ceived 250 systemic steroids, and oxygen. The intervention group response to standard therapy consisting of nebulized albuterol, controlled trial in which children with acute asthma were old admitted with acute asthma.

standardized inpatient asthma care for children with status repeated doses of nebulized ipratropium bromide (IB) to some of the other inhaled steroid compounds, such as fluticasone and budesonide, as long-term follow-up, especially because this therapy would require shots every 2 to 4 Weeks. Practically, IP compliance will be important factors, as well as efficacy and safety, as we continue to study these new therapies.

WANDA PHIPATANAKUL, MD
Boston, MA

IPRATROPUM BROMIDE PLUS NEBULIZED ALBUTEROL FOR THE TREATMENT OF HOSPITALIZED CHILDREN WITH ACUTE ASTHMA


Objective. To ascertain whether the addition of repeated doses of nebulized ipratropium bromide (IB) to standardized inpatient asthma care for children with status asthmatics would improve clinical outcome.

Study Population. A total of 210 children 1 to 18 years old admitted with acute asthma.

Methods. This was randomized, double-blind, placebo-controlled trial in which children with acute asthma were assigned to receive either ipratropium or placebo in addition to standard therapy consisting of nebulized albuterol, systemic steroids, and oxygen. The intervention group received 250 µg IB combined with each albuterol treatment by jet nebulization in a dosing schedule as determined an algorithm. The placebo group received isotonic saline instead of IB.

Results. There were no significant differences between the therapeutic groups in hospital length of stay (P = .46) asthma care pathway progression (P = .37) the need for additional therapy, or adverse effects. Children greater than 6 years (N = 70) treated with IB had shorter mean hospital length of stay (P = .03) and progressed more rapidly in the asthma care pathway (P = .02) than children in the placebo group, although these differences were no longer significant after data were adjusted for baseline differences.

Conclusion. The addition of repeated doses of nebulized IB to a standardized regimen of systemic steroids and albuterol offers no significant advantage in terms of clinical outcome for the treatment of hospitalized children with acute asthma.

Reviewer’s Comments. The literature on IB in adult asthma remains unclear. Emergency room studies have yielded conflicting results, with some showing shorter lengths of stay and reduced rates of hospitalization and others showing no effect. This is an excellent study of inpatient asthma that demonstrates little effect, although there was a trend toward more effect in older children. There are likely to be individual patients who respond more to IB than others although it has not yet been possible to identify those patients before the initiation of treatment. It still seems reasonable to use IB in patients showing little response to their first β-agonist treatments to determine if that individual patient may benefit from its use.

CHRISTOPHER RANDOLPH, MD
Waterbury, CT

EFFICACY OF IV THEOPHYLLINE IN CHILDREN WITH SEVERE STATUS ASTHMATICUS


Purpose of the Study. To determine if the addition of intravenous (IV) theophylline to an aggressive treatment regimen of inhaled and IV beta-agonists, inhaled ipratropium and IV methylprednisolone would enhance the recovery of children with severe status asthmatics admitted to the pediatric intensive care unit (PICU).

Study Population. Forty-seven children with a diagnosis of status asthmatics who were admitted to the Cardinal Glennon Children’s Hospital in St Louis PICU for ≥2 hours. All subjects were in severe distress with a modified Wood-Downes clinical asthma score (CAS) of ≥5. Subjects’ age range was 13 months to 17 years.

Methods. Subjects were enrolled who fulfilled the above criteria. In brief, the CAS includes measures of oxygenation, breath sounds, accessory muscle use, expiratory wheezing, and cerebral function. Admission to the PICU was determined by inadequate response to repeated albuterol treatments and the ED and critical care staff. Subjects were randomly assigned to receive in addition to their regular aggressive treatment (denoted above in purpose of study) either IV aminophylline 7 mg/kg loading dose followed by age adjusted rates of 0.5–0.65 mg/kg/hr or no additional treatment (controls). Theophylline levels were kept between 12 to 17 µg/mL. The CAS evaluations were performed by investigators blinded to the treatment and were performed twice daily by 1 of 4 investigators. The PICU attending and resident team were all aware of the treatment assignment and made all medical decisions related to the subjects. CAS was suspended in the event of intubation and resumed on extubation. Nursing staff was queried regarding side effects of the subjects.

Results. There was no significant difference between the theophylline and control groups with respect to age, sex, race, home medications, past use of hospital resources, origin (ED or ward), ED treatment, or time of admission. The baseline CAS scores were not different. Six subjects required mechanical ventilation (3 in each group), although the 3 control subjects were intubated after treatment and the 3 in the theophylline group before treatment was begun. Subjects receiving IV theophylline had a significant decrease in time to reach CAS ≤3 and a greater percentage change in respiratory rate than control subjects during the first 12 hours in the PICU. Theophylline did not significantly influence the time to meet PICU discharge criteria among patients not receiving mechanical ventilation, but in those requiring intubation, the PICU stay was reduced. There was no significant difference in adverse effects between the 2 groups, except and increase in complaints of emesis in the theophylline group and increase in tremor in the control group.

Conclusions. Contrary to the National Heart Lung and Blood Institute guidelines for treatment of status asthmati-
cure in children, this study suggests that critically ill children with severe status asthmaticus may benefit from the addition of IV theophylline to β-agonist, anticholinergic, and corticosteroid therapies. Additional studies may examine the administration of theophylline to select patients in the ED unresponsive to conventional therapy or in patients known to be high risk for respiratory failure.

**Reviewer’s Comments.** This is the first prospective randomized trial of IV theophylline limited to children admitted to the PICU. Other studies in hospitalized (noncritical care) asthmatic children failed to show a benefit with the addition of theophylline to conventional treatment. It is possible that the benefit of the addition of theophylline is dependent on the severity of their illness. Adult studies have shown the improvement in spirometry with the addition of a methylxanthine is related to the degree of airway narrowing. The addition of theophylline may serve to reduce the incidence of respiratory failure and mechanical ventilation in children with severe status asthmaticus. The authors note that not blinding the medical team to the treatment may have influenced the results to some degree, but for safety reasons, they did not feel that was war-

Mary Beth Bollinger, DO
Baltimore, MD

**Immunology**

**IMMUNODEFICIENCY DISEASES**

**THE CARBOXYL TERMINUS OF THE GRANULOCYTE COLONY-STIMULATING FACTOR RECEPTOR, TRUNCATED IN PATIENTS WITH SEVERE CONGENITAL NEUTROPENIA/ACUTE MYELOID LEUKEMIA, IS REQUIRED FOR SH2-CONTAINING PHOSPHATASE-1 SUPPRESSION OF STAT ACTIVATION**


**Purpose of the Study.** Some patients with severe congenital neutropenia harbor mutations in the carboxyl terminus of the granulocyte colony-stimulating factor (G-CSF) receptor. It is this subgroup of patients with severe congenital neutropenia that is markedly predisposed to acute myeloid leukemia. This predisposition poses a significant hurdle to management. Patients with severe congenital neutropenia are typically treated with G-CSF. In this subgroup, G-CSF could drive leukemogenesis and is contraindicated. This study examines the mechanism underlying the predisposition to malignancy.

**Methods.** Cell lines transfected with both wild-type and mutant G-CSF receptor cDNAs and SHP-1 negative cell lines were used to examine the effect of the mutation on signaling function. Electrophoretic mobility shift assays, Western blots, and transient transfections using reporter constructs were performed.

**Results.** The mutant receptors are paradoxically associated with an increased proliferative response to G-CSF despite the differentialistic block in neutrophil development. The G-CSF receptor contains no intrinsic signaling activity, but activates Src family kinases, STAT 3/5, MAP kinases, and PI3 kinase. SHP-1 acts as a negative regulator. The mutant receptors are unable to interact effectively with SHP-1. The consequences of this impaired negative regulation are prolonged responses in the STAT pathways but not other signaling pathways. The exaggerated responses in the STAT pathways would explain the survival advantage of these cells and their hyperproliferation.

**Conclusion.** Failure of the mutant G-CSF receptors to interact effectively with the negative regulator SHP-1 appears to underlie the predisposition to acute myeloid leukemia.

**Reviewer’s Comments.** This study represents an important advance in our understanding of the secondary malignancies occurring in patients with severe congenital neutropenia. It should allow improved risk stratification for patients and could ultimately lead to improved management.

Kathleen E. Sullivan, MD, PhD
Philadelphia, PA

**MUTATION OF A NEW GENE ENCODING A PUTATIVE PYRIN-LIKE PROTEIN CAUSES FAMILIAL COLD AUTOINFLAMMATORY SYNDROME AND MUCKLE-WELLS SYNDROME**


**Purpose of the Study.** To identify the genes for familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).

**Study Population.** Three families with FCAS and 1 family with MWS.

**Methods.** Genomic DNA isolation, identification of coding region, DNA sequencing, and mutation detection. Protein prediction programs were also performed.

**Results.** Four distinct mutations of the CIAS1 Gene on chromosome 1q44 were identified. The gene encodes a newly identified protein called cryopyrin.

**Conclusion.** Mutations of the CIAS1 Gene encoding cryopyrin cause at least two distinct but similar cold-sensitive diseases, including FCAS and MWS.

**Reviewers’ Comments.** This exciting discovery has led to the identification of a new protein, aptly named “cryopyrin,” that links cold temperature exposure to inflammation. In this report, mutations of the cryopyrin gene were identified in family members with 2 rare autosomal dominant conditions that are “autoinflammatory” disorders (ie, conditions with recurrent inflammatory symptoms in the absence of autoantibodies): FCAS and MWS. Recently, FCAS—also known as familial cold urticaria and familial polymorphous cold eruption—has been well-described by the same authors. The FCAS clinical picture includes: skin rash (100%), arthralgia (96%), fever (93%), conjunctivitis (84%), disease onset in the first 6 months of life (95%), an average time delay between cold exposure and the onset of symptoms of 2.5 hours, and an average episode duration of 12 hours (Hoffman HM, et al. J Allergy Clin Immunol. 2001;108:615–620). In contrast, MWS leads to progressive sensorineural deafness, amyloidosis of the kidneys and other organs, fevers, chills, rigors, malaise, and chronic recurrent urticaria. The reason for the 2 distinct clinical entities associated with mutations in the same gene still need to be explored. For more discussion, see a brief editorial entitled “A fever gene comes in from the cold” by Kastner and O'Shea on pages 241–242 of the same issue.

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Efficacy of IV Theophylline in Children with Severe Status Asthmaticus

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