Allergy and inflammation
Allergic population

- hyper-producers of IgE
- consistently increasing
- western societies: ~20% of general population
Allergic population

- Older siblings
- Daycare centres
- Farming environment
- Helminth infections
- Microbial exposure (LPS)

Birth

T_{h2}

Only child

Urban lifestyle

“Sterile” clean environment

Healthy

Allergies
Asthma
Eczema
Rhinitis

T_{h1}

T_{h2}

Nature Reviews | Immunology
Allergic triggers

- Skin Contact: poison plants, animal dander, pollen, latex
- Injection: bee sting, medication
- Ingestion: medication, nuts & shellfish
- Inhalation: pollen, dust, mold & mildew, animal dander
Allergic triggers

“abnormal” over-reaction to “normal” exposures
Allergic reactions

basophils, blood cells

IgE, allergen

Mast cell, tissue cells
Allergic reactions

The first time the allergy-prone person runs across an allergen such as ragweed,

he or she makes large amounts of ragweed IgE antibody.

These IgE molecules attach themselves to mast cells.

The second time that person has a brush with ragweed,

the IgE-primed mast cell will release its powerful chemicals,

and the person will suffer the wheezing and/or sneezing, runny nose, watery eyes, and itching of allergy.
## Allergic symptoms

<table>
<thead>
<tr>
<th>food allergies</th>
<th>airborne allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>mouth/pharynx itching</td>
<td>runny nose</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>mucus production</td>
</tr>
<tr>
<td>nausea, vomiting</td>
<td>sneezing</td>
</tr>
<tr>
<td>↓ BP</td>
<td>itching eyes, nose, throat</td>
</tr>
<tr>
<td>respiratory symptoms</td>
<td>watering eyes</td>
</tr>
<tr>
<td>dermatological symptoms</td>
<td>conjunctivitis</td>
</tr>
</tbody>
</table>
Allergy types/presentations

- allergic rhinitis (inflammation of nasal mucous membranes)
- allergic conjunctivitis
- atopic eczema/contact dermatitis
- anaphylactic reaction (shock)
- asthma
Allergic rhinitis

- Local exposure to allergen (inhaled)
- Interaction with mast cells
- Release of histamine, leukotrienes, chemotactic factors
- Local edema, cellular infiltration, mucosal thickening

**Signs and symptoms of allergic rhinitis**
- Sneezing, nasal irritation, watery nose, congestion
Allergic rhinitis

allergic rhinitis

Nasal cavity: normal

Nasal cavity: allergic rhinitis
Non-pharmacological Tx
Non-pharmacological Tx

- avoiding/minimizing exposure to allergen
- immunotherapy = desensitization (↓ IgE, ↑ IgG)
Pharmacotherapy - allergic rhinitis

- $H_1$-receptor blockers (antihistamines)
- $\alpha$-adrenergic agonists (AAAs)
- Intranasal corticosteroids (INCs)
- Cromolyn/nedocromil
- Leukotriene modifiers
Pharmacotherapy - allergic rhinitis

• $H_1$-receptor blockers (antihistamines)
• $\alpha$-adrenergic agonists (AAAs)
• intranasal corticosteroids (INC)
• cromolyn/nedocromil
• leukotriene modifiers
Pharmacotherapy - allergic rhinitis

H₁-receptor blockers (antihistamines)

• block histamine binding to H₁ receptors
• most effective vs. sneezing and watery nose
• ineffective vs. congestion
• oral/nasal administration

• 1ˢᵗ generation: additional anticholinergic properties and CNS ADEs
• 2ⁿᵈ generation: less anticholinergic/CNS ADEs, longer action
Pharmacotherapy - allergic rhinitis

\( H_1 \)-receptor blockers (antihistamines) - 1\(^{st}\) generation

- chlorpheniramine (\textit{Ahiston\textsuperscript{®}}, \textit{Acamol-Tsinun\textsuperscript{®}}, \textit{Dexamol-Cold\textsuperscript{®}})
- diphenhydramine (\textit{various combination products})
- hydroxizine (\textit{Otarex\textsuperscript{®}})
- anticholinergic properties:
  - sedation, drowsiness, dry mouth/eyes, urinary hesitation
- CNS effects (lipophillic):
  - memory, confusion, motor function
  - children, rare: stimulation
Pharmacotherapy - allergic rhinitis

**H₁-receptor blockers** (antihistamines) - 2nd generation

- cetirizine (*Zytrec®, Histazine®*)
- loratadine (*Lorastine®*) → *desloratadine* (*Aerius®*)

  metabolites: less CNS ADEs than parent?

- fexofenadine (*Telfast®*) (terfandine metabolite)
- azelastine (*Rhinolast®*) - spray
  (antiinflammatory: vs. congestion; rapid onset: “rescue”; bitter taste)
Pharmacotherapy - allergic rhinitis

**H₁-receptor blockers** (antihistamines) - 2nd generation

- lesser anticholinergic effects (dry eyes)
- less CNS penetration (lipophobic): less/non-sedating
- less effective against congestion (vs. INCs)
Pharmacotherapy - allergic rhinitis

- $H_1$-receptor blockers (antihistamines)
- $\alpha$-adrenergic agonists (AAAs)
- intranasal corticosteroids (INCs)
- cromolyn/nedocromil
- leukotriene modifiers
Pharmacotherapy - allergic rhinitis

α-adrenergic agonists (AAAs)

“nasal decongestants”, “sympathomimetics”

- phenylephrine (combinations: Alnase®, Vibroci®l, Sinaf®)
- oxymetazoline (Alrin®, Rhinoclir®)
- xylometazoline (Otrivin®): long-acting
- pseudoephedrine (Sinufed®, various combinations),
Pharmacotherapy - allergic rhinitis

α-adrenergic agonists (AAAs)

- vasoconstrictors: reduce edema, congestion
- mostly intranasal use (pseudoephedrine - oral)
- pseudoephedrine:
  additional beta-agonist effect: bronchial relaxation, ↑ HR

<table>
<thead>
<tr>
<th>AAA</th>
<th>duration</th>
<th>frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenylephrine</td>
<td>0.5-4hr</td>
<td>4-6/day</td>
</tr>
<tr>
<td>xylometazoline</td>
<td>10hr</td>
<td>2/day</td>
</tr>
<tr>
<td>pseudoephedrine</td>
<td>6-8hr</td>
<td>2-4/d</td>
</tr>
</tbody>
</table>
Pharmacotherapy - allergic rhinitis

α-adrenergic agonists (AAAs)

• ADEs: limited with intranasal administration; potential:
  - CNS effects: headache, insomnia, excitability
  - ↑ BP, HR
  - local effect: dryness, irritation, itching

• PD DDIs (low probability with local administration)
Pharmacotherapy - allergic rhinitis

α-adrenergic agonists (AAAs)

- high dose/prolonged use
- down-regulation of local $\alpha_1$ receptors
- loss of pharmacological effect
- rebound congestion
- rhinitis medicamentosa
Pharmacotherapy - allergic rhinitis

• $H_1$-receptor blockers (antihistamines)
• $\alpha$-adrenergic agonists (AAAs)
• intranasal corticosteroids (INCs)
• cromolyn/nedocromil
• leukotriene modifiers
Pharmacotherapy - allergic rhinitis

Intranasal corticosteroids (INCs)

- fluticasone (*Flixonase®, Allegro®*)
- mometasone (*Nasonex®*)
- budesonide (*Nasocort®*)
- betamethasone (*Betnesol®*)

3rd generation

2nd generation

1st generation
Pharmacotherapy - allergic rhinitis

**Intranasal corticosteroids (INCrs)**

- inhibition of allergic inflammation
- advanced INCs (mometasone, fluticasone):

  - ↓ lipophilicity
  - ↓ systemic bioavailability (<2%)
  - ↓ systemic adverse effects
Pharmacotherapy - allergic rhinitis

Intranasal corticosteroids (INCs)

• inhibition of allergic inflammation

• 1998 meta-analysis:
  “significantly greater relieve of congestion, nasal discharge, sneezing, nasal itch, postnasal drip, and total nasal symptoms than oral antihistamines.”

• ADEs:
  - systemic - rare
  - local - irritation, itching, dryness, burning sensation

• once-daily: prefer at night
Pharmacotherapy - allergic rhinitis

- $H_1$-receptor blockers (antihistamines)
- $\alpha$-adrenergic agonists (AAAs)
- Intranasal corticosteroids (INCs)
- Cromolyn/nedocromil
- Leukotriene modifiers
Pharmacotherapy - allergic rhinitis

Cromolyn/nedocromil

• “mast-cell stabilizers”
• effective only as prevention/prophylaxis
  - prior to allergy season
  - prior to exposure to known allergen
• in mild cases may be corticosteroid-sparing (young children)
• frequent dosing required (3-4/day)
• main advantage: safety (children, pregnancy, elderly)
Pharmacotherapy - allergic rhinitis

• $H_1$-receptor blockers (antihistamines)
• α-adrenergic agonists (AAAs)
• intranasal corticosteroids (INCs)
• cromolyn/nedocromil

• leukotriene modifiers
Pharmacotherapy - allergic rhinitis

Leukotriene modifiers

• mainly effective vs. congestion
• useful in patients
  - intolerant of intranasal administration
  - with concomitant asthma
Pharmacotherapy - allergic rhinitis

Therapeutic considerations

• INCs usually 1\textsuperscript{st}-line: superior efficacy vs. all symptoms
• antihistamines ineffective vs. congestion
  
  2\textsuperscript{nd}-generation (“non-sedating”) safer than 1\textsuperscript{st} generation
• AAAs for short-term use only
• cromolyn ineffective for acute relief
• leukotriene modifiers: limited data
• combination products
# Pharmacotherapy - allergic rhinitis

## Therapeutic considerations - special populations

<table>
<thead>
<tr>
<th>population</th>
<th>1(^{\text{st}})-line</th>
<th>2(^{\text{nd}})-line</th>
<th>3(^{\text{rd}}) line</th>
</tr>
</thead>
<tbody>
<tr>
<td>children &lt;3yr</td>
<td>cromolyn</td>
<td>2(^{\text{nd}})-gen. AH</td>
<td>INC</td>
</tr>
<tr>
<td>concomitant asthma</td>
<td>leukotriene modifier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>elderly</td>
<td>INC</td>
<td>2(^{\text{nd}})-gen. AH</td>
<td></td>
</tr>
<tr>
<td>pregnancy</td>
<td>cromolyn</td>
<td>2(^{\text{nd}})-gen. AH (budesonide?)</td>
<td></td>
</tr>
</tbody>
</table>

AH - antihistamine; INC - intranasal corticosteroid
Pharmacotherapy – allergy

DRUGS FOR EXAM

- chlorpheniramine
- loratadine
- oxymetazoline
- pseudoephedrine
- (fluticasone)
- (cromolyn)
- (montelukast)
Anti-inflammatory drugs
Inflammatory process

1. stimulus (cut)
2. Initial local vasoconstriction (↓ blood loss)
3. vasodilation, local immune/inflammatory reaction (heat, redness)
4. swelling and pain
5. damage repair, inflammatory response gradually subsides
6. healing

Anti-inflammatory drugs
Inflammatory process

- **calor**
- **dolor**
- **rubor**
- **tumor**

Anti-inflammatory drugs
Inflammation - presentation

Anti-inflammatory drugs
Prostaglandins in inflammation

**The prostaglandin pathway**

- Stimulus → Phospholipase A₂ → Phospholipids → Arachidonic Acid
- Lipoxygenases: 12-HETE, 15-HETE, LTA₄ → LTB₄, LTC₄, LTD₄, LTE₄
- Cyclooxygenase: COX-1 and COX-2 → PGH₂ → PGE₂, PGF₂α, PGD₂, TxA₂

**Anti-inflammatory drugs**

- COX-1 gene transcription
- COX-2 gene transcription

**Induced by:**
- Oxidative stress
- Injury
- Ischemia
- Seizures
- Neurodegenerative diseases

**Glucocorticoids:**

- mRNA → Membrane phospholipids → Arachidonic acid
- Nonsteroidal anti-inflammatory drugs (NSAIDS)
- Selective COX-2 inhibitors

**Lipoxygenase pathway**

- Membrane phospholipids → Arachidonic acid → 5-Lipoxygenase → Leukotrienes

**COX unrelated to leukotriene production**
COX-1 vs. COX-2

Anti-inflammatory drugs
Anti-inflammatory drugs

Anti-inflammatory drug classes

• “classical” NSAIDs
• COX-2 inhibitors
  • leukotriene modifiers
  • corticosteroids (Olga...)

Anti-inflammatory drugs
"Classical" NSAIDs

- inhibition of COX enzymes
- decreased PG synthesis
- suppression of inflammatory processes
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

- prototypic NSAID
- synthesized 1853, introduced as Aspirin 1899, mechanism elucidated 1971
Acute allergic inflammation

COX active site

Ser

OH

Acetylation

COX [INACTIVE]

Acetyl group attacks Ser hydroxyl residue

Acetylsalicylic acid (aspirin)
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

\[
\text{acetyl salicylic acid} + \text{COX} \rightarrow \text{salicylate} + \text{acetyl-COX}
\]

**Diagram**
- Aspirin interacts with COX, blocking the pathway for prostaglandin formation.
- Acetyl binding is irreversible.

**Legend**
- **acetyl**: irreversible binding.
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

\[
\text{acetyl} \text{salicylic acid} + \text{COX} \rightarrow \text{acetyl} + \text{salicylate}-\text{COX}
\]
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

- resultant effect varies per action site
- **anti-inflammatory effect**: peripheral target sites
- inhibition of PG-mediated inflammatory cascade

Inflammatory process

PG release

Inflammation: pain, swelling, heat, redness
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

- resultant effect varies per action site
- **antipyretic effect**: central thermoregulation

Anti-inflammatory drugs
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

- resultant effect varies per site
- **analgesic effect**: peripheral sites

```
<table>
<thead>
<tr>
<th>inflammatory process</th>
<th>PG release</th>
</tr>
</thead>
<tbody>
<tr>
<td>histamine, bradykinin, other mediators</td>
<td></td>
</tr>
<tr>
<td>sensitization of sensory nerve endings</td>
<td></td>
</tr>
</tbody>
</table>
```
“Classical” NSAIDs

Aspirin (acetylsalicylic acid, ASA)

undesired effects:

- **respiratory**: elevated CO$_2$, increased ventilation
  (high-dose: respiratory alkalosis; toxic doses: respiratory acidosis)

- **GI**: increased gastric acid secretion, nausea, vomiting
  (PGs↓ gastric acid secretion and ↑ secretion of protective mucus)

- **kidney**: Na$^+$/$\text{H}_2\text{O}$ retention, edema, hyperkalemia
  (PGs regulate and maintain renal blood flow)
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

undesired effects: **platelets**

irreversible aggregation inhibition

bleeding complications
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

PK/PD:

- oral administration (food, fluids)
- peak: 30-40 min
- platelets inactivation evident: 1hr
- irreversible inactivation – long PD $T_{1/2}$
- non-CYP hepatic metabolism
- renal excretion
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

additional ADEs:

- dermatological
- Reye’s syndrome (<15yr) [?]
- hypersensitivity (allergic) reactions
- tinnitus/hearing loss
- hepatotoxicity (reversible)
- rebound headache in chronic use vs. headache
“Classical” NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

salicylism:

<table>
<thead>
<tr>
<th>Level</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>headache, drowsiness, dizziness, tinnitus/hearing loss</td>
</tr>
<tr>
<td>Moderate</td>
<td>thirst, visual impairment, uncontrolled hand movements</td>
</tr>
<tr>
<td>Severe</td>
<td>seizures, hallucinations, severe nervousness, excitement, confusion, wheezing/shortness of breath, unexplained fever</td>
</tr>
</tbody>
</table>
“Classical” NSAIDs

Aspirin (acetylsalicylic acid, ASA)

intoxication

- **lethal**: 150 mg/dl (vasomotor collapse, coma, dehydration)
- **severe**: 100 mg/dl (tinnitus, central hyperventilation)
- **mild**: 50 mg/dl
- **10 mg/dl**: analgesic, antipyretic, antiplatelet

salicylate plasma concentration (mg/dl)
"Classical" NSAIDs

**Aspirin** (acetylsalicylic acid, ASA)

DDIs: PD

- other drugs affecting renal function
- other NSAIDs
- other drugs affecting platelets/coagulation
- hypoglycemics (↑ insulin secretion)
- corticosteroids (↓ salicylate clearance)
- antihypertensives (sodium/water retention)
- SSRIs/SNRIs (antiplatelet effect)
“Classical” NSAIDs

Aspirin (acetylsalicylic acid, ASA)

place in therapy

• diminishing use as antipyretic/analgesic (safety)
• other salicylates used for several inflammatory states (such as rheumatoid arthritis, inflammatory bowel disease)
• local use vs. cutaneous inflammation (methyl salicylate)
“Classical” NSAIDs

Other NSAIDs

• propionic acid derivatives:
  - ibuprofen (Nurofen®, Advil®, Adex®, Artofen®)
  - naproxen (Narocin®, Naxyn®, Point®)

• acetic acid derivatives:
  - indomethacin (Indomed®, Indocin®, Indovis®)
  - diclofenac (Voltaren®, Abitren®)
“Classical” NSAIDs

Other NSAIDs

• oxicams:
  - piroxicam (Brexin®, Feldene Gel®)
  - norloxicam (Xefo®)

• naphthylalkylanone: nabumetone (Relifex®, Nabuco®)

• pyranocarboxylic acid: etodolac (Etopan®)

• nimesulide (Mesulid®)
“Classical” NSAIDs

Other NSAIDs

• mechanism: similar to that of aspirin
  - **reversible** binding to COX
  - differing COX-1/COX-2 selectivity
"Classical" NSAIDs

Other NSAIDs
• simple vs. time-dependent competition

-aspirin-
irreversible binding

COX

competitive binding

arachidonic acid

simple competitors

ibuprofen
naproksen
piroxicam

tight binding,
slow self-dissociation

time-dependent competitors

diclofenac
indomethacin
"Classical" NSAIDs

Other NSAIDs
- potent anti-inflammatory effect
- effective antipyretics
- relatively mild analgesic effect
"Classical" NSAIDs

GI toxicity

<table>
<thead>
<tr>
<th>presentation</th>
<th>frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>minor endoscopic lesions</td>
<td>65%</td>
</tr>
<tr>
<td>symptomatic ulcer, bleeding, perforation</td>
<td>3-6mo 1%</td>
</tr>
</tbody>
</table>

• probably safer: nabumetone, etodolac, oxicams
“Classical” NSAIDs

GI toxicity

- **local effect** (acidity)
- **systemic effect** (COX inhibition)

- nabumetone (non-acidic prodrug)
- increased COX-2 selectivity
## “Classical” NSAIDs

<table>
<thead>
<tr>
<th>T&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>NSAID</th>
<th>specific ADEs</th>
<th>↑ effect of</th>
<th>↓ effect of</th>
</tr>
</thead>
<tbody>
<tr>
<td>short</td>
<td>ibuprofen</td>
<td>aseptic meningitis</td>
<td>dig, warf, Li,</td>
<td>diuretics</td>
</tr>
<tr>
<td></td>
<td>indomethacin</td>
<td>↑ GI/CNS effects</td>
<td>Li</td>
<td>furosemide anti-HTNs</td>
</tr>
<tr>
<td>intermediate</td>
<td>diclofenac</td>
<td>↑ LFTs</td>
<td>warf, dig, Li, hypogly</td>
<td>diuretics</td>
</tr>
<tr>
<td></td>
<td>etodolac</td>
<td>---</td>
<td>dig, Li</td>
<td>diuretics</td>
</tr>
<tr>
<td></td>
<td>naproxen</td>
<td>pulmonary infiltrates</td>
<td>warf, Li, ACEIs</td>
<td>---</td>
</tr>
<tr>
<td>long</td>
<td>nabumatone</td>
<td>---</td>
<td>warf,</td>
<td>diuretics</td>
</tr>
<tr>
<td></td>
<td>piroxicam</td>
<td>---</td>
<td>Li</td>
<td>diuretics</td>
</tr>
</tbody>
</table>

dig - digoxin; warf - warfarin; Li - lithium; hypogly – hypoglycemics; **PK PD**
“Classical” NSAIDs

Choosing an NSAID

- indication
- clinical data (evidence-based)
- ADEs/DDIs
- patient factors
- cost
- trial and error...

similar properties - varying effects
Cyclooxygenase pathway

Anti-inflammatory drugs

Therapeutic disadvantages of selected NSAIDs*

Upper GI disturbances are common

No antipyretic effect

Very potent; should be used only after less toxic agents have proven ineffective

CNS disturbances common

Therapeutic advantages of selected NSAIDs

Salicylates:
- Aspirin
- Salicylate salts
- Diflunisal

Acetic acids:
- Indomethacin
- Sulindac
- Tolmetin

Propionic acids:
- Ibuprofen
- Fenoprofen
- Flurbiprofen
- Ketoprofen
- Naproxen
- Oxaprozin

Oxicams:
- Piroxicam
- Meloxicam

Fenamates:
- Mefenamic acid
- Meclomenamic acid

COX-2 inhibitors
- Celecoxib

Lower GI irritation

Less GI irritation than aspirin

Low cost; long history of safety

Long half-life permits daily or twice daily dosing

Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs.
COX-1 vs. COX-2

- **Arachidonic Acid**
  - **COX-1** (Constitutive)
    - Inhibition undesirable
    - Homeostatic functions: Gastrointestinal tract, Renal tract, Platelet Function, Macrophage differentiation
  - **COX-2** (Induced)
    - Inhibition desirable
    - Inflammation
  - Cytokines IL-1, TNF Growth factors
  - Glucocorticoids

**Anti-inflammatory drugs**
COX-2 selectivity

Small, sharp, aspirin-like drugs fit in mouths of both COX-1 and COX-2

Big, blunt drugs fit only into the mouth of COX-2

Narrow-mouthed COX-1

Wide-mouthed COX-2
Selective COX-2 inhibitors

- celecoxib (*Celebra®*, *Celcox®*)
- etoricoxib (*Arcoxia®*)
- **rofecoxib (Vioxx®)**
- valdecoxib (*Bextra®*)
COX-2 selectivity is relative...

some “NSAIDs” are more COX-2 selective than “COX-2 selective inhibitors”...
Selective COX-2 inhibitors

etoricoxib

• oral administration, good absorption
• hepatic CYP metabolism
• mostly-renal clearance
• $T_{1/2} \sim 22\text{hr}$ (once-daily)
• minor GI ADEs, dizziness, peripheral edema, $\uparrow BP$
• DDIs - $\uparrow$ lithium, theophylline levels
  - $\uparrow$ warfarin effect
  - $\downarrow$ anti-HTN effect of diuretics, ACEIs
Selective COX-2 inhibitors

- similar efficacy to that of NSAIDs
- main advantage: decreased GI toxicity
- other ADEs: generally similar to NSAIDs
- no anti-platelet effect
- CV risk: small BP increase, edema, renal effects
- caution if combined with aspirin (CHD/CVA prevention)
Selective COX-2 inhibitors

• some COX-2 selective inhibitors withdrawn:
  - rofecoxib (cardiovascular/renal toxicity in long-term use)
  - valdecoxib (cardiovascular/renal toxicity in short-term use, severe skin reactions)

[ - nimesulide (hepatotoxicity) ]

Anti-inflammatory drugs
Selective COX-2 inhibitors

- some COX-2 selective inhibitors withdrawn:

  - complex, dynamic inter-relations
  - incomplete mechanistic data
  - limited long-term clinical data

an over-simplification
Prostaglandins in inflammation

choosing an anti-inflammatory

Risk factors for NSAID gastropathy
- Age >65 years
- Anti-coagulant use
- Prior GI bleeding
- Use of oral steroids

No
Cheapest NSAID
Lowest dosage
Shortest period

Yes
Do you really want to give an NSAID?

NSAID + PPI
eg, naproxen + omeprazole

or

NSAID + Misoprostol
eg, naproxen + misoprostol 100 mcg
twice daily

or

Celecoxib
Never twice daily
Always ≤200 mg/day
Pharmacotherapy – anti-inflammatory drugs

DRUGS FOR EXAM

- aspirin
- naproxen
- etoricoxib