

## Translating Best Evidence into Best Care

EDITOR'S NOTE: *Journals reviewed for this issue: Archives of Disease in Childhood, Archives of Pediatrics and Adolescent Medicine, British Medical Journal, Journal of the American Medical Association, The Journal of Pediatrics, The Lancet, New England Journal of Medicine, Pediatric Infectious Diseases Journal, and Pediatrics.* Gurpreet K. Rana, BSc, MLIS, Taubman Medical Library, University of Michigan, contributed to the review and selection of this month's abstracts.

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### Nasal steroids helpful for short-term treatment of children with obstructive sleep apnea

Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics* 2008;122:e149-55.

**Question** Among children with mild obstructive sleep apnea syndrome (OSAS), do intranasal corticosteroids improve sleep-related disturbances better than placebo?

**Design** Randomized crossover trial.

**Setting** University of Louisville.

**Participants** Sixty-two children with polysomnographically diagnosed mild OSAS.

**Intervention** Intranasal budesonide (32  $\mu\text{g}$  per nostril at bedtime) or placebo for 6 weeks, followed by an additional 6-week treatment in the alternative treatment arm after allowing for a 2-week washout period.

**Outcomes** Polysomnographic assessment and radiographs for assessment of adenoid size.

**Main Results** There were significant improvements in both polysomnographic measures (sleep latency, slow-wave sleep, and rapid-eye-movement sleep), in the magnitude of respiratory disturbance (apnea/hypopnea index, nadir pulse oxygen saturation), and in adenoid size among the 48 children who completed the treatment phase, compared with 32 children who received placebo in their initial arm, with normalization of sleep measures in 54.1% of the treated children. Furthermore, discontinuation of treatment for 8 weeks for 25 children revealed a sustained duration of the initial treatment effect.

**Conclusions** A 6-week treatment with intranasal budesonide effectively reduced the severity of mild obstructive sleep apnea syndrome and the magnitude of the underlying adenoidal hypertrophy, and this effect persisted for at least 8

weeks after cessation of therapy. These findings justify the use of topical steroids as the initial therapeutic option in otherwise healthy children with mild obstructive sleep apnea.

**Commentary** This study adds to a small but growing body of evidence,<sup>1,2</sup> which suggests that nasal corticosteroids may represent an effective short-term treatment for OSAS in children. The authors found that 6 weeks of intranasal budesonide treatment in children with mild OSAS resulted in normalization of the polysomnogram (PSG) in 54% of treated children and that improvements in PSG parameters and adenoidal size were maintained 8 weeks after completion of active treatment. Strengths of the study derive from its use of polysomnography and other objective assessment measures at 3 points within the double-blind, placebo-controlled, crossover protocol and from its use of rigorous selection criteria to ensure that the severity of OSAS for children in the cohort was truly uniform. Limitations of the study are modest. A substantial proportion of children in this study—23 of 62—were already receiving antihistamines or immunotherapy. Although these subjects were required to continue their existing therapy for the duration of the study protocol, it is unclear whether these subjects might represent children with allergic rhinitis or other conditions that might preferentially respond to use of nasal steroids. In spite of these encouraging results, further study will be required to determine the optimal role of nasal steroids in the treatment of pediatric OSAS and whether this treatment is safe and effective for long-term, as well as short-term, use.

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## Regular use of inhaled corticosteroids controls symptoms of mild persistent asthma, but with growth effect

Turpeinen M, Nikander K, Pelkonen AS, Syvänen P, Sorva R, Raitio H, Malmberg P. Daily versus as-needed inhaled corticosteroid for mild persistent asthma (The Helsinki early intervention childhood asthma study). *Arch Dis Child* 2008; 93:654-9.

**Question** Among children with mild persistent asthma, is the use of daily versus as-needed inhaled budesonide more effective in controlling asthma symptoms?

**Design** Randomized controlled trial.

**Setting** Helsinki University Hospital, Finland.

**Participants** One hundred seventy-six children, aged 5 to 10 years with newly detected asthma.

**Intervention** Children were randomized to 1 of 3 treatment groups: (1) continuous budesonide (400 mg twice daily for 1 month, 200 mg twice daily for months 2 to 6, 100 mg twice daily for months 7 to 18); (2) budesonide, identical treatment to group 1 during months 1 to 6, then budesonide for exacerbations as needed for months 7 to 18; and (3) disodium cromoglycate (DSCG) 10 mg 3 times daily for months 1 to 18. Exacerbations were treated with budesonide 400 mg twice daily for 2 weeks.

**Outcomes** Lung function, the number of exacerbations, and growth.

**Main Results** Compared with DSCG the initial regular budesonide treatment resulted in significantly improved lung function, fewer exacerbations, and a small but significant decline in growth velocity. After 18 months, however, the lung function improvements did not differ between the groups. During months 7 to 18, patients receiving continuous budesonide treatment had significantly fewer exacerbations (mean 0.97), compared with 1.69 in group 2 and 1.58 in group 3. The number of asthma-free days did not differ between regular and intermittent budesonide treatment. Growth velocity was normalized during continuous low-dose budesonide and budesonide therapy given as needed. The latter was associated with catch-up growth.

**Conclusions** Regular use of budesonide afforded better asthma control but had a more systemic effect than did use of budesonide as needed. The dose of inhaled corticosteroid (ICS) could be reduced as soon as asthma is controlled. Some children do not seem to need continuous ICS treatment.

**Commentary** This study addresses an important question of whether intermittent use of ICS in children with mild persistent asthma can achieve similar control of their symptoms as the continuous use of ICS with potentially fewer side effects. These results replicate those found by Boushey et al<sup>1</sup> in a similar study performed in adults with mild asthma. There was no significant difference in peak expiratory flow

(PEF) measurements between continuous and intermittent ICS or DSCG group at any time point. However, the use of PEF measurements as an asthma outcome has been recently questioned given its variability and lack of correlation with other outcomes. Turpeinen et al<sup>2</sup> also did not demonstrate difference between the groups in pulmonary function. Conversely, the clinical burden of asthma (symptom-free days, number of exacerbations, and time to first exacerbation) was significantly decreased in children treated with continuous ICS compared with intermittent ICS and DSCG treatment groups. It can be argued that clinical symptom burden may be the most relevant measures of childhood asthma control given the number of children with persistent asthma that have normal or near-normal lung function.<sup>2</sup> Children treated with continuous ICS demonstrated a significantly decreased mean height velocity after 18 months of the study compared with children treated with DSCG. It should be noted that the height difference was small (1 cm) and similar to the difference found in other studies of children with persistent asthma treated with ICS.<sup>2</sup> Of note is that the study included only Caucasian children, so the results may not be generalized to a non-Caucasian population. Thus the results of the study confirm the results from previous studies that continuous treatment with ICS is associated with significantly better asthma control than treatments with DSCG or intermittent treatment. In making the decision to use continuous ICS in children with asthma, the burden of the disease should be weighed against the potential side effects.

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## Risk of death is not increased in children with simple febrile seizures

Vestergaard M, Giørtz Pedersen M, Østergaard JR, Bøcker Pedersen C, Olsen J, Christensen J. Death in children with febrile seizures: a population-based cohort study. *Lancet* 2008;372:457-63.

**Question** Among children with febrile seizures, is there an increased risk of death?

**Design** Population-based cohort study with a nested case-control study.

**Setting** Denmark.

**Participants** A total of 1 675 643 children born between January 1, 1977, and December 31, 2004. The case-control

portion of the study included 8172 children who died and 40 860 individually-matched control subjects.

**Intervention** Children were followed up from 3 months of age until death, emigration, or August 31, 2005.

**Outcomes** Overall and cause-specific death after first febrile seizures, estimated with survival analyses.

**Main Results** Of the children who died, there were 232 deaths among 55 215 children with a history of febrile seizures. The mortality rate ratio was 80% higher during the first year (adjusted mortality rate ratio 1.80 [95% CI 1.31-2.40]) and 90% higher during the second year (1.89 [1.27-2.70]) after the first febrile seizure; thereafter it was close to that noted for the general population. A total of 132 of 100 000 children (95% CI 102-163) died within 2 years of a febrile seizure compared with 67 (57-76) deaths per 100 000 children without a history of this disorder. In the nested case-control study, children with simple ( $\leq 15$  minutes and no recurrence within 24 hours) febrile seizures had a mortality rate similar to that of the background population (adjusted mortality rate ratio 1.09 [95% CI 0.72-1.64]), whereas the mortality rate was increased for those with complex ( $> 15$  minutes or recurrence within 24 hours) febrile seizures (1.99 [1.24-3.21]). This finding was partly explained by preexisting neurologic abnormalities and subsequent epilepsy.

**Conclusions** The long-term mortality rate is not increased in children with febrile seizures, but there seems to be a small excess mortality rate during the 2 years after complex febrile seizures. Parents should be reassured that death after febrile seizures is very rare, even in children at high risk.

**Commentary** Despite the general acceptance that children with febrile seizures have a good prognosis, the hypothesis persists that febrile seizures are linked to sudden death through a common infectious or environmental agent, anatomic abnormality, or genetic susceptibility to fever. The shared susceptibility hypothesis has found little support, however, from large epidemiologic studies that showed sudden infant death syndrome (SIDS) and febrile seizures occur in different populations. SIDS is more frequent in African-American children, for example, whereas this higher risk is not mirrored in febrile seizures. SIDS and febrile seizures do not seem to occur together in families. In this study, Vestergaard et al tested the hypothesis that febrile seizures are associated with an increased risk of death by examining mortality data from nationwide registries in Denmark. The investigators found that in children who had febrile seizures, there was an increased risk of death in the 2 years after the first febrile seizure, but that the absolute risk was still very low. In a nested case control study, they reviewed medical records to obtain more clinical information than is available in registry data. They found that the increased risk of death after febrile seizure was seen only in children with complex febrile seizures and in those with underlying neurologic abnormalities. This well-conducted study again seems to refute, for

children with simple febrile seizures, the idea of a shared cause between febrile seizures and sudden death. The study nevertheless suggests there may be a subset of children— notably those with complex features and underlying neurologic abnormalities—which might warrant closer attention and follow-up.

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## Magnesium treatment of mothers may decrease the incidence of cerebral palsy in at-risk infants

Rouse DJ, Hirtz DG, Thom E, Vamer MW, Spong CY, Mercer BM, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008;359:895-905.

**Question** Among women at high risk for preterm birth, does the use of magnesium sulfate decrease the risk of cerebral palsy in their children?

**Design** Randomized controlled trial.

**Setting** Twenty participating Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network sites across the United States.

**Participants** A total of 2241 women at imminent risk for delivery between 24 and 31 weeks of gestation.

**Intervention** Magnesium sulfate, administered intravenously as a 6-g bolus followed by a constant infusion of 2 g per hour, or matching placebo.

**Outcomes** The composite of stillbirth or infant death by 1 year of corrected age or moderate or severe cerebral palsy at or beyond 2 years of corrected age.

**Main Results** The rate of the primary outcome was not significantly different in the magnesium sulfate group and the placebo group (11.3% and 11.7%, respectively; relative risk, 0.97; 95% confidence interval [CI], 0.77 to 1.23). However, in a prespecified secondary analysis, moderate or severe cerebral palsy occurred significantly less frequently in the magnesium sulfate group (1.9% vs 3.5%; relative risk, 0.55; 95% CI, 0.32 to 0.95, number needed to treat = 63). The risk of death did not differ significantly between the groups (9.5% vs 8.5%; relative risk, 1.12; 95% CI, 0.85 to 1.47). No woman had a life-threatening event.

**Conclusions** Fetal exposure to magnesium sulfate before anticipated early preterm delivery did not reduce the combined risk of moderate or severe cerebral palsy or death, although the rate of cerebral palsy was reduced among survivors.

**Commentary** This study upholds the typical high standards of design and execution one expects from a collaborative from the National Institutes of Health. The conclusion of this

study is congruent with the Cochrane review,<sup>1</sup> concluding the null hypothesis for death or cerebral palsy, as well as a reduction in severity of cerebral palsy. Decisions to use magnesium are made by obstetricians; when dealing with this treatment they must consider the potential risk for both infant and maternal harm. Doyle's meta-analysis suggests significant maternal adverse outcomes do occur in the treatment group, including maternal tachycardia and hypotension. The lack of such finding in this trial is worthy of discussion. If maternal harm occurs, pediatricians must ask whether the potential risks to 63 mothers (ie, the number needed to treat) are balanced against the value of preventing one case of cerebral palsy? Additionally, it may make biologic sense that neurologic deaths may be prevented by magnesium, but it is also worrisome that magnesium therapy may contribute to neonatal harm (such as the effect of maternal hypotension on the fetus). The data from this study hints at this concern with a 1.6% reduction in CP incidence (3.5% in control vs 1.9% in treatment group) accompanied by a 1% increase in neonatal death (8.5% in control vs 9.5% in treatment group). These seem to be conflicting results when evaluating magnesium's benefits to the neonate. That is, is cerebral palsy prevented only to result in more neonatal deaths? Knowing the cause of neonatal death would be interesting and is required if one is worried about the intervention being the cause of the incremental deaths. If neonatal neurologic death is not prevented by magnesium, one could question the use of death or cerebral palsy as the principal outcome measure. This underscores the difficulty one encounters in designing such studies. Because it is a large, well designed and executed study, there should be abundant data available to explore such questions leading to hypothesis generation and better designed studies in this area.

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## Physical therapy is effective for deformational plagiocephaly

van Vlimmeren LA, van der Graaf Y, Boere-Boonekamp MM, L'Hoir MP, Helders PJM, Engelbert RHH. Effect of pediatric physical therapy on deformational plagiocephaly in children with positional preference: a randomized controlled trial. *Arch Pediatr Adolesc Med* 2008;162:712-8.

**Question** Among infants with a positional preference for their head, does physical therapy decrease the prevalence of positional preference and deformational plagiocephaly (DP) at 6 and 12 months, compared with no active intervention?

**Design** Randomized controlled trial.

**Setting** Physical therapy department in a single hospital in the Netherlands.

**Participants** Sixty-five sequential infants referred at 7 weeks of age to physical therapy with positional DP.

**Intervention** Infants were randomly assigned (stratified by sex) to a 4-week course of 8 physical therapy sessions designed by the authors to address positional preferences, including parent counseling, exercises for motor development, "tummy time," and an educational brochure. Those in the placebo group received only the educational brochure.

**Outcomes** The primary outcome was severe DP assessed by plagiocephalometry. The secondary outcomes were positional preference, motor development, and cervical passive range of motion. The physical therapists performing the therapy were blinded to the outcome assessors, but no mention was made of whether the outcome assessors were blinded to treatment group.

**Main Results** The primary outcome of severe plagiocephaly decreased in the treatment group from 55% at age 7 weeks to 24% at 12 months compared with 63% to 56% in the control (leaflet-only) group (number needed to treat [NNT] = 4). Secondary outcomes were similar between the 2 groups, except intervention parents were better at positioning their infants and gave them more tummy time compared with the control group.

**Conclusions** A 4-month standardized pediatric physical therapy program to treat positional preference significantly reduced the prevalence of severe deformational plagiocephaly when initiated by 2 months of age.

**Commentary** Van Vlimmeren et al randomized 65 children with positional plagiocephaly to a 4-month course of physical therapy or simply receiving a patient education handout. The participants were quite young, at 7 weeks, and although the authors noted baseline characteristics to be "similar" between the 2 groups, there was a trend toward the control group infants having more positional preference. Patients were randomized and intention to treat was followed. However, no mention of allocation concealment or blinding of outcome assessors was made, even for the subjective secondary outcomes. The NNT of 4 is quite impressive for such a benign intervention, and physical therapy can be quite reassuring to parents as a "hands-on" treatment. However, the outcome of severe plagiocephaly was defined by objective head measurements and not by a more clinically meaningful measure such as parent-reported satisfaction. The improvement in secondary outcomes is to be expected because it simply measured how well the parents understood the physical therapists' instructions. A meta-analysis published in the same issue showed that molding therapy with helmets was superior to repositioning therapy for positional plagiocephaly.<sup>1</sup> However, the treatments in the 7 studies included in the meta-analysis were begun at an average age of 6 months, about the age the patients in the van Vlimmeren trial were completing their

course of physical therapy. Thus it makes sense for young infants with severe positional plagiocephaly to first undergo a course of physical therapy. Only if this should fail to produce the desired results after a few months should serious consideration and referral for molding therapy be considered. Interestingly, the trials in the meta-analysis point toward the same outcomes for positional treatments as molding by 2 years of age. Unfortunately, for those children who do not respond by 2 years of age to any treatment, surgery is usually the only viable option.

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### **Escalating dose indomethacin for prophylactic closure of patent ductus arteriosus does not improve closure rates and is associated with increased complications**

Jegatheesan P, Ianus V, Buchh B, Yoon G, Chome N, Ewig A, et al. Increased indomethacin dosing for persistent patent ductus arteriosus in preterm infants: A multicenter, randomized, controlled trial. *J Pediatr* 2008;153:183-9.

**Question** Among extremely premature infants whose patent ductus arteriosus (PDA) failed to close with a conventional dosing regimen of indomethacin, does a higher dose increase the rate of PDA closure without increasing the rate of other morbidities?

**Design** Randomized controlled trial.

**Setting** Four university hospitals in the United States.

**Participants** One hundred five infants (<28 weeks gestation) who received a conventional, prophylactic 3-dose course of indomethacin who had continued evidence of persistent ductus patency on an echocardiogram obtained before the third prophylactic indomethacin dose.

**Intervention** Infants received an extended 3-day course of either low-dose (0.1 mg/kg/d) or higher-dose (0.2 or 0.5 mg/kg/d) indomethacin.

**Outcomes** Closure of the PDA, as documented by an echocardiogram obtained 24 hours after the last dose of study drug.

**Main Results** Despite increasing serum indomethacin concentrations by 2.9-fold in the higher-dose group, there was no significant decrease in the rate of persistent PDA (low = 52%; higher = 45%,  $P = .50$ ). The higher-dose group had a significantly higher occurrence of serum creatinine above 2 mg/100 mL (low = 6%, higher = 19%,  $P < .05$ ) and moderate/severe retinopathy of prematurity (ROP) (low = 15%, higher = 36%,  $P < .025$ ). The incidence of moderate/severe ROP was directly related to the poststudy indomethacin concentrations (odds ratio = 1.75, confidence interval: 1.15-2.68,  $P < .01$ ).

**Conclusions** Increasing indomethacin concentrations above the levels achieved with a conventional dosing regimen had little effect on the rate of PDA closure but was associated with higher rates of moderate/severe ROP and renal compromise.

**Commentary** PDA is a common concern in premature infants and can be associated with significant morbidity. Previous studies have suggested greater success with escalating-dose indomethacin. This well-designed, randomized controlled trial sought to determine the efficacy of this practice. Although the increased dose significantly increased indomethacin levels, no benefit was seen in terms of ductal closure, with increased risk of toxicity in the form of renal dysfunction and retinopathy of prematurity. Even though it is possible that a larger sample size may have resulted in a significant increase in the rate of ductal closure, the toxicity seen with higher doses precluded further enrollment in this study. It is possible that the treatment effect of higher-dose indomethacin shown in previous studies may have been due to duration of therapy as opposed to increased dose.

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