Variation in the use of mechanical ventilation for asthma: How big a gap?*

In this issue of *Pediatric Critical Care Medicine*, Dr. Carroll and colleagues (1) present a retrospective cohort study of children with severe asthma treated in a regional pediatric intensive care unit (PICU). Children who received their initial care in a community hospital were three times more likely to be intubated (relative risk ratio 3.3, 95% confidence interval 1.5–7.5) compared with children whose initial care was in a children's hospital. Based on asthma severity scores, PICU and total hospital length of stay, and duration of supplemental oxygen, patient severity did not differ by site of original care. Furthermore, the authors showed that among intubated patients, the intensity of asthma therapies tended to be less, as was the time of treatment before intubation at the community hospital compared with the children's hospital. Finally, the severity of hypercarbia before intubation at the community hospital was significantly less. These data suggest that some intubated children could have been managed without invasive mechanical ventilation.

Like other reports (2, 3), this study shows that practice management for severe asthma varies and that criteria for intubation and mechanical ventilation are neither clear nor uniform. The authors focus on the 27 (18%) children who were intubated; however, information on care intensity for children who were not intubated would also be helpful and could strengthen the authors' assertion that initial asthma care in a children's hospital is more aggressive for all patients with severe asthma and that such intensive effort decreases the need for invasive mechanical support. Likewise, tolerance of hypercarbia, relative degrees of hypoxia, and severity of respiratory distress for the entire cohort would again add to the evidence that asthma care in the children's hospital limited use of intubation and mechanical ventilation for children of similar disease severity. The authors only provide summary statistics for venous blood gases for the intubated patients, and the reader does not know the severity of hypercapnia for patients who were not intubated. The pathway reported by the Global Initiative for Asthma suggests that a $Paco_2$ >45 mm Hg should prompt intensive care admission, and progression of the flow chart suggests possible intubation and mechanical ventilation (4). It would be useful to know if the proportion of patients with CO_2 levels above this threshold differed by site of initial care.

Dr. Carroll and colleagues (1) report low use of mainstay therapies (4). Only 45% of children treated at a community hospital received corticosteroids compared with 86% at the children's hospital before intubation. Anti-inflammatory therapy is the cornerstone for severe asthma management, and systemic administration is recommended for all patients (4). Administration of corticosteroids results in early clinical effects (1–2 hrs) (5). Only limited information on other asthma therapies was reported. For instance, maximal hourly dose of inhaled albuterol is not reported. Likewise, use of inhaled anticholinergics, another recommended therapy for severe asthma episodes (4), is not reported. Finally, uses of methylxanthines, magnesium, heliox, and noninvasive ventilation are not reported.

Current consensus guidelines endorse use of systemic β-agonist, magnesium, and methylxanthines at a "consideration" level for support among children with a severe exacerbation (4). A recent meta-analysis regarding administration of magnesium in the emergency department for status asthmaticus concluded that magnesium sulfate administration significantly decreased risk of hospital admission. The pooled risk estimate for admission was 0.29 (95% confidence interval, 0.14–0.59, $p = .0006$), and the number needed to treat to avoid one hospitalization was four (95% confidence interval, 3–8) (6). However, less is known regarding magnesium and improvement in pulmonary function tests among children hospitalized for status asthmaticus. Methylxanthines have well-described toxicity (e.g., nausea and dysrhythmias); however, two randomized studies among PICU patients reported that addition of methylxanthines to systemic steroids and β-agonists resulted in more rapid improvement in asthma symptoms (7, 8). The Cochrane Collaborative concluded that in "children with a severe asthma exacerbation, the addition of intravenous aminophylline to beta-2 agonists and glucocorticoids (with or without anticholinergics) improves lung function within 6 hrs of treatment" (9). Neither of these "second-tier" therapies is discussed by Dr. Carroll and colleagues (1), and they either are not used in this community for severe asthma or are not reported.

Dr. Carroll and colleagues (1) do report use of intravenous or subcutaneous β-agonists, which tended to be more commonly used at the children's hospital (86% vs. 45%). Systemic β-agonists are the most commonly used second-tier therapy nationally (3). Systemic administration is appealing when the patient has severe airway obstruction and delivery of inhaled medications to the airways may be diminished. Reports on use of salbutamol in the emergency department (10) and terbutaline (11) in the PICU have shown benefit with decreased asthma symptoms, and the medications have an acceptable safety profile.

Another therapy that the authors do not mention is noninvasive ventilation. This is interesting, because two of the authors reported a case series of five children treated in 2002 to 2004 with noninvasive positive pressure ventilation for their care during a severe asthma exacerbation (12). It is unclear

*See also p. 91.

Key Words: status asthmaticus; mechanical ventilation; variation; noninvasive ventilation; β-agonists

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from the present report whether these children were excluded or included. Use of noninvasive ventilation is labor intensive and incurs similar costs compared with invasive ventilation, but its use in a retrospective cohort study was associated with lower need for invasive ventilation (3). Other reports of noninvasive mechanical ventilation among children with lower airway obstruction suggest that it can be used safely with lower rates of complications compared with invasive ventilation (13).

This report adds to the evidence that indications for intubation among children with severe asthma need further refinement, and it suggests that some patients who are intubated could be treated with less invasive measures. Furthermore, it suggests that pediatric critical care providers may be more tolerant of respiratory distress compared with adult emergency department physicians and may be willing to allow patients more time to improve before institution of mechanical support. Efforts to avoid mechanical ventilation including multiple drug regimens, heliox, and noninvasive positive pressure ventilation require familiarity with use of these therapies not available in most community settings, such that some discrepancy in care is likely unavoidable.

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Understanding the role of von Willebrand factor and its cleaving protease ADAM TS13 in the pathophysiology of critical illness*

Most clinicians are well aware of von Willebrand's disease, the disorder associated with umbilical cord and surgical procedure bleeding. This disease is sometimes caused by a complete absence of von Willebrand factor (vWF) multimer but is most times caused by congenitally based severe truncation of the vWF multimer. The vWF multimer is an accordion-like protein made by endothelium and, to a lesser extent, platelets/megakaryocytes to facilitate the formation of a platelet plug at the site of vascular injury. When focal injury occurs, circulating vWF multimers encounter shear stress and unfold from an accordion to a long molecule that attracts platelets at the site of stress. These long multimers are subsequently proteolyzed by circulating vWF cleaving protease, now known as ADAM TS 13. The longer the size of the vWF multimer (e.g., ultralarge vWF), the greater the platelet binding and thrombosis; the shorter the size of the vWF multimer, the lesser the platelet binding. If longer vWF multimers are never present, as is the case in von Willebrand's disease, then bleeding occurs because the ability to form platelet thrombosis is severely impaired.

In the normal host, the endothelium produces ultralarge vWF multimers when activated by focal trauma or inflammation. Being extremely thrombogenic, the ultralarge vWF multimer forms the strongest platelet clotting at the site of injury. This effectively reverses bleeding at the site of vascular injury. However, it can also cause pathology when endothelium is systemically activated or injured. For example, thrombotic thrombocytopenic purpura occurs when systemic endothelium activation results in the release of ultralarge vWF multimers in a patient with a congenital or acquired absence of ADAM TS 13 activity. Patients with this disorder present with thrombocytopenia and multiple organ failure including renal failure and neurologic failure/

*See also p. 96.

Key Words: von Willebrand's disease; endothelium; ADAM TS13

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