What's in this week's issue?
Week of August 15 - 19, 2022

SPOTLIGHT: A Breath of Fresh Corticosteroids?
Treatment of COVID-19 Infection with Inhaled Ciclesonide

- What Outcomes Should Newborn Providers Be Aware of for Newborns of Pregnant Women with SARS-CoV-2?

- The Risk of Neurodevelopmental Disorders in Children with Perinatal Acetaminophen Exposure

- Core Temperature and Gait Instability: The New Predictors of Exertional Heat Stroke?
Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial


Copyright © 2022 by Family Physicians Inquiries Network, Inc.

KEY TAKEAWAY: Inhaled ciclesonide therapy for outpatients with COVID-19 infection may reduce COVID-related emergency department (ED) visits and hospitalizations but does not shorten time to resolution of symptoms.

STUDY DESIGN: Phase three, multicenter, double-blind RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Inhaled corticosteroids, such as ciclesonide, are used for the treatment of numerous respiratory diseases. Ciclesonide has anti-viral properties and demonstrated limited efficacy in the treatment of severe COVID-19. However, the efficacy of ciclesonide in reducing time to alleviation of symptoms in patients with mild to moderate COVID-19 is unclear.

PATIENTS: Outpatients with symptomatic COVID-19 infection

INTERVENTION: Inhaled ciclesonide

CONTROL: Inhaled placebo

OUTCOME: Time to symptom resolution

Secondary Outcomes: ED visits, hospitalizations, all-cause mortality, percentage of patients with complete symptom resolution

METHODS (BRIEF DESCRIPTION):

- Participants were enrolled at 10 centers.
- Non-hospitalized, COVID-19 positive, and symptomatic patients ages 12 years old and older were enrolled within 72 hours of a positive COVID-19 diagnosis.
- Patients were randomized to receive either ciclesonide metered-dose inhaler (MDI) at the highest recommended daily dose of 320 µg two times daily for 30 days or placebo MDI for 30 days.
- Participants self-administered ciclesonide or placebo at home and monitored oxygen saturation with a pulse oximeter.
- Daily symptom logs were kept by the patients for 30 days using a 4-point symptom severity scale (where a higher score indicates worse severity) on an electronic smartphone diary application.

- Participants were contacted at regular intervals for a health care check by a clinician.
- Investigators also assessed patients for adverse effects through 60 days.

INTERVENTION (# IN THE GROUP): 197

COMPARISON (# IN THE GROUP): 203

FOLLOW UP PERIOD: 60 days

RESULTS:

Primary Outcome –

- Ciclesonide MDI did not improve time to symptom resolution in comparison to placebo (median time of 19 days for both groups; HR 1.1; 95% CI, 0.84–1.4).

Secondary Outcomes –

- Ciclesonide MDI was associated with a decreased frequency of subsequent ED visits or hospitalizations related to COVID-19 infection in comparison to placebo (1% vs 5.4%; odds ratio 0.18; 95% CI, 0.04–0.85).
- Ciclesonide MDI was not associated with total hospitalizations or death, all-cause mortality, or percentage of patients with symptom resolution at day seven, 14, or 30.

LIMITATIONS:

- The study evaluated for complete symptom resolution, not for time of return to normal activities or resolution of severe symptoms.
- Symptoms may have been incorrectly assigned to COVID-19 or adverse events.
- Patients 12 years old and older were included, but only 4% of participants were under 18 years old, which limited analysis in pediatric patients.
- White patients were overrepresented in general.
- More patients with diabetes and asthma were present in the intervention group than the control group.

Emily Welder, MD
UI Hospitals and Clinics:
The University of Iowa Hospitals and Clinics
Iowa City, IA
**KEY TAKEAWAY:** Maternal SARS-CoV-2 infection during pregnancy is associated with the newborn experiencing NICU care, any neonatal morbidities of respiratory distress syndrome, any neonatal respiratory disorder, and hyperbilirubinemia.

**STUDY DESIGN:** Cohort study

**LEVEL OF EVIDENCE:** STEP 3

**BRIEF BACKGROUND INFORMATION:** COVID-19 infections in pregnancy have unknown effects on the fetus. Further research is needed to guide treatment and prevention.

**PATIENTS:** Neonates of pregnant women

**INTERVENTION:** Pregnant women diagnosed with SARS-CoV-2

**CONTROL:** Pregnant women negative for SARS-CoV-2

**OUTCOME:** Admission to NICU, respiratory distress syndrome, any neonatal respiratory disorder, hyperbilirubinemia requiring treatment, hospital neonatal mortality, breastfeeding rates, length of stay, resuscitation, infant positivity

**METHODS (BRIEF DESCRIPTION):**
- The Swedish Pregnancy Register, Neonatal Quality Register, and Register for Communicable Diseases were utilized in Sweden for tracking maternal SARS-CoV-2 infections and neonatal outcomes.
- All hospitals in Sweden (an unreported number) were included except for four that do not report to the national registry.
- The exposure was infants exposed to SARS-CoV-2 by mothers testing positive for SARS-CoV-2 from conception to one week after birth.
- From March to June 2020, only pregnant women admitted for hospital care with symptoms of COVID-19 were tested with PCR tests. In June 2020, a general testing strategy was implemented that included outpatient testing with PCR of pregnant women receiving prenatal care and contact tracing in addition to continued inpatient testing.
- Some (unknown number) but not all hospitals tested all women admitted for delivery.

- The neonatal period was defined as early neonatal (0–6 days), late neonatal (7–28 days), and post neonatal.

**INTERVENTION (# IN THE GROUP):** 2,323

**COMPARISON (# IN THE GROUP):** 85,836

**FOLLOW UP PERIOD:** 28 days after delivery

**RESULTS:**
- Maternal SARS-CoV-2 test positivity compared to SARS-CoV-2 negative mothers was significantly associated with newborns experiencing:
  - Higher admission for neonatal care (12% vs 8.4%, respectively; odds ratio [OR] 1.5; 95% CI, 1.3–1.7)
  - Respiratory distress syndrome (1.2% vs 0.5%, respectively; OR 2.4; 95% CI, 1.5–3.8)
  - Any neonatal respiratory disorder (2.8% vs 2.0%; OR 1.4; 95% CI, 1.1–1.9)
  - Treated hyperbilirubinemia (3.6% vs 2.5%; OR 1.5; 95% CI, 1.1–1.9)

- Maternal SARS-CoV-2 infection was not associated with hospital neonatal mortality, breastfeeding rates at discharge, length of stay in neonatal care, resuscitation, and infant positivity.

**LIMITATIONS:**
- Small number of SARS-CoV-2 maternal infections relative to the entire sample size of mothers who delivered in Sweden during the study time. This underpowers the study.
- COVID-19 can be asymptomatic, and therefore skewed the data. The women presenting for care with term and near-term infants had a higher likelihood of being tested, and, therefore, were more likely to test positive. This may overestimate risks with SARS-CoV-2 test positivity in near-term and term infants.
- There are no guidelines in Sweden to test for SARS-CoV-2 in asymptomatic pregnant women.
- No data reflecting on outcomes regarding severity of SARS-CoV-2 infection, which may have significance in the outcomes of patients that is not accounted for.
- Infants of the comparison group were only tested if suspicion for maternal infection, which introduces detection bias.

Keenan Kuckler, MD
University of Wyoming FMRP – Casper
Casper, WY
Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure with Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood


**KEY TAKEAWAY:** There is an association between acetaminophen exposure in the peripartum period and development of ADHD or autism spectrum disorder (ASD) in a dose-dependent fashion. While awaiting further data to establish or negate any causal relationship, physicians should be considerate about acetaminophen prescriptions.

**STUDY DESIGN:** Longitudinal cohort study

**LEVEL OF EVIDENCE:** STEP 3

**BRIEF BACKGROUND INFORMATION:** Acetaminophen is the most used analgesic and antipyretic among mothers during pregnancy and infants in early life. There are several human and rodent studies showing acetaminophen crosses the placental barrier, has toxic effects on cortical neurons, inhibits fetal testosterone which disrupts brain development, and selectively inhibits cyclooxygenase 2 which may affect multiple brain functions. There is also an association between maternal self-reported acetaminophen use and risk of ADHD. More research on acetaminophen and pregnant women is needed.

**PATIENTS:** Children exposed to acetaminophen in-utero

**INTERVENTION:** Dose-dependent exposure to acetaminophen and its metabolites

**CONTROL:** Reduced exposure

**OUTCOME:** Diagnosis of ADHD, ASD, both ADHD/ASD, developmental disability in childhood

**METHODS (BRIEF DESCRIPTION):**

- Mother-infant dyads with sufficient cord plasma samples and core metabolite measurements were identified from the Boston Birth Cohort. Of these dyads, infants that have continued to receive primary care or specialty care at the BMC past six months of age were invited to participate.
- EMR was used to identify patients with ADHD only, ASD only, ADHD and ASD, and neurodevelopmental disorders using documented ICD 9 and ICD 10 codes.

- Maternal nonclinical and demographic variables were obtained via standard interview questionnaire. Clinical information is obtained from EMR.
- Unchanged acetaminophen and acetaminophen metabolites were measured in the cord blood.
- Exclusion criteria: Contraception via in vitro fertilization, non-singleton pregnancies, deliveries induced by maternal trauma and newborns with major birth defects
- Potential confounders adjusted for in analysis: maternal age at birth, maternal race/ethnicity, maternal education level, marital status, stress during pregnancy, smoking before/during pregnancy, alcohol use before/during pregnancy, maternal BMI, parity, breastfeeding, ever use of illicit drugs, maternal fever during pregnancy, early childhood lead levels, child’s sex, delivery type, preterm birth and birth weight
- Statistical analyses were used to compare the five groups (ADHD only, ASD only, ADHD and ASD, other developmental disabilities, and no developmental disability).

**INTERVENTION (# IN THE GROUP):** 996

**COMPARISON (# IN THE GROUP):** 327

**FOLLOW UP PERIOD:** Six months of age up to 21 years old

**RESULTS:**

- All cord acetaminophen metabolites had positive association with risk of ADHD diagnosis in a dose-dependent manner. Children with cord acetaminophen burden in the second tertial (OR 2.3; 95% CI, 1.4–3.7) and third tertial (OR 2.9; 95% CI, 1.8–4.7) had higher risk of ADHD compared to the first tertial.
- ASD only (OR 3.6; 95% CI, 1.6–8.6) and ASD/ADHD (OR 3.4; 95% CI, 1.3–9.9) had higher odds in the third tertial.
- Results were consistent across possible confounders.

**LIMITATIONS:**

- As a cohort study, only an association between exposure to acetaminophen during the antepartum period and risk of ADHD, ASD or both can be drawn, but direct causality cannot be established.
- Since this is an observational study, it is unable to exclude confounders such as genetic and
environmental factors

- Given that acetaminophen has a half-life of three hours, this data only reflects exposure in the peripartum period.
- Metabolome panel used to detect the different acetaminophen metabolites did not measure acetaminophen sulfate, one of the major metabolites.
- There was no true unexposed control group

Melat Gebremichael, MD & Priya Raghavan, MD
MedStar Health/Georgetown-
Washington Hospital Center
Washington, DC
Gait instability and estimated core temperature predict exertional heat stroke


Copyright © 2022 by Family Physicians Inquiries Network, Inc.

**KEY TAKEAWAY:** Using an exertional heat stroke risk algorithm that includes body core temperature and gait irregularity may predict exertional heat stroke a few minutes before a collapse.

**STUDY DESIGN:** Prospective cohort study

**LEVEL OF EVIDENCE:** STEP 4

**BRIEF BACKGROUND INFORMATION:** High-intensity activities place athletes, workers, and military personnel who must train and perform in hot environments at risk for exertional heat stroke (EHS). Rapid recognition, cooling, and advanced treatment is key to surviving EHS without medical complications. Being able to identify individuals with prodromal signs of EHS and referring them to appropriate medical care could reduce the incidence and severity of EHS.

**PATIENTS:** US military personnel from various military units participating in outdoor exercises

**INTERVENTION:** Patients who developed EHS

**CONTROL:** Patients who did not develop EHS

**OUTCOME:** Estimated core temperature (ECTemp), gait instability score, EHS risk prediction

**METHODS (BRIEF DESCRIPTION):**

- 1,806 US military personnel (1,701 men and 105 women) from various military units were monitored via custom torso-worn physiological monitoring systems, which recorded heart rate and triaxial accelerometry, during high-intensity military training activities (four- and five-mile runs, seven- and 12-mile ruck marches).
- 3,422 high EHS-risk training datasets were analyzed over two years (2018-2019).
- ECTemp was computed according to an algorithm that used a series of heart rate measurements.
- Gait instability score was derived from a three-axis accelerometry data set.
- EHS risk prediction was developed using three EHS classifiers: ECTemp alone, gait instability scores alone, or the two measures combined.

**INTERVENTION (# IN THE GROUP):** 6

**COMPARISON (# IN THE GROUP):** 3,416

**FOLLOW UP PERIOD:** One-time Immediate evaluation after training activity

**RESULTS:**

**Primary Outcome** –

- ECTemp in individuals who developed EHS was higher compared to those who did not develop EHS.
- Individuals who suffered EHS: ECTemp ranged from 39.2°C to 40.8°C (data analysis only presented as a figure).
- Individuals who developed EHS had higher gait instability scores compared to those without EHS (data analysis only presented as a figure).
- EHS prediction using ECTemp alone had a false-positive rate of 2.7%.
- EHS prediction using a gait instability alone was 2.7%.
- EHS prediction using a combination of ECTemp and gait instability was 0.9% for a prediction interval of 30 sec.

**Secondary Outcome** –

- EHS risk algorithm predicted EHS cases 3.5 mins prior to the EHS occurrence.
- There were no common risk factors for the EHS cases, such as WetBulb Globe Temperature (WBT), air temperature, relative humidity, BMI, or inadequate hydration.

**LIMITATIONS:**

- EHS is rare, so the EHS risk is developed only using six subjects.
- Due to the large number of non-EHS cases (n=3,416), there were zero false-negatives. Since the false-negative rate was undetermined, the true efficacy of the EHS risk algorithm was not assessed.
- ‘False-positive’ label in this study refers to cases where subsequent collapse did not occur. It is unknown whether these individuals with significantly irregular collapse developed exertional heat illness without EHS or suffered from a musculoskeletal injury.
- EHS risk score is based on the ability to establish a normal gait in individuals, such as run or ruck marches, so the EHS risk score is less applicable to those who work intermittently, such as firefighting.
Melinda W. Ng, MD & Whay-Yih Cheng, DO
David Grant USAF Medical Center - Travis AFB FMRC
Fairfield, CA

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