GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of May 30 - June 3, 2022

SPOTLIGHT: More than a Grain of Salt for Patients with Chronic Heart Failure

- Metformin May Be Superior to Insulin in GDM
- Caring for Patients: PoCUS for Foot and Ankle Fractures
- Taking the Headache Out of Choosing Pharmacologic Therapy for Pediatric Migraines

More than a Grain of Salt for Patients with Chronic Heart Failure

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial

Ezekowitz JA, Colin-Ramirez E, Ross H, et al. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. *Lancet.* 2022; 399(10333):1391–1400. doi:10.1016/S0140-6736(22)00369-5

KEY TAKEAWAY: Among patients with chronic heart failure, a low sodium diet does not reduce cardiovascular-related hospitalizations, emergency room visits, or all-cause death as compared to usual dietary advice.

STUDY DESIGN: Multicountry, unblinded, randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding, trial stopped early)

BRIEF BACKGROUND INFORMATION: Clinicians and guidelines routinely recommend a low sodium diet for patients with heart failure. Although excess sodium is often identified as a reason for worsening heart failure symptoms, randomized trials to date have not demonstrated a clinically significant benefit of a low salt diet for these patients.

PATIENTS: Adults with New York Heart Association (NYHA) functional class II and III chronic heart failure

INTERVENTION: Target sodium intake <1,500 mg/day

CONTROL: Usual care

OUTCOME: Cardiovascular (CV)-related hospitalizations, CV-related emergency department (ED) visits, all-cause death

Secondary Outcome: Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, NYHA functional class, 6-minute walk distance at 12 months

METHODS (BRIEF DESCRIPTION):

- Adults at multiple centers on optimally tolerated medical therapy were assigned to either a low sodium diet (<1,500 mg/day) and education or usual care (general dietary advice by treating clinician).
  - Participants, investigators, and clinicians were unblinded to treatment group.
- Demographics
  - Participants had a mean age of 67 years old, median ejection fraction of 36%, over half resided in Canada, and 33% were female.
  - Median sodium intake was similar at baseline (2,286 mg/day in intervention group vs 2,119 mg/day in usual care group) but lower in the intervention group at 12 months (1,658 mg/day vs 2,073 mg/day in usual care).
- A masked committee assessed the primary outcome over 12 months. Blinded outcome assessors assessed quality of life and safety endpoints at 12 months.
  - KCCQ scores range from 0-100 for each measure, with 5-point change defined as the minimal clinically important difference.

INTERVENTION (# IN THE GROUP): 397

COMPARISON (# IN THE GROUP): 409

FOLLOW UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- No difference between the two groups for the primary outcome at 12 months (15% in low salt group vs 17% in usual care group, hazard ratio [HR] 0.89; 95% CI, 0.63–1.3).

Secondary Outcome –

- No difference in all-cause death between the two groups at 12 months.
- The intervention group had a statistically significant improvement in mean difference from baseline to 12 months for KCCQ overall summary score (3.4 points; 95% CI, 0.79–6), clinical summary score (3.3 points; 95% CI, 0.74–5.8), and physical limitation score (3.8 points; 95% CI, 0.67–6.9) as compared to usual care group.
- There was a statistically significant improvement in change in NYHA class intervention vs usual care group (odds ratio 0.59; 95% CI, 0.40–0.86) but no difference in 6-minute walk distance or safety outcomes.

LIMITATIONS:

- Participants, investigators, and clinicians were unblinded to assigned treatment group.
- Trial ended early at interim analysis at 12 months due to futility and COVID-19 pandemic.
- Investigators did not collect information on racial and ethnic backgrounds of the participants.
- The statistically significant differences in secondary outcomes are unlikely to be clinically meaningful.

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Metformin May Be Superior to Insulin in GDM

Metformin for gestational diabetes study: metformin vs insulin in gestational diabetes: glycemic control and obstetrical and perinatal outcomes: randomized prospective trial

Picón-César MJ, Molina-Vega M, Suárez-Arana M, et al. Metformin for gestational diabetes study: metformin vs insulin in gestational diabetes: glycemic control and obstetrical and perinatal outcomes: randomized prospective trial. *Am J Obstet Gynecol.* 2021; 225(5):517.e1-517.e17. doi:10.1016/j.ajog.2021.04.229

KEY TAKEAWAY: Metformin can provide equivalent glycemic control in GDM to insulin, with fewer episodes of hypoglycemia, slightly better postprandial glycemia, and equivalent or better obstetrical and perinatal outcomes.

STUDY DESIGN: Multicenter, open-label, parallel arms, randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Despite being first line treatment for diabetes in nonpregnant patients, oral medications are not commonly used in pregnancy because of concern that they will cross the placenta and may have long-term metabolic effects on the fetus. Because of this, the ADA recommends insulin as the treatment of choice for gestational diabetes. Previous research has shown metformin to be effective with few long-term effects on the baby. This study further evaluated efficacy and safety of metformin compared to insulin for GDM, adding systematic evaluation of hypoglycemia.

PATIENTS: Pregnant women with gestational diabetes mellitus

INTERVENTION: Metformin

CONTROL: Insulin detemir and/or insulin aspart

OUTCOME: Glycemic control, mode of labor/delivery
Secondary Outcomes: Maternal weight gain, treatment acceptability, adverse events

METHODS (BRIEF DESCRIPTION):

- Pregnant women 18 to 45 years old with a singleton fetus diagnosed with A2 gestational diabetes between 14 and 35 weeks GA were included. Women with fasting glucose levels over 120 mg/dL and with GI disorders were excluded.
- Each patient was randomly assigned to receive either metformin or insulin at standard starting doses and received a home blood glucose meter. Both groups had dose titration using a standard schedule.
- Standard growth and well-being assessments of the fetus were performed.
- Blood glucose, creatinine, liver enzymes, A1c, lipids, TSH, and vitamin B12 were obtained at inclusion, 35 and 37 weeks GA, and 8-12 weeks postpartum
- At the postpartum visit, a 75 g oral glucose tolerance test was performed.
- Primary Outcomes: Maternal fasting glucose, postprandial glucose, hypoglycemic episodes, hypertensive disorders, type of labor, mode of delivery, prematurity, macrosomia, LGA, NICU, NRDS, hypoglycemia, jaundice
- Secondary Outcomes: Maternal weight gain, fetal growth, congenital abnormalities, satisfaction with treatment

INTERVENTION (# IN THE GROUP): 97
COMPARISON (# IN THE GROUP): 99

FOLLOW UP PERIOD: Last visit 8–12 weeks postpartum

RESULTS:

Primary Outcome –

- Glycemic Control:
  - The difference between metformin vs insulin groups for glycemic control after two weeks and at 35–37 GA was not statistically significant.
  - The metformin group had significantly lower post-prandial glucose levels:
    - After lunch at two weeks (117 mg/dL vs 124 mg/dL, *P*=0.003)
    - After dinner at two weeks (121 mg/dL vs 126 mg/dL, *P*=0.041)
    - After dinner at 35–37 GA (118 mg/dL vs 127 mg/dL, *P*=0.001).
  - Patients on metformin vs insulin group were significantly less likely to have a hypoglycemic event (18% vs 56%, OR 6.1, 95% CI, 3.1–12).
- Mode of labor and delivery:
  - Patients on metformin were less likely to have an induction of labor or a cesarian section:
    - 60 insulin group patients were induced (29 elective) vs 43 metformin group patients (17 elective) (*P*=.029).
    - 38 insulin group patients had NSVD vs 58 metformin group patients (*P*=.795).
    - 51 insulin group patients went to C-section (14 elective) vs 26 metformin patients (9 elective) (*P*=.001).

Secondary Outcome –

- Maternal weight gain was significantly less in the metformin group, with average weight gain (1.4 kg vs 3.9 kg, *P*<.001).
- Treatment acceptability was significantly higher with metformin vs insulin (70% vs 32%, *P*<.001).
- Metformin vs insulin was significantly more likely to cause GI complaints (63% vs 42%, *P*=.006).

LIMITATIONS:

- Open-label may have caused doctors to assume worse GDM profiles in patients on insulin which may have biased decision-making around delivery method.
- Patients with fasting glucose >120 mg/dL and with gastrointestinal disorders were excluded, cannot generalize results to women in these categories.

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Caring for Patients: PoCUS for Foot and Ankle Fractures

Point-of-care bedside ultrasound examination for the exclusion of clinically significant ankle and fifth metatarsal bone fractures; a single blinded prospective diagnostic cohort study

Crombach A, Azizi N, Lameijer H, El Moumni M, Ter Maaten JC. Point-of-care bedside ultrasound examination for the exclusion of clinically significant ankle and fifth metatarsal bone fractures; a single blinded prospective diagnostic cohort study. *J Foot Ankle Res*. 2020; 13(1):19. Published 2020 May 7. doi:10.1186/s13047-020-00387-y

KEY TAKEAWAY: Standardized ankle PoCUS in combination with Ottawa Ankle rules completed by an experienced sonographer offers comparable sensitivity and specificity to radiograph imaging for ankle and fifth metatarsal fractures in emergency care situations.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Ankle and foot injuries are a common emergency department (ED) complaint often resulting in unnecessary radiation exposure and visit costs. Ottawa Ankle Rules (OAR) is a known tool offering high sensitivity and low specificity in acute ankle/foot fractures. Previous research in un-blinded PoCUS studies have shown promise for improvement in fracture specificity.

PATIENTS: Adult patients in the ED with acute ankle or foot trauma

INTERVENTION: PoCUS of ankle to assess for fracture

CONTROL: Radiograph of the ankle

OUTCOME: Sensitivity and specificity of fracture identification by sonographers of all experience levels
Secondary Outcome: Sensitivity and specificity of fracture identification by expert sonographers

METHODS (BRIEF DESCRIPTION):

- Patients were >17 years old who presented to the Netherland ED with acute ankle trauma occurring <48 hours beforehand and demonstrated positive OAR.
- After triage, sonographer (either an ED resident, physician, or expert) completed standardized ankle PoCUS without knowledge of clinical history or known presence of fracture.
- Another ED provider blinded to PoCUS result cared for the patient and obtained radiographs of the ankle.
- Radiologists blinded to PoCUS result read the radiographs and determined if fracture was present.
- Comparison between PoCUS and radiograph for sensitivity and specificity of detecting fractures.

INTERVENTION (# IN THE GROUP): 158

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Compared to fracture identified by radiograph, ankle PoCUS across all sonographers had a:
  - Sensitivity of 80% (95% CI, 63–92%)
  - Specificity of 90% (95% CI, 84–95%)
  - Positive LR 8.3
  - Negative LR 0.22

Secondary Outcome –

- Compared to fractures identified on radiograph, Ankle PoCUS done by an expert sonographer had a:
  - Sensitivity of 83% (95% CI, 66–93%)
  - Specificity of 99% (95% CI, 96–100%)
  - Positive LR 104
  - Negative LR 0.17

LIMITATIONS:

- Study completed in tertiary teaching hospital Emergency Department.
- Ultrasound machine malfunctioned during the study.
- Many ineligible patients due to missing data related to ultrasound malfunction resulting in smaller study size.
- Complete blinding could not occur due to clinical findings witnessed while completing ultrasound and clinical history provided to radiologists.

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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 US Army Medical Department, the Army at large, or the Department of Defense.

Taking the Headache Out of Choosing Pharmacologic Therapy for Pediatric Migraines

Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis

Locher C, Kossowsky J, Koechlin H, et al. Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis. *JAMA Pediatr.* 2020; 174(4):341–349. doi:10.1001/jamapediatrics.2019.5856

KEY TAKEAWAY: There is insufficient evidence to support the use of the prophylactic pharmacological therapy for pediatric migraines.

STUDY DESIGN: Systematic review and meta-analysis of 23 RCTs (N=2,217)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to significant heterogeneity)

BRIEF BACKGROUND INFORMATION: Pediatric migraines are a common occurrence with a rate of 23% in adolescents and an increasing prevalence with age. Debilitating headaches can have a significant impact on a child's ability to perform at school, participate in extracurricular activities, and take part in social gatherings. Current recommendations are based on research on adult migraine patients, as research with pediatric migraine patients is limited and inconclusive.

PATIENTS: Pediatric patients with episodic migraines

INTERVENTION: Pharmacological agents as prophylactic treatment

CONTROL: Placebo

OUTCOME: Efficacy

Secondary Outcome: Safety acceptability

METHODS (BRIEF DESCRIPTION):

- A comprehensive literature search included RCTs as well as existing systematic reviews on similar topics.
- Studies that were included looked at populations <18 years old with prior diagnosis of episodic migraines (with or without aura).
- Studies selected for inclusion were head-to-head comparisons of two pharmacologic agents or a pharmacologic agent compared to placebo.
- Interventions included 13 pharmacological agents belonging to the categories of β-blockers, anticonvulsants, antidepressants, antihistamines, calcium channel blockers, natural supplements, and placebo.

INTERVENTION (# IN THE GROUP): 1,698

COMPARISON (# IN THE GROUP): 519

FOLLOW UP PERIOD: Eight weeks to six months

RESULTS:

Primary Outcome –

- Propanol and topiramate were significantly more effective than other pharmacological interventions (19 trials, N=1,541; SMD 0.6; 95% CI, 0.03–1.2 / SMD 0.59; 95% CI, 0.03–1.2).
  - However, long-term analysis revealed no significant difference compared to placebo.

Secondary Outcome –

- The acceptability of prophylactic pharmacotherapy was not statistically different compared to placebo (19 trials, N=1,641; RR 0.49; 95% CI, 0.12–2 for riboflavin to RR 1.50; 95% CI, 0.70–3.2 for sodium valproate).
- Safety was not significantly different between prophylactic pharmacotherapy and placebo with treatment discontinuation for adverse effects (11 trials, N=1,069; RR 0.78; 95% CI, 0.02-38 for riboflavin to RR 7.0; 95% CI, 0.38–128 for flunarizine).

LIMITATIONS:

- 7 of the 12 pharmacological agents were tested on less than 100 patients.
- There was significant heterogeneity due to difference in intervention dosing, length of treatment, and reporting methods.
- Potential that young children are not able to accurately differentiate a migraine from other types of headaches, possibly impacting primary and secondary outcomes.

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