GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

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Bitter About Penicillin Allergies?

Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients with Low-Risk Penicillin Allergy: The PALACE Randomized Clinical Trial

Copaescu AM, Vogrin S, James F, et al. Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy: The PALACE Randomized Clinical Trial. *JAMA Intern Med*. 2023;183(9):944-952. doi:10.1001/jamainternmed.2023.2986

KEY TAKEAWAY: A direct oral penicillin challenge is a time and cost-effective strategy in determining true penicillin allergy for those at low risk. This is noninferior to the standard of care involving the two-stage skin testing followed by oral challenge.

STUDY DESIGN: Parallel, two-arm, noninferiority, open-label, randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Penicillin allergies can often be self-reported and unverified, and have been associated with increased antibiotic resistance, higher medical costs, and poorer health outcomes. This study aimed to identify a safe, convenient, and cost-effective way to test those with low-risk penicillin allergy with a direct oral challenge compared to standard of care.

PATIENTS: Patients ≥18 years old with a labeled penicillin allergy and PEN-FAST score of <3

INTERVENTION: Direct oral penicillin challenge

CONTROL: Penicillin skin testing followed by oral challenge if negative

PRIMARY OUTCOME: Physician-verified positive oral penicillin challenge

Secondary Outcome: Feasibility, safety, efficacy

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from six international outpatient sites (3 in North America and 3 in Australia).
- Eligible patients were ≥18 years old with penicillin allergy and calculated PEN-FAST (point-of-care risk assessment for penicillin allergy) score <3.
- PEN-FAST is a validated tool that enables point-of-care risk assessment for adults reporting penicillin allergies. A score <3 can identify low-risk penicillin allergy.
    - ≤5 since reaction (2 points)
    - Anaphylaxis or angioedema (2 points)
    - Severe cutaneous adverse reaction (2 points)
    - Treatment required for reaction (1 point)
- Patients were ineligible if they had a history of anaphylaxis to any drug, a history of spontaneous urticaria or mast cell disease, or had a history of severe delayed organ or skin reactions.
- Patients were randomized 1:1 to direct oral challenge or prick followed by intradermal testing, then oral challenge.
- Patients with direct oral challenge were directly observed with measurements of vitals at baseline and at 60 minutes.
- Five days post challenge, participants were contacted to report on delayed adverse events.
- Patients in the skin testing group were pricked and monitored with standardized procedures.
- The primary outcome was a physician-verified positive oral penicillin challenge which included an immune-mediated reaction within the hour. A positive skin test was defined as a ≥3 mm wheel and ≥5 mm compared to the negative control.
- Feasibility was defined as the proportion of patients referred to allergy that were eligible for intervention, the proportion of patients consenting to participate and the proportion of patients randomized to the intervention who had the intervention delivered as per the protocol.
- Safety was defined as the proportion of patients who experienced an antibiotic-associated immune mediated adverse event, the proportion of patients who experienced an antibiotic associated, non-immune mediated adverse event.
- Efficacy was defined as penicillin allergy de-labeling post randomization.

INTERVENTION (# IN THE GROUP): 187

COMPARISON (# IN THE GROUP): 190

FOLLOW-UP PERIOD: Five days

RESULTS:

Primary Outcome –

- Direct oral penicillin challenge in low-risk patients was noninferior to skin testing followed by oral

challenge (risk difference [RD] 0.008; 90% CI, –1.2 to 1.2).

Secondary Outcome –

- 446 of 643 screened patients were eligible to participate (69%; 95% CI, 66–73) and 382 of 446 eligible patients were enrolled (86%; 95%, CI 82–89).
- Of the 382 randomized patients, the intervention per protocol was completed for 351 patients (92%; 95% CI, 87–94).
- Of the 382 randomized patients, the intervention per protocol was completed for 351 patients (92%; 95% CI, 87–94).
- Within five days following oral penicillin challenge, there was no significant difference in cumulative adverse events, immune mediated adverse events, and efficacy between the intervention and control.

LIMITATIONS:

- Most participants had a PEN-FAST score of zero or one, limiting generalizability to those with an overall score of <2.
- Those with a past medical history of anaphylaxis in general were excluded.
- Open label required due to intervention of oral only vs skin and oral testing likely affected the primary outcome.
- The study had a relatively small sample size.
- Observation for adverse events was limited to one hour in-person and five days reported, then reviewed only retrospectively based on documentation.

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Getting to the Heart of It: Childhood Food Insecurity and Adverse Cardiovascular Health in Adulthood

Early Childhood Food Insecurity and Cardiovascular Health in Young Adulthood

Lam EL, Gauen AM, Kandula NR, et al. Early Childhood Food Insecurity and Cardiovascular Health in Young Adulthood. *JAMA Cardiol*. 2025;10(8):762-769. doi:10.1001/jamacardio.2025.1062

KEY TAKEAWAY: Early childhood food insecurity is associated with worse cardiovascular health in young adulthood compared to no food insecurity in childhood. The household Supplemental Nutrition Assistance Program (SNAP) participation moderates the effect of food insecurity on cardiovascular health (CVH).

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Prior evidence suggests that food insecurity is associated with CVH outcomes in adults. Whether childhood food insecurity is associated with CVH across the lifespan is unclear, but previous studies suggest that SNAP participation in childhood may reduce incidence of metabolic syndrome in adulthood. This study aimed to evaluate whether childhood food insecurity is associated with adult CVH.

PATIENTS: Children with food insecurity

INTERVENTION: Household food insecurity

CONTROL: No household food insecurity

PRIMARY OUTCOME: CVH in young adulthood

Secondary Outcome: Specific subcategories of CVH, and cardiovascular-kidney-metabolic syndrome (CKM)

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria: Children born in large United States cities, with an oversampling (3:1) of births to unmarried parents, resulting in a cohort that is highly representative of low-income and racially minoritized families.
- Data collection began at birth (in 1998) with subsequent periodic follow-up assessments through 15 years old, using both telephone and home visits.
- Food insecurity was assessed at three years old, or five years old or both, using the US Department of Agriculture Food Insecurity Survey, defined as high, marginal, low or very low food insecurity.
- SNAP participation was also assessed.
- CVH was evaluated in young adulthood using the American Heart Association Life's Essential 8 (LE8). Scores range from 0–100 including components for diet, physical activity, tobacco exposure, body mass index (BMI) ≥30, non-high density lipoprotein (HDL) ≥ 130 mg/dL, hemoglobin A1C (HbA1c) ≥5.7%, and systolic blood pressure (SBP) ≥130 mmHg, where a higher score represents better CVH.
- CKM syndrome was defined as:
  - Stage 0: No risk factors
  - Stage 1: Excess and/or dysfunctional adiposity
  - Stage 2: Metabolic risk factors and/or chronic kidney disease (CKD)
  - Combined stages 3 and 4: Subclinical or clinical cardiovascular disease
- Multivariable regression was used to examine associations between early childhood food insecurity, SNAP participation, and young adult cardiovascular health outcomes, adjusting for relevant sociodemographic and clinical covariates (sex, mother's household income at 5 years old, mother's highest educational attainment at 5 years old, and mother's age at child's birth).
- The statistical measure of association was a β-coefficient for each continuous outcome, and odds ratio for binary outcomes.

INTERVENTION (# IN THE GROUP): 649

COMPARISON (# IN THE GROUP): 422

FOLLOW-UP PERIOD: Mean 22 years

RESULTS:

Primary Outcome –

- Childhood food insecurity was associated with lower cardiovascular health compared to no food insecurity (β –2.2; 95% CI, –4.0 to –0.4).
- Childhood food insecurity increased the odds of obesity (BMI>30) compared to no food insecurity (odds ratio [OR] 1.4; 95% CI, 1.1–1.8).
- Food insecurity and CVH were higher among those not enrolled in SNAP participation.
  - No SNAP participation (β –4.9; 95% CI, –7.6 to –2.3)
  - SNAP participation (β 1.0; 95% CI, –1.6 to 3.7)

- Food insecurity was associated with a lower cardiovascular health among female participants (β −2.4; 95% CI, −4.8 to −0.03), but not among male participants.

Secondary Outcome –

- Food insecurity was associated with a lower BMI compared to no food insecurity (β –4.9; 95% CI, –9.6 to –0.3).
- Food insecurity was not significantly associated with subscores for diet, physical activity, tobacco, cholesterol, glucose, or blood pressure.
- Food insecurity increased the chance of CKM stages 1, 3, and 4, but not with stages 0 or 2.
    - CKM stage 1 (adjusted odds ratio [aOR] 1.4; 95% CI, 1.04–2.0)
    - CKM stage 3 and 4 (aOR 1.6; 95% CI, 1.1–2.5)

LIMITATIONS:

- This was not a randomized study, so there may be residual confounders not measured including parental health status, neighborhood environment, other social determinants of health, which may influence both food insecurity and cardiovascular outcomes.
- Limited generalizability given the study oversampled nonmarital births in large United States cities.
- Food insecurity was assessed only at early points (3 years old and 5 years old) which may not capture the chronicity or variability of food insecurity exposure.

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Exposure to Cannabis in Utero has Unhealthy Outcomes

Neonatal Outcomes Associated with in Utero Cannabis Exposure: A Population-based Retrospective Cohort Study

Avalos LA, Adams SR, Alexeeff SE, et al. Neonatal Outcomes Associated with in Utero Cannabis Exposure: A Population-based Retrospective Cohort. *Am J Obstet Gynecol*. 2024;231(1):132.e1-132.e13. doi:10.1016/j.ajog.2023.11.1232

KEY TAKEAWAY: Cannabis exposure in utero is associated with increased odds of neonates that are small for gestational age, low birth weight, late premature and/or admitted to the neonatal intensive care unit (NICU).

STUDY DESIGN: Population-based retrospective cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Prenatal cannabis use in the United States (US) is increasing especially in pregnant young adults and teens. Cannabis is being legalized for medical or recreational use. Current research posits conflicting results regarding maternal cannabis use. This study evaluated the associations between in utero cannabis exposure and neonatal outcomes.

PATIENTS: Neonates

INTERVENTION: Maternal cannabis use in pregnancy

CONTROL: No cannabis use in pregnancy

PRIMARY OUTCOME: Neonates that are born small for gestational age (SGA), having low birth weight (LBW), requiring oxygen after birth, late preterm and NICU admission

METHODS (BRIEF DESCRIPTION):

- Data from electronic health records (EHRs) of pregnant individuals in the Kaiser Permanente Northern California (KPNC) integrated health system were screened for infants of singleton pregnancies born between January 1, 2011, and July 31, 2020.
- The cohort of infants resulted from single pregnancies of patients who had a KPNC health plan during some point in the pregnancy, had attended at least one prenatal visit in the KPNC system and responded to a questionnaire about prenatal cannabis use and or had a urine toxicology test ran.
- Covariates were age at pregnancy onset, neighborhood deprivation index, insurance type, self-reported race and ethnicity, educational attainment, alcohol exposure in pregnancy, nicotine use, opioid use, stimulate and anxiety or sleep medicine use, adequacy of prenatal care by the Kotelchuck index, obesity status, and maternal co-morbidities.
- Dose and frequency were calculated from self-report surveys, with mode of consumption not considered.
- Exposure was defined as having a positive drug screen or self-reported cannabis use during pregnancy.
- LBW was defined as infant birthweight <2,500 g
- SGA (10th percentile) was estimated based on the sex- and gestational age-specific birthweight distributions of the 2017 US natality files.
- Preterm birth was defined as birth <37 weeks of gestation
- Early moderate preterm was defined as birth <34 weeks of gestation
- NICU admission was defined as an admission for high acuity or for lower acuity ≥4 hours and was measured with a binary variable (Yes/No).
- Respiratory support indicated for high-acuity patients who received noninvasive ventilation, endotracheal ventilation, or other respiratory support during the birth hospitalization, and was measured with a binary variable (Yes/No).
- DAGitty web application was used to determine whether a variable was a cofounder, collider, mediator or none of these.
- Results were reported as the odds of LBW, SGA, early preterm, late preterm, those admitted to the NICU, and those requiring respiratory support in the setting of cannabis exposure vs non exposure.

INTERVENTION (# IN THE GROUP): 22,624

COMPARISON (# IN THE GROUP): 342,300

FOLLOW-UP PERIOD: During birth hospitalization

RESULTS:

Primary Outcome –

- Babies born to mothers who used cannabis during pregnancy had increased odds of being LBW, SGA,

early moderate preterm, preterm, and requiring NICU admission, compared with those who were not exposed.
    - LBW (adjusted odds ratio [aOR] 1.2; 95% CI, 1.1–1.3)
    - SGA (aOR 1.2; 95% CI, 1.2–1.3)
    - NICU admission (aOR 1.1; 95% CI, 1.01–1.1)
    - Preterm birth (aOR 1.1; 95% CI, 1.01–1.1)
    - Early moderate preterm birth (aOR 1.1; 95% CI, 1.01–1.2)
- The odds of babies born to mothers who used cannabis during pregnancy compared with those who were not exposed to cannabis having respiratory support was not significant (aOR 1.1; 95% CI, 1.0–1.2).

LIMITATIONS:

- No information was provided by the study on duration, concentration of exposure, or mode of consumption of the cannabis.
- It was possible that there was misclassification of cannabis use because cannabis can be excreted in the urine for greater then 30 days after consumption.
- Self-reported frequency and duration of use may be unreliable as there is stigma around cannabis use and pregnancy. This could lead to under reporting of cannabis use in self-reported surveys.

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