GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of September 26 - 30, 2022

SPOTLIGHT: Blood Pressure Targets for Chronic Hypertension in Pregnancy

Blood Pressure Targets for Chronic Hypertension in Pregnancy

Treatment for Mild Chronic Hypertension during Pregnancy

Tita AT, Szychowski JM, Boggess K, et al. Treatment for Mild Chronic Hypertension during Pregnancy. *N Engl J Med*. 2022;386(19):1781-1792. doi:10.1056/NEJMoa2201295

KEY TAKEAWAY: In women with mild chronic hypertension, a blood pressure goal of <140/90 improves pregnancy outcomes without compromising fetal growth.

STUDY DESIGN: Multi-center, nonblinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Goal blood pressures for pregnant patients with mild chronic hypertension are unclear, with guidelines varying among organizations. It is not known whether maternal or neonatal status is best optimized by continuing existing antihypertensive medications or treating only when blood pressures become severely elevated.

PATIENTS: Pregnant women <23 weeks gestational age with mild chronic hypertension

INTERVENTION: Initiation of antihypertensive therapy to target a blood pressure goal of <140/90

CONTROL: Initiation of antihypertensive therapy at blood pressure of ≥160/105

PRIMARY OUTCOMES: Efficacy outcome: Composite of pre-eclampsia with severe features, delivery before 35 weeks gestational age due to medical indications, placental abruption, and fetal/neonatal death

Safety outcome: Small for gestational age

METHODS (BRIEF DESCRIPTION):

- Eligible patients included pregnant women <23 weeks gestation with either new diagnosis or known history of chronic hypertension.
- The study defined "new chronic hypertension" as blood pressure (BP) >140/90 prior to 20 weeks gestation, measured at least twice with at least four hours between readings; and defined "known chronic hypertension" as prior documentation of elevated BP along with history of (or current treatment with) blood-pressure lowering treatments (medications or lifestyle interventions).
- The study excluded patients with any of the following: severe BP elevations (≥160/105) at randomization, secondary hypertension, requiring >1 medication to control BP, multiple gestation, and high-risk conditions necessitating lower BP goals.
- Baseline demographics of the study population included an average age of 32 years, average BMI of 38, with 45% of patients taking aspirin at baseline.
- Each group was treated to target their BP goal using typical medications used in pregnancy (primarily labetalol or long acting nifedipine, or if requested by patient, amlodipine or methyldopa).
- BPs were measured with automated cuffs in a standardized manner at follow up visits, and up-titration of medications occurred as indicated based on measured BP.
- Small for gestational age was defined as birth weight under 10th percentile for gestational age and sex.
- Primary outcomes were measured from time of randomization to two weeks postpartum.
- Patients were asked about both maternal and infant events including readmissions or unscheduled visits to the clinic or ED.
- Those assessing primary efficacy outcomes were blinded to study group assignment.

INTERVENTION (# IN THE GROUP): 1,208

COMPARISON (# IN THE GROUP): 1,200

FOLLOW UP PERIOD: Two weeks postpartum

RESULTS:

- Targeting a BP goal <140/90 reduced the risk of adverse maternal outcomes compared to a target of ≥160/105 (adjusted risk ratio 0.82; 95% CI, 0.74-0.92; NNT=15).
- No significant difference between groups in the safety outcome of newborn measuring small for gestational age.

LIMITATIONS:

- The major limitation of the study was that patients and care providers were not blinded to study group or BP goals.
- The study also used clinically measured blood pressures, rather than readings obtained at home, raising concern for possible white-coat hypertension.

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The Sound of SILENCE: Does Prophylactic Scopolamine Prevent Death Rattle in Dying Patients?

Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life: The SILENCE Randomized Clinical Trial

van Esch HJ, van Zuylen L, Geijteman ECT, et al. Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life: The SILENCE Randomized Clinical Trial. *JAMA*. 2021;326(13):1268-1276. doi:10.1001/jama.2021.14785

KEY TAKEAWAY: Scopolamine butylbromide reduces the incidence of death rattle without adverse effects.

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

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current clinical guidelines recommend anticholinergics to reduce death rattle. As anticholinergics decrease mucus production without necessarily effecting already produced mucus, a prophylactic dose may be more helpful.

PATIENTS: Adults admitted to hospice who had entered the dying phase

INTERVENTION: Scopolamine butylbromide

CONTROL: Physiological saline

PRIMARY OUTCOME: Primary outcomes: incidence of death rattle Secondary outcomes: incidence of death rattle and adverse side effects at 48 hours, and length of dying phase

METHODS (BRIEF DESCRIPTION):

- The study was a multicenter clinical trial involving 5 different hospice centers.
- Patients were recruited for the trial when they had a life expectancy of at least three days, understood they would stay in hospice until death, and were able to consent.
- Patients were randomly assigned to receive 20 mg/mL scopolamine butylbromide or 1 mL of physiological saline (placebo).
- Family members, health care professionals, and researchers were blinded to the study as well as the medication and placebo were provided in identical looking packaging.
- When the patient entered the dying phase, as determined by a health professional, they were administered scopolamine or placebo four times a day through an indwelling subcutaneous catheter.
- After receiving either scopolamine or placebo, the primary measurement was the occurrence of a grade 2 or higher death rattle measured at two consecutive time points at an interval of four hours.
- The secondary outcomes measured the occurrence of death rattle at 48 hours to also include any of side effects (i.e., restlessness, dry mouth, or urinary retention) and length of dying phase.
- Restlessness was measured using both the Care Program for the dying (CPD) and Vancouver Interaction and Calmness Scale (VICS); for both scales, a higher score suggested more restlessness.

INTERVENTION (# IN THE GROUP): 79

COMPARISON (# IN THE GROUP): 78

FOLLOW UP PERIOD: From hospice admission through death

RESULTS:

Primary Outcome

- Scopolamine significantly decreased the development of death rattle compared to the placebo (13% vs 27% respectively, p=.02).

Secondary Outcomes

- Scopolamine significantly lowered cumulative incidence of death rattle at 48 hours compared to placebo (8% vs 17% respectively, p=0.03).
- Scopolamine did not cause more adverse effects in patients when compared to placebo.
  - Restlessness: CPD score (23 pts vs 19, p=0.48) VICS score (7 pts vs 7, p=0.98)
  - Dry mouth: (8 pts vs 12, p=0.34)
  - Urinary retention: (20 pts vs 15, p=0.60)
  - Scopolamine significantly increased the length of dying phase compared to placebo (42.8 hrs vs 29.5 hrs respectively, p=.04)

LIMITATIONS:

- Only 10% of patients who were admitted to hospice facilities participating in the study were included the final analysis.
- As respiratory infection was an exclusion criterion, the results may not apply to hospice patients with a respiratory infection.
- No validated tool exists for assessing the onset of the dying phase, it was a clinical decision made by health care professionals.
- Subcutaneous administration of the medication may not always be feasible or desirable, however the use of

a patch for medication delivery has not been studied.
- Only one hospice participated for the entirety of the study which also happened to be the largest hospice. As a result, almost 73% of the study participants were from the same hospice.

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Tirzepatide Improves HbA1c in Patients with Type 2 Diabetes Treated with Insulin Glargine

Effect of Subcutaneous Tirzepatide vs Placebo added to Titrated Insulin Glargine on Glycemic Control in Patients with Type 2 Diabetes

Dahl D, Onishi Y, Norwood P, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. *JAMA*. 2022;327(6):534-545. doi:10.1001/jama.2022.0078

KEY TAKEAWAY: The addition of subcutaneous tirzepatide, compared to placebo, results in improved glycemic control after 40 weeks in patients with type 2 diabetes and inadequate glycemic control despite treatment with insulin glargine.

STUDY DESIGN: Randomized, double-blind, parallel, multicenter, placebo-controlled study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Tirzepatide is a novel, once-weekly dual glucose-dependent insulinotropic polypeptide and selective glucagon-like peptide-1 (GLP-1) receptor agonist. Tirzepatide has been shown to reduce hemoglobin A1c (HbA1c) and body weight when compared to semaglutide (1 mg), insulin degludec, and insulin glargine, when added to oral glucose-lowering medications. This study evaluated the efficacy and safety of three different doses of tirzepatide when added to titrated basal insulin glargine (with or without metformin).

PATIENTS: Adults with type 2 diabetes and inadequate glycemic control with once-daily insulin glargine with or without metformin

INTERVENTION: Once-weekly subcutaneous injections of 5-mg, 10-mg, or 15 mg tirzepatide

CONTROL: Placebo

PRIMARY OUTCOME: Mean change from baseline HbA1c

Secondary outcomes: HbA1c < 7% at study end, body weight change from baseline, fasting serum glucose change from baseline

METHODS (BRIEF DESCRIPTION):

- Enrolled patients at 45 sites in the U.S. and its territories, Europe, and Japan.
- Inclusion criteria: Baseline HbA1c 7.0% to 10.5%, BMI at least 23, and stable once daily insulin glargine dose >20 IU or >0.25 IU/kg.
- Patients were randomized in a 1:1:1:1 ratio to receive once-weekly injections of tirzepatide or placebo for 40 weeks.
- During the initial four weeks insulin glargine doses were kept unchanged, except for safety reasons.
- To reduce hypoglycemia risk, all patients with HbA1c ≤ 8.0 were required to reduce their basal glargine dose by 20% after randomization.
- Insulin doses were adjusted per the study's treat-to-target algorithm during weeks 5-40.
- Patients using metformin at baseline were continued on the same dose and formulation for the entire study.
- Tirzepatide doses were gradually titrated to facilitate gastrointestinal tolerability, starting with a 2.5 mg dose and increasing by 2.5 mg every four weeks until the patient reached their randomly assigned dose.
- The comparison group received matching doses of placebo using an identical injection device.

INTERVENTION (# IN THE GROUP):

- 5 mg: 116
- 10 mg: 119
- 15 mg: 120

COMPARISON (# IN THE GROUP): 120

FOLLOW UP PERIOD: 40 weeks followed by four-week safety follow-up period

RESULTS:

Primary outcome –

- Change in HbA1c was larger with all doses of tirzepatide than placebo
  - 5 mg: -2.1% (difference -1.2%, 95% CI, -1.5% to -1.0%)
  - 10 mg: -2.4% (difference -1.5%, 95% CI, -1.8% to -1.3%)
  - 15 mg: -2.3% (difference -1.5%, 95% CI, -1.7% to -1.2%)

Secondary Outcomes –

- More patients treated with tirzepatide had an HBA1c < 7.0% than those receiving placebo
  - 5mg: 87% (OR 15, 95% CI, 7.0-31)
  - 10 mg: 87% (OR 20, 95% CI, 9.2-40)
  - 15 mg: 85% (OR 12, 95% CI, 5.6-23)
- Patient's receiving tirzepatide had a change in body weight from baseline while patients receiving placebo experienced weight gain
  - 5 mg: -5.4 kg (difference -7, 95% CI, -8.7 to -5.4)
  - 10 mg: -8 kg (difference -9.1, 95% CI, -10.7 to -7.5)

- 15 mg: -9 kg (difference -10.5, 95% CI, -12 to -8.8)
- There was a greater change in fasting serum blood glucose in the tirzepatide group than the placebo group
  - 5 mg: -58 mg/dL (difference -19, 95% CI, -27 to -11)
  - 10 mg: -64.0 mg/dL (difference -25, 95% CI, -32 to -17)
  - 15 mg: -63 mg/dL (difference -23, 95% CI, -31 to -16)

LIMITATIONS:

- Sample may not have been representative of diabetic patients in many clinical settings.
  - Some racial or ethnic groups were underrepresented
  - Average age of participants was 61 years old
  - Large number of exclusion criteria.
- Lack of insulin adjustment in first 4 weeks may have favored the tirzepatide group.
- Gastrointestinal adverse events were self-reported.
- Improved glycemic control with little or no change in insulin dose, and gastrointestinal side effects may have partially affected blinding.
- No proactive insulin dose reduction when at HbA1c goal while on tirzepatide to explore if tirzepitide could be insulin sparing.

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"Shouldn't I Get an Antibiotic for My Cold?"

Reducing Expectations for Antibiotics in Patients with Upper Respiratory Tract Infections: A Primary Care Randomized Controlled Trial

Perera AI, Thomas MG, Petrie KJ, et al. Reducing Expectations for Antibiotics in Patients with Upper Respiratory Tract Infections: A Primary Care Randomized Controlled Trial. Ann Fam Med. 2021;19(3):232-239. doi:10.1370/afm.2672

KEY TAKEAWAY: Patients with upper respiratory infection (URI) symptoms who receive education on antibiotic futility or adverse effects of antibiotics are less likely to expect to receive antibiotics, but this has no effect on whether patients receive an antibiotic.

STUDY DESIGN: Three-arm blinded randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Antibiotics are frequently inappropriately prescribed for treatment of URI despite the risks of harm including promoting antibiotic resistance. One contributing factor is patient expectation to receive antibiotics for URI, based in patients' underestimation of harms of antibiotics and belief that antibiotics are necessary. It is unknown whether educational interventions might reduce patient expectations for antibiotics and reduce antibiotic prescriptions for URI.

PATIENTS: Adults and children with URI symptoms

INTERVENTION: Brief presentations on either futility of antibiotics or side effects of antibiotics

CONTROL: Brief presentation about healthy lifestyle choices (topic not related to antibiotics)

PRIMARY OUTCOME: Patient expectation to receive an antibiotic prescription

Secondary Outcomes: Patient belief about the efficacy of antibiotics for URI and frequency of antibiotic prescriptions

METHODS (BRIEF DESCRIPTION):

- Three-arm blinded RCT measuring effects of brief educational presentations administered in two wealthy urban family practice clinics in New Zealand.
- Participants were adults with URI symptoms (N=234) or parents of children ages 0-7yrs (N=91) with URI symptoms who were being seen by a prescribing physician.
- Participants completed brief Likert-scale surveys immediately before and after viewing one of three brief (six slides, approximately one minute) tablet-based presentations. The surveys measured beliefs about antibiotics and expectation to receive antibiotics. This occurred prior to meeting with the provider.
- Masking/Blinding: Participants were not informed of the aims of the study. Upon consent, each was randomized to view one of three presentations, with a 1:1:1 allocation. Physicians were aware of the study but blinded to whether a patient consented to participate and, if applicable, which tablet-based presentation a patient had viewed.
- Study Arms:
- Arm 1 (Futility): presentation included information about futility of antibiotics for URI treatment and symptomatic treatments (nasal spray, throat lozenge) for URI
- Arm 2 (Adverse effects): information about potential side effects of antibiotics and alternative treatments for URI
- Arm 3 (Control): information about healthy lifestyle choices, unrelated to antibiotics or URI.
- To measure frequency of antibiotic prescriptions, patients were asked immediately after the visit if they had received an antibiotic prescription. This data was compared to individual prescription data from the National Pharmaceutical Collection database during the seven days after the visit.
- The Kruskal-Wallis test was used to compare differences between median scores of the 3 groups. Cohen d represents the standardized mean difference calculated from the Kruskal-Wallis test. A Cohen d effect of 0.2 is considered small, 0.5 medium, and 0.8 a large effect.

INTERVENTION (# IN THE GROUP):

- Arm 1 (Futility): 119
- Arm 2 (Adverse effects): 104

COMPARISON (# IN THE GROUP): 102

FOLLOW UP PERIOD: Seven days after the clinic visit

RESULTS:

Primary Outcome –

- Participants who viewed an intervention presentation (futility or adverse effects) had significant reduction in expectation to receive antibiotics compared to those in the control group (Kruskal-Wallis *H*=37, Cohen

d=0.7, *P*<.001).

Secondary Outcomes –

- Participants who viewed an intervention presentation were also significantly less likely to believe that antibiotics are effective for URI compared to those in the control group (Kruskal-Wallis *H*=31.4, Cohen *d*=0.6, *P*<.001).
- There were no significant differences in rates of antibiotic prescriptions between the intervention and control groups, as assessed by both participant post-visit surveys and review of the national pharmacy database.

LIMITATIONS:

- Study population is centered in a wealthy, educated urban area in New Zealand.
- Two clinics from which the study population was drawn had lower rates of antibiotic prescription than the New Zealand national average.
- While blinded to participation and allocation, physicians were aware that the study was being conducted in their clinic.

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