Clinical Briefs in Primary Care™

The essential monthly primary care update

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Can Appendicitis be Cured with Antibiotics Alone?

Source: Vons C, et al. *Lancet* 2011;377:1573-1579.

Sometimes, acute appendicitis (AAP) just goes away. We know this because of abdominal explorations that disclose evidence of chronic appendicitis, indicative of one or more prior episodes. Four randomized trials support the relevance of antibiotic treatment for AAP, but definitive conclusions about the appropriate role of antibiotics in AAP treatment have been limited by aspects of previous study design.

Vons et al performed a controlled trial of adult patients with CT-confirmed uncomplicated AAP who were randomized to antibiotics (amoxicillin/clavulanic acid 3-4 g/d) or surgery. Although one group was assigned to surgery alone, the surgical group also actually received a single parenteral 2 g dose of amoxicillin/clavulanic acid at induction of anesthesia; additionally, if complicated appendicitis was discovered at surgery (i.e., the appendicitis had progressed or was misdiagnosed by CT), antibiotics were subsequently administered even in the surgery group.

Peritonitis within 30 days of intervention — the primary endpoint of the trial — occurred more often in the antibiotic group (8% vs 2%), hence the noninferiority of antibiotic treatment was NOT confirmed. If future tools can do a better job of identifying those who truly have uncomplicated appendicitis, antibiotics may prove to be a more valuable first-line treatment. ■

Antihypertensive Medication Nonadherence and Blood Pressure

Source: Rose AJ, et al. *J Clin Hypertens* 2011;6:416-421.

It comes as no surprise that when patients do not take their blood pressure (BP) medication, a lapse in BP control is anticipated. On the other hand, when a patient presents with an elevated BP and acknowledges omitted doses, it is difficult to be sure whether the observed elevation in BP is solely due to recent omissions, an underlying worsening of BP (requiring an augmentation rather than just simple restoration of treatment), rebound BP elevation, or some combination of these elements. To gain a more concrete insight into the anticipated impact of omitted BP medication in a typical patient population, Rose et al reviewed data from a population (n = 869) enrolled in a trial investigating the effects of physician communication on BP control. A component of the study design was utilization of medication bottles with memory caps that recorded timing and frequency of opening, providing a detailed view of medication administration.

When comparing BP after a 7-day period of poor adherence (< 60% of prescribed medication administered) to a prior period of excellent adherence, BP was 12/7 mmHg higher immediately following the week of poor adherence.

Clinical inertia — failure to intensify treatment despite suboptimal goal attainment — is sometimes innocently propagated by clinician uncertainty about whether uncontrolled BP should simply be attributed to missed doses or needs treatment augmentation. The authors suggest that clinicians consider a maximum BP excursion of 15/8 mmHg as potentially likely due to poor medication adherence, and that when BP elevation is greater than this amount, consider augmentation of antihypertensive treatment rather than simply encouraging better adherence to the existing regimen. ■

PDE5 Inhibition and Cognitive Function

Source: Shim YS, et al. *Int J Impot Res* 2011;23:109-114.

The therapeutic realm of PDE5 inhibitors has expanded to include not only erectile dysfunction (ED) but also pulmonary hypertension. Animal studies have identified PDE5 activity in the brain, which can be impacted by currently available PDE5 inhibitors since they readily cross the blood-brain barrier. In the animal CNS, increased cyclic GMP (a pharmacodynamic effect of PDE5 inhibition) is seen in pathways associated with memory; studies have confirmed enhanced cognition in animals with impaired cognition related to diabetes, anticholinergic medications, and hyperammonemia who are treated with PDE5 inhibitors.

Udenafil is a PDE5 inhibitor not available in the United States but already in use in other countries (e.g., Korea, Russia) for treatment of ED. Shim et al undertook a trial of udenafil in men with ED but without known cognitive dysfunction (n = 30). Subjects underwent a battery of tests of cognitive function at baseline and 8 weeks later. Testing metrics included measures of general cognitive function,

verbal learning for episodic memory, and frontal executive function.

Several tests of cognitive function showed statistically significant improvement. Cognitive function improvement was greater in men whose sexual function scores improved the most. The authors suggest further exploration of the effects of PDE5 inhibition on cerebral flow to gain greater understanding of the favorable cognitive effects they have demonstrated. ■

What Things are Making us Gain Weight?

Source: Mozaffarian D, et al. *N Engl J Med* 2011;364:2392-2404.

Since two-thirds of Americans are overweight or obese, most of us should probably be trying to better understand why. Perhaps the observation that the daily number of calories per capita continues to increase, while daily energy expenditure dwindles, is enough to satisfy the casual observer. Or is the *character* of caloric intake — such as high glycemic index carbohydrate vs low — a critical factor? As yet, despite simple answers (just reduce calories), there are few simple solutions (folks cannot/will not adhere to calorie-based dietary restrictions).

Might it help to identify commonplace "culprit" foods — that is, dietary components associated most often with weight gain, rather that just total calorie counts?

Based on follow-up of healthy U.S. adults during observational periods lasting as long as 20 years (n = 120,877), Mozaffarian et al determined that several commonplace dietary and lifestyle factors were associated with weight gain. For instance, over a 4-year interval, for every additional daily serving of potato chips, there was a 1.69 lb weight gain. Sugar-sweetened beverages were next on the list of items associated with weight gain. Perhaps, not surprisingly, physical activity, fruits, grains, nuts, and vegetables were inversely associated with weight.

Despite widespread public awareness of the health consequences of being overweight and obesity, most are not able — using currently advised methods — to reverse the trend for weight gain. Whether targeting elimination of specific dietary components (e.g., sugar-sweetened beverages) and/or the augmentation of selected favorable components (e.g., nuts, grains, fruits) will prove to be effective remains to be determined. ■

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Disease-Modifying Antirheumatic Drugs and Risk for Developing Diabetes

Source: Solomon DH, et al. *JAMA* 2011; 305:2525-2531.

Prior to the advent of disease-modifying antirheumatic drugs (DMARDs), the possibilities for remission of disorders like rheumatoid arthritis (RA) and severe psoriasis (PSOR) were remote. Along with the welcome dramatic clinical improvements seen with DMARDs, concerns about adverse effects — such as adversities associated with either the consequences of their immunomodulatory activity or direct toxic effects — require a high level of vigilance. Recently, however, there has been recognition that biologic DMARDs such as TNF inhibitors or hydroxychloroquine, when used in RA or PSOR, might be associated with a lesser risk of diabetes.

Solomon et al performed a retrospective study of RA/PSOR patients who began treatment with a DMARD (n = 121,280) in the United States and Canada. Compared with nonbiologic DMARDs (examples include sulfasalazine, leflunomide, cyclosporine, and others), use of biologic DMARDs was associated with a 23%-46% lesser risk of new-onset diabetes. Because cardiovascular (CV) risk is magnified in persons with RA, treatment choices may be influenced by consideration of agents less likely to further augment CV risk through induction of diabetes. ■

The Ipswich Touch Test for Diabetic Peripheral Neuropathy

Source: Rayman G, et al. *Diabetes Care* 2011;34:1517-1518.

Type 2 diabetes (DM2) remains the #1 cause of atraumatic limb amputation in the United States. The primary cause of foot ulcers that progress to limb loss is diabetic neuropathy, which decreases sensory awareness of tissue trauma, allowing destruction to progress without warning signs that would otherwise stimulate seeking care for injuries or infections. Albeit consistently recommended by consensus guidelines, routine examination of the feet remains markedly suboptimal by both clinicians and patients alike. Although monofilament and tuning fork testing are highly effective in identifying the presence of diabetic neuropathy, they also remain underutilized.

The Ipswich Touch Test (named after the United Kingdom Hospital in which it was developed) is performed by "lightly touching/resting the tip of the index finger for 1-2 seconds on the tips of the first, third, and fifth toes and the dorsum of the hallux." The presence of neuropathy is defined by this method as having two or more of the eight sites (four sites on each foot) being insensate.

The gold-standard for identification of diabetic neuropathy in this trial was vibration perception threshold as determined by a neurothesiometer. Both monofilament and the Ipswich Touch Test were highly sensitive and had strong positive-predictive value for the presence of neuropathy. When the Ipswich Touch Test compared with monofilament testing, there was near-perfect agreement. As discussed by the authors, perhaps the lack of requirement for specialized measurement tools will prompt clinicians to be more consistently proactive in seeking to define diabetic neuropathy in the feet. ■