THE LATEST ON ASTHMA MEDICATIONS--FROM SABA'S TO BIOLOGICS AND BEYOND

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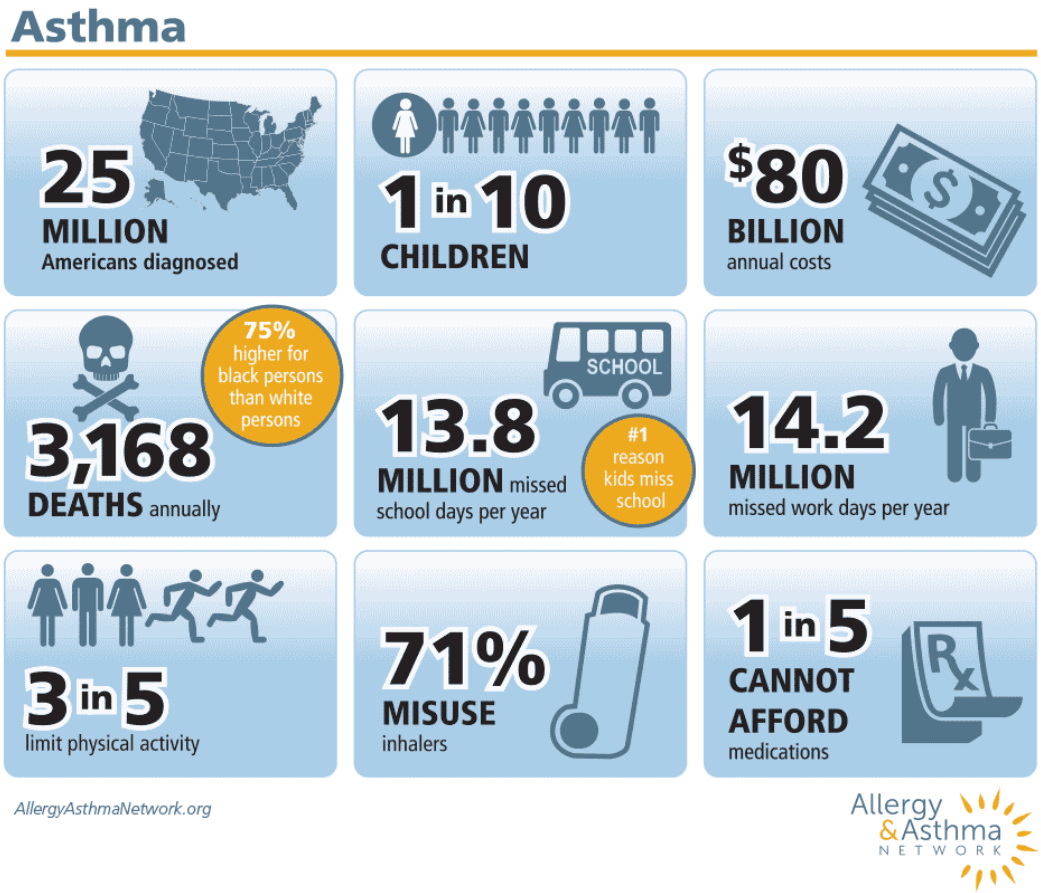
Learning Objectives

- Summarize the Epidemiology & Pathophysiology of Asthma
- Briefly Describe the Evolution of Asthma Medications
- Describe the Current Asthma Medication Arsenal
- Review Delivery Systems
- Examine Special considerations
  - Delivery with mechanical ventilation
  - Continuous inhaled bronchodilator therapy
- Review How to Choose a Pharmacologic Approach
- Review Likely Future Developments
- Provide Additional Resources

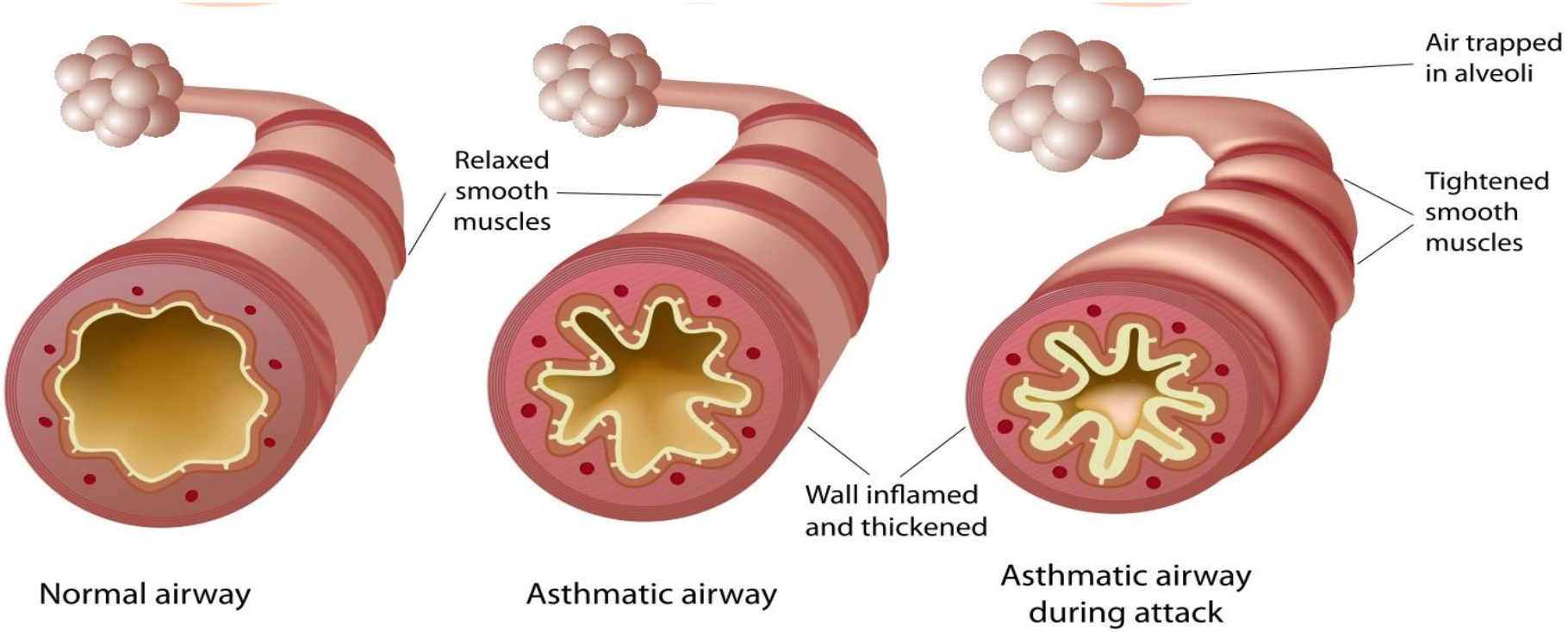
Asthma Epidemiology



Asthma Basics

- Definition
  - A clinical syndrome characterized by:
    - Airway obstruction, which is partially or completely reversible either spontaneously or with treatment.
    - Airway hyperresponsiveness (AHR) to various stimuli Incidence
    - Airway inflammation
      - Bronchial Smooth Muscle Constriction
      - Airway Wall Swelling
      - Excessive Mucous
- Incidence
  - In 2020, Approx. 22 million adults and 7 million children reported having asthma
  - Accounts for:
    - 2 million ED visits Annually
    - 3500 deaths / year

Asthma Pathophysiology



Exacerbations

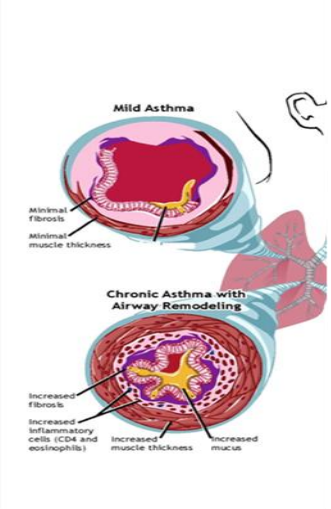
- Acute worsening of symptoms and lung function
- May occur as a result of a trigger such as viral infection, allergen, noncompliance, pollution, irritants, etc
- The best treatment is **early recognition and intervention** – RT's should be in tune to subtle changes that may provide an opportunity to intervene
- Risk factors for asthma related deaths
  - 2 hospitalizations
  - 3 ED visits
  - 2 SABA cannisters per month
  - No asthma action plan, previous severe exacerbation (ICU/intubation) and non adherence

Why Exacerbations are Bad

- Diminishes Patient's and Family ***Quality of Life***
  - Lost School
  - Lost work days
  - Co-morbidities—e.g. depression,
- Increases potentially ***avoidable burden*** on our health system.
- If frequent, may result in permanent airway changes known as ***Airway Remodeling***

airway remodeling

- Many patients with intermittent symptoms have normal lung function in-between
- A subset develops irreversible airflow obstruction from airway remodeling
- Use of ICS decreases inflammation, OCS use, decline in lung function by reducing exacerbations and decreases the rate ratio of death



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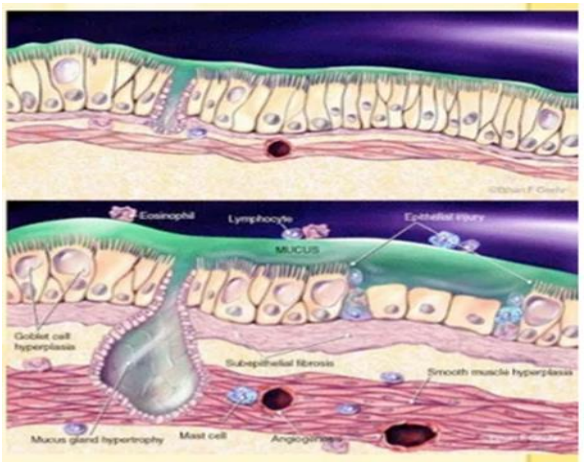


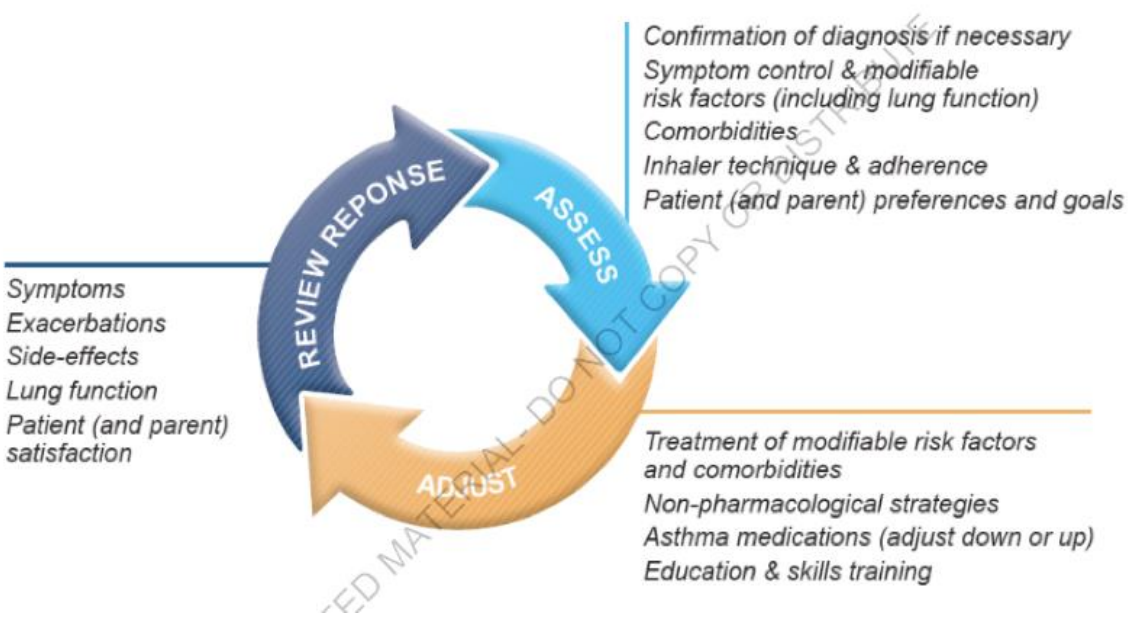
Asthma: Management

- Four important components recommended by the ***National Asthma Education Program (NAEP)*** expert panel:
  - Objective measurements and monitoring of lung function
  - ***Pharmacologic therapy***
  - Environmental control
  - Patient education

Asthma: Management (Cont)

- Control of asthma is defined as:
  - Minimal to no chronic diurnal or nocturnal symptoms
  - Infrequent exacerbations
  - ***Minimal to no need for beta-2 agonists***
  - No limitation to exercise activity
  - PEFR or FEV_1 greater than 80% predicted with less than 20% diurnal variation
  - ***Minimal to no adverse effects of medication***

Treatment of asthma



Milestones in Asthma Medication Evolution

- ***1950's & 1960: Catecholamine adrenergic bronchodilators are the mainstay in Asthma treatment.***
  - Very Short Acting
  - Many Side effects (tachycardia, tremors)
  - Examples: Subcutaneous epinephrine, epinephrine (Primatene Mist), Metaproterenol (Alupent)
- ***1970's & 1980's***:
  - Non-catecholamine adrenergic bronchodilators are introduced and gain a foothold (e.g. Albuterol)
  - Inhaled steroids gain in popularity.
  - Mast cell Stabilizers Introduced (Cromolyn Sodium-Intal)
- ***Late 1990' s and early 2000's:***
  - Much larger emphasis on Asthma education, management and prevention.
  - Leukotriene inhibitors introduced (e.g., Singulair)
  - Levalbuterol (Xopenex) Introduced
    - Never gained a strong foothold - Cost and Similar effectiveness to Albuterol
  - Adrenergics De-emphasized-Use > 2 times per week = unstable Asthma
  - 2010 CFC-based propellants phased out in favor of HFA (Hydrofluroalkane)
- **2010-2020's:**
  - Explosion in Combination DPI's
  - Biologics (Monoclonal Antibodies) introduced and Gain in popularity

Adrenergic Bronchodilators - Indications

- Indications for use
  - Short-acting agents (rescue agents)
    - For relief of acute reversible airflow obstruction
  - Long-acting agents
    - For maintenance bronchodilation in patients with obstructive lung disease
  - Racemic epinephrine
    - To reduce airway swelling after extubation or during croup or epiglottitis
    - To control airway bleeding during endoscopy

Adrenergic Bronchodilators – Mechanism of Action

- Mechanism of action and effects
  - Alpha-receptor stimulation: causes vasoconstriction and vasopressor effect
  - Beta-1-receptor stimulation: causes increased heart rate and heart contractility
  - Beta-2-receptor stimulation: relaxes bronchial smooth muscle, stimulates mucociliary activity, and has some inhibitory action on inflammatory mediator release

Adrenergic Bronchodilators – Three Subgroups

- Three subgroups:
  - Ultra–short acting catecholamine agents
    - Racemic epinephrine
    - Lacks beta-2 specificity
    - Cardiac side effects common
    - Has strong alpha-1 activity and vasoconstricting effect
    - Metabolized rapidly by enzyme catechol o-methyltransferase (COMT)
  - Short-acting noncatecholamine agents
    - Albuterol and levalbuterol
    - Beta-2-specific agents
    - Duration of action is about 4-6 hours
    - Suited for maintenance therapy
  - Long-acting adrenergic bronchodilators
    - Salmeterol, formoterol, arformoterol
    - Duration of action is about 12 hours
    - Mechanism allows for persistent receptor stimulation over a prolonged period of hours
    - Indacaterol and olodaterol have a 24-hour duration (ultra-long-acting)
    - Vilanterol is ultra-long-acting available in combinations

Adrenergic Bronchodilators – Adverse Effects

Adverse effects (most common)

- Tremors
- Headache
- Insomnia
- Nervousness

Adverse effects (potential)

- Dizziness
- Hypokalemia
- Loss of bronchoprotection
- Nausea
- Tolerance (tachyphylaxis)
- Worsening of ventilation/perfusion ratio

Adrenergic Bronchodilators

- Common Dosing/Frequency: 2.5 mg Albuterol/3 mls nss, Q4-6H
- Assessment of bronchodilator therapy
  - Based on indications for aerosol agent
  - Vital signs, breath sounds, and breathing pattern should be evaluated before and after treatment
  - Patient's subjective response is important to evaluate

Anticholinergic Bronchodilators

- A second-line category of bronchodilator for Asthma
  - Slower on-set
  - Longer duration of therapy
  - A cholinergic blocking agent is effective only if bronchoconstriction exists due to cholinergic activity, which is less common in asthma
- First-line treatment for COPD
  - Maintenance treatment in COPD
  - Combined with a beta-agonist is indicated for use in patients with COPD receiving regular treatment who require additional bronchodilation for relief of airflow obstruction.
- Examples:
  - Ipratropium Bromide-Atrovent, tiotropium bromide, aclidinium bromide, glycopyrrolate bromide, umeclidinium bromide
  - **Common Dose/Frequency-0.5 mg in 3 mls nss, Q6-8 hrs**
- Combined anticholinergic and beta-agonist
  - Ipratropium bromide and albuterol, umeclidinium bromide and vilanterol, glycopyrrolate bromide and formoterol, tiotropium bromide and olodaterol,

Inhaled Corticosteroids

- Indications and purposes
  - Orally inhaled preparations used for antiinflammatory maintenance therapy of persistent asthma and severe COPD
  - Use of intranasal steroids is for control of allergic and nonallergic rhinitis.
- Mechanism of action
  - Lipid-soluble drugs that act on intracellular receptors
  - Full antiinflammatory effects require hours to days
  - Will not provide immediate relief of dyspnea from airways obstruction

Inhaled Corticosteroids -- Adverse Effects

- Systemic
  - Adrenal insufficiency
  - Extrapulmonary allergy
  - Acute asthma
  - HPA suppression (minimal, dose dependent)
  - Growth retardation
  - Osteoporosis
- Local (Topical)
  - Oral fungal infections
  - Dysphonia
  - Cough, bronchoconstriction
  - Incorrect use of MDI

Inhaled Corticosteroids

- Assessment of drug therapy
  - Use strategies for assessment similar to those used for evaluation of bronchodilators
  - In addition
    - Make sure patient understands importance of consistent use and not to use it as rescue drug
    - Instruct patient in use of peak flowmeter
    - Assess patient for side effects

Commonly Used Inhaled Corticosteroids

- Inhaled corticosteroids
  - Beclomethasone dipropionate (QVAR Redihaler)
  - Ciclesonide (Alvesco)
  - Flunisolide hemihydrate (Aerospan)
  - Fluticasone propionate (Flovent HFA; Flovent Diskus; Armonair Respiclick)
  - Fluticasone furoate (Arnuity Ellipta)
  - Budesonide (Pulmicort Flexhaler; Pulmicort Respules)
  - Mometasone furoate (Asmanex Twisthaler; Asmanex HFA)

Inhaled Corticosteroids

- Combinations
  - Fluticasone propionate/salmeterol (Advair Diskus; Advair HFA; AirDuo Respiclick)
  - Budesonide/formoterol fumarate HFA (Symbicort)
  - Mometasone furoate/formoterol fumarate HFA (Dulera)
  - Fluticasone furoate/vilanterol (Breo Ellipta)
  - Fluticasone furoate/umeclidinium/ vilanterol (Trelegy Ellipta)

Nonsteroidal Antiasthma Drugs

- Growing class of drugs for treatment of asthma
- These include:
  - Mast cell stabilizers (cromolyn sodium)
  - Antileukotrienes, also termed *leukotriene modifiers* (zafirlukast, zileuton, montelukast)
  - Monoclonal antibodies or anti-IgE agents (benralizumab, mepolizumab, omalizumab and relizumab)
- Indications for use
  - Prophylactic management (control) of persistent asthma
  - Offer no benefit for acute airways obstruction in asthma
  - Cromolyn sodium and antileukotrienes may be used as alternative to steroids in patients with persistent asthma symptoms
  - Monoclonal antibodies are available for consideration in correct population

Nonsteroidal Antiasthma Drugs

- Mechanism of action
  - Cromolyn sodium inhibits degranulation of mast cells in response to allergic and nonallergic stimuli
    - Prevents release of histamine and other mediators of antihistamine
  - Zafirlukast and montelukast act as leukotriene receptor antagonists and are selective competitive antagonists of leukotriene receptors
    - Causes bronchoconstriction, mucus secretion, vascular permeability, and plasma exudation into airway
    - Drug inhibits reactions induced by exercise, cold air, allergens, and aspirin

Nonsteroidal Antiasthma Drugs

- Mechanism of action
  - Zileuton inhibits 5-lipoxygenase enzyme, which catalyzes formation of leukotriene from arachidonic acid
  - Omalizumab inhibits attachment of IgE to mast cells and basophils, reducing release of chemical mediators of allergic response
  - Enralizumab, mepolizumab and reslizumab blocks interleukin-5 (IL-5) changing the signaling of IL-5 reducing eosinophils

Nonsteroidal Antiasthma Drugs

- Adverse effects
  - Antileukotriene agents
    - Headache
    - Dyspepsia
    - Liver enzyme elevation
  - Monoclonal antibodies
    - Injection site
    - Viral infections
    - Headache
    - Sinusitis
    - Pharyngitis

Delivery Devices -- Pressurized Metered Dose Inhalers

- Technique for use of pMDI
  - Most patients do not use proper technique
  - Thorough education of patient can take up to 30 minutes
  - MDI should be actuated at beginning of inspiration with mouthpiece held 4 cm in front of open mouth
- Technique for use of pMDI
  - Concerns with open-mouth technique
    - Ipratropium bromide administration along with poor coordination can result in drug being sprayed into eyes
    - Anticholinergic agents have been associated with increased ocular pressure
    - Steroid pMDIs can increase incidence of opportunistic oral yeast infection and dysphonia

Pressurized Metered Dose Inhalers – Enhancing Drug Delivery

- pMDI accessory devices
  - Basic concepts for spacer devices include: (1) small volume adapters, (2) open tube designs, (3) bag reservoirs, and (4) valved holding chambers
  - All spacers add distance between the pMDI and the mouth, reducing the initial forward velocity of the pMDI droplets
  - Spacers
    - Simple valveless extension device that adds distance between pMDI outlet and patient's mouth
    - Reduces oropharyngeal deposition and need for hand-breath coordination
- pMDI accessory devices
  - Holding chambers
    - Incorporate one or more valves that prevent aerosol in chamber from being cleared on exhalation
    - Provide less oropharyngeal deposition, higher respirable drug dosages, and better protection from poor hand-breath coordination than simple spacers

Holding Chambers

Courtesy Monaghan/Trudell Medical, London, Canada.

Treatment troubles - technique

Improper inhaler technique is associated with poor asthma control and frequent emergency department visits

Hamdan AL-Jahdali, Anwar Ahmed, Abdullah AL-Harbi, Mohd Khan, Salim Baharoon, Salih Bin Salih, Rabih Halwani & Saleh Al-Muhsen

- **Study Features**
  - 450 patients who visited the ED in two Saudi Arabia academic hospitals
  - 176 (39.1%) were males
  - Mean age of 42.3 ±16.7 years
  - Mean duration of asthma was 155.9 ± 127.1 weeks.
- **Results:**
  - Improper use of asthma inhaler devices was observed in 203(45%)
  - Improper use was associated with:
    - Irregular clinic follow-ups (p = 0.0001)
    - Lack of asthma education (p = 0.0009)
    - Uncontrolled asthma ACT (score ≤ 15) (p = 0.001)
    - Three or more ED visits (p = 0.0497)
    - Duration of asthma of less than 52 weeks (p = 0.005).
- **Lack of education (OR =1.65) and lack of regular follow-up (OR =1.73) were the most likely factor to lead to bad technique**

Hamdan Al-Jahdali, et al. Improper inhaler technique is associated with poor asthma control and frequent emergency department visits. Allergy, Asthma & Clinical Immunology **volume 9, Article number: 8 (2013)**

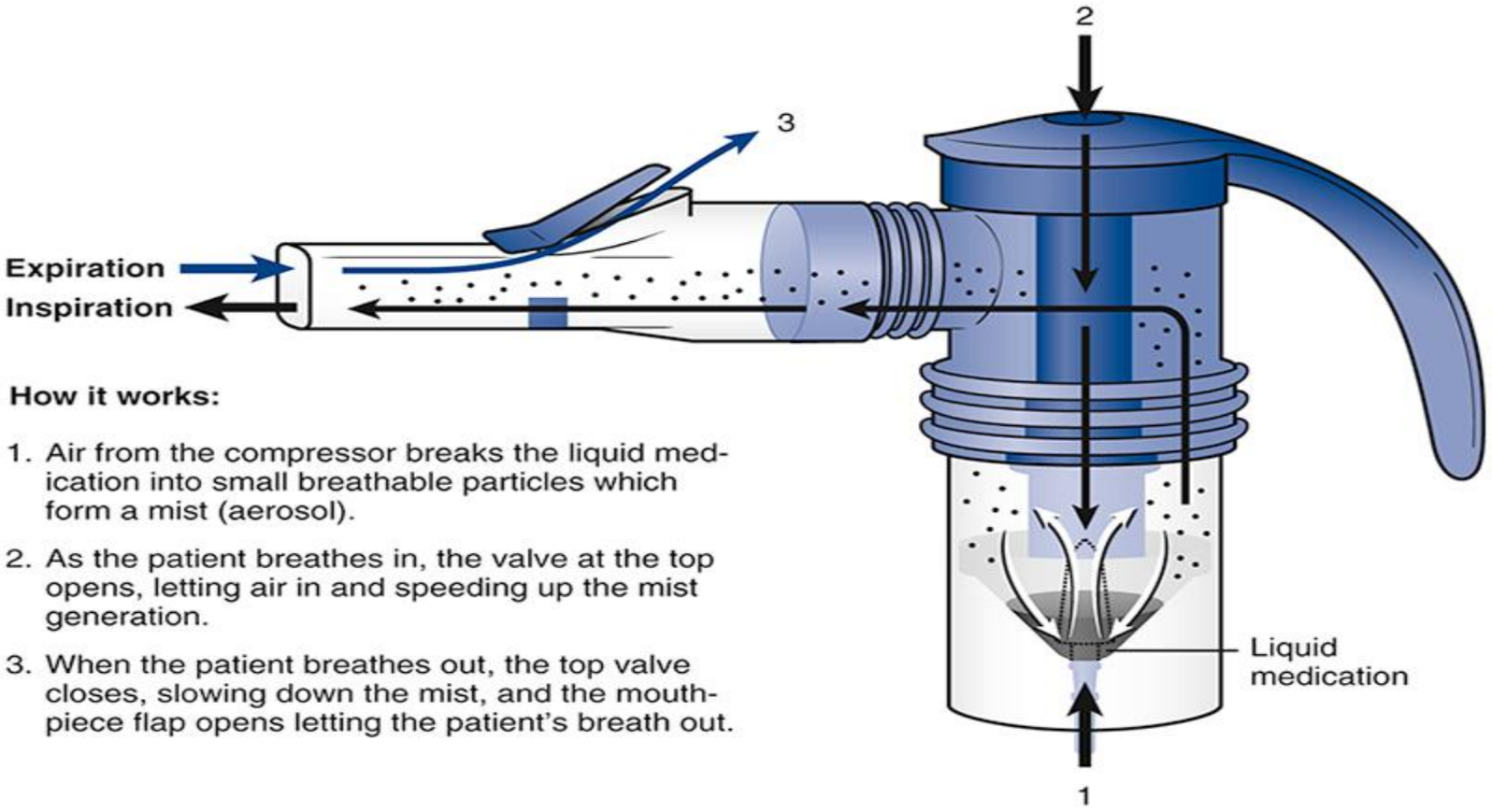
Pneumatic (Jet) Nebulizers

- Most nebulizers are powered by high-pressure oxygen or air
  - Provided by portable compressor, compressed gas cylinder, or 50-psi wall outlet
- Factors affecting nebulizer performance
  - Nebulizer design
  - Flow
  - Gas source
  - Density
  - Humidity and temperature
  - Characteristics of drug formulation

Pneumatic (Jet) Nebulizers

- Small-volume nebulizers (SVN)
  - Four categories
    1. Continuous nebulizer with simple reservoir
    - May increase inhaled dose by 5% to 10%, or increase inhaled dose from 10% to 11% with 6-inch piece of reservoir tube
    2. Continuous nebulizer with collection reservoir bag
    - Bag reservoirs hold aerosol generated during exhalation
    - Allows small particles to remain in suspension for inhalation with next breath while larger particles rain out
    - Attributed to 30% to 50% increase in inhaled dose
    3. Breath enhanced (BE)
    - Generate aerosol continuously, utilizing system of vents and one-way valves
    4. Breath actuated nebulizer (BAN)
    - Can increase inhaled aerosol mass by three- to fourfold over conventional continuous nebulization

Breath Actuated SVN



How it works:

1. Air from the compressor breaks the liquid medication into small breathable particles which form a mist (aerosol).
2. As the patient breathes in, the valve at the top opens, letting air in and speeding up the mist generation.
3. When the patient breathes out, the top valve closes, slowing down the mist, and the mouthpiece flap opens letting the patient's breath out.

From Cairo JM, Pilbeam SP: *Mosby's respiratory care equipment*, ed 8, St. Louis, 2009, Mosby.

Pneumatic (Jet) Nebulizers

- Small-volume nebulizers (SVN)
  - Technique
    - Slow inspiratory flow optimizes SVN aerosol deposition
    - Selection of delivery method (mask or mouthpiece) is based on patient ability, preference, and comfort
  - Infection control issues
    - Nebulizers should be cleaned and disinfected, or rinsed with sterile water, and air dried between uses

Dry Powder Inhalers

- Breath-actuated dosing system
- Patient creates aerosol by drawing air through dose of finely milled drug powder
- Dispersion of powder into respirable particles depends on creation of turbulent flow in inhaler
  - Flow is function of ability of patient to inhale powder with sufficiently high inspiratory flow rate
- Do not use propellants and do not require hand-breath coordination needed for pMDIs

Dry Powder Inhalers

- Categorized based on design of their dose containers
  - Unit-dose DPI
    - Aerolizer and Handihaler dispense individual doses of drug from punctured gelatin capsules
  - Multiple-unit dose DPI
    - Diskhaler contains case of four or eight individual blister packets of medication on disk inserted into inhaler
  - Multiple dose Drug Reservoir DPI
    - Twisthaler, Flexhaler, and Diskus are preloaded with quantity of pure drug sufficient for dispensing 120 doses of medication

Dry Powder Inhalers

- Factors affecting DPI performance and drug delivery include
  - Intrinsic resistance and inspiratory flow rate
  - Exposure to humidity and moisture
  - Patient's inspiratory flow ability
- Technique for use of DPI
  - Patients must generate inspiratory flow rate of at least 40-60 L/min to produce respirable powder aerosol
  - DPIs should not be used by infants, small children, those who cannot follow instructions, and patients with severe airway obstruction
  - Requires cleaning in accordance with product label

DPI Examples

Ellipta

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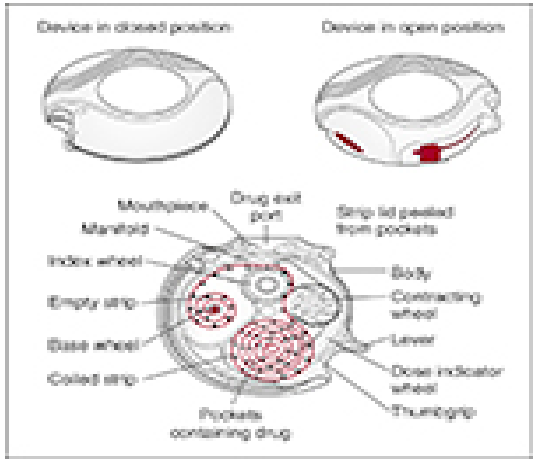
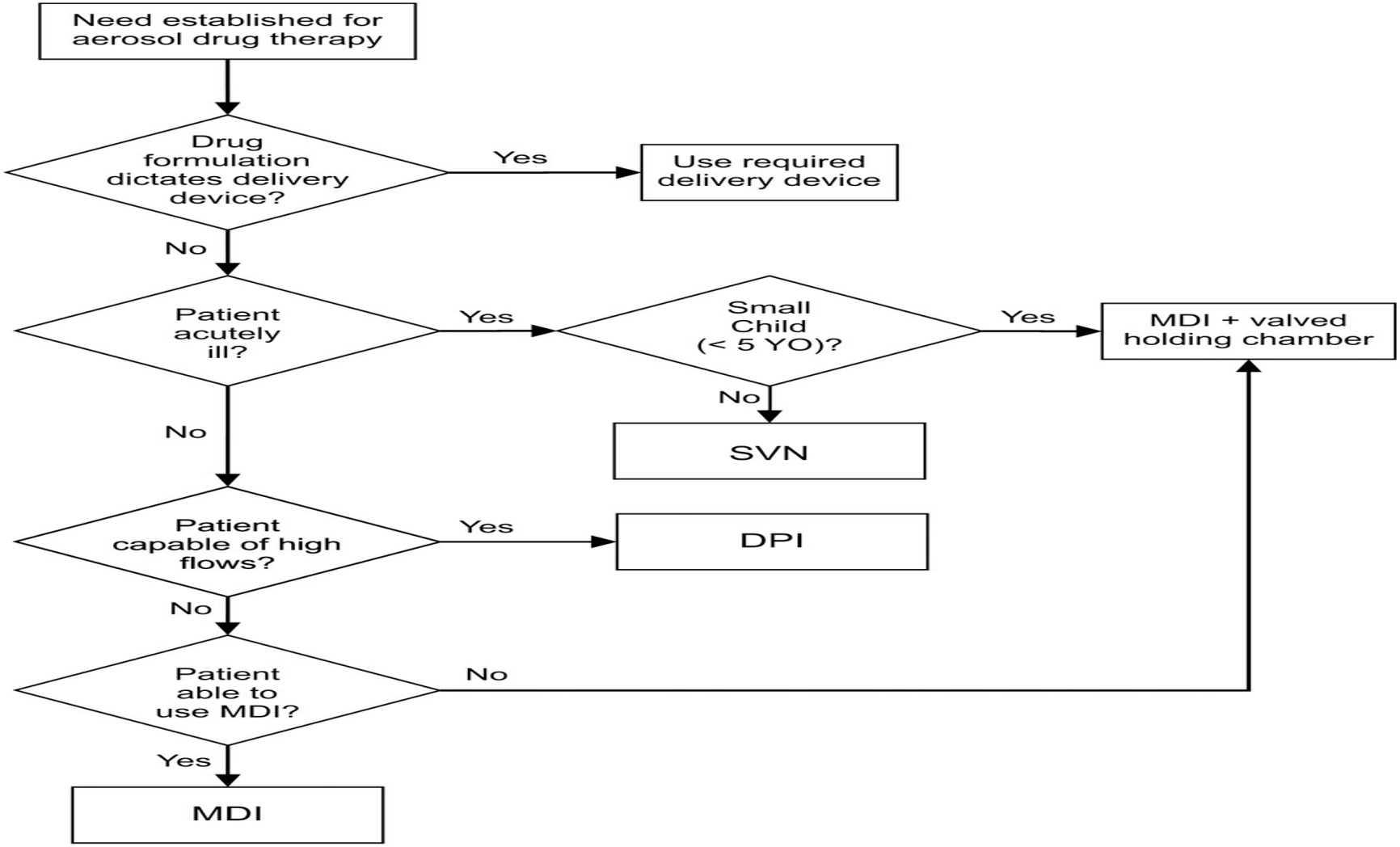
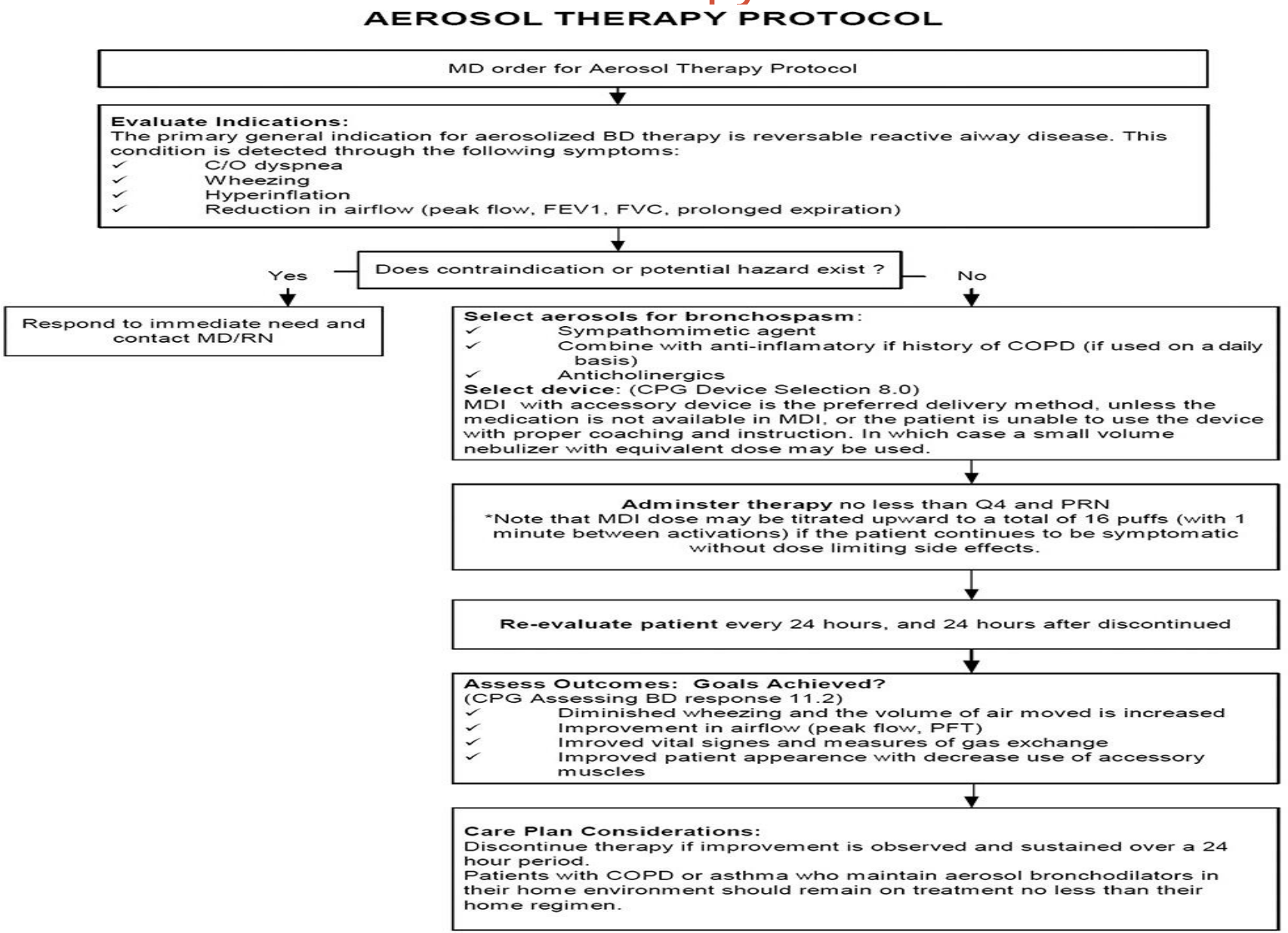


Add Table 40.3 here—Advantages & Disadancges of Delivery Systems

Selecting a Delivery System/Device



Bronchodilator Protocol Therapy



Special Considerations-Children & Infants

- Infants and children
  - Smaller airway diameter than adults
  - Breathing rate is faster
  - Nose breathing filters out large particles
  - Lower minute volumes
  - Devices requiring cooperation (e.g., MDI's, DPI's) should be avoided in young children and infants.
  - Patient cooperation and ability varies with age and developmental ability
    - Crying reduces lower airway deposition of aerosol medication
    - Blow-by should be avoided

Special Considerations –Continuous Nebulization

- Continuous nebulization for refractory bronchospasm
  - CBT with nebulized albuterol doses ranging from 5-20 mg/hour have proved to be safe for adult and pediatric patients with severe asthma
  - Patient carefully assessed every 30 minutes for first 2 hours; then hourly
    - Patient must be observed for adverse drug responses
  - Positive response indicated by increase in PEFR of at least 10% after first hour of therapy
    - Goal is at least 50% of predicted value

Special Considerations –Mechanically Ventilated

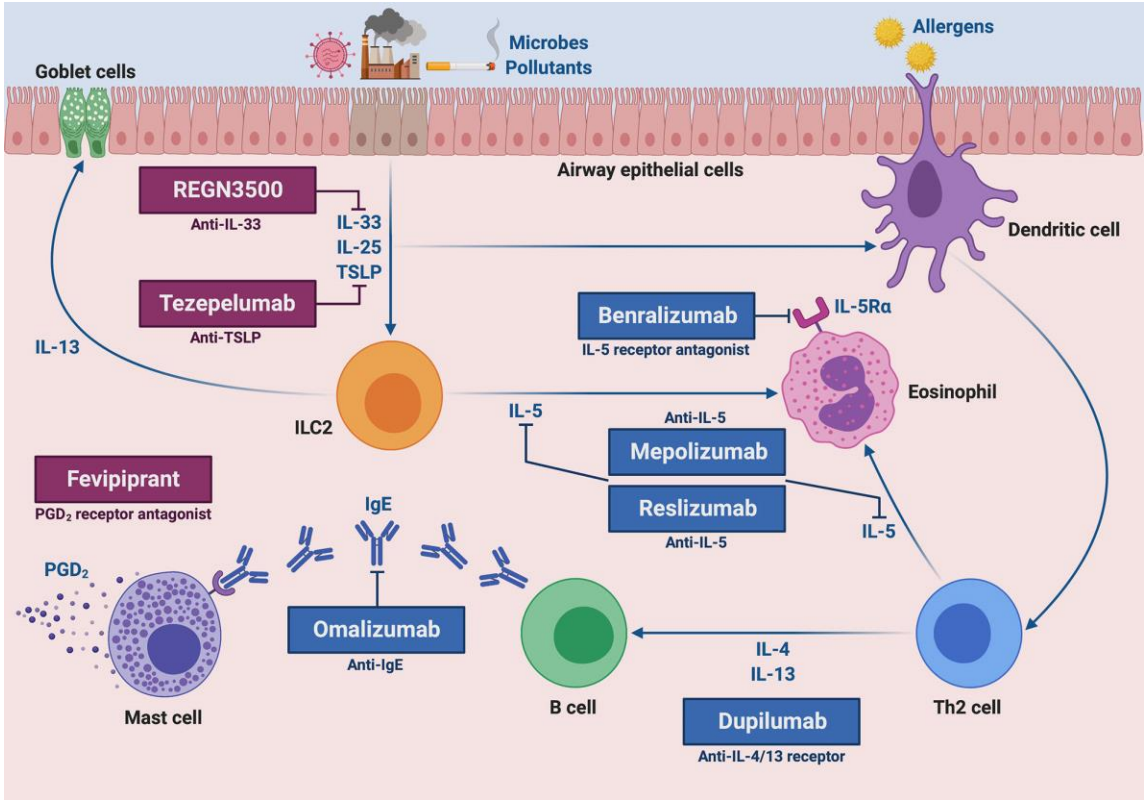
- Placement of aerosol generators in the ventilator circuit can have a substantial impact on the available lung dose of drug
  - During adult ventilation without bias flow
    - Vibrating Mesh (Aerogen) should be placed on the dry side of humidifier
    - SVN's should be placed 18 to 24 inches from the patient in the inspiratory limb
  - In contrast, MDI's are more efficient when placed close to the patient at the circuit wye

- Aerosol administration to mechanically ventilated patients
  - Techniques used for assessing response to bronchodilator
    - Measure change in difference between peak and plateau pressures
      - Drop in peak pressure during mechanical ventilation suggests effective bronchodilation
    - Automatic positive end-expiratory pressure levels may decrease in response to bronchodilators
    - Breath-to-breath variations

Biologic therapy

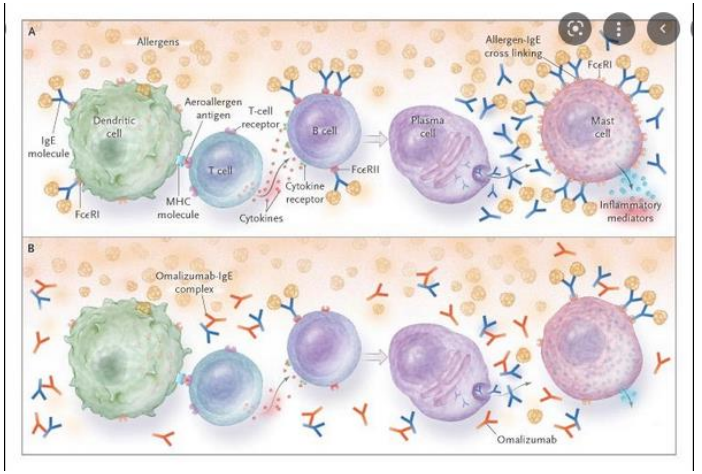
- Life changing for many of our patients
- Currently, there are agents that target anti-IgE, anti-IL 5, anti-IL5R, anti-IL-4R/13 and anti-TSLP (thymic stromal lymphopoietin)
- There are no head to head trials
- Choice is based heavily on suspected phenotype, concurrent disease, IgE level, eosinophils, patient preference (home vs. observed) and personal experience

Molecular targets of Biologic therapy



Biologic therapy – Omelizumab (Xolair)

- **The OG** anti-IgE therapy
- Forms complexes to prevent binding to mast cells
- Approval for over **6 yo with IgE 30-700** IU/mL, positive allergen testing and incomplete control of mod-severe asthma
- SubQ every 2-4 weeks - **Self administered** or observed
- Decrease the rate of asthma exacerbations by 25%
- May cause sustained improvement in FEV1 at 5, 7 and 9 years
- Improvement in symptom control, QoL, OCS use, and a lower loss of working and school days has also been shown



Sally Wenzel. Treatment of severe asthma in adolescents and adults. UpToDate. Sep 15 2022.
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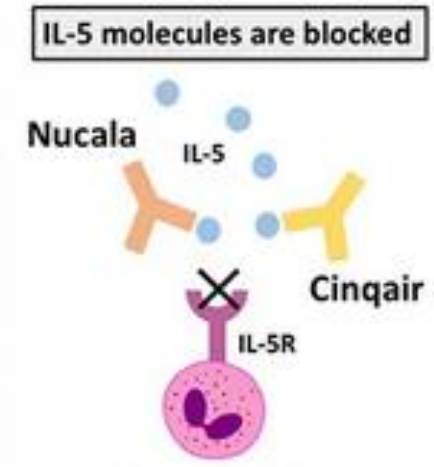
Strunk et al. Omalizumab for asthma. June 22, 2006. N Engl J Med 2006; 354:2689-2695

Mepolizumab (Nucala)

- Anti-IL 5
- Over **6 yo** with severe asthma with eosinophilia > 150/microL (preferably >300)
- Also approved for chronic **rhinosinusitis and nasal polyposis**
- SubQ 100 mg every 4 weeks and can be **self-administered** or observed
- Significant reduction in exacerbations (50-60% reduction)
- Improved QoL
- Steroid reduction of 50% compared with placebo



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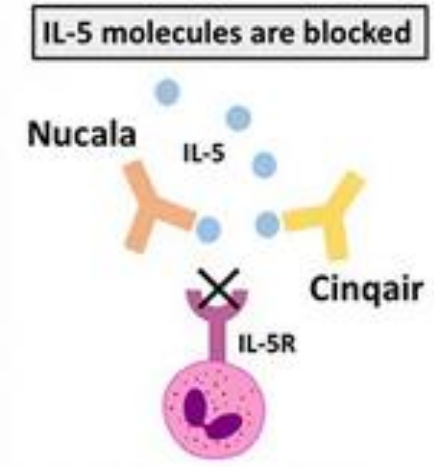
Reslizumab (Cinqair)

- Anti IL-5
- Over **18 yo** with severe asthma with eos > 400
- **IV administration** over 20-50 minutes every 4 weeks
- Decrease in exacerbation by 50%, improved symptoms and QoL and improved FEV1 (115-220 mL)
- Limited data shows a reduction in steroid use (250 vs 610 mg over 52 weeks



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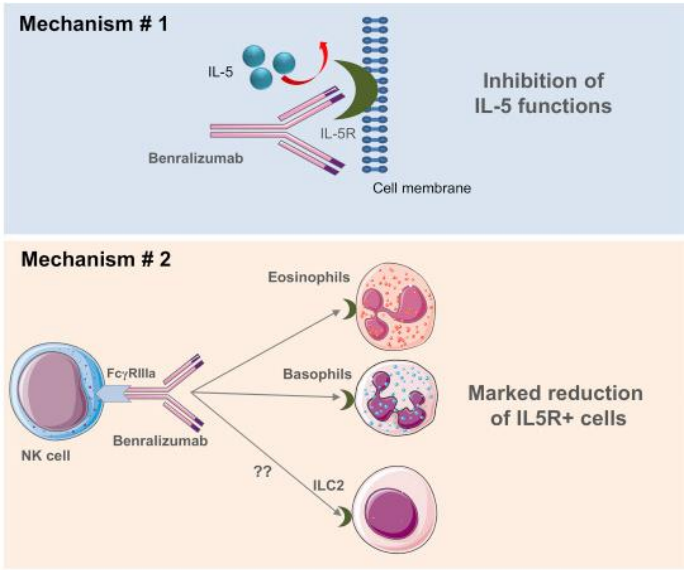
Benralizumab - Fasenra

- Anti IL-5 receptor alpha works to **both** block IL-5 from binding and to induce apoptosis of eosinophils
- Over 12 yo with severe asthma and eos > 150 cell/microL
- SubQ q4 weeks for 3 doses and **then every 8 weeks** and can be self-administered
- **Reduces exacerbations** with RR 0.49, 0.51 or 0.55 depending on the study. This was most pronounced if eos > 300
- Steroid reduction by 75% and elimination in 62% of patient



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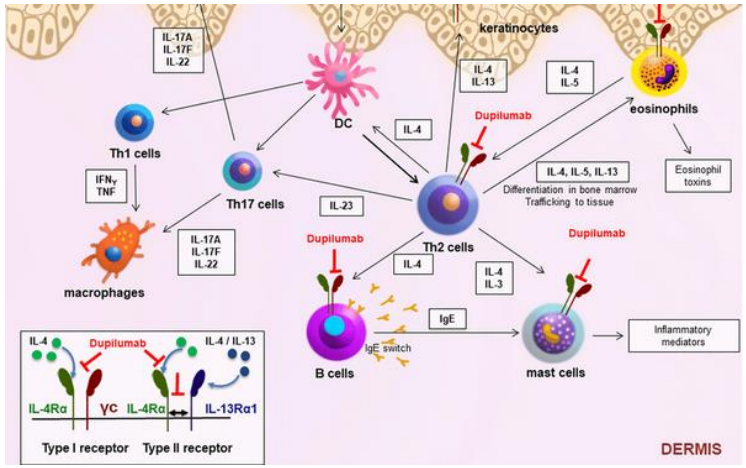
Dupilumab (Dupixent)

- Anti IL-4 receptor alpha subunit
- Inhibits both IL-4 and IL-13
- Approved for **moderate-severe** with eos > 150 in patient > 6 yo
- Also used for **eczema, chronic rhinosinusitis, nasal polypsis,** eosinophilic esophagitis and prurigo nodularis
- Decreases exacerbations by 67% (eos > 300), 40% (150-300) and –4% (< 150)
- Decreases steroid dose by 70% vs 42% in placebo
- Increases FEV1 by 150 mL



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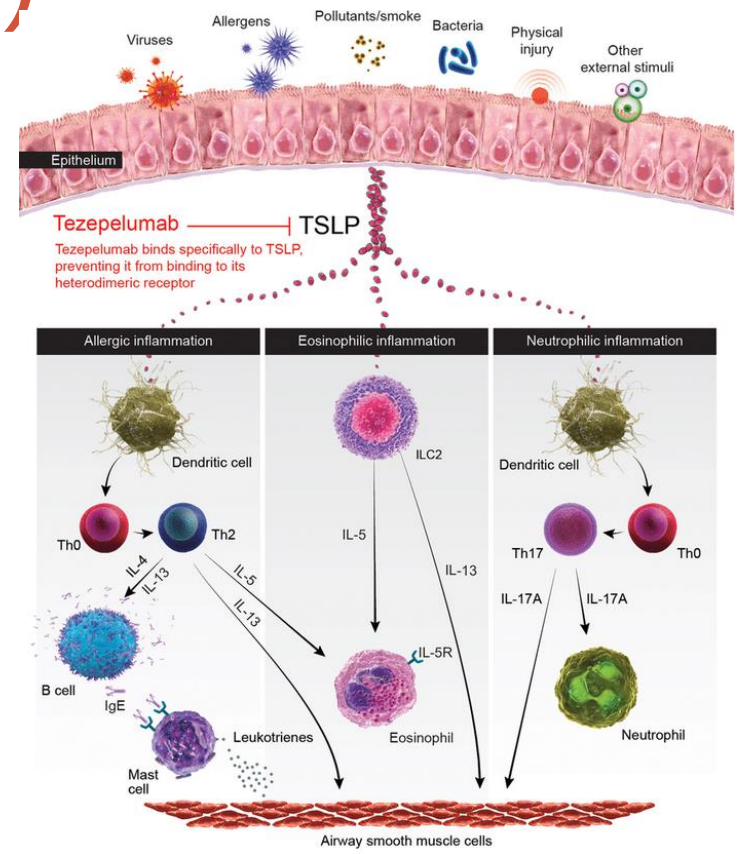
Tezepelumab (Tezspire)

- Newly approved anti thymic stromal lymphopoietin (TSLP) - a cytokine produced from the epithelial cells
- Severe asthma over the age of 12 with no requirement for FeNO or eos
- SubQ every 4 weeks
- 56-71% reduction in exacerbations
- Reduced ED visits (1.2% vs 3.6%)
- Reduction in steroid use was only apparent for eos>150



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Licensed biological therapies	Targets	Molecular mechanisms of action	Effects in the control of severe asthma
Omalizumab	IgE	Generation of IgE/anti-IgE immune complexes that inhibit IgE-mediated allergic cascade	↓ Exacerbations ↑ Quality of life and symptom control ↑ FEV1
Mepolizumab	IL-5	Prevention of IL-5 binding to IL-5Rα	↓ Blood and sputum eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↓ OCS intake ↑ FEV1
Reslizumab	IL-5	Prevention of IL-5 binding to IL-5Rα	↓ Blood and sputum eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↑ FEV1
Benralizumab	IL-5Rα	Blockade of IL-5Rα ADCC-induced eosinophil apoptosis	↓ Blood eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↓ OCS intake ↑ FEV1
Dupilumab	IL-4Rα	Dual receptor antagonism of IL-4/IL-13	↓ Exacerbations ↓ OCS intake ↑ FEV1

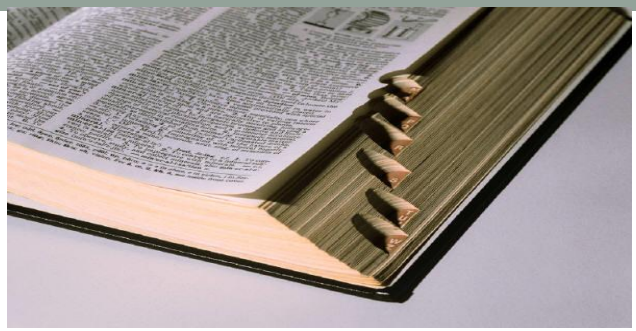
Controlling Environmental Contamination

- Exposures:
  - Nebulized drugs may enter room directly from nebulizer or during patient exhalation
  - Continuous pneumatic nebulizers produce greatest amount of second-hand aerosol
- Controlling Exposures:
  - Use of one-way valves and filters can help
  - Negative-pressure rooms and treatment booths are useful strategies
  - Personal protective equipment is recommended when caring for patient with disease that can be spread by airborne route

Take Home Points

- Asthma still accounts for a significant amount of morbidity for patient and lost productivity (for patients and caregivers)
- However, we have come a long way in Asthma management
- Much greater emphasis on management & prevention.
- However, there is still more work to be done.
- Stay abreast of developments…knowledge is empowerment from which our patients can benefit!!!

Selected References



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