Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

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Efficacy of Roflumilast in Asians with COPD

Source: Zheng J, et al. *Chest* 2014;145: 44-52.

Site-specific phosphodiesterase (PDE) inhibition is now a standard component of pharmacotherapy. Because PDE5 is selectively located in the genital area, PDE5 inhibition (e.g., sildenafil, tadalafil, vardenafil) can improve circulatory flow and enhance sexual function. PDE3 is located dominantly in the circulation of the lower legs, enabling the PDE3 inhibitor cilostazol to improve circulation in patients with intermittent claudication. PDE6 is located in the retina, such that sildenafil (which has PDE5 and PDE6 inhibition activity) can produce blue visual effects. PDE4 is located in the pulmonary system, and PDE4 inhibition has recently been added to the pharmacotherapy of chronic obstructive pulmonary disease (COPD) in the form of roflumilast.

In the United States, roflumilast is FDA-approved for reducing COPD exacerbations. Although registration trials have shown modest bronchodilatory activity from PDE4 inhibition, the degree of bronchodilation produced by the PDE4 inhibitor roflumilast is below the threshold required by the FDA to be specifically labeled as a bronchodilator.

Ethnically diverse responses to pharmacotherapy are increasingly recognized to be of clinical significance. For instance, there are clinically meaningful differences in the metabolism of theophylline between American children and Chinese children. Zheng et al evaluated the effects of roflumilast treatment of COPD in an Asian population.

The efficacy of roflumilast in this all-Asian population was consistent with prior published results in non-Asian populations. Unless the current and evolving smoking status of much of Asia (especially men) experiences a prominent reversal — some recent reports indicate that as many as 50% of adult Chinese men are smokers — we can anticipate the need for a full complement of COPD treatments in the coming decades. ■

Atopic Dermatitis Patients Should Avoid Some Topical Preservatives

Source: Shaughnessy CN, et al. *J Am Acad Dermatol* 2014;70:102-107.

The course of atopic dermatitis (AD) can vary from being a minimally distracting nuisance to calamitous. Often becoming apparent even in infancy, the course of AD is characterized by lifelong recurrences of pruritic dermatitis most commonly on the hands, face, scalp, and trunk. Unfortunately, there is no known cure for AD, although combinations of immune-modulating drugs — topical and systemic — can usually provide good symptomatic control.

It has not gone unnoticed that persons with AD are often hyper-responsive to a variety of topical irritants, including everyday contact items like wool clothing. Similarly, AD subjects have been shown to be more burdened with induction of contact dermatitis from the most commonly recognized contact allergens (e.g., metals such as nickel).

Following that line of thought, Shaughnessy et al sought to determine whether AD patients would also be more sensitive to commonplace preservatives found in topical creams, emollients, and moisturizers that are encountered in day-to-day living in such products as makeup, sunscreen, and hand lotions.

Using a panel of recognized skin-sensitizing preservatives, the investigators performed patch testing on patients suspected of allergic contact dermatitis (n = 2453). The panel of allergens included the seven most commonly recognized preservatives responsible for allergic contact dermatitis.

AD patients were significantly more likely than non-AD patients to have positive patch tests. The category of topical agents known as formaldehyde releasers (e.g., quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin) was disproportionately represented among the sensitizing agents in AD subjects, and the authors suggest that AD patients be advised to avoid products containing these agents. ■

A More Confident 'Maybe' for the Role of Genotyping in Warfarin Therapy

Source: Pirmohamed M, et al. *N Engl J Med* 2013;369:2294-2303.

It is difficult to contest the excellence of warfarin for risk reduction in atrial fibrillation (average stroke reduction approximately 66%; mortality reduction 26%). Nonetheless, maintenance therapy with warfarin is complicated by drug in-

teractions, dietary interactions, and the foibles of inconsistent medication administration in even the best of hands. The consequences of significant bleeding — especially intracranial bleeding — have spawned a variety of plans for initial dosing and subsequent dose adjustment, each method seeking the most prompt and safe pathway for achieving a therapeutic level of anticoagulation while avoiding over-anticoagulation.

A good deal of the variation in response to warfarin is due to genetic metabolic pathways, particularly CYP2C9 and VKORC1. Identification of individual genetic makeup in reference to these pathways could help predict (at least in theory) doses of warfarin necessary to achieve therapeutic anticoagulation.

First, the good news. In the clinical trial by Pirmohamed et al (n = 455) in which genotyping was performed, there was a statistically significant increase in time in the therapeutic range (67.3%) vs traditional warfarin dosing (60.3%). Additionally, the incidence of excessive anticoagulation was less in the group whose dosing was based on genotyping.

The bad news, however, is that in the same issue of the *New England Journal of Medicine* another trial (n = 1015) that compared pharmacogenetic-based warfarin dosing vs standard dosing found no difference between methodologies (*N Engl J Med* 2013;369:2283-2293). Counterintuitively, in black patients in the latter trial, maintenance of a therapeutic INR was actually less in the pharmacogenetic-based group.

At the current time, you and I do not have to worry about sorting this out, since current guidelines do not advocate routine genetic testing. The status of pharmacogenetic warfarin management remains controversial. ■

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Simple Steps to Better Oral Hygiene in the Long-Term Care Facility

Source: Gutkowski S. *Ann Long-Term Care: Clin Care Aging* 2013;21:26-28.

Although oral hygiene may not seem to be as much a "major league" issue as cardiovascular disease (CVD), diabetes, or dyslipidemia, poor oral hygiene status has actually been linked to important outcomes, including pneumonia and CVD. Although the mechanisms are incompletely understood, gingival and periodontal inflammation seen in persons with poor oral hygiene is associated with worse CVD outcomes, perhaps due to systemic consequences of local inflammation.

Of course, there are other consequences to poor oral hygiene including tooth loss, halitosis, and eating difficulties. Yet, there has been little attention paid in the medical literature to simple steps that might improve oral health in long-term care facilities. Although mechanical tooth-brushing on a regular basis would doubtless be helpful, this would be a somewhat labor-intensive intervention for staff to participate in.

Gutkowski performed a small pilot study based on the premise that xylitol, a five-carbon sugar commonly found in many fruits and vegetables, might be helpful to improve oral hygiene, since oropharyngeal bacteria are not able to use five-carbon sugars to create their self-protective biofilm in which they establish long-term residence, leading to tooth decay, calculus, and periodontal disease. Since xylitol is readily available in chewing gum, and many adults of all ages find chewing gum to be a pleasant activity, a pilot trial (n = 6) to ascertain the effect on oral biofilm through xylitol gum chewed twice daily for 3 months was undertaken. In addition to the xylitol gum, residents were also asked to apply a calcium/phosphorus-containing mineral paste called "MI Paste" twice daily, to additionally help prevent tooth decay.

At the end of the 3 months, there was a readily visible (as seen through the use of dental disclosure tablets) improvement in biofilm levels. Simple steps may make important inroads in oral health for persons in long-term care facilities. ■

Is There a Link Between Psoriasis and Hyperuricemia?

Source: Gisondi P, et al. *J Am Acad Dermatol* 2014;70:127-130.

Whether elevated uric acid (UA) levels merit our attention as a cardiovascular (CV) risk factor is a long-embattled issue. Data accruing from the Framingham Heart Study, beginning in 1948, found that UA was associated with CV disease, but we must remember that such an association does not prove causation. Even if such a causal role is confirmed, it remains to be determined whether modulation of UA will be both safe and effective.

Both rheumatoid arthritis (RA) and psoriasis (with our without psoriatic arthritis) are commonly categorized as rheumatologic disorders because of their relatedness through abnormal immunologic pathways. Indeed, the identification of increased CV risk in patients with psoriasis followed quickly on the heels of more widespread appreciation of the important magnification of CV risk imparted by RA.

Despite the recognition that psoriasis and RA are associated with increased CV risk, the mechanism(s) for this risk remains ill-defined — hence, the understandable exploration of the incidence of hyperuricemia in psoriatic patients.

Gisondi et al compared serum UA levels in consecutive patients with psoriasis (n = 119) vs controls (n = 119). Asymptomatic hyeruricemia was almost three times as common in psoriasis patients (19%) as controls (7%). Additionally, the mean serum UA levels were significantly higher in psoriasis patients than controls (5.6 md/dL vs 4.9 mg/dL).

Psoriasis is typified by accelerated turnover of skin cells, which could contribute to serum UA. Whether elevations of UA cause or contribute to the observed increase in CVD seen in psoriasis patients remains to be determined. ■