GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

**Week of May 2 - 6, 2022**

### SPOTLIGHT: Acute Respiratory Tract Infections in Children: Are Antibiotics Effective?

- Oral Anticoagulants for the Prevention of Recurrent Thromboembolism among Chronic Kidney Disease Patients
- Acute Back Pain? Consider Battlefield Acupuncture
- Is Prenatal Bariatric Surgery Worth the Risk?
- Are Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2) Better than Sulfonylureas in Patients with Type 2 Diabetes?

# Acute Respiratory Tract Infections in Children: Are Antibiotics Effective?

**Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomized, placebo-controlled trial**

Little P, Francis NA, Stuart B, et al. Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial. *Lancet.* 2021; 398(10309):1417–1426. doi:10.1016/S0140-6736(21)01431-8



KEY TAKEAWAY: Antibiotics do not provide a clinical benefit when used to treat uncomplicated lower respiratory tract infections in children.

STUDY DESIGN: Double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Antibiotics are commonly prescribed in the pediatric population to treat uncomplicated respiratory tract infections. However, there is very little evidence of effectiveness of antibiotics. Antibiotic resistance is a growing health concern, so stewardship is of utmost importance.

PATIENTS: Children with lower respiratory infection

INTERVENTION: Amoxicillin

CONTROL: Placebo

OUTCOME: Duration of bad/worse symptoms

Secondary Outcome: Severity, duration

METHODS (BRIEF DESCRIPTION):

- Eligible children were six months to 12 years old who presented to primary care with acute lower respiratory tract infection, where pneumonia was not suspected, and with symptoms less than 21 days.
- Exclusion criteria: non-infectious cause or almost certain viral cause, immune compromised, antibiotic use in previous 30 days
- Patients randomly assigned in 1:1 ratio to either receive amoxicillin 50 mg/kg per day or placebo in three divided oral doses for seven days.
- Parents kept a diary of symptoms and daily activities for at least one week and for as long as symptoms persisted for up to four weeks.
- Symptoms included: cough, phlegm, shortness of breath, wheezing, runny nose, trouble sleeping, feeling unwell, fever, interference with normal activities
- Symptoms were rated from 0 (no problem) to 6 (as bad as it could be).

INTERVENTION (# IN THE GROUP): 221

COMPARISON (# IN THE GROUP): 211

FOLLOW UP PERIOD: Four weeks

RESULTS:

Primary Outcome –

- There was no difference in median duration of moderately bad or worse symptoms between the antibiotic or placebo groups (5 days vs 6 days, respectively; HR 1.1; 95% CI, 0.9–1.4).

Secondary Outcome –

- The antibiotic group had slightly better symptom severity 2–4 days after seeing a doctor (1.8 vs 2.1; Mean difference -0.28; 95% CI, -0.51 to -0.04)
- There was no difference in median duration of symptoms between the antibiotic or placebo groups (7 days vs 8 days, respectively; HR 1.1; 95% CI, 0.86–1.3).

LIMITATIONS:

- Not powered to be able to assess complications of treatment with antibiotics.
- Follow up rate of 73% raises concern for possible attrition bias.

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# Oral Anticoagulants for the Prevention of Recurrent Thromboembolism among Chronic Kidney Disease Patients

**Using oral anticoagulants among chronic kidney disease patients to prevent recurrent venous thromboembolism: A systematic review and meta-analysis**

Alhousani M, Malik SU, Abu-Hashyeh A, et al. Using oral anticoagulants among chronic kidney disease patients to prevent recurrent venous thromboembolism: A systematic review and meta-analysis. *Thromb Res*. 2021; 198:103_114. doi:10.1016/j.thromres.2020.11.036



KEY TAKEAWAY: Direct Oral Anticoagulants (DOACs) carry less risk for bleeding compared with Vitamin K Antagonists (VKAs) and Low Molecular Weight Heparins (LMWH). Additionally, DOACs are not inferior to other anticoagulants for the secondary prevention of venous thromboembolism (VTE) among CKD patients.

STUDY DESIGN: Meta-analysis of 10 RCT (N=10,840)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: VTE causes significant harm to both hospitalized and community-dwelling patients. Thrombus prophylaxis poses a particular challenge among CKD patients, who are at an increased risk of both clotting and bleeding. DOACs, have been shown to be effective and have a low bleeding side effect profile, but are underutilized in this patient population.

PATIENTS: Patients with CKD (stratified by serum creatinine, or SCr) and a history of VTE

INTERVENTION: Oral anticoagulation

CONTROL: Other anticoagulants or placebo

OUTCOME: Prevention of VTE, occurrence of bleeding

METHODS (BRIEF DESCRIPTION):

- Literature review of phase I, II, and III RCTs
- Studies compared various modes of anticoagulation (DOACs, LMWH, and VKAs) to one another and/or to placebo for secondary prevention of VTE among CKD patients stratified by severity of disease (based on SCr).
- Data from 10 different studies were pooled into four interventions versus comparison groups as described below, with varied dosing among several different DOACs, and standard dosing for VKAs and LMWHs.
- Outcomes included prevention of secondary thrombus (efficacy) and incidence of clinically relevant bleeding (safety).

INTERVENTION VS COMPARISON (# IN THE GROUP):

- DOACs (640) vs Placebo (485)
- DOACs (3,761) vs VKAs and LMWHs (3,798)
- LMWHs (484) vs VKAs (512)
- DOACs and VKAs (1,275) vs LMWH (1,236)

FOLLOW UP PERIOD: Three to 48 months

RESULTS:

- In CKD patients with a history of VTE…
  - DOACs significantly reduced the occurrence of recurrent VTE compared with placebo (2 trials, N=1,125; RR: 0.20, 95% CI, 0.09–0.46, I2 = 14%) at any level of renal impairment.
  - DOACs and VKAs are equally effective for reducing the occurrence of recurrent VTE (5 trials, N=7,559; RR:0.83, 95% CI, 0.60–1.1, I2 = 34%) at any level of renal impairment.
  - LMWH and OACs in general are equally effective for reducing the occurrence of recurrent VTE (3 trials, N=2,511; RR:1.5, 95% CI, 0.79–2.8, I2 = 78%) at any level of renal impairment.
  - DOACs compared with VKAs were associated with:
    - A lower risk of major bleeding (3 trials, N=6,044; RR:1.5, 95% CI, 0.79–2.8, I2 = 78%) at any level of renal impairment
    - A lower risk of non-major clinically relevant bleeding (5 trials, N=7,559; RR: 0.71, 95% CI, 0.52–0.96, I2 = 53%) at mild levels of renal impairment
    - No significant difference in risk of intracranial bleeding in patients with mild or moderate levels of renal impairment (2 trials, N=1,962; RR: 0.68, 95% CI, 0.19–2.4, I2 = 0%)

LIMITATIONS:

- Studies were selected based on collection of baseline SCr data, some levels of Cr clearance were better represented than others from one trial to the next.
- There was evidence for significant heterogeneity among studies with respect to:
  - Follow up duration
  - Baseline characteristics of patients
  - Other risk factors for VTE besides CKD
- The study only collected RCTs in English.
- No qualitative analysis on the rigor of studies selected is described.

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# Acute Back Pain? Consider Battlefield Acupuncture

**Battlefield Acupuncture Versus Standard Pharmacologic Treatment of Low Back Pain in the Emergency Department: A Randomized Controlled Trial**

Johnston K, Bonjour T, Powell J, April MD. Battlefield Acupuncture Versus Standard Pharmacologic Treatment of Low Back Pain in the Emergency Department: A Randomized Controlled Trial. *J Emerg Med.* 2021; 61(4):406–415. doi:10.1016/j.jemermed.2021.07.017



**KEY TAKEAWAY:** Battlefield Acupuncture (BFA) may result in more pain reduction for acute back pain compared to common pain medications, although effects may be small.

**STUDY DESIGN:** Single-center study, nonblinded, randomized controlled trial

**LEVEL OF EVIDENCE:** STEP 3 (downgraded due to small study and results with small clinical significance)

**BRIEF BACKGROUND INFORMATION:** 2.3% of all Emergency Department (ED) visits are for treatment of low back pain. The American College of Physicians recommends clinicians preferentially use nonpharmacologic treatment before resorting to opioid and nonopioid medications. BFA, a specific type of auricular acupuncture, is an emerging nonpharmacologic treatment option being studied for various pain syndromes in adults. Previously only one randomized trial has demonstrated effectiveness in ED patients with back pain.

**PATIENTS:** Adults with acute back pain
**INTERVENTION:** Battlefield acupuncture (BFA)
**CONTROL:** Standard pharmacologic therapies
**OUTCOME:** Pain reduction
Secondary Outcomes: Patient satisfaction and function, rescue medication use

**METHODS (BRIEF DESCRIPTION):**

- A convenience sample of adults 18-55 years old presented to Brooke Army Medical Center ED with atraumatic back pain of less than three months duration with pain score of at least 30 mm on a 100 mm Visual Analogue Scale (VAS).
- Patients were randomized to either BFA or a control arm.
- In the BFA arm, the treating clinician sequentially placed five acupuncture needles into the auricle of each ear using acupoint zones in accordance with the U.S. Air Force Acupuncture and Integrative Medicine Center protocol.
- In the control arm, the treating clinician could choose between predefined medications and doses, including acetaminophen 325-1000 mg oral, diclofenac 50-75 mg oral, diazepam 5-10 mg oral or IV, hydrocodone 5mg oral, or ketorolac 30-60 mg IM.
- Patients completed the VAS and Back Pain Functional Scale (BPFS) before and 30-40 minutes after the pain intervention. Patients then completed a VAS and BPFS and reported any rescue pain medication use after ED discharge via phone.

**INTERVENTION (# IN THE GROUP):** 26
**COMPARISON (# IN THE GROUP):** 26

**FOLLOW UP PERIOD:** 48-72 hours

**RESULTS:**
Primary Outcome –

- 30 minutes after the treatments, BFA proved to reduce pain more than the pharmacologic treatment (effect size difference 12 mm; 95% CI, 0.1–24).

Secondary Outcomes –

- BFA did not reduce pain more than the pharmacologic treatment 48-72 hours post-intervention.
- Fewer patients in the BFA group used rescue medications after ED discharge compared to the control group (effect size difference 17%; 95% CI, 1.0–32).
- There were no adverse effects reported in either group.

**LIMITATIONS:**

- The primary outcome had a very wide confidence interval, calling into question the precision of the results.
- This was a small study, powered to an arguably small analgesic effect of only 12 mm on the VAS.
- The study suffered from lack of blinding and a possible selection bias, as the investigators recruited a convenience sample of potential study subjects rather than systematically collecting data on every patient meeting inclusion criterion.
- This was a single-center study with a narrow patient population.
- The BFA group had a greater muscle relaxer use prior to ED visit than the control group.
- The control group received a broad range of therapies, and the investigators did not collect

data regarding which of the predefined medications were given to each patient in the control arm.

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*The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy of the Department of Defense, Department of Army, US Army Medical Department, or the US Government.*

# Is Prenatal Bariatric Surgery Worth the Risk?

**Perinatal outcomes after bariatric surgery**

Getahun D, Fassett MJ, Jacobsen SJ, et al. Perinatal outcomes after bariatric surgery. *Am J Obstet Gynecol*. 2022; 226(1):121.e1-121.e16. doi:10.1016/j.ajog.2021.06.087



KEY TAKEAWAY: Preconception counseling for obese women who qualify should include risks and benefits of Bariatric Surgery (BS) in addition to lifestyle modifications. Prenatal BS is associated with lower risks for many adverse outcomes, but also increases the risk for SGA infants and postpartum hemorrhage.

STUDY DESIGN: Retrospective cohort study via EMR review

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Severe obesity (BMI >35) affects all races and ethnicities and is rising in prevalence. Obesity impairs fertility and is associated with increased risk for several adverse perinatal outcomes. The most effective treatment for obesity is bariatric surgery, but its effects on perinatal outcomes are not yet well understood.

PATIENTS: Pregnant women with severe obesity

INTERVENTION: Bariatric Surgery (VSG, RYGB or gastric banding) any time prior to pregnancy

CONTROL: No Bariatric Surgery

OUTCOME: Perinatal outcomes

METHODS (BRIEF DESCRIPTION):

- Population-based, retrospective cohort review of Kaiser Permanente Southern California hospitals and outpatient clinic and Bariatric Registry EHR (electronic health record) review
- Outcomes for severely obese pregnant women with a history of BS were compared to those of severely obese pregnant women who were eligible for but did not receive BS (based on KPSC registry).
- Perinatal outcomes evaluated included gestational diabetes, preeclampsia, eclampsia, placenta previa, placental abruption, abnormal fetal heart rate tracings, premature rupture of membranes, cesarean delivery, chorioamnionitis, large for gestational age, NICU admission, and postpartum hemorrhage.
- Exclusion criteria: Non-KPSC members for >90 days during the pregnancy, multiple gestation pregnancies, maternal age <18 years old, gestational ages <20 weeks, patients without pre-pregnancy BMI data, patients without BS and pre-pregnancy BMI <35, and patients who underwent BS during pregnancy

INTERVENTION (# IN THE GROUP): 1,886

COMPARISON (# IN THE GROUP): 18,327

FOLLOW UP PERIOD: Through hospital delivery and initial infant hospital stay

RESULTS:

Prenatal bariatric surgery for severe obesity was associated with lower risk of:

- Cesarean delivery by 9.5% (aOR 0.65; 95% CI, 0.59–0.72)
- Gestational Diabetes by 8.8% (aOR 0.60; 95% CI, 0.53–0.69)
- Pre-eclampsia and eclampsia by 12% (aOR 0.53; 95% CI, 0.46–0.6)
- Chorioamnionitis by 1.8% (aOR 0.45; 95% CI, 0.32–0.63)
- Large for Gestation neonate by 12% (aOR 0.23; 95% CI, 0.19–0.29)
- Macrosomia by 11% (aOR 0.24; 95% CI, 0.19–0.30)
- NICU admission by 4.2% (aOR 0.70; 95% CI, 0.61–0.81)

Prenatal bariatric surgery for severe obesity was associated with increased risk of:

- Small for gestational age (SGA) neonates by 8.3% (aOR 2.5; 95% CI, 2.2–2.8)
- Postpartum hemorrhage by 0.9% (aOR, 1.8; 95% CI, 1.3–2.5)

These effects varied based on the time interval between BS and subsequent pregnancy, with some benefits decreasing with longer intervals.

LIMITATIONS:

- Potential selection bias related to healthier patients being chosen to undergo BS.
- Potential for inadequately controlled confounding effect of smoking due to potentially unreliable self-reported data.
- Inability to determine the confounding effects of nutrition and behavioral factors, those undergoing BS may have undergone significant behavioral changes that drove the outcomes seen rather than the effects of the intervention itself.
- Effects of timing of BS relative to pregnancy on some outcomes are difficult to explain.

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# Are Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2) Better than Sulfonylureas in Patients with Type 2 Diabetes?

**Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonylureas in Patients With Type 2 Diabetes**

Xie Y, Bowe B, Gibson AK, McGill JB, Maddukuri G, Al-Aly Z. Comparative Effectiveness of Sodium-Glucose Cotransporter 2 Inhibitors vs Sulfonylureas in Patients With Type 2 Diabetes [published correction appears in JAMA Intern Med. 2021 Sep 13;:null]. *JAMA Intern Med*. 2021; 181(8):1043–1053. doi:10.1001/jamainternmed.2021.2488



KEY TAKEAWAY: Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2) treatment along with metformin was associated with a reduced risk of all-cause mortality compared with sulfonylureas.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Sulfonylureas are the most common anti-hyperglycemic medications used alongside metformin. However, evidence suggests that SGLT2 inhibitors benefit patients with diabetes beyond the improvement of glycemic control, with decreased incidence of cardiovascular disease and renal protection. Further, there is evidence of these benefits in patients without diabetes. To date, there is a lack of clinical data and experiments comparing SGLT2 inhibitors and sulfonylureas.

PATIENTS: Patients using metformin for type II diabetes treatment

INTERVENTION: Adjunct therapy with SGLT2 inhibitor

CONTROL: Adjunct therapy with sulfonylurea

OUTCOME: All-cause mortality

METHODS (BRIEF DESCRIPTION):

- Patients with diabetes using metformin were identified using data from the Veteran Affairs Health Care System.
- Exclusion criteria included previous prescription of SGLT2 inhibitor or sulfonylurea, type I diabetes, stage 3 chronic kidney disease, or kidney transplant.
- 23,870 individuals received adjunct treatment with SGLT2 inhibitors and 104,423 individuals received adjunct treatment with sulfonylureas (mean age 65 years old; 95% male).
- Time until death was the outcome of the study.

INTERVENTION (# IN THE GROUP): 23,870

COMPARISON (# IN THE GROUP): 104,423

FOLLOW UP PERIOD: Through death or administrative end (January 31, 2021).

RESULTS:

- Metformin + SGLT2 inhibitor reduced the risk of death more than metformin + sulfonylureas (N=128,293; HR 0.77; 95% CI, 0.70–0.85).
- Because of their advantages in reducing complication costs and gains in quality-adjusted life-years, SGLT2 inhibitors are considered to be cost-saving or cost-effective despite higher treatment cost.

LIMITATIONS:

- Since this is an observational study, true causality cannot be determined.
- Data was collected by chart review which provides additional limitations.
- Data was obtained from the US Department of Veterans Affairs to build the cohort study was mostly comprised of older, White, male participants, limiting the generalizability of study findings.
- Group using SGLT2 inhibitors were older and had a higher burden of several comorbidities, including cardiovascular and kidney disease, which might cause residual confounding.

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