GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 3 - Issue 26

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of June 26 - 30, 2023

SPOTLIGHT: Comparing Currently Available Novel Oral Antivirals for COVID-19

Comparing Currently Available Novel Oral Antivirals for COVID-19

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy and Safety of Three New Oral Antiviral Treatment (molnupiravir, Fluvoxamine and Paxlovid) for COVID-19: A Meta-Analysis

Wen W, Chen C, Tang J, et al. (2022). Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine and Paxlovid) for covid-19a meta-analysis. *Annals of Medicine*. 2022;54(1):516-523. doi:10.1080/07853890.2022.2034936

KEY TAKEAWAY: Novel oral antiviral medications (molnupiravir, fluvoxamine, and Paxlovid) are effective in decreasing mortality and hospitalizations in COVID-19 patients without significant adverse effects.

STUDY DESIGN: Meta-analysis of eight randomized controlled trials (N=6,788)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: COVID-19 remains inadequately controlled at this time. With the increasing demand across the world, new antiviral medications have been proposed due to their relatively increased efficacy and safety. Three presently available novel oral agents (molnupiravir, fluvoxamine, Paxlovid) were selected to study for mortality and hospitalization benefits.

PATIENTS: Patients diagnosed with COVID-19 infection

INTERVENTION: Molnupiravir, fluvoxamine, paxlovid

CONTROL: Placebo

PRIMARY OUTCOME: Mortality, hospitalizations

Secondary Outcome: Adverse events

METHODS (BRIEF DESCRIPTION):

- Of 6,788 COVID-19 patients, 2,440 received novel oral antiviral agents, and 2,348 received placebo.
- No specific demographic information was shared by the authors.
- Patients received molnupiravir, fluvoxamine, or paxlovid under the RCT format (specific dosing information not shared in this research).
- Research outcome (deaths, hospitalizations) assessed and aggregated.
- Incidence of adverse effects including nausea, vomiting, diarrhea, arthralgia, myalgia, deep vein thrombosis, and pulmonary embolism from experimental and control group compare.

INTERVENTION (# IN THE GROUP): 2,440

COMPARISON (# IN THE GROUP): 2,348

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Novel antiviral COVID-19 treatments reduced the risk of overall risk for death or hospitalization compared to placebo treatment (odds ratio [OR] 0.33; 95% CI, 0.22–0.49; I^2=43%).
- Novel antiviral COVID-19 treatment reduced mortality compared to placebo treatment (OR 0.41; 95% CI, 0.26–0.64; I^2=44%).
- Novel antiviral COVID-19 treatment reduced hospitalizations compared to placebo treatment (OR 0.20; 95% CI, 0.09–0.43; I^2=9%).
  - Molnupiravir: OR 0.22 (95% CI, 0.10–0.48)
  - Fluvoxamine: OR 0.45 (95% CI, 0.28–0.72)
  - Paxlovid: OR 0.05 (95% CI, 0.00–0.81)

Secondary Outcome –

- There was no difference in adverse events including nausea, vomiting, diarrhea, arthralgia, myalgia, deep vein thrombosis, and pulmonary embolism between the antiviral treatment and placebo.

LIMITATIONS:

- Two of the articles included were established by the pharmaceutical company that produced the medication.
- Patient demographic information is unavailable, and it is difficult to judge the involvement of confounding variables.
- Barriers to implementing these interventions included limited attendance, lack of participant buy-in, and language-related challenges.

Michael Wu, DO
Cahaba – UAB FMRP Bessemer
Centreville, AL

What Parameters Influence the Effect of Cold-Water Immersion on Muscle Soreness? An Updated Systematic Review and Meta-Analysis

Batista NP, de Carvalho FA, Machado AF, Micheletti JK, Pastre CM. What parameters influence the effect of cold-water immersion on muscle soreness? An updated systematic review and meta-analysis. *Clin J Sport Med*. 2023 Jan 1;33(1):13-25. doi: 10.1097/JSM.0000000000001081.

KEY TAKEAWAY: Regardless of water temperature and cold-water immersion (CWI) protocol, CWI with less than 15 minutes significantly reduces muscle soreness in both immediate and delayed effects. Immediate effects of CWI are superior in endurance exercises; however, delayed effects of CWI are superior in both endurance and resistance exercises.

STUDY DESIGN: Systemic review and meta-analysis of randomized controlled trials (N=1,590)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to low-quality studies with no patient information)

BRIEF BACKGROUND INFORMATION: CWI has been widely used in sports science to facilitate recovery after training. CWI has the potential benefits of lowering both muscle temperature and hydrostatic pressure, which results in decreased muscle edema, less post-exercise pain, and therefore, improved recovery. However, most CWI studies do not necessarily examine the efficacy of CWI. Hence, the purpose of this study is to determine the efficacy of CWI on muscle soreness compared with a control condition regarding water temperature, immersion time, CWI protocol, and type of exercise.

PATIENTS: Athletes and nonathletes

INTERVENTION: Cold-water immersion (CWI)

CONTROL: No attempt to accelerate recovery

PRIMARY OUTCOME: Muscle soreness

METHODS (BRIEF DESCRIPTION):

- Patient demographics were not provided.
- Studies were included if they were RCTs evaluating both immediate effects (immediately after CWI) and delayed effects (24 and 48 hours after exercise).
- Studies were excluded if they did not use a visual analog scale, did not include CWI, or associated with other techniques, did not have a control group, or used CWI application before the exercise.
- Interventions included subgroups in terms of water temperature, immersion time, CWI protocol, and type of exercise to cause fatigue.
    - Water temperature for both immediate and delayed effects: Moderate cold (10–15 °C) and severe cold (5–9 °C).
    - Immersion time for both immediate and delayed effects:
        - Short immersion (≤10 minutes), medium immersion (11–15 minutes), and longer immersion (16–20 minutes).
    - CWI protocol for both immediate and delayed effects:
        - Intermittent application and continuous application.
    - Type of exercise for immediate and delayed effects:
        - Endurance exercise and resistance exercise.
- Outcome was measured by assessing muscle soreness after CWI via a visual analog scale (VAS) from 0 to 10, with a higher number indicating a high level of muscle soreness.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: 48 hours

RESULTS:

Primary Outcome –

- Regardless of the water temperature, CWI was more likely to reduce muscle soreness than control:
    - Immediate effects:
        - Severe cold (mean difference [MD] 0.99; 95% CI, 0.38–1.6; I^2=54%)
        - Moderate cold (MD 1.0; 95% CI, 0.44–1.6; I^2=87%)
    - Delayed effects:
        - Severe cold (MD 0.68; 95% CI, 0.09–1.3; I^2=37%)
        - Moderate cold (MD 1.2; 95% CI, 0.61–1.8; I^2=92%)
- CWI with short and medium immersion was significantly more likely to reduce muscle soreness

than control, but no significant difference in longer immersion:
    - Immediate effects:
        - Short immersion (MD 0.80; 95% CI, 0.18–1.4; I^2=85%)
        - Medium immersion (MD 1.6; 95% CI, 0.70–2.5; I^2=80%)
    - Delayed effects:
        - Short immersion (MD 1.3; 95% CI, 0.51–2.0; I^2=92%)
        - Medium immersion (MD 1.0; 95% CI, 0.08–2.0; I^2=89%)
- Regardless of CWI protocol, CWI was significantly more likely to reduce muscle soreness than control:
    - Immediate effects:
        - Intermittent application (MD 1.5; 95% CI, 0.66–2.3; I^2=50%)
        - Continuous application (MD 0.92; 95% CI, 0.35–1.5; I^2=85%)
    - Delayed effects:
        - Intermittent application (MD 1.9; 95% CI, 0.44–3.3; I^2=90%)
        - Continuous application (MD 0.86; 95% CI, 0.27–1.5; I^2=92%)
- For endurance exercise, CWI was significantly more likely to reduce muscle soreness in both immediate and delayed effects than control. For resistance exercise, CWI was significantly more likely to reduce muscle soreness ONLY in delayed effects than control:
    - Immediate effects:
        - Endurance exercise (MD 1.1; 95% CI, 0.57–1.6; I^2=79%)
    - Delayed effects:
        - Endurance exercise (MD 0.97; 95% CI, 0.30–1.6; I^2=91%)
        - Resistance exercise (MD 1.4; 95% CI, 0.45–2.3; I^2 = 91%)

LIMITATIONS:

- For RCTs with participants exercising for multiple days, only the first session was taken into consideration.
- No longer time periods (e.g., weeks, months, etc.) were evaluated.
- Participant demographics including age, gender, ethnicity, and comorbidities were not clearly stated.
- Nearly 80% of the studies that had endurance exercise were carried out with athletes, so the results did not accurately apply to the general population.
- Magnitude of the effect, dose-response gradient, and influence of all plausible residual confounding were not assessed.

Jiayang Xiao, MD
PIH Health Downey FMR
Downey, CA

Is Lung Ultrasound Reliable for Diagnosis of Community-Acquired Pneumonia?

Lung Ultrasound Performed by Primary Care Physicians for Clinically Suspected Community-Acquired Pneumonia: A Multicenter Prospective Study

Rodríguez-Contreras FJ, Calvo-Cebrián A, Díaz-Lázaro J, et al. Lung Ultrasound Performed by Primary Care Physicians for Clinically Suspected Community-Acquired Pneumonia: A Multicenter Prospective Study. *Ann Fam Med*. 2022;20(3):227-236. doi:10.1370/afm.2796

KEY TAKEAWAY: Utilization of lung ultrasound may be effective in diagnosing suspected community-acquired pneumonia in the primary care setting.

STUDY DESIGN: Prospective, observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Community-acquired pneumonia (CAP) is a common and potentially serious pulmonary infection that is often diagnosed in primary care settings. Lung ultrasound (US) is potentially a reliable and cost-effective tool for the diagnosis of CAP, but studies in outpatient offices are limited. This study evaluated the diagnostic accuracy of lung ultrasound performed by primary care physicians (PCPs) in patients with clinically suspected CAP.

PATIENTS: Patients with suspected pneumonia

INTERVENTION: Lung ultrasound

CONTROL: Chest X-ray

PRIMARY OUTCOME: Diagnostic accuracy of lung ultrasound

METHODS (BRIEF DESCRIPTION):

- This was a prospective observational cohort study conducted across 12 primary care offices in Spain.
- Twenty-eight physicians (21 family physicians and 7 pediatricians), with a median of 85 hours of accredited US training including a dedicated five-hour lung US course, participated.
- Patients aged five years or older with clinically suspected CAP with fever and/or cough were included.
- Patients with known pneumonia, recent hospitalization, chronic lung disease, or recent antibiotic use were excluded.
- Patients had a median age of 47 years, 51.2% were female, fever (≥38°C) was present in 70.7% of patients, while 97.6% had a cough, crackles were heard in 59.8% of patients and the median peripheral oxygen saturation was 97%.
- Participants underwent standardized point-of-care lung US performed by trained PCPs, then immediately completed a chest X-ray interpreted by a radiologist.
- Lung US was positive if consolidation (≥1cm) or asymmetric B-line pattern was seen.
- Chest x-ray was positive if consolidation or interstitial pattern was officially reported.
- The sensitivity, specificity, predictive values (PV), and likelihood ratios (LR) of lung US diagnostic accuracy were calculated.

INTERVENTION (# IN THE GROUP): 82 (patients served as their own controls)

COMPARISON (# IN THE GROUP): 82

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Lung US and chest X-ray results demonstrated significant diagnostic correlation (odds ratio [OR] 10.2; 95% CI, 3.3–31).
- Lung US sensitivity was 0.88 (95% CI, 0.75–0.95).
- Lung US specificity was 0.59 (95% CI, 0.43–0.72).
- Lung US had a positive PV of 0.68 (95% CI, 0.55–0.79) and a negative PV of 0.83 (95% CI, 0.66–0.92).
- Lung US had a positive LR of 2.12 (95% CI, 1.45–3.10) and a negative LR of 0.21 (95% CI, 0.09–0.49).
- The median time to perform the lung US was 10 minutes.

LIMITATIONS:

- The study had a small sample size.
- As lung US was not compared to the gold-standard chest CT, it is possible that some consolidations visible on US were not evident on chest x-ray, potentially incorrectly increasing the false positive rate of US.
- There was no assessment of point of care lung US accuracy with an expert sonographer.
- There was no clinical follow-up to establish final diagnosis or illness severity.

Hussein Jumhour, MD
St. Joseph's Health, Department of Family Medicine
Paterson, NJ

One Rep Max or One Rep Trash? Pre-Workout vs Caffeine Supplements on Strength Endurance

Effects of Multi-Ingredient Pre-Workout Supplement and Caffeine on Bench Press Performance: A Single-Blind Cross-Over Study

Kruszewski M, Merchelski M, Kruszewski A, et.al. Effects of Multi-Ingredient Pre-Workout Supplement and Caffeine on Bench Press Performance: A Single-Blind Cross-Over Study. *Nutrients*. 2022 Apr 22;14(9):1750.

KEY TAKEAWAY: In resistance-trained males, strength endurance was greater with caffeine supplementation compared to multi-ingredient pre-workout supplements (MIPS).

STUDY DESIGN: Single-blinded crossover study

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: Multi-ingredient pre-workout supplements (MIPS) and caffeine are popular workout supplements that have individually shown some benefit in improving exercise performance. Few studies have compared the effects of MIPS versus caffeine alone.

PATIENTS: 16- to 40-year-old males in good health

INTERVENTION: Weight-based MIPS

CONTROL: Caffeine alone

PRIMARY OUTCOME: Strength endurance, state of mind, arousal, perceived exertion

Secondary Outcome: Financial impact of MIPS vs caffeine-alone

METHODS (BRIEF DESCRIPTION):

- The study was conducted at the Jozef Pilsudski University of Physical Education in Warsaw, Poland.
- Participants had to have at least one year of experience in bench press training and have no history of adverse side effects from any of the MIPS ingredients. The mean weight for the participants was 83.9 kg. The mean years of experience was 5.6.
- Participants were required to stop any additional physical activities and refrain from taking any additional pharmacologic or nutritional supplements.
- Data was collected over three visits. At the first visit, participants received no supplementation and performed 10 repetitions using their individual bench press weight. After 48 hours, participants completed two additional visits in which they were given either MIPS or caffeine. The second and third visits were separated by at least 72 hours.
- Thirty minutes after supplementation consumption, participants performed a standardized warm-up followed by five bench press sets to failure. Pre- and post-training psychologic assessments were administered.
    - FS – an 11-point scale about state of mind. Scores range from +5 to -5 where +5 is very good and -5 is very bad
    - FAS – a 6-point arousal scale where 1 is low and 6 is high
    - sRPE – an 11-point scale of perceived exertion where 0 is rest and 10 is maximum
- The dose used for caffeine and MIPS was 6 mg/kg of body weight. MIPS ingredients included beta-alanine, L-citrulline malate, arginine alpha-ketoglutarate, L-taurine, L-tyrosine, and 300 mg of caffeine.
- A search in an online database (Allegro.pl) was used to obtain and compare the cost of the most commonly used caffeine supplements (at least 200 mg) and MIPS containing at least 200 mg of caffeine.

INTERVENTION (# IN THE GROUP): 15

COMPARISON (# IN THE GROUP): 15

FOLLOW-UP PERIOD: None

RESULTS:

Primary Outcome –

- Total repetition volume was higher with caffeine supplementation compared to MIPS (37 vs 36, *P*=.04).
- There were no significant differences between caffeine and MIPS in state of mind, arousal, or perceived exertion.

Secondary Outcome –

- The mean price per portion of MIPS was 10 times higher than caffeine in pill form and 50 times higher than caffeine in powder form.

LIMITATIONS:

- The study had a small sample size, only included male patients, and tested one exercise type.

- The study was conducted over a very short period (days) and did not assess performance over a longer period (weeks to months).

Sean Seipel, MD
Naval Medical Center Camp Lejeune FMR
Camp Lejeune, NC

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Navy Medical Department, the Navy at large, or the Department of Defense.