GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: A Link Between Autism Spectrum Disorder and Acetaminophen: No Longer a Complete Mystery

A Link Between Autism Spectrum Disorder and Acetaminophen: No Longer a Complete Mystery

A Systematic Review of the Link Between Autism Spectrum Disorder and Acetaminophen: A Mystery to Resolve

Khan FY, Kabiraj G, Ahmed MA, et al. A Systematic Review of the Link Between Autism Spectrum Disorder and Acetaminophen: A Mystery to Resolve. *Cureus*. 2022;14(7):e26995. Published 2022 Jul 18. doi:10.7759/cureus.26995

KEY TAKEAWAY: There is a consistent association between acetaminophen use during pregnancy and adverse neurodevelopmental outcomes, including autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). Further studies are needed to better understand its mechanism of action, verify causality, and identify a safer analgesic alternative.

STUDY DESIGN: Systematic review of 13 prospective cohort studies, one narrative review article, one systematic review, and one meta-analysis. (N=284,317)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Most medications are not adequately investigated in human pregnancies even though some drugs taken during pregnancy have been linked to ASD. Acetaminophen is the most common medication taken during pregnancy but its relationship to ASD was not first studied until more recently. Research now shows that if taken during pregnancy, acetaminophen may affect the immune system and impair neurodevelopmental outcomes. This systemic review aims to analyze and summarize the data available regarding the use of acetaminophen during pregnancy and its effects on neurodevelopmental outcomes.

PATIENTS: Women in their reproductive years and children

INTERVENTION: Maternal prenatal use of acetaminophen

CONTROL: No use of acetaminophen during pregnancy

PRIMARY OUTCOME: Adverse neurodevelopmental outcomes

METHODS (BRIEF DESCRIPTION):

- The PRISMA 2020 checklist was used to compile relevant human population studies using PubMed/Medline/PubMed Central, Science Direct, and Google Scholar.
- Studies published in English from the past five years were included and all geographical areas were considered.
- Patient demographics included women in their reproductive years (mainly 16+) and children
- The intervention was measured as the maternal use of acetaminophen pre-pregnancy and during pregnancy for varying lengths of time.
- The control was no use of acetaminophen during pregnancy.
- Adverse neurodevelopmental disorders included ASD and ADHD.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Variable

RESULTS:

Primary Outcome –

- All 16 studies showed a consistent association between acetaminophen use during pregnancy and adverse neurodevelopmental outcomes in children, including ASD and ADHD, especially with a longer duration of acetaminophen use (numerical and statistical results not provided).

LIMITATIONS:

- There were limited studies that discussed the mechanisms of acetaminophen leading to neurodevelopmental disorders, so acetaminophen's relationship to the pathophysiology of these disorders is not well understood.

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Should Food be Thy Medicine?

Effect of an Intensive Food-As-Medicine Program on Health and Health Care Use: A Randomized Clinical Trial

Doyle J, Alsan M, Skelley N, Lu Y, Cawley J. Effect of an Intensive Food-as-Medicine Program on Health and Health Care Use: A Randomized Clinical Trial. *JAMA Intern Med.* 2024;184(2):154-163. Doi:10.1001/jamainternmed.2023.6670

KEY TAKEAWAY: In diabetics with an HbA1c ≥8.0% and food insecurities, an intensive food-as-medicine program that includes groceries, dietitian consultations, education, and health coaching does not significantly decrease HbA1c levels compared to standard medical care.

STUDY DESIGN: Stratified randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Food insecurity has been a target to improve patient outcomes and reduce healthcare costs in diet-related chronic diseases such as type 2 diabetes mellitus (DM2). Observational food-as-medicine programs have been found to improve food insecurity. This study assesses that food-as-medicine programs' impacts on health and healthcare use are uncertain.

PATIENTS: Type 2 diabetic patients with food insecurity

INTERVENTION: Intensive food-as-medicine program

CONTROL: Standard diabetes care

PRIMARY OUTCOME: HbA1c

Secondary Outcome: Biometric measures (weight, blood pressure, cholesterol, triglycerides, and fasting glucose), health care use

METHODS (BRIEF DESCRIPTION):

- Patients in the mid-Atlantic diagnosed with DM2 had an HbA1c ≥8%, experienced food insecurity, resided in a rural or urban setting serviced by the program, and received care in the program's connected healthcare system were included in the study.
- Patients were randomized to one of two groups:
  - Starting the program immediately
  - Starting the program in six months (control)
- Patients who started the program immediately had weekly clinic visits which consisted of the following:
  - Dieticians distributed 10 meals per week per patient and each member of the patient's household with food choices.
  - Patients received education on diet and diabetes from dieticians.
  - Routine preventative care was provided by nursing.
- Patients who were starting the program in six months received brochures on food banks.
- HbA1c measured at approximately six and 12 months.

INTERVENTION (# IN THE GROUP): 170

COMPARISON (# IN THE GROUP): 179

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- The food-as-medicine program did not affect HbA1c at six months compared to usual care (between-group adjusted mean difference [MD] –0.10; 95% CI, –0.46 to 0.25).

Secondary Outcome –

- There were no significant differences between the food-as-medicine program and usual care in blood pressure, cholesterol, triglycerides, fasting glucose, hospitalization, ED use, or insurance claims.
- Food-as-medicine significantly increased weight compared to usual care at six months (adjusted MD 2.0 kg; 95% CI, 0.07–3.8).
  - There was no significant difference by 12 months.
- Food-as-medicine increased outpatient visits compared to usual care at six months (adjusted MD 1.0; 95% CI, 0.07–3.8).
  - There was no significant difference at 12 months.

LIMITATIONS:

- Conducted during the COVID-19 pandemic.
- Inclusion criteria for HbA1c cutoff may have had a propensity to decrease with standard care at baseline.
- The study was conducted at a health system that may have already had effective glycemic care for the control group.

- Social-desirability bias: The control group may have changed behaviors to compensate for not being enrolled in the treatment program immediately.
- Lack of details in dietary consumption to verify if provided food was consumed.
- Limited follow-up where the intervention results may have had significant outcomes beyond six to 12 months.

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Preventing Recurrent UTI in Women Using Vaginal Estrogen

Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women: A Randomized Clinical Trial

Ferrante KL, Wasenda EJ, Jung CE, Adams-Piper ER, Lukacz ES. Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women: A Randomized Clinical Trial. *Female Pelvic Med Reconstr Surg*. 2021;27(2):112-117. doi:10.1097/SPV.0000000000000749

KEY TAKEAWAY: Vaginal estrogen reduces UTI occurrence in post-menopausal women with recurrent UTI.

STUDY DESIGN: Investigator-initiated, multicenter, single-blind, randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size and single-blind design)

BRIEF BACKGROUND INFORMATION: Recurrent UTIs (rUTI) are common in post-menopausal females. Few studies are available to evaluate the current dosing and efficacy of vaginal creams in this population for the prevention of rUTI. The goal of this study was to determine the efficacy of vaginal estrogen in post-menopausal women for the prevention of rUTI.

PATIENTS: Post-menopausal females with a diagnosis of recurrent UTI

INTERVENTION: Vaginal estrogen cream or ring

CONTROL: Placebo cream

PRIMARY OUTCOME: UTI occurrence

METHODS (BRIEF DESCRIPTION):

- Participants 18–100 years old were selected based on post-menopausal status and documented diagnosis of recurrent UTI.
- Participants were excluded if they had used vaginal androgen, progestin, or estrogen products within six months or if the patient used medications or supplements for the prevention of UTI within three months before the study.
- Individuals were then randomized in a 1:1:1 ratio to the following groups:
  - Vaginal estrogen cream
  - Vaginal estrogen ring
  - Placebo cream
- The primary outcome of UTI occurrence was assessed by the number of occurrences of UTI in women treated with vaginal estrogen vs placebo.

INTERVENTION (# IN THE GROUP): 16

COMPARISON (# IN THE GROUP): 11

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Women treated with vaginal estrogen cream had fewer UTIs compared to placebo (50% vs 91%, respectively; *p*=.041).
- Women treated with vaginal estrogen ring had fewer UTIs compared to placebo (38% vs 91%, respectively; *p*=.041).

LIMITATIONS:

- Participant recruitment was limited by lack of referral due to the absence of documented UTI and biases from providers willing to refer patients due to the current widespread use of vaginal estrogen for the prevention of rUTI in local areas.
- Modifications to study design included: Decreased wash-out period to two months after using any vaginal hormones and one month if the patient used drugs/supplements known to prevent UTI, only one culture-proven UTI of three documented UTIs in 12 months or one culture-proven UTI of two documented UTIs in six months.
- Small sample size
- Single-blinded study
- The vaginal estrogen ring was likely not fully blinded in the study during placement.
- There was no comparison of effectiveness between modes of estrogen delivery.

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(In)Direct with First-Attempt Intubations: Video and Direct Laryngoscopy

Video vs Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults

Prekker ME, Driver BE, Trent SA, et al. Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults. *N Engl J Med*. 2023;389(5):418-429. doi:10.1056/NEJMoa2301601

KEY TAKEAWAY: Successful tracheal intubation on the first attempt occurred more often using video laryngoscopy than direct laryngoscopy.

STUDY DESIGN: Randomized, unmasked, multisite trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unmasked study design)

BRIEF BACKGROUND INFORMATION: Most intubations are attempted with direct laryngoscopy; however, video laryngoscopy has gradually increased. Current studies comparing the use of video and direct laryngoscopy demonstrate inconsistent results. Successful intubation on the first attempt is meaningful because it is associated with better outcomes for critically ill patients, compared to those whose intubation was not successful on the first attempt. This study sought to demonstrate which type of laryngoscopy is associated with higher rates of successful first-attempt intubation.

PATIENTS: Adults undergoing intubation

INTERVENTION: Video laryngoscopy

CONTROL: Direct laryngoscopy

PRIMARY OUTCOME: Success on the first trial of intubation

Secondary Outcome: Severe complications within two minutes of intubation, success per prior experience

METHODS (BRIEF DESCRIPTION):

- Eligible patients were adults in emergency departments (ED) and intensive care units (ICU), who were critically ill and requiring intubation with a laryngoscope, from 17 sites in the United States.
- Patients who were pregnant, incarcerated, or detained, or required intubation before randomization were excluded, as well as those where the provider decided one type of laryngoscope was required or not appropriate.
- Participants had a mean age of 55 years old, 35% were female, 70% of intubations occurred in the ED, and primary indications for intubation were altered mental status (45%) and acute respiratory failure (30%).
- Patients were randomized in a 1:1 ratio, either intubation with video laryngoscopy (intervention group) or with direct laryngoscopy (control group).
- The primary outcome was binary, whether there was a successful endotracheal tube placement with one insertion attempt.
    - This was defined by a single insertion of the endotracheal tube (ETT) into the trachea (with a single tube in the mouth or bougie followed by insertion of an ETT into the mouth).
- Secondary outcome was the number of intubations that had a severe complication occurring between induction and two minutes following intubation, specifically SpO2 <80%, systolic blood pressure <65 mmHg, new or increased vasopressor requirement, cardiac arrest, and/or death.
- The experience of operator was grouped by the number of prior intubations (<25, 25–100, >100).

INTERVENTION (# IN THE GROUP): 705

COMPARISON (# IN THE GROUP): 712

FOLLOW-UP PERIOD: Two minutes after intubation

RESULTS:

Primary Outcome –

- Successful first attempt of intubation occurred more often with video laryngoscopy compared to direct laryngoscopy (85% vs 71%, respectively; absolute risk difference 14%; 95% CI, 9.9–19).

Secondary Outcome –

- There was no difference in the incidence of severe complications between video and direct laryngoscopy groups.
- Among operator groups with fewer previous intubations (<25 and 25–100), there was more often successful first-attempt intubation using video laryngoscopy compared to direct laryngoscopy (80% vs 54% and 86% vs 74%, respectively).
- In the operator group with greater previous intubations (>100), there was no significant difference in first-attempt success.

LIMITATIONS:

- Large amounts of the procedure, including equipment and protocol (blade type, brand of laryngoscope, whether bougie was used, method to determine intubation success), were left to provider discretion.
- Providers performing the intubations were predominantly emergency medicine residents and critical care fellows (92%).
- The subgroup analysis of operators was not reported with absolute risk differences, so conclusions cannot be drawn.

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Blood-Glucose Management in ICU Settings: Does Stringency Matter?

Tight Blood-Glucose Control Without Early Parenteral Nutrition in the ICU

Gunst J, Debaveye Y, Güiza F, et al. Tight Blood-Glucose Control without Early Parenteral Nutrition in the ICU. *N Engl J Med*. 2023;389(13):1180-1190. doi:10.1056/NEJMoa2304855

KEY TAKEAWAY: Tight glucose control does not affect ICU length of stay or 90-day mortality in ICU patients who did not receive early parenteral nutrition.

STUDY DESIGN: Randomized, large, multicenter, controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unblinded study design)

BRIEF BACKGROUND INFORMATION: Hyperglycemia is a common finding in the ICU that is associated with poor outcomes. Previous studies have shown that strict glucose control has led to positive and negative effects for patients in the ICU. In the outpatient setting, strict glucose control is known to be important in secondary prevention. With strict use of insulin, hypoglycemia events can likely occur more often, which is detrimental. This study aimed to explore how different levels of sugar control affect recovery times in the ICU.

PATIENTS: Adult ICU patients

INTERVENTION: Tight glucose control

CONTROL: Liberal glucose control

PRIMARY OUTCOME: ICU length of stay, 90-day mortality

Secondary Outcome: ICU-acquired acute kidney injury, liver dysfunction

METHODS (BRIEF DESCRIPTION):

- Patients 55–75 years old admitted to the ICU between September 2018 and August 2022 were included in this study.
  - 60% were male.
- Patients were randomly assigned to the liberal glucose control or tight glucose control group in a 1:1 ratio.
  - Tight glucose control group: Blood glucose optimized between 80–110 mg/dl using a computer algorithm managing insulin doses. Measurement of blood glucose occurred every 1–4 hours based on the algorithm.
  - Liberal glucose control group: Insulin initiated if blood-glucose was >215 mg/dl. The ideal blood glucose range was 180–215 mg/dl. Blood glucose was measured at least every four hours a day.
- Blood glucose was measured with arterial blood gas.
- Insulin was administered using continuous infusion through a central venous catheter.
- Upon ICU admission, parenteral nutrition was refrained for 1 week.
- The duration of ICU care was assessed by computing the period of admission until discharge from the ICU, or until vital organ support was no longer necessary.
- 90-day mortality was used as a safety outcome.
- The secondary outcome measured ICU-acquired acute kidney injury and liver dysfunction.
  - Incidence of acute kidney injury was measured by incidences of stage three acute renal failure and the use of renal replacement therapy.
  - Incidence of liver dysfunction was measured using gamma-glutamyl transferase, alkaline phosphatase, bilirubin, AST, and ALT plasma levels.

INTERVENTION (# IN THE GROUP): 4,608

COMPARISON (# IN THE GROUP): 4,622

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Tight glucose control did not yield a significant impact on ICU length of stay when compared to liberal glucose control (mean score 6 vs 7 days, respectively; relative risk [RR] 0; 95% CI, –1 to 0).
- Tight glucose control group did not yield a significant impact on mortality within 90 days compared to liberal glucose control (11% vs 10%, respectively; *P*=.51).

Secondary Outcome –

- ICU-acquired acute kidney injury was greater in the liberal glucose control group compared to the tight glucose control group (8.6% vs 7.2%, respectively; RR 0.84; 95% CI, 0.73–0.97).
- Liver dysfunction had a higher incidence in the liberal glucose control group compared to the tight

glucose control group (33% vs 28%, respectively; RR 0.86; 95% CI, 0.81–0.92).

LIMITATIONS:

- Possible confounding variables to the primary outcome may have been affected by the shortage of ICU beds during the COVID-19 pandemic.
- This was not a blind study for the caregivers, who knew the treatment assignment.
- Variable discharge from ICU criteria

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Benefits of Osteopathic Manipulative Treatment in Patients with Chronic Lower Back Pain

Osteopathic Manipulative Treatment of Patients with Chronic Low Back Pain in the United States: A Retrospective Cohort Study

Licciardone JC, Moore S, Fix K, Blair LG, Ta K. Osteopathic manipulative treatment of patients with chronic low back pain in the United States: a retrospective cohort study. *J Osteopath Med.* 2023;123(5):259-267. Published 2023 Feb 3. doi:10.1515/jom-2022-0212

KEY TAKEAWAY: Spinal manipulation may reduce pain and improve quality of life in patients with chronic lower back pain.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Chronic lower back pain is the leading cause of disability and can impair quality of life. This study assesses if integrating osteopathic manipulative treatment (OMT) into care improves back pain and quality of life.

PATIENTS: Adults with chronic lower back pain

INTERVENTION: OMT

CONTROL: No OMT

PRIMARY OUTCOME: Pain intensity, pain impact, physical function, health-related quality of life

METHODS (BRIEF DESCRIPTION):

- Adults 21–79 years old from the Pain Registry for Epidemiological, Clinical, and Interventional Studies and Innovation who were followed over a 12-month period from April 2016 to April 2022 (n=1,358).
- Patients reported their physician type (osteopathic or allopathic) and use of spinal manipulative treatment. Any patients treated by an osteopathic physician and reporting spinal manipulation were considered the treatment group, while patients treated by an allopathic physician or an osteopathic physician not using spinal manipulation were the control.
- Pain intensity was measured by a 1–10 scale of daily low back pain.
- Pain impact was measured by the pain intensity measurement and the Patient-Reported Outcomes Measure Information System.
- Physical function was measured with the Roland-Morris Disability Questionnaire.
- Health-related quality of life was measured by sleep disturbance, pain interference, anxiety, depression, and low energy/fatigue (SPADE) cluster.
- Higher numbers on all measures represented worse pain or functional outcomes.

INTERVENTION (# IN THE GROUP): 187

COMPARISON (# IN THE GROUP): 1,171

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- OMT improved the following compared to no OMT:
  - Pain intensity (delta change per ANOVA 0.62; 95% CI, 0.24–0.99)
  - Pain impact (delta change per ANOVA 3.1; 95% CI, 1.2–5.1)
  - Physical function (delta change per ANOVA 2.2; 95% CI, 0.93–3.6)
  - Health-related quality of life (delta change per ANOVA 1.5; 95% CI, 0.02–3.1)

LIMITATIONS:

- Participants were not randomized at enrollment.
- Patients may have had OMT before enrollment which affected outcomes.
- Specific methods of OMT were not tracked, all treatment was recorded as “spinal manipulation”.
- Treatment with an osteopath with spinal manipulation was self-reported by the patients.

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