GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

Volume 2 - Issue 16

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of April 18 - 22, 2022

SPOTLIGHT: Whooping the Cough - When is the Optimal Timing of Pertussis Vaccination in Pregnancy or Early Infancy to Prevent Newborn Pertussis Infection?

Whooping the Cough: When is the Optimal Timing of Pertussis Vaccination in Pregnancy or Early Infancy to Prevent Newborn Pertussis Infection?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

The optimal strategy for pertussis vaccination: a systematic review and meta-analysis of randomized control trials and real-world data

Nguyen HS, Vo NP, Chen SY, Tam KW. The optimal strategy for pertussis vaccination: a systematic review and meta-analysis of randomized control trials and real-world data. *Am J Obstet Gynecol.* 2022; 226(1):52–67.e10. doi:10.1016/j.ajog.2021.06.096

KEY TAKEAWAY: Pertussis vaccination of pregnant mothers or newborns provides a safe and universally available intervention to boost immunity against a potentially life-threatening infection.

STUDY DESIGN: Systematic review and meta-analysis of 10 RCTs, 14 cohort studies, and five case-control studies

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Pertussis infection, also known as "whooping cough", can be severe and life-threatening in the first 90 days of a newborn's life. This systematic review and meta-analysis examined the efficacy of vaccinating pregnant women and/or newborns in rates of pertussis illness in this age group.

PATIENTS: Pregnant women or newborns

INTERVENTION: Pertussis vaccination

CONTROL: No vaccination

OUTCOME: Immunogenicity, incidence of pertussis, serious adverse events

Secondary Outcome: Timing of pertussis vaccine

METHODS (BRIEF DESCRIPTION):

- PubMed or MEDLINE, Embase, the Cochrane library databases, ClinicalTrials.gov, and other relevant papers were searched.
- Included studies analyzed efficacy, immunogenicity, or severe adverse events (SAEs) of pertussis vaccination.
- The studies were compared in two general groups:
  - Mothers who received pertussis vaccination vs those who did not (6 RCTs, 13 cohort studies, 5 case-control studies)
  - Infants vaccinated at birth vs those who were not (4 RCTs and 1 cohort study)

INTERVENTION (# IN THE GROUP):

- Immunogenicity evaluation: 1,953
- Evaluation of vaccine efficacy: 222,910

COMPARISON (# IN THE GROUP): 174,360

FOLLOW UP PERIOD: Not available

RESULTS:

Primary Outcomes –

- Maternal immunization significantly reduced pertussis incidence rate in children zero to three months old (7 trials, N=111,513; OR 0.22; 95% CI, 0.14–0.33).
- Vaccine efficacy for children up to three months old was 78% (95% CI, 67–86).
- Vaccination at birth increased concentrations of:
  - Anti-PT IgG: SMD 0.55 (95% CI, 0.33–0.77)
  - Anti-FHA IgG: SMD 0.52 (95% CI, 0.33–0.77)
- There was no statistical difference in SAEs.
  - Mothers: 7 trials, N=8,854; RR 1.2; 95% CI, 0.76–1.8
  - Infants: 1 trial, N=564; RR 0.77; 95% CI, 0.42–1.4

Secondary Outcomes –

- There was a lack of studies with power to determine the optimal timing of pertussis vaccination in pregnancy.

LIMITATIONS:

- There was no consensus on the optimal timing for pertussis vaccination during pregnancy.
- Preterm infants were not included in the data.
- Direct comparison of immunogenicity of pertussis vaccination in pregnancy versus at birth was not completed.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

Breastmilk as COVID-19 Medicine? Antibodies Found in Human Milk Neutralize SARS-CoV-2 Virus

Association of Human Milk Antibody Induction, Persistence, and Neutralizing Capacity With Sars-Cov-2 Infection vs. mRNA Vaccination

Young BE, Seppo AE, Diaz N, et al. Association of Human Milk Antibody Induction, Persistence, and Neutralizing Capacity With SARS-CoV-2 Infection vs mRNA Vaccination. *JAMA Pediatr.* 2022; 176(2):159–168. doi:10.1001/jamapediatrics.2021.4897

KEY TAKEAWAY: Antibodies acquired through COVID-19 infection and vaccination manifest in different patterns in human milk, but both may be able to neutralize SARs-CoV-2.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: SARS-CoV-2 has rarely been detectable in human milk suggesting vertical transmission of the virus through breast milk is unlikely. Scant information is available regarding the effects of SARS-CoV-2 on human breast milk with respect to patterns of antibody production and neutralizing capability of SARS-CoV-2 wild type virus.

PATIENTS: Lactating individuals with an infant six months old or younger

INTERVENTION: Vaccinated lactating individuals

CONTROL: Unvaccinated lactating individuals with COVID-19

OUTCOME: Comparison of patterns of antibody production post COVID-19 infection vs. post vaccination, as well as ability of human milk to neutralize SARS-CoV-2 virus in each group.

METHODS (BRIEF DESCRIPTION):

- Infection Cohort:
  - Individuals 18 years or older currently lactating with an infant 6 months old or younger, who were diagnosed with COVID-19 within the previous 14 days (between July 2020 and April 2021).
- Participants provided human breast milk samples from their home on day 0 (date milk collection materials received), 3, 7, 10, 28, and 90.
- Vaccinated Cohort:
  - Participants in vaccinated cohort were lactating health care professionals who were recieving the first dose of COVID-19 vaccine (Moderna or Pfizer-BioNtech) between December 2020 and January 2021.
  - Participants were excluded if they had history of previous COVID-19 infection.
  - Milk sample was collected prior to vaccination, 18 days after the first dose, 18 days after the second dose, and 90 days after the second dose.
- Both Cohorts:
  - Total RNA extracted from milk received was analyzed via reverse transcription quantitative PCR against SARS-CoV-2, and concentrations of IgA and IgG were assessed.
  - Random subsets of samples who had the highest immune response during the first month from their respective cohorts (10 from infection and 20 from vaccinated) were chosen to measure microneutralization against SARS-CoV-2 in plates coated with the virus.

INTERVENTION (# IN THE GROUP): 30

COMPARISON (# IN THE GROUP): 47

FOLLOW UP PERIOD: 90 days

RESULTS:

- COVID-19 infection resulted in the following antibody responses:
  - Initial IgA and IgG response with increasing levels to 90 days (n=33)
    - IgA response: day 0: 34 AU vs day 90: 75 AU ($P<.001$)
    - IgG response: day 0: 1.6 AU vs day 90: 32 Au ($P<.001$)
  - Poor IgA response with no IgG response (n=5)
    - IgA response: day 0: 16 UA vs day 90: 9.9 AU ($P<.54$)
    - IgG response: day 0: 1 AU vs day 90: 1.2 AU ($P<.09$)
- COVID-19 vaccination resulted in:
  - Robust IgG response at 18 days after the first dose (1.3 AU pre-vaccination vs 12.0 AU at 18 days; $P=.001$)
  - IgG response had a slight decrease after 90 days to 29 AU.
  - Similar IgA response compared to infection.
- When comparing the two groups, the following results were reported without numerical or statistical analysis presented:
  - Vaccinated group had larger and more uniform IgG response that seemed to decrease slightly over time.
  - Infection group had more variable antibody pattern

but with greater IgA response.
    - SARS-CoV-2 mRNA was not detected in any milk sample from either group.
    - Human milk demonstrated neutralizing capability in both vaccinated and infection cohorts but with slightly higher activity in infection group.

LIMITATIONS:

- Most participants in infection group recruited from social media which preselected candidates with time and ability to participate in social media, limiting generalizability.
- Only health care professionals were in the study, introducing bias secondary to greater average age and higher education level.
- There was an exclusion criterion of infant age <six months in infection group vs. no upper limit of infant age in vaccination group.
- Participant pool not very diverse: 69/77 identified as Caucasian

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Oral Microbiome Therapy Can Reduce Recurrent *Clostridioides difficile* Infection

SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection

Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection. *N Engl J Med*. 2022; 386(3):220–229. doi:10.1056/NEJMoa2106516

KEY TAKEAWAY: Oral administration of SER-109 has improved risk reduction of recurrent *Clostridioides difficile* infection compared to placebo, when given to patients with symptom resolution after treatment with standard-of-care antibiotics.

STUDY DESIGN: Phase III, double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current standard of care for recurrent *C. difficile* infection consists of oral antibiotic therapy, but this does not kill *C. difficile* spores and leads to changes in the gastrointestinal microbiome. Other spore forming bacteria may inhibit the ability of *C. difficile* spores to germinate. Administration of oral microbiome therapy with other spore forming bacteria may produce a more durable clinical response.

PATIENTS: Patients who had three or more episodes of *C. difficile* infection

INTERVENTION: SER-109

CONTROL: Placebo

OUTCOME: Recurrence of *C. difficile* infection

METHODS (BRIEF DESCRIPTION):

- 182 total study participants 18 years old or older
- Diagnosed with three or more episodes of *C. difficile* (including a current acute episode) and had received 10 to 21 days of standard antibiotic therapy.
- Three days of four capsules daily oral SER-109 or placebo were administered.
- Recurrence was monitored and classified as three or more loose stools per day for two consecutive days and a positive toxin assay.
  - This was monitored for eight weeks.
- Adverse events were evaluated periodically during any clinical encounter.

INTERVENTION (# IN THE GROUP): 89

COMPARISON (# IN THE GROUP): 93

FOLLOW UP PERIOD: Eight weeks

RESULTS:

- SER-109 decreased the risk of *C. difficile* infection recurrence at 8 weeks compared to placebo (12% vs 40%, respectively; relative risk 0.32; 95% CI 0.18–0.58).
- There were no serious adverse events or deaths related to use of SER-109.

LIMITATIONS:

- The study consisted of low representation from minority populations, so generalizability to minority populations, including Black and Hispanic patients, is limited.
- Absence of a stool specimen before antibiotic treatment limits full study of the impact of SER-109 on microbiome prior to antibiotics.

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Internet Delivered CBT for Social Anxiety Disorder in Children

Therapist-Guided Internet-Delivered Cognitive Behavioral Therapy vs Internet-Delivered Supportive Therapy for Children and Adolescents with Social Anxiety Disorder: A Randomized Clinical Trial

Nordh M, Wahlund T, Jolstedt M, et al. Therapist-Guided Internet-Delivered Cognitive Behavioral Therapy vs Internet-Delivered Supportive Therapy for Children and Adolescents With Social Anxiety Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2021; 78(7):705–713. doi:10.1001/jamapsychiatry.2021.0469

KEY TAKEAWAY: ICBT is a more efficacious and cost-effective treatment modality for children and adolescents with Social Anxiety Disorder when contrasted to an active comparative model of ISUPPORT.

STUDY DESIGN: Single-blind, superiority, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Social anxiety disorder (SAD), particularly with childhood and adolescent onset, has lasting effects on the individual as well as large cost implications on society. While Cognitive Behavioral Therapy (CBT) is the first-line evidence-based treatment for SAD, it remains limited due to resources and accessibility. Therapist-guided internet-delivered CBT has overcome certain barriers, yet its efficacy has not been analyzed.

PATIENTS: Children and adolescents diagnosed with SAD

INTERVENTION: Therapist-guided internet-delivered cognitive behavioral therapy (ICBT)

CONTROL: Therapist-guided internet-delivered supportive therapy (ISUPPORT)

OUTCOME: SAD symptom severity

Secondary Outcomes: Depression and anxiety symptoms, functioning, quality of life, cost

METHODS (BRIEF DESCRIPTION):

- Study participants were children (10-14 years old) and adolescents (15-17 years old) with principal diagnosis of SAD.
  - Parents were included as co-participants, primarily reporting on anxiety symptoms and general functioning observed in children and adolescents during the study.
- Study participants excluded those with other psychological conditions or those who had received CBT within the last six months.
- Study participants and their parents were randomly assigned either to 10 weeks of ICBT or ISUPPORT. Each consisted of 10 online modules for the study participants, five online modules for the parents, and three video call therapy sessions for the study participants and parents.
- Study assessors were blinded to treatment allotment and assessed ADIS-C at the pre-treatment, 10-week trial, and 3-month follow-up.
- A blind Clinician Severity Rating (CSR) score derived from ADIS-C was the primary measurement of efficacy. CSR ranged from 0-8 with ≥4 meeting classification as a clinical case.
- Utilizing Cohen *d* (standardized mean difference), between group effect size was categorized by range: small (*d*=0.2–0.5), moderate (*d*=0.5–0.8) and large (*d*= ≥0.8). *d*= <0.2 was deemed negligible even if statistically significant.
- Secondary outcomes were measured using masked assessor-rated Clinical Global Impression-Improvement (CGI-I) to determine SAD improvement relative to pre-treatment, Children's Global Assessment Scale (CGAS) to assess global functioning, Work and Social Adjustment Scale-Parent Version (WSAS-P) to measure general functioning, and child-reported Child Health Utility 9D (CHU9D) to assess quality of life.

INTERVENTION (# IN THE GROUP): 51

COMPARISON (# IN THE GROUP): 52

FOLLOW UP PERIOD: 10-week trial with a 3-month follow-up period

RESULTS:

Primary Outcomes –

- ICBT reduced SAD symptom severity more than ISUPPORT (*d*=0.67; moderate effect).

Secondary Outcomes –

- ICBT improved the following over ISUPPORT:
  - Self-reported SAD: Child-reported *d*=0.64 (moderate effect) and parent-reported *d*=0.83 (large effect)
  - Anxiety and depression symptoms: Child-reported *d*=0.78 (moderate effect) and parent-reported *d*= 0.78 (moderate effect)
  - Functioning: Assessor-reported *d*=0.39 (small effect) and parent-reported *d*=0.48 (small effect)
- ICBT did not affect child-reported quality of life over ISUPPORT (*d*=0.21).

- ICBT was significantly more cost effective than ISUPPORT.
- Cost effectiveness ratio incorporating total societal cost differences and differences in remitter status was −$20,428 (95% CI, −$22,246 to −$18,610).

LIMITATIONS:

- Small sample size per treatment allotment
- Participants in this study were referrals either from healthcare professionals or self-referrals; thus, could be interpreted as self-selecting.
- Study was restricted to families living in Sweden; therefore, the data is not generalizable to other geographic or demographic populations.

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Posterior Left Pericardiotomy: A Promising Procedure to Prevent Postop Atrial Fibrillation

Posterior left pericardiotomy for the prevention of atrial fibrillation after cardiac surgery: an adaptive, single-centre, single-blind, randomized, controlled trial

Gaudino M, Sanna T, Ballman KV, et al. Posterior left pericardiotomy for the prevention of atrial fibrillation after cardiac surgery: an adaptive, single-centre, single-blind, randomised, controlled trial. *Lancet*. 2021; 398(10316):2075–2083. doi:10.1016/S0140-6736(21)02490-9

KEY TAKEAWAY: Posterior left pericardiotomy is a safe and simple surgical procedure that drains the pericardial space into the left pleural cavity. When performed in conjunction with cardiac surgery for coronary arteries, aortic valve, or ascending aorta, it is highly effective at reducing the incidence of atrial fibrillation.

STUDY DESIGN: Adaptive, single-blind RCT

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Atrial fibrillation is the most common complication of cardiac surgery. Postoperative pericardial effusions can trigger atrial fibrillation, leading to extended hospital stays, stroke, and death. Previous studies have shown promise for posterior left pericardiotomy in reducing postoperative atrial fibrillation but lacked consistent data and methodology.

PATIENTS: Adults undergoing primary elective cardiac surgery

INTERVENTION: Posterior left pericardiotomy

CONTROL: No intervention

OUTCOME: Postoperative atrial fibrillation

Secondary Outcomes: Need for postoperative antiarrhythmic medicine, need for systemic anticoagulation due to atrial fibrillation, need for postoperative electrical cardioversion, time in atrial fibrillation, duration of hospital stay, any postoperative atrial arrhythmia

METHODS (BRIEF DESCRIPTION):

- Included patients were those undergoing primary elective cardiac surgery involving carotid arteries, aortic valves, or ascending aorta without history of atrial fibrillation or other arrhythmias.
- Patients were excluded if they were undergoing mitral or tricuspid valve surgery, had pre-existing left pleural disease, chest deformity, or were having repeat or other minimally invasive procedures.
- Eligible participants were randomly assigned 1:1 and risk stratified using CHA2DS2-VASC to either posterior left pericardiotomy or no intervention during the planned procedure by computer generated randomization.
- Patients and assessors were blinded to treatment assignments.
- Patients completed planned surgery with posterior left pericardiotomy or no intervention.
- Continuous cardiac rhythm assessment was performed as was daily 12 lead EKG during hospitalization to assess for atrial arrhythmia.
- Follow up performed within 30 days of hospitalization.

INTERVENTION (# IN THE GROUP): 212

COMPARISON (# IN THE GROUP): 208

FOLLOW UP PERIOD: 30 days after hospital discharge

RESULTS:

Primary Outcome –

- Posterior left pericardiotomy significantly reduced the incidence of postoperative atrial fibrillation when compared to no intervention (17% vs 32%; RR 0.55; 95% CI, 0.39–0.78).

Secondary Outcomes –

- Posterior left pericardiotomy decreased the need for antiarrhythmic medications (17% vs 31%; RR 0.55; 95% CI, 0.38–0.79).
- Posterior left pericardiotomy decreased the need for systemic anticoagulation (6% vs 14%; RR 0.44; 95% CI, 0.24–0.82).
- Postoperative atrial arrhythmias were more frequent in the no intervention group (33% vs 21%; RR 0.65; 95% CI, 0.47–0.90).
- Median time (in hours) in atrial fibrillation, duration of hospital stay, and need for postoperative electrical cardioversion were comparable for both groups.

LIMITATIONS:

- Only low risk patients were included in the study.
- Level of evidence downgraded to STEP 3 because patient-oriented outcomes, such as morbidity or mortality, were not examined.
- The study was only performed at a single site.
- Treatment effect may be lower if only focused on symptomatic episodes of arrhythmia.

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