

Name: Acetylsalicylic Acid/Aspirin**Class:** Salicylate**Mech.:** Irrevers. acetylation of cyclooxygenase → inhib. of prostaglandin synth. → ↓ prostaglandins, thromboxanes, & prostacyclins → analgesia, inhib. of platelet aggregation, anti-inflammatory effects, anti-pyresis, stim. of central resp. center.**Absorption:** Rapidly absorbed in stomach and upper intestine. Also absorbed through skin. pKa = 3.5, so gastric acid → ↑ absorption. Enteric coating may delay absorption.**Dist.:** pH-dependent passive (non-ionic) diffusion. Active transport in renal tubules. 90% bound to albumin.**Metab.:** Hydrolyzed by tissue/blood esterases. Conjugated in liver.**Excretion, t_{1/2}:** Salicylate & metabolites excreted in urine. pH-dependent—30% excretion in alkaline urine, 2% in acidic urine. Low doses (600 mg) = 1st order; t_{1/2} = 3-5 hr. High doses (4 g/d) = 0 order, t_{1/2} = 15 hr.**Utility: Analgesia**—mild-mod. pain, somatic pain. No dependence or tolerance. Low efficacy for visceral pain. **Anti-inflammatory**—also a mech. of analgesia.**Anti-pyresis**—inhib. bacterial pyrogens in CNS; blocks hypothalamic response to IL-1. ↓ **Platelet aggregation**—2° to inhib. of thromboxane synth.**Aspirin cont.****Toxicity/S.E.s:** GI bleeding and ulceration—usu. due to high doses, but may occur w/lower doses. Painless bleeding may cause iron-deficiency anemia.

Hypersensitivity—usu. in patients w/nasal polyps, asthma, or chronic urticaria → urticaria, angioedema, hypotension. Bleeding—C/i w/severe hepatic damage, vit. K deficiency, hemophilia. Hepatotoxicity w/CT disorders. May be involved in Reye's Synd.; not recommended for kids w/chicken pox or influenza.

Pregnancy—reduced birth weight, ↑ perinatal mortality, ante/post-partum hemorrhage, prolonged gestation. Renal effects—low doses → ↓ uric acid excretion; high doses → ↑ uric acid excretion. Poisoning—acute → resp. alkalosis (hyperventilation), metabolic acidosis (fixed anion). Correlates w/plasma conc. Chronic → higher brain conc. than in acute poisoning; greater toxicity than plasma conc. would suggest. More resistant to treatment than acute poisoning.

Drug Interactions: Alcohol → ↑ gastric bleeding. Displacement of oral hypoglycemia drugs, NSAIDs, methotrexate, phenytoin, oral anti-coagulants, & sulfonamides from protein binding sites.**Special Features:** May exacerbate acute gout attacks.**Name: Methylsalicylate (Oil of Wintergreen)****Class:** Salicylate**Mech.:****Absorption:** Absorbed transdermally.**Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Used in foods...may be toxic.**Utility:** Used in liniments for cutaneous counterirritation.**Special Features:****Name: Salicylamide****Class:** Salicylate**Mech.:****Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:****Utility:****Special Features:** May exacerbate acute gout attacks.

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Name: Ibuprofen (Advil, Motrin, Nuprin) (OTC)

Class: NSAID

Mech.: Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).

Absorption: Oral. Absorbed from stomach and upper intestine. Peak conc. 1-2 hr.

Dist.: Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd.

Metab.: 1° = liver. Phase I (oxid.) & Phase II (conjug.).

Excretion, t_{1/2}: Metabolites in urine. Renal failure → retention of glucuronide metabolites → potential for toxic accumulation of orig. compound. t_{1/2} = 2-3 hr.

Toxicity/S.E.s: GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures.

Utility: Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout.

Name: Indomethacin (Indocin)

Class: NSAID

Mech.: Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).

Absorption: Oral. Absorbed from stomach and upper intestine. Peak conc. 1-2 hr.

Dist.: Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd.

Metab.: 1° = liver. Phase I (oxid.) & Phase II (conjug.).

Excretion, t_{1/2}: Metabolites in urine, bile, & feces. Renal failure → retention of glucuronide metabolites → potential for toxic accum. of orig. compound. t_{1/2} = 4-5 hr. Decreased clearance w/hepatic/renal impairment & in the elderly.

Toxicity/S.E.s: GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures. Use limited by toxicity. 100% cross-reactivity with aspirin.

Utility: Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout.

Special Features: Most commonly used NSAID for acute gout attack due to short peak time & rapid clearance.

Name: Sulindac (Clinoril)

Class: NSAID

Mech.: Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).

Absorption: Oral. Absorbed from stomach and upper intestine. Peak conc. 1-2 hr.

Dist.: Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd.

Metab.: 1° = liver. Phase I (oxid.) & Phase II (conjug.).

Excretion, t_{1/2}: Metabolites in urine, bile, feces. Renal failure → retention of glucuronide metabolites → potential for toxic accumulation of orig. compound. t_{1/2} = 8-16 hr. Decreased clearance w/hepatic impairment and in the elderly.

Toxicity/S.E.s: GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis, but less likely to cause kidney effects than other NSAIDs. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures.

Utility: Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout.

Special Features: Pro drug (converted to an active metabolite).

Name: Flurbiprofen (Ansaid)

Class: NSAID

Mech.: Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).

Absorption: Oral. Absorbed from stomach and upper intestine. Peak conc. 1-5 hr.

Dist.: Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd.

Metab.: 1° = liver. Phase I (oxid.) & Phase II (conjug.).

Excretion, t_{1/2}: Metabolites in urine. Renal failure → retention of glucuronide metabolites → potential for toxic accumulation of orig. compound. t_{1/2} = 5 hr.

Toxicity/S.E.s: GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures.

Utility: Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout.

Name: Naproxen (Naprosyn)**Class:** NSAID**Mech.:** Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).**Absorption:** Oral. Absorbed from stomach and upper intestine. Peak conc. 2-4 hr.**Dist.:** Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd.**Metab.:** 1° = liver. Phase I (oxid.) & Phase II (conjug.).**Excretion, t_{1/2}:** Metabolites in urine. Renal failure → retention of glucuronide metabolites→potential for toxic accumulation of orig. compound. t_{1/2} = 12-15 hr. Clearance decreased w/renal/hepatic impairment & in the elderly.**Toxicity/S.E.s:** GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures.**Utility:** Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout.**Name: Piroxicam (Feldene)****Class:** NSAID**Mech.:** Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).**Absorption:** Oral. Absorbed from stomach and upper intestine. Peak conc. 3-5 hr.**Dist.:** Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd.**Metab.:** 1° = liver. Phase I (oxid.) & Phase II (conjug.).**Excretion, t_{1/2}:** Metabolites in urine. Renal failure → retention of glucuronide metabolites→potential for toxic accumulation of orig. compound. t_{1/2} = 30-86 hr.**Toxicity/S.E.s:** GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures.**Utility:** Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout.**Name: Diflunisal (Dolobid)****Class:** Salicylate.**Mech.:** Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).**Absorption:** Oral. Absorbed from stomach and upper intestine. Peak conc. 2-3 hr.**Dist.:** Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd. No CNS.**Metab.:** 1° = liver. Phase I (oxid.) & Phase II (conjug.).**Excretion, t_{1/2}:** Metabolites in urine. Renal failure → retention of glucuronide metabolites→potential for toxic accumulation of orig. compound. t_{1/2} = 11-15 hr. Clearance decreased w/renal impairment & in the elderly.**Toxicity/S.E.s:** GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures.**Utility:** Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout.**Special Features:** Not metab. to salicylate, ∴ no salicylate intoxication. No CNS → no antipyretic properties. 3-4x more potent than aspirin.**Name: Ketorolac (Toradol)****Class:** NSAID**Mech.:** Inhibition of cyclooxygenase → inhibition of prostaglandin synthesis. Also inhib. of PMN adhesion, aggregation, & activation (ramifications uncertain).**Absorption:** Parenteral only.**Dist.:** Weak acid (pKa <5). ~90% protein binding. Vd ≅ albumin Vd.**Metab.:** 1° = liver. Phase I (oxid.) & Phase II (conjug.).**Excretion, t_{1/2}:** Metabolites in urine. Renal failure → retention of glucuronide metabolites → potential for toxic accumulation of orig. compound.**Toxicity/S.E.s:** GI—esophagitis & esophageal strictures; gastroduodenal erosions, ulceration, hemorrhage, & perforation; ileal inflammation, strictures, hemorrhage, & perforation; colon hemorrhage and exacerbation of inflammatory bowel disease. Hypersensitivity—possible cross-reaction w/aspirin. Inhib. of platelet aggregation. Kidney—Na⁺ retention, hemodynamic renal failure, interstitial nephritis. CNS—dizziness, tinnitus, headache, aseptic meningitis. Overdose—Acute is less serious than w/aspirin, but may cause metabolic acidosis & seizures.**Utility:** Treat pain, inflammation, dysmenorrhea, patent ductus arteriosus, acute gout. May be as effective as morphine or meperidine for short-term relief of mod.-severe pain.

Name: Gold (Auranofin, Aurothioglucose)**Class:** Slow-Acting Antirheumatic Agent**Mech.:** Unknown. May involve alteration of macrophage fxn.**Absorption:** Auranofin—oral. Aurathioglucose—IM.**Dist.:** 95% protein bound.**Metab.:****Excretion, t_{1/2}:** 65% in urine, 35% feces. 5-6 days.**Toxicity/S.E.s:** Affects about 1/3 of patients. Mucocutaneous—pruritis & dermatitis. Renal—proteinuria, nephrotic synd., hematuria. Hematologic—eosinophilia, thrombocytopenia, aplastic anemia.**Utility:** Treatment of patients w/rheumatoid arthritis who are unresponsive to NSAIDs or whose symptoms persist despite maximal tolerated doses of NSAIDs.**Special Features:****Name: D-penicillamine (Cuprimine)****Class:** Slow-Acting Antirheumatic Agent**Mech.:** Unknown. Suppresses/modifies immune system & interacts w/leukocyte membrane receptors. Also chelates heavy metals (e.g., Pb, Hg, As, Cu).**Absorption:** Oral.**Dist.:** 80% protein bound.**Metab.:****Excretion, t_{1/2}:** Urine.**Toxicity/S.E.s:** Mucocutaneous—pruritis, dermatitis. Renal—proteinuria, nephrotic synd. Hematologic—thrombocytopenia, aplastic anemia. Pulmonary—hemorrhagic pneumonitis.**Utility:** Treatment of patients w/rheumatoid arthritis who are unresponsive to NSAIDs or whose symptoms persist despite maximal tolerated doses of NSAIDs.**Special Features:****Name: Methotrexate (Rheumatrex)****Class:** Slow-Acting Antirheumatic Agent (Antimetabolite)**Mech.:** Inhib. dihydrofolate reductase → inhib. of formation of tetrahydrofolic acid → ↓ synth of purines, thymidylic acid, methionine, and serine → ↓ DNA/RNA/protein synth. → eventual cell death.**Absorption:** Oral, IV, IM, IT.**Dist.:** No CNS unless administered IT.**Metab.:** **Excretion, t_{1/2}:****Toxicity/S.E.s:** Stomatitis, myelosuppression, erythema, rash, urticaria, alopecia, n/v/d. Long term use may → hepatic fibrosis. High doses may → crystalluria. Patient must be well hydrated and have alkaline urine to avoid renal toxicity. Also pulmonary toxicity in children. IT admin. → subacute meningeal irritation, stiff neck, headache, fever; rarely seizures, encephalopathy, paraplegia. C/i w/pregnancy (teratogenic).**Utility:** Low doses useful in treating rheumatoid arthritis and severe psoriasis. Effective against acute lymphocytic leukemia, choriocarcinoma, Burkitt's lymphoma, breast cancer, head/neck carcinomas. High doses are curative for osteogenic sarcoma and choriocarcinoma.**Name: Hydroxychloroquine (Plaquenil)****Class:** Slow-Acting Antirheumatic Agent (Anti-Malarial Agent)**Mech.:** Unknown. Inhib. nucleic acid synth, stabilizes lysosomal membranes, traps free radicals.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** GI upset, pruritis, headaches, visual disturbances, discoloration of nail beds and mucous membranes.**Utility:** Treat rheumatoid arthritis that has been unresponsive to NSAIDs. Also used to treat rheumatoid arthritis in conjunction w/an NSAID (allows use of lower dose of hydroxychloroquine).**Special Features:**

Name: Sulfasalazine (Azulfidine)**Class:** Sulfonamide (Slow-Acting Antirheumatic Agent)**Mech.:** Comp. inhib. of PABA incorp. into dihydropteridic acid → inhib. of folic acid.**Absorption:** Poorly absorbed in GI tract.**Distribution:** GI tract**Metab.:** Hydrolyzed to active form by intest. bacteria.**Excretion, t_{1/2}:** feces**Toxicity/S.E.s:** Interferes w/normal flora → ↓ vit. K synth.**Utility:** Active in bowel lumen. Used prior to surgery to reduce microbe population. Treat inflammatory bowel disease, rheumatoid arthritis.**Special Features:** Broken down in intestines to liberate 5-aminosalicylate (anti-inflammatory).**Name: Levamisole (Ergamisol)****Class:** Slow-Acting Antirheumatic Agent (Veterinary Anti-Helminthic Agent)**Mech.:** Enhances cell-mediated immune responses (↑ chemotaxis & phagocytosis of PMNs and Mφs, ↑ T cell fxn). How these effects ameliorate RA is unknown.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Rash (most common), leukopenia, agranulocytosis, thrombocytopenia, influenza-like illnesses, mouth ulcers, n/v.**Utility:** Treat rheumatoid arthritis (off-label use).**Special Features:****Name: Probenecid (Benemid)****Class:** Anti-Gout Agent (Uricosuric Agent)**Mech.:** Blocks proximal tubular reabsorption of uric acid.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:** Reabsorbed by renal tubules & metabolized slowly.**Toxicity/S.E.s:** GI irritation (not severe). Skin rash. Rare aplastic anemia.**Utility:** Treat gout via increased urinary excretion of uric acid. Blocks tubular secretion of penicillin; may be used to increase penicillin levels.**Special Features:** At low doses, probenecid blocks proximal tubule secretion of uric acid.**Name: Sulfinpyrazone (Anturane)****Class:** Anti-Gout Agent (Uricosuric Agent)**Mech.:** Blocks proximal tubular reabsorption of uric acid.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:** Rapidly excreted by the kidneys.**Toxicity/S.E.s:** GI irritation (not severe). Skin rash. Rare aplastic anemia.**Utility:** Treat gout via increased urinary excretion of uric acid.**Special Features:** At low doses, sulfinpyrazone blocks proximal tubule secretion of uric acid.

Name: Allopurinol (Zyloprim)**Class:** Anti-Gout Agent**Mech.:** Inhibits xanthine oxidase → ↓ production of uric acid.**Absorption:** Well absorbed orally.**Dist.:****Metab.:** Metab. by xanthine oxidase to a longer acting active metabolite.**Excretion, t_{1/2}:****Toxicity/S.E.s:** GI intolerance, skin rash.**Drug Interactions:** Inhib. metab. of oral anticoagulants. Xanthine oxidase inactivates 6-mercaptopurine & azathioprine (cancer chemotherapeutic drugs). ∴ doses must be lowered when patient takes allopurinol.**Utility:** Treat chronic tophaceous gout, gout patients w/high excretion of uric acid, patients who cannot use probenecid or sulfinpyrazone, recurrent renal uric acid stones, renal impairment, grossly elevated serum acid concentrations (>13 mg/dL). Use also w/cancer chemotherapy to prevent urate nephropathy.**Special Features:****Name: Colchicine****Class:** Anti-Gout Agent**Mech.:** Binds to tubulin → inhib. of leukocyte migration & phagocytosis → ↓ inflamm. response.**Absorption:** Rapidly absorbed orally.**Dist.:****Metab.:****Excretion, t_{1/2}:** Urine & feces.**Toxicity/S.E.s:** GI intolerance (n/v/d).**Utility:** Treat acute gout attacks. Use to prevent acute attacks while initiating allopurinol or probenecid therapy.**Special Features:** Not analgesic. No effect on uric acid production or excretion.**Name: Acetaminophen (Tylenol)****Class:** Para-aminophenol (OTC)**Mech.:** Weak inhib. of peripheral prostaglandin synth. More effective CNS cyclooxygenase inhib. → antipyretic and analgesic properties.**Absorption:** Oral → rapid & complete w/peak in 30-60 min. Not a weak acid.**Dist.:** Dist. throughout body fluids. Protein binding (20-50%) not significant.**Metab.:** No zero-order kinetics. Phase II conjug. w/glucuronic acid & sulfate. Phase I oxid. → N-acetyl-benzoquinoneimine. Reacts w/sulfhydryl groups, but normally inactivated by glutathione (except in overdose).**Excretion, t_{1/2}:** Majority excreted as conjug. metabolites in urine. Not related to urine pH. 2 hr.**Toxicity/S.E.s:** Overdose → depletion of hepatic glutathione → rxn. w/sulfhydryl groups of hepatic proteins → hepatic necrosis. Also renal tubular necrosis. Treatment w/N-acetylcysteine w/in 10 hr. of overdose can be life-saving.**Utility:** Analgesic and antipyretic efficacies comparable to aspirin.**Special Features:** Para-aminophenol prototype. Often used w/other analgesics (e.g., Tylenol + Codeine). Weak peripheral inhib. → weak anti-inflammatory activity. No urocosuric or anti-platelet effects.**Name: Phenacetin****Class:** Para-aminophenol**Mech.:** Converted to acetaminophen. Weak inhib. of peripheral prostaglandin synth. More effective CNS cyclooxygenase inhib. → antipyretic and analgesic properties.**Absorption:** Oral → rapid & complete. Not a weak acid.**Dist.:** Dist. throughout body fluids. Protein binding (20-50%) not significant.**Metab.:** No zero-order kinetics. Phase II conjug. w/glucuronic acid & sulfate. Phase I oxid. → N-acetyl-benzoquinoneimine. Reacts w/sulfhydryl groups, but normally inactivated by glutathione (except in overdose).**Excretion, t_{1/2}:** Majority excreted as conjug. metabolites in urine. Not related to urine pH.**Toxicity/S.E.s:** Nephropathy assoc. w/chronic use. Overdose → depletion of hepatic glutathione → rxn. w/sulfhydryl groups of hepatic proteins → hepatic necrosis. Also renal tubular necrosis. Treatment w/N-acetylcysteine w/in 10 hr. of overdose can be life-saving.**Utility:** Analgesic and antipyretic efficacies comparable to aspirin.**Special Features:** No longer prescribable in US due to renal toxicity. Weak peripheral inhib. → weak anti-inflammatory activity. No urocosuric or anti-platelet effects.

Name: Cyclosporine (Sandimmune)**Class:** Immunosuppressant**Mech.:** Binds to calmodulin and a cytoplasmic cytophilin → selective inhib. of transcription of IL-2 gene → inhib. of IL-2 prod. & release from T4 cells, inhib. of proliferation of T8 cells, block of T4 activation of B cells.**Absorption:** Oral → highly variable and incomplete absorption.**Dist.:** Large Vd. Binds in tissues. 60-70% contained in RBCs.**Metab.:** Extensive hepatic metab involving cyt. P450 enzymes. 17 metabolites known. Drug levels monitored by RIA or HPLC.**Excretion, t_{1/2}:** Biliary excretion, minor renal excretion.**Toxicity/S.E.s:** Nephrotoxicity (main toxicity), hepatotoxicity, hirsutism, gingival hyperplasia, neurotoxicity, altered coagulability. But little (if any) bone marrow suppression. Drug interactions—rifampin & phenobarbital → induction of hepatic metab. Erythromycin → inhib. of hepatic metab. Ketoconazole & amphotericin → ↓ clearance.**Utility:** Prolong organ transplants (1° use). Suppress cell-med. diseases. Possible benefit w/early treatment of IDDM.**Special Features:****Name: OKT3 (Muromonab-CD3)****Class:** Immunosuppressant**Mech.:** Opsonizes T cells, modulates CD3 antigen recognition complex on T cells, blocks CTL killer function.**Absorption:** IV**Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Chills, fever, thrombocytopenia, erythema, pruritis, hypersensitivity rxns, anti-OKT3 antibody production (∴ only given for 1-2 weeks).**Utility:** Prevent or reverse acute allograft rejection.**Special Features:** Murine monoclonal antibody against CD3 on T cells.**Name: Prednisone****Class:** Corticosteroid (Immunosuppressant)**Mech.:** Inhib. of IL-1 & TNF synth/release from Mφs → ↓ activation of T cells and Mφs, ↓ PMN fxn, ↓ T cell-dependent Ab production, ↓ complement activity, ↓ activity & release of kinins.**Absorption:** Oral**Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Suppressed pituitary adrenal fxn, hypertension, weight gain, peptic ulcer, GI bleeding, euphoric personality changes, cataracts, hyperglycemia.**Utility:** Immunosuppression. Primarily employed to induce remission in patients w/acute lymphocytic leukemia, and for treatment of lymphomas. Treat hypercalcemia due to vit. D intox., sarcoidosis, or specific cancers (e.g., lymphoproliferative) (30-60 mg/d).**Special Features:****Name: Methylprednisone****Class:** Corticosteroid (Immunosuppressant)**Mech.:** Inhib. of IL-1 & TNF synth/release from Mφs → ↓ activation of T cells and Mφs, ↓ PMN fxn, ↓ T cell-dependent Ab production, ↓ complement activity, ↓ activity & release of kinins.**Absorption:** Parenteral**Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Suppressed pituitary adrenal fxn, hypertension, weight gain, peptic ulcer, GI bleeding, euphoric personality changes, cataracts, hyperglycemia.**Utility:** Immunosuppression. Primarily employed to induce remission in patients w/acute lymphocytic leukemia, and in treatment of lymphomas.**Special Features:**

Name: Azathioprine (Imuran)

Class: Immunosuppressant (Antimetabolite)

Mech.: Converted to 6-mercaptopurine (thiol analog of hypoxanthine) → inhib. of purine synth. → cytotoxicity to dividing cells → ↓ lymphocyte proliferation → inhib. of cellular and humoral immunity.

Absorption:

Dist.:

Metab.:

Excretion, t_{1/2}:

Toxicity/S.E.s: Bone marrow depression (main toxicity), n/v/d, hepatotoxicity.

Utility: Primarily used in maintenance of remission in acute lymphoblastic leukemia.

Special Features:

Name: Cyclophosphamide (Cytosan)

Class: Immunosuppressant (Alkylating Agent) (Cancer Chemotherapeutic Agent)

Mech.: Activated via hepatic P450 metabolism → phosphoramidate mustard. Phosphoramidate mustard alkylates DNA → cytotoxicity to dividing cells.

Absorption: Oral

Dist.:

Metab.:

Excretion, t_{1/2}:

Toxicity/S.E.s: Bone marrow depression (esp. leukocytosis), hemorrhagic cystitis (may → bladder fibrosis), n/v/d, alopecia, amenorrhea, testicular atrophy, sterility. Possible secondary malignancies years later.

Utility: Cancer chemotherapy, nephrotic syndrome, intractable rheumatoid arthritis.

Special Features: Therapeutic effect independent of level of P450 activity.

Name: Antilymphocyte Globulin (ALG)

Class: Immunosuppressant

Mech.: Polyclonal antibody to human lymphocytes (not selective to CD3) → destruction and inactivation of lymphocytes.

Absorption:

Dist.:

Metab.:

Excretion, t_{1/2}:

Toxicity/S.E.s: Chills, fever, thrombocytopenia, erythema, pruritis, hypersensitivity rxns, anti-ALG antibody production (∴ only given for 1-2 weeks).

Utility: Prevent or reverse acute allograft rejection.

Special Features:

Name: G-CSF (Filgrastim)

Class: Immunostimulant

Mech.: Promotes growth & differentiation of granulocyte precursors.

Absorption:

Dist.:

Metab.:

Excretion, t_{1/2}:

Toxicity/S.E.s: Bone pain, fever, anti-CSF antibodies.

Utility: Restore hematopoiesis (FDA-approved to treat neutropenia), augment host defenses, esp. after cancer therapy.

Special Features:

Name: GM-CSF (Sargramostim)**Class:** Immunostimulant**Mech.:** Stim. bone marrow production of precursors to PMNs, monocytes, platelets. Also activates PMNs, eosinophils, and monocytes.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Fever, dermatologic rxns, splenomegaly.**Utility:** FDA-approved to increase myeloid recovery rate after bone marrow transplantation. Also used for hematological reconstitution after autologous bone marrow transplants and treatments w/bone marrow cytotoxic drugs.**Special Features:** Greater severity of immunologic S.E.s than w/G-CSF.**Name: Erythropoietin (Epoetin Alfa, Epogen)****Class:** Immunostimulant**Mech.:** Stim. division/differentiation of erythroid progenitors in bone marrow.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Usu. well-tolerated. Low incidence of hypertension, headache, seizures. Rare hypersensitivity rxns.**Utility:** Treat anemia assoc. w/chronic renal failure, AZT therapy, cancer and chemotherapy. Supplemental iron eventually required in therapy.**Special Features:** Manufactured by recombinant DNA technology. Identical to human erythropoietin.**Name: Interferon α** **Class:** Immunostimulant**Mech.:** Binds to cell-surface receptors → inhib. of viral replication, inhib. of cell proliferation.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Fever w/chills; dose-related leukopenia, thrombocytopenia; fatigue, malaise, anorexia, weight loss, alopecia, transient elevation of liver enzymes. High doses may → transient & reversible nephrotoxicity.**Utility:** IFN α 2A is approved for mgt. of hairy cell leukemia. Also useful for chronic hepatitis B, virally induced tumors, recurrent varicella zoster, HSV keratitis, Kaposi's sarcoma, cutaneous T cell lymphoma.**Special Features:** Produced by mononuclear leukocytes. Interferon production is induced by dsRNA (poly I:C), amplitgen (mismatched nucleotides), LPS.**Name: Interferon β** **Class:** Immunostimulant**Mech.:** Binds to cell-surface receptors → inhib. of viral replication, inhib. of cell proliferation.**Absorption:****Dist.:****Metab.:****Excretion, t_{1/2}:****Toxicity/S.E.s:** Fever w/chills; dose-related leukopenia, thrombocytopenia; fatigue, malaise, anorexia, weight loss, alopecia, transient elevation of liver enzymes. High doses may → transient & reversible nephrotoxicity.**Utility:** Used to treat for chronic hepatitis B, virally induced tumors, recurrent varicella zoster, HSV keratitis, Kaposi's sarcoma, hairy cell leukemia, cutaneous T cell lymphoma.**Special Features:** Produced by fibroblasts. Interferon production is induced by dsRNA (poly I:C), amplitgen (mismatched nucleotides), LPS.

Name: Interferon γ **Class:** Immunostimulant**Mech.:** Binds to cell-surface receptors \rightarrow activation of NK cells and M ϕ s, promotion of conversion to TH₁ cells.**Absorption:****Dist.:****Metab.:****Excretion, t $\frac{1}{2}$:****Toxicity/S.E.s:** Fever w/chills; dose-related leukopenia, thrombocytopenia; fatigue, malaise, anorexia, weight loss, alopecia, transient elevation of liver enzymes. High doses may \rightarrow transient & reversible nephrotoxicity.**Utility:** Used to treat for chronic hepatitis B, virally induced tumors, recurrent varicella zoster, HSV keratitis, Kaposi's sarcoma, hairy cell leukemia, cutaneous T cell lymphoma.**Special Features:** Produced by memory TH₁ cells and NK cells. Interferon production is induced by dsRNA (poly I:C), amplitigen (mismatched nucleotides), LPS.**Name: Bacillus Calumet-Guerin (BCG)****Class:** Immunostimulant**Mech.:** Viable strain of Mycobacterium bovis. Enhances M ϕ activity, promotes M ϕ tumoricidal activity.**Absorption:****Dist.:****Metab.:****Excretion, t $\frac{1}{2}$:****Toxicity/S.E.s:****Utility:** Treat bladder carcinoma and melanomas.**Special Features:****Name: Misoprostol (Cytotec)****Class:** Gastric Protectant (Prostaglandin)**Mech.:** Analog of prostaglandin E₁. Inhib. secretion of HCl. Stimulates secretion of mucus & HCO₃ (cytoprotective).**Absorption:****Dist.:****Metab.:****Excretion, t $\frac{1}{2}$:****Toxicity/S.E.s:** Diarrhea, nausea. Produces uterine contractions. \therefore c/i during pregnancy.**Utility:** Only agent approved for prevention of gastric ulcers induced by NSAIDs. Less effective than H₂ antagonists for acute treatment of peptic ulcers.**Special Features:**

How, if some day or night a demon were to sneak after you into your loneliest loneliness and say to you, "This life as you now live it and have lived it, you will have to live once more and innumerable times more; and there will be nothing new in it, but every pain and every joy and every thought and sigh and everything immeasurably small or great in your life must return to you—all in the same succession and sequence—even this spider and this moonlight between the trees, and even this moment and I myself. The eternal hourglass of existence is turned over and over, and you with it, a dust grain of dust." Would you not throw yourself down and gnash your teeth and curse the demon who spoke thus? Or did you once experience a tremendous moment when you would have answered him, "You are a god, and never have I heard anything more godly." If this thought were to gain possession of you, it would change you, as you are, or perhaps crush you. The question in each and every thing, "Do you want this once more and innumerable times more?" would weigh upon your actions as the greatest stress. Or how well disposed would you have to become to yourself and to life to *crave nothing more fervently* than this ultimate eternal confirmation and seal?

—Friedrich Nietzsche