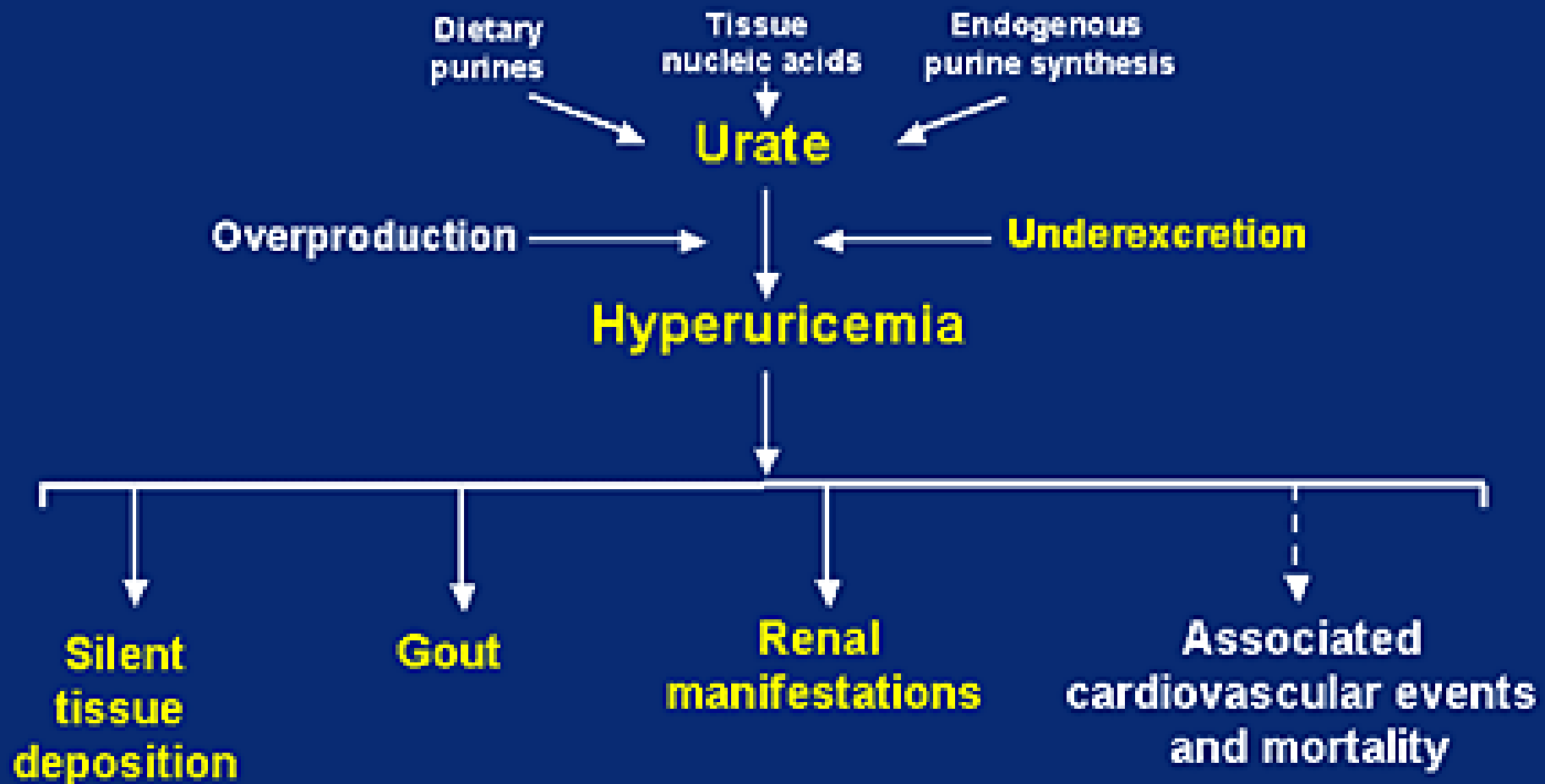
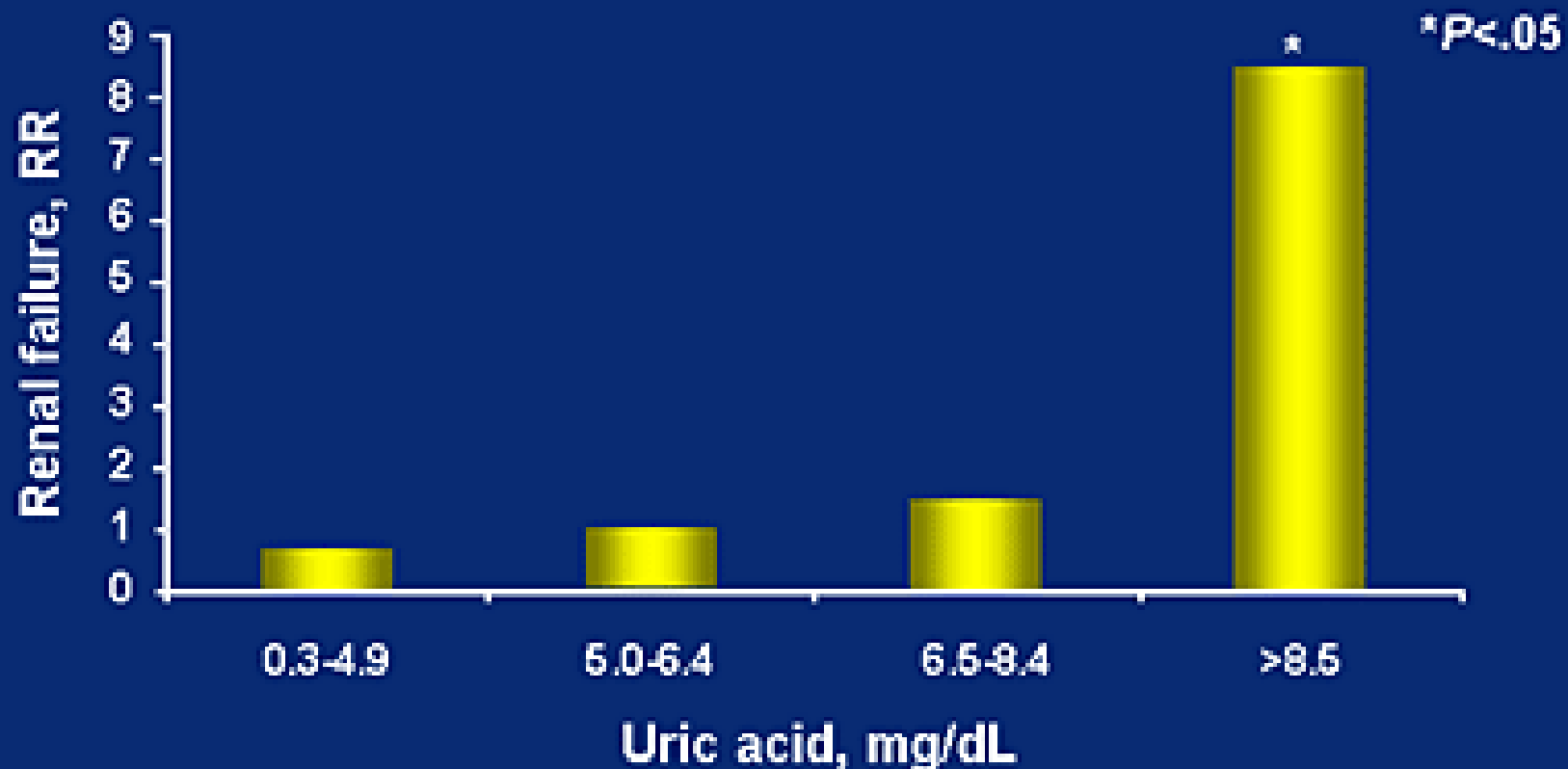


Review of the Hyperuricemia Cascade



Uric Acid and Risk of Renal Failure

Study of 49,413 Japanese male railroad workers, 5-year follow-up



RR = relative risk.

Tomita et al. *J Epidemiol.* 2000;10:403-409.

Serum Uric Acid Predicts Hypertension

Study	Population	Relative Risk
Khan (1972)	10,000 males	2-fold risk at 5 years
Selby (1990)	2062 subjects	2-fold risk at 6 years
Hunt (1991)	1482 adults	2-fold risk at 7 years
Jossa (1994)	619 male workers	2-fold risk at 12 years
Taniguchi (2001)	6356 males	2-fold risk at 10 years
Masuo (2003)	433 male workers	A 1.0 mg/dL change in sUA predicts a 27 mmHg increase in systolic BP at 5 years
Nakanishsi (2003)	2310 males	1.6-fold risk at 6 years

Conclusions

- An elevation in sUA independently predicts renal failure in subjects with IgA nephropathy and in normal subjects
- **Experimental hyperuricemia** causes interstitial and glomerular injury via a crystal-independent mechanism
- **Experimental studies** suggest uric acid activates the renin-angiotensin system, inhibits nitric oxide, and causes glomerular hypertension

Summary

- **The most common cause of hyperuricemia is underexcretion by the kidney**
- **Our understanding of the mechanisms responsible for renal handling of uric acid is greatly improving**
- **Hyperuricemia may have a direct effect on kidney function and hypertension**

Review of Gout

One Chronic Disease, Best Described by 4 Stages

**Asymptomatic
hyperuricemia**

**Elevated serum
urate with no
clinical gout**



Acute flares

**Acute inflammation
from urate
crystal
phagocytosis**

**Intercritical
segments**

**Intervals
between flares**

**Advanced
gout**

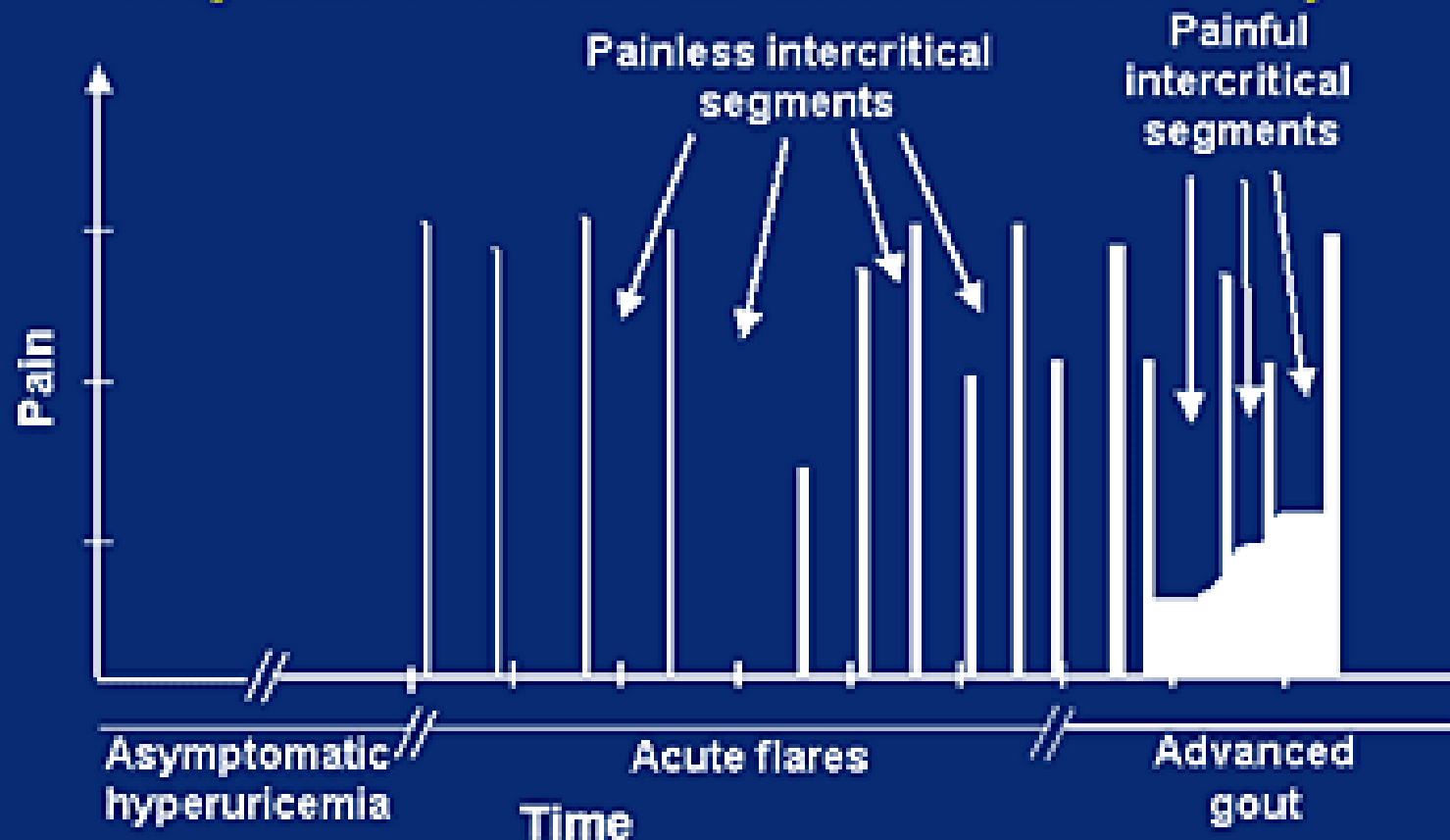
**Long-term gouty
complications of
uncontrolled
hyperuricemia**

**Silent tissue crystal
deposition may begin**

Uncontrolled hyperuricemia

Uncontrolled Hyperuricemia Causes Gout to Progress

Untreated, chronic hyperuricemia increases body urate stores and advances disease severity



Adapted from Klippel et al, eds. In: *Primer on the Rheumatic Diseases*. 12th ed. Arthritis Foundation; 2001:313.

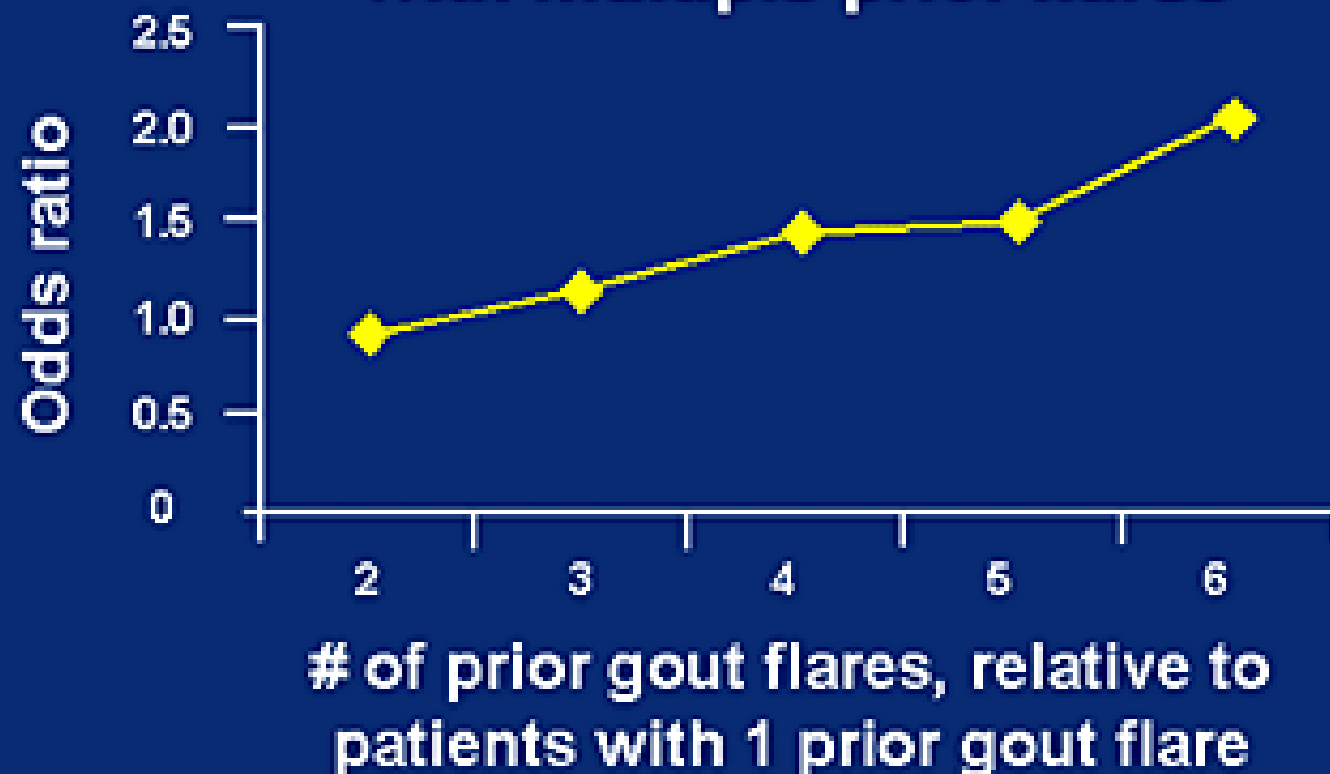
Uncontrolled Hyperuricemia and the Progression of Gout

Serum urate and the risk of acute flares

- Retrospective managed care study (n=5942)
- Patients with **sUA ≥ 6 mg/dL**
 - **59% more likely** to have a flare than those with sUA <6 mg/dL
- Patients **on allopurinol with sUA ≥ 6 mg/dL**
 - **75% more likely** to have a flare than those with sUA <6 mg/dL

Uncontrolled Hyperuricemia and the Progression of Gout

Risk of recurrent flares increases with multiple prior flares



Sarawate et al. Poster presented at the ACR Meeting 2005. San Diego, CA.

Uncontrolled Hyperuricemia and the Progression of Gout

- Increased urate deposition may progress hidden damage to
 - Joint damage
 - ♦ Chronic arthritis
 - ♦ Radiographic changes
 - Development of tophi
 - Renal manifestations



Erosions and hypertrophic adjacent bone

Uncontrolled Hyperuricemia, Progressing Gout, and Their Impact on QOL (cont'd)

- **Acute flares**


- Interfered with work, recreational activities, and movement in 50% of patients

- **Intercritical segments**

- 25% reported pain when not experiencing a flare

- **Advanced gout**

- Worse concern and pain scores with ≥ 1 tophi vs no tophi ($P < .002$)
- Worse scores in all 4 domains with sUA > 10 mg/dL vs sUA < 9.0 mg/dL ($P < .007$)



QOL declines as gout progresses

Uncontrolled Hyperuricemia, Progressing Gout, and Their Economic Impact

- Study of the economic impact of gout (n=1085)
- Employees with gout (vs those without) had
 - 4.6 more absence days per year
 - 2.1% lower mean annual productivity
- **Proper gout management will result in**
 - **Decreased absenteeism**
 - **Increased productivity**

Special Considerations for Diagnosing Gout

- **Look for gout, even if**
 - sUA levels are normal
 - The symptoms present in a woman
 - The flare is polyarticular and chronic
 - The involved joint is atypical (eg, Heberden's nodes)
- **Do not treat to diagnose**
 - Other types of acute arthritis may also respond to colchicine

Comorbidities Associated With Hyperuricemia

- Renal manifestations¹
- Obesity²
- Metabolic syndrome³
- Diabetes mellitus⁴
- Heart failure⁵
- Hyperlipidemia²
- Hypertension⁶
- Cardiovascular disease⁷

1. Vazquez-Mellado et al. *Best Pract Res Clin Rheumatol*. 2004;18:111-124.

2. Nakanishi et al. *Int J Epidemiol*. 1999;28:888-893.

3. Ford et al. *JAMA*. 2002;287:356-359.

4. Boyko et al. *Diabetes Care*. 2000;23:1242-1248.

5. Anker et al. *Circulation*. 2003;107:1991-1997.

6. Gavin et al. *Am J Cardiovasc Drugs*. 2003;3:309-314.

7. Niskanen et al. *Arch Intern Med*. 2004;164:1546-1551.

Review of Risk Factors for the Development of Gout

- Male gender
- Postmenopausal women
- Advanced age
- Drugs (eg, diuretics, cyclosporine)
- Hypertension¹
- Posttransplant patients
- High alcohol intake²
 - Highest risk with beer consumption
- High body mass index¹
- Diet high in meat and seafood³

1. Choi et al. *Arch Int Med*. 2005;165:742-747.

2. Choi et al. *Lancet*. 2004;363:1277-1281.

3. Choi et al. *N Engl J Med*. 2004;350:1093-1103.

Dietary and Lifestyle Recommendations for Gout May Not Replace Treatment

- <20% of patients make sustained lifestyle changes¹
- A primary prevention strategy **may not be an effective secondary prevention strategy** in patients with existing disorders²

1. Levinger et al. *Ann Intern Med.* 2001;135:386-391

2. Choi et al. *Curr Rheum Rep.* 2005;7:220-226.

Conclusions

- **Gout is a significant problem**
 - **Uncontrolled gout can cause**
 - ◆ **Serious clinical manifestations**
 - ◆ **Poor QOL**
 - ◆ **Negative economic effects**
 - **Growing incidence and prevalence**
 - **Additional risk factors being confirmed**
 - **Associated with multiple comorbidities**

Conclusions (cont'd)

- In order to control gout
 - Check for gout in all undiagnosed joint disorders
 - Search for unrecognized comorbidities associated with gout
 - Manage gout as a chronic, progressive disease
 - Encourage lifestyle changes in gout patients
 - ◆ This may not replace pharmacologic treatments

Review of the Treatment Goals for Gout

- **Terminate the acute flare as rapidly as possible**
- **Protect against further attacks**
 - Reduce the chance of crystal-induced inflammation
- **Treat the hyperuricemia and ultimately prevent flares and disease progression**
 - Provide long-term correction of the metabolic problem
 - Lower the serum urate sufficiently to deplete the total body urate pool

Terminating the Acute Flare

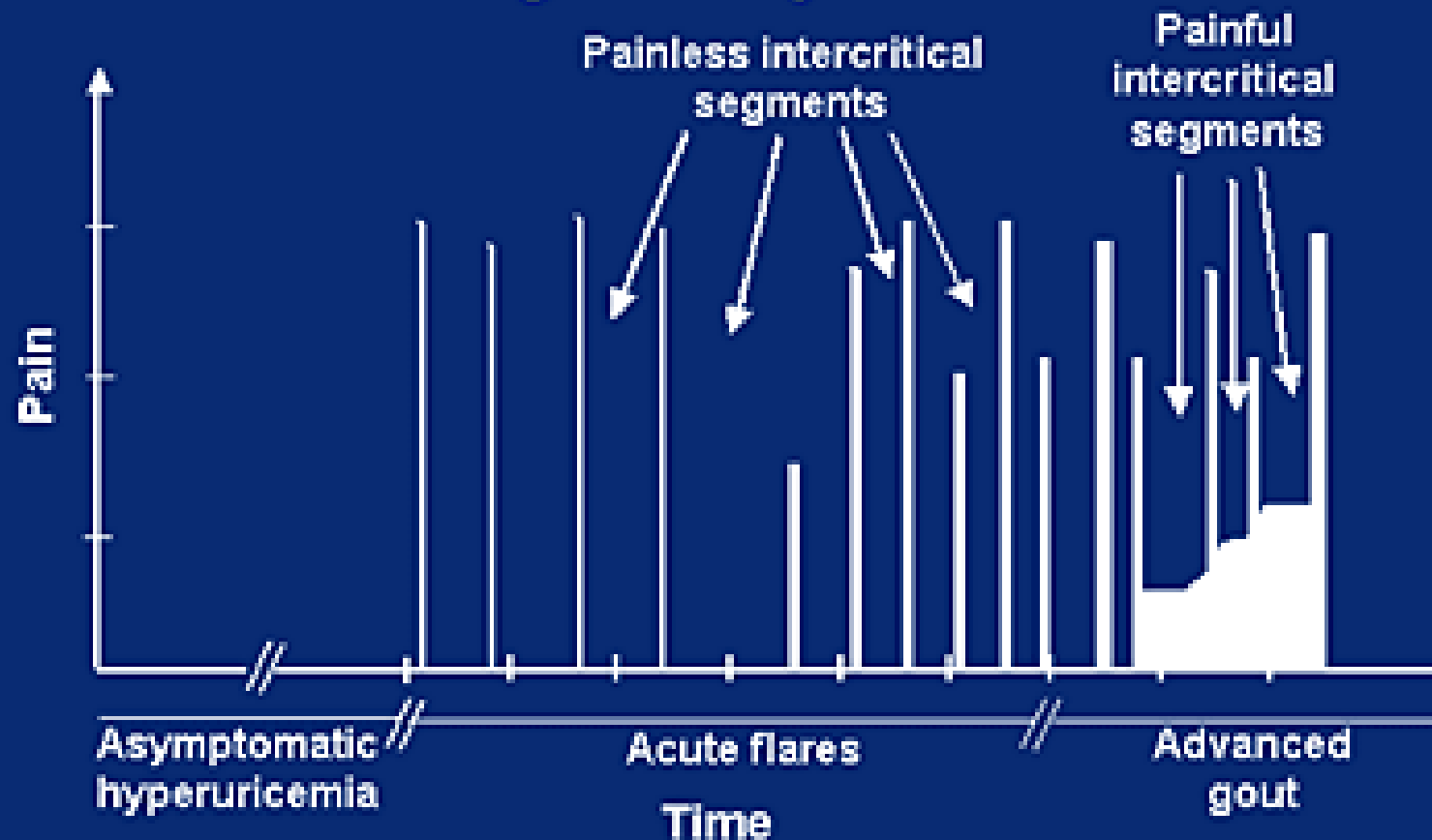
- Resolution of acute flare by controlling crystal-induced inflammation and pain
 - **Not a cure for gout**
 - ♦ Only resolves the symptoms
 - ♦ Urate crystals remain in the joint
 - Serum urate should NOT be lowered during the flare
 - Medication options
 - ♦ NSAIDs, oral colchicine, corticosteroids, ACTH
- The critical issues are
 - Considering contraindications due to comorbidities
 - Rapid initiation of therapy
 - Adequate dosing
 - Appropriate duration of therapy

Considerations When Initiating Urate-Lowering Therapy

- **Serum urate level**
 - If very high, you may want to initiate early
- **Patient preferences**
- **Comorbidities**
- **Uncontrolled hyperuricemia can cause**
 - Silent tissue deposition and hidden damage that is difficult to predict
 - Progression of gout to irreversible joint damage and tophi

Gout Can Progress as Hyperuricemia Remains Uncontrolled

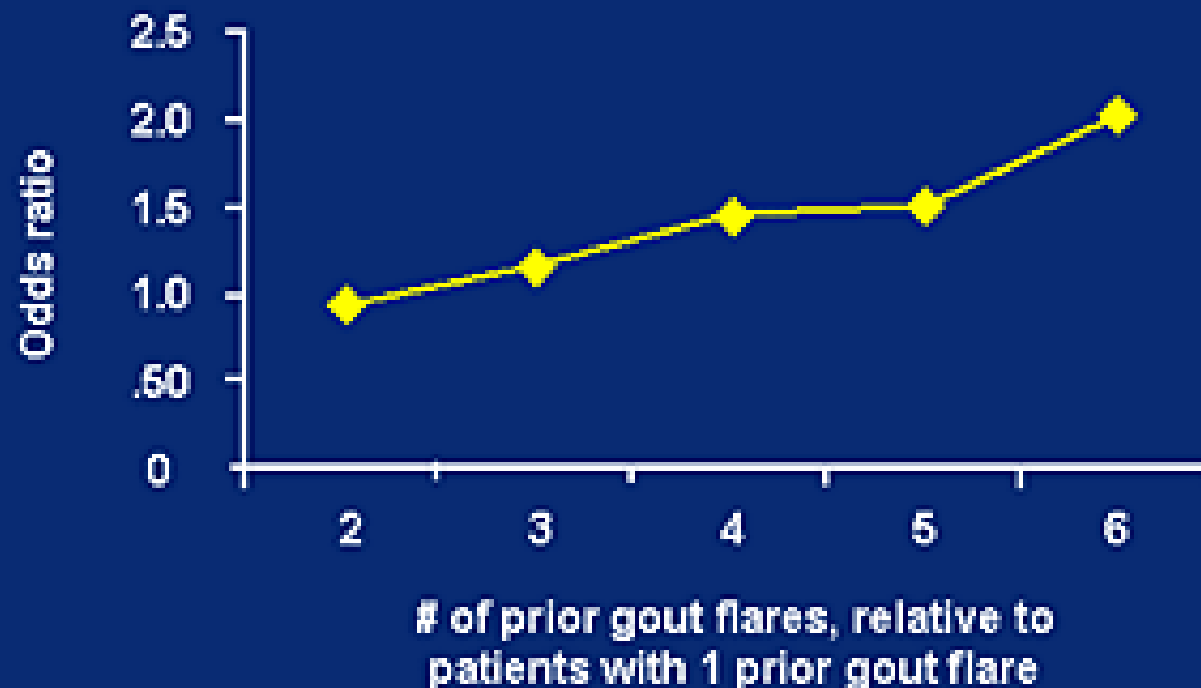
Body urate stores increase over time, potentially advancing the severity of the disease



Adapted from Klippel et al, eds. In: *Primer on the Rheumatic Diseases*. 12th ed. Arthritis Foundation; 2001:313.

The Risk of Recurrent Flares Increases With Multiple Prior Flares

Retrospective managed care study of gout patients
(n=5942)



Sarawate et al. Poster presented at the ACR Meeting 2005. San Diego, CA.

Initiating Urate-Lowering Therapy at the Right Time

- Discuss urate-lowering therapy with the patient after the first attack
- Strongly encourage it after the second attack
- Initiate therapy if advanced manifestations are present
 - eg, tophi, chronic arthritis, nephrolithiasis

Choosing an Appropriate Urate-Lowering Agent

- The ideal urate-lowering agent should
 - Achieve sUA <6.0 mg/dL to ultimately prevent flares and disease progression
 - Be associated with minimal adverse events
 - Be able to be used widely in patients suffering from hyperuricemia and gout

Proven Importance of Continuous Lowering of Serum Urate to <6.0 mg/dL

Achieving sUA <6.0 mg/dL demonstrates

No recurrence of or fewer acute flares

- ✓ Shoji et al (*Arthritis Care Res*, 2004)
- ✓ Loebel et al (*Ann Rheum Dis*, 1974)
- ✓ Becker et al (*Arthritis Rheum*, 2004)

Less crystals in joints

- ✓ Li-Yu et al (*J Rheum*, 2001)

Reduction in tophus size

- ✓ Perez-Ruiz et al (*Arthritis Rheum*, 2002)
- ✓ McCarthy et al (*Arthritis Rheum*, 1991)
- ✓ Schumacher et al (*Arthritis Rheum*, 2004)
- ✓ Becker et al (*Arthritis Rheum*, 2004)
- ✓ Wortmann et al (*ACR Poster*, 2005)

No recurrence of tophaceous deposits

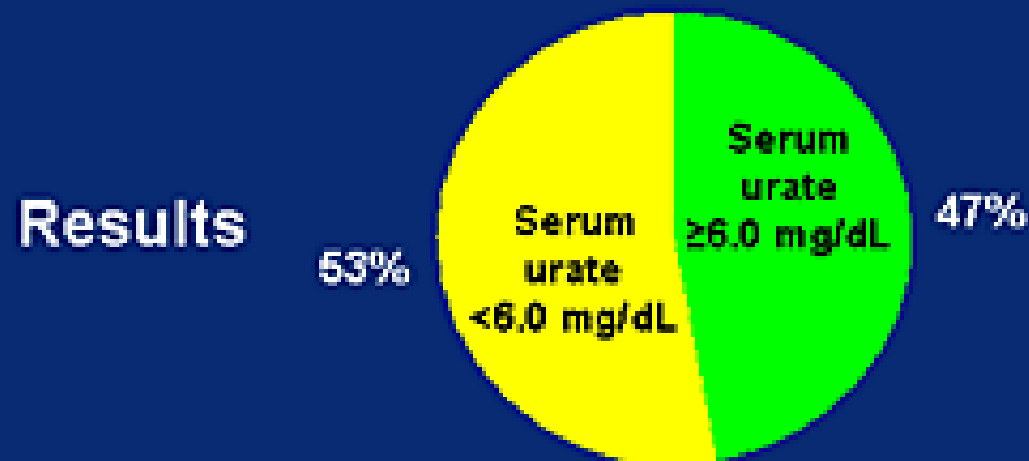
- ✓ van Lieshout-Zuidema et al (*J Rheum*, 1993)
- ✓ Gast et al (*Clinical Rheum*, 1987)

Limitations to Existing Arsenal of Urate-Lowering Agents

	Allopurinol	Uricosurics
Renal function an issue	✓	✓
Risk of nephrolithiasis		✓
Multiple doses daily required		✓
Drug interactions	✓	✓
Target serum urate not always achieved	✓	✓
Potentially fatal hypersensitivity syndrome	✓	
Nonselective enzyme inhibition	✓	

Target Serum Urate Levels Not Always Achieved With Allopurinol

- Allopurinol given to patients with gout¹
 - 49 patients given standard doses of allopurinol (300 mg/day)



Urate-Lowering Therapy and Acute Flare Prevention

- Urate-lowering therapy increases incidence of acute flares
 - May be caused by potent reduction in urate levels
- Prevention of acute flares
 - Co-treatment with prophylactic agents partially prevents flares
 - Achieving and maintaining sUA <6.0 mg/dL over time decreases flares requiring treatment

Protecting Against Acute Flares

Suggestions

- Initiate urate-lowering therapy with a prophylactic agent
 - Continue prophylaxis until
 - ♦ The patient is attack free
AND
 - ♦ Visible tophi are gone
AND
 - ♦ The patient maintains an **sUA <6.0 mg/dL** for ~6 months
- Even after prophylaxis, patients are still susceptible to flares
 - Prepare the patient for potential recurrence

Monitoring Patients on Urate-Lowering Therapy

- After administering a urate-lowering drug, concentration begins to decrease within 1-2 days
- To assure sUA <6.0 mg/dL is achieved
 - Monitor sUA every 2-4 weeks after initiating urate-lowering therapy until levels reach <6.0 mg/dL
 - Continue to monitor every 6-12 months after target sUA is achieved
- Assess for any adverse reactions to the drug used

Conclusions

A comprehensive treatment strategy needs to be initiated

1. Treat acute flares with anti-inflammatory agents
2. Initiate urate-lowering therapy at the ideal time for each patient (usually weeks after any flare has subsided)
 - ◆ Consider therapy in early disease due to unpredictable silent tissue deposition and disease progression
 - ◆ Take immediate action in advanced and tophaceous disease
3. Include discussion of lifestyle changes

Conclusions

4. Choose an appropriate agent

- **Effective**
 - Target <6.0 mg/dL
- **Consider safety**
- **New agents may improve the treatment of gout**
 - Easier to use in renal disease
 - Use in patients allergic to allopurinol

Conclusions

- 5. Protect against flares that occur with urate lowering**
 - Initiate a prophylactic agent at the start of urate-lowering therapy
 - Continue prophylaxis for an appropriate duration
- 6. Follow-up monitoring of sUA**
 - Assure that the patient achieves sUA <6.0 mg/dL early in therapy
 - Continue to monitor every 6-12 months after sUA <6.0 mg/dL is achieved