GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Strokes and LDL-C Reduction - An Intensely Important Topic

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Strokes and LDL-C Reduction: An Intensely Important Topic

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Between Intensity of Low-Density Lipoprotein Cholesterol Reduction with Statin-Based Therapies and Secondary Stroke Prevention: A Meta-analysis of Randomized Clinical Trials

Lee M, Cheng CY, Wu YL, Lee JD, Hsu CY, Ovbiagele B. Association Between Intensity of Low-Density Lipoprotein Cholesterol Reduction With Statin-Based Therapies and Secondary Stroke Prevention: A Meta-analysis of Randomized Clinical Trials. JAMA Neurol. 2022; 79(4):349-358.

KEY TAKEAWAY: More intensive low-density lipoprotein cholesterol (LDL-C) lowering therapy shows a greater reduction in the risk of recurrent stroke.

STUDY DESIGN: Meta-analysis of 11 randomized clinical trials (RCTs) (N=20,163)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to studies not directly answering the research question and small sample sizes of included studies)

BRIEF BACKGROUND INFORMATION: Recurrent stroke is a common occurrence. This study analyzed whether more intensive or less intensive LDL-C lowering therapies decrease the risk of recurrent stroke.

PATIENTS: Patients with a history of stroke

INTERVENTION: More intensive LDL-C lowering therapy

CONTROL: Less intensive LDL-C lowering therapy

PRIMARY OUTCOME: Recurrent stroke

Secondary Outcome: Major adverse cardiovascular events (MACE), hemorrhagic stroke

METHODS (BRIEF DESCRIPTION):

- Comprehensive literature search for RCTs that included:
  - Patients with a history of stroke or TIA.
  - Compared more intensive vs less intensive LDL-C lowering statin-based therapies.
    - The study did not define what more versus less intensive therapies specifically included.
  - Recurrent stroke was used as an endpoint.
  - The duration of treatment was at least six months.

INTERVENTION (# IN THE GROUP): 10,085

COMPARISON (# IN THE GROUP): 10,078

FOLLOW-UP PERIOD: 1–6.1 years

RESULTS:

Primary Outcome –

- Compared to less intensive approaches, more intensive LDL-C lowering statin-based therapies reduced the risk of:
  - Stroke (11 trials, n=20,163; relative risk [RR] 0.88; 95% CI, 0.80–0.96)
  - Myocardial infarction (7 trials, n=15,448; RR 0.73; 95% CI, 0.62–0.86)

Secondary Outcome –

- Compared to less intensive approaches, more intensive LDL-C lowering statin-based therapies reduced the risk of MACE (8 trials, n=18,708; RR 0.83; 95% CI, 0.78–0.89).
- Intensive approaches increased the risk of hemorrhagic stroke compared to less intensive approaches (8 trials; n=18,708; RR 1.5; 95% CI, 1.1–1.9).
- There was no significant difference in all-cause mortality between the LDL-C lowering strategies (5 trials, n=10,034; RR 1.0; 95% CI, 0.90–1.2).

LIMITATIONS:

- The included studies were completed in high-income countries and excluded studies with >10% of patients having end-stage renal disease, limiting generalizability.
- Several studies did not blind the interventions.
- The sample sizes of the included studies varied widely, with three of the studies having less than 200 participants.

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Clinical Symptoms in Pediatric UTI: When to Consider Treating

Clinical Features for the Diagnosis of Pediatric Urinary Tract Infections

Boon H, Van den Bruel A, Struyf T, Gillemot A, Bullens D, Verbakel J. Clinical Features for the Diagnosis of Pediatric Urinary Tract Infections: Systematic Review and Meta-Analysis. *Ann Fam Med*. 2021;19 (5) 437-446; DOI: 10.1370/afm.2684

KEY TAKEAWAY: In otherwise healthy ambulatory pediatric care populations, urinary tract infection should be strongly considered in patients with cloudy urine, dysuria, urinary frequency, or bed-wetting; conversely, diaper rash, stridor, or circumcision can be used to rule out urinary tract infections.

STUDY DESIGN: Systematic review and meta-analysis of 35 cross-sectional, case-control, and retrospective cohort studies (N=78,427)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: UTIs are common in the pediatric population, representing up to 6% of acute illnesses in children under five years old. Presenting symptoms are often non-specific, especially in toddlers and infants who are preverbal. Delays in diagnosis increase the risk of systemic infections and permanent renal injury. Current AAP guidelines recommend urine sampling for all acutely ill children who: are prescribed antibiotics, are younger than 3 months, are 3–24 months and not low risk on a risk stratification tool or are older than 24 months with a sign and symptom-based strategy. There is limited evidence on whether AAP or European-based guidelines accurately identify patients who would benefit from testing.

PATIENTS: Children in an ambulatory care setting

INTERVENTION: Symptoms, clinical features, or clinical prediction rules

CONTROL: absence of symptoms and features

PRIMARY OUTCOME: Positive urine culture

METHODS (BRIEF DESCRIPTION):

- A literature search identified prospective cross-sectional diagnostic accuracy studies, diagnostic nested case-control studies, and retrospective cohort studies.
- Inclusion criteria: Studies comparing diagnostic accuracy of clinical features of UTI in pediatric patients, pediatric patients age <18 years in an ambulatory care setting.
- Those with 58 specific symptoms or clinical features and the use of six clinical prediction rules were compared to those without determining if the diagnostic tool was useful and effective for identifying UTI.
- 2014 European Association of Urology (EAU) Urinary Tract Infections in Children guidelines were used as a reference standard for positive urine culture results.
- Positive and negative likelihood ratios and post-test probabilities were calculated for each clinical finding or symptom and each clinical prediction rule.
- Results were reported as Useful for Ruling Out UTI (Substantially Decreased Likelihood, LR– ≤0.25) or Useful for Ruling in UTI (Substantially Increased Likelihood, LR+ ≥4).

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The following clinical features and prediction rules were useful for ruling out urinary tract infections:
  - Circumcision (negative likelihood ratio [LR–] 0.24; 95% CI, 0.08–0.72)
  - Stridor (LR– 0.2; 95% CI, 0.05–0.81)
  - Diaper rash (LR– 0.13; 95% CI, 0.02–0.92)
  - Gorelick scale <2 (LR– 0.11; 95% CI, 0.01–0.81)
- The following clinical features and prediction rules were useful for ruling in urinary tract infections:
  - Cloudy urine (positive likelihood ratio [LR+] 4.6; 95% CI, 3.7–5.6)
  - Malodorous urine (LR+ 4.1; 95% CI, 2.3–7.5)
  - DUTY clean-catch score ≥5 (LR+ 9.6; 95% CI, 7.1–13)
  - Hematuria might be useful for ruling in UTI, but findings were limited by study heterogeneity.
  - Suprapubic tenderness, loin tenderness, capillary refill time >3 seconds, and no fluid intake might be useful for ruling in UTI but were each only reported in one study.

- The exclusion of studies including children >5 years old did not affect outcome findings.

LIMITATIONS:

- Heterogeneity existed between studies.
- Overall moderate to high risk of bias due to selection bias from retrospective sampling.
- Cloudy and malodorous urine were reported mostly in high-prevalence studies and included in only one low-prevalence study.
- Exclusion of one of four studies evaluating malodorous urine decreased the LR+ of this clinical finding to 2.9 (95% CI, 1.6–5.2).
- Clinical decision-making tools still require external validation.

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Antidepressants: A Little Bit Goes a Long Way

No Benefit from Flexible Titration above Minimum Licensed Dose in Prescribing Antidepressants for Major Depression: Systematic Review

Furukawa TA, Salanti G, Cowen PJ, Leucht S, Cipriani A. No benefit from flexible titration above minimum licensed dose in prescribing antidepressants for major depression: systematic review. *Acta Psychiatr Scand*. 2020 May;141(5):401-409. DOI: 10.1111/acps.13145.

KEY TAKEAWAY: Fixed, minimum, FDA-approved dosing of antidepressants is as effective as flexible dosing regimens during the acute phase of major depression.

STUDY DESIGN: Systematic review and meta-analysis of 123 placebo-controlled randomized trials (RCTs) (N= 29,420)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to averages rather than individual patient data used in meta-analysis)

BRIEF BACKGROUND INFORMATION: Second-generation antidepressants are recommended for the initial treatment of major depression; however, guidelines vary on appropriate dosing strategies (fixed vs. flexible titration). In terms of efficacy, tolerability, and acceptability, fixed vs. flexible dosing of antidepressants warrants further comparison.

PATIENTS: Adults with major depressive disorder

INTERVENTION: Fixed-dose studies

CONTROL: Flexible-dose studies

PRIMARY OUTCOME: ≥50% reduction in depression

Secondary Outcome: Depression severity, drop-outs due to tolerability and acceptability

METHODS (BRIEF DESCRIPTION):

- Adults, diagnosed with acute phase of major depression from six countries were included.
- Patients with multiple psychiatric disorders were excluded from this study.
- Studies included SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline), venlafaxine, or mirtazapine at fixed-minimal doses (intervention) vs. placebo or flexible-titration doses vs. placebo (control).
- Both primary and secondary outcomes were analyzed using Ratio of Odds Ratios (RORs), which compares the fixed-dosing Odds Ratio (OR) and flexible-dosing OR of the same antidepressant.

INTERVENTION (# IN THE GROUP): 66 RCTs

COMPARISON (# IN THE GROUP): 77 RCTs

FOLLOW-UP PERIOD: Eight weeks

RESULTS:

Primary Outcome –

- Flexible-dosing of antidepressants provided no advantage compared to minimum-licensed dosing in terms of effectiveness:
  - SSRIs: ROR 0.96 (95% CI, 0.73–1.3)
  - Venlafaxine: ROR 1.2 (95% CI, 0.96–1.6)
  - Mirtazapine: ROR 0.77 (95% CI, 0.33–1.8)

Secondary Outcome –

- Flexible-dosing of antidepressants provided no advantage compared to minimum-licensed dosing in terms of tolerability and acceptability.

LIMITATIONS:

- The conclusions apply to the group average, rather than the individual patients.
- Individual characteristics such as age, weight, comorbidities, and past antidepressant usage were not considered.
- Some antidepressants had fewer studies, so they had wider confidence intervals.

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Probiotics Can Improve Atopic Dermatitis in Infants and Toddlers

The Effectiveness of Probiotic *Lactobacillus rhamnosus* and *Lactobacillus casei* Strains in Children with Atopic Dermatitis and Cow's Milk Protein Allergy

Cukrowska B, Ceregra A, Maciorkowska E, et al. The Effectiveness of Probiotic *Lactobacillus rhamnosus* and *Lactobacillus casei* Strains in Children with Atopic Dermatitis and Cow's Milk Protein Allergy: A Multicenter, Randomized, Double Blind, Placebo Controlled Study. *Nutrients*. 2021;13(4):1169. Published 2021 Apr 1. doi:10.3390/nu13041169

KEY TAKEAWAY: Probiotics containing *Lactobacillus sp* may be effective in the treatment and prevention of atopic dermatitis in children less than two years old, particularly in those with allergen sensitization.

STUDY DESIGN: Multi-site, randomized, double-blind, placebo-controlled, parallel-group study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: In recent decades, the incidence of food allergies and atopic dermatitis has increased in developed countries. This may be multifactorial and potentially related to diet, increased use of antibiotics and detergents, and decreased incidence of infectious diseases, among other factors. Pediatric atopic dermatitis appears to be associated with a narrow spectrum of bacteria in the gastrointestinal (GI) tract.

PATIENTS: Children <2 years old with severe atopic dermatitis

INTERVENTION: Probiotics

CONTROL: Placebo

PRIMARY OUTCOME: Atopic dermatitis symptom severity, clinical improvement

Secondary Outcome: Levels of serum IgE and allergen-specific IgE

METHODS (BRIEF DESCRIPTION):

- Patients were less than two years old, with the diagnosis of atopic dermatitis.
- Both groups maintained a diet free of cow's milk protein.
- The intervention group received standard of care for skin regimen with emollients and use of other pharmacotherapy as appropriate.
- Study subjects received a daily mixture of three probiotic strains containing 1 billion CFU consisting of 50% *lactobacillus casei* and 50% *lactobacillus rhamnosus*. The placebo group received maltodextrin. Both preparations were identical in appearance.
- SCORAD assessments by a blinded investigator were completed at the initial visit, three months, and nine months follow-up. SCORAD index comprised of grading objective symptoms from 0–3 including erythema, edema, scratches, oozing/crusting, lichenification, and skin dryness (60% of SCORAD), total body surface area involved estimated by use of the rule of nines (20%), and subjective pruritus and insomnia secondary to allergic manifestations (20%).
- Primary outcome: Change of symptom severity as measured by the SCORAD index and change in the proportion of subjects with improvement, no change, or worsening. A SCORAD change of greater than 30% from the initial score was of clinical significance for the study.
- Secondary outcome: Levels of serum IgE and allergen-specific IgE were also measured via MAST immuno-blot assay initially and at a nine-month follow-up.

INTERVENTION (# IN THE GROUP): 66

COMPARISON (# IN THE GROUP): 68

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Probiotics decreased symptom severity compared to placebo at three months (OR 2.6; 95% CI, 1.1–5.8; NNT=5.9).
- Probiotic treatment was less likely to result in no improvement compared to placebo (OR 0.25; 95% CI, 0.07–0.99).

Secondary Outcome –

- Most children had sensitization to multiple allergens based on allergen-specific IgE levels.
- Mean baseline and nine-month total IgE levels were not significantly different between groups.
- Subjects with allergen sensitization in the probiotic group vs placebo group were markedly more likely

to see an improved SCORAD index (OR 6.0; 95% CI, 1.9–20).

LIMITATIONS:

- 36% and 30% of subjects of intervention and control groups, respectively, dropped out between the three- and nine-month follow-up points.
- Subjectivity related to obtaining the SCORAD index, though mitigated by using blinded specialists.
- Lack of ability to maintain systematic consistent administration of study drugs.
- Inconsistency concerning verifying if subjects used other dietary supplementation during the study.

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Vaccination Matters in Pregnancy: Maternal Outcomes of COVID-19 Infection

Maternal Outcomes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Vaccinated Compared with Unvaccinated Pregnant Patients

Morgan JA, Biggio JR Jr, Martin JK, et al. Maternal Outcomes After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Vaccinated Compared with Unvaccinated Pregnant Patients. *Obstet Gynecol*. 2022;139(1):107-109. doi:10.1097/AOG.0000000000004621

KEY TAKEAWAY: Fully vaccinated pregnant patients had a lower risk of developing severe or critical COVID-19 infections in comparison to unvaccinated individuals.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Breakthrough infections in vaccinated individuals were common during the 4th "delta" wave of the COVID-19 pandemic. Pregnancy is known to increase the risk for severe disease, yet the uptake of vaccination in this high-risk population remains low. This study highlights the importance of vaccination against severe and critical COVID-19 infections, especially in pregnant individuals.

PATIENTS: Pregnant women

INTERVENTION: SARS-CoV-2 vaccination

CONTROL: No SARS-CoV-2 vaccination

PRIMARY OUTCOME: Severe or critical COVID-19 infections

Secondary Outcome: COVID-19 infection requiring supplemental oxygen, intensive care unit admission, or use of adjunctive medical therapy

METHODS (BRIEF DESCRIPTION):

- Patients included women 22–38 years old. Demographics were broken down by age, race, pre-pregnancy BMI, current smoking status, and comorbidities including diabetes, hypertension, cardiac disease, HIV, and asthma.
- Vaccinated patients were significantly older, much more likely to be White/non-Hispanic, have a lower BMI, and were less likely to be active smokers.
- Objective confirmation of vaccination status was performed using a state-wide immunization reporting network.
- COVID-19 vaccinations included Pfizer, Moderna, and Johnson & Johnson.
- SARS-CoV-2 infections were evaluated based on severity as defined by SpO2 <94% on room air, a respiratory rate greater than 30 breaths per minute, PaO_2/FiO_2 <300 mmHg, or lung infiltrates greater than 50%. Critical illness was defined as respiratory failure, septic shock, or multiple organ failure.
- Outcomes were measured based on the severity of the COVID-19 illness, the need for supplemental oxygen, and ICU admissions.

INTERVENTION (# IN THE GROUP): 1,332

COMPARISON (# IN THE GROUP): 8,760

FOLLOW-UP PERIOD: Two months

RESULTS:

Primary Outcome –

- Vaccinated patients had a lower rate of severe or critical COVID-19 infection compared to unvaccinated patients (adjusted odds ratio [aOR] 0.10; 95% CI, 0.01–0.49).

Secondary Outcome –

- Vaccinated patients had a lower rate of severe COVID-19 infection compared to unvaccinated patients (aOR 0.11; 95% CI, 0.01–0.53).
- Vaccinated patients had a lower rate for any positive SARS-CoV-2 infection compared to unvaccinated patients (aOR 0.31; 95% CI, 0.18–0.51).
- The vaccinated group had no cases of critical COVID-19 infection, stillbirth, maternal death, supplemental oxygen use, ICU admission, or Tocilizumab use.

LIMITATIONS:

- The study only included data from the Oshner Health System in Louisiana. Test results or treatment which occurred in other health systems would have been missed.
- The timing of vaccination and amount of prenatal care during pregnancy were not reported and may have been additional confounders that were not adjusted for.
- The analyzed population only had a 13.2% vaccination rate.

- The results were from a specific variant and wave of the pandemic that may have been more severe in its manifestations than later waves, which could alter the significance of the association.

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