Asthma: Experience counts ?
Airway Obstruction

19 yr old, mild asthmatic
Silent chest
Mechanism of dynamic hyperinflation in the setting of severe airflow obstruction. Reproduced with permission from Levy and coworkers [7].
Homer – *Iliad* 2700 years ago:
A warrior dies at the end of battle with “asthma and perspiration”

Hippocrates – 460-360 BC
asthma, dyspnea, tachypnea, orthopnea used interchangeably

Aretaeus of Cappodocia – ? 50 – 130 AD
“cheeks are ruddy, eyes protuberant as if from strangulation....
they breathe standing as if desiring to draw in all the air they can possibly inhale”.

Marketos and Ballas. J Asthma 1982
More recently

John Floyer - 1698
“laborious respiration with lifting of the shoulders and wheezing”

Stewart and Gibson – 1896 (Stedman. 20th Century Practice)
“The treatment of asthma involves the treatment of patients between and during fits.

1. To allay the spasm during the paroxysm;
2. To find out and remove the exciting cause....
3. to treat the complications and sequelae”.

From Chu and Drazen. 
Am J Respir Crit Care Med 2005
Pathophysiology

Bronchospasm
Mucosal oedema
Mucous plugging
Asthma Pharmacotherapy

1. Anticholinergic Belladonna related alkaloids
2. Non-anticholinergic bronchodilator stimulation
3. Corticosteroids
4. Specifically targeted asthma treatments
   (cromones, antileukotrienes, anti-IgE)
Stewart and Gibson – 1896 (Stedman. 20th Century Practice)
Primary treatment was the use of belladonna alkaloids; often delivered by smoking ‘asthma cigarettes’.

*Smoking tobacco benefits a few, but the addition of a little Stramonium to tobacco is of far greater service*

Osler – 1914 *Belladonna* “may be given in solution or in the form of cigarettes.... contains some plant of the order *Solanaceae*. .. excellent cigarettes are now manufactured and asthmatics try various sorts...”

‘Smoking Weed a century before Trudeau’
Stramonium
Osler: Hypodermic injections of Pilocarpine are effective in the treatment of asthma

Solanaceae: Nightshade family

Many alkaloids with invaluable pharmaceutical properties: anti-cholinergic (scopalamine, hyoscine)
Ipratropium Bromide (Atrovent)

• Introduced in the 1980’s
  Trial by Easton et al; COPD; compared with albuterol; equipotent NEJM 1986

• Not FDA approved for rescue treatment of asthma
• Nor approved in Canada

Mechanism of action not clear but likely inhibition of reflex bronchospasm mediated by cholinergic pathways
Non-anticholinergic Bronchodilators

Methyl Xanthines: Aminophylline

- coffee – mentioned in Osler *Principles and Practice of Medicine* 1914
- introduced in 1940s non selective phosphodiesterase inhibitor (increase cAMP)
- many other mechanisms of action
- small therapeutic window – risks considered greater than benefits

Direct Adrenergic Bronchodilators

- Dramatic response to IV adrenaline in 3 patients not responding to usual treatment
  Melland B. *Lancet* 1910
- Ephedrine used in 1926
- MDI introduced in 1950s for adrenaline and isoproterenol associated with epidemic of deaths
Nebulised adrenaline introduced in 1930s

Specific $\beta_2$ agonists for inhalation developed in 1960s and 70s

Terbutaline and Salbutamol
Rapid onset and longer duration of action

Selective long acting $\beta_2$ agonists developed used in conjunction with other agents (fenoterol, salmetrol)
FIG. 1. Mean change in PaCO₂ during iv infusion of salbutamol (n = 11) and isoproterenol (n = 31) in those patients that responded to bronchodilator therapy.
Fig. 2. Percentage change in heart rate with time, in patients successfully treated with iv salbutamol (n=11) and isoproterenol (n = 31).

Bohn et al. Crit Care Med. 1984
"..there is no doubt that in the 5 cases reported, corticotrophin and cortisone brought about changes that could not have been produced with any other known method of treatment"
What were we doing?
# Severe Acute Asthma in a Pediatric Intensive Care Unit: Six Years’ Experience

89 patients (125 admissions)
41 ventilated (33%)
77% Hypercapnia (PaCO$_2$ > 45)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_2$ agonists (nebulized)</td>
<td>100%</td>
</tr>
<tr>
<td>Theophylline</td>
<td>99%</td>
</tr>
<tr>
<td>Steroids</td>
<td>94%</td>
</tr>
<tr>
<td>Ipratropium Bromide</td>
<td>10%</td>
</tr>
<tr>
<td>Salbutamol IV</td>
<td>38%</td>
</tr>
<tr>
<td>Isoproterenol IV</td>
<td>10%</td>
</tr>
</tbody>
</table>

Outcome..... is excellent provided optimal use of bronchodilators and steroids and Judicious selection for those requiring ventilation

Stein R et al. Pediatrics 1989
Efficacy, results and Complications in Mechanical Ventilation of Children with Severe Asthma

79 Admitted over 32 months
19 ventilated

Aminophylline
Nebulised salbutamol
Hydocortisone
IV salbutamol
IV Isoproterenol

Muscle relaxation:
Strictly controlled with Pancuronium

Principles of Ventilation

• Avoid air trapping
• Slow rate
  - long expiratory time
  - short inspiratory time
• Tolerate high $\text{CO}_2$ (Darioli and Paret. ARRD. 1984)
• Correct Hypoxemia
• Beware dynamic hyperinflation
Since then........
Measurement of intrinsic positive end-expiratory pressure. Reproduced with permission from The McGraw-Hill Companies [64].
Mechanism of dynamic hyperinflation in the setting of severe airflow obstruction. Reproduced with permission from Levy and coworkers [7].

Stather et al. Critical Care. 2005
Bronchoscopy

Mucous plugs and casts

Allow for toilette and instillation of mucolytic

Safe
Well tolerated
Decreased time to extubation and LOS in ICU

Maggi JC et al. Paediatr Pulmon 2012
Khan M. Chest 2014
Why Is Mg Good for Asthma?

- Direct bronchodilator
- Calcium antagonist
- Inhibits acetylcholine release from nerve terminals
- Inhibits histamine release
- Up-regulates $\beta_2$ receptors
- Reduces neutrophils in inflammatory response
Magnesium

Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial

Colin Powell, Ruwanthi Kolamunnage-Dona, John Lowe, Angela Boland, Stavros Petrou, Iolo Doull, Kerenza Hood, Paula Williamson, on behalf of the MAGNETIC study group

Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial

Steve Goodacre, Judith Cohen, Mike Bradburn, Alasdair Gray, Jonathan Benger, Timothy Coats, on behalf of the 3Mg Research Team*
Magnesium

Overall the two trials need to be considered in view of all of the evidence.

Both nebulised and inhaled MgSO$_4$ *seem* efficacious in children with severe acute asthma.

...evidence of efficacy of inhaled MgSO$_4$ in adults is limited.

IV MgSO$_4$ should *be restricted* to those patients with severe asthma not responsive to bronchodilators.

Rowe B. Lancet 2013
Isoflurane-JHU PICU Experience

• 18/268 (6.7%) of patients admitted required mechanical ventilation
• 7/18 (39%) treated with isoflurane – mean duration 14 H
• 3/7 (43%) of patients required vasopressor therapy for hypotension
• All patients who received isoflurane had an increase in pH and decrease CO₂
• 5/7 (71%) were extubated within 24 H of isoflurane initiation
• One child died from severe anoxic brain injury sustained prior to arrival to the PICU
Isoflurane Effects-JHU PICU

Mean Change in pCO2 with Isoflurane Administration

Similar improvements in pH
## ECLS for Asthma

<table>
<thead>
<tr>
<th></th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>256</td>
<td>245</td>
</tr>
<tr>
<td>Mean (years)</td>
<td>7.05</td>
<td>40.2</td>
</tr>
<tr>
<td>% VV vs VA</td>
<td>62</td>
<td>77</td>
</tr>
<tr>
<td>Duration Mean (days)</td>
<td>7</td>
<td>7.6</td>
</tr>
<tr>
<td>% Discharged Alive*</td>
<td>77</td>
<td>75</td>
</tr>
</tbody>
</table>
ECMO Runs Reported to ELSO with Asthma

Number of runs reported to ELSO
How are we doing?
Critical Care for Pediatric Asthma: Wide Care Variability and Challenges for study

13,552 patients reviewed 2004-2008

Ipratropium 41-84%
Terbutaline 11-74%
MgSO4 23-64%
Xanthines 0-46%

60% Intubated before PICU admission
Use of NIV more in non – academic sites
Complications were rare
Mortality more rare

Bratton et al. PCCM 2012
Fatal and Near-Fatal Asthma in Children

- 5 yr review of 261 children
- 178 (69%) intubated prior to admission
- 218 (84%) no complications
- 11 (4%) deaths – 10 pre hospital arrest

- NIV in 16%
- Heliox 30%
- Inhalational anaesthetic 3%
- Bronchoscopy 7%
- ECMO in 3 patients

If you come to us......

1987
Inhaled ß-agonists
IV Salbutamol
IV steroids
Inhaled anticholinergic

Ventilation
Muscle relaxation
Less permissive hypercapnia

2014
MgSO₄
Ipratropium
More permissive CO₂
NIV

Less intubation
Higher tolerance
Despite variability in practice, overwhelming majority do well
Most deaths are sudden severe asthma outside our domain

Near-Fatal Asthma:
An Ounce of Prevention May be Worth More than a Pound of Cure

Lee and Brilli et al. J Pediatr 2012
Asthma Management Continuum
Children (6 years and over) and Adults

- **Controlled**
  - Fast-acting Bronchodilator on Demand
  - Environmental Control, Education and Written Action Plan
  - **Confirm Diagnosis**

- **Uncontrolled**
  - Adjust Therapy to Achieve and Maintain Control
  - Regularly Reassess
    - Control
    - Spirometry or PEF
    - Inhaler technique
    - Adherence
    - Triggers
    - Comorbidities

### Inhaled Corticosteroid (ICS)*
*Second-Line: Leukotriene Receptor Antagonist (LTRA)*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose</th>
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<tbody>
<tr>
<td>≥12 yrs</td>
<td>≤250 mcg/day†</td>
</tr>
<tr>
<td>6-11 yrs</td>
<td>≤200 mcg/day†</td>
</tr>
<tr>
<td>6-11 yrs</td>
<td>251 – 500 mcg/day†</td>
</tr>
<tr>
<td></td>
<td>201 – 400 mcg/day†</td>
</tr>
<tr>
<td>≥12 yrs</td>
<td>&gt;500 mcg/day †</td>
</tr>
</tbody>
</table>

- **≥12 yrs:** Add LABA*
- **6-11 yrs:** Increase ICS
- **≥12 yrs:** Add LTRA
- **6-11 yrs:** Add LTRA

- **Anti-IgE‡**
- Prednisone

† HFA Beclomethasone or equivalent; *Second-line: LTRA; ‡ Approved for 12 years and over
Experience counts?