Translating Best Evidence into Best Care

EDITOR'S NOTE: Studies for this issue were identified using the Clinical Queries feature of PubMed, searching *JAMA Pediatrics* and *The Journal of Pediatrics*, and using customized EvidenceUpdates alerts.

EVIDENCE-BASED MEDICINE PEARL: BLOCK RANDOMIZATION: Standard randomization may be problematic in a multisite study, where small sites contribute few patients. When the sample size is small, patients may be over-assigned to one study group. To minimize this group-allocation skewing, investigators use forced, equal allocation, where a computer generates small, equal-group allocation sets, called blocks. For example, in a two-group study, a block of eight has 4 slots each for groups "A" and "B," ordered randomly, such as ABABAABB, with consecutive patients assigned in that order. Every 8 patients are thereby equally assigned to groups A and B. Although this approach is a less "pure" form of randomization, as no individual patient has an equal chance of assignment to either group, it is accepted as valid and helps avoid an aspect of site-specific bias. Please piece by Leung on page 777 regarding article Simpson EL et al (*J Allergy Clin Immunol* 2014;134:818-23), for an example of a randomized controlled trial employing block randomization.

LITERATURE SEARCH PEARL: THE GREY LITERATURE: If you are interested in finding an unpublished clinical research manuscript, a health policy report, a report of a clinical trial protocol, a dissertation, a government or business report — or any hard-to-get, noncommercially-published document—you need to enter the realm of the "grey literature." Access to the grey literature is not always straightforward. However, access may be important (eg, identifying unpublished studies in preparation for guideline development). Smoothing out the literature search path are a number of resources available online. The New York Academy of Medicine (http://www.greylit.org) provides links to databases for a variety of health related matters, including health policy, prevention, and global health, as well as the bimonthly Grey Literature Report. New York University Libraries website has a Grey Literature page (http://guides.nyu.edu/greylithealth) with links to a number of portals, some of which access clinical trials both in the US and globally, Centers for Disease Control and Prevention reports, dissertations, health-related organizations that produce various types of documents and presentations, research in progress, and proceedings of meetings. Finally, GreyNet International via its GreySource index (http://www.greynet.org/greysourceindex.html) provides links to the grey literature on many topics including biomedical.

—Jordan Hupert, MD

Porphylactic emollient use beginning at birth prevents atopic dermatitis

Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol.* 2014;134:818-23.

Question Among infants at high risk for atopic dermatitis (AD), what is the therapeutic efficacy of prophylactic emollient use beginning soon after birth, compared with no use, on development of atopic dermatitis?

Design Block randomized controlled trial.

Setting Portland, Oregon, and 3 acute National Health Service hospital trusts, United Kingdom.

Participants Infants within 3 weeks of birth at high risk of AD (family history of atopic disease).

Intervention Emollients or none for 6 months.

Outcomes The incidence of AD at 6 months.

Main Results Number needed to treat (NNT) with emollients to prevent one patient from developing AD, not accounting for patients lost to follow-up (LTFU): 5 (95% CI 3-23). NNT assuming all patients LTFU in both groups developed AD: NNT 6 (95% CI 3-1138). NNT, worst-case scenario (treatment LTFU developed AD, control did not): 19 (95% CI 5-infinity).

Conclusions Emollient therapy from birth prevents atopic dermatitis at 6 months of age.

Commentary Recent advances demonstrate that AD is associated with skin barrier defects that may contribute to the local inflammatory response by allowing penetration of allergens and microbes into AD skin.[1] As there is no cure for this common skin disease, there has been considerable interest in whether atopic dermatitis may be prevented. The finding by Simpson et al that emollient therapy from birth can reduce the incidence of AD is important. The reliability of this observation is strengthened by a second, independent paper published in the same issue of *The Journal of Allergy and Clinical Immunology*, demonstrating that daily emollient versus control therapy in a randomized controlled trial of 108 subjects in Japan resulted in significant reduction of AD.[2] If these studies are confirmed in larger trials, emollient therapy from birth may be a simple intervention that may reduce the prevalence of AD. This would provide an opportunity to observe whether reduction in AD interferes with the onset

of the atopic march, where AD evolves into food allergy, asthma, and allergic rhinitis. Importantly, both of these studies were relatively short-term without follow-up off emollient therapy. Therefore, it is not known whether emollients truly prevent AD or AD might still occur after emollient therapy is stopped.

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2. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol 2014;134:824-30.

Antibiotic prophylaxis prevents urinary tract infection recurrence

Hoberman A, Greenfield SP, Mattoo TK, Keren R, Mathews R, Pohl HG, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med.* 2014;370:2367-76.

Question Among children with vesicoureteral reflux, what is the efficacy of antibiotic prophylaxis, compared with placebo, in preventing urinary tract infection (UTI) recurrence?

Design Randomized controlled trial.

Setting 19 clinical sites across the US.

Participants Children with UTI, 2-17 months of age, who also have vesicoureteral reflux.

Intervention Prophylaxis with trimethoprim–sulfamethoxazole vs placebo.

Outcomes Recurrent UTI.

Main Results Recurrent UTI developed in 13% vs 24% of children (prophylaxis vs placebo). Number need to treat, 10 (95% CI, 6 to 22). Renal scarring did not differ significantly.

Conclusions Antimicrobial prophylaxis was associated with a reduced risk of UTI recurrence.

Commentary In the early 1990s, during a national seminar on UTI in children, I pointed out that the evidence base supporting the use of antimicrobials to prevent UTI was very weak and suggested that placebo-controlled trials were warranted. A senior pediatric nephrologist recommended (fairly strongly) that I be seated and warned the audience that if my heretical views were acted on, there would be an epidemic of end-stage kidney failure from preventable UTI-associated kidney damage (so-called "reflux nephropathy"). My, how things have changed! Now we have seen a flurry of placebo-controlled trials and the American Academy of Pediatrics issuing of guidelines against the use of antibiotics to prevent UTI in young children with reflux.[1] Hoberman et al consolidate substantially what we know about the effect of antimicrobials (specifically trimethoprim-sulfamethoxazole) for the prevention of UTI in children, albeit in a select group of children at risk—those with vesicoureteral reflux. Antimicrobials reduce the risk of UTI recurrence by about one-half and that effect is very consistent across a broad range of children, but if recurrent UTI occurs, resistant pathogens are more likely. These results are entirely consistent with the other placebo-controlled trials,[2] but extend our knowledge by demonstrating that the effect on new kidney damage ("scarring") is likely to be negligible at best. The implications of the study are clear: (1) antimicrobial prophylaxis does reduce UTI recurrence but is very unlikely to prevent new scarring; (2) the guidelines of the American Academy of Pediatrics need a substantial revision as a matter of urgency; (3) we do not need any more placebo-controlled trials of antimicrobials, but trials of different antimicrobials are required; and (4) not all children with a single index UTI need prophylaxis (only 40% of children had a recurrence). Children likely to benefit include those with recurrent UTI, very young children, or whose first infection was particularly serious.

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2. Williams G. Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. [Review][Update of Cochrane Database Syst Rev. 2006;CD001534; PMID: 16855971] Cochrane Database of Systematic Reviews. (3):CD001534, 2011.

Pulse oximetry based decisions increase hospitalization in bronchiolitis

Schuh S, Freedman S, Coates A, Allen U, Parkin PC, Stephens D, et al. Effect of oximetry on hospitalization in bronchiolitis: a randomized clinical trial. *JAMA*. 2014;312:712-8.

Question Among otherwise healthy infants with bronchiolitis, what is the influence of the pulse oximetry value on hospital admission rates from the emergency department (ED)?

Design Block-randomized controlled trial.

Setting ED in Toronto, Canada.

Participants Otherwise healthy infants, 4 weeks –12 months, with first episode of mild to moderate bronchiolitis (true saturations $\geq$ 88%).

Intervention Pulse oximetry with true, versus falsely-elevated (by 3 points) displayed values.