Clinical Briefs in Primary Care™

The essential monthly primary care update

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Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 11, NUMBER 12 PAGES 23-24 DECEMBER 2006

Global Consequences of Smoking

Source: Teo KK, et al. *Lancet*. 2006; 368:647-658.

In the United States, COPD is the 4th leading cause of death. Widespread public education about smoking toxicity has not decreased COPD mortality, and since 2000 the number of women who die from COPD has eclipsed men.

Worldwide, more men than women suffer toxicity from smoking, with an average life shortening of 22 years for those who succumb to smoking-related disease. Currently, persons in developing countries comprise 82% of all smokers worldwide.

The INTERHEART study is a case-control study which recruited participants from 52 countries in Asia, Europe, the Middle-East, Africa, Australia, and the Americas. The cohorts compared were persons with first acute MI (n = 15,152) and age/sex-matched controls.

The odds ratio for non-fatal MI in current smokers was approximately 3 times that of non smokers. After smoking cessation, this risk was almost halved by 3 years time, but was never reduced to the level of risk of lifelong non-smokers.

Second-hand smoke was also directly associated with increased risk for MI in a graded fashion: even a 'low' level of exposure (1-7 hours/week) was associated with a 24% increased odds ratio for MI, and persons in the highest quartile of exposure (more than 22 hours/week) had a 62% increased odds ratio. Developing countries do not have well established policies to educate the public about health risks of smoking. The majority of life lost in the decades to come will be in developing countries; development of effective cessation programs, public education to prevent the acquisition of a tobacco habit, and heightened public awareness of risks to non-smokers are critically needed. ■

Celecoxib for Prevention of Sporadic Colorectal Adenomas

Source: Bertagnolli MM, et al. *N Engl J Med*. 2006;355:873-884.

The knowledge that colonic adenoma express tumorigenic cyclooxygenase-2 (COX-2), whereas healthy colonic mucosa does not, led to clinical trials in high-risk populations which have confirmed that COX-2 inhibition reduces colorectal cancer (CCA). For persons with familial adenomatous polyposis, a population with exaggerated CCA risk, celecoxib has shown antitumor activity. Whether the antitumor activity of celecoxib might be useful in prevention of new adenomas for persons who have already had one adenoma detected—but do not have familial adenomatous polyposis—was the subject of this trial.

Patients (n = 2,035) were randomized to receive celecoxib (200 mg b.i.d. or 400 mg b.i.d.) or placebo and were followed for three years, with colonoscopy at years one and three.

Celecoxib was associated with statistically significant reductions in new adenomas: a 33% relative reduction at 200 mg b.i.d., and 38% reduction at 400 mg b.i.d. compared to placebo. Attesting to the elevated risk of new adenomas in this population is the > 60% incidence of new adenomas amongst the placebo group.

Unfortunately, an increase in cardiovascular risk (2.6-3.4 risk ratio increase) was seen in this middle aged population (mean age = 59 years). Although risk reduction for new adenomas is evident, competing cardiovascular risk must temper enthusiasm for these favorable results. ■

Trends in Herpes Simplex Prevalence

Source: Xu F, et al. *JAMA*. 2006;296: 964-973.

Early thinking about herpes simplex virus (HSV) simplified pathology into anogenital lesions, which were caused by HSV type 2 (HSV-2), and orofacial lesions which were caused by HSV type 1 (HSV-1). Increasingly, it became clear that either virus could cause lesions at either site, although the preponderance of pathogen-specific sites was still consistent with the earlier thinking. The use of HSV typing was based upon the observation that HSV-1 anogenital lesions have a less frequent recurrence pattern. Although genital HSV-2 is usually sexually transmitted, either type of HSV may be acquired by non-sexual means, and most acquisition is asymptomatic.

Since 1994, overall HSV-2 seroprevalence has declined almost 20% and HSV-1 seroprevalence has decreased 6.9%. On the other hand, there has been a more than four-fold increase in the percentage of individuals whose anogenital HSV is attributable to HSV-1 (ie, they have been diagnosed with

genital herpes, but are HSV-2 seronegative), albeit the absolute percentage remains low.

Highly effective antiviral therapies to reduce HSV transmission and recurrences are available, and promising results for an HSV vaccine have been reported. Because HSV-2 infection is associated with increased risk for HIV acquisition, enhanced methods for HSV prevention are a priority. ■

Diabetes Prevention: 7 Ways to Leave Your Sugar

Source: The DREAM Trial Investigators. *Lancet*. 2006;368:1096-1105.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) appear to be the steps directly preceding the development of overt diabetes. Randomized clinical trials have demonstrated that several different interventions can reduce the development of diabetes for persons with IFG or IGT: acarbose, diet and exercise, or metformin. The thiazolidinedione troglitazone has also demonstrated efficacy, but was withdrawn from the market due to liver toxicity. Functional similarities between troglitazone and rosiglitazone (ROS) suggest that the latter should also be effective to prevent progression from IFG/IGT to frank diabetes, without the attendant risk of hepatic dysfunction.

The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication)Trial randomized 5808 persons with either IGT or IFG (as determined by 75 g oral GTT) to ROS or placebo. Dosing of ROS was 4 mg/d × 2 months then 8 mg/d × 3 years.

ROS treatment reduced the composite primary end point (incident diabetes or death) by 60%, and the specific secondary end point of new onset diabetes by 62% ($P < 0.0001$ for each). Risk reduction was similar whether the subject entered the trial with IFG or IGT. Clinicians now have numerous evidence-based pathways from which to choose if they wish to intervene in persons with IFG or IGT to prevent diabetes. ■

Mortality Amongst Persons with Hepatitis B or Hepatitis C

Source: Amin J, et al. *Lancet*. 2006;368:938-945.

Both hepatitis B (HEPB) and hepatitis C (HEPc) may progress to advanced liver disease, but little data have addressed the long-term mortality associated with these infections. The Notifiable Diseases Database of Australia provides an opportunity to retrospectively examine outcomes in persons with hepatitis.

During the 1990-2002 period, 117,547 persons were identified with HEPb or HEPc. Standardized mortality ratios were greatly magnified for death from liver disease in persons with either HEPb or HEPc, and risk was compounded when co-infected with both. For instance, persons with HEPb incurred a risk of liver-related death was 12-fold greater than age-matched persons without HEPb; for HEPb/HEPc coinfection, risk was magnified 33-fold.

One (perhaps) surprising data point emerged from this study: in persons with HEPc, risk of dying from illicit drug-related causes was actually greater than liver-related causes. Because 80% of HEPc in Australia is acquired through intravenous drug use, continued substance use remains a problem whose mortality outweighs that of the HEPc disease process itself. ■

Medical Management of Kidney Stones

Source: Hollingsworth JM, et al. *Lancet*. 2006;368:1171-1179.

Kidney stones (KST) are epidemiologically important in the United States, being responsible for almost 2 million annual office or emergency department visits in recent years. Small distal ureteral stones (< 5 mm) will spontaneously pass most of the time, but surgical treatment is sometimes required.

Calcium channel blockers (CCB) and alpha-blockers (ALB) have physiologically appealing activity that could enhance likelihood of stone expulsion: they decrease ureteral smooth muscle spasm, while allowing continued physiologic ureteral peristalsis.

Hollingsworth et al report upon a literature search of all randomized controlled trials (n = 417) of CCB or ALB to treat kidney stones (total patient n = 693). The pooled data indicate a 65% greater likelihood of stone passage in persons receiving CCBs or ALB than in persons treated with simple analgesia (eg, NSAIDs or other analgesics).

Most of the clinical trials employing CCB or ALB have been published in subspecialty literature. The authors suggest that the available evidence supports inclusion of medical therapy (alpha blockers or calcium channel blockers) to enhance likelihood of KST passage. Tamsulosin and nifedipine were the most commonly reported agents representative of ALB and CCB respectively. Because both classes of drugs have a high degree of familiarity to clinicians, and the adverse effect profiles are excellent, CCB/ALB treatment may reduce the need for surgical intervention in persons suffering KST and deserve consideration by primary care clinicians as appropriate medical therapy. ■

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