

Respirations

Winter 2006

Season greetings! And thanks to all those who read and gave us feedback on our inaugural offering of *Respirations*. We were thrilled to hear from you so please keep those comments and questions coming!

For anyone involved in pediatric healthcare, “‘Tis the season to be wheezy!” would probably seem like appropriate alternative lyrics to the Welsh classic. So in this edition, I will review the hot off the press concepts in the treatment of RSV bronchiolitis while John will describe a case on wheezing that was not asthma. LCK (choolr@stlo.mercy.net)

RSV bronchiolitis: Time for a different approach!

In 1963, Reynolds and Cook concluded “Oxygen is vitally important in bronchiolitis and there is little evidence that any other treatment is useful.” Over the last forty years despite advances in many fields of medicine, the mantra for the treatment of RSV bronchiolitis has been supportive care with supplemental oxygen, minimal handling of the infant, and the use of intravenous fluids and ventilatory support when necessary. Any other intervention outside of these basic measures could be the topic of much debate. Perhaps because of the similarity between RSV bronchiolitis and asthma, a variety of bronchodilators have been considered. It appears that beta-adrenergic bronchodilators like albuterol may give short-term relief of symptoms in some individual patients. Nebulized epinephrine is postulated to offer even additional benefit over albuterol due to added alpha-adrenergic vasoconstrictor effects on mucosal edema perhaps in the nose as well as the lower airways. However in a Cochrane Database Systematic Review, of five inpatient and three outpatient studies, the authors found only slight improvements in clinical scores and oxygen saturations compared to albuterol and placebo among outpatients. Nebulized epinephrine did not alter the need for hospitalization. There has been no apparent clinical benefit from the additional of Ipratropium to beta-agonists in the treatment of bronchiolitis. So, since L-epinephrine is the biologically active component of racemic epinephrine and is also significantly cheaper, my personal preference is to try 0.5 ml/kg of 1:1000 solution diluted in 3 ml normal saline (max dose: ≤ 4 yrs 2.5ml/dose) every 4-6 hours.

Although the pathophysiology of RSV bronchiolitis involves significant airway inflammation, the data supporting the use of systemic and inhaled glucocorticoids is disappointingly weak. The American Academy of Pediatrics does not recommend using glucocorticoids for the treatment of RSV symptoms. However increased understanding of the type of airway inflammation present in RSV bronchiolitis might explain our clinical observations. Steroids fail to down-regulate RSV-induced secretion of interleukin (IL) 8 which

plays an important role in neutrophilic airway inflammation. A recent double-blind, placebo-controlled (DBPC) study¹ however demonstrated a shorter hospital stay (6.5 ± 1.7 d versus 9.1 ± 1.9 d) among premature infants with RSV bronchiolitis receiving nebulized dexamethasone 0.25mg + epinephrine over saline placebo + epinephrine.

Three years ago, Bisgaard et al.² reported a significant increase in symptom-free days and nights during the month following RSV infection in children 3 to 36 months of age treated with montelukast (22%) versus placebo (4%). The youngest infant was 3 months of age and treatment was initiated within seven days of symptoms onset.

A more recent and very intriguing DBPC study³ looked at the effects of clarithromycin on the “steroid-resistant” inflammation of RSV bronchiolitis. Tahan et al. demonstrated significant reductions in hospital duration, need for supplemental oxygen and rescue bronchodilator treatments among infants who received clarithromycin. Clinical improvements were accompanied and perhaps explained by significant reductions in the cytokines IL-4, IL-8 and eotaxin (eosinophil chemotactic agent) while enhanced interferon gamma production was noted. Clarithromycin, one of the newer macrolides, is known to have immunomodulatory effects via inhibition of NF-KB activation. Knowing that RSV infection evades the human adaptive immune system by skewing the Th1/Th2 cytokine balance towards increased levels of Th2 cytokines with subsequent increased tendency for allergic asthma, the putative benefits of clarithromycin may even go beyond an improvement in immediate bronchiolitis symptoms.

Besides from the potential immunomodulatory benefits of clarithromycin, antibiotics are generally not indicated in the treatment of uncomplicated RSV bronchiolitis. However, studies⁴ of infants who require mechanical ventilation with severe RSV show as high as 40% bacterial contamination or infection of the lower airways. The most commonly isolated organism being *Haemophilus influenzae*.

Finally a few words on non-pharmacological interventions: (1) Khoshoo et al. found an increased risk of primary aspiration in previously healthy infants (3-12 months) during RSV bronchiolitis. The addition of rice cereal decreased the aspiration risk but practically this may lead to more difficulty as the infant tries to suck the thickened formula through the nipple. A reasonable and not overly cautious approach is to consider nasogastric tube feeds or intravenous fluids in infants with respiratory rates consistently >60 breaths per minute. (2) Chest physiotherapy is of no proven benefit in the management of RSV bronchiolitis. (3) And please remember, you can always call your friendly neighborhood pulmonologists! LCK

References:

1. Acta Paediatrica 2005; 94: 866-871
2. Am J Respir Crit Care Med 2003; 167: 379-383
3. Eur Respir J 2006 Oct 18; [Epub ahead of print]
4. Thorax 2006; 61: 611-615

Illustrative Case

Mary is an 11 year-old girl with a two year history of intermittent exercise-induced dyspnea. She describes chest discomfort and difficulty catching her breath only with activity such as running in gym. There is an occasional cough and “wheeze”. Her respiratory difficulty seems worse during inspiration. Specifically she feels unable to “get an adequate breath in”. Throat pain is noted but there is no hoarseness or change in voice. She has no history of neck trauma. Albuterol has neither prevented nor relieved her symptoms. Her symptoms typically resolve within 20 minutes of resting. She also has a history of gastroesophageal reflux disease, anxiety and vague somatic complaints including muscle aches and weakness. A previous rheumatology workup was normal.

Since Mary’s symptoms were triggered by exercise, we chose to perform an exercise challenge. Her baseline spirometry was normal. However while running on the treadmill, Mary developed inspiratory “wheeze” and complained of throat pain. Her oxyhemoglobin saturation decreased into the upper 80’s. Flexible laryngoscopy done while she was symptomatic demonstrated normal upper airway anatomy but paradoxical adduction of her vocal cords during inspiration. Post-exercise spirometry showed no reduction in her forced expiratory volume in one second that would suggest asthma.

Discussion—Mary displayed many classical signs and symptoms of vocal cord dysfunction (VCD). By definition VCD is paradoxical adduction of the vocal cords particularly during inhalation that reduces air flow at the level of the larynx. Dyspnea occurs as the individual fails to perceive a sensation of air movement that matches his/her respiratory efforts. VCD occurs on a wide severity spectrum ranging from brief self-resolving stridor to rare cases that required intubation and/or tracheotomy. VCD often masquerades as asthma which results not only in unnecessary pharmaceutical prescription but frequent emergency room visits and hospitalizations. Steroids and adrenergic bronchodilators are ineffective. VCD is common—a study evaluating 117 children aged 6-21 years of age with exercise-induced dyspnea found slightly more children with VCD (13 of 117) than with true exercise-induced bronchospasm (11 of 117)¹. Asthma and VCD are also not mutually exclusive of each other. Studies have shown asthma to be present in as many as 20-50% in patients with VCD². Treatment begins with recognizing the correct cause of the patient’s symptoms.

Note that visualization of the upper airway when the patient is asymptomatic is not normally diagnostic. VCD is a “functional” disorder and the vocal cords may only be seen moving abnormally when the patient is experiencing symptoms. Spirometry done to exclude asthma is also usually normal except there may be a suggestion of variable (i.e. not fixed) extrathoracic airway obstruction on the inspiratory limb of the flow/volume loops. Education is extremely important for the patient and parents. We believe a detailed age-appropriate description of the pathophysiology aids the child’s understanding of how to relieve and prevent symptoms from reoccurring. Alternative breathing techniques are taught to the child. In more refractory cases a multidisciplinary team approach with speech therapy and psychology is available. Treatment of co-morbid conditions such as asthma, rhinitis, and gastroesophageal reflux is important. There has been one report³ of six patients with VCD responding preferentially to pre-exercise ipratropium MDI over albuterol. Long-term outcome appears quite favorable. JFS

References:

1. Ann Allergy Asthma Immunol. 2005; 94:366-371.
2. Am J Respir Crit Care Med. 1995; 152:1382-1386.
3. Ann Allergy Asthma Immunol. 2006; 96:794-799.

Diagnostic Tool Talk

Although persistent asthma is a disease of chronic airway inflammation and treatment is geared towards its reduction, there are few clinical tools available that easily measure and monitor airway inflammation. Spirometry for example reflects airway caliber and may appear normal even when significant inflammation is present, especially if the patient is using long-acting bronchodilators.

The fraction of exhaled nitric oxide (FeNO) present in one’s breath correlates with the degree of airway eosinophilia as well as bronchial hyper-reactivity to agents such as methacholine. Increased FeNO levels are a result of *inducible* nitric oxide synthetase seen during oxidative stress and eosinophilic airway inflammation. An elevated FeNO is therefore useful to distinguish patients with untreated asthma from the individual without asthma. FeNO can also be used to assess efficacy of treatment, whether the dose of ICS is sufficient, adherence to therapy and to predict the patient’s risk for an acute exacerbation (such as when weaning ICS dose). FeNO measurement is easy to perform and can be done in cooperative children as young as 3 years.

Nurse Joan’s Corner

Did you know that if a MDI is stored in a valve-down position for a few hours there may be less medicine available in the first puff, even if you shake it before hand? To avoid this problem, instruct patients to store MDIs in the valve-up position. If a canister was stored valve-down for more than four hours, don’t count the first puff. ©

