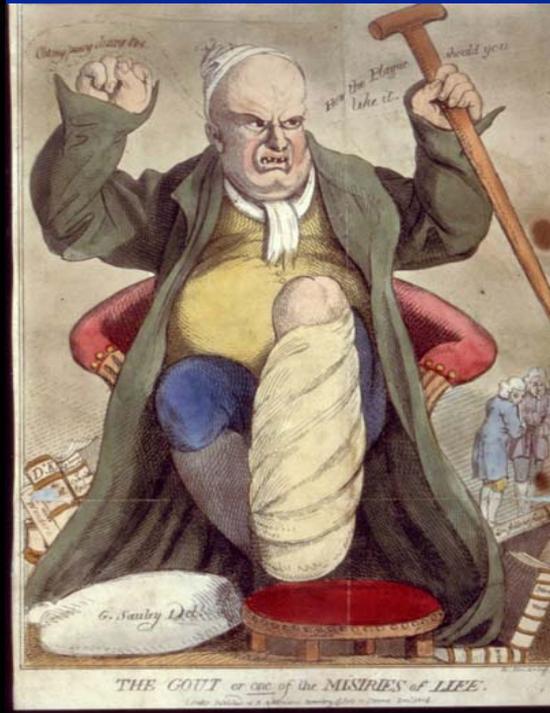


Clinical Overview of Gout

John J. Cush, MD
Baylor Research Institute, Dallas, TX



Gout

- 1st described 5th century BC – Hippocrates described gout as “the king of diseases and the disease of kings”
- Disorder of urate metabolism, with resultant hyperuricemia and deposition of monosodium urate (MSU) crystals in joints and soft tissues.

Societal Burden

- Prevalence in US and UK ~1%, Dutch 3%
 - ❖ Men >> Women
- National Arthritis Data WorkGroup estimates
 - ❖ 3.1 million have self reported gout in last yr (6.1 million Ever)
- In 1981, 37 million lost work days in US*
- 2003 Kim et al estimates the annual cost of Acute Gout is \$27,378,494 in the USA
 - Probable underestimate as women excluded & not all indirect and intangible costs included

Piscavet HSJ, Ann Rheum Dis 2003; 62: 644

Lawrence RC Arthritis Rheum. 2008 58:26

Roubenoff et al, JAMA 1981

Kim KY Clin Ther. 2003 Jun;25(6):1593-617

Gout Epidemiology-

- Men: Peak onset is 40-50 yrs
 - ❖ most common inflammatory arthritis in men
- Women: peak onset is post-menopausal
 - ❖ Less than have 15% onset prior to menopause
- Prevalence influenced by hormonal, geographic, racial, genetic, dietary, background conditions:
 - ❖ Males > Females. Estrogen is uricosuric
 - ❖ Populations: Maori, Tokelauan migrants, Filipinos, Taiwan males, etc (genetics or dietary)
 - ❖ Renal transplant (2-13%); HTN (\uparrow RR \geq 2.7)
 - ❖ Seasonal: Gout more often in spring (possibly summer)

Frequency of Gout Increasing?

Author	Population	1 st Era Incidence rate	2 nd Era Incidence rate
NHIS	Self-report (prevalence)	1969	1996
		5/1000	9.4/1000
Arromdee	Rochester MN	1977-78	1995-96
		45/100,000	62.3/100,00
Wallace Wortmann	USA Managed Care	1990	1999
		2.9/1000	5.2/1000

Testing? Increasing life-span? Insulin resistance? Obesity?

Increasing Prevalence of Gout

- Increased longevity
- Increased prevalence of Hypertension
- Increased use diuretics and low dose ASA
- Dietary trends
- Alcohol consumption
- Obesity epidemic
- Increased prevalence of Metabolic syndrome
- Increased organ transplantation, CsA use
- Increased survival in CAD and CHF

Prevalence of Gout

Age (years)	Men 3.4 Million Population %	Women 1.7 Mill Population %
20-29	0.2	0.6
30-39	2.1	0.1
40-49	2.2	0.6
50-59	5.7	2.3
60-69	9.1	3.5
70-79	10.8	4.7
<u>></u> 80	8.6	5.6

NHANES III 1988-94

Gout

Associations:

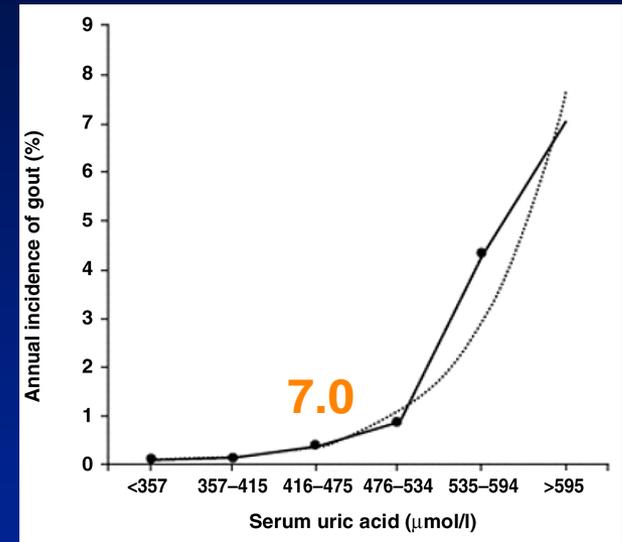
- Hypertension
- Obesity
- Diabetes
- Renal insufficiency
- Diuretics & CHF
- Alcohol consumption
- Lead exposure
- Family history
- Sweetened Soft drinks
- Males

Precipitants:

- Alcohol (beer, not wine)
- Hospitalization (fever, Poly)
- Surgery: joint replacement, carpal tunnel release
- Drugs: Diuretics, ASA, IV NTG, PZA, GCSF, CyA
- Total parenteral nutrition
- Septic arthritis, reactive arthritis, lupus, elderly

Serum Uric Acid & Incidence of Gout*

Serum Urate mg/dl	Gout attack/yr/1000	5 year cumulative
< 7.0	0.8	5
7.0 – 7.9	0.9	6
8.0 – 8.9	4.1	9.8
> 9.0	49 (4.9%)	220 (22%)



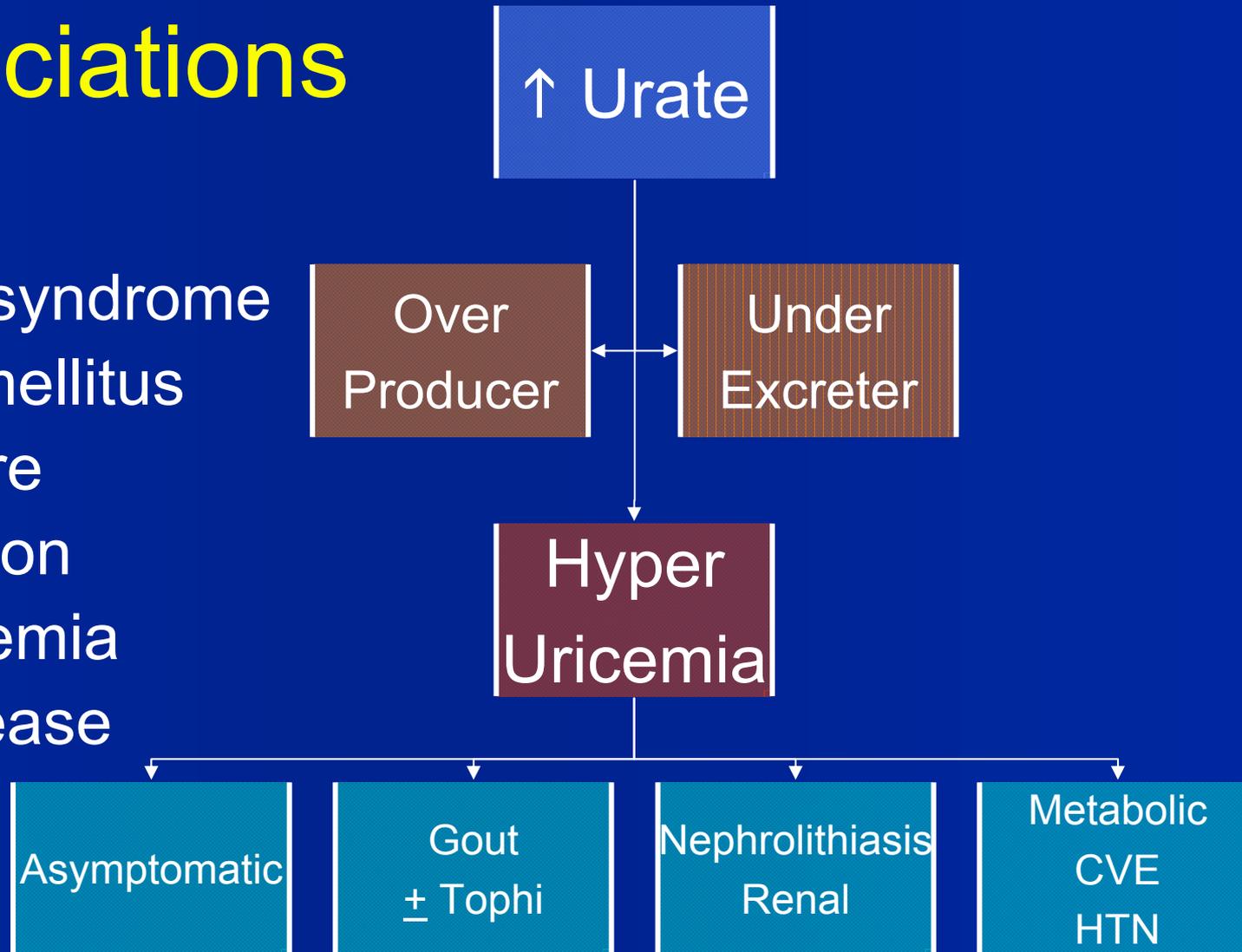
*Campion EW et al (1963-87) Am J Med 82:421-26, 1987

Saag K, Choi. Arthritis Res Ther. 2006;8 Suppl 1:S2

Hyperuricemia Associations

- Obesity
- Metabolic syndrome
- Diabetes mellitus
- Heart failure
- Hypertension
- Hyperlipidemia
- Renal Disease

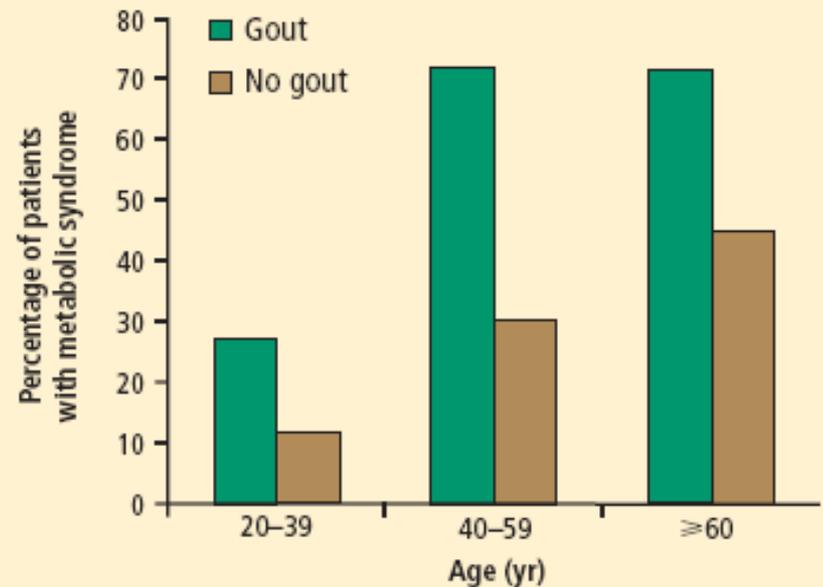
- ❖ CRI
- ❖ ESRD



Gout and Metabolic Syndrome

- ↑↑ Frequency of gout & metabolic syndrome
 - ❖ Common = Obesity epidemic
- BMI>35 assoc > 3-7X risk Gout
- Gout→60% ↑risk of CVD(men)
- No known assoc w/ insulin resistance & dyslipidemia
- ?Hyperuricemia:an independant risk factor for CVD? HTN? Renal Dz?
 - ❖ Causal or circumstantial relationships?

Gout associated with higher prevalence of metabolic syndrome across age groups

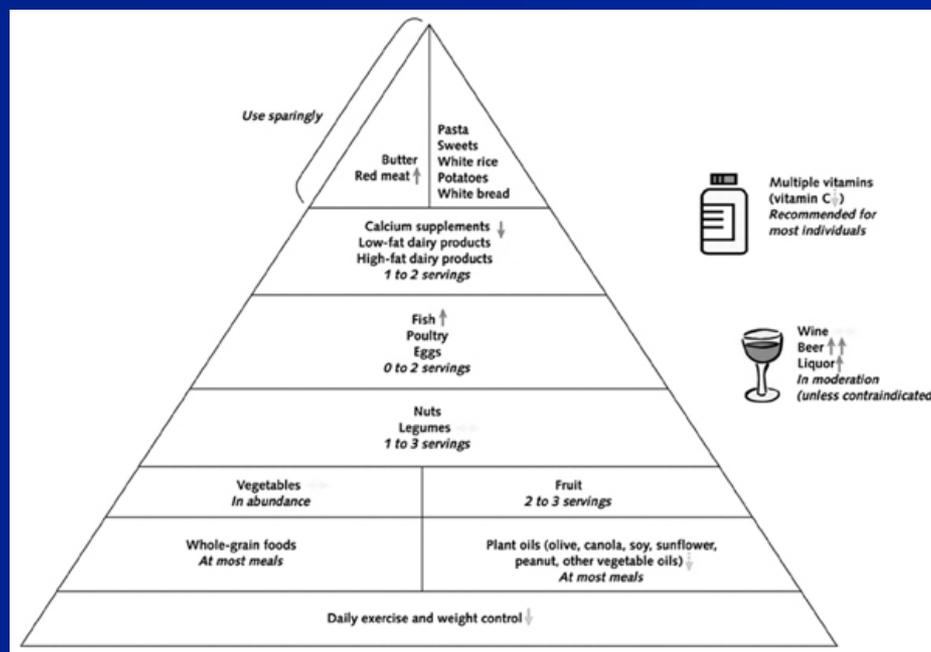


Diet and Gout

High Purine Diet

All Meats, Anchovies
Seafood, herring, sardines
Yeast, beer, alcohol,
sweetbreads

Beans, peas, lentils,
oatmeal, spinach,
asparagus, cauliflower,
mushrooms



- Survey of 47150 males over 12 yrs. (no prior hx Gout). Identified 730 new cases of gout

❖ Comparing highest /lowest quintiles:

- Meat intake
- Seafood intake
- Dairy products
- Not associated: Purine Vegetables & protein intake

RR

1.41 (1.07-1.86)

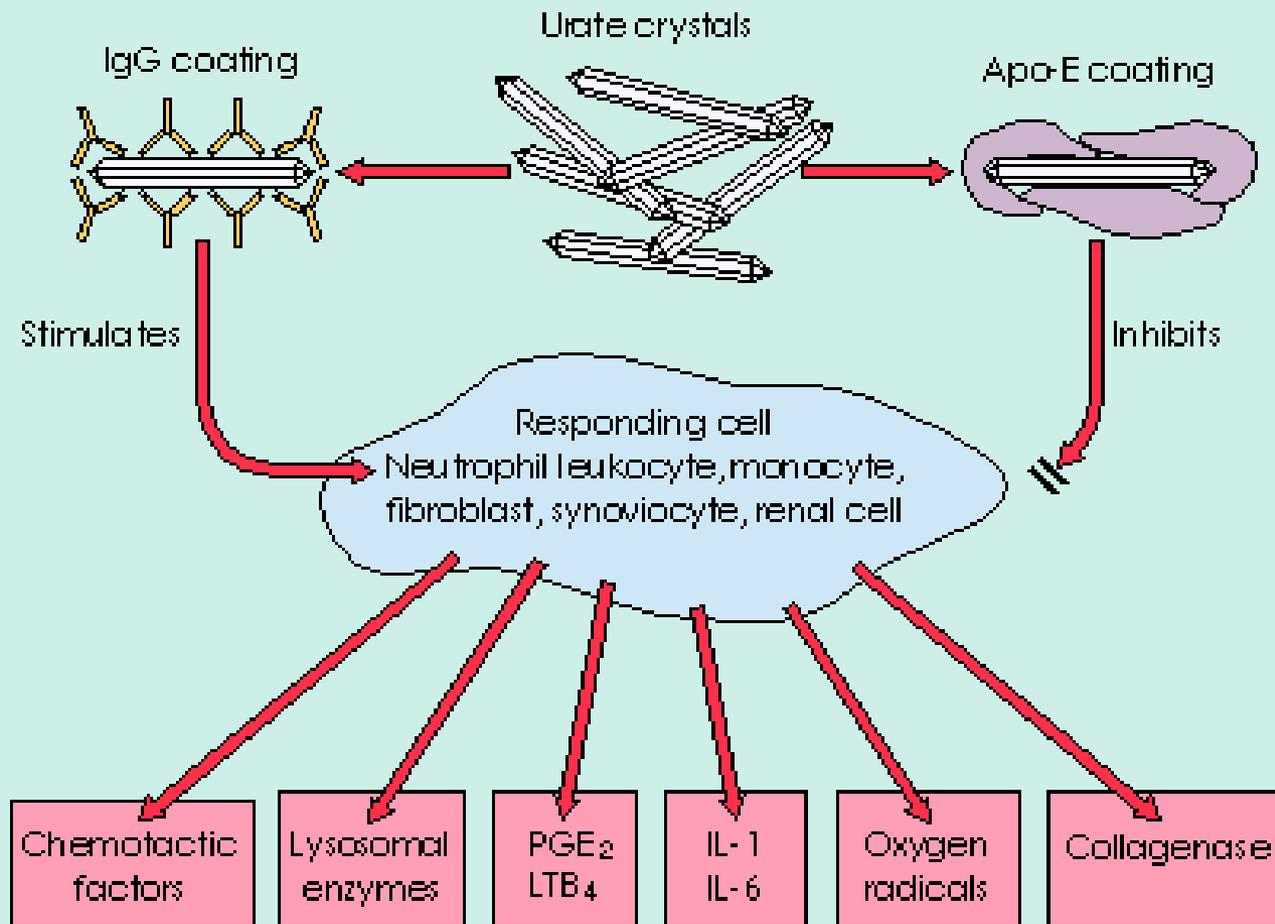
1.51 (1.17 – 1.95)

0.56 (0.42-0.74)

Choy on Gout

- Alcohol
 - ❖ Dose related Risk of gout (>50g/d, RR=2.53).
 - Increased w/ Beer (1.49/12oz); Wine 1.04/4 oz ser
- Obesity: womens health study
 - ❖ BMI 30-34 → RR 4.69
 - ❖ BMI >35 → RR 7.25
 - ❖ HTN and diuretic use increased RR 4.1-4.8
- Sweetened (Fructose) Soft Drinks
 - ❖ ≥ 2 Servings/day RR 1.85 (diet drinks not assoc.)

INFLAMMATORY MEDIATORS PRODUCED IN RESPONSE TO URATE CRYSTALS



Phases of Gout

- Asymptomatic hyperuricemia: elevated uric acid without evidence of gout, nephrolithiasis.
 - higher levels increase risk
- Acute: intermittent/recurrent, LE, ascending, inflammatory mono/oligoarthritis, “Podagra”
- Intercritical gout: intervals between attacks
 - Tissue deposition continues
- Tophaceous gout: chronic, large volume accumulation of MSU crystals (tophi) tissues
- Renal: nephrolithiasis, gouty nephropathy, uric acid nephropathy

Acute (Classic) Gout

- Acute, severe pain, warmth, inflammation, Limited motion → cant walk, cant put sheet on it.
- Podagra(50-90%): pain/swell warmth in 1st MTP
 - ❖ Other Joints: MTP, tarsus, ankle, knee
- Initially lower extremity monoarthritis (80-90%)
- w/ repeated attacks → arthropathy ascends
 - ❖ (initially a polyarthritis in elderly, women, myelo-proliferative disorders, Cyclosporine)
- Associated with fever, leukocytosis, high ESR or C-reactive protein levels.
- Chronology: untreated attacks last 7-14 days. Acute gout risk of repeat attack estimated to be 78% w/in 2 yrs

Natural Hx of Acute Attack

Bellamy N, et al. Br J Clin Pharmacol 24:33-6, 1987

- 11 volunteers with acute podagra studied x 7d
 - ❖ 2 withdrew on day 4 for severe pain
 - ❖ 9 remaining showed improvement
 - Pain improved by day 5
 - Swelling improved by day 7
 - Tenderness improved in 7/9 by day 7 (2 persisted)
 - But only 3 noted resolution of pain during 7d study
- Implications for clinical trial endpoints?
 - ❖ Pain improvement/resolution by day 7
 - ❖ Resolution of symptoms, return to normal activity

Gouty Tophi

- Incidence has decreased over last few decades
- Seen in 25-50% of untreated patients (after 10-20yrs)
- Location: Olecranon, bursae, digits, helix of ear
- Damages bone, periarticular structures and soft tissues
- Palpable measure of total body urate load



Gout: Diagnostics

- Crystal identification is diagnostic
- Laboratory Findings
 - ❖ 40-49% will have normal uric acid levels
 - ❖ Common: Leukocytosis; ESR and CRP elevated
 - ❖ Usual indices of inflammation absent (↓alb, Hgb)
- Radiographic findings
 - ❖ Soft tissue swelling
 - (Opacities = tophi)
 - ❖ Normal Joint space
 - ❖ Erosions: nonarticular, punched out, Sclerotic margins, overhanging edge



Uric Acid

- Random hyperuricemia ≠ gout (likely CRI, diuretic use)
- Acute attack: Urate levels may be normal, low or high
- 40-49% of acute gouty attacks are **normouricemic**
 - ❖ Mechanism: increased excretion of uric acid
 - Increased Urate excretion mediated by IL-6, inflammation
 - Urano W, et al. J Rheumatol 29:1950-3, 2002
 - Schlesinger N, et al. J Rheumatol 24: 2265-6, 1997
- Negative association between Gout – RA
 - ❖ Few reports of both coexisting in literature
 - ❖ RF preferentially binds MSU coated with IgG and inhibited neutrophil chemiluminescence (RF may block interaction of crystal bound IgG and Fc recpt)

1977 ARA Criteria for Diagnosis of Gout

- Urate crystals*: Intraarticular or Tophus
 - ❖ Plus any 6 of following:
 - > 1 attack acute arthritis;
 - Maximal inflammation w/in 1day;
 - Erythema over joint;
 - Podagra;
 - Hx of podagra;
 - Unilateral tarsal involvement;
 - Tophus;
 - Hyperuricemia;
 - Asymmetric swelling on exam/ xray;
 - Subcortical cyst w/o erosion;
 - Joint fluid culture negative during attack

* Wallace et al 1977 (sensitivity 84.4%, specificity 100%)

Practical Diagnosis of Gout

Acute/recurrent inflammatory mono-/oligoarthritis

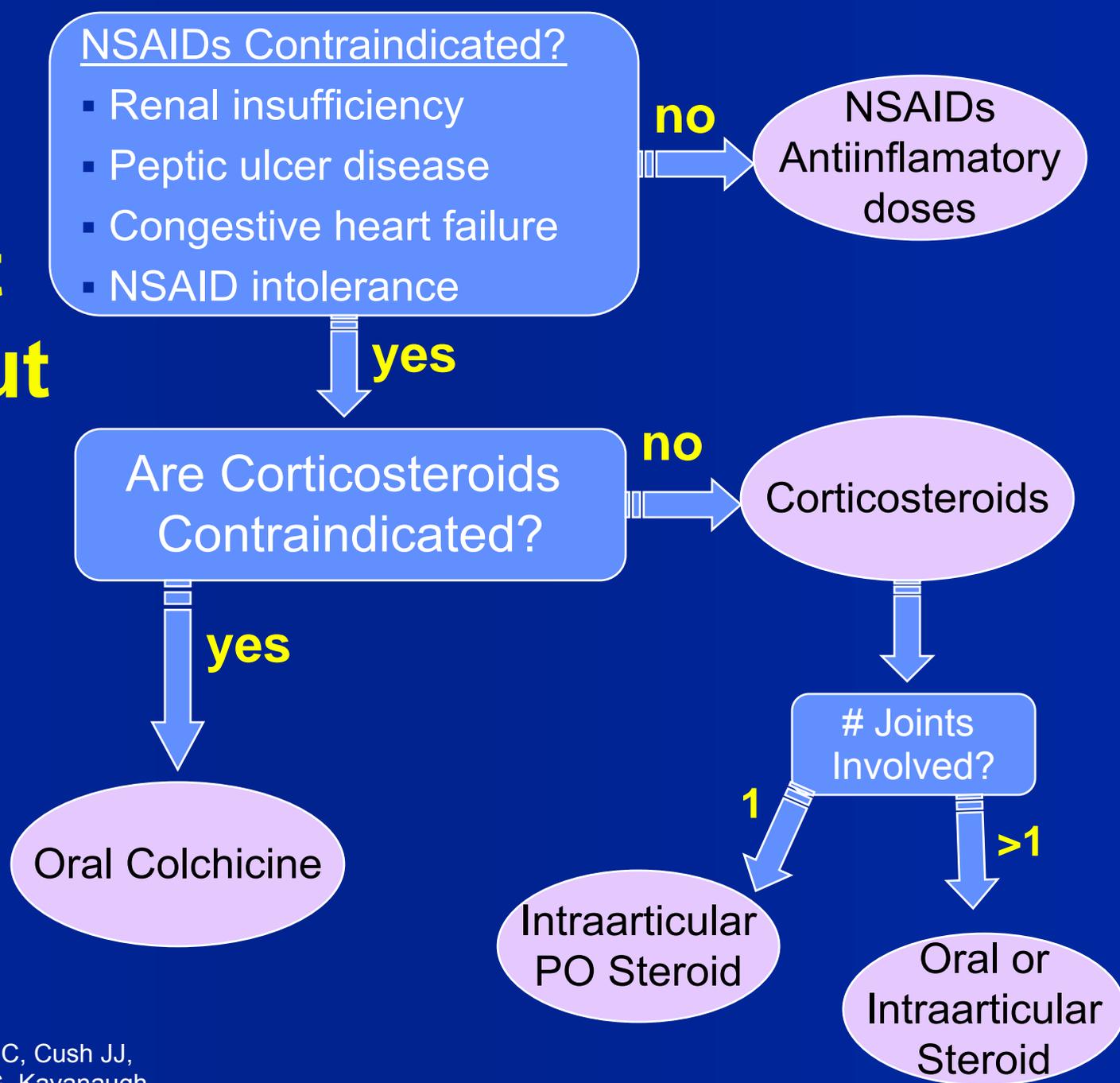
- With evidence of MSU crystal identification
OR
- ❖ One of the following:
 - History of prior intermittent like attacks
 - Evidence of hyperuricemia
 - X-ray evidence of antecedent gouty damage



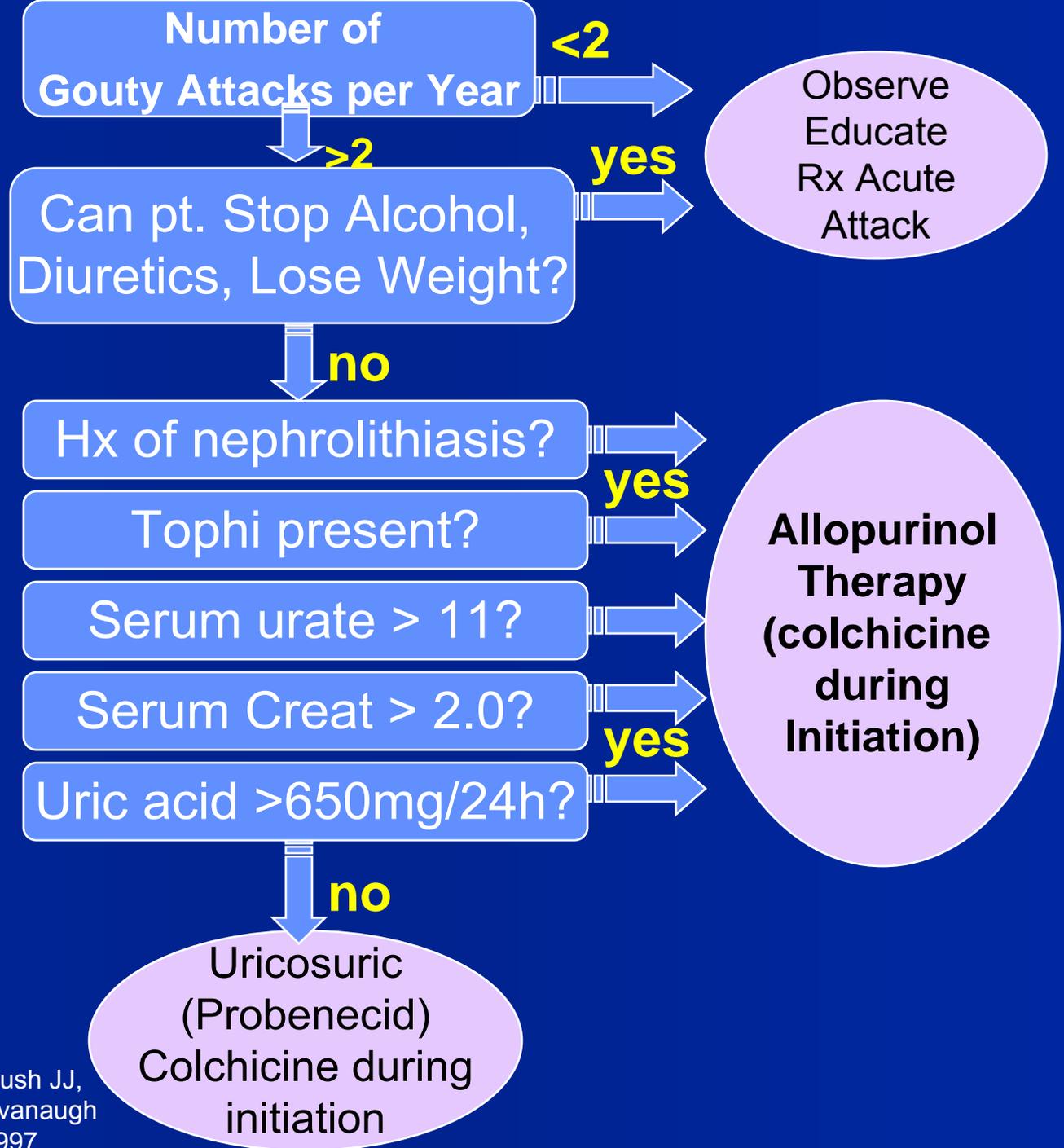
Goals of Treatment

- Rapidly terminate the acute flare
- Protect against further flares
 - ❖ Reduce the chance of crystal-induced inflammation
- Treat the hyperuricemia to prevent disease progression
 - ❖ Serum urate < 6.0 to prevent attacks

Treatment Acute Gout



Treatment of Interval Gout

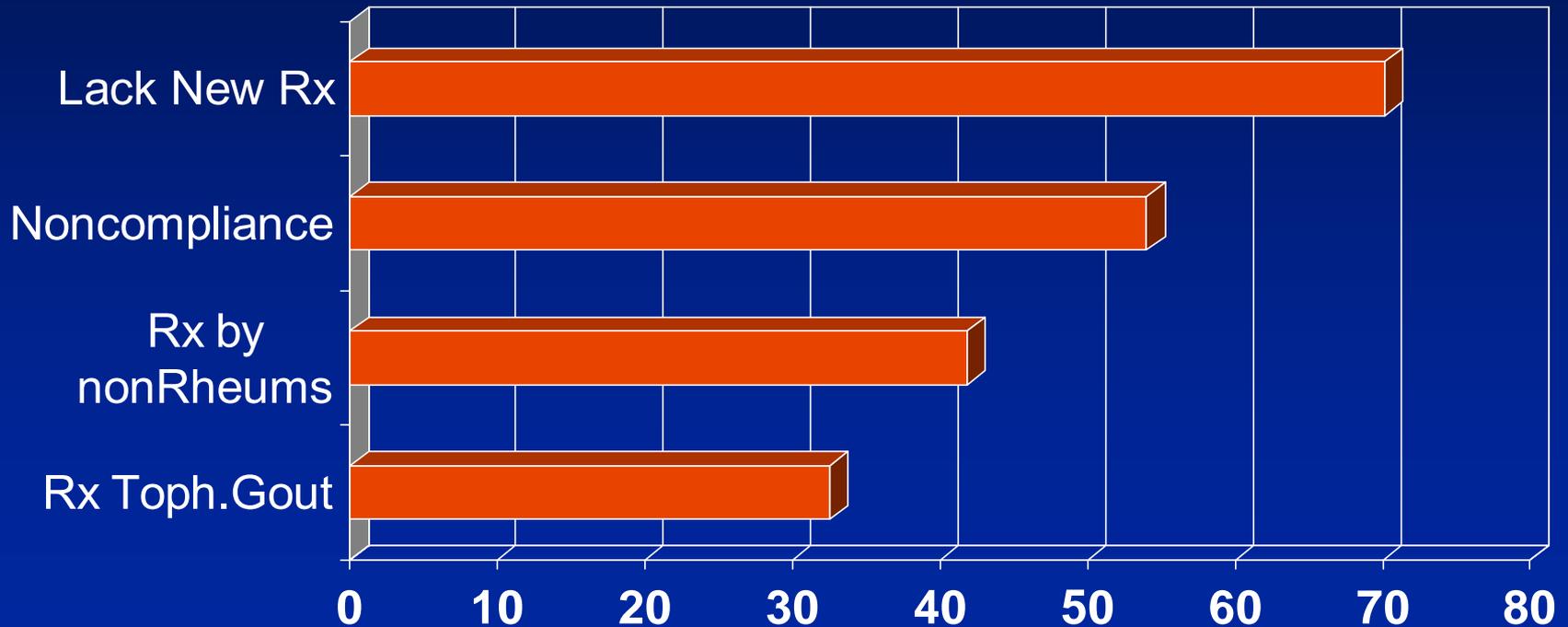


Gout – Sad and Sorry Truths

- Totally Treatable and Preventable
- Largely Dx & managed by PCPs and ER Physicians
 - ❖ Cant/wont do arthrocentesis
- Very few managed by Rheumatologists
 - ❖ only those with severe, recalcitrant, chronic disease
 - ❖ Rheum referral more accurate dx, shorter Sx duration (3.1day), shorter hospitalization (7.4 days), lower hospitalization costs (\$5995 less)*
 - ❖ Krishnan showed 2/3 visits to PCP and 1.3% to Rheumatology
- Many MDs equate hyperuricemia = gout
- Most believe that colchicine is the drug of choice**
- Significant amount of inappropriate management

Survey of 484 US Rheumatologists

Most disappointing in the care of gout pts?



Survey completed 5/13/08

Gout: management

- Acute Rx: NSAIDs > steroids > colchicine (oral only)
- Steroids: PO, IM, intraarticular
- > 2-3 attacks/year → Chronic Rx; Urate lowering Rx
- Chronic Rx: allopurinol, probenecid, colchicine
- Probenecid: uricosuric, promotes excretion
 - ❖ Don't use with CRI, nephrolithiasis or Tophaceous gout
- Colchicine: (diarrhea) decr. PMN motility
- Allopurinol: decrease formation - use w/ CRF, renal stones, Tophaceous gout, Uric acid > 11



* Adjust dose for renal insufficiency

- Return to Main