# Internal Medicine RESEARCH REVIEW™

Making Education Easy

Issue 69 – 2021


## In this issue:



**Abbreviations used in this issue**

**COVID-19** = coronavirus disease 2019
**CV** = cardiovascular
**HF** = heart failure
**PPI** = proton pump inhibitor
**RCT** = randomised controlled trial
**SARS-COV-2** = severe acute respiratory syndrome coronavirus 2
**SNRI** = serotonin-noradrenaline (norepinephrine) reuptake inhibitor

## Welcome to issue 69 of Internal Medicine Research Review.

Several of the research papers selected for this issue focus on the current COVID-19 pandemic: we see convalescent plasma but not azithromycin may be helpful in its treatment, and we also see the results of a phase 3 trial of one of a number of vaccines being developed. This issue also includes NZ research reporting reduced hospital admissions among individuals residing in homes where the EECA subsidy had been used to install insulation. Researchers from the US have also described their experiences running a virtual hospital. There is also a randomised Spanish study reporting that focused ultrasound subthalamotomy in one hemisphere can improve motor features of Parkinson's disease in patients with asymmetric signs.

We hope you enjoy this issue, and we welcome your comments and feedback.

Kind regards


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## Use of proton pump inhibitors to treat persistent throat symptoms

**Authors:** O'Hara J et al.


**Summary:** This randomised, placebo-controlled trial examined the use of the PPI lansoprazole for 16 weeks in 346 patients with persistent throat symptoms. There was no significant difference between the lansoprazole and placebo arms for improvement in mean Reflux Symptom Index score at the end of treatment (17.4 vs. 15.6) or for any secondary outcome measure, including Reflux Symptom Index score at 12 months (16.0 vs. 13.6).


**Comment:** The concept of a link between gastro-oesophageal reflux disease and throat and voice symptoms is entrenched in the clinical community, and persistent throat symptoms are often treated with PPIs. In this UK-based, medium-sized multicentre RCT among patients with persistent throat symptoms, the use of lansoprazole compared with placebo didn't result in improving the persistent throat symptoms. Based on this study, the use of PPIs for persistent throat symptoms couldn't be recommended.

***Reference: BMJ 2021;372:m4903***
Abstract

### Independent commentary by Dr Sisira Jayathissa

Dr Sisira Jayathissa is a General Physician and a Geriatrician. He is also the clinical director of medicine and community health at the Hutt Valley DHB. He is actively involved in both undergraduate and postgraduate medical education in the Wellington region.
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## Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY)

**Authors:** RECOVERY Collaborative Group

**Summary:** Patients hospitalised with COVID-19 were randomised to usual standard of care with (n=2582) or without (n=5181) oral or intravenous azithromycin 500mg once daily for 10 days or until discharge as part of the larger open-label RECOVERY trial investigating a range of treatments. The 28-day mortality rate in both the azithromycin and placebo arms was 22% (rate ratio 0.97 [95% CI 0.87, 1.07]), and there was no significant between-group difference for median duration of hospital stay (10 vs. 11 days), the proportion discharged alive within 28 days (rate ratio 1.04 [0.98, 1.10]), or for the proportion meeting the composite endpoint of invasive mechanical ventilation or death among those not on invasive mechanical ventilation at baseline (risk ratio 0.95 [0.87, 1.03]).

**Comment:** Multiple drug therapies have been studied in COVID-19 without significant benefit. This large RCT comparing azithromycin and placebo failed to show any clinical benefit. The use of azithromycin was based on its perceived clinical benefit related to immunomodulatory actions. Based on these results, azithromycin couldn't be recommended as a treatment for hospitalised patients with COVID-19 not suffering from a bacterial infection.

***Reference: Lancet 2021;397:605–12***
Abstract

## Trial of dexamethasone for chronic subdural hematoma

**Authors:** Hutchinson PJ et al., for the British Neurosurgical Trainee Research Collaborative and Dex-CSDH Trial Collaborators

**Summary:** Adults with symptomatic chronic subdural haematoma were randomised to receive oral dexamethasone 8mg twice daily tapered over 2 weeks (evaluable n=341) or placebo (evaluable n=339); 94% of the participants underwent surgical evacuation of their haematoma during the index admission at the discretion of the treating clinician. For the primary outcome, the proportion of dexamethasone recipients with a modified Rankin scale score of 0–3 at 6 months (favourable outcome) was lower than the proportion of placebo recipients (83.9% vs. 90.3% [p=0.01]), but so was the proportion with available data who underwent repeat surgery for haematoma recurrence (1.7% vs. 7.1%). Dexamethasone recipients experienced more adverse events than placebo recipients.

**Comment:** Glucocorticoids have been used to treat chronic subdural haematoma, but there is limited evidence for effectiveness. In this medium-sized, double-blind RCT, use of a 14-day course of dexamethasone was associated with less favourable outcomes and increased side effects. Dexamethasone couldn't be recommended for routine use in patients with chronic subdural haematoma.

***Reference: N Engl J Med 2020;383:2616–27***
Abstract

## Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis

**Authors:** Ferreira GE et al.

**Summary:** A total of 33 trials were included in this systematic review and meta-analysis to investigate the efficacy and safety of antidepressants for back and osteoarthritis pain compared with placebo. Pain and disability were primary outcomes in the included trials, and these scores were converted to a scale of 0 (no pain or disability) to 100 (worst pain or disability). SNRIs reduced both back pain (mean difference –5.30 [95% CI –7.31, –3.30; moderate certainty) and osteoarthritis pain (–9.72 [–12.75, –6.69]; low certainty) at 3–13 weeks. Very low certainty evidence showed that SNRIs reduced sciatica at ≤2 weeks (–18.60, [95% CI –31.87, –5.33]) but not at 3–13 weeks (–17.50 [–42.90, 7.89]). Tricyclic antidepressants did not reduce sciatica at ≤2 weeks (–7.55 [95% CI –18.25, 3.15]) but did at 3–13 weeks (–15.95 [–31.52, –0.39]) and 3–12 months (–27.0 [–36.11, –17.89]; low-to-very low certainty). SNRIs reduced disability from back pain at 3–13 weeks (–3.55 [95% CI –5.22, –1.88]; moderate certainty) and disability due to osteoarthritis at ≤2 weeks (–5.10 [–7.31, –2.89]; moderate certainty). Pain and disability from back pain were not reduced by tricyclic antidepressants.

**Comment:** This meta-analysis of RCTs compared the effects of antidepressant drugs with placebo among more than 5000 participants with low back or neck pain, sciatica, or hip or knee osteoarthritis. Drug treatments are largely ineffective for back pain and osteoarthritis, and have the potential for harm. We need to find better strategies to treat patients with these disorders to manage their pain without recourse to the prescribing relatively ineffective medicines.

***Reference: BMJ 2021;372:m4825***
Abstract

## Association between home insulation and hospital admission rates

**Authors:** Fyfe C et al.

**Summary:** This NZ quasi-experimental retrospective cohort study used linked datasets to evaluate a national intervention programme to investigate whether retrofitting home insulation would reduce cold-associated hospital admission rates among 994,317 residents of 204,405 houses participating in the EECA's Warm-up New Zealand: Heat Smart retrofit programme (2009–2014). There were 234,873 hospital admissions during the study period, and the rates increased in both the intervention and control groups across all population categories and conditions, with the exception of acute hospital admissions among Pacific peoples (rate ratio 0.94 [95% CI 0.90, 0.98]), and those with asthma (0.92 [0.86, 0.99]), CV disease (0.90 [0.88, 0.93]) or ischaemic heart disease in adults >65 years old (0.79 [0.74, 0.84]). Postintervention increases were lower in the intervention versus the control group (relative rate ratio 0.89 [95% CI 0.88, 0.90]), representing 9.26 fewer hospital admissions per 1000 people. These effects were more pronounced in patients with respiratory disease (relative rate ratio 0.85 [95% CI 0.81, 0.90]), asthma (0.80 [0.70, 0.90]) or ischaemic heart disease in those >65 years old (0.75 [0.66, 0.83]).

**Comment:** This large NZ-based cohort study provides valuable insight to the value of good public policy into housing stock. Improved insulation of houses was associated with a reduction in hospital admissions mainly related to respiratory problems. The study design creates a chance of significant bias, but they have been minimised. Health professionals need to be aware of living environments of their patients, especially those with respiratory conditions, and must proactively work with other agencies to improve home environments.

***Reference: BMJ 2020;371:m4571***
Abstract



## Early high-titer plasma therapy to prevent severe COVID-19 in older adults

**Authors:** Libster R et al., for the Fundación INFANT-COVID-19 Group

**Summary:** Older adults who had presented within 72 hours after mild COVID-19 symptoms started were randomised to receive convalescent plasma with high IgG titres against SARS-COV-2 (n=80) or placebo (n=80) in this trial; enrolment was terminated before planned due to the declining rate of COVID-19 cases in the trial's catchment area. Compared with placebo, a smaller proportion of convalescent plasma recipients developed severe respiratory disease (respiratory rate ≥30 breaths per minute and/or oxygen saturation <93% on ambient air; primary endpoint; 16% vs. 31%; relative risk 0.52 [95% CI 0.29, 0.94]), with a greater effect seen when participants who developed severe respiratory disease before their study infusion were excluded (relative risk 0.40 [0.20, 0.81]). There were no solicited adverse events recorded.

**Comment:** Using antibody-rich convalescent serum has been used against infections for a long period. The effectiveness of such therapy in COVID-19 is starting to emerge. In this small RCT, the use of convalescent plasma with high titres of antibodies against SARS-COV-2 in infected patients administered within 72 hours after the onset of symptoms reduced the risk of progression to severe respiratory disease. The authors didn't assess the long-term outcomes. Early administration of antibody-rich convalescent plasma seems to be a reasonable treatment option in patients with COVID-19.

***Reference: N Engl J Med 2021;384:610–8***
Abstract

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## Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine

**Authors:** Baden LR et al., for the COVE Study Group

**Summary:** Individuals deemed to be at high risk for SARS-COV-2 infection or its complications were randomised to receive two intramuscular injections of the mRNA-1273 vaccine 100µg against SARS-COV-2 (n=15,210) or placebo (n=15,210) 28 days apart in this phase 3 trial, with >96% of participants receiving both their injections, and 2.2% having serological and/or virological evidence of SARS-COV-2 infection at baseline. Compared with placebo, symptomatic COVID-19 illness occurred in significantly fewer mRNA-1273 vaccine recipients (3.3 vs. 56.5 per 1000 person-years,) providing vaccine efficacy of 94.1% (p<0.001); the efficacy of the vaccine was similar across key secondary analyses, including assessment 14 days after the first dose, inclusion of participants with evidence of SARS-COV-2 infection at baseline, and in participants aged ≥65 years. All 30 participants who developed severe COVID-19, including one fatality, were from the placebo group. The mRNA-1273 vaccine was associated with more moderate, transient reactogenicity, but serious adverse events were rare and occurred at similar incidences between the two groups.

**Comment:** This large phase 3 RCT was conducted to determine the efficacy and safety of the mRNA-1273 SARS-COV-2 vaccine (Moderna) compared with placebo. The results showed good short-term vaccine efficacy. However, questions remain unanswered on long-term efficacy, the potential for unknown side effects, efficacy against major mutant viruses and the ability to protect against asymptomatic infections. However, the development of a number of effective vaccines over a short period should be applauded.

***Reference: N Engl J Med 2021;384:403–16***
Abstract

## Insights from rapid deployment of a 'virtual hospital' as standard care during the COVID-19 pandemic

**Authors:** Sitammagari K et al.

**Summary:** The development and rapid deployment of a virtual hospital programme (Atrium Health hospital at home) within a large US healthcare system was described. The programme comprised proactive home monitoring and hospital-level care via a virtual observation unit and a virtual acute care unit in the home settings of 1477 eligible patients with COVID-19. The median 'length of stay' for the patients was 11 days. Among 1293 patients (88%) who received care in the virtual observation unit only, 40 (3%) required inpatient hospitalisation, and of these, 40% were admitted to an ICU, 18% required ventilator support and 5% died during their hospital admission. Among 184 patients (12%) admitted to the virtual acute care unit, 11% required intravenous fluids, 9% received antibiotics, 22% required respiratory inhaler or nebuliser treatments and 22% received supplemental oxygen. Of the 24 patients (13%) from this group who needed to be admitted to a conventional hospital, 42% required ICU admission, 3% required a ventilator and none died.

**Comment:** Telehealth has become increasingly important during this century, especially during the pandemic. There have been barriers to telehealth, including the inability to have proper consultations. This study showed the ability of a robust telehealth system combined with backup for managing health issues in a selected patient population. As many other medical interventions, telehealth needs to evolve with good clinical governance to be safe and effective.

***Reference: Ann Intern Med 2021;174:192–9***
Abstract



## Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease

**Authors:** Martínez-Fernández R et al.

**Summary:** This Spanish study investigated the efficacy of focused ultrasound subthalamotomy in patients with markedly asymmetric Parkinson's disease who had motor signs not fully controlled by medication or who were ineligible for deep-brain stimulation. The participants were randomised to undergo MRI-guided focused ultrasound subthalamotomy on the side opposite their main motor signs (n=27) or a sham procedure (n=13). The primary efficacy outcome of mean Movement Disorder Society – Unified Parkinson's Disease Rating Scale part III score for the more affected body side in the off-medication state decreased from 19.9 at baseline to 9.9 at 4 months in the active-treatment group and from 18.7 to 17.1 in the control group (between-group difference, 8.1 points [p<0.001]). Adverse events that persisted at 4 months in the focused ultrasound subthalamotomy group were dyskinesia in the off-medication state (n=3) and on-medication state (n=1), weakness on the treated side (n=2), speech disturbance (n=3), facial weakness (n=1) and gait disturbance (n=2).

**Comment:** This small two-centre, sham-controlled RCT involving relatively young Parkinson's disease patients showed focused ultrasound subthalamotomy has resulted in improved motor features of Parkinson's disease on the more affected side. However, adverse events were frequent and persisted in several patients. Given the young age of the patients and irreversible nature of ultrasound-related damage, this new treatment method needs to be compared against other invasive treatments prior to being accepted into regular clinical practice.

***Reference: N Engl J Med 2020;383:2501–13***
Abstract

## Ferric carboxymaltose for iron deficiency at discharge after acute heart failure

**Authors:** Ponikowski P et al., on behalf of the AFFIRM-AHF Investigators

**Summary:** Adults hospitalised for acute HF who were iron deficient and had a left ventricular ejection fraction of <50% were randomised to receive intravenous ferric carboxymaltose (dose set according to extent of iron deficiency; evaluable n=558) or placebo (evaluable n=550) for ≤24 weeks in this trial. The difference between the ferric carboxymaltose and placebo groups for primary outcome events (composite of total hospitalisations for HF and CV-related death during the 52-week postrandomisation period) failed to reach statistical significance (57.2 vs. 72.5 per 100 patient-years [p=0.059]), with no significant between-group difference in the risk of CV-related death (hazard ratio 0.96 [95% CI 0.70, 1.32]), but significantly lower risks of hospitalisation for HF (rate ratio 0.74 [0.58, 0.94]) and a composite of first HF hospitalisation or CV-related death (32% vs. 38%; hazard ratio 0.80 [0.66, 0.98]). The respective serious adverse event rates in the ferric carboxymaltose and placebo arms were 45% and 51%.

**Comment:** In this large double-blind RCT among patients with iron deficiency, and who had stabilised after an episode of acute HF, treatment with ferric carboxymaltose was safe and reduced the risk of HF hospitalisation without an effect on the risk of CV death and side effects. Interestingly, this benefit was shown in the patients without laboratory-confirmed anaemia. There appeared to be no attempt to address the cause of iron deficiency. All these factors need to be considered prior to considering ferric carboxymaltose treatment for all patients with systolic HF and biochemical iron deficiency.

***Reference: Lancet 2020;396:1895–904***
Abstract

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