

Tanner Nissly, DO;
Shailendra Prasad,
MBBS, MPH

Department of Family
Medicine and Community
Health, University of
Minnesota, Minneapolis

PURLS EDITOR
James Stevermer,
MD, MSPH

Department of Family
Medicine, University of
Missouri at Columbia

This asthma treatment has a lasting side effect in children

A new study finds that when children with asthma use inhaled corticosteroids, the effect on growth may not be temporary, as once thought.

PRACTICE CHANGER

Before prescribing inhaled corticosteroids (ICS) for a child with asthma, tell the patient—and parents—that their use could lead to a small but permanent effect on adult height.¹

STRENGTH OF RECOMMENDATIONS

B: Based on one prospective study.

Kelly HW, Sternberg AL, Lescher R, et al; CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med*. 2012;367:904-912.

ILLUSTRATIVE CASE

A 10-year-old boy is brought in by his father for asthma follow-up. The child uses an albuterol inhaler, but has had increased coughing and wheezing recently. You are ready to step up his asthma therapy to include ICS. But the patient's father questions this, noting that he recently read that steroids may reduce a child's growth. How should you respond?

Inhaled corticosteroids (ICS) are a mainstay in the treatment of asthma ranging from mild persistent to severe. Standards of care for asthma treatment involve a stepwise approach, with ICS added if symptoms are not controlled with short-acting beta antagonists alone.² In addition, monotherapy with ICS is more effective for controlling symptoms than leukotriene inhibitors or other controller medications, while also decreasing hospitalizations and nocturnal

awakenings and improving quality of life—with few side effects.³

What we know about ICS and children's growth

One adverse effect of ICS, however, is that of “decreased linear growth velocity”⁴—ie, slowing the rate at which children grow. Until recently, children were thought to “catch up” later in life, either by growing for a longer period of time than they would had they not taken ICS or by growing at an increased velocity after ICS medications are discontinued.⁴⁻⁶

STUDY SUMMARY

The effect on growth is small, but long-lasting

Kelly et al conducted a prospective observational cohort study that followed 943 (90.7%) participants in the Childhood Asthma Management Program (CAMP) in the years after the randomized controlled trial (RCT) ended.

A double-blind, placebo-controlled RCT, CAMP studied the linear growth of 1041 children with mild-to-moderate persistent asthma who were divided into 3 treatment groups: One group received 200 mcg inhaled budesonide twice daily; a second group received 8 mg inhaled nedocromil twice daily; and a third group received placebo. Albuterol was used symptomatically by all 3 groups.⁷ The children ranged in age from 5 to 13 years at the start of the study;

98 patients—split evenly among the 3 treatment arms—were lost to follow-up.

During the 4 to 6 years of the CAMP trial, the budesonide group received a mean total of 636 mg ICS, whereas the nedocromil and placebo groups received an average of 88.5 and 109.4 mg ICS, respectively. After the RCT ended, all participants had standardized asthma treatment, receiving mean adjusted total doses of ICS of 381 mg for the budesonide group, 347.9 mg for the nedocromil group, and 355 mg for the placebo group.

Patients' height was measured every 6 months for the next 4.5 years, and once or twice a year thereafter until they reached adult height (at a mean age of 24.9 ± 2.7 years).

ICS users were a half inch shorter

Long-term ICS use was linked to a lower adult height. The adjusted mean height was 171.1 cm for the budesonide group vs 172.3 cm for those on placebo, a difference of 1.2 cm, or 0.47 inch (95% confidence interval [CI], -1.9 to -0.5 ; $P = .001$); the mean adult height in the nedocromil group (172.1 cm) was similar to that of the placebo group (-0.2 cm; 95% CI, -0.9 to 0.5 ; $P = .61$).

The lower adult height in the ICS group did not vary significantly based on sex, age at trial entry, race, or duration of asthma prior to trial entry; however, dose was a key factor. A larger daily dose of budesonide—particularly in the first 2 years of the RCT—was associated with a lower adult height (about -0.1 cm for each mcg/kg in that 2-year time frame). This was consistent with results from studies that looked at other types of ICS (beclomethasone, fluticasone, and mometasone).⁸⁻¹¹

The study also showed that growth velocity was reduced in the first 2 years of assigned treatment with budesonide, and this was primarily among prepubertal participants. After the initial 2-year slowing in growth rate, the children resumed growing at normal speeds.

WHAT'S NEW?

Now we know:

Children don't "catch up"

Retrospective studies have reported that children on ICS for mild persistent to moder-

ate asthma would have an initial slowing in growth velocity but then "catch up" by growing for a longer period of time.³⁻⁵ This is the first prospective study with good follow-up to show that ICS use affects long-term growth and adult height. While the effect is not large, some children and their families might be concerned about it.

CAVEATS

ICS use was atypical

The randomized controlled portion of the study used a prescribed dose of budesonide without regard to symptoms. This is not the typical pattern of ICS use. In addition, compliance with ICS varies significantly.¹² Because the effect on adult height appears to be dose dependent, however, we think the results of this study are valid.

In addition, there was a placebo control group (and big differences in exposure to ICS) only for the duration of the RCT. During the subsequent study, all patients received equivalent doses of ICS. This means that the variation in mean adult height achieved can be primarily ascribed to participants' use of ICS during the 4- to 6-year CAMP trial. Of note, the effect of ICS was greatest in prepubertal participants, so there may be a diminished effect as teens approach their final height.

The study did not look at the effect of ICS use in patients with severe asthma—the group most likely to use ICS. However, the benefits of ICS for those with severe asthma likely outweigh any negative effects on adult height.

CHALLENGES TO IMPLEMENTATION

What to tell patients

The message we convey to patients (and parents) about ICS use is a nuanced one. We can stress that ICS remain very important in the treatment of asthma and, while it appears that their use causes a slight decrease in adult height, most children with persistent asthma benefit from ICS. **JFP**

ACKNOWLEDGEMENT

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Re-



This is the first prospective study with good follow-up to show that ICS use affects long-term growth and adult height.

search Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources

or the National Institutes of Health.

Copyright © 2013 Family Physicians Inquiries Network. All rights reserved.

References

1. Kelly HW, Sternberg AL, Lescher R, et al; CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med.* 2012;367:904-912.
2. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health National Heart, Lung and Blood Institute: National Asthma Education and Prevention Program, 2007. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdlm.pdf>. Accessed August 15, 2013.
3. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev.* 2012;(5):CD002314.
4. Agertoft L, Pedersen S. Effect of long-term treatment with budesonide on adult height in children with asthma. *N Engl J Med.* 2000;343:1064-1069.
5. Van Bever HP, Desager KN, Lijssens N, et al. Does treatment of asthmatic children with inhaled corticosteroids affect their adult height? *Pediatr Pulmonol.* 1999;27:369-375.
6. Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol.* 1997;99:466-474.
7. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med.* 2000;343:1054-1063.
8. Tinkelman DG, Reed CE, Nelson HS, et al. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics.* 1993;92:64-77.
9. Verberne AA, Frost C, Roorda RJ, et al. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med.* 1997;156:688-695.
10. Allen DB, Bronsky EA, LaForce CF, et al. Growth in asthmatic children treated with fluticasone propionate. *J Pediatr.* 1998;132:472-477.
11. Skoner DP, Meltzer EO, Milgrom H, et al. Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4-9 years old with mild persistent asthma. *J Asthma.* 2011;48:848-859.
12. Cochrane MG, Bala MV, Downs KE, et al. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation technique. *Chest.* 2000;117:542-550.

Probiotics and antibiotics: A PURL update



In "Prescribing an antibiotic? Pair it with probiotics" (*J Fam Pract.* 2013;62:148-150), we summarized a systematic review and meta-analysis showing probiotics to be effective in preventing antibiotic-associated diarrhea (AAD). The study further found that AAD caused by *Clostridium difficile* infection (CDI) was less likely in patients receiving probiotics, with a number needed to treat of 25 to prevent one CDI, an important cause of morbidity and mortality. However, the authors of the study noted several caveats, including low adherence to follow-up.

Thus, we would like to call your attention to a more recent meta-analysis¹ (including 20 RCTs with a total of 3818 immunocompetent patients) focused solely on the prevention of CDI with probiotics. It showed a decreased incidence of both *C difficile*-associated diarrhea and CDI infection with probiotic use in both

children and adults (relative risk=0.34; 95% confidence interval, 0.24-0.49). The strains of probiotics in the RCTs included *Bifidobacterium*, *Lactobacillus*, *Saccharomyces*, and *Streptococcus* species with at least 10 billion colony-forming units, with multiple strains used in some trials. There were no serious adverse effects attributed to probiotic use. This report, as well as a 2013 Cochrane review² with consistent results, confirms the benefits of probiotics for patients taking antibiotics, especially those at risk of CDI.

Kate Rowland, MD, MS; Dionna Brown, MD; Bernard Ewigman, MD, MSPH
The University of Chicago

1. Johnston BC, Ma SY, Goldenberg JZ, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:877-888.
2. Goldenberg JZ, Ma SS, Saxton JD, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev.* 2013;(5):CD006095