The Ins and Outs of Respiratory Medicines

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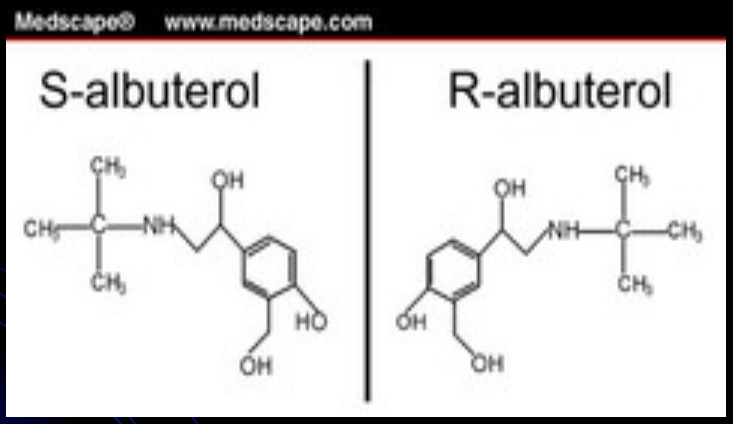
Albuterol

Racemic epinephrine

Levalbuterol

Albuterol - Levalbuterol



Albuterol/Levalbuterol

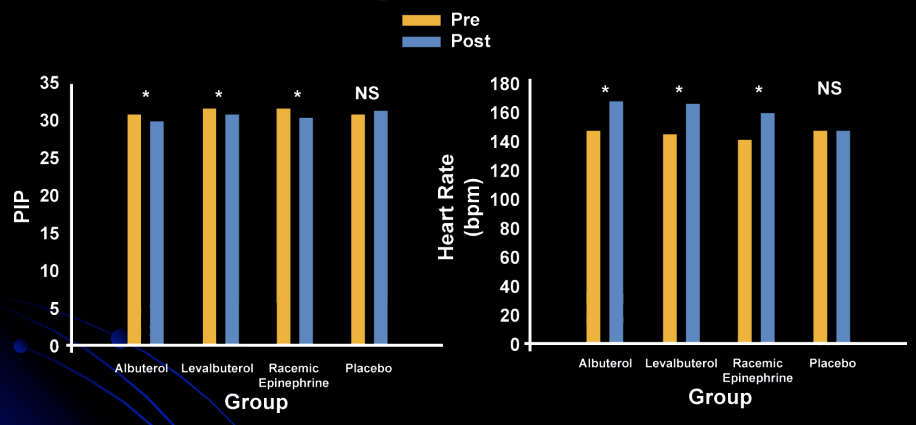
- What is the advantage of Levalbuterol > albuterol?

Comparing Bronchodilators

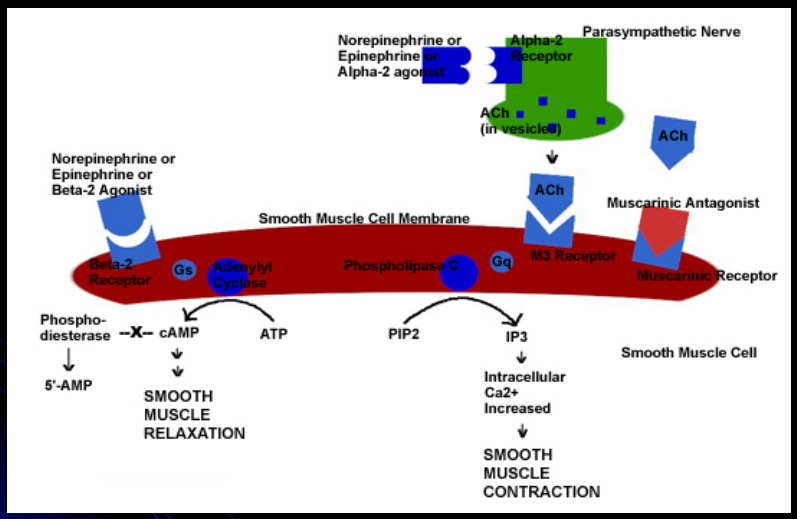
- 22 mechanically ventilated patients with RSV bronchiolitis enrolled in RCT
  - Albuterol, levalbuterol, racemic epinephrine, placebo
- Significant reductions in PIP and resistance after treatment with all 3 agents
  - Small reductions (lack clinical significance)
  - No superiority between agents
- Significant increase in heart rate after each treatment
  - Equivalent increases

RCT = randomized controlled trial; PIP = peak inspiratory pressure.
Levin DL, et al. *Pediatr Crit Care Med.* 2008;9(6):598-604.

Comparing Bronchodilators



*P<.05.
NS = not significant.
Levin DL, et al. *Pediatr Crit Care Med.* 2008;9(6):598-604.



Albuterol

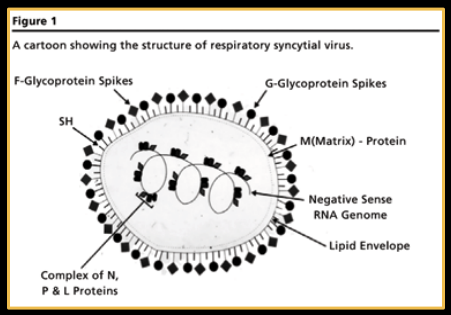
- How does albuterol work?
- Relaxing respiratory smooth muscles
- What do we know about neonates?
- Immature respiratory smooth muscles

Albuterol in Bronchiolitis

- >100 studies evaluating its use
- No consistent benefit
- No randomization for history of asthma

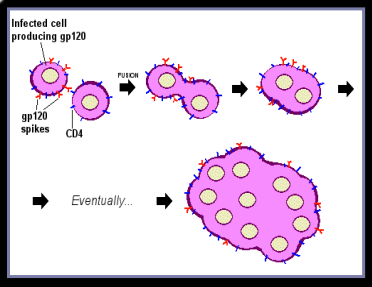
RSV—The Virus

- RSV must enter the host cell to reproduce
- Protein F
  - Glycoprotein projection on the RSV surface
  - Fusing the RSV viral envelope and the host cell
- Infected cells then begin to fuse to one another, producing a large incompetent cell (syncytium)
- Protein G
  - Allows virus to enter the cell



Smyth RL, et al. *Lancet*. 2006;368:312-322.

Viral Pathogenesis

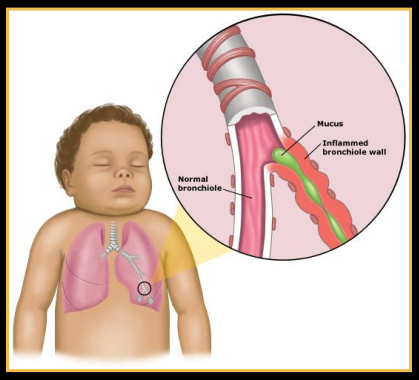


- RSV directly damages the cells in the epithelium or walls of the airways
- Once the RSV virus fuses the cell membranes and forms syncytia (multinucleated cells), they are partially resistant to host defense mechanisms
- Syncytia formation causes eventual sloughing of these cells into the airway lumen

Smyth RL, et al. *Lancet.* 2006;368:312-322.

Viral Pathogenesis

- The respiratory epithelial cells initially regenerate as nonciliated cells that cannot sweep cellular debris and mucus out of the airway lumen
- As a result, mucous plugs may partially or fully obstruct the bronchioles
- Pneumonia occurs when this process extends into the alveoli
- Proliferation of goblet cells results in excessive mucus production
- Tissue edema and mucus production occur simultaneously



Long SS. *Pediatric Infectious Diseases: Bronchiolitis.* 3rd ed. Churchill Livingstone; 2008.

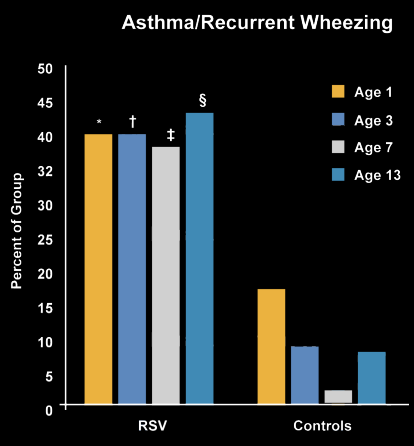
What Are the Long-term Health Consequences of RSV?

- Increased risk of respiratory conditions
  - Greater bronchial reactivity
  - Continued, more frequent wheezing
  - Prolonged inflammatory response
  - Hyperactive airway disease

Sigurs N, et al. *Am J Resp Crit Care Med.* 2000;161:1501-1507. Meissner HC, et al. *Pediatr Infec Dis J.* 1999;18:223-231. Sampalis JS. *J Pediatr.* 2003;143:150-156. Leader S, et al. *Pediatr Infect Dis J.* 2002;21:629-632. Black CP. *Respir Care.* 2003;48:209-231.

RSV Disease in Infancy Is an Important Risk Factor for Asthma/Recurrent Wheezing up to 13 Years of Age

- 47 children hospitalized for RSV LRI in the first year of life
- 93 controls with no RSV LRI
- Risk of wheezing was significantly higher at 13 years compared with controls (*P*<.001)



*P=.003; †P<.001; ‡P<.0001; §P<.001.
LRI = lower respiratory infection.
Sigurs N, et al. *Pediatrics.* 1995;95:500-505. Sigurs N, et al. *Am J Resp Crit Care Med.* 2000;161:1501-1507. Sigurs N, et al. *Am J Respir Crit Care Med.* 2005;171:137-141.

RSV Infection and Asthma

- Exploring the association between severe RSV infection and asthma
- A registry-based twin study
- N = 8280 twin pairs from 1994 to 2000, followed for development of asthma after RSV
- RSV infection that is severe enough to warrant hospitalization does not cause asthma, but is an indicator of the genetic predisposition to asthma

Thomsen SF, et al. *Am J Respir Crit Care Med.* 2009;179(12):1091-1097.

- Perhaps patients with a genetic predisposition to asthma are the ones that have a response to albuterol

Recommendations for Steroids

- AAP guidelines do NOT recommend routine use of steroids for the management of RSV bronchiolitis
- AAP Red Book: "... steroids are not effective nor indicated for RSV bronchiolitis in previously healthy infants"
- May consider if underlying BPD, lung disease

American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis. *Pediatrics.* 2006;118(4):1774-1793.

What this may mean clinically

- Physicians may add steroids on to the treatment of bronchiolitis in term infants with low risk factors for hospital admission for RSV
- There is no Double blind randomized clinical evidence that this beneficial

Audience Response Question

Which medications have been documented in clinical trials to shorten the length of hospital stay?

1. Albuterol/levalbuterol
2. Racemic epinephrine
3. Hypertonic saline
4. Ribavirin
5. All of the above
6. None of the above

Hypertonic saline

- What does the term hypertonic saline mean?
- What percent?

- Cystic Fibrosis - 7%
- RSV bronchiolitis – 3%

Hypertonic Saline in Bronchiolitis

- Hypertonic saline (3 %) inhalations
- Mechanism of action
  - Viscosity reduction
  - Stimulation of cilial beat by releasing prostaglandin E2
  - Absorption of water from mucus to reduce edema of airway
  - Sputum induction and cough

Zhang L, et al. *Cochrane Database Syst Rev.* 2008;4:CD006458.

Hypothesis for the Use of Hypertonic Saline (HS) 3%

- Decreases mucosal edema
- Decreases the concentration of inflammatory mediators
- Mechanically clears inspissated mucus
- Improvement in overall mucociliary function and transport
- Helps clear mucus in cystic fibrosis patients

Nebulized 3% HS in Ambulatory Children with Viral Bronchiolitis

- Randomized, double-blind, placebo controlled in 70 infants
- Group 1: Terbutaline added to 0.9% saline
- Group 2: Terbutaline added to 3% saline

- Exclusion Criteria:
  - Cardiac illness
  - Chronic respiratory disease
  - Previous wheezing episode
  - Age > 24 months
  - Oxygen saturation <96% on room air
  - Need for hospitalization

Sarrell E, Tal G, Witzling M, et al.

Results

- Primary outcomes:
  - (1) Difference in the decline in CS scores from baseline between the two groups every day (and the change in CS scores after the inhalations each day)

CS Scores	Terbutaline + 0.9% Saline	Terbutaline + 3% Saline	p value
Day 1 (baseline)	6.4 ± 1.8	6.6 ± 1.5	NS
Day 2	5.2 ± 1.9	3.9 ± 1.5	< 0.005
Day 3	4.8 ± 2.3	2.1 ± 2.2	
Day 4	3.8 ± 2.5	1.1 ± 2.2	
Day 5	2.9 ± 2.7	0.9 ± 2.2	

*CS scores also differed significantly after inhalation treatments in favor of the group with 3% saline especially on days 1 ($p < 0.005$) & 2 ($p = 0.01$).

Sarrell E, Tal G, Witzling M, et al.

Results

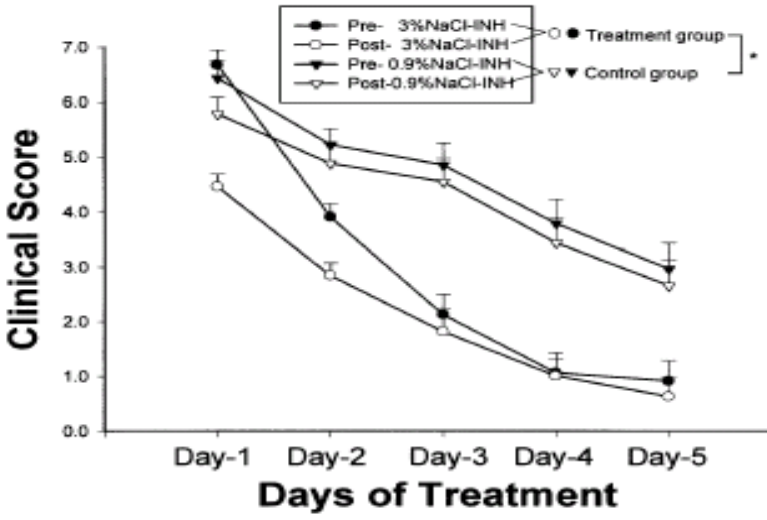


FIGURE 1. After the baseline measurement on the first day, the CS score differed significantly between the two groups: terbutaline/3% NaCl (treatment group) vs terbutaline/0.9% NaCl (control group). *$p < 0.005$. INH = inhalation.

Sarrell E, Tal G, Witzling M, et al.

Results

- (2) Difference in hospitalization rate
  - 2 patients in 3% saline group
  - 3 patients in 0.9% saline group
  - Did not reach statistical significance

Sarrell E, Tal G, Witzling M, et al.

Nebulized 3% HS in Hospitalized Infants with Viral Bronchiolitis

- Randomized, double-blind, controlled trial in 52 hospitalized infants
- Group 1: Epinephrine in 0.9% saline solution
- Group 2: Epinephrine in 3% saline solution
- q8h

- Exclusion Criteria:
  - Cardiac disease
  - Chronic respiratory disease
  - Previous wheezing episode
  - Age > 12 months
  - Oxygen saturation of room air < 85%
  - Obtunded conciousness
  - Progressive respiratory failure requiring mechanical ventilation

Mandelberg A, Tal G, Witzling M, et al

Results

- Primary outcome:
  - Duration of hospitalization
  - Change in clinical severity score after inhalations each day

	Epinephrine + 0.9% Saline	Epinephrine + 3% Saline	p value
Duration of hospital stay in days	4 ± 1.9	3 ± 1.2	< 0.05
CS Scores (baseline)	8.08 ± 1.3	8.29 ± 1.3	NS
↓ in CS after tx (Day 1)	3.5%	7.3%	< 0.001
↓ in CS after tx (Day 2)	2%	8.9%	
↓ in CS after tx (Day 3)	4%	10%	

Mandelberg A, Tal G, Witzling M, et al

Results

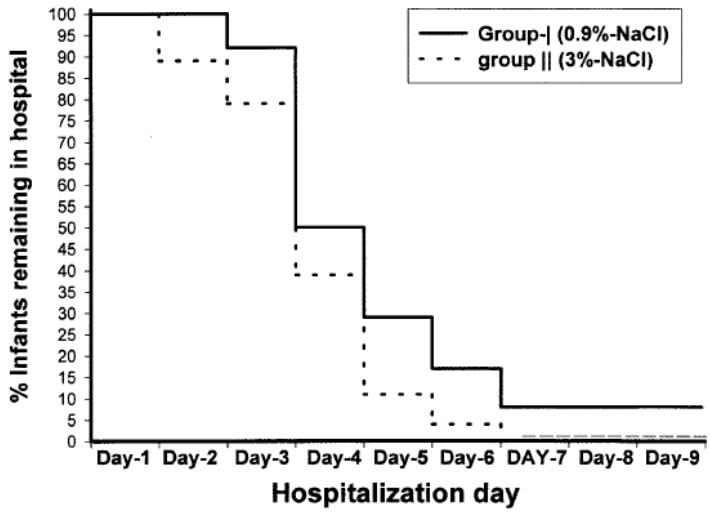


FIGURE 1. The percentage of infants remaining in the hospital each day for each group.

Mandelberg A, Tal G, Witzling M, et al

Results Continued

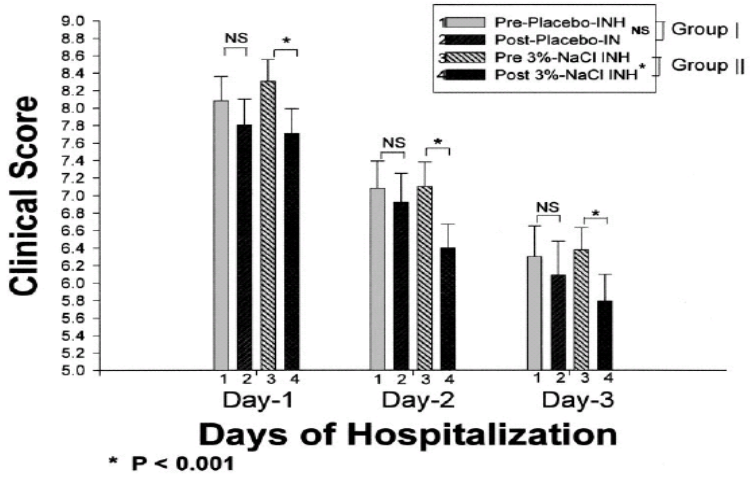


FIGURE 2. The clinical severity scores in group 1 and group 2. The fall of the clinical score after the inhalation therapy was NS in group 1 on the first, second, and third days after hospital admission. In group 2, significant differences were observed on each of the first 3 days ($p < 0.001$). Also, these falls in clinical scores differed significantly between the two groups on each of these days. IN, INH = inhalation.

Mandelberg A, Tal G, Witzling M, et al

Nebulized HS in the Treatment of Viral Bronchiolitis in Infants

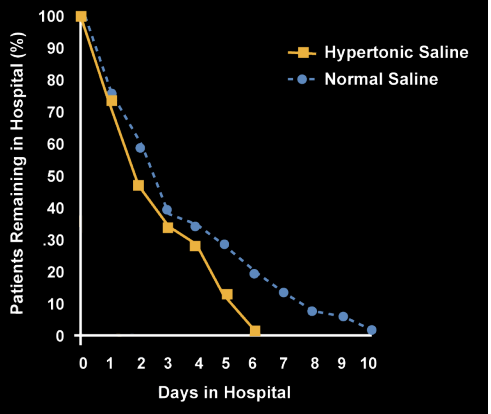
- Prospective, randomized, double-blinded, controlled, multicenter trial in 96 infants
- Group 1: Nebulized 3% saline solution
- Group 2: Nebulized 0.9% saline solution
- Q2h x 3 doses, q4h x 5 doses then q6h until discharge

- Exclusion Criteria:
  - Previous wheezing episode
  - Chronic cardiopulmonary disease or immunodeficiency
  - Critical illness at presentation requiring admission to intensive care
  - Use of nebulized HS within previous 12 hours
  - Premature birth (gestation age $\leq$ 34 weeks)

Kuzik B, Al Qadhi S, Kent S, et al

Hypertonic Saline for Bronchiolitis

- Reduction in LOS 26% with hypertonic saline
  - 2.6 $\pm$ 1.9 days (hypertonic saline) vs 3.5 $\pm$ 2.9 days (normal saline)
- Trend for greater improvement in infants <6 months



Kuzik BA, et al. *J Pediatr.* 2007;151(3):266-270.

Nebulized HS without Adjunctive Bronchodilators in Children with Bronchiolitis

- Retrospective cohort study of infants hospitalized with bronchiolitis
- N = 158 patients
  - 4 excluded (BPD-2, CLD-1, trisomy 21-1)
- Exclusion Criteria:
  - Bronchopulmonary dysplasia
  - Chronic lung disease
  - Neuromuscular impairment
  - Immunodeficiency
  - Congenital heart disease

Ralston S, Hill V, and Martinez M.

Results

- Primary outcome:
  - Rate of adverse reactions to 3% saline solution
  - Methods of delivery of therapy
    - With bronchodilators, within 4 hours after bronchodilator administration, or alone
- Four respiratory adverse events occurred among 377 doses administered without adjunctive bronchodilators (1% adverse event rate)

Ralston S, Hill V, and Martinez M.

Results

TABLE 3. Adverse Event Rates Associated With Nebulized 3% Saline Solution Administered Without Adjunctive Bronchodilators ($N = 377$)

Type of Event	Rate, Estimate (95% CI), %
Any documented event	1.0 (0.3–2.8)
Events resulting in discontinuation of therapy	0.5 (0.02–2)
Events characterized as bronchospasm	0.3 (<0.01–1.6)

Ralston S, Hill V, and Martinez M.

Clinical Recommendations

- Use of 3% HS should be considered in patients with viral bronchiolitis
  - Decreases length of hospital stay by approximately 1 day
  - Reduces the clinical severity score
  - Can be added to albuterol or epinephrine
  - Safe

Conclusions

- Evidence suggests that hypertonic saline 3% administered early and regularly in mild to moderate bronchiolitis results in decreased severity of symptoms and can reduce the total hospital stay
- The most common dose in clinical trials was 4 ml 3% saline
  - Q8h or q6h

Asthma

Wheezing

Daily or Intermittent Budesonide in preschool children with Recurrent Wheezing

NEJM; 2011:365(21):1990-2001

- N=278
- Age 12 to 53 months
- During the previous year
  - At least 4 episodes of wheezing
  - At least 3 episodes of wheesing and use of a controller medication for > 3 months
  - Positive values on a modified API
  - At least one exacerbation requiring systemic corticosteroids, urgert or emergency care, or hospitalization

Daily or Intermittent Budesonide in preschool children with Recurrent Wheezing

NEJM; 2011:365(21):1990-2001

- Randomized
  - Intermittent high dose regimen (1 mg twice daily for 7 days)
  - 500 mcg nightly
  - Matching placebos
- No significant difference
  - Frequency of exacerbations (0.95 vs 0.97) exacerbations per year
  - Time to 1st exacerbation
  - Mean exposure of budesoide was 104 mg less with the intermittent regimen

- What is the effect of administration of inhaled corticosteroids on adult height?

Effect of Inhaled Glucocorticoids In childhood on adult height

NEJM. 2012;367:904-12

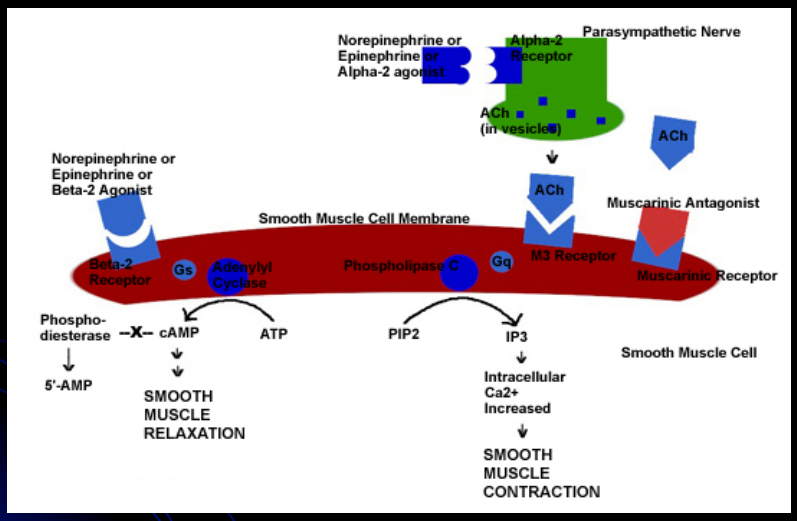
- Measured adult height in 904/1041 of the participants (90.6%) in the Childhood Asthma Management Program
  - Mean adult height was 1.2 cm lower
    - Larger daily dose in the 1st 2 years had a greater effect on adult height
    - Decrease was not progressive or cumulative
    - Greater in whites than other races
    - Greater the younger at study entry

Ipratropium in status asthmaticus

- Albuterol 2.5 mg + ipratropium 500 mcg inhaled q20 minutes x 3 doses compared to albuterol 2.5 mg
  - Statistical reduction in hospital admissions

Mechanism

- Frequent Albuterol rescue threapy is associated with:
  - Down regulation of Beta receptors



Corticosteroids in status asthmaticus

- 2 mg/kg/24h
  - Maximum 60 mg/24h
- Why do we give corticosteroids in asthma exacerbations?

Corticosteroids in asthma

- Up-regulate beta-receptors
- 4 hours
- Anti-inflammatory effect
- 24 – 36 hours

Tiotropium in asthma poorly controlled with standard combination therapy

NEJM. 2012: September 3rd

- N=912 patients
  - Inhaled corticosteroids and LABA
  - Compared the effect on lung function and exacerbations of adding tiotropium 5 mcg or placebo x 48 weeks
  - FEV1 80% or less
  - Hx: 1 severe exacerbation in the past year

Tiotropium in asthma poorly controlled with standard combination therapy

NEJM. 2012: September 3rd

- Mean FEV1 62%
- Mean age 53 years
  - Time to 1st exacerbation 282 vs 226 days
    - Overall reduction 21%
  - Change in peak FEV1 from baseline
    - 86 ± 34 ml in trial 1 (p = 0.01)
    - 154 ± 32 ml in trial 2 (p = 0.001)
    - Modest sustained bronchiodilation

Step-up therapy for children with uncontrolled asthma receiving corticosteroids

NEJM: 2010:362:975-85

- 182 children – 100 mcg fluticasone BID
  - 3 blinded stop up therapies in random order for 16 weeks
    - 250 mcg fluticasone BID
    - 100 mcg fluticasone + LABA
    - 100 mcg fluticasone + LTA (5 or 10 mg montelukast)
  - Exacerbations
  - Asthma control days
  - FEV1

Step-up therapy for children with uncontrolled asthma receiving corticosteroids

NEJM: 2010:362:975-85

- Nearly all children had a differential response to each therapy
  - LABA > ICS or LTA
    - Better control at baseline predicted a better response to LABA
    - White race – better response to LABA
    - Black patients least response to LTA

Questions?