

A Patient with Complicated Ulcerative Colitis: Individualizing Drug Therapy

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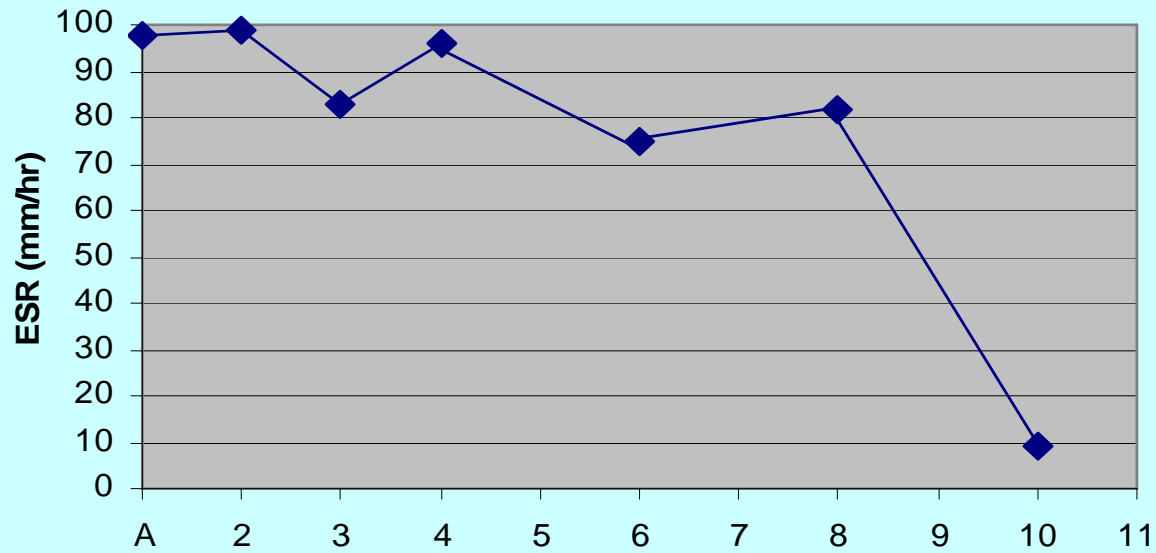
Patient's Problem List

- Ulcerative Colitis Dx 2001
 - Acute Weight Loss (~ 9 Kg x 45d)
 - Acute Pancreatitis
 - Pain Control
 - Nutrition and Anemia
 - Family Centered Care
 - Medication Compliance
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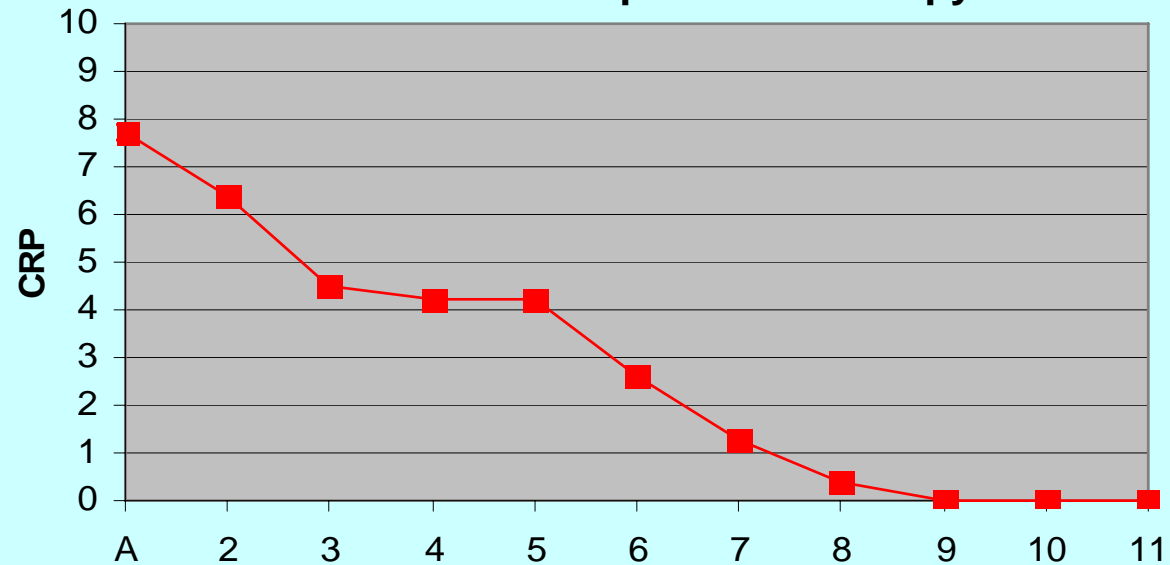
Hospital Course

- Pt admitted to the ward to the GI service
 - Placed NPO, PIC inserted & TPN started
 - Pancreatic US (OSH 3 days PTA): nl biliary tract & gall bladder, w/a diffusely prominate pancrease w/o focal lesions; CXR – nl
 - Abd CT (no contrast) – Suggestive of pancreatitis
 - Clin Pharm consut D2: Re-initiate azathioprine, mesalamine enema at HS, hold oral GCS
 - ? of drug induced pancreatitis: consult ped pharm (D2)
 - Demerol® 30 mg IV Q 4H prn pain
 - Pt improved with resolution of abdominal pain and continual decrease in request for Demerol®; improving labs
 - Rx additions: Nexium 20 mg IV QD; methylprednisolone 8 mg IV Q8h (D4)
 - Disproportionate decrease in WBC relative to other “inflammatory” markers
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Patient's ESR Response to Therapy

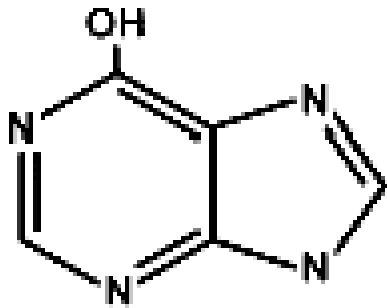


Patient's CRP Response to Therapy

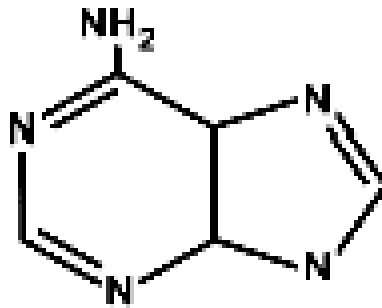


Commonly Prescribed Medications Associated with Drug-Induced Pancreatitis

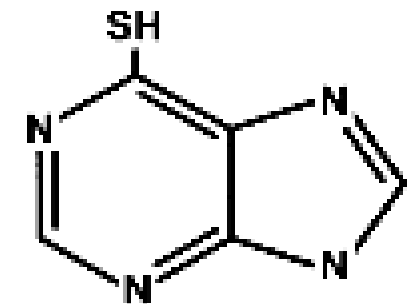
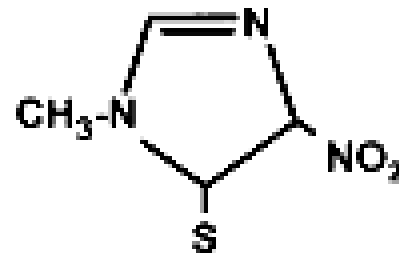
Medication	# of Reported Cases	Top 100 Med Rank
Hydrocodone APAP	55	1
Premarin [®]	42	5
Prempro [®]	42	42
Estradiol	42	77
Ortho-Tri Cyclen [®]	42	25
Furosemide	21	7
HCTZ	12	10
Prednisone	10	27
Methyl Pred	10	92



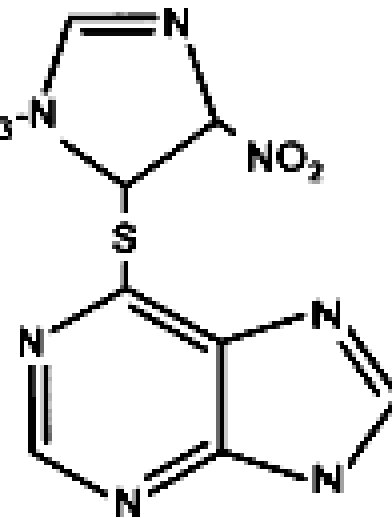
Hypoxanthine



Adenine



6-Mercaptopurine

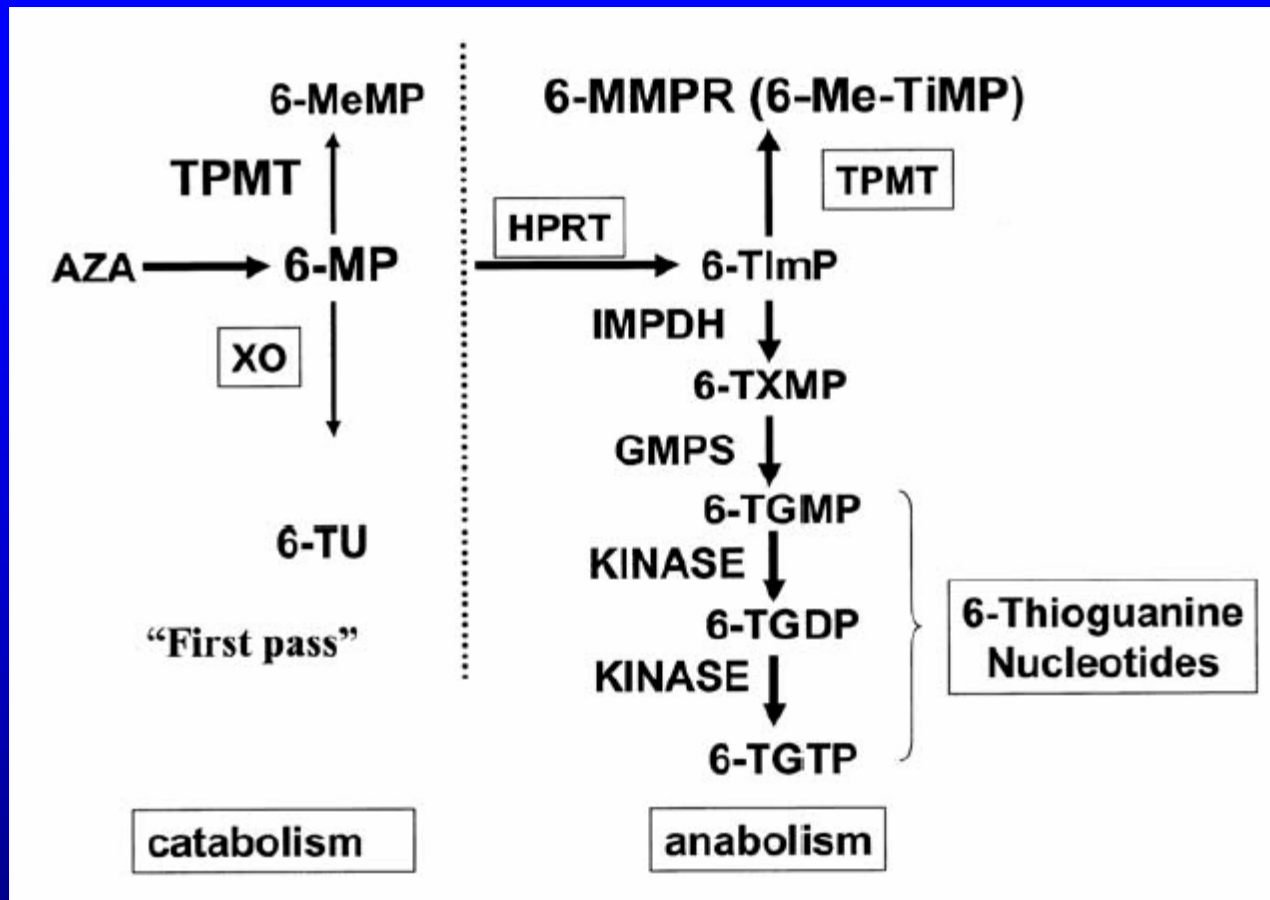


Azathioprine

Chemical structure of adenine nucleotide and its derivatives hypoxanthine, 6-mercaptopurine, and azathioprine.

Azathioprine

- Developed in 1950
 - Attempt to improve upon 6MP PK
 - Focus primarily bioavailability
 - 55% 6MP by MW & 88% AZA converted to 6MP
 - Disposition Characteristics
 - Rapid, non-enzymatic conversion by sulphhydryl containing compds in plasma & tissue
 - AZA F = 25-85% (50-72%) vs 6MP = 5-37%
 - T_{1/2}: AZA - 12 min, 6MP - 0.7-2hrs
 - Other Characteristics
 - AZA possesses some immunosuppressant activity
 - Dose dependent toxicity
 - Bone marrow: neutropenia, anemia, thrombocytopenia
 - Mucositis, hypersensitivity
 - Lab monitoring for efficacy/safety
-



Thiopurine metabolism. Oral AZA is rapidly converted to 6-MP by a nonenzymatic process. Initial 6-MP transformations occur along competing catabolic (XO, xanthine oxidase; TPMT) and anabolic (HPRT, hypoxanthine phosphoribosyltransferase) enzymatic pathways. Once formed, 6-thiosine 5'-monophosphate (6-TImP) is further catalyzed by inosine monophosphate dehydrogenase (IMPDH), and guanosine monophosphate synthetase (GMPS) and the di- and tri-derivatives of 6-thioguanosine 5'-monophosphate (6-TGMP) formed by their respective kinases. T-TU, 6-thiouric acid.

Thiopurine, S-Methyltransferase (TPMT)

- Cytosolic Enzyme
 - Catalyzes S-methylation of aromatic and heterocyclic sulfhydryl compds
 - AZA, 6MP, TG
 - Primarily located in hematopoietic tissues
 - Genetic Polymorphism
 - 90% High, 10% Intermediate, 0.3% Low or No
 - Effective in guiding dose
 - Clear population differences in frequency
 - *1/*1 wild type ~ 89% (normal)
 - *1/*3 heterozygotes ~10-11% (reduced activity)
 - *3/*3 homozygous for variant allele ~ 0.3% no activity
 - Laboratory Assessment
 - Measure enzyme activity: radiochemical or by HPLC
 - Denaturing HPLC, RT-PCR, molecular haplotyping, arrayed primer extension (APEX) assays
-

TPMT allele frequencies in various populations

Population	No. patients	Allele frequency				Genotype frequencies (%)		
		TPMT*1	TPMT*2	TPMT*3 A	TPMT*3 C	W/M	W/W	M/M
Ghanaians	217	0.924	0	0	0.076	85.2	14.3	0.005
Kenyans	101	0.946	0	0	0.054	89.1	10.9	0
British Caucasian	199	0.948	0.005	0.045	0.002	89.1	10.1	0
NZ Caucasian	100	0.950	0	0.05	0	91	8	1
Swedish [†]	800	0.956	0.00063	0.0375	0.0044	91.25	8.75	0
Argentinian [‡]	147	0.960	0.0068	0.031	0	91.8	8.2	0
Colombian	140	0.960	0.0038	0.036	0	92.1	7.9	0
African-Americans [§]	248	0.962	0.004	0.008	0.024	92.7	7.3	0
American Caucasian	282	0.964	0.002	0.032	0.002	92.9	7.1	0
Saami	194	0.969	0	0	0.031	93.8	6.2	0
Chinese	192	0.977	0	0	0.023	95.3	4.7	0
Malay [¶]	200	0.975	0	0	0.023			
Egyptian	200	0.984	0	0.003	0.013	93.6	6.4	0
Japanese	522	0.984	0	0	0.016	97.1	2.5	0.38
Indian	200	0.987	0	0.005	0.008			
South-east Asians	300	0.993	0.0017	0	0.050	90.5	9.0	0.5
Taiwanese	249	0.994	0	0	0.014	94.0	6.0	0
South-west Asians (British)	99	0.990	0	0.01	0	98.0	2.0	0

TPMT, thiopurine methyltransferase.

TPMT: Genotype-Phenotype (Dis)cordance

- 98% concordance between gene-phen
 - Genotype highly sensitive (90%) & specific (99%) in I.D. pts with 1 or 2 non-functional alleles
 - ↑ reports ↓ concordance with low enzyme activity
 - Enzyme Activity
 - Measured in RBC's
 - Radiochemical or HPLC-based activity assay
 - Influenced by recent blood transfusion, uremia
 - Activity varies over time in individuals
 - Drugs: AZA, diuretics ↑; 5 ASA compds ↓
 - Genotype
 - Will ID vast majority of pts ↓ activity
 - Will miss rare variant allele pts
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TPMT Activity and Toxicity

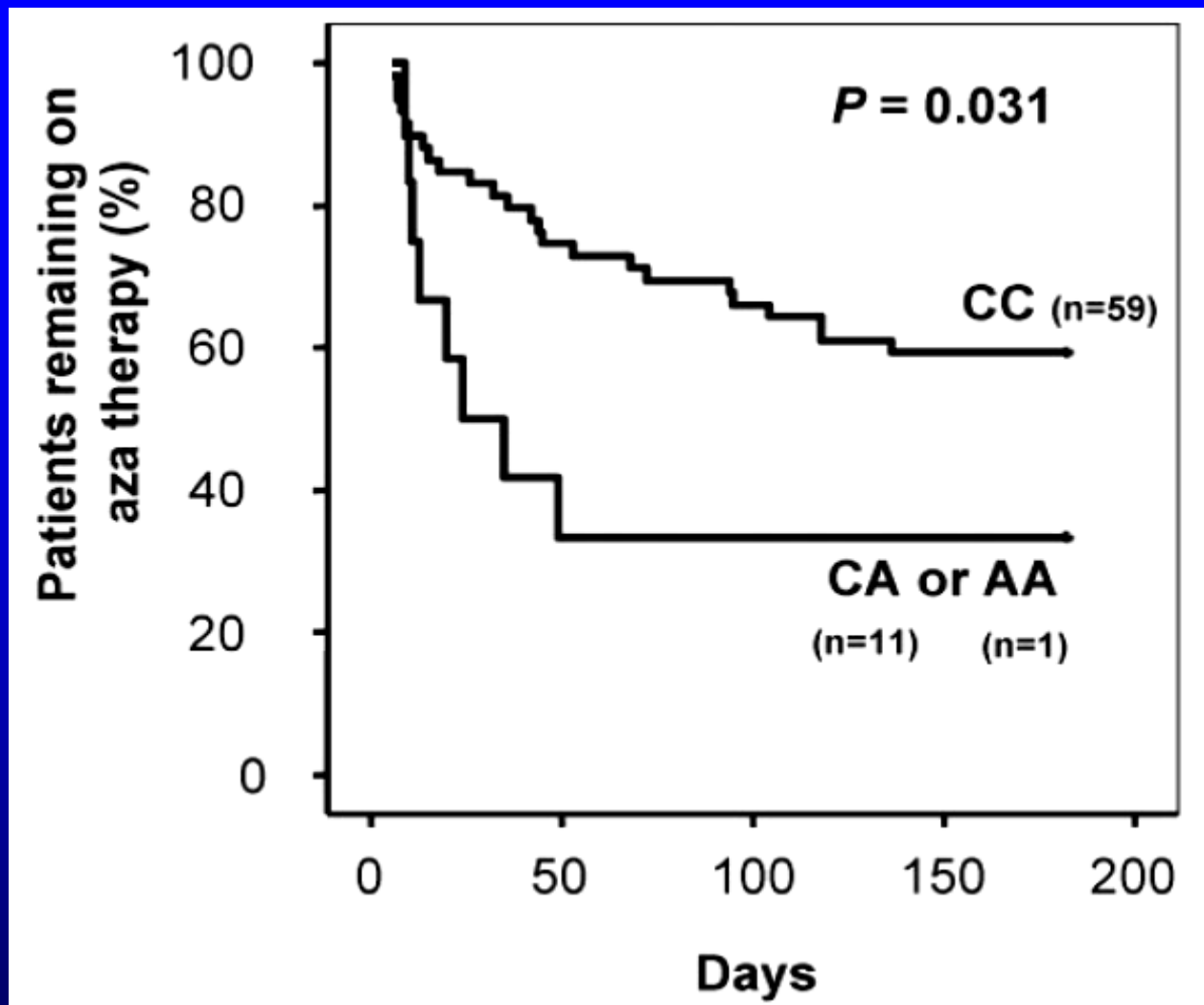
- Myelotoxicity
 - Incidence and magnitude directly related to drug dose and TPMT activity
 - ? TPMT activity pre-Rx
 - 30 +% myelotox – geno/pheno correlation
 - Factors other than TPMT activity determines total risk
 - Other Adverse Effects
 - N, V, infection, ↑ LFT's, “hypersensitivity”
 - Poor correlation with TPMT activity
 - Prevailing Perspective
 - Good relationship for myelotoxicity
 - Poor correlation for non-myelotoxicity
 - Good correlation with efficacy / relapse
 - Directs drug dose
-

Relationship Between TPMT Phenotype Patients and Side Effects: AZA or 6-MP Intolerant

TPMT Phenotype	Type of Toxicity M(%)		
	Hematopoietic	Liver	Mucositis
Deficient (n=6)	6 (100)	0	2 (33.3)
Intermediate (n=9)	9 (100)	3 (33.3)	1 (11.1)
High (n=8)	6 (75)	3 (37.5)	1 (12.5)

23 Phenotype, 20 genotype: Concordance: Deficient-100%; Intermediate-60% (n=8)

Evans WE, et al. J Clin Oncol 19:2293, 2001.



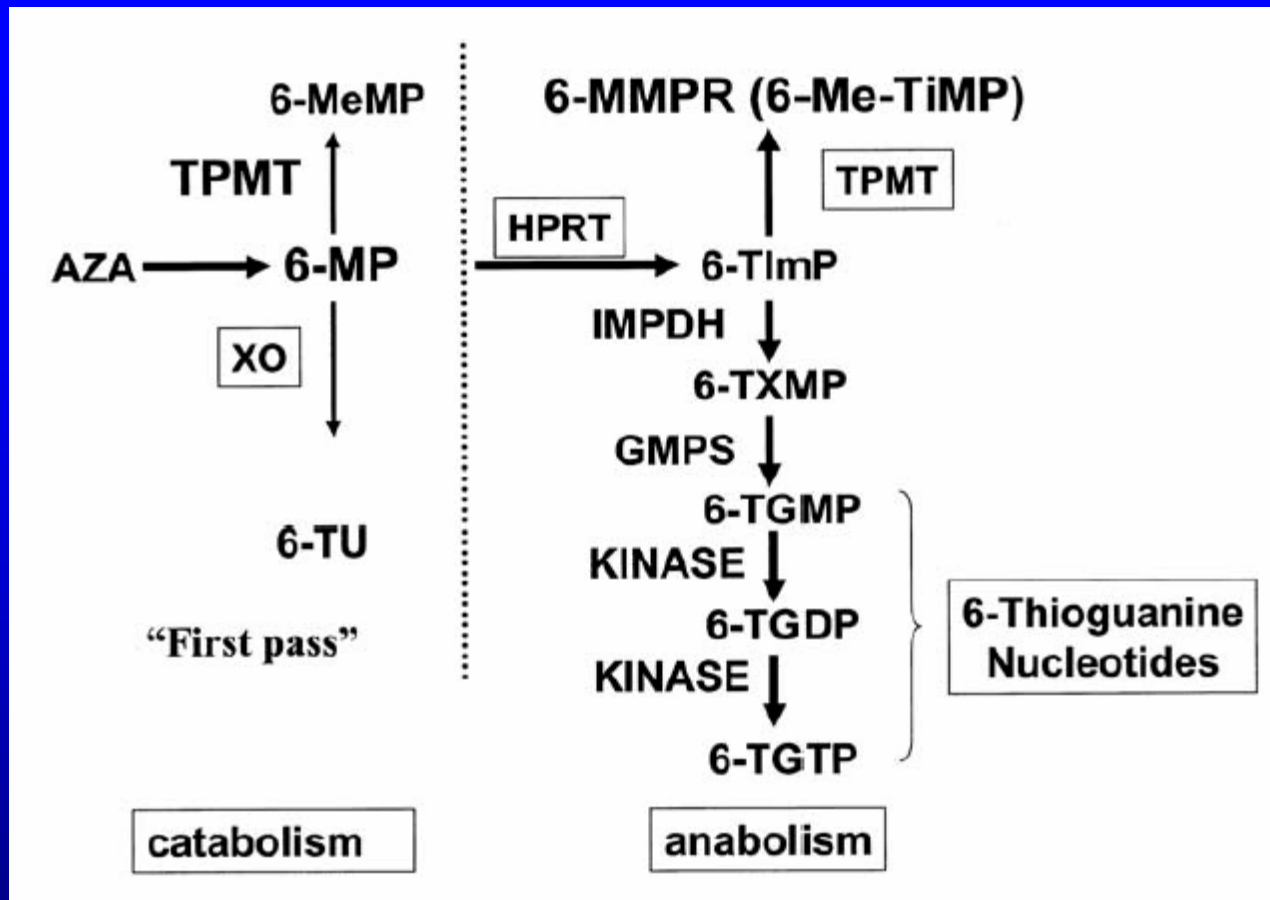
Time-to-event (survival) curve showing probability of remaining on aza therapy stratified according to *ITPA* 94C>A status.

CC, wild type; CA, heterozygous mutation; AA, homozygous mutation.

Von Ahsen N, et al.; *Clin Chem* 51:2282, 2005.

Inosine Triphosphate Pyrophosphatase Genotype

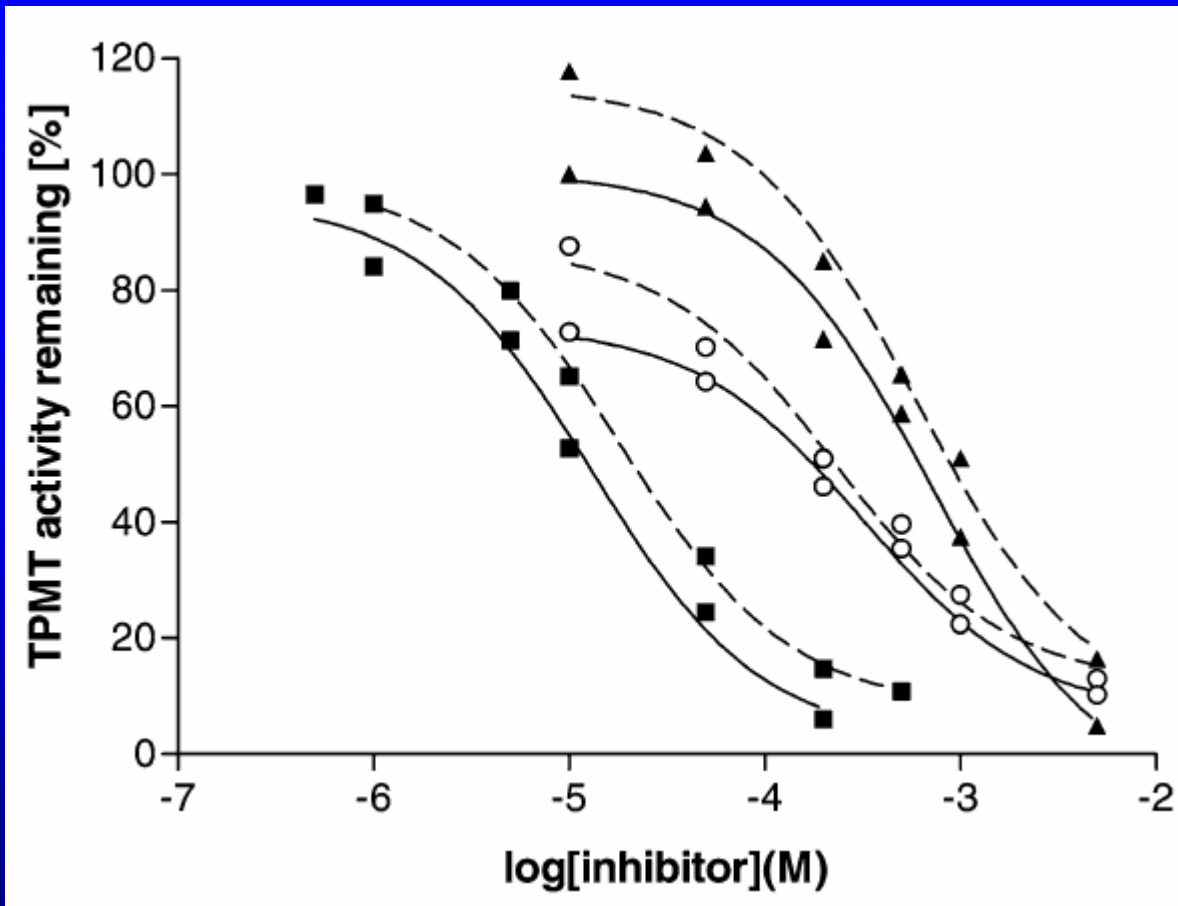
- Recently variant alleles identified
 - Associated with thiopurine Rx toxicity
 - Non-myelotoxicity
 - Reduced activity
 - Accumulation of 6-thioinosine triphosphate pyrophosphate (6-TITP)
 - Catalyzes ITP-IMP: recycles 6-thio purines
 - Data evolving regarding bedside application
 - ITPA 94C > a deficient allele strong TP-tox correlation
 - OR: rash 10.3, pancreatitis 6.2, allergic-type reactions 4.7
-



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Thioguanine Nucleotide Concentrations

- TGN-Distal metabolites
 - Active, cytotoxic
 - Accumulate in tissues and incorporated into nucleic acids
 - Incorporates fraudulent metabolites in RNA & DNA
 - Inhibits purine synthesis
 - RBC Enzyme Concentrations
 - Inversely correlates with TPMT activity
 - Low []'s associated with relapse (↑ dose)
 - High []'s associated with toxicity (↓ dose)
 - Target [] range disease & severity dependent (ALL vs IBD vs RA, others)
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Inhibition of thiopurine methyltransferase (TPMT) activity in red blood cells (RBCs) of two representative azathioprine (AZA)-free patients with inflammatory bowel disease (IBD) by furosemide (*filled square*), piretanide (*open circle*) and AZA (*filled triangle*). *Solid lines* TPMT activity (54 units), *broken lines* TPMT activity (23 units).

Hematologic Parameters in Adults with Crohn's Disease on Azathioprine

Parameter	REMISSION		p Value
	Yes (n=14)	No (n=31)	
WBC	5,350 (2,106)	8,918 (3,858)	0.004
Lymphocytes (%)	16.6 (6.8)	9.6 (5.8)	0.005
Granulocytes (%)	73 (8.7)	81 (6.9)	0.007

Data presented as mean (\pm SD)

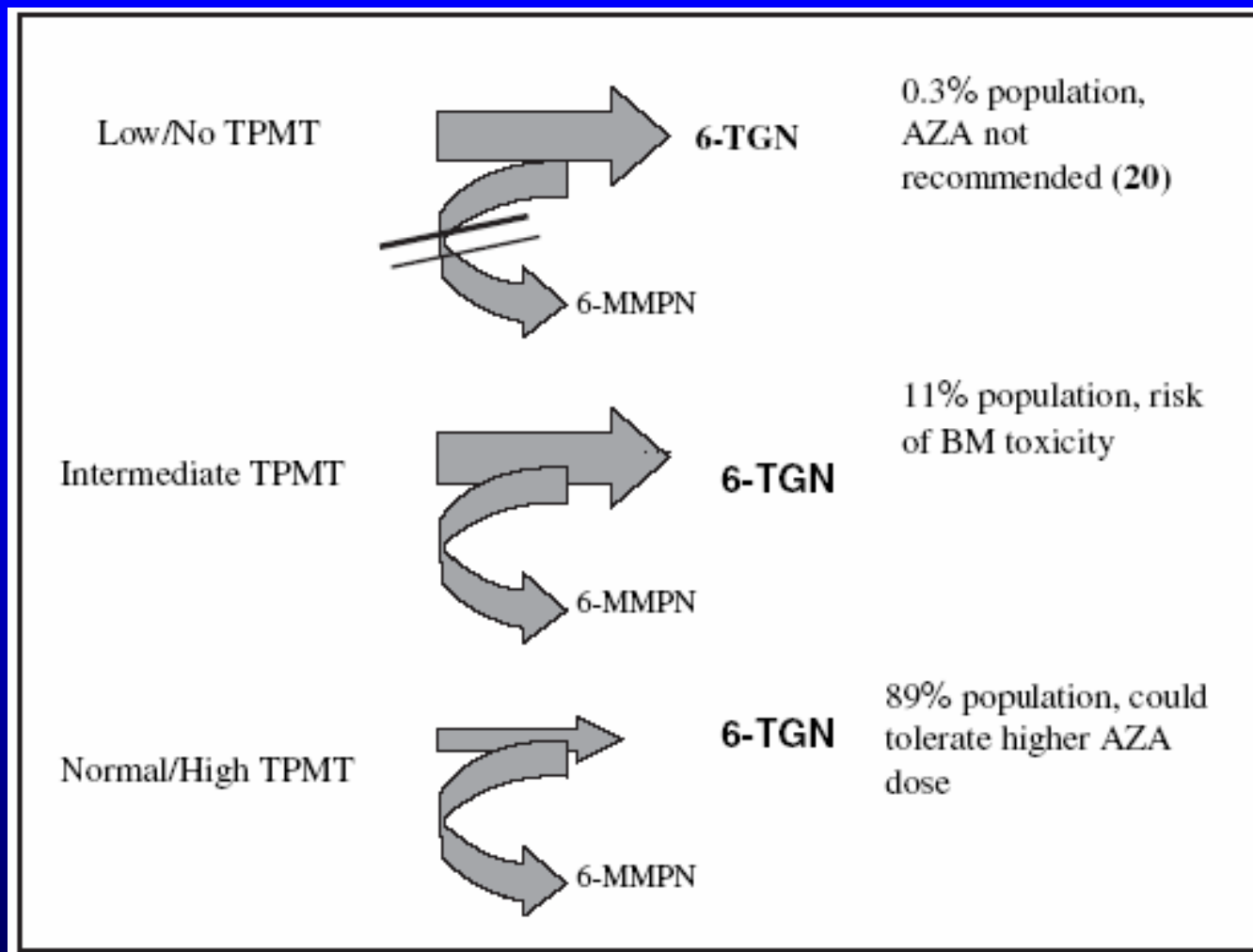
Hematologic Parameters in Adults with Ulcerative Colitis on Azathioprine

Parameter	REMISSION		p Value
	Yes (n=13)	No (n=27)	
WBC	6,045 (1,165)	8,767 (2,356)	0.003
Lymphocytes (%)	20 (5.3)	12 (5.6)	0.001
Granulocytes (%)	69 (6.1)	79 (8.9)	0.004

Data presented as mean (\pm SD)

Suggested Azathioprine Treatment Doses Based Upon Erythrocyte TPMT Activity

TMT Activity	~ % of Population	Azathioprine Dose (mg)
Deficient (very low / absent)	0.3	No Rx or ↓ by 90%
Intermediate	11	↓ Dose by 15-50%
Normal or “High”	89	Standard Rx



TPMT enzyme activity according to its genotype and concomitant 6-TG nucleotide production in the general population.