GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: RSV Vaccination in Pregnancy: Safely Inducing an Immune Response in 2 People with 1 Vaccine

RSV Vaccination in Pregnancy: Safely Inducing an Immune Response in 2 People with 1 Vaccine

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Safety and Immunogenicity of an Investigational Respiratory Syncytial Virus Vaccine (RSVPreF3) in Mothers and Their Infants: A Phase 2 Randomized Trial

Bebia Z, Reyes O, Jeanfreau R, et al. Safety and Immunogenicity of an Investigational Respiratory Syncytial Virus Vaccine (RSVPreF3) in Mothers and Their Infants: A Phase 2 Randomized Trial. *J Infect Dis.* 2023;228(3):299-310. doi:10.1093/infdis/jiad024

KEY TAKEAWAY: One dose of the RSVPreF3 vaccine during the late 2nd trimester or early 3rd trimester of pregnancy is safe and induces a strong maternal immune response that is subsequently transferred to their newborns.

STUDY DESIGN: Randomized, observer-blind, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Respiratory syncytial virus (RSV) infections in young children lead to a significant number of hospitalizations and even deaths, especially in children <6 months old. Maternal vaccination against diseases such as influenza, tetanus, diphtheria, pertussis, and COVID-19 in pregnancy has been proven to safely produce a passive immune response in infants. This study aims to determine the safety of a novel RSV vaccine and its ability to induce an immune response in mothers and their newborns.

PATIENTS: Women with singleton pregnancies

INTERVENTION: Unadjuvanted RSVPreF3 vaccine

CONTROL: Placebo vaccine

PRIMARY OUTCOME: Safety of single RSV vaccine dose; increase in level of anti-RSV antibodies pre-vaccination, 31 days post-vaccination, and at delivery for mothers; and placental transfer ratio at birth for infants

METHODS (BRIEF DESCRIPTION):

- Healthy women 18–40 years old with no congenital malformations or genetic abnormalities were eligible for this study.
- Women were excluded from the study if there were complications with the pregnancy, had a history of preterm birth or ≥2 spontaneous abortions, had acute viral illnesses, had previously received an RSV vaccine, or were immunocompromised.
- Participants were randomized to receive 60 µg or 120 µg of unadjuvanted RSVPreF3 vaccine or placebo between 28 weeks, zero days gestation, and 33 weeks, six days gestation.
- Participants were monitored for 60 minutes post-vaccination for any adverse effects.
- Specific solicited injection site reactions including pain, erythema, and swelling as well as systemic reactions including fatigue, headache, nausea, vomiting, diarrhea, abdominal pain, and fever were recorded up to seven days post-vaccination. These were all considered to be causally related to the vaccine.
- Other unsolicited reactions could be reported up to 30 days post-vaccination. Pregnancy complications such as fetal distress and hypertensive disorders of pregnancy, birth outcomes, and congenital anomalies were also recorded.
- Maternal blood samples were obtained at day one (pre-vaccination), day 31, delivery, and day 43 post-delivery and assessed for the presence and amount of anti-RSVPreF3 IgG antibodies using an ELISA.
- Similarly, infant blood samples were obtained at birth (cord blood or blood sample within 3 days of birth), and day of life 43, 121, and 181 and assessed for the presence and amount of anti-RSVPreF3 IgG antibodies using an ELISA.
- Immunogenicity data was assessed using per-protocol analysis.
- Analyses were performed using the two-sample t-test. All analyses used the statistical analysis systems life science analytics framework software.

INTERVENTION (# IN THE GROUP):

- 60 µg RSVPreF3 vaccine: 70
- 120 µg RSVPreF3 vaccine: 75

COMPARISON (# IN THE GROUP): 68

FOLLOW-UP PERIOD:

- Mother: 43 days post-delivery
- Infant: 181 days post-birth

RESULTS:

Primary Outcome –

- There was no difference in pregnancy-related or neonatal adverse events between vaccine and

placebo groups (statistical results presented via figure).

- Anti-RSV antibodies increased 13-fold compared to pre-vaccination levels for the 60 µg vaccine group at 31 days post-vaccination.
- Anti-RSV antibodies increased 15-fold for the 120 µg vaccine group at 31 days post-vaccination.
- Infant's placental transfer ratios for anti-RSV antibodies were higher compared to the placebo group:
  - 60 µg vaccine group: 1.6
  - 120 µg vaccine group: 1.9

LIMITATIONS:

- The COVID-19 pandemic led to the early termination of study enrollment and the study fell short of its enrollment goal.
- Social distancing and masking during the COVID-19 pandemic led to decreased transmission of RSV and the study was thus unable to assess the vaccine's impact on individuals who contracted RSV.

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Damages of Doxorubicin in Cancer Patients: Will Statins Save the Day?

Statins and Left Ventricular Ejection Fraction Following Doxorubicin Treatment

Hundley WG, D'Agostino R Jr, Crotts T, et al. Statins and Left Ventricular Ejection Fraction Following Doxorubicin Treatment. *NEJM Evid.* 2022;1(9):10.1056/evidoa2200097. doi:10.1056/evidoa2200097

KEY TAKEAWAY: Doxorubicin does not decrease left ventricular ejection fraction (LVEF) in patients with breast cancer and lymphoma without a prior indication for atorvastatin therapy.

STUDY DESIGN: Randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Doxorubicin is a chemotherapeutic drug that can cause myocardial damage and left ventricular dysfunction. Observational studies have shown that patients taking statins for prior known cardiovascular indications have higher LVEF after doxorubicin treatment than patients who do not. Little is known about the benefits of statin therapy on LVEF after doxorubicin treatment in patients without prior cardiovascular indications.

PATIENTS: Adults with breast cancer and lymphoma without indications for statin therapy

INTERVENTION: Atorvastatin

CONTROL: Placebo

PRIMARY OUTCOME: Decline in LVEF

Secondary Outcome: Cognitive function, serum markers of inflammation, renin

METHODS (BRIEF DESCRIPTION):

- Women and men >21 years old diagnosed with lymphoma (stages 1–4) or breast cancer (stages 1–3) set to undergo doxorubicin treatment, with a survival expectation of >2 years were included in the study.
- Patients were blinded and randomized to one of the following treatments:
  - 40 mg atorvastatin daily PO for 24–27 months
  - Placebo
- Treatments were self-administered 48 hours before starting doxorubicin therapy. Participants recorded adherence in a medication diary. They also returned their pill bottles and the residual pills were counted at six and 24 months.
- Outcomes were measured at pretreatment, six, 12, 18, and 24 months.
- LVEF measurements were assessed using cardiac magnetic resonance imaging.
  - Readers were blinded to all patient identifiers.
- Cognitive function was measured using the Hopkins Verbal Learning Test-Revised (HVLT-R). Scores range from 0–36, a score of 36 representing 100% recall.

INTERVENTION (# IN THE GROUP): 139

COMPARISON (# IN THE GROUP): 140

FOLLOW-UP PERIOD: 24 months

RESULTS:

Primary Outcome –

- Statin therapy did not significantly prevent LVEF decline in patients receiving doxorubicin therapy when compared to placebo at 24 months (mean difference –0.08%; 95% CI, –1.8 to 1.7).

Secondary Outcome –

- There was no significant difference in cognitive function, renin, or serum markers of inflammation between the placebo and statin groups.

LIMITATIONS:

- A large number of patients dropped out of the trial, and several were noncompliant, many of whom cited "feeling overwhelmed" by tests and cancer treatments as their reason for withdrawal.
- Statins were administered only 24–48 hours before initiating doxorubicin therapy. Thus, it is unknown whether or not long-term statin therapy before doxorubicin treatment would reduce the decline in LVEF.
- The study did not measure the progression of coronary artery disease, a major etiology of LVEF decline.

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Forget New Shoes, New Knees Are All You Need

A High Physical Activity Level After Total Knee Arthroplasty Does Not Increase the Risk of Revision Surgery During the First Twelve Years: A Systematic Review with Meta-Analysis and GRADE

Kornuijt A, Kuijer PPFM, van Drumpt RA, Siebelt M, Lenssen AF, van der Weegen W. A high physical activity level after total knee arthroplasty does not increase the risk of revision surgery during the first twelve years: A systematic review with meta-analysis and GRADE. *Knee*. 2022;39:168-184. doi:10.1016/j.knee.2022.08.004

KEY TAKEAWAY: High physical activity after total knee replacement does not increase the risk of revision surgery for the first twelve years.

STUDY DESIGN: Systematic review and meta-analysis of five cohort studies and one case-control study (N=4,874)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to the design of included studies)

BRIEF BACKGROUND INFORMATION: The longevity of knee implants after total knee arthroplasty (TKA) has associations with surgical factors. However, high physical activity (HPA) is a more patient-related factor for the longevity of the implants. HPA levels may lead to increased wear and tear of the implant possibly leading to aseptic loosening which is the most common cause for knee revision surgery. This review examines the association between activity levels and the risk of revision surgery at medium and long-term follow-up for patients with a TKA surgery.

PATIENTS: Adults with total knee replacement

INTERVENTION: HPA level

CONTROL: Low physical activity (LPA) level

PRIMARY OUTCOME: Rate of revision surgery of total knee replacement

METHODS (BRIEF DESCRIPTION):

- Studies were searched by using electronic databases Pubmed and Embase and selected studies were hand-searched.
- Patients included adults who received primary TKA surgery.
- Recreational and sports activity levels were measured postoperatively with a well-defined activity instrument.
- The study described at least two distinctly different activity levels.
- Activity levels were compared related to the risk of revision surgery, revision rate at medium (3–10 years) or long-term follow-up (>10 years).
- The outcome looked at the association between physical activity level and revision rate.

INTERVENTION (# IN THE GROUP): 2,169

COMPARISON (# IN THE GROUP): 2,705

FOLLOW-UP PERIOD: 4–12 years

RESULTS:

Primary Outcome –

- High physical activity level was not a risk factor for all-cause revision surgery (risk ratio [RR] 0.62; 95% CI, 0.24–1.6).

Secondary Outcome –

- There was no association between high physical activity level and an increased risk of revision surgery due to aseptic loosening (RR 1.3; 95% CI, 0.34–5.2).

LIMITATIONS:

- A variety of questionnaires was used in the included studies to measure activity levels.
- The definition of high-level activity was heterogeneously defined throughout all studies.
- Confounding factors may influence TKA implant survival.

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Nasal Esketamine: A Whiff of Hope for Treatment-Resistant Depression

Esketamine Nasal Spray Versus Quetiapine for Treatment-Resistant Depression

Reif A, Bitter I, Buyze J, et al. Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant Depression. *N Engl J Med*. 2023;389(14):1298-1309. doi:10.1056/NEJMoa2304145

KEY TAKEAWAY: Esketamine is more effective for treatment-resistant depression than quetiapine; it appears more patients achieve early remission and are less likely to discontinue therapy.

STUDY DESIGN: Multisite, single-blind, randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to unblinded participants and clinicians)

BRIEF BACKGROUND INFORMATION: Treatment-resistant depression occurs in about 10–30% of patients with major depressive disorder (MDD) and is associated with higher rates of hospitalization, suicidality, and mortality. Second-generation antipsychotics are a common treatment modality but have significant movement and metabolic side effects. This trial compared the efficacy of nasal esketamine and oral quetiapine on depression remission.

PATIENTS: Adults with treatment-resistant depression

INTERVENTION: Nasal esketamine

CONTROL: Oral quetiapine

PRIMARY OUTCOME: Depression remission

Secondary Outcome: Safety and discontinuation rates

METHODS (BRIEF DESCRIPTION):

- Patients 18–74 years old were recruited from 171 sites in 24 countries with treatment-resistant MDD.
- Inclusion criteria were (1) Diagnostic and Statistical Manual of Mental Disorders- Fifth Edition (DSM-V) criteria for MDD without psychotic features, (2) a score of 34 or higher on the Inventory of Depressive Symptomatology-Clinician Rated scale (scores 0–84), (3) less than 25% reduction in symptoms from 2–6 consecutive antidepressant (AD) treatments (with agents from at least 2 different classes) during the current episode of depression.
- All patients were allowed to continue with selective serotonin reuptake inhibitors (SSRI) or serotonin and norepinephrine reuptake inhibitors (SNRI).
- Patients with certain psychiatric disorders (psychosis, bipolar, autism spectrum, intellectual disorders), certain personality disorders (borderline, antisocial, histrionic, narcissistic), treatment with high doses of quetiapine (>50 mg daily) or esketamine during the current episode, and patients who had no signs of clinical improvement on their current antidepressant treatment were excluded.
- The mean age in the esketamine group was 44 years, with 33% male, and 39% had failed ≥3 treatments.
- The mean age in the quetiapine group was 46 years with 65% men, and 38% had failed ≥3 treatments.
- In the intervention group, participants self-administered nasal esketamine under supervision at a treatment site at increasing doses (28–84 mg).
    - Treatments were twice weekly during weeks 1–4, weekly during weeks 5–8, and weekly/bi-weekly during weeks 9–32.
- The comparison group self-administered quetiapine XR daily at home (50–300 mg).
    - Weekly to bi-weekly medication compliance counseling was provided.
- Remission was defined by a score ≤10 on the Montgomery-Asberg Depression Rating scale (MADRS); scores range from 0–60 with higher indicating more severe depression at eight weeks.
- Safety analysis identified adverse events for all patients who received at least one dose of any treatment.

INTERVENTION (# IN THE GROUP): 336

COMPARISON (# IN THE GROUP): 340

FOLLOW-UP PERIOD: 32 weeks

RESULTS:

Primary Outcome –

- Participants who received esketamine had higher rates of remission at week eight as compared to those who received quetiapine (27 vs 18%, respectively; adjusted odds ratio (aOR) 1.7; 95% CI, 1.2–2.5, NNT=11).

Secondary Outcome –

- Patients who received esketamine reported more adverse events compared to patients who received quetiapine (92% vs 78%, respectively), but patients

who received esketamine were less likely to discontinue treatment due to adverse events compared to patients who received quetiapine (4.2% vs 11%, respectively).

LIMITATIONS:

- Esketamine availability and affordability may limit access for patients.
- Esketamine requires frequent in-person supervised treatments and may have addictive potential.
- The study was funded by Janssen.

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Efficacy of Oral vs Vaginal Misoprostol for Labor Induction

Vaginal Compared with Oral Misoprostol Induction at Term: A Cluster Randomized Controlled Trial

Adhikari EH, McGuire J, Lo J, McIntire DD, Spong CY, Nelson DB. Vaginal Compared With Oral Misoprostol Induction at Term: A Cluster Randomized Controlled Trial. *Obstet Gynecol.* 2024;143(2):256-264. doi:10.1097/AOG.0000000000005464

KEY TAKEAWAY: There was no significant difference in vaginal delivery rates with oral vs vaginal misoprostol for labor induction, although vaginal misoprostol led to a decreased need for oxytocin during labor induction.

STUDY DESIGN: Single-center, non-blinded, cluster-randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding)

BRIEF BACKGROUND INFORMATION: Misoprostol is a commonly used cervical ripening agent for labor induction, however, few standardized protocols exist to determine the best administration route or optimal dosage to use to achieve a higher rate of vaginal deliveries and reduce the need for oxytocin.

PATIENTS: Pregnant women at >37 weeks gestational age

INTERVENTION: Vaginal misoprostol

CONTROL: Oral misoprostol

PRIMARY OUTCOME: Rate of vaginal delivery

Secondary Outcome: Maternal outcomes included time to delivery, oxytocin use, labor epidural use, cesarean delivery, chorioamnionitis, tachysystole-associated fetal distress, excess blood loss, transfusion, endometritis, uterine rupture, unplanned hysterectomy, surgical site infections. Neonatal outcomes included acidosis, five-minute APGAR score, need for NICU, need for intubation, and sepsis.

METHODS (BRIEF DESCRIPTION):

- The study was completed at a large academic center in Texas.
- Participants were eligible if they were nulliparous or multiparous with uncomplicated singleton pregnancies with no major fetal anomalies or vertex presentation, were dilated at 2 cm or less, and had intact membranes.
- Participants were randomized into the following two treatment groups:
  - Vaginal misoprostol protocol: 25 mcg every three hours, up to five doses (max dose 125 mcg)
  - Oral Misoprostol protocol: 100 mcg every four hours, up to two doses (max dose 200 mcg)
- After misoprostol initiation, patients were transitioned to oxytocin if the following criteria were met: Non-reassuring fetal heart tracing, active labor (defined as 4 cm dilated or more), four or more painful contractions in 10 minutes, meconium-stained amniotic fluid.
- Oxytocin was also initiated three or four hours after administration of the maximum dose of vaginal or oral misoprostol if 3–5 contractions were not achieved in 10 minutes.
- Primary and secondary outcomes were obtained through a medical record review by the research team.
- Secondary maternal outcomes included time to delivery, oxytocin use, labor epidural use, cesarean delivery, chorioamnionitis, tachysystole-associated fetal distress, excess blood loss, transfusion, endometritis, uterine rupture, unplanned hysterectomy, surgical site infections.
- Secondary neonatal outcomes included acidosis, five-minute APGAR score, need for NICU, need for intubation, and sepsis.

INTERVENTION (# IN THE GROUP): 1,322

COMPARISON (# IN THE GROUP): 1,224

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- There was no difference in vaginal delivery rates between vaginal and oral misoprostol (78% vs 77%, respectively; adjusted relative risk [aRR] 1.0; 95% CI, 0.97–1.1).

Secondary Outcome –

- Oxytocin use before delivery was less in the vaginal misoprostol group compared to the oral misoprostol group (69% vs 78%, respectively; aRR 0.88; 95% CI, 0.84–0.92).

- The vaginal misoprostol group had less tachysystole-associated fetal distress when compared to the oral misoprostol group (3.5% vs 5.9%, respectively; aRR 0.59; 95% CI, 0.40–0.87).
- There were higher NICU admission rates in the vaginal misoprostol group compared to the oral misoprostol group (2% vs 1%, respectively; aRR 2.1; 95% CI, 1.1–4.1).
- There was no significant difference between the two groups in all other secondary maternal and fetal outcomes.

LIMITATIONS:

- The study defined active labor as cervical dilation of 4 cm instead of the more widely accepted 6 cm dilation.
- The study is less generalizable as it was a single-center, unblinded study.
- 95% of enrolled patients had a BMI of ≥31 which may not be inclusive of the general population.

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