

Pathophysiology		Pathophysiology (cont)		Pathophysiology (cont)		Uric Acid Lowering Therapies (cont)	
<b>Gout is a common and complex form of</b>	arthritis	Nucleotides	Monomers: phosphate, base, ribose	Uric acid	3 oxygens	Purine like XO	Allopurinol
<b>Characterization of Gout</b>	sudden, severe attacks of pain, swelling, redness and tenderness in one or more joints, most often in the big toe	<b>Purines</b>	Guanine and Adenine	Xanthine is catalyzed by xanthine oxidase into	uric acid	Non-Purine (specific) like XO	Febuxostat
<b>How Uric Acid normally is eliminated in the body</b>	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 builds up.	<b>Purine Ring Structure</b>	double ring structure	Uric Acid Pka	5.3, weak organic acid	Xanthine Oxidase enzyme	protein is large, Mol Weight 270 kDa
<b>Build up of Uric Acid characterization</b>	forming sharp, needlelike uric acid crystals in a joint or surrounding tissue that cause pain, inflammation and swelling	<b>Pyrimidine Ring Structure</b>	single ring	Uric Acid pH	7.4 (virtually all uric acid is in its DE-protonated and much more soluble urate form)	<b>active sites of Xanthine Oxidase.</b>	molybdenum atoms are contained as molybdopterin cofactors
<b>Nucleic Acid components</b>	Sugar, phosphate, nitrogenous base	<b>Formation of Uric Acid</b>	purine breakdown	<b>Function of Xanthine Oxidase</b>	Uric acid Synthesis	Allopurinol metabolite	Oxypurinol. Analogues of hypoxanthine and xanthine.
		<b>Purine Foods</b>	liver, shellfish, alcohol			<b>Molybdopterin</b>	class of cofactors found in most molybdenum-containing and all tungsten-containing enzymes
		<b>Xanthine oxidase</b>	Enzyme required to produce uric acid by the breakdown of purine nucleotides	<b>Uric Acid Lowering Therapies</b>		Synonyms for molybdopterin are:	MPT and pyranopterin-dithiolate.
		Hypoxanthine is catalyzed by xanthine oxidase into	Xanthine	Inhibition of Xanthine Oxidase	Reduces UA generation	suicide inhibitor of XO	oxipurinol
		<b>Xanthine Oxidase catalyzes</b>	the breakdown reaction of hypoxanthine and xanthine into uric acid	Inhibition of URA1 and GLU9	Reduce UA reabsorption in kidney		
		AMP get converted to	hypoxanthine	Adding Uricase	Convert UA to Allantoin		
		GMP is converted into	Xanthine	<b>First line Urate lowering therapy</b>	Xanthine Oxidase Inhibitors		
		Hypoxanthine	1 oxygen atom	<b>Second line</b>	Benzbromarone, Probenecid, pegloticase		
		Xanthine	2 oxygen	<b>Benzbromarone</b>	Increase renal urate excretion		
				<b>Probenecid</b>	Increase renal urate excretion		
				<b>Pegloticase</b>	UA degradation		
						<b>Uric Acid Reabsorption Inhibitor</b>	
						major urate reabsorption transporter	Urate anion transporter 1 URAT1 (SLC22A12 gene)
						<b>Location of Uric Acid Reabsorption Inhibition</b>	<b>Proximal Convoluted Tubule (PCT)</b>



### Uric Acid Reabsorption Inhibitor (cont)

**Uric Acid Reabsorption Inhibition**

**URAT1** OAT transporter family. Anion exchanger that specifically reabsorbs uric acid from the PCT in exchange for Cl

**GLUT9** glucose transporter family. proximal tubule of kidney, transports uric acid across basolateral membrane into the blood

**GLUT9a vs GLUT9b** differs at N-terminal domain

**Probenecid** acts by inhibiting URAT 1 and GLUT 9 transporters

**Prototypical uricosuric drug**

**Benzbromarone** Potent uricosuric. More potent than probenecid.

### Uricases

**Uricase** the enzyme responsible for the breaking down of urate to the more water-soluble allantoin was somehow lost during the evolution of man.

**Pegloticase** porcine recombinant polyethylene-glucol conjugated uricase

**Pegloticase MOA** genetically altered variant of Escherichia coli, catalyzing uric acid to the water-soluble purine metabolite allantoin

**Uric acid is** Oxidized \_\_\_\_\_ to allantoin



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