake**
- **Purine-rich vegetables are acceptable**
- **Low-fat dairy products, coffee, and wine may be protective**

Choi HK et al. Curr Opin Rheumatol 2005;17:341 / BMJ 2008;336:309

Indications for Chronic Treatment of Symptomatic Hyperuricemia

- > 2 or 3 attacks of gouty arthritis within 1-2 years: lifestyle modifications after the 1st attack
- Chronic gouty arthritis with bony erosions
- Tophaceous gout
- Renal stones: uric acid or calcium
- Prevention of uric acid nephropathy in the tumor lysis syndrome

Mikuls TR et al. Arthritis Rheum 2004;50:937

Indications for Allopurinol over Uricosurics

- Overproducers: > 700 mg uric acid / 24 hr urine
- Tophaceous gout
- Renal stones: uric acid or calcium
- Renal insufficiency: CrCl < 50 uricosurics are ineffective
- Prophylaxis against tumor lysis syndrome
- Hyperuricemia secondary to myeloproliferative diseases
- Failure or intolerance of uricosuric medications

Uricosurics (probenecid)

- Indications: underexcretors with adequate renal function not on > 81 mg/day of ASA
- Contraindications:
  - CrCl < 50: drug is ineffective
  - Age > 65: diminished CrCl
  - Uric acid nephrolithiasis or overproducers of uric acid
  - ASA usage > 81 mg/day: negates the drug's uricosuric actions

Urate-lowering Therapy (ULT)

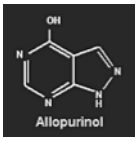
- Do not use to treat an acute attack of gout or start in the setting of an acute attack (wait 2-4 weeks)
- If an acute attack occurs while on these medications, continue these meds while treating the acute attack; adjust these medications after the acute attack subsides
- Patients starting urate-lowering therapy should be on prophylactic colchicine or low-dose daily NSAID therapy for the first 6 to 12 months to minimize the 24% risk of acute gouty attacks precipitated by urate-lowering therapy (Borstad GC et al. J Rheumatol 2004;31:2429)

Allopurinol Dosing / Renal Insufficiency

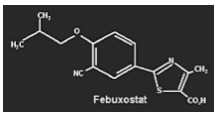
- CrCl 0 ml/min: 100 mg q3d
- CrCl 10 ml/min: 100 mg q2d
- CrCl 30 ml/min: 100 mg qd Hande et al. Am J Med 1984
- CrCl 60 ml/min: 200 mg qd
- CrCl 90 ml/min: 300 mg qd (scant data >300 mg/d)
- 100 mg/day for every 30 ml/min of CrCl
- Titrate slowly (start with 100 mg/day) with goal sUA < 6.0 mg/dl (Perez-Ruiz F et al. Arthritis Rheum 2007;57:1324)
- Reports of no association between dose and risk of hypersensitivity syndrome/toxicity (Dalbeth N et al. J Rheumatol 2006;33:1646 / Stamp LK et al. Arthritis Rheum 2011;63:412)
- Evaluate risks/benefits in CKD; febuxostat is an option

Allopurinol: Drug Interactions

- Ampicillin: 3- to 10-fold risk of rash
- Thiazides: potentiate allopurinol toxicity
- Warfarin: prolonged half-life
- Theophylline: prolonged half-life
- Cyclophosphamide: enhanced bone marrow suppression
- Azathioprine / 6-mercaptopurine:
  - Degradation of these purine analogues blocked by inhibiting xanthine oxidase
  - Use with allopurinol not advised; azathioprine dose reduction of 75%



Febuxostat (Uloric®)



- Dosing: 40 mg/d with ↑ to 80 mg if needed for goal sUA
- More selective xanthine oxidase inhibitor ($175/mos)
- Metabolized mainly in the liver; allopurinol metabolites are renally excreted
- Can be used in mild CKD 2 to moderate CKD 3 (CrCl 30-59 ml/min); data in CKD 4 not yet published
- AE rates not different from allopurinol except cardiovascular events 0.74/100 pt-yrs vs 0.60/100 pt-yrs: causality not established

Gout: Points to Remember

- Lifestyle modifications are recommended for gout
- Assess the patient's comorbid medical conditions including renal and hepatic function to guide the safest treatment options for acute gout and symptomatic hyperuricemia with a goal sUA < 6.0 mg/dl.
- Acute gout (pill-in-the-pocket): NSAIDs, colchicine, corticosteroids
- Indications for lifelong ULT:
  - 2 or more gout attacks/year
  - Tophaceous gout
  - Uric acid renal stones
- Never start, stop, or adjust ULT during an acute flare

Gout: Points to Remember

- ULT:
  - Start low and gradually titrate to goal sUA
  - Prophylactic colchicine or low-dose NSAID for at least 6-12 months
- Febuxostat:
  - Intolerant to allopurinol or difficult to achieve goal sUA
  - CKD with CrCl > 30 ml/min; no dose adjustment needed
- Pegloticase: refractory to conventional ULT

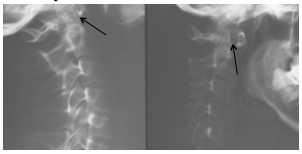
Gout quality of care indicators: Mikuls TR et al. Arthritis Rheum 2004;50:937, Zhang W et al. Ann Rheum Dis 2006;65:1312, Jordan KM et al. Rheumatology 2007;46:1372.

Perioperative Evaluation and Inpatient Management of Immunosuppression in Rheumatic Diseases

- A 48-year-old man with a 20-year history of seropositive, nodular, erosive RA presents for elective total hip arthroplasty (THA). He is on MTX 20 mg/wk, anti-TNF therapy, and chronic prednisone 5 mg/d. You are consulted by Orthopedics for preoperative assessment and medication management.
- All of the following are appropriate <u>except</u>:
  1. Cardiovascular risk assessment
  2. Lateral C-spine with flexion and extension views
  3. Perioperative stress-dose steroids
  4. Continue MTX and anti-TNF therapy to prevent a RA flare
  5. Hold MTX and anti-TNF therapy

Pre- and Perioperative Management of Patients with Rheumatic Diseases

- RA is associated with a 60% increased risk of CV death compared with the general population (Meune C et al. Rheumatology 2009;48:1309). Risk stratification is necessary.
- RA: rule out C1-C2 subluxation prior to intubation with lateral C-spine with flexion and extension views



Medication Management: Glucocorticoids

- Glucocorticoids: prolonged (> 3 weeks) use resulting in adrenal insufficiency:
  - Hydrocortisone 100 mg IV q8h perioperatively then slow dose reduction over 48 hours until able to take regular oral dose (moderate and major surgical stress)
  - Cochrane Review: 2 randomized controlled trials involving 37 patients reported that supplemental perioperative steroids were *not* required in surgical pts with adrenal insufficiency. Cannot support or refute use (Cochrane Database Syst Rev 2009;4:CD005367; Marik PE et al. Arch Surg 2008;143:1222)
- Risk of adrenal insufficiency outweighs short-term high-dose steroids

Medication Management: NSAIDs

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs): Should be stopped at least 5 half-lives prior to surgery:
  - T ½ 2-6 h stop 1-2 days before (ibuprofen, diclofenac, indomethacin)
  - T ½ 7-15 h stop 2-3 days before (naproxen, sulindac, celecoxib)
  - T ½ > 20 h stop 7-10 days before (meloxicam, nabumetone, piroxicam)

Douketis JD et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). Chest 2008;133:299S

Medication Management: ASA and Clopidogrel
American College of Chest Physicians 2008

- For pts not at high risk for cardiac events, recommend interruption of above anti-platelet agents 7-10 days prior to surgery (Grade 1C)
- High risk of cardiac events (exclusive of coronary stents) and noncardiac surgery: cont ASA up to and beyond surgery; d/c clopidogrel 5-10 days prior (2C)
- CABG: continue ASA; d/c clopidogrel 5-10 days prior (1C)
- Bare metal coronary stenting within 6 weeks: cont ASA and clopidogrel; drug-eluting stent within 12 months: cont ASA and clopidogrel (1C)

Medication Management: DMARDs

- Methotrexate (orthopedic surgery trials):
  - Concern for ↑ infections and ↓ wound healing
  - Several retrospective trials conclude that continued MTX therapy may be safe in the perioperative period. Problematic:
    - Retrospective nature and small number of pts
    - Comparisons: with and without MTX while others evaluated continuing vs d/cing MTX
    - Different durations of interruption and MTX doses
    - No data for pts on combination DMARD rx

Murata K et al. Mod Rheumatol 2006;16:14, Pieringer H et al. Clin Rheumatol 2008;27:1217, Heldmann F et al. Clin Exp Rheumatol 2010;28:S110

Medication Management: DMARDs

- Methotrexate (2 prospective trials):
  - 32 pts undergoing THA: 4/16 local infections if continued MTX versus 0/26 infections if MTX held week before and after; no ↑ flares. (Carpenter MT et al. Orthopedics 1996;19:207)
  - 388 pts (orthopedic surgeries) – infections:
    - Continued MTX (median dose 7.5-10 mg/wk): 2%
    - MTX held 2 wks before and after: 15%
    - RA not on MTX but on other DMARDs: 10.5%

    (Grennan DM et al. Ann Rheum Dis 2001;60:214)
- Multiple confounders: severity of RA, inflammatory burden, comorbities, duration and site of surgery, primary or revision surgery. Recommendation: HOLD MTX wk before and after

Medication Management: Anti-TNFs

- Anti-TNF therapy is associated with an increased risk of serious skin and soft tissue infections (IRR 4.28). Dixon WG et al. Arthritis Rheum 2006;54:2368
- Current anti-TNF agents:
  - Infliximab: t ½ 10 days
  - Etanercept: t ½ 4 days
  - Adalimumab: t ½ 20 days
  - Certolizumab: t ½ 14 days
  - Golimumab: t ½ 14 days

Medication Management: Anti-TNFs

- Retrospective studies suggest that continued use of anti-TNFs does not ↑ the risk of postoperative infections or wound healing. den Broeder AA et al. J Rheumatol 2007;34:689, Goh L et al. Rheumatol Int 2011 [Epub]
- Other retrospective studies report an ↑ risk of surgical infections with continued use of anti-TNF agents. Giles JT et al. Arthritis Rheum 2006;55:333, Kawakami K et al. Rheumatology 2010;49:341.
- These studies are limited by their retrospective nature, small sample sizes, different comparison groups, and lack of uniform drugs and dosing

Bongartz T. J Rheumatol 2007;34:4, Pappas DA et al. Curr Opin Rheumatol 2008;20:450

Medication Management: Anti-TNFs

- Need randomized trials in which drug discontinuation can be determined, exposure times measured, and outcomes prospectively observed
- In this situation of uncertainty, major Rheumatology Societies recommend withholding anti-TNF agents perioperatively considering the morbidity of orthopedic surgical site infections
- Recommendations:
  - Hold anti-TNF therapy agents for 3-5 half lives preoperatively and restart in 2-3 wks if adequate wound healing: 2 wks for etanercept, and 4 wks for infliximab, adalimumab, certolizumab, and golimumab *Pappas DA et al. Curr Opin Rheumatol 2008;20:450*

Points to Remember

- There is an increased incidence of cardiovascular events in patients with rheumatic diseases
- Patients with RA should be screened for C1-C2 subluxation prior to elective intubation
- Perioperative stress-dose steroids are indicated for patients on chronic corticosteroids
- Most DMARDs are safe to continue perioperatively unless infection present or there is a risk for neutropenia. Exceptions are MTX, anti-TNF agents, and other biologics which should be held.

What is the Diagnosis?

- 45-year-old man presents initially with nodular skin lesions followed by painful necrotic purpura affecting his ears and extremities. WBC 1.2.

1. Wegener's granulomatosis
2. Cutaneous polyarteritis nodosa
3. Levamisole-adulterated cocaine
4. Henoch-Schönlein purpura
5. Weber-Christian disease

Cutaneous Vasculopathy in Users of Levamisole-Adulterated Cocaine

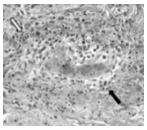
- Levamisole:
  - Immunomodulatory properties: used to treat RA in the 1970s and colon ca with 5-FU in the 1990s
  - Removed from the US market in 2000 because of the potential for agranulocytosis
  - Veterinary use as an anthelminth agent
- USA 2009: 69% of cocaine adulterated with levamisole to enhance euphoric and addictive effects

Levamisole-Adulterated Cocaine Vasculopathy

- Retiform purpura with propensity to involve the ears
- Hypercoagulability: transient antiphospholipid antibodies (aPLs)
- Leukopenia or neutropenia: > 50% cases
- + ANCAs (high titer) reactive to multiple target antigens:
  - p-ANCA and/or c-ANCA
  - Myeloperoxidase (MPO) and/or Proteinase 3 (PR3)
  - Absent anti-neutrophil elastase characteristic of cocaine-induced midline destructive lesion

Levamisole-Adulterated Cocaine Vasculopathy

- Skin biopsy: leukocytoclastic vasculitis
- Utox for cocaine (2-3 day window)
- Treatment:
  - Cocaine cessation (smoking and snorting) and supportive care
  - Low to high dose steroids
  - Extensive skin necrosis reported with cocaine re-challenge



Ullrich K et al. J Clin Rheumatol 2011;17:193
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Gross RL et al. Clin Rheumatol 2011; June 25 [Epub]
Milman N et al. Arthritis Care Res 2011;63:1195