Anti-inflammatory, Antipyretic, and Analgesic Agents

Chapter 36
Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. When healing is complete, the inflammatory process usually subsides.
However, inappropriate activation of the immune system can result in inflammation, leading to immune mediated diseases such as rheumatoid arthritis (RA).
In RA, WBCs initiates an inflammatory attack as in the followings:

A) Activation of WBCs $\rightarrow$ activation of T-lymphocytes which will recruit & activate monocytes & macrophages.
B) Macrophages & monocytes secrete pro-inflammatory cytokines, including tumor necrosis factor (TNF-α) & interleukin (IL-1) into synovial cavity.
1) ↑ cellular infiltration into the endothelium due to release of histamins, kinins & vasodilatory prostglandins.
2) ↑ production of c-reactive protein by hepatocytes (a marker for inflammation).

3) ↑ production of proteolytic enzymes (collagenase & metalloproteinase) by chondrocytes (cells that maintain cartilage) → degradation of cartilages & joint space narrowing.
Normal joint space

Narrowed joint space
4) ↑ osteoclast activity (osteoclasts regulate bone breakdown), result in focal bone erosions & bone demineralization around joints.
5) Heart, lungs & liver are adversely affected.

C) B-lymphocytes also involved which produced rheumatoid factor (inflammatory factors) & other autoantibodies which maintain inflammation.
These defensive reactions will cause progressive tissue injury resulting in joint damage & erosions.
II. PROSTAGLANDINS

Membrane Phospholipids

activated PL-A₂

Arachidonic Acid

COX

PGG₂

PGH₂

Lipoxigenase

Leukotrienes
& Lipoxins

- Prostaglandins D₂, E₂, and F₂a
- Prostacyclin (PGI₂)
- Thromboxanes (e.g., TXA₂)
Prostaglandins and related compounds are produced by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action.
Arachidonic acid, a 20-carbon fatty acid, is the primary precursor of the prostaglandins and related compounds. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid.
1. Cyclooxygenase pathway:

Eicosanoids (prostaglandins, thromboxanes, and prostacyclins) are synthesized via the cyclooxygenase pathway. Two related isofoms of the cyclooxygenase enzymes have been described.
Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids, it is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions.
Whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation.
COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation.
COX-2 expression is induced by inflammatory mediators like TNF-α and IL-1, but can also be pharmacologically inhibited by glucocorticoids, which may contribute to the significant anti-inflammatory effects of these drugs.
2. Lipoxygenase pathway:

Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes or lipoxins, depending on the tissue. Antileukotriene drugs, such as zileuton, zafirlukast, and montelukast, are useful for the treatment of moderate to severe asthma.
Prostaglandins: Therapeutic uses

Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G- coupled proteins.
Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and
mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes.
1. **Alprostadil**: Alprostadil is a PGE1 that is naturally produced in tissues, such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus.
Therapeutically, alprostadil can be used to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible.
(ductus arteriosus is a blood vessel connecting the pulmonary artery to the proximal descending aorta which normally closed after birth).
PGE1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart.
Local administration of *alprostadil* in the urethra (suppository) or into the corpus cavernosa (injection) can produce an erection suitable for intercourse. These effects are mediated by an increase in intracellular cAMP leading to activation of protein kinase and smooth muscle relaxation.
When used for the treatment of erectile dysfunction, *alprostadil can produce symptomatic hypotension, dizziness, and syncope*. When administered intravenously (IV) in neonates, apnea, fever, sepsis, and seizures have been reported.
2. **Lubiprostone**: It is a PGE1 derivative used for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation.
Lubiprostone stimulates chloride channels (ClC-2) in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion and increases intestinal motility.
3. Misoprostol: it is a PGE1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. The drug decreases the incidence of gastric and duodenal ulcers caused by NSAIDs.
Misoprostol is contraindicated during pregnancy because it induced contraction of the uterus. Misoprostol is also used off-label in obstetric settings for labor induction. Other common side effects are: diarrhea, abdominal pain, spotting (in women), and headache.
4. Prostaglandin F$_2$α analogs

Bimatoprost, latanoprost, tafluprost & travoprost are PGF2α analogs that are indicated for the treatment of open angle glaucoma and elevated intraocular pressure. They are administered as ophthalmic solutions once a day and are as effective as timolol or better in reducing intraocular pressure.
Bimatoprost increases eyelash prominence, length, and darkness and has also been approved for the treatment of eyelash hypotrichosis (predominantly loss or reduction).
5. Prostacyclin (PGI$_2$) analogs

Epoprostenol [ee-poe-PROST-en-ol], the pharmaceutical form of naturally occurring prostacyclin, and the synthetic analogs of prostacyclin (iloprost [EYE-loe-prost] and treprostinil [tre-PROS-ti-nil]) are potent pulmonary vasodilators that are used for the treatment of pulmonary arterial hypertension.
Epoprostenol and treprostinil are administered as a continuous intravenous infusion, and treprostinil may also be administered orally or via inhalation or subcutaneous infusion. Inhaled iloprost requires frequent dosing due to the short half-life.
Side effects: Dizziness, headache, flushing and fainting are usually the most common side effects. Bronchospasm and cough can also occur after iloprost inhalation.
I. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities.
They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis.
A. Aspirin and other salicylic acid derivatives

Aspirin is a weak organic acid that is unique among the NSAIDs in that it irreversibly acetylates (and, thus, inactivates) cyclooxygenase.
Aspirin is rapidly deacetylated by esterases in the body, thereby producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.
The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of prostaglandin synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites.
Aspirin decrease the synthesis of PGE2 which responsible for sensitization of the nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.
Actions & Therapeutic uses of Aspirin

a. Anti-inflammatory, antipyretic & analgesic uses.
Salicylic acid derivatives used in treatment of
rheumatoid fever, osteoarthritis (degeneration of
the cartilage & aggravated by impaired blood
supply) & rheumatoid arthritis (chronic
inflammation).
Healthy knee joint  Osteoarthritis
In rheumatoid arthritis, the same joints usually are affected on both sides of the body. This symmetry doesn't typically occur in osteoarthritis, so it's common for only one hand or knee to be painful.
Aspirin commonly use in analgesia of headache, arthralgia (neurologic pain in joints) & myalgia (pain in the muscle). It is use for low to moderate pain arise from musculoskeletal rather than arise from the viscera.
b. External application: salicylic acid used topically to treat corns, calluses & warts.

c. Cardiovascular applications: aspirin used to inhibit platelet aggregation so used prophylactically in treatment of:
1) Reduce the risk of transient ischemic attacks (TIAs), stroke & M.I.
2) Reduce the risk of death in those having M.I.

TXA₂ (thromboxane A₂) release from the platelets with PGs by the effect of COX enzyme. TXA₂ enhance platelet aggregation whereas PGI₂ decrease it is aggregation.
Low doses (doses less than 325 mg; many classify it as doses of 75 to 162 mg commonly 81 mg) of aspirin are used prophylactically to reduce the risk of recurrent cardiovascular events and/or death in patients with previous MI or unstable angina pectoris.
Aspirin can irreversibly inhibit thromboxane $A_2$ production in platelets via acetylation of COX enzyme. Platelets have no nuclei so they are unable for synthesizing new enzyme & the lack of thromboxane persists for the life time of platelets (3-7 days).
Meanwhile the inhibition of COX enzyme in the endothelial cells for synthesis of PGI$_2$ can be overcome by re-synthesis again of new enzyme, thus PGI$_2$ available for antiplatelet action.
Pharmacokinetics:

After oral administration, the un-ionized salicylates are passively absorbed partly from the stomach and mostly from the upper small intestine (dissolution of the tablets is favored at the higher pH of the gut).
Salicylates must be avoided in children and teenagers (less than 20 years old) with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome.
Reye syndrome or Reye's syndrome is a potentially fatal syndrome that has numerous detrimental effects to many organs, especially the brain and liver, as well as causing a lower than usual level of blood sugar (hypoglycemia). The classic features are a rash, vomiting, and liver damage.
For long-term myocardial infarction prophylaxis, the dose is 81 to 162 mg/day; for those with RA or osteoarthritis, the initial dose is 3 grams/day; for stroke prophylaxis, the dose is 50 to 325 mg/day; and in a patient having an acute myocardial infarction, the dose is 162 to 325 mg of nonenteric-coated aspirin chewed and swallowed immediately.
Adverse effects:

a. **Gastrointestinal**: The most common GI effects of the salicylates are epigastric distress, nausea, and vomiting.

b. **Blood**: The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA2, resulting in inhibition of platelet aggregation and a prolonged bleeding time. For this reason, aspirin should not be taken for at least 1 week prior to surgery.
c. Respiration: In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic acidosis.

d. Hypersensitivity: Approximately 15 percent of patients taking aspirin experience hypersensitivity reactions, include urticaria, bronchoconstriction, and angioedema. Fatal anaphylactic shock is rare.

e. Reye syndrome
B. Propionic acid derivatives

Ibuprofen  [eye-byoo-PROE-fen], naproxen [nah-PROX-en], fenoprofen [fen-oh-PROE-fen], ketoprofen [key-toe-PROE-fen], flurbiprofen [flur-bye-PROE-fen], and oxaprozin [ox-ah-PROEzin].
All of these drugs possess anti-inflammatory, analgesic, and anti-pyretic activity. Additionally, they can alter platelet function and prolong bleeding time. They have gained wide acceptance in the chronic treatment of RA and osteoarthritis, because their GI effects are generally less intense than those of aspirin.
C. Acetic acid derivatives

They include indomethacin [in-doe-METH-a-sin], sulindac [sul-IN-dak], and etodolac [eh-TOE-doh-lak]. All have anti-inflammatory, analgesic, and antipyretic activity.
D. Oxicam derivatives

Piroxicam [peer-OX-i-kam] and meloxicam [mel-OX-i-kam] are used to treat RA, ankylosing spondylitis (rigidity of the spine), and osteoarthritis. They have long half-lives, which permits once-daily administration.
Meloxicam inhibits both COX-1 and COX-2, with preferential binding for COX-2, and at low to moderate doses shows less GI irritation than piroxicam. However, at high doses, meloxicam is a nonselective NSAID, inhibiting both COX-1 and COX-2.
E. Fenamates

Mefenamic [meh-FEN-a-mick] acid and meclofenamate [meh-KLO-fena- mate] have no advantages over other NSAIDs as anti-inflammatory agents. Their side effects, such as diarrhea, can be severe, and they are associated with inflammation of the bowel.
F. Heteroaryl acetic acids

Diclofenac [dye-KLO-feh-nak] and tolmetin [tole-MET-in] are approved for long-term use in the treatment of RA, osteoarthritis, and ankylosing spondylitis (rheumatoid disease chiefly of young males in which there are abnormal pain & rigidity of intervertebral hip).
Ketorolac [key-toe-ROLE-ak] is a potent analgesic but has moderate anti-inflammatory effects. It is available for oral administration, for intramuscular use in the treatment of postoperative pain, and for topical use for allergic conjunctivitis.
G. Nabumetone

Nabumetone [na-BYOO-meh-tone] is indicated for the treatment of RA and osteoarthritis and is associated with a low incidence of adverse effects. Nabumetone is metabolized by the liver to an active metabolite, which displays anti-inflammatory, antipyretic, and analgesic activities.
H. Celecoxib

Celecoxib [sel-eh-COCKS-ib] is significantly more selective for inhibition of COX-2 than of COX-1. This selectivity against COX-2 provides a therapeutic advantage over nonselective COX inhibitors, allowing the proper management of chronic inflammatory conditions.
**Celecoxib** is approved for treatment of RA, osteoarthritis, acute to moderate pain, and for adjuvant treatment of patients with familial adenomatous polyposis (is an inherited condition in which numerous adenomatous polyps form mainly in the epithelium of the large intestine) to reduce the number of adenomatous colorectal polyps.
Unlike aspirin, celecoxib does not inhibit platelet aggregation and does not increase bleeding time. Celecoxib has both similar efficacy to NSAIDs in the treatment of pain and in the risk for cardiovascular events. Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects.
II. ACETAMINOPHEN

Acetaminophen [a-SEAT-a-MIN-oh-fen], (N-acetyl-p-aminophenol, or APAP) inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties.
Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity.
Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin for those patients with gastric complaints, those in whom prolongation of bleeding time would be a disadvantage, and those who do not require the anti-inflammatory action of aspirin.
Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (recall that aspirin increases the risk of Reye syndrome).
Acetaminophen is virtually free of any significant adverse effects. Large doses of acetaminophen make the available glutathione in the liver becomes depleted.
Thus the administration of N-acetylcysteine, which contains sulfhydryl groups can be lifesaving if administered within 10 hours of the overdose.
III. DISEASE-MODIFYING ANTIRHEUMATIC AGENTS (DMARDs)

DMARDs are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues.
A. Methotrexate

It is an immunosuppressant, and this may account for its effectiveness in autoimmune diseases. It is used alone or in combination therapy for treatment of patients with rheumatoid or psoriatic arthritis.
Psoriatic Arthritis Of The Fourth Toe
The dose of methotrexate that required for treatment is much lower than that required for treatment of cancer.

Adverse effects: nausea, mucosal ulceration, cytopenia (reduction in the number of blood cells).
B. Hydroxychloroquine

This agent is also used in the treatment of lupus & malaria. It is used for mild RA, often combined with methotrexate. Its mechanism of action may include inhibition of phospholipase A2 and platelet aggregation, membrane stabilization, effects on the immune system, and antioxidant activity.
C. Leflunomide

Leflunomide (le-FLOO-no-mide) is an immunomodulatory agent that preferentially causes cell arrest through reversible inhibition of dihydroorotate dehydrogenase (DHODH) resulting in the inhibition of DNA synthesis which required for proliferation of lymphocytes.
Leflunomide reduce pain & inflammation associated with the disease but also appear to slow the progression of structural damage.
D. Minocycline

Minocycline [mi-noe-SYE-kleen], a tetracycline antibiotic, is considered to be a DMARD. Although minocycline has been shown to be effective in the treatment of early RA, it is generally not utilized as first-line therapy. Minocycline can be used as monotherapy or in combination with other DMARDs.
E. Sulfasalazine

Sulfasalazine [sul-fa-SAΗ-la-zeen] is also used for early, mild RA in combination with hydroxychloroquine and methotrexate. Onset of activity is 1 to 3 months, and it is associated with leukopenia (neutropenia). Its mechanism of action in treating RA is unclear.
F. Glucocorticoids

Glucocorticoids are potent anti-inflammatory drugs that are commonly used in patients with RA to bridge the time until DMARDs are effective. Doses up to 10 mg of prednisone are usually used. Timely dose reductions and cessation are necessary to avoid adverse effects associated with long-term use.
IV. BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS

Interleukin-1 and TNF-α are pro-inflammatory cytokines involved in the pathogenesis of RA.
When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis.
A. Adalimumab

Adalimumab [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to TNF-α, thereby interfering with endogenous TNF-α activity by blocking its binding to the surface receptors.
Use of adalimumab results in reductions in the concentrations of matrix metaloproteinase MMP-1 (collagenase), MMP-3 (stromelysin-1), C reactive protein, and markers of cartilage and synovium turnover.
This agent is indicated for treatment of moderate to severe RA, either as monotherapy or in combination with methotrexate. It is also indicated for psoriatic arthritis, ankylosing spondylitis, and Crohn disease (inflammatory bowel disease (IBD) that may affect any part of the gastrointestinal tract from mouth to anus).
Adalimumab is administered subcutaneously weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, or increased risk of infection.
B. Certolizumab pegol

Certolizumab [ser-toe-LIZ-oo-mab] is a unique TNF-α blocker that contains a Fab fragment of a humanized antibody and is a potent neutralizer of TNF-α biological actions.
It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via subcutaneous injection. It has similar indications to adalimumab. Adverse effects are similar to other TNF-α inhibitors.
C. Etanercept

Etanercept [ee-TAN-er-cept] is a genetically engineered recombinant fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF receptors.
This agent is approved for use in patients with moderate to severe RA, either alone or in combination with methotrexate. It is also approved for use in patients with polyarticular-course juvenile RA, psoriatic arthritis, ankylosing spondylitis, and psoriasis.
Etanercept is well tolerated. It can produce local inflammation at the site of injection. Etanercept is given subcutaneously twice a week.
D. Golimumab

Golimumab [goe-LIM-ue-mab] neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors.
This compound is administered subcutaneously once a month in combination with methotrexate or other nonbiologic DMARDs. Golimumab may increase hepatic enzymes.
Reactivation of hepatitis B may occur in chronic carriers. As with other TNF-α inhibitors, this drug may increase the risk of malignancies and serious infections.
E. Infliximab

Infliximab (in-FLIX-i-mab) is a monoclonal antibody that binds specifically to human TNF-α, and inhibits binding with its receptors.
Infliximab is approved for use in combination with methotrexate in patients with RA who have had inadequate response to methotrexate monotherapy.
This agent is not indicated for use alone, because monotherapy allows the body to develop anti-infliximab antibodies, with a reduction in efficacy. Adverse effects include fever, chills, pruritis or urticaria.
F. Abatacept

T lymphocytes need two interactions to become activated:

1) the antigen-presenting cell (that is, macrophages or B cells) must interact with the receptor on the T cell and

2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell.
Initiation/amplification of the antigen-specific response

T cell

DC

Cytokines

Target of immune potentiatior and delivery system

Vaccines

Nature Reviews | Drug Discovery
Abatacept [a-BAT-ah-cept] is a soluble recombinant fusion protein that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation. This agent is indicated for patients with moderate to severe RA who have had an inadequate response to DMARDs or TNF-α inhibitors.
Abatacept is administered as an IV infusion every 4 weeks. Common adverse effects include headache, upper respiratory infections, nasopharyngitis, and nausea. Concurrent use with TNF-α inhibitors is not recommended due to increased risk of serious infections.
G. Rituximab

It is a monoclonal antibody that directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, resulting in B-cell depletion.
This agent is indicated for use in combination with methotrexate to reduce signs and symptoms of moderate to severe RA.
Rituximab is administered as two 1000-mg IV infusions separated by 2 weeks. To reduce the severity of infusion reactions, methylprednisolone at 100 mg IV or its equivalent is administered 30 minutes prior to each infusion. Urticaria, hypotension & angioedema are adverse effects.
H. Tocilizumab

Tocilizumab [toe-si-LIZ-ue-mab] is a monoclonal antibody that inhibits the actions of IL-6 by blocking the IL-6 receptor.
Tocilizumab is administered as an intravenous infusion every 4 weeks. The drug can be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs for patients with moderate to severe RA.
I. Tofacitinib

Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane.
Cytokines, growth factors, interferons, ILs, and erythropoietin can lead to an increase in Janus kinase activity and activation of the immune system.
Tofacitinib [toe-fa-SYE-ti-nib] is an oral inhibitor of Janus kinases indicated for the treatment of moderate to severe RA in patients who have had an inadequate response or intolerance to methotrexate. Hemoglobin concentrations must be greater than 9 g/dL to start tofacitinib and must be monitored during therapy due to the risk for anemia.
Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment. Tofacitinib treatment may also increase the risk for secondary malignancy, opportunistic infections, renal, or hepatic dysfunction.
J. **Anakinra** [an-a-KIN-ra] is an IL-1 receptor antagonist. It leads to a modest reduction in the signs and symptoms of moderate to severe RA in patients who have failed one or more DMARDs. This agent is associated with neutropenia and is infrequently used in the treatment of RA.
Gout is a metabolic disorder characterized by high levels of uric acid in the blood. Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney.
The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals. This process generates oxygen metabolites, which damage tissues, resulting in the release of lysosomal enzymes that evoke an inflammatory response.
In addition, there is increased production of lactate in the synovial tissues. The resulting local decrease in pH fosters further deposition of urate crystals. The cause of hyperuricemia is an overproduction of uric acid relative to the patient’s ability to excrete it.
Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (below 6 mg/dL), thus preventing the deposition of urate crystals.
A. Treatment of acute gout

It can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. Acute attacks are treated with indomethacin to decrease movement of granulocytes into the affected area.
NSAIDs other than indomethacin are also effective at decreasing pain and inflammation. [Note: Aspirin is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney.]
Intraarticular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting.
Systemic corticosteroid therapy for more widespread joint involvement. Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).
B. Treatment of chronic gout

Chronic gout can be caused by:

1) A genetic defect, such as one resulting in an increase in the rate of purine synthesis.

2) Renal deficiency

3) Lesch-Nyhan syndrome (inherited disease characterized by impaired renal function).

4) Excessive production of uric acid associated with cancer chemotherapy.
A. Colchicine

Colchicine [KOL-chi-seen], a plant alkaloid, has been used for the treatment of acute gouty attacks as well as chronic gout. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.
Colchicine does not prevent the progression of gout to acute gouty arthritis, but it does have a suppressive, prophylactic effect that reduces the frequency of acute attacks and relieves pain.
Mechanism of action:

1. Colchicine binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their migration into the affected area.

2. Furthermore, colchicine blocks cell division by binding to mitotic spindles. Colchicine also inhibits the synthesis and release of the leukotrienes.
B. Allopurinol

Allopurinol [al-oh-PURE-i-nole] is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase.
Allopurinol is effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after treatment with chemotherapeutic agents) or in renal disease.
Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions of allopurinol.
C. Febuxostat

Febuxostat [feb-UX-o-stat] is a new xanthine oxidase inhibitor. Although it is structurally unrelated to allopurinol, it has the same indications as those of allopurinol. Its adverse effect profile is similar to that of allopurinol.
D. Probenecid

It is a uricosuric drug. It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption.
Probenecid blocks the tubular secretion of penicillin and is sometimes used to increase levels of β-lactam antibiotics. It also inhibits excretion of naproxen, ketoprofen, and indomethacin. It should be avoided if creatinine clearance is less than 50 ml/min.
E. Pegloticase [peg-LOE-ti-kase] is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys.
Pegloticase is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks.
DRUGS USED TO TREAT HEADACHE

The most common types of headaches are migraine, tension-type, and cluster headaches. Migraine can usually be distinguished from cluster headaches and tension-type headaches by its characteristics.
<table>
<thead>
<tr>
<th></th>
<th><strong>MIGRAINE</strong></th>
<th><strong>CLUSTER</strong></th>
<th><strong>TENSION TYPE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Females more often than males</td>
<td>Males more often than females</td>
<td>Females more often than males</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Variable</td>
<td>During sleep</td>
<td>Under stress</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Usually unilateral</td>
<td>Behind or around one eye</td>
<td>Bilateral in band around head</td>
</tr>
<tr>
<td><strong>Character and severity</strong></td>
<td>Pulsating, throbbing</td>
<td>Excruciating, sharp, steady</td>
<td>Dull, persistent, tightening</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2–72 hours per episode</td>
<td>15–90 minutes per episode</td>
<td>30 minutes to 7 days per episode</td>
</tr>
<tr>
<td><strong>Associated symptoms</strong></td>
<td>Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting</td>
<td>Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes</td>
<td>Mild intolerance to light and noise, anorexia</td>
</tr>
</tbody>
</table>

**Figure 36.21**
Characteristics of migraine, cluster, and tension-type headaches.
Migraines, for example, present as a pulsatile, throbbing pain, whereas cluster headaches present as excruciating, sharp, steady pain. This is in contrast to tension-type headaches, which present as dull pain, with a persistent, tightening feeling in the head.
Patients with severe migraine headaches report one to five attacks per month of moderate to severe pain, usually unilateral. The headaches significantly affect quality of life and result in considerable health care costs.
Management of headaches involves avoidance of headache triggers (for example, alcohol, chocolate, and stress) and use of abortive treatments for acute headaches, as well as prophylactic therapy in patients with frequent or severe migraines.
The causes of migraine are believed to be related to a mix of environmental & genetic factors. Psychological conditions are associated including depression, anxiety & bipolar disorder.
Types of migraine

There are two main types of migraine headaches. The first, *migraine without aura* (previously called common migraine), is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours.
These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound), approximately 85% of migraines patients do not have aura.
In the second type, migraine with aura (previously called classic migraine), the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly, these symptoms are visual, occurring approximately 20 to 40 minutes before headache pain begins.
The pain of both types of migraine may be due to extracranial and intracranial arterial dilation. This stretching leads to release of neuroactive molecules, such as substance P.
Phases of Migraine

1. **Asymptomatic phase:**
   Between attacks, no symptoms or pathologic features are evident.

2. **Prodromal Phase:** Visual disturbances that precede the actual headache which associated with arterial vasoconstriction & release of serotonin.

3. **Headache Phase:** Pain, nausea & vomiting which associated with cerebral vasodilation & lower than normal levels of serotonin.
1. **Triptans:** This class of drugs includes sumatriptan [SOO-ma-triptan], naratriptan [NAR-a-trip-tan], rizatriptan [rye-za-TRIP-tan], eletriptan [EH-leh-trip-tan], almotriptan [AL-moh-trip-tan], frovatriptan (frova-TRIP-tan), and zolmitriptan [zole-ma-TRIP-tan].
The triptans are serotonin agonists, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature in which probably suppress the release of sensory neuropeptide such as substance P.
Sumatriptan is given subcutaneously, intranasally, or orally. Zolmitriptan is available orally and by nasal spray. [Note: All other are taken orally.]
Significant elevation of blood pressure and cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration.
Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw.
2. **Ergot alkaloids:** Ergotamine [er-GOT-a-meen] and dihydroergotamine [dye-hye-droe-er-GOT-a-meen], a semisynthetic derivatives of ergotamine, are ergot alkaloids approved for the treatment of migraine headaches.
The action of the ergot alkaloids is complex, with ability to bind to 5-HT1 receptors, α receptors, and dopamine receptors. 5-HT1 receptors located on intracranial blood vessels are targets that cause vasoconstriction with the use of these agents.
Ergotamine is currently available sublingually and is mostly effective when used in the early stages of the migraine. It is also available as an oral tablet or suppository containing both ergotamine and caffeine. Ergotamine is used with strict daily and weekly dosage limits due to its ability to cause dependence and rebound headaches.
Dihydroergotamine is administered intravenously or intranasally and has an efficacy similar to that of sumatriptan. The use of dihydroergotamine is limited to severe cases of migraines. Nausea is a common adverse effect. Ergotamine and dihydroergotamine are contraindicated in patients with angina and peripheral vascular disease because they are significant vasoconstrictors.
3. Prophylaxis for migraine headache

Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs. Propranolol is the drug of choice, but other β-blockers, particularly metoprolol, atenolol, & nadolol, have been shown to be effective.
Other agents used in prophylaxis which reduce the frequency & severity of migraine attacks include tricyclic anti-depressants (amitriptyline), anti-convulsant (divalproex) & calcium channel blocker (verapamil) [appears to block serotonin re-uptake].
Drugs for tension & cluster headache

Analgesics such as NSAIDs (for example, naproxen and ibuprofen), acetaminophen, and aspirin are used for symptomatic relief of tension headaches. Acetaminophen and/or aspirin may also be combined with caffeine. [Note: Caffeine is believed to increase the central effectiveness of acetaminophen and aspirin.]
Butalbital, a barbiturate, in combination with acetaminophen or aspirin with or without caffeine is also used in tension headaches. Inhalation of 100% oxygen and triptans (especially sumatriptan) are used as first-line abortive strategies for cluster headache.
THANK YOU FOR LISTENING