The Inflammatory Response

• A general definition inflammation is the response of vascularized tissue to injury.
• First described in the first century A.D. and revised in the 20th century as follows – known as the triple response:
  – redness: the local dilation of blood vessels, occurring in seconds
  – flare: a reddish color several centimeters from the site, occurring 15-30 seconds after injury
  – wheal: local swelling, occurring in minutes

• The process of inflammation, producing the visible results is caused by the following four major categories of activity:
  – increased vascular permeability: produces and exudates into surrounding tissues
  – leukocytic infiltration: the emigration of white cells through capillary walls (diapedesis) in response to attractant chemicals (chemotaxis)
  – phagocytosis: white cells and macrophages ingest and process foreign material, such as bacteria
  – mediator cascade: histamine and chemoattractant factors are released at the site of the injury and various inflammatory mediators are generated
Inflammation in the Airway

- Airway inflammation can occur in the lungs in response to a variety of causes
  - direct trauma (GSW, stabbing)
  - indirect trauma (blunt chest injury)
  - inhalation of noxious or toxic substances (chlorine gas, smoke)
  - respiratory infections and systemic infections producing sepsis and septic shock with acute respiratory distress syndrome (ARDS)
  - allergic and non-allergic stimulation in asthma

Inflammation in the Airway

- The two most common inflammatory diseases of the airway are chronic bronchitis and asthma
- Asthmatic reactions are distinguished into an early-phase and late-phase reaction
- Following an insult to the asthmatic airway by an allergen, cold air, viral infection or noxious gas, there is evidence that the early-phase response is caused by immunoglobulin E (IgE)-dependent activation of mast cells, which can release inflammatory mediators
- The immediate response is bronchoconstriction, which peaks at around 15 minutes and declines over the next hour

Inflammation in the Airway

- Although this bronchoconstriction may self-limit or respond to β agonists, the progression of cellular events can continue
- Mast cell mediators and the release of cytokines recruit other inflammatory cells (eosinophils, basophils, monocytes/macrophages, lymphocytes) and other cytokines, causing the late-phase response
- During this late-phase response, mast cells and recruited inflammatory cells release a range of inflammatory mediators
- The late-phase response occurs 6-8 hrs. after a challenge and may last up to 24 hrs.
Corticosteroids

- Adrenocorticosteroids are naturally occurring hormones secreted by the adrenal cortex. They are classified into three groups according to chemical structure and major physiological effects:
  - glucocorticosteroids (anti-inflammatory and immunosuppressant actions)
  - mineralocorticosteroids (maintenance of fluid and electrolyte balance)
  - sex hormones
- Of these, the glucocorticosteroids are the primary ones used in respiratory care for their anti-inflammatory properties.

Corticosteroids

- Mechanism of action:
  - Pharmacologic actions are varied. The major actions pertaining to respiratory care are:
    - anti-inflammatory action - inhibits the formation and release of inflammatory mediators by interfering with the degranulation of the mast cell
    - increased sympathomimetic effects - inhibits COMT
    - enhanced ciliary transport - increase mucus secretion by altering mucus composition
    - enhanced sympathomimetic responsiveness - indirectly stimulates cAMP production by restoring responsiveness to β-adrenergic stimulation
    - improved sense of well being

Corticosteroids

- Indications:
  - asthma – recommended for maintenance and control therapy of chronic asthma, identified in the NAEPP EPR-II as Step 2 asthma (greater than 2 days/week of symptoms, greater than 2 nights/month with symptoms, FEV1 or PEF 80% ± 20% or greater)
  - COPD – not currently recommended by the American Thoracic Society for other than acute exacerbations; however, many COPD patients report lessened symptoms when taking aerosol corticosteroids
  - active interstitial lung disease
  - neonatal respiratory distress syndrome
  - ARDS
  - aspiration pneumonitis
Corticosteroids

- Contraindications
  - hypersensitivity to any of the formulation’s ingredients
  - systemic fungal infections
  - pts. with psychoses
  - PUD
  - acute glomerulonephritis
  - herpes simplex of the eye
  - severe diabetes mellitus

- Precautions
  - not indicated for the rapid relief of bronchospasm
  - if recommended aerosol dosages are exceeded (generally ≥ 1000 µg/day), the HPA transport mechanism may be affected
  - during pregnancy, use only if benefits outweigh the potential risks to the fetus
  - prolonged therapy may result in Cushingoid syndrome (moon face, edema, hump back) with adrenal insufficiency
  - when tapering dosages, watch for withdrawal syndrome: anorexia, nausea, vomiting, lethargy, headache, hypotension
  - administer PO forms with food
  - local administration is preferred when indicated
  - long-term therapy requires lowest effective do

- Adverse reactions (systemic administration)
  - suppression of the HPA system and adrenal cortex
  - fluid and electrolyte imbalance - Na+ and fluid retention, edema, hypokalemia, met. Alkalosis
  - cardiovascular - fat embolism, thromboembolism, arrhythmias, syncope, hypertension
  - GI - pancreatitis, abdominal distention, nausea, vomiting, weight gain, PUD, perforation of the small and large bowels
  - CNS - headache, vertigo, insomnia, restlessness, seizures, mood swings, depression, euphoria
  - musculoskeletal - muscle wasting, muscle pain, osteoporosis, delayed healing
  - misc. - growth suppression, obesity, Cushingoid appearance, hyperglycemia, diabetes, immunosuppression, cataract formation, increased WBC
Corticosteroids

- Adverse reactions (aerosol administration)
  - local - throat irritation, hoarseness, dry mouth, coughing, oropharyngeal fungal infection (Candida albicans or Aspergillus niger), rinsing and gargling after administration may prevent this infection
  - systemic - suppression of HPA mechanism
  - other - bronchospasm, rashes

Aerosol Corticosteroids

Beclomethasone Dipropionate
- brand names: Beclovent, Vancenil, Vancenil HFA Double strength
- dosage form
  - MDI: 42 µg/actuation
  - MDI: 84 µg/actuation
  - Intranasal MDI: 42 µg/actuation
  - Intranasal spray: 4.42%
- dosage
  - MDI (42 µg): adults: 2 inhalations tid or qid; children: 1-2 inhalations tid or qid
  - MDI (84 µg): adults and children ≥ 6 yrs: 2 inhalations bid
  - Intranasal MDI: adults: 1 inhalation each nostril bid; children 6-12 yrs.: 1 inhalation each nostril bid
  - Intranasal spray: adults: 1-2 inhalations each nostril bid; children 6-12 yrs.: 1 inhalation each nostril bid

Beclomethasone Dipropionate HFA
- brand name: QVAR
- dosage form
  - MDI: 40 µg/actuation, 80 µg/actuation
- dosage
  - adults ≥ 12 yr.: 40-80 µg bid*, 40-160 µg bid**
    - * recommended starting dose if on bronchodilators alone
    - ** recommended starting dose if on inhaled corticosteroids previously

Aerosol Corticosteroids

Beclomethasone Dipropionate HFA
- brand name: QVAR
- dosage form
  - MDI: 40 µg/actuation, 80 µg/actuation
- dosage
  - adults ≥ 12 yr.: 40-80 µg bid*, 40-160 µg bid**
    - * recommended starting dose if on bronchodilators alone
    - ** recommended starting dose if on inhaled corticosteroids previously
Aerosol Corticosteroids

- **Flunisolide**
  - brand names: AeroBid, AeroBid-M, Nasalide, Nasarel (intranasal; see p. 210)
  - dosage form
    - MDI: 200 µg/actuation
  - dosage
    - adults and children ≥ 6 yrs.: 2 inhalations bid (am and pm)

Aerosol Corticosteroids

- **Fluticasone Propionate**
  - brand names: Flovent, Flovent Rotadisk; Advair, Flonase (intranasal; see p. 210)
  - dosage form
    - MDI: 44, 110 or 220 µg/actuation
    - DPI (Rotadisk): 50, 100, 250 µg/inhalation
    - DPI (Advair): 100, 250 or 500 µg/inhalation (with 50 µg salmeterol)
  - dosage
    - (Rotadisk): adults 100 µg bid*, 100-250 µg bid**, 1000 µg bid***, children 4-11 yr.: 50 µg bid
    - (Advair): adults and children ≥ 12 yr.: one inhalation 100 µg q 12h (starting dose if not currently on inhaled corticosteroids)
      - * recommended starting dose if on bronchodilators alone
      - ** recommended starting dose if on inhaled corticosteroids previously
      - *** recommended starting dose if on oral corticosteroids previously

Aerosol Corticosteroids

- **Triamcinolone Acetonide**
  - brand names: Azmacort, Nasacort (intranasal; see p. 210)
  - dosage form
    - MDI: 100 µg/actuation
  - dosage
    - adults: 2 inhalations tid or qid
    - children: 1-2 inhalations tid or qid
Aerosol Corticosteroids

- **Budesonide**
  - brand names: Pulmicort Turbuhaler (DPI), Pulmicort Respules (nebulizer solution), Rhinocort (intranasal; see p. 210)
  - dosage form:
    - DPI: 200 µg/actuation
    - SVN: 0.25 mg/2ml; 0.5 mg/2ml unit dose respules
  - dosage:
    - SVN: adults: 1 respule daily, children 6-12 yrs.: 0.5 mg or 1 mg once daily or twice daily in divided doses
    - * recommended starting dose if on bronchodilators alone
    - ** recommended starting dose if on inhaled corticosteroids previously
    - *** recommended starting dose if on oral corticosteroids previously

Oral, IV & IM Corticosteroids

- **Dexamethasone**
  - brand names: Decadron, Hexadrol
  - mode of action: potent, long-acting anti-inflammatory agent; rapidly absorbed after oral administration
  - dosage forms: oral, IV

- **Hydrocortisone Sodium Succinate**
  - brand names: Solu-Cortef
  - mode of action: relatively short-acting anti-inflammatory agent; normal daily secretion of hydrocortisone in humans is 10-25 mg; normal plasma level is 5-30 mg/100; used in the tx of status asthmaticus and other acute chest diseases
  - onset of action: app. 60 min.; peak action: app. 5 hrs.; excreted within 12 hrs.
  - dosage forms: oral, IV, IM

Oral, IV & IM Corticosteroids

- **Methylprednisone**
  - brand names: Solu-Medrol (IV, IM), Medrol (oral)
  - mode of action: potent intermediate-acting anti-inflammatory agent; alternate drug to hydrocortisone for hypersensitivity reactions, status asthmaticus, aspiration pneumonitis, ARDS
  - onset of action: slow, 12-24 hrs.
  - duration: long, up to 1 week
  - dosage form: oral, IV, IM

- **Prednisone**
  - brand names: Orasone, Deltasone, Meticorten
  - mode of action: intermediate-acting anti-inflammatory agent; 3-5 times more potent than hydrocortisone; metabolized to its active form: prednisolone in the liver
  - dosage form: oral
Oral, IV & IM Corticosteroids

- Prednisolone
  - brand names: Delta-Cortef, Sterane, Hydeltrasol
  - mode of action: essentially the same as prednisone; one of the more commonly used corticosteroids for allergic and inflammatory conditions
  - dosage form: oral, IV, IM