Status Asthmaticus in practice

Robert Silverman MD, MS
What Is Asthma?

• A chronic condition
• Characterized by respiratory complaints ranging in course from episodic to persistent, and from mild to incapacitating
• A spectrum of vulnerability to triggers
• Poorly controlled asthma can lead to more severe episodes, hospitalizations, or death
Asthma Fact Sheet
Global

• About 300 million people in the world currently have asthma

• It is estimated that there may be an additional 100 million people with asthma by 2025

• About 255,000 people died of asthma in 2005

• Asthma accounts for about 1 in every 250 deaths worldwide

Global Burden of Asthma, GINA, 2004
Impact Of Asthma

- 29.8 million people in US diagnosed with asthma in their lifetime
- 19.8 million currently diagnosed with asthma
- 11.0 million have experienced an asthma “attack” in the previous 12 months

Impact of asthma in the USA

• 1.9 million ED visits
• 484,000 hospitalizations
• 4,261 deaths

2002, CDC National Center for Health Statistics
Economic Data: Hospitalizations

- Average cost of an asthma hospitalization has increased from $5662 in 1993 to $10,036 in 2002

- This has occurred even though the LOS has decreased from 4.9 to 3.8 days

- 58% of all hospitalizations are in adults aged 25 and older; 72% of all hospitalization costs incurred in same age groups

- Total asthma expenditures: 50% for hospitalizations

Frequency of Emergency Room Visits
Hospital Emergency Room Visits for Asthma in the Past Year

- Total (N=2509): 23%
- Adults (n=1788): 19%
- Children (n=721): 32%

Base: All respondents (unweighted N=2509).
Frequency of Hospitalization Hospitalized for Asthma in the Past Year

- Total (N=2509): 9%
- Adults (n=1788): 7%
- Children (n=721): 12%

Base: All respondents (unweighted N=2509).
Pathology of Asthma

Normal Lungs  Asthma

Source: "What You and Your Family Can Do About Asthma" by the Global Initiative For Asthma
Created and funded by NIH/NHLBI
What is status asthmaticus?

- 37 year old female; asthma since childhood
- Has asthma symptoms at least several times a week
- Uses her albuterol inhaler to treat episodically
- Comes to ER 2-3 times/year for asthma worsening
- Hospitalized every 2 years for asthma
- Had some cold/upper respiratory infection symptoms 4-5 days ago
- Starting using her ‘pump’ more frequently 3-4 days ago because of increasing shortness of breath and wheezing
Status Asthmaticus

- She started using her pump every 2-3 hours about 2 days ago
- Unable to sleep for past 2 nights because of difficulty breathing
- Unable to care for kids or go to work for past 2 days
- Using her pump every hour, without relief, until she ran out of her medications
- Couldn’t get an appointment to see her doctor that day
- Family convinced her to go to the ER
Typical profile

- She had difficulty walking into the ER because of shortness of breath
- Has difficulty finishing her sentences because she can’t catch her breath
- Using all the muscles in her neck and chest wall to force air into her lungs
- Is wheezing audibly every time she breathes
- Has a very fast pulse and less oxygen in her bloodstream than normal
- Feels like she can’t get any air in
- Her FEV% predicted in 24% (normal =100%)
Treatment

- Treatment consists of bronchodilators
- Beta-agonists (proventil, albuterol) are the mainstay of therapy: ‘gold standard’
- Work quickly, can be given in repeated doses, are well tolerated
- Typically administered as a nebulizer; given every 20-60 minutes in the ED
- Most potent treatments for acute asthma
- All other treatments are considered adjuncts to beta-agonists
Other treatments

- Ipratropium
- Magnesium
- Leukotriene modifiers
- Steroids
Treatments

• 2 bronchodilator treatments were given
• Her FEV1 improved only to 30%
• She was still very uncomfortable and struggling
• She was admitted to the PCU for observation and further treatment
FEV1 Response to Treatment Over Time: Divided by Median FEV1 (40.5%) at Time 60

Time (minutes)

FEV1 % Predicted

Below Median
Above Median
Summary

- Beta-agonists are the mainstay of treatment for acute asthma
- Systemic steroids may take hours or longer to work, and the response is variable
- Even with bronchodilator and steroid-based therapy, ED treatment failures range up to 20%.
- Therefore, additional treatments are needed to prevent hospitalization, ICU admissions, or near-fatal/fatal asthma.
Study Objectives

• Determine if MN-221 can improve outcomes in asthmatics who are refractory to standard care
• Improve FEV1 (lung function)
• Hasten recovery
• Prevent hospitalization
• Prevent admissions to the ICU
• Prevent further deterioration of asthma
FEV1 Response By Treatment

FEV1 % Predicted

Time (minutes)

T 0  T 20  T 40  T 60  T 120  T 180  T 240  T 360

Standard
Therapy 1
Therapy 2
Therapy 3
Therapy 4
Intravenous Sympathomimetics
Intravenous beta-agonists
IV albuterol, epinephrine, terbutaline

- Concept: the drug class of beta-agonists are the most effective treatments for acute asthma
- Delivering the treatments intravenously may deliver more drug and to obstructed areas of the lung
- Can be used in children who are not responding to usual beta-agonist nebulizer therapy
- Less frequently used in adults because of concern of side effects (rapid heart rates)
- MN-221 may be more effective and have fewer side effects than currently available IV beta-agonists, making it more desirable for both children and adults
IV epinephrine in adult ED patients

- ED of Western Hospital (250 beds, census 32,000), Melbourne Australia
- Age 18-55 years, triage levels 1-3
- 220/1169 (19%) patients received IV epinephrine
- Side effects: chest pain in 2 patients (no EKG changes or enzymes); 2 SVT
Comparison of FEV1 Response Between 4 Groups

**Group 1:** initial FEV1 < 30% and Δ FEV over 60 minutes < 11.

**Group 2:** initial FEV1 < 30% and Δ FEV over 60 minutes ≥ 11.

**Group 3:** initial FEV1 ≥ 30% and Δ FEV over 60 minutes < 10.

**Group 4:** initial FEV1 ≥ 30% and Δ FEV over 60 minutes ≥ 10.

<table>
<thead>
<tr>
<th></th>
<th>NEB Group (n = 22)</th>
<th>IV Group (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>41 ± 17</td>
<td>39 ± 13</td>
</tr>
<tr>
<td>Males/females</td>
<td>10/12</td>
<td>17/8</td>
</tr>
<tr>
<td>Duration of asthma, yr</td>
<td>14 ± 13</td>
<td>14 ± 12</td>
</tr>
<tr>
<td>Previous ICU hospitalization, n (%)</td>
<td>14 (64)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Oral steroids, n (%)</td>
<td>5 (22)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Duration of attack, h</td>
<td>14 ± 12</td>
<td>14 ± 16</td>
</tr>
<tr>
<td>Range, h</td>
<td>2–48</td>
<td>1.5–72</td>
</tr>
<tr>
<td>Number of β-agonist inhalations</td>
<td>14 ± 11</td>
<td>19 ± 20</td>
</tr>
<tr>
<td>PEF, L/min</td>
<td>59 ± 61</td>
<td>78 ± 76</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>51 ± 8</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>118 ± 19</td>
<td>115 ± 19</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>152 ± 28</td>
<td>153 ± 28</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>89 ± 14</td>
<td>88 ± 17</td>
</tr>
<tr>
<td>Clinical index (0 to 15)</td>
<td>10.0 ± 2.1</td>
<td>10.2 ± 2.3</td>
</tr>
<tr>
<td>Plasma albuterol concentration, µg/L</td>
<td>2.9 ± 2.4</td>
<td>3.6 ± 6.1</td>
</tr>
</tbody>
</table>

* Definition of abbreviations: PEF = peak expiratory flow; PaCO₂ = arterial carbon dioxide pressure.
* The results are mean ± SD. The groups do not differ statistically for any of the parameters.
Figure 1. Peak expiratory flow (PEF), PaCO₂ values, and clinical index ratings (C1) before and after 1 h of treatment in the NEB group (solid line) and in the IV group (broken line). Mean values are indicated for both groups.

Fig. 1. – Timing of treatment, recording of effects and blood analysis. Salb: salbutamol; inhal: inhalation; PEF: peak expiratory flow; HR: heart rate; BP: blood pressure; bw: body weight.

**Table 1.** – Patient characteristics on entry into the study (mean±sd or percentage of patients)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nebulization (n=87)</th>
<th>Infusion (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>58±12</td>
<td>55±13</td>
</tr>
<tr>
<td>Males</td>
<td>49%</td>
<td>56%</td>
</tr>
<tr>
<td>PEF l·min⁻¹</td>
<td>170±47</td>
<td>166±70</td>
</tr>
<tr>
<td>PEF % of predicted</td>
<td>33±9</td>
<td>31±8</td>
</tr>
<tr>
<td>Pulse rate beats·min⁻¹</td>
<td>112±9</td>
<td>111±10</td>
</tr>
<tr>
<td>Blood pressure systolic mmHg</td>
<td>145±20</td>
<td>140±21</td>
</tr>
<tr>
<td>Blood pressure diastolic mmHg</td>
<td>87±11</td>
<td>88±12</td>
</tr>
<tr>
<td>β₂-agonists dose aerosol</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>β₂-agonists</td>
<td>37%</td>
<td>43%</td>
</tr>
<tr>
<td>β₂-agonists nebulization</td>
<td>11%</td>
<td>21% p&lt;0.05</td>
</tr>
<tr>
<td>Theophylline oral</td>
<td>80%</td>
<td>76%</td>
</tr>
<tr>
<td>Corticosteroids inhalation</td>
<td>67%</td>
<td>62%</td>
</tr>
<tr>
<td>Corticosteroids oral</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Ipratropium inhalation</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

| Plasma terbutaline level n mol·l⁻¹ (n=124) | 22±18 | 24±20 |
| Plasma salbutamol level n mol·l⁻¹ (n=119)  | 30±29 | 24±26 |
| Plasma theophylline level μ mol·l⁻¹ (n=138) | 35±22 | 34±25 |

PEF: peak expiratory flow.
Fig. 2. – PEF in patients treated with inhaled salbutamol (A) and intravenously infused salbutamol (B). Significance levels refer to individual changes from initial values (*p<0.05; ***p <0.001). PEF: peak expiratory flow; Salb: salbutamol.

Fig. 4. – Pulse rate in patients treated with inhaled salbutamol (A) and intravenously infused salbutamol (B). Significance levels refer to individual changes from initial values (***: p<0.001).

Comparison of intravenous and nebulized salbutamol in treatment of severe asthma

Results before and after receiving salbutamol (10 milligrams) by nebulizer or by intravenous infusion (900 micrograms over 45 minutes). Blood gas pressures measured while breathing 40% oxygen.

Intravenous and nebulized salbutamol treatment in severe acute asthma

<table>
<thead>
<tr>
<th>Salbutamol treatment</th>
<th>Intravenous</th>
<th>Nebulised</th>
</tr>
</thead>
<tbody>
<tr>
<td>No and sex</td>
<td>26M, 11F</td>
<td>23M, 12F</td>
</tr>
<tr>
<td>No atopic</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Mean (range) age (years)</td>
<td>37 (16-69)</td>
<td>35 (16-66)</td>
</tr>
<tr>
<td>Mean (SD) peak flow rate (l/min):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>91 (37.2)</td>
<td>111 (53.4)</td>
</tr>
<tr>
<td>On discharge</td>
<td>360 (160)</td>
<td>359 (107)</td>
</tr>
<tr>
<td>Peak flow rate on admission expressed as % of predicted mean (SD)</td>
<td>20.4 (6.9)</td>
<td>24 (9.1)</td>
</tr>
<tr>
<td>Mean (SD) blood gas tension on admission (kPa):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen tension</td>
<td>8.8 (1.1)</td>
<td>9.1 (1.2)</td>
</tr>
<tr>
<td>Carbon dioxide tension</td>
<td>4.9 (1.0)</td>
<td>4.7 (0.7)</td>
</tr>
</tbody>
</table>

Type and severity of asthma in patients treated with intravenous and nebulized salbutamol

Cheong et al., Intravenous beta agonist in severe acute asthma., *British Medical Journal*, 1988: 297: 448-450, Table 1.
Intravenous and nebulized salbutamol treatment in severe acute asthma

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Intravenous group</th>
<th>Nebulised group</th>
<th>Difference (significance)</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0 (p&gt;0.1)</td>
<td>-3.5 to 3.6</td>
</tr>
<tr>
<td>0.5</td>
<td>6.3 (5.9)</td>
<td>6.3 (8.5)</td>
<td>0.0 (p&gt;0.1)</td>
<td>-3.9 to 8.6</td>
</tr>
<tr>
<td>1.5</td>
<td>13.2 (12.4)</td>
<td>10.9 (13.9)</td>
<td>2.3 (p&gt;0.01)</td>
<td>-0.2 to 13.5</td>
</tr>
<tr>
<td>2.5</td>
<td>17.3 (15.6)</td>
<td>10.6 (13.3)</td>
<td>6.7 (p&gt;0.05)</td>
<td>0.7 to 16.7</td>
</tr>
<tr>
<td>3.5</td>
<td>20.7 (19.8)</td>
<td>12.0 (13.5)</td>
<td>8.7 (p&lt;0.025)</td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>25.2 (19.9)</td>
<td>14.3 (15.9)</td>
<td>10.9 (p&lt;0.01)</td>
<td>2.4 to 19.1</td>
</tr>
</tbody>
</table>

Percentage increase in peak flow rate in patients treated with salbutamol intravenously and via nebulizer. Intravenous group shows a greater increase in peak flow rate (25.2% versus 14.3% after 4-5 hours).

Cheong et al., Intravenous beta agonist in severe acute asthma., British Medical Journal, 1988: 297: 448-450, Table 2.
Changes in pulse rate in intravenous salbutamol group and nebulized salbutamol group

IV Salbutamol
Browne et al Lancet 1997 349:301-05

• Children who failed 5.0mg nebulized salbutamol were randomized into 5.0mg nebulized salbutamol every 20 minutes with or without 15mcg/kg salbutamol over 10 minutes. All received IV steroids

• Phase two began at 2 hours, where an aggressive inpatient regimen of continuous salbutamol was given to all patients

• Total n=29
Intravenous salbutamol treatment for severe acute asthma

Signs of acute severe asthma in patients treated with salbutamol intravenously and via nebulizer

Browne et al., Randomised trial of intravenous salbutamol in early management of severe acute asthma in children, *The Lancet*, 1997: 349: 301-305, Fig. 2.
3 arms: Standard care in children plus:
- IV salbutamol 15mcg/kg, or
- Inhaled ipratropium 250mcg x 3, or
- IV salbutamol plus inhaled ipratropium

All patients received IV steroids and repeat nebulized salbutamol

Results: recovery time shorter for IV salbutamol than inhaled ipratropium

Adding nebulized ipratropium to IV salbutamol did not improve outcome
## Leading Causes of Death, U.S. 2004

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Deaths</td>
<td>2,397,615</td>
</tr>
<tr>
<td>Heart disease*</td>
<td>652,486</td>
</tr>
<tr>
<td>Cancer</td>
<td>553,888</td>
</tr>
<tr>
<td>Cerebrovascular diseases (stroke)</td>
<td>150,074</td>
</tr>
<tr>
<td>COPD and allied conditions†</td>
<td>121,987</td>
</tr>
<tr>
<td>Accidents</td>
<td>112,012</td>
</tr>
<tr>
<td>Diabetes</td>
<td>73,138</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>65,965</td>
</tr>
<tr>
<td>Influenza and pneumonia</td>
<td>59,664</td>
</tr>
<tr>
<td>Nephritis</td>
<td>42,480</td>
</tr>
<tr>
<td>Septicemia</td>
<td>33,373</td>
</tr>
<tr>
<td>All other causes of death</td>
<td>532,648</td>
</tr>
</tbody>
</table>

* Includes 451,326 deaths from CHD.
† Chronic lower respiratory diseases.

Prevalence of current asthma, by age group and sex, Australia, 2001

## Hospitalizations For Asthma 1999/US (CDC)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Number</th>
<th>Rate/10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>105,000</td>
<td>55</td>
</tr>
<tr>
<td>5-14</td>
<td>85,000</td>
<td>22</td>
</tr>
<tr>
<td>15-34</td>
<td>77,000</td>
<td>10</td>
</tr>
<tr>
<td>35-64</td>
<td>138,000</td>
<td>13</td>
</tr>
<tr>
<td>≥65</td>
<td>73,000</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>478,000</td>
<td>18</td>
</tr>
</tbody>
</table>
Eotaxin Expression After Airway Challenge

FEV1 % Predicted: Response to Treatment Over 6 Hours

Time (minutes) vs. FEV1 % Predicted
Pathobiology

Airflow Limitation Is The Result Of Acute And Chronic Processes

• Acute
  – bronchoconstriction
  – airway edema
  – airway secretions
  – mucous plug formation
  – autopsy data: inflammation present in small and large airways
Ranking of the Prevalence of Current Asthma Symptoms in Adults by Country

Masoli et al., The global burden of asthma, *Allergy*, 2004, Fig. 3 (Written Questionnaire, 20-44 year old adults)
Clinical practice guidelines recommendations and survey responses for management of asthma in Australia and New Zealand

Archives of Disease in Childhood 2008; 93:307-312.