Status asthmaticus in the medical intensive care unit: A 30-year experience

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Summary
Objectives: To investigate the characteristics, trends in management (permissive hypercapnia; mechanical ventilation (MV); neuromuscular blockade) and their impact on complications and outcomes in Status Asthmaticus (SA).

Methods: We performed a retrospective observational study of subjects admitted with SA to a single multidisciplinary MICU over a 30-year period. All laboratory, radiologic, respiratory care, physician notes and orders were extracted from an electronic medical record (EMR) maintained during the entire duration of the study.

Results: Two hundred and twenty-seven subjects were admitted with 280 episodes of SA. While subjects reflected our regional population (52% Hispanic), African Americans were over-represented (22%) and Caucasians under-represented (21%). Thirty-eight percent reported childhood asthma, 27% were steroid dependent (10% in the last 10 years), and 18% had a recent steroid taper. One hundred and thirty-nine (61.2%) required intubation. The duration of hospitalization was similar between mechanically ventilated and non-ventilated subjects (5.8 ± 4.41 vs. 6.8 ± 7.22 days; p = 0.07). The overall complication rate remained low irrespective of the use of permissive hypercapnia or mode of mechanical ventilation (overall mortality 0.4%; pneumothorax 2.5%; pneumonia 2.9%). The frequency of SA declined significantly in the last 10 years of the study (12.4 vs. 3.2 cases/year).

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Introduction

Status asthmaticus (SA) is a life-threatening condition characterized by progressive respiratory failure due to asthma that is unresponsive to standard therapeutic measures. While overall mortality from asthma has failed to decline, there is minimal literature regarding the outcome of SA once patients reach the ICU. Most investigators report mortality rates of 6–38% with more recent studies reporting mortality less than 10%. Several reports suggest that mechanical ventilation (MV) in SA is associated with significant morbidity and mortality. Many patients admitted with SA will require ICU level care. Severe bronchoconstriction, mucous plugging, and air trapping make these patients challenging to manage, and optimal treatment strategies have not yet been delineated. In particular, ventilator strategies and complication rates are not well defined. However, the NAEP guidelines suggest that “permissive hypercapnia” or “controlled hypoventilation” should be utilized to reduce the risk of barotrauma. The goal of the present study was to characterize the clinical course of subjects with SA being treated in the ICU. To our knowledge, this study represents the largest reported series of SA in the literature. Our data span three decades, allowing a unique opportunity to study changes in prevalence, outcomes, and treatment strategies in SA.

Materials and methods

This study involves a retrospective review of 280 hospital admissions in 227 patients admitted to the medical ICU of the University of Texas Health Science Center — San Antonio between December 1980 through January of 2010 with severe exacerbation of asthma. The University Hospital is a 650 bed, urban, academic hospital located in San Antonio, Texas. The MICU is a 20-bed unit providing care for critically ill medical patients. An electronic medical record allowed for data collection including age, race, sex, use and type of MV, laboratory and radiographic reports, length of hospital stay, complications, and mortality.

All patients met the American Thoracic Society criteria for the diagnosis of asthma. Patient with a 10-pack year history of cigarette use or greater were excluded. Patients were considered to have recurrent SA if they had any prior ICU admissions for exacerbation of asthma. Adult-onset asthma was characterized as asthma that developed after age 17. A recent steroid taper was defined as oral corticosteroids within four weeks prior to admission.

Decisions regarding invasive or non-invasive ventilation were based on the judgment of the emergency department (ED) or ICU attending physician. In the first two decades most patients were treated with tidal volumes of 10–12 ml/kg. In the last decade low tidal volume strategies with permissive hypercapnia were exclusively employed. Ventilatory modes and settings were left to the discretion of the ICU attending. The use of neuromuscular blockers in SA patients is discouraged at our institution unless necessary for intubation to allow ventilator synchrony.

This research protocol was approved by the IRB of The University of Texas Health Science Center at San Antonio (# HSC20100125E). Statistical analysis was performed using Stata Statistical Software, version 9.3 (StataCorp, College Station, Texas). Comparisons between groups were made using Student’s t test, Fischer’s Exact Test, and analysis of variance (ANOVA). Results are expressed as mean ± standard deviation. All p-values <0.05 were considered significant.

Results

Between 1980 and 2010, 227 patients were admitted to the MICU with 280 episodes of SA. The average age of our population was 37.3 ± 14.87 years (range 16–77), with 147 (65%) female patients and 80 (35%) male patients. Ethnic groups included 118 (52%) Hispanic, 51 (22%) African American, 48 (21%) Caucasian and 12 (5%) others. The average age of asthma onset was 37.3 ± 14.9 years and 62% of all patients had adult-onset asthma. Recurrent SA was noted in 34 patients, yielding a rate of 15%. Among patients with recurrent disease, 20 had 2 episodes, 10 had 3 episodes, three had 4 episodes, and one had 5 episodes. Overall, 62 (27%) were steroid dependent, yet only 3/32 (9%) studied in the past 10 years were steroid dependent. A recent steroid taper was reported in 41 patients (18%) (Table 1).

The overall duration of asthma symptoms prior to admission was 3.65 ± 2.81 days, and duration of hospitalization was 5.77 ± 3.81 days. In our series, 139 patients (61.2%) required intubation and mechanical ventilation and 3 (1%) required non-invasive positive pressure ventilation. Length of time on MV was 3.42 days (range 8 h to 12 days), however, duration of hospitalization was not different between groups. Table 2 outlines differences in length of hospital stay, peak pH, lowest pH, and duration of symptoms between ventilated and non-ventilated patients.

The mode of ventilation and tidal volume varied greatly depending on the time period of the study. During the first 20 years, most patients (111/117) were treated with synchronized intermittent mandatory ventilation (SIMV); the remaining with assist control (ACV) or pressure control ventilation (PCV). During this time period, the average tidal volume was 725 ml (range 600–1000 ml) and peak pressures averaged 46.5 cm H2O (range 20–107 cm H2O). Only two patients were treated with PCV, both with poor outcomes (one acute myocardial infarction and death, another with anoxic brain injury). In the last 10 years, the majority (16/22) of patients were treated with continuous
Data are presented as mean ± SD or no. (%).

- Asthma onset before 17 yrs of age.
- Total 53 recurrent episodes in 34 subjects: 20 (2 episodes); 10 (3 episodes); and 1 (5 episodes).
- Oral corticosteroids use — no. (%) Steroid dependent Recent steroid taper
- Subjects— no. (%) 34 (15%) 53 (19%)
- Episodes — no. (%) 10 (3 episodes); 3 (4episodes); and 1 (5 episodes).
- Recent steroid taper: 41 (18%) mechanical ventilation (AC/CMV). SIMV was utilized in only four patients and PCV was used in the remaining two. Extrapolating from controlled hypoventilation data that was published during this time period, patients in the last 10 years were treated with lower tidal volumes. The average tidal volume in the more recent cohort was 545 ml (range 450–640 ml). The rate of neuromuscular blockade, and the preferential use of assist control ventilation.

## Discussion

The management of SA in the MICU has evolved in recent years despite a lack of randomized controlled trials to guide optimal therapy in these patients. The present study is unique in that it was conducted over a 30-year time period. The long-term nature of our study provides valuable information regarding the impact of recent trends in asthma management including permissive hypercapnia, avoidance of neuromuscular blockade, and the preferential use of assist control ventilation.

The demographics of our subjects with SA are in agreement with prior observations that note SA is more common in female patients and more common in African Americans. Sixty-five percent of our subjects were female and African American subjects were over-represented (22% vs. 6% in our patient population). Little data exist regarding the onset of asthma in subjects with SA and our study found the average age of onset of asthma to be 37.3 ± 14.9 years with 62% of subjects being identified with adult-onset asthma. One important finding in our study was the incidence of subjects presenting with recurrent SA (15%) and supports the concept that prior ICU admission for severe asthma is a major risk factor for life-threatening asthma. Additionally, exacerbation of asthma while receiving steroids or after a recent steroid taper should be assessed in the ED since 18% of our subjects presented during or after a steroid taper.
Our study supports the recent literature suggesting that the overall mortality rate in SA has declined significantly from early reports. As seen in previous studies, most deaths in patients with SA are related to secondary complications in the MICU or failure to receive appropriate care rather than refractory asthma itself. Some authors have concluded that the historically high morbidity and mortality rates associated with severe asthma were related to complications from MV. It has also been suggested that controlled hypoventilation strategies are a primary cause of improvements in clinical outcomes. Surprisingly, mortality rates did not differ between the earlier cohorts in which larger tidal volumes were employed compared to the more recent cohort which relied on permissive hypercapnia. Though the preferential use of assist control ventilation and permissive hypercapnia are widely accepted practices, this strategy of MV did not have a significant impact on mortality in the present study and this study was unable to establish clear benefit or harm related to the use of permissive hypercapnia.

The decision to use AC/CMV or SIMV modes of ventilation is perhaps even more controversial. Our study found no difference in outcomes between these two modes of ventilation. The use of PCV was not well studied in our population but was associated with poorer outcomes in our study, as the two most serious complications during the first 20 yrs of our study (death and anoxic brain injury) occurred in these patients. It is not clear whether the complications were related to the choice of ventilator mode, or if the use of PCV served as a marker for patients who were more severely ill. The successful use of PCV has been reported in a recent pediatric study of SA. Based on the current study the use of either AC/CMV or SIMV ventilator modes seem to be reasonable choices, and we recommend avoiding PCV until this mode of ventilation is studied in adults with SA. Adequate oxygenation, avoidance of dynamic hyperinflation, and close attention to inspiratory flow rates, $I/E$ ratio, and plateau pressures are likely far more important principles than the mode of ventilation utilized.

The use of neuromuscular blockade (NMB) in subjects intubated for SA is strongly discouraged. Leatherman et al. found an incidence of muscle weakness in asthmatic patients treated with NMB and steroids of 29%. A study by Adnet et al. evaluated the morbidity of intubated asthmatic patients receiving long-term (greater than 12 h) neuromuscular blockade in a retrospective cohort study from five centers. The occurrence of ventilator associated pneumonia, post-intubation myopathy, and duration of ICU stay was significantly higher in the neuromuscular blockade group. Additionally, multiple logistic regressions showed that neuromuscular blockade was the only independent predictor of overall morbidity and occurred in 18% in the neuromuscular group vs. 2% in the steroid only group. In our study neuromuscular blockade was predominately used at the time of intubation and only three subjects received neuromuscular blockade for greater than 12 h. Our overall rate of myopathy in subject receiving neuromuscular blockade of 19% (data not shown) was similar to that reported by Adnet et al. A recent study by Kessler et al., demonstrated that the risk of myopathy in SA was not correlated with the duration of NMB. Even subjects receiving NMB for $\leq$ 2 h had a 14% incidence of clinically significant weakness which was not significantly greater than subjects receiving more than 24 h of NMB.

Among the other complications noted during our study, electrolyte abnormalities were the most frequent (17–35%) but were mild and well tolerated. Pneumonia occurred in 2.9% of patients, and was more commonly seen in the recent cohort of patients (9.4% as compared to 2.0%). Hypotension was noted in 1.6% of patients overall, with a statistically significant increase during the last 10 years (9.4% vs. 4.8%). Most episodes of hypotension occurred immediately post-intubation and the duration of hypotension was generally very short. Complications in the immediate postintubation period are well described and dysrrhythmias or hypotension occurred in 10% of subjects in the report by Zimmerman et al. Early studies reported the risk of pneumothorax between 10 and 30% but recent studies suggest rates of 2–6%. Our study supports the more recent studies since pneumothorax occurred in 7/280 episodes of SA (2.5%). Three of these cases occurred in the ED prior to MV and were felt to be secondary to aggressive bag valve mask resuscitation of the patients immediately after intubation. No cases of pneumothorax were identified in the more recent cohort, where smaller tidal volumes were employed. Aside from pneumothorax, other serious complications included death, anoxic encephalopathy, and myocardial infarction. The rates for all severe complications, however, were low (ranging from 0.4% to 2.5%).

### Table 3 Complications of status asthmaticus.

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<tbody>
<tr>
<td>Death</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Anoxic encephalopathy</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>7 (2.8%)</td>
<td>0</td>
<td>7 (2.5%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (1.6%)</td>
<td>2 (6.3%)</td>
<td>6 (2.1%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>12 (4.8%)</td>
<td>3 (9.4%)</td>
<td>15 (5.4%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (2.0%)</td>
<td>3 (9.4%)</td>
<td>8 (2.9%)</td>
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<tr>
<td>Hypokalemia</td>
<td>89 (35%)</td>
<td>9 (28%)</td>
<td>98 (35%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>45 (18%)</td>
<td>3 (9.4%)</td>
<td>48 (17%)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>114 (46%)</td>
<td>6 (18%)</td>
<td>120 (43%)</td>
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- From myocardial infarction with secondary massive GI after anticoagulation.
- Glucose over 150 mg/dl.
One of the most striking findings in our study is the sharp decline in the occurrence of SA at our institution. From 1980 to 1999 our institution treated an average of 12.4 ICU patients with SA per year. During 2000–2010 this number dropped to 3.2 cases per year. It is well known that asthma prevalence and hospitalization rates are both increasing despite recent therapeutic advancements. The dramatic reduction in SA seen at our institution is likely multifactorial. Widespread use of inhaled corticosteroids, improved access to care, and advancements in ED management of asthma are factors that likely contributed to this decline. In support of this concept, a prospective asthma disease management study from our institution revealed that approximately 70% of asthmatics treated at our institution comply with their inhaled corticosteroid therapy. Despite the increasing prevalence of asthma, many patients who receive timely and appropriate care can likely avoid progression to SA.

Our study has several limitations. First, it is a single institution study with a retrospective design. Second, due to geographic location our population consisted primarily of Hispanic patients, who may have milder disease than other ethnic groups. As a result, it may be difficult to generalize our findings to other populations. Additionally, it could be argued that our extremely low mortality rate despite a high incidence of MV represents unnecessary intubation in some patients. We feel that this explanation is unlikely considering that the reasons for intubation included respiratory arrest (19%), CO₂ narcosis (4%), and progressive hypercapnia (52%). Only 25% of patients were intubated due to clinical tiring without worsening hypercapnia. Furthermore, significantly higher pCO₂ and lower pH values among intubated patients suggest that these patients were more acutely ill than those who avoided invasive MV.

In conclusion, our study demonstrates that outcomes for SA should be good/excellent once patients reach the ICU. Despite our frequent use of MV, mortality and complications remained low. Additionally, MV did not significantly increase the duration of hospitalization.

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Conflicts of interest

The authors have no actual or potential conflict of interest disclosure of any personal or financial support or author involvement with organization(s) with financial interest in the subject matter.

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