Pathophysiology

Gout is a common and complex form of	arthritis
Character-ization of Gout	sudden, severe attacks of pain, swelling, redness and tenderness in one or more joints, most often in the big toe
How Uric Acid normally is eliminated in the body	dissolves in the blood and passes through the kidneys into the urine. If too much is produced, the kidneys excrete too little uric acid, which it then bbuilds up.
Build up of Uric Acid character-ization	forming sharp, needlelike uric acid crystals in a joint or surrou-nding tissue that cause pain, inflammation and swelling
Nucleic Acid components	Sugar, phosphate, nitrogenous base

Pathophysiology (cont)

Nucleo-tides	Monomers: phosphate, base, ribose
Purines	Guanine and Adenine
Purine Ring Structure	double ring structure
Pyrimadine	Cytosine, Thymine, Uracil
Pyrimadine Ring Structure	single ring
Formation of Uric Acid	purine breakdown
Purine Foods	liver, shellfish, alcohol
Xanthine oxidase	Enzyme required to produce uric acid by the breakdown of purine nucelotides
Hypoxa-nthine is catalyzed by xantine oxidase into	Xanthine
Xanthine Oxidase catalyzes	the breakdown reaction of hypoxanthine and xanthine into uric acid
AMP get converted to	hypoxanthine
GMP is converted into	Xanthine
Hypoxa-nthine	1 oxygen atom
Xanthine	2 oxygen

Pathophysiology (cont)

Uric acid	3 oxygens
Xanthine is catalyzed by xanthine oxidase itno	uric acid
Uric Acid Pka	5.3, weak organic acid
Uric Acid pH	7.4 (virtually **all uric acid is in its DE-protonated and much more soluble urate form**
Function of Xanthine Oxidase	Uric acid Synthesis

Uric Acid Lowering Therapies

Inhibition of Xanthine Oxidase	Reduces UA *generation*
Inhibition of URA1 and GLU9	Reduce UA *reabsorption* in kidney
Adding Uricase	Convert UA to Allantoin
First line Urate lowering therapy	Xanthine Oxidase Inhibitors
Second line	Benzbromarone, Probenecid, pegloticase
Benzbr-omarone	Increase renal urate excretion
Probenecid	Increase renal urate excretion
Pegloticase	UA degradation

Uric Acid Lowering Therapies (cont)

Purine like XOI	Allopurinol
Non-Purine (specific) like XOI	Febuxostat
Xanthine Oxidase enzyme	protein is large, Mol Weight 270 kDa
active sites of Xanthine Oxidase.	molybdenum atoms are contained as molybdopterin cofactors
Allopu-rinol metabolite	Oxypurinol. Analogues of hypoxanthine and xanthine.
Molybd-opterins	class of cofactors found in most molybdenum-cont-aining and all tungsten-con-taining enzymes
Synonyms for molybd-opterin are:	MPT and pyrano-pterin-dithiolate.
suicide inhibitor of XO	oxipurinol

Uric Acid Reabsorption Inhibitor

major urate reabsorption transporter	Urate anion transporter 1 URAT1 (SLC22A12 gene)
Location of Uric Acid Reabsorption Inhibition	**Proximal Convoluted Tubule (PCT)**

Uric Acid Reabsorption Inhibitor (cont)	
Uric Acid Reabso-rption Inhibition	Inhibit URAT1 and GLUT9
URAT1	OAT transporter family. Anion exchanger that specifically reabsorbs uric acid fro mthe PCT in exchange for Cl
GLUT9	glucose transp-orter family. proximal tubule of kidney, transports uric acid across basolacteral membrane into the blood
GLUT9a vs GLUT9b	differs at N-terminal domain
Probenecid	acts by inhibiting URAT 1 and GLUT 9 transp-orters
Protot-ypical uricosuric drug	probenecid
Benzob-romarone	Potent uricosuric. More potent than probenecid.

Uricases	
Uricase	the enzyme respon-sible for the breaking down of urate to the more water-soluble allantoin was somehow lost during the evolution of man.
Peglot-icase	porcine recombinant polyethylene-glucol conjugated uricase
Peglot-icase MOA	genetically altered variant of Escher-ichia coli, catalyzing uric acid to the water-soluble purine metabolite allantoin
Uric acid is ____ to allantoin	Oxidized