GP RESEARCH REVIEW™

Making Education Easy

Issue 168 – 2021

In this issue:

Abbreviations used in this issue
CI = confidence interval
COVID-19 = coronavirus disease-2019
HR = hazard ratio
PCR = polymerase-chain-reaction
RR = risk ratio
SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

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Welcome to Issue 168 of GP Research Review.

Further evidence has emerged that hydroxychloroquine is ineffective in preventing the transmission of SARS-CoV-2 infection among contacts of confirmed COVID-19 patients. Furthermore, hydroxychloroquine has exhibited a treatment-related adverse event rate of 56.1%. In the Natural Health section, Dr Chris Tofield has reviewed two interesting studies, one showing the benefits of *Curcuma longa* extract for knee osteoarthritis and the other egg consumption and the risk of cardiovascular events.

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

Jim

Assoc Professor Jim Reid
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A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19

Authors: Mitjà O et al

Summary: This Spanish open-label, cluster-randomised trial tested the effect of hydroxychloroquine (800mg followed by 400mg daily for 6 days) in the prevention SARS-CoV-2 infection among 2314 asymptomatic contacts of polymerase-chain-reaction (PCR)-confirmed COVID-19 patients (n = 672). There were no differences between treatment groups in incidence of PCR-confirmed, symptomatic COVID-19 (hydroxychloroquine 5.7%; usual-care 6.2%; RR 0.86; 95% CI 0.52-1.42), nor a difference in incidence of SARS-CoV-2 infection defined by symptoms compatible with COVID-19 or a positive PCR test regardless of symptoms (18.7% vs 17.8%). Adverse event rates were higher in hydroxychloroquine than usual-care recipients (56.1% vs 5.9%), but there were no treatment-related serious adverse events.

Comment: Another one! Not only is hydroxychloroquine useless for the treatment of COVID-19, it has a similar profile for its use in prevention. It was also spectacular in the incidence of adverse effects (56.1% vs 5.9% against the placebo group)!!!

Reference: N Engl J Med. 2021;384(5):417-427
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 postgraduate work at the University of Miami in Florida, USA. **For full bio CLICK HERE.**

This Research Review has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 1 CME credit for the General Practice Educational Programme (GPEP) and Continuing Professional Development (CPD) purposes. You can record your CME credits in your **RNZCGP Dashboard**

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE.**

Association between use of macrolides in pregnancy and risk of major birth defects: Nationwide, register based cohort study

Authors: Andersson NW et al.

Summary: This Danish register-based cohort study (n = 1,192,539; 1997-2016) assessed the relationship between the use during pregnancy of macrolide antibiotics (n = 13,019) versus phenoxymethylpenicillin (propensity matched 1:1) or no antibiotic use (propensity matched 1:4) and the risk of major birth defects. Across the matched pregnancies, there were 457 infants born with major birth defects after macrolides use (35.1 per 1000 pregnancies) versus 481 infants (37.0 per 1000 pregnancies) after penicillin use (RR 0.95; 95% CI 0.84-1.08); absolute risk difference per 1000 pregnancies of -1.8 (95% CI -6.4 to 2.7). Major birth defect risk was not increased among women using macrolides during versus recently before becoming pregnant (RR 1.00; 95% CI 0.88-1.14) or versus women who did not use any antibiotics (RR 1.05; 95% CI 0.95-1.17).

Comment: This is a very large study that demonstrates the safety of use of the macrolide antibiotics (e.g., erythromycin, roxithromycin, azithromycin) in pregnancy. This is in line with recommendations made in the New Zealand Formulary.

Reference: BMJ. 2021;372:n107
Abstract

Statin treatment and muscle symptoms: Series of randomised, placebo controlled n-of-1 trials

Authors: Herrett E et al.

Summary: This UK series of double-blinded trials across 50 sites examined the effect of reintroduction of statins (six 2-month treatment periods with atorvastatin 20mg daily or placebo) on muscle symptoms in 200 people who had recently stopped or were considering stopping statins because of muscle symptoms. Muscle symptoms on a visual analogue scale (0-10) were provided by 151 participants for at least one statin and one placebo period. Overall, there were no differences in muscle symptom scores between statin and placebo periods (mean difference -0.11; 95% CI -0.36 to 0.14). Withdrawal because of intolerable muscle symptoms occurred in 18 (9%) participants during a statin period and 13 (7%) participants during a placebo period. Two-thirds of those completing the trial restarted long-term statin treatment.

Comment: There is, in my experience, a strong folk law in existence, fanned by a radio talkback host, about the side effects of statins. Callers complain of dementia, tiredness, and most of all, muscle pains. While I have no doubt that for some these are very real, but in others…? This double-blind, placebo-controlled, cross-over study in statin recipients who had previously suffered from muscle pains, demonstrated that over the study periods, there was no difference in muscle symptom scores between those on 20mg atorvastatin and placebo. However, I do note that there was a higher drop-out rate among those during their statin periods. Still inconclusive…

Reference: BMJ. 2021;372:n135
Abstract

Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial

Authors: RECOVERY Collaborative Group

Summary: In the UK multicentre, randomised, controlled, open-label, adaptive platform RECOVERY trial, azithromycin 500mg once daily was tested to see if its immunomodulatory actions would benefit patients admitted to hospital with COVID-19. In total, 2582 patients received azithromycin and 5181 usual care (mean age 65.3 years; 38% women). Overall, 22% of both groups of patients died within 28 days (RR 0.97; 95% CI 0.87-1.07). There was no difference in duration of hospital stay (median 10 vs 11 days) or proportion discharged alive within 28 days (RR 1.04; 95% CI 0.98-1.10). In those not receiving invasive mechanical ventilation at baseline, there was no difference in the proportion meeting a composite endpoint of invasive mechanical ventilation or death (RR 0.95; 95% CI 0.87-1.03).

Comment: COVID-19 is dominating the medical literature at present. This time another blank on the effectiveness of use of azithromycin. It should be kept for the treatment of appropriate infection.

Reference: Lancet. 2021;397(10274):605-612
Abstract

Effect of high-intensity strength training on knee pain and knee joint compressive forces among adults with knee osteoarthritis: The START randomized clinical trial

Authors: Messier SP et al.

Summary: This US, single-centre, assessor-blinded randomised clinical trial compared high-intensity (n = 127) versus low-intensity (n = 126) strength training versus control (n = 124; providing attention, social interaction and health education) in patients with knee osteoarthritis. Over an 18-month follow-up, 320 patients (85%) completed the trial. Mean adjusted (sex, baseline BMI, baseline outcome values) Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) knee pain scores did not differ between the high-intensity strength training and control (5.1 vs 4.9; adjusted difference 0.2; 95% CI -0.6 to 1.1) or low-intensity groups (5.1 vs 4.4; adjusted difference 0.7; 95% CI -0.1 to 1.6). Nor did mean knee joint compressive forces differ between groups (2453 vs 2512 N; adjusted difference -58; 95% CI -282 to 165 N: 2453 vs 2475 N; adjusted difference -21; 95% CI -235 to 193 N). Non-serious adverse events occurred in 87 participants (53 high-intensity; 30 low-intensity; 4 control) and serious adverse events unrelated to the study in 13 participants (5 high-intensity; 3 low-intensity; 5 control).

Comment: There has been some enthusiasm for the use of high-intensity knee strengthening exercises for the treatment of osteoarthritis of the knee. This study looked at the effect on knee pain of high-intensity versus low-intensity exercise. The outcome was that there was no difference between the two groups as far as pain is concerned, but there was no measurement of disease outcome, especially with reference to need for future joint replacement.

Reference: JAMA. 2021;325(7):646-657
Abstract

Evaluation of time to benefit of statins for the primary prevention of cardiovascular events in adults aged 50 to 75 years: A meta-analysis

Authors: Yourman LC et al.

Summary: This survival meta-analysis of statin randomised clinical trials was conducted to determine the time to benefit for prevention of a first major adverse cardiovascular event (MACE) based on 8 studies (n = 65,383; 66.3% male; mean age 55-69 years; mean length of follow-up 2-6 years). Only 1 study demonstrated a decrease in all-cause mortality with statins. Meta-analysis indicated that 2.5 (95% CI 1.7-3.4) years of statin treatment were needed to avoid 1 MACE per 100 patients. To prevent 1 MACE per 200 patients, the time to benefit was 1.3 years (95% CI 1.0-1.7), and to avoid 1 MACE per 500 patients was 0.8 years (95% CI 0.5-1.0).

Comment: This study reinforces the limited capacity of statins to primarily prevent a first MACE. This was a meta-analysis of only 8 trials conducted in primary care which included 65,000 odd patients aged between 50 and 75 years who did not have established cardiovascular disease. Statins did not provide any benefit in preventing mortality, and in addition it required the treatment of 100 participants for 2.5 years to prevent one MACE.

Reference: JAMA Intern Med. 2021;181(2):179-185
Abstract

Immunosuppression as a risk factor for COVID-19: A meta-analysis

Authors: Tassone D et al.

Summary: This random-effects meta-analysis examined whether immunosuppressed patients were at higher risk of COVID-19 based on 6 studies (n = 10,049). Prevalence of immunosuppression ranged from 0.126% to 1.357% in these study cohorts. The pooled analysis included 64 (0.637%) immunosuppressed patients with COVID-19. The observed-to-expected ratio of immunosuppression among patients with COVID-19 relative to the general community was 0.12 (95% CI 0.05-0.27) and did not indicate an increased risk.

Comment: COVID-19 again. Medically-induced immunosuppression is common, not only patients on all monoclonal antibodies, but also all on disease modifying antirheumatic drugs (DMARDS), and systemic steroids to name a few. It was previously accepted that these patients were at increased risk of an infection by COVID-19, but this paper, a meta-analysis involving 10,000 patients, demonstrated that they are not at increased risk of contracting the disease.

Reference: Intern Med J. 2021;51(2):199-205
Abstract

Impact of fast-food outlet density on incidence of myocardial infarction in the Hunter region

Authors: Saluja T et al.

Summary: This Australian retrospective cohort study (1996-2013) examined the role of fast-food outlet density as an environmental risk factor for myocardial infarction (MI) using data from the Hunter Cardiac and Stroke Outcomes unit in New South Wales. Fast-food outlet density per local government area was positively correlated with MI rates in both single and multivariate models adjusting for age, obesity, hyperlipidaemia, hypertension, smoking status, diabetes and socioeconomic status ($p < 0.001$). An increase of one fast-food outlet per local government area corresponded with 4.07 additional MIs per 100,000 people per year (95% CI 3.86-4.28).

Comment: This is an interesting study that looked at the relationship of fast-food outlet density (number of fast-food shops) and the incidence of MI in an area. Using MI as the sole indicator, there was a direct relationship between fast food outlet density and the rate of MI. This was apparent in both rural and metropolitan areas, and was also apparent after multivariate adjustment for cardiovascular risk factors. In a nutshell – the more fast food shops the more MI in the community!!

Reference: Intern Med J. 2021;51(2):243-248
Abstract

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Influenza Vaccine for Older Adults - E-Learning Module

Our latest E-Learning Module endorsed by the RNZCGP and College of Nurses is now available to complete just in time for the 2021 influenza season.

This is based on the **Research Review Product Review of MF59®-Adjuvanted Inactivated Quadrivalent Influenza Vaccine for Older Adults (Fluad Quad®),** with expert commentary by Infectious disease expert Professor Tim Blackmore.

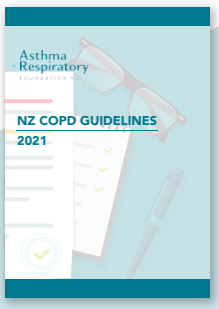
This review summarises data relevant to the use of the MF59-Adjuvanted inactivated quadrivalent influenza vaccine (Fluad® Quad) for the prevention of seasonal influenza in adults aged ≥65 years, against the background of a high burden of disease in older adults and factors that can reduce vaccine effectiveness.
CLICK here to read the review

GPs: START MODULE

NURSES: START MODULE

New Zealand COPD Guidelines

The **NZ COPD Guidelines** have been developed by the Asthma and Respiratory Foundation's (ARFNZ) working group of respiratory health experts led by Dr Stuart Jones from Middlemore Hospital and Professor Bob Hancox from the University of Otago, with the goal of improving diagnosis, and laying out clear recommendations for assessment and management of this respiratory disease.



Download the NZ COPD Guidelines here

EVIDENCE-BASED NATURAL HEALTH
by Dr Chris Tofield

Effectiveness of *Curcuma longa* extract for the treatment of symptoms and effusion–synovitis of knee osteoarthritis

Authors: Wang Z et al.

Summary: This Australian single-centre, randomised, double-blind, placebo-controlled trial examined the use of *Curcuma longa* extract for reducing knee symptoms and effusion-synovitis in 70 patients with symptomatic knee osteoarthritis and ultrasonography-defined knee effusion-synovitis. *Curcuma longa* extract improved visual analogue scale pain score versus placebo by -9.1 mm (95% CI -17.8 to -0.4 mm; $p = 0.039$), but had no effect on effusion-synovitis volume (3.2 mL; 95% CI -0.3 to 6.8). The extract also improved WOMAC knee pain (-47.2 mm; 95% CI -81.2 to -13.2 mm; $p = 0.006$), but not lateral femoral cartilage T2 relaxation time (-0.4 ms; 95% CI -1.1 to 0.3). Adverse event incidences did not differ between extract (n = 14; 39%) and placebo (n = 18; 53%) recipients.

Comment: Curcumin is a constituent of turmeric, which in turns comes from the root of the *Curcuma longa* plant in the ginger family. Most of you will be aware of the various anti-inflammatory and antioxidant properties of curcumin, though we're still needing studies in humans to demonstrate effects on clinical outcomes. Enter this small Tasmanian study showing some improvements in knee pain in osteoarthritis, a first step in the right direction.

Reference: Ann Intern Med. 2020;173(11):861-869
Abstract

Association between egg consumption and risk of cardiovascular outcomes: A systematic review and meta-analysis

Authors: Krittanawong C et al.

Summary: This meta-analysis examined the relationship between egg consumption and overall cardiovascular disease events based on 23 prospective studies (n = 1,415,839) with a median follow-up of 12.28 years. In total, there were 123,660 cases, and 157,324 cardiovascular disease events included in the analysis. Consumption of more than 1 egg per day versus no or 1 egg per day, was not associated with a change in risk of overall cardiovascular disease events (HR 0.99; 95% CI 0.93-1.06). However, egg consumption >1 egg per day was associated with a decreased risk of coronary artery disease (HR 0.89; 95% CI 0.86-0.93; $p < 0.001$).

Comment: Eggs have gone in and out of favour over the years, confusing the general population as well as health practitioners. This led the NZ Nutrition Foundation to produce a lengthy white paper back in 2014, stating that one to two eggs a day was acceptable for healthy people. Yet uncertainty remained. Now we have this 2020 meta-analysis of 23 studies (finally?) concluding that more than one egg a day was actually beneficial for cardiac health. It will be interesting to see if this stance changes again in a few years.

Reference: Am J Med. 2021;134(1):76-83.e2
Abstract

Dr Christopher Tofield

Dr Tofield completed his medical training at St Bartholomew's and the Royal London Hospital in London. He has extensive experience in general practice, spent several years in clinical research, has published several medical papers, is clinical advisor to Bay of Plenty District Health Board and practices skin cancer medicine and surgery. Chris also has a background in medical writing and editing and while at medical school published a medical textbook on pharmacology. Chris is responsible for sourcing and short-listing national and international studies for GP Research Review. He also selects papers and provides commentary for the Natural Health section in GP Research Review.

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