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Welcome to the eighty-seventh issue of GP Research Review.

The use of antibacterial prophylaxis to prevent urinary tract infection (UTI) recurrences in children with vesicoureteral reflux (VUR) remains controversial. However, unequivocal evidence published recently in the *NEJM* has attested to the benefits of such treatment. The research involved children (aged 2–71 months) who were diagnosed with VUR following a first or second episode of UTI. Those who were treated with trimethoprim/sulphamethoxazole over a 2-year period to prevent infections were far less likely to have recurrent UTI compared with those who received placebo. Moreover, certain subgroups of children derived more benefit than others from antibacterial prophylaxis, particularly those with bladder and bowel dysfunction at study entry, and those who had a fever with their initial UTI.

A large, prospective cohort study from France suggests that premenopausal women who have “very many” moles may have a significantly higher risk of breast cancer than women who have no moles. Perhaps in future screening scores for breast cancer will include number of moles as an important marker.

The PrediMed study from Spain shows that an increase in extra virgin olive oil and nut intake in the context of a Mediterranean diet results in fewer adverse cardiovascular (CV) events (stroke, myocardial infarction, and CV death). The higher the daily olive oil intake, the greater the risk reduction.

I hope you enjoy this issue and I welcome your comments and feedback.

Kind Regards
Jim

Associate Professor Jim Reid
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Antimicrobial prophylaxis for children with vesicoureteral reflux

**Authors:** RMUR Trial Investigators

**Summary:** The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial enrolled 607 children aged 2–71 months who were diagnosed with vesicoureteral reflux (VUR) following a first or second episode of urinary tract infection (UTI). The children were randomised to receive trimethoprim/sulphamethoxazole or placebo. Recurrent UTI developed in 39 of 302 children (13%) who received prophylaxis as compared with 72 of 305 children (24%) who received placebo (relative risk 0.55; 95% CI, 0.38 to 0.78). Prophylaxis reduced the risk of recurrences by 50% (hazard ratio [HR] 0.50; 95% CI, 0.34 to 0.74) and was particularly effective in children whose index infection was febrile (HR 0.41; 95% CI, 0.26 to 0.64) and in those with baseline bladder and bowel dysfunction (HR 0.21; 95% CI, 0.08 to 0.58). The occurrence of renal scarring did not differ between the groups (11.9% for the prophylactic group and 10.2% for the placebo group). Among 87 children with a first recurrence caused by *Escherichia coli*, the proportion of isolates that were resistant to trimethoprim/sulphamethoxazole was 63% in the prophylaxis group and 19% in the placebo group.

**Comment:** This study has a “yes/but” result. The risk of recurrence of infection was essentially halved with prophylaxis, but in the group whose first recurrence was caused by *E. coli*, there was a high (63%) development of resistance to trimethoprim/sulphamethoxazole. There was no difference in the development of renal scarring between the placebo and prophylactic group. The real conclusion is that the cause of the vesicoureteral reflux should be primarily addressed.


**Abstract**

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Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes

Authors: Roumij CL et al.

Summary: Data were retrospectively analysed from the national Veterans Health Index databases, which included 178,341 veterans with diabetes initially treated with metformin from 2001 through 2008 who subsequently added either insulin (n=2948) or a sulphonylurea (n=39,990). The aim of the study was to compare the risk between therapies of a composite primary outcome of acute myocardial infarction (AMI), stroke hospitalisation, or all-cause death. Additional propensity score matched analysis was performed on a subset of 2436 veterans in the insulin group and 12,180 veterans in the sulphonylurea group. Patients had received metformin for a median of 14 months before treatment intensification; median follow-up after this addition was 14 months. There were 172 vs 634 events for the primary outcome among patients who added insulin vs sulphonylureas, respectively (42.7 vs 32.8 events per 1000 person-years; adjusted hazard ratio [aHR], 1.30; 95% CI, 1.07 to 1.58; p=0.009). AMI and stroke rates were statistically similar, 41 vs 229 events (10.2 and 11.9 events per 1000 person-years; aHR, 1.44; 95% CI, 0.91 to 2.28; p=0.01). There were 54 vs 258 secondary death rates were 137 vs 444 events, respectively (33.7 and 0.88; 95% CI, 0.59 to 1.30; p=0.52), whereas all-cause death rates were 22.8 events per 1000 person-years; aHR, 1.15 to 1.79; p=0.001). There were 54 vs 258 secondary outcomes: AMI, stroke hospitalisations, or cardiovascular deaths (22.8 vs 22.5 events per 1000 person-years; aHR, 0.49; 95% CI, 0.71 to 1.34; p=0.87).

Comment: I have commented on over 850 papers during the Research Review series, and (I think) this is the first one in which my interpretation has not been correct. Thank you for the “spotter’s” emailing about this. On reflection, and reading this paper again – insulin did not win “hands down” and the opposite is the case. Beware the sample size as the sulphonylurea set numbers greatly outnumber the insulin one, and this is of course reflected in the absolute numbers of events. In a nutshell there basically was no statistical difference in rate of AMI, stroke, or cardiovascular deaths in the two groups, but all-cause mortality was markedly increased in those on insulin.

Reference: JAMA 2014;311(22):2288-96

How do GPs want to learn in the digital era?

Authors: Yee M et al.

Summary: A total of 2500 GPs in Australia participated in a national survey conducted in 2012 that questioned their preferences for continuing medical education (CME) activities and motivation for choice. The vast majority (95%) preferred learning in a group rather than on their own. The analysis identified that 83% preferred face-to-face lecture-based formats, 70% preferred interactive group discussions, 66% preferred one-to-one learning with an expert, and 55% preferred online self-education. Relevance to clinical practice was the key motivation for participation (80%).

Comment: My feeling is that we are in a transition period. The oldies (that’s me – though I am barely run-in) “learned” by listening to pearls of wisdom being dropped from above in lectures. Damned if I can remember much from lectures I have attended. The problem is that there are many ways that people learn and we are all individuals. What is apparent from someone who has spent his whole professional life in medical education is – to teach is not to ensure learning occurs; to learn does not necessarily mean understanding occurs, and understanding is not to do; but to do and understand is to remember. We all do this in different ways and in another 10 years when a new generation of doctors is upon us we will continue to advance our learning styles – but it will still be individual.


Impact of changes to reimbursement of fixed combinations of inhaled corticosteroids and long-acting β2-agonists in obstructive lung diseases

Authors: Bjørnsson ÓUS et al.

Summary: Outcomes are reported from an evaluation of the effects of a cost-saving policy change introduced by the Icelandic government in 2010 that limited reimbursement of fixed inhaled corticosteroids/long-acting β2-agonist (ICS/LABA) combinations. The policy change took effect on 1 January 2010 (index date); data for the year preceding and following this date were analysed in 8241 patients with controlled/partially controlled asthma and/or chronic obstructive pulmonary disease (COPD) who had been dispensed an ICS/LABA during 2009. Following the policy change, 47.8% fewer fixed ICS/LABA combinations were dispensed during the post-index period among patients whose asthma and/or COPD was controlled/partially controlled during the pre-index period. There were also fewer ICS monocomponents dispensed. After the policy change, 48.6% of patients were no longer receiving any respiratory medications. This led to reduced disease control, as demonstrated by more healthcare visits (44.0%) as well as more oral corticosteroid (76.3%) and short-acting β2-agonist (SABA; 51.2%) dispensations.

Comment: An interesting outcome. From the prescribing figures it seems that there was a significant overall reduction in control of asthma/COPD with reference to the increase in systemic steroid and short-acting bronchodilator prescribing. It is somewhat concerning that nearly 50% of respiratory patients are reported as receiving no treatment following the policy change. It would be interesting to look further at time off work, hospital admissions, acute presentations, and ED visits. Maybe – just maybe – the savings are expensive in terms of overall health economics.


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The effect of L-thyroxine substitution on lipid profile, glucose homeostasis, inflammation and coagulation in patients with subclinical hypothyroidism

Authors: Anagnostis P et al.

Summary: The effects of L-thyroxine therapy on lipidaemic profile, coagulation markers, high-sensitivity C-reactive protein (hsCRP) and glucose homeostasis are reported for 32 patients (mean age 52.1 years) with subclinical hypothyroidism. At baseline, mean thyroid-stimulating hormone (TSH) levels were 6.79 mIU/mL. At 6 months, after restoration of euthyroidism, significant reductions from baseline were observed in systolic blood pressure (BP; from 135.2 to 129.7 mmHg; p=0.03) and diastolic BP (from 79.5 to 72.1 mmHg; p=0.03) only in those patients with baseline TSH levels >7 mIU/mL. L-thyroxine therapy had no significant effect upon body weight, total cholesterol, LDL or HDL cholesterol, triglycerides, apolipoprotein B, fasting plasma glucose or insulin, homeostasis model assessment-insulin resistance (HOMA-IR), hsCRP, antithrombin III, protein C, protein S, fibrinogen or homocysteine levels, except for a decrease in apolipoprotein A1 (p=0.04) and an increase in lipoprotein (a) levels (p=0.02).

Comment: Subclinical hypothyroidism is not that uncommon. Patients who present with atypical symptoms often have a thyroid-stimulating hormone test done as part of a screen. If it is high, full thyroid function tests are undertaken (T3 and T4 levels) and the result is that frequently they fall into the "grey" area of being neither one thing nor the other, or perhaps "just within the range of normality". This study suggests that if patients are normotensive then watchful expectancy may be the way to go. If BP is elevated, it may be worthwhile for a trial of thyroxine replacement to see if this reduces BP.


Abstract

The value of routine radiography in patients with knee osteoarthritis consulting primary health care: a study of agreement

Authors: Skou ST et al.

Summary: This Danish study explored agreement between the radiographic and clinical diagnosis in knee osteoarthritis (OA), as well as the ability of radiography to rule out serious pathology in clinical knee OA. The analysis involved referral forms from GPs and radiographs of 1334 patients aged >40 years not previously diagnosed with knee OA. A Cohen’s kappa was used to examine the agreement between primary indication for radiographic referral (± clinical knee OA; Kellgren and Lawrence score ≥1). The strength of the agreement was 0.106 to 0.298, with the kappa was used to examine the agreement between primary indication for radiographic referral (± clinical knee OA; Kellgren and Lawrence score ≥1). The strength of the agreement was 0.106 to 0.298, with the lowest agreement in the youngest patients and the highest in the oldest patients. An evaluation of radiographic features in a subset of 997 patients with clinical knee OA identified conditions needing further investigation or specific treatment.

Comment: This is a complex issue involving patient expectation, specialist requirement, allocation of points for surgery, and as the authors suggest, ruling out other diagnosis or serious pathology. I can only imagine the retort, if I referred a patient to an orthopaedic surgeon for opinion for consideration for joint replacement without an x-ray. But I agree that the film seldom adds to the decision outcome – maybe a need for consideration for radiologists, generalists, and orthopaedic surgeons to rethink.


Abstract

Effects of changing guidelines on prescribing aspirin for primary prevention of cardiovascular events

Authors: Hissett J et al.

Summary: De-identified electronic health record (EHR) data were obtained for 131,050 individuals >17 years of age with a known diagnosis of cardiovascular disease (CVD) or at increased risk of CVD, as determined by diagnostic, demographic, and clinical data collected from 33 primary care practices in 11 different clinical organisations spread across 6 states in the USA. Changes in recorded aspirin use were observed among the patients across 4 time periods (time 1: 1 January 2007 to 31 December 2007; time 2: 1 January 2008 to 31 December 2008; time 3: 1 January 2009 to 31 May 2010; and time 4: 1 June 2010 to 31 May 2011). From 2007 to 2011, aspirin usage reflected in the EHR increased for the entire population and for each individual high-risk diagnosis. The percentage of the population initiating aspirin therapy for primary prevention within a year of diagnosis of CVD risk factors or CVD “equivalency” increased between 2007 and 2011. Aspirin usage also increased steadily over the 4-year period among those with a new diagnosis of CVD, indicating no negative impact from new negative primary prevention studies.

Comment: This is yet another study questioning the use of aspirin as a prophylactic measure in patients who do not have established CVD. The current evidence suggests that the risk of adverse effects of aspirin in those without established CVD (including diabetics) is greater than any preventive benefit. Note that this does not apply for established disease.

Reference: J Am Board Fam Med 2014;27(1):78-86

Abstract

Independent commentary by Associate Professor Jim Reid.

Jim Reid graduated in medicine at the University of Otago Medical School in Dunedin New Zealand. He had previously trained as a pharmacist. He undertook his postgraduate work at the University of Miami in Florida. Currently he is Head of Rural Health and Deputy Dean of the School at the Dunedin School of Medicine. He has a private family medicine practice at the Caversham Medical Centre, Dunedin, New Zealand.

For full bio CLICK HERE.
Association between melanocytic nevi and risk of breast diseases: the French E3N Prospective Cohort

Authors: Kvasnikoff M et al.

Summary: The French E3N study followed 89,902 women aged 40–65 years from June 1990 to June 2008, exploring associations between number of naevi and breast cancer risk. At study entry, women were categorised by number of naevi (none; a few; many; very many). During the study period, 5956 breast cancers (including 5245 invasive tumours) were diagnosed. In Cox proportional hazards regression models adjusted for age, education, and known breast cancer risk factors, women with “very many” naevi had a significantly higher breast cancer risk (HR 1.13; 95% CI, 1.01 to 1.27 vs “none”; \( \beta_{\text{naevi}}=0.04 \)), although significance was lost after adjustment for personal history of benign breast disease or family history of breast cancer. The 10-year absolute risk of invasive breast cancer increased from 3749 per 100,000 women without naevi to 4124 per 100,000 women with “very many” naevi. The association was restricted to premenopausal women (HR 1.40, 95% CI, 1.07 to 1.85). The numerical value of “very many” is not evaluated in this study, and of course family history etc. is important. But this is an important observation – women with a large number of naevi have a significantly increased risk of breast cancer. The 10-year absolute risk of invasive breast cancer increased from 3749 per 100,000 women without naevi to 4124 per 100,000 women with “very many” naevi. The association was restricted to premenopausal women (HR 1.40, \( \beta_{\text{naevi}}=0.04 \)), even after full adjustment (HR 1.34; \( \beta_{\text{naevi}}=0.03 \)), but did not differ according to breast cancer type or hormone receptor status. Significantly positive dose–response relationships were observed between number of naevi and history of breast cancer type or hormone receptor status. The associations between number of naevi and breast cancer risk were significant in the Mediterranean diet intervention groups and not in the control group.

Comment: Fascinating! The message from this study is that when undertaking skin checks for naevi, look out for the woman with a large number of naevi. The numerical value of “very many” is not evaluated in this study, and of course family history etc. is important. But this is an important observation – women with multiple naevi are at greater risk of benign and malignant breast disease.


Abstract

Evidence-based natural health by Dr Chris Tofield

Olive oil intake and risk of cardiovascular disease and mortality in the PREDIMED study

Authors: Guasch-Ferré M et al.

Summary: This analysis included 7216 men and women aged 55–80 years participating in the PREvención con Dieta MEDITerránea (PREDIMED) study, assigned at baseline to 1 of 3 interventions: Mediterranean Diets supplemented with nuts or extra-virgin olive oil, or a control low-fat diet. None of the participants had CVD at enrolment, but they were at high CV risk because of the presence of type 2 diabetes or ≥3 of the following risk factors: current smoking, hypertension, high LDL cholesterol, low HDL cholesterol, overweight or obesity, and family history of premature CVD (stroke, myocardial infarction and CV death). The study aimed to assess the association between total olive oil intake, its varieties (extra virgin and common olive oil) and the risk of CVD and mortality. Over a median follow-up of 4.8 years, 277 CV events and 323 deaths were recorded. Participants in the highest energy-adjusted tertile of baseline total olive oil and extra-virgin olive oil consumption had a 35% (HR 0.65; 95% CI, 0.47 to 0.89) and 39% (HR 0.61; 95% CI, 0.44 to 0.85) lower risk of major CV events, respectively, compared to those in the reference. Higher baseline total olive oil consumption was associated with a 48% reduction in the risk of CV mortality (HR 0.52; 95% CI, 0.29 to 0.93). Each increase of 10 g/day in extra-virgin olive oil consumption was associated with a 10% reduction in the risk of CV events and a 7% reduction in mortality risk. No significant associations were found for cancer and all-cause mortality. The associations between CV events and extra virgin olive oil intake were significant in the Mediterranean diet intervention groups and not in the control group.

Comment: Interestingly, the olive oil group in this study did better than the low-fat diet group. And not only that, but the greater the daily olive oil intake, the lower the CV risk. Should we now be steering our high-risk patients (or anyone else for that matter) away from the green top milk and recommend more olive oil instead? Food for thought.


Abstract

Effects of ginger for nausea and vomiting in early pregnancy

Authors: Thomson M et al.

Summary: This meta-analysis of randomised, placebo-controlled trials using ginger for nausea and vomiting in early pregnancy (NVEP) included 6 studies (508 subjects; 256 received ginger and 252 received placebo). Use of ginger (<1 g daily) for ≥4 days was found to be associated with a 5-fold likelihood of improvement in NVEP. Use of ginger (≥1 g daily) for ≥4 days was associated with a 10-fold reduction in the risk of nausea and vomiting. ginger is a very popular choice for pregnant women suffering from nausea or vomiting. According to this Canadian meta-analysis, however, you need to ingest approximately 1 g of ginger a day for it to be effective. That’s around 8 or 9 Griffin’s ginger biscuits a day, at 0.12 g ginger per biscuit. Healthy munching.


Abstract

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