New Developments in Gout

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Conflict of Interest Declaration

- I have no actual or potential conflict of interest in relation to this activity.

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Objectives

- Review the etiology and pathophysiology of gout.
- List current treatment options for gout prophylaxis and treatment.
- Discuss new treatment options for gout.

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Self-Assessment Question 1

Which statement regarding colchicine is TRUE?

a) Colchicine has been FDA approved for the treatment of gout for centuries and is considered to be the Drug Of Choice for acute attacks.
b) Colchicine is safe to use in patients with renal and hepatic impairment.
c) The majority of patients taking colchicine cannot tolerate the frequent GI side effects, including nausea, vomiting and diarrhea.
d) Intravenous colchicine is readily available in the U.S. and is an ideal choice for patients that cannot tolerate the GI toxicities associated with oral colchicines.

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Self-Assessment Question 2

Which statement regarding the management of chronic gout is TRUE?

a) Prophylactic therapy can safely be initiated while a patient is having an acute attack.
b) Patients that have had two or more acute attacks within a year, have evidence of tophi or joint destruction, or have uric acid kidney stones qualify for prophylactic therapy.
c) Uricosurics, such as Probenecid and Sulfinpyrazone, are effective in treating both underexcreters and overproducers of uric acid.
d) Febuxostat has shown to be more effective in controlling gout flares than allopurinol because it is a more selective xanthine oxidase inhibitor.

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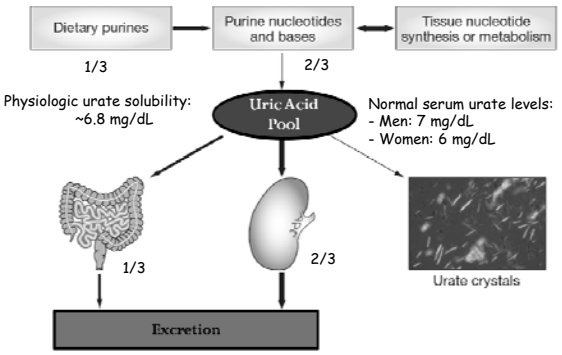
Gout Etiology[1]



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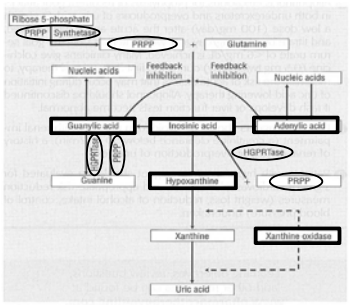
Uric Acid Overproducers[2]



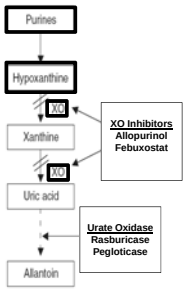


FIGURE 96-1. Purine metabolism. (HGPRT, hypoxanthine-guanine phosphoribosyltransferase; PRPP, phosphoribosyl pyrophosphate.)

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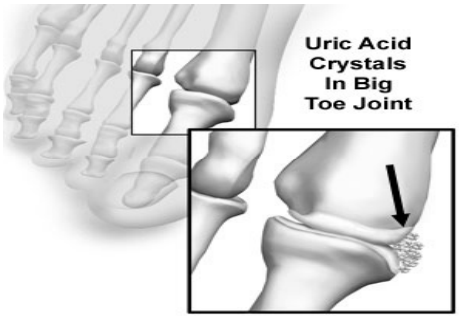
What Is Causing The Pain?



http://www.squidoo.com/gout_information_treatment. Accessed March 25, 2011

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Gout Risk Factors[2,3]

- Age
- Gender
- Dietary habits
  - Overindulging, obesity, fasting
  - Food is NOT likely the only culprit
- Metabolic syndrome
  - Hypertension, hyperlipidemia, obesity, insulin resistance
- Injury or trauma

- **Not a comprehensive list**

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TABLE 96-1 Conditions Associated with Hyperuricemia[2]

Primary gout	Obesity
Diabetic ketoacidosis	Sarcoidosis
Myeloproliferative disorders	Congestive heart failure
Lactic acidosis	Renal dysfunction
Lymphoproliferative disorders	Down syndrome
Starvation	Lead toxicity
Chronic hemolytic anemia	Hyperparathyroidism
Toxemia of pregnancy	Acute alcoholism
Pernicious anemia	Hypoparathyroidism
Glycogen storage disease type 1	Acromegaly
Psoriasis	Hypothyroidism
Hypoxanthine-guanine phosphoribosyltransferase deficiency	Phosphoribosylpyrophosphate synthetase overactivity
Polycythemia vera	Beryllosis
Renal transplantation	

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Drugs Capable of Inducing Hyperuricemia and Gout[2]

(Table 96-2)

- Diuretics
- Nicotinic acid
- Salicylates (<2g/day)
- Ethanol
- Pyrazinamide
- Levodopa
- Ethambutol
- Cytotoxic drugs
- Cyclosporine

Not a comprehensive list

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Lifestyle and Gout[3]

Hyperuricemia

- [serum urate] > 7mg/dL = abnormal;
- ↑risk for gout
- Asymptomatic/ incidental finding = typically no therapy necessary

Gout

- Hyperuricemia **at some point** in the disease
- Monosodium urate crystals
- Symptomatic = clinical gout

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Acute Gouty Arthritis

- Sudden onset of excruciating joint pain/arthritis
  - Develops in 1 day; often at night
- + other signs of inflammation = redness, swelling, warmth, tenderness of the joint
- Typically affects a single joint
  - Toe, ankle, or knee
  - Toe>insteps>ankles>heels>knees>wrists>fingers>elbows[2]
- Generally improves completely over a few days to several weeks EVEN IF UNTREATED

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Chronic Tophaceous Gout

- May develop in patients who have repeated attacks of gout over many years
- Large #'s of urate crystals collect in joints, bones, and cartilage → nodule/mass is AKA tophus (plural tophi)
- Tophi are usually not painful or tender
  - Can cause erosion/deformity of the bone
  - Can become inflamed and cause symptoms similar to acute gouty attack

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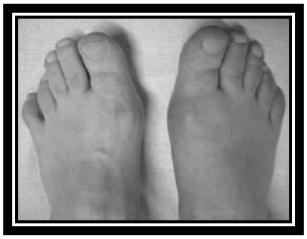
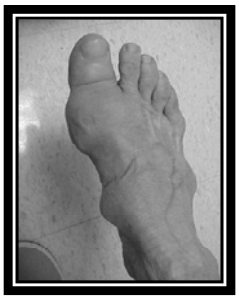
Acute Gout vs.Tophaceous Gout





Left photo: http://www.medicalfinals.co.uk/QuizJanuary2007Answers.html Accessed March 25, 2011.
Right photo: http://knol.google.com/k/gout# Accessed March 25, 2011.

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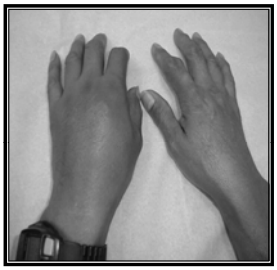
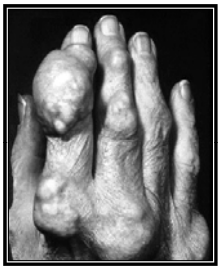
Acute Gout vs.Tophaceous Gout





Left Photo: http://www.cureyourgout.com/ Accessed March 25, 2011.
Right Photo: http://www.hopkins-arthritis.org/arthritis-info/gout/clinincal-presentation-and-diagnosis.html Accessed March 25, 2011.

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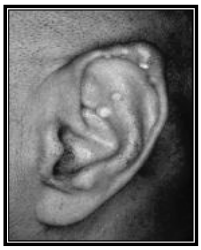
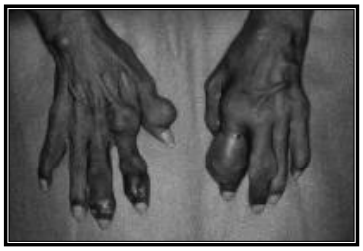
Tophaceous Gout[4]



Tophaceous deposits in ear.



Chronic tophaceous gout in an untreated patient with end-stage renal disease.

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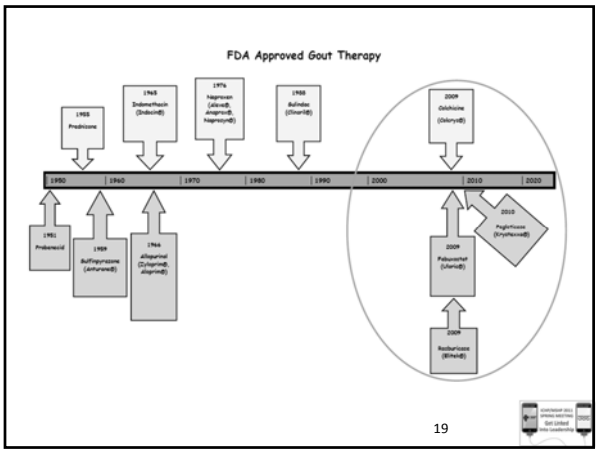

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Key Concepts for Gout Management

- Acute treatment only takes care of symptoms of gout. It does not lower uric acid levels.
- Prophylaxis therapy lowers uric acid levels.
  - Patients must qualify for prophylactic therapy.
- Uric acid lowering therapy can trigger acute attacks.

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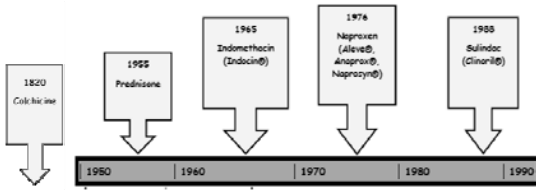
Management of Acute Gout



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Management of Acute Gout – NSAIDs

- **Place in therapy:** acute attacks (DOC if no CIs); prophylaxis
- **Things to consider**: An NSAID is an NSAID is an NSAID
  - The earlier the better (w/in 12-24H of pain onset)
  - Highest dose for 2-3 days, then decrease over ~2 weeks
  - Continue NSAIDs for at least 48 hours after resolution of symptoms[4]
- **CIs:** hx of hypersensitivity, hx/active GI bleed/ulceration, pregnancy/breastfeeding, coagulation defects
- **Caution:** cardiac (HF, CAD), renal or hepatic impairment, elderly, anticoagulation use, uncontrolled HTN
- **Monitoring:** creatinine, blood pressure, disorientation LFTs, CBC, BUN, GI side effects
- **What about COX-1 vs COX-2 inhibitors?**
  - Above applies PLUS cardiovascular safety concerns and increased cost

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Management of Acute Gout - colchicine

- **Place in therapy:** 2nd line option for acute attacks; prophylaxis
- **Things to consider:** favorable effects when initiated w/in 24-48hrs of jt. sx onset (>48H success ↓ SUBSTANTIALLY)[4]
- **PO administration only:** 0.6mg dosages were historically given Qhour until joint sx resolve, GI sx develop (e.g., abdominal discomfort/diarrhea/nausea/vomiting), OR total max dose of 6-8mg is reached[2,5]
  - GI SEs typically ALWAYS occur before relief of attack is achieved[4]
- Will discuss Colcrys® (colchicine) further in "new" treatment options for gout

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Management of Acute Gout - Corticosteroids

- **Place in therapy:** 3rd line therapy for acute attacks; prophylaxis
- **Things to consider:** multiple routes of administration[4]
  - **PO:** for patients with multiple joint involvement; taper recommended; typically symptom improvement in 12-24 hours
  - **Intra-articular:** best for gout limited to 1-2 joints; dose depends on joint size; joint infection must be ruled out first
  - **IM:** best for patients unable to take po medications
- **Steroid precautions:** CNS effects - delerium, depression, insomnia (frail/elderly), diabetic (hyperglycemia), bleeding or GI disorders (hemorrhage, peptic ulcers, wt gain), CVD (fluid rtn, HTN), active infection, renal or hepatic dysfunction; long-term use = osteoporosis and cataracts[5]

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Management of Chronic Gout

- Candidates for prophylactic therapy[2]
  - Recurrent attacks (≥2 attacks/year)
  - Evidence of tophi or joint destruction
  - Uric acid nephrolithiasis
- Uric acid = strongest modifiable risk factor for acute gout
- Prophylactic therapy involves:
  - ↑ uric acid excretion
  - ↓ uric acid production

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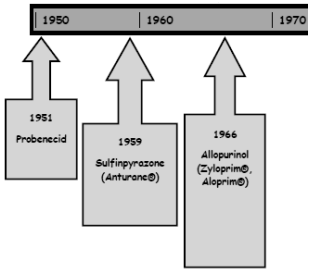
Management of Chronic Gout



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Management of Chronic Gout
Uricosuric Agent - Probenecid

- **Place in therapy:** prophylaxis; indicated for underexcretors
- **Things to consider**[2,5]**:**
  - Can cause stone formation; adequate hydration (2L/day)is essential
  - **SEs:** GI (ulcers), rash, precipitation of acute attacks, stones, enhanced anticoagulation effect
  - **DIs:** inhibits secretion of many drugs = antibiotics, sulfonamides, indomethacin, etc.
  - **CI:** CrCl<30 mL/min, hx of kidney stones, overproducers, concomitant use with salicylates (ASA blocks the effect of probenecid), past or present blood dyscrasias

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Management of Chronic Gout
Uricosuric Agent - Sulfinpyrazone

- **Place in therapy:** prophylaxis; indicated for underexcretors
  - Probenecid typically better tolerated; sulfinpyrazone can be an alternative or used in addition to maximum doses of Probenecid[5]
- **Things to consider:**
  - Similar SE, DI, and CI profile as Probenecid
  - Some formulations contain sulfites = anaphylaxis, asthmatic attacks

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Management of Chronic Gout
Xanthine Oxidase Inhibitor - Allopurinol

- **Place in therapy:** prophylaxis; indicated for overproducers and underexcretors; secondary hyperuricemia associated with chemotherapy (IV)
- **Things to consider:** DOC for patients with a hx of stones, renal insufficiency, lympho/myeloproliferative disorders, overproducers, intolerance or allergy to uricosurics
- **Dosage:** dictated by severity of the disease and renal function
  - **Initiation:** 100mg po daily, then increase dose by 100mg every 1-4 weeks until target serum uric acid level is achieved[5]
    - ↑ frequency of acute attacks = mobilizes uric acid stores
    - Should take oral formulations with plenty of fluid
  - Most commonly prescribed dosage is 300mg po daily[4]
    - This may be suboptimal for efficacy

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Management of Chronic Gout
Xanthine Oxidase Inhibitor - Allopurinol

- **SEs**: rash, leucopenia, some GI (N/V), rarely "allopurinol hypersensitivity syndrome" = severe rash, hepatitis, interstitial nephritis = dose related (20% mortality)[2]
  - DC if rash develops or LFTs become abnormal
- **DIs:** ↑ serum concentrations of allopurinol when co-administered with thiazides/loop diuretics; allopurinol can ↑ concentrations of didanosine, theophylline, azathioprine, coumadin; antacids ↓ absorption of allopurinol[5]
- **Monitoring:** CBC, serum uric acid levels, hepatic and renal function
  - Typically serum uric acid levels checked monthly; dose is increased monthly until target serum uric acid level is achieved.
  - It is essential to verify compliance before increasing the dose

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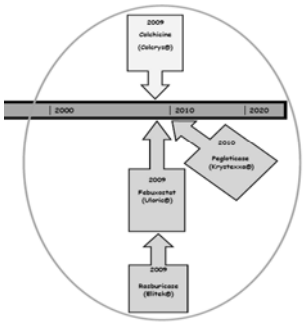
New Treatment Options for Gout



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"New" Treatment Options for Gout
Colcrys® (colchicine)[5]

- **Approved indication(s):** acute gouty attacks, prophylaxis
- **Treatment dosing:** 1.2mg at first sign of flare, wait 1 hr then 0.6mg (maximum 1.8 mg within 1 hr)
- **Prophylactic dosing:** 0.6 mg Qday or BID (maximum 1.2 mg/day)
- **Side effects:** GI most notable (e.g., nausea, vomiting, diarrhea, anorexia)
- **Warnings/Precautions:** blood dyscrasias, GI symptoms (dose reduction), myotoxicities (e.g., renal dysfunction, elderly, and concomitant use with cyclosporin, verapamil, diltiazem, fibrates, statins = >myopathy)
- **Monitoring:** CBC, renal and hepatic function tests

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Self-Assessment Question 1

Which statement regarding colchicine is TRUE?

a) Colchicine has been FDA approved for the treatment of gout for centuries and is considered to be the Drug Of Choice for acute attacks.
b) Colchicine is safe to use in patients with renal and hepatic impairment.
c) The majority of patients taking colchicine cannot tolerate the frequent GI side effects, including nausea, vomiting and diarrhea.
d) Intravenous colchicine is readily available in the U.S. and is an ideal choice for patients that cannot tolerate the GI toxicities associated with oral colchicines.

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New Treatment Options for Gout Uloric® (febuxostat)

- **Approved indication(s):** prophylaxis
- **Comparison to allopurinol:** Uloric is more selective in inhibiting xanthine oxidase ≠ reduction in gout flares; > discontinuation of Uloric due to ↑ LFTs[6]
- **Prophylactic dosing:** 40mg po Qday; may increase to 80mg po BID after 2 weeks if serum uric acid level not <6mg/dL
  - Precipitates acute gouty attacks: recommend NSAIDs/colchicine w/initiation of therapy and continue for up to 6 months [6]
  - 40mg Qday = 300mg Qday allopurinol; 80mg Qday was more effective vs. allopurinol 300mg Qday in reaching goal serum uric acid levels <6 mg/dL [6]

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New Treatment Options for Gout Uloric® (febuxostat)

- **Side effects:** rash, elevated LFTs, and arthralgia most notable[5]
- **Warnings/Precautions:** causal relationship not established[5,6]
  - Increased reports of MI, stroke, CV deaths compared to Allopurinol
- **Monitoring:** signs and symptoms of MI, stroke; LFTs at baseline, 2 months, 4 months, then periodically, serum uric acid levels at baseline and 2 weeks post initiation

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Self-Assessment Question 2

Which statement regarding the management of chronic gout is TRUE?

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New Treatment Options for Gout
Urate Oxidase - Elitek® (rasburicase)[5]

- **Approved indication(s):** hyperuricemia associated with malignancy
- **Manufacturer recommended dosing:** I.V. 0.2 mg/kg once daily for up to 5 days (dosing guided by patient's risk of tumor lysis syndrome = low, intermediate or high)
- **Side effects:** cardiovascular (peripheral edema, fluid overload), CNS (fever, HA, anxiety), rash, hypo/hyper-phosphatemia, GI (diarrhea, constipation, mucositis, nausea, vomiting, abdominal pain), elevated LFTs, hyperbilirubinemia, and infection most notable
- **Warnings/Precautions:** Black boxed warnings for anaphylaxis, hemolysis (CI: G6PD deficiency), methemoglobinemia, uric acid degradation , immunogenicity
- **Monitoring:** plasma uric acid levels (4 hrs post admin. and Q6-8 hrs until TLS resolved), CBC, G6PD deficiency, hypersensitivity rxn

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New Treatment Options for Gout
Urate Oxidase - Krystexxa® (pegloticase)[5]

- **Approved indication(s):** refractory gout
  - Precipitates acute gouty attacks: initiate NSAIDs/colchicine ≥1 wk prior to initiation and continue for ≥6 months
  - Requires premedication with antihistamines and corticosteroids
- **Manufacturer recommended dosing:** I.V. 8 mg every 2 weeks
- **SEs:** antibody formation, bruising, urticaria, nausea, vomiting, constipation, infusion reactions (anaphylaxis) most notable
- **Warnings/Precautions:** Black boxed warnings for anaphylaxis, hemolysis (CI: G6PD deficiency), methemoglobinemia; caution in heart failure patients due to exacerbations; immunogenicity
- **Monitoring:** CBC, G6PD deficiency, hypersensitivity reaction

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Gout Therapy Cost Considerations[7]

- **Colcrys® (colchicine)**
  - 0.6 mg (30 tablets) = ~$170
- **Prednisone**
  - All strengths (30 tablets) = <$20
- **Allopurinol**
  - All strengths (100 tablets) = <$25
- **Zyloprim®**
  - All strengths (30 tablets) = <$80
- **Uloric® (febuxostat)**
  - 40 mg (30 tablets) = ~$175

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References

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QUESTIONS?

ICHP/MSHP 2011 Spring Meeting
Clinical Pearls Session – New Developments In Gout
Tatum Mead, PharmD
121-000-11-015-L01-P

Post Test Questions:

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