GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 12 - 16, 2021

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A Shorter-Course Antimicrobial Therapy for Pediatric Community-Acquired Pneumonia May Be as Effective

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Short-course antimicrobial therapy for pediatric community-acquired pneumonia: The SAFER randomized clinical trial

Pernica JM, Harman S, Kam AJ, et al. Short-Course Antimicrobial Therapy for Pediatric Community-Acquired Pneumonia: The SAFER Randomized Clinical Trial. *JAMA Pediatr*. 2021; 175(5):475–482. doi:10.1001/jamapediatrics.2020.6735

KEY TAKEAWAY: In previously healthy children diagnosed with community-acquired pneumonia (CAP), a five day course of high-dose amoxicillin had comparable outcomes to a traditional 10 day course.
STUDY DESIGN: Two center, parallel group, non-inferiority randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The standard for outpatient treatment of pediatric community-acquired pneumonia has traditionally been a 10 day course of antimicrobial therapy. Multiple RCTs support short-course antibiotic treatment of adults with CAP. However, studies in the pediatric population have previously been limited by small size, lack of blinding, or poor study design.

PATIENTS: Children diagnosed with CAP and treated in outpatient setting
INTERVENTION: Five days of high-dose amoxicillin followed by five days of placebo
CONTROL: 10 days of high-dose amoxicillin
OUTCOME: Clinical cure at 14 to 21 days

METHODS (BRIEF DESCRIPTION):

- Children aged 6 months to 10 years treated outpatient for CAP
- CAP defined as:
  - Fever within 48 hours of presentation
  - Tachypnea, increased work of breathing, or auscultatory findings
  - CXR findings of CAP per ED physician interpretation
  - Primary diagnosis of CAP by ED physician
- Exclusion criteria included comorbidities that would predispose to severe disease or pneumonia of unusual origin, previous Beta-lactam antibiotic therapy, or illness requiring hospitalization.
- Patients given five days of amoxicillin plus five days of placebo vs five days of amoxicillin plus five days of amoxicillin of different formulation
- Treatment failure was defined by persistent fever at 96 hours and those patients received a full 10 day course.
- Patients returned at days 14 to 21 for primary outcome measurement. Caregivers were called one month after enrollment.
- Primary outcome: Initial improvement during first four days, improvement of symptoms at 14–21 days follow up, no more than one fever spike after day four, no hospital admission or additional antibacterial needed.
- Secondary outcome: Rate of caregiver work absenteeism, child absenteeism, and drug adverse reactions

INTERVENTION (# IN THE GROUP): 140 participants with 126 included in primary analysis
COMPARISON (# IN THE GROUP): 141 participants with 126 included in primary analysis

FOLLOW UP PERIOD: 1 month

RESULTS:

- Short course antibiotic therapy (5 days) for uncomplicated pediatric CAP is comparable to standard care (10 days) (Risk Difference 0.023; 97.5% one-sided CL, –0.087)
- Caregiver work absenteeism was lower in short course antibiotic therapy (Incident Rate Ratio 0.076; 95% CI, 0.66–0.87)
- All other secondary outcomes were similar between groups.

LIMITATIONS:

- Difficult to definitively diagnose bacterial pneumonia
- 10% were lost to follow up
- Not sufficient power to show non-inferiority of primary outcome of study
- Results cannot be generalized to treating CAP in low and middle income countries

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E-cigarettes, a New Path for Smoking Cessation?

Effect of e-cigarettes plus counseling vs counseling alone on smoking cessation: a randomized clinical trial

Eisenberg MJ, Hébert-Losier A, Windle SB, et al. Effect of e-Cigarettes plus Counseling vs Counseling Alone on Smoking Cessation: A Randomized Clinical Trial. *JAMA*. 2020; 324(18):1844–1854. doi:10.1001/jama.2020.18889

KEY TAKEAWAY: Use of electronic cigarettes (e-cigarettes) plus counseling vs counseling alone shows no long-term increase in smoking abstinence beyond 12 weeks among adults motivated to quit.
STUDY DESIGN: Randomized clinical trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Smokers use e-cigarettes as a tool for smoking cessation, however the efficacy for smoking cessation remains controversial and not well studied.

PATIENTS: Adult cigarette smokers
INTERVENTION: Nicotine e-cigarettes or non-nicotine e-cigarettes plus individualized counseling
CONTROL: Individualized counseling
OUTCOME: Smoking abstinence as defined by zero cigarettes smoked

METHODS (BRIEF DESCRIPTION):

- 274 out of the 801 screened adults met inclusion criteria:
  - ≥18 years old
  - Smoked a mean of 10 cigarettes or more per day
  - Had a moderate to strong desire and intention to attempt to quit as indicated by a Motivation to Stop Scale level of 5 or higher
- Exclusion criteria:
  - Used smoking cessation therapy in the past 30 days
  - Had an e-cigarette in the past 60 days
  - Had ever used an e-cigarette for 7 or more days consecutively
- Patients were randomized into nicotine e-cigarettes, non-nicotine e-cigarettes, or no e-cigarettes, with all participants receiving individualized counseling.
- The primary endpoint was point prevalence abstinence (7-day recall, biochemically validated using expired carbon monoxide) at 12 weeks, with trial secondary outcomes through 24 weeks.
  - The trial was scheduled to last for 52 weeks, however shortages and delays in e-cigarette manufacturing resulted in early termination of the study, with primary endpoint reduced from 52 weeks to 12 weeks.
- Secondary outcomes were measured at various follow-ups:
  - Point prevalence abstinence
  - Adverse events
  - Continuous abstinence daily cigarette consumption change
  - Serious adverse events
  - Treatment adherence
  - Dropouts due to adverse events
- Participants lost to follow-up were presumed to be smoking.

INTERVENTION (# IN THE GROUP):
Nicotine e-cigarettes: 128
Non-nicotine e-cigarettes: 127
COMPARISON (# IN THE GROUP): 121

FOLLOW UP PERIOD: Primary endpoint of 12 weeks, with outcomes through 24 weeks reported as secondary endpoint

RESULTS: E-cigarettes provided no significant increase to the level of smoking abstinence beyond the primary endpoint of 12 weeks when compared to 24 week follow-up.

- At 12 weeks, the nicotine e-cigarettes plus counseling group had increased smoking abstinence compared to the control group (22% vs 9.1%; Risk Difference [RD] 13; 95% CI, 4.0–22).
  - At 24 weeks the difference was no longer significant (17% vs 9.9%; RD 7.3; 95% CI, –1.2 to 16).
- There was no significant difference between the non-nicotine e-cigarettes plus counseling group and the counseling only group at 12 weeks (17% vs 9.1%; RD 8.2; 95% CI, –0.1 to 17)
  - The point prevalence abstinence between groups was significantly greater at 24 weeks (21% vs 9.9%; RD 11; 95% CI, 1.8–19).

- Adverse events were common among all groups with cough (64%) and dry mouth (53%) being the most common.

LIMITATIONS:

- Early termination of the trial.
- Lost to follow-up rates were the highest among those who received counseling alone.
- E-cigarettes used in the trial were not commercially available e-cigarettes, but e-cigarettes specifically designed for the study.

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Should We Forget About Verubecestat?

Randomized trial of Verubecestat for prodromal Alzheimer's disease

Egan MF, Kost J, Voss T, et al. Randomized Trial of Verubecestat for Prodromal Alzheimer's Disease. *N Engl J Med*. 2019; 380(15):1408–1420. doi:10.1056/NEJMoa1812840

KEY TAKEAWAY: Verubecestat, a BACE-1 & BACE-2 inhibitor, does not benefit clinical outcomes and may even worsen cognition and daily function in patients with prodromal Alzheimer's disease.

STUDY DESIGN: Multisite, randomized, double-blind, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The amyloid hypothesis of Alzheimer's disease attributes the accumulation of amyloid-beta (Aβ) in the brain to Alzheimer's disease. Verubecestat blocks the cleavage of the amyloid precursor protein and has been shown to inhibit Aβ. In previous studies, Verubecestat also showed some regression of amyloid plaques, however no indication of disease deceleration was observed. Given the reduction in Aβ, it was hypothesized that Verubecestat may improve clinical outcomes in patients identified earlier in their disease process.

PATIENTS: 50–85 year old patients with memory loss

INTERVENTION: Verubecestat tablet 12 mg or 40 mg daily

CONTROL: Oral placebo

OUTCOME: Cognitive and daily function

METHODS (BRIEF DESCRIPTION):

- Patients did not meet criteria for dementia but had subjective memory loss for one year and had the presence of brain amyloid on a PET scan. Independent review confirmed diagnosis of prodromal Alzheimer's disease
- Patients from 238 centers in 22 countries were randomly assigned in a 1:1:1 ratio to receive oral Verubecestat at 12 mg daily, 40 mg daily, or placebo.
- Trial groups were randomly assigned via computer-generated schedule and stratified according to geographic region, baseline memory score, and the use of cholinesterase-inhibiting medications. Biomarker sub-studies of brain volume measures and amyloid burden were also collected.
- All patients were administered identical appearing tablets.
- Patients who completed 104 trial weeks progressed to part 2 (extension period – planned duration for up to 5 years).
- Patients in the placebo group were switched to the 40 mg dose, while patients in the experimental groups continued at same dose concentration.
- Cognition and daily function measured by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB; 0–18; 18=worst outcomes)

INTERVENTION (# IN THE GROUP):

- 12 mg/d: 485
- 40 mg/d: 484

COMPARISON (# IN THE GROUP): 485

FOLLOW UP PERIOD: 104 weeks

RESULTS: The trial was terminated early after failure to support hypothesis of superiority over placebo.

- There was no difference in cognitive and daily function between the 12 mg intervention group compared to placebo (1.6 vs 1.7; *P*=.67).
- The 40 mg intervention group had worse cognitive and daily function outcomes compared to placebo (2.0 vs 1.6; *P*=.01).

LIMITATIONS: The primary limitation of the study was early termination due to patients experiencing worse clinical outcomes on the study drug versus placebo.

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Decreasing Distress in Pediatric Emergency Departments: Potential Consideration

The effect of a cartoon and information video about intravenous insertion on pain and fear in children aged 6 to 12 years in the pediatric emergency unit: a randomized controlled trial

Düzkaya DS, Bozkurt G, Ulupınar S, Uysal G, Uçar S, Uysalol M. The Effect of a Cartoon and an Information Video About Intravenous Insertion on Pain and Fear in Children Aged 6 to 12 Years in the Pediatric Emergency Unit: A Randomized Controlled Trial. *J Emerg Nurs*. 2021; 47(1):76–87. doi:10.1016/j.jen.2020.04.011

KEY TAKEAWAY: Informational videos or cartoons are effective in reducing pain and fear during intravenous access in children.

STUDY DESIGN: Experimental randomized controlled clinical trial

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Needle sticks are common procedures in the emergency department and cause children pain and fear. Previous studies demonstrate that perceived pain can have permanent effects on physiologic and behavioral response to pain later in life. Distraction techniques could decrease pain and fear.

PATIENTS: Children 6–12 years old

INTERVENTION: Viewing an informational video before or a cartoon during IV insertion

CONTROL: IV insertion with no video

OUTCOME: Mean pain and fear levels reported by children

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Conscious patients from one emergency department in Istanbul, Turkey
- Exclusion Criteria: Sedatives, anticonvulsants, analgesics, previous hospitalization, chronic or life-threatening diseases
- Power analysis determined sample size.
- IV placed by research nurse.
- Obtained before and after IV insertion:
  - *Wong-Baker FACES*: Pain scored to numeric values given to various cartoon faces that best illustrates physical pain, 0–10, higher score = more pain
  - *Children's Fear Scale*: Showing cartoon faces that best illustrates emotions, 0–4, higher score = more anxiety
- Group One: Viewed informational video before IV access. Video was created with accordant developmental level of children and reviewed by pediatric nursing experts.
- Group Two: Children chose one of two popular cartoon options and viewed the cartoon during IV insertion.
- Group Three (Control): IV access without videos
- One-way analysis of variance, chi-square test and intra-class correlation coefficient measured + analyzed data

INTERVENTION (# IN THE GROUP):

- Video: 159
- Cartoon: 159

COMPARISON (# IN THE GROUP): 159

FOLLOW UP PERIOD: December 2017 – July 2018

RESULTS:

- Informational video and cartoon groups had lower child mean pain and fear scores compared to control group:
  - Mean pain scores before vs after IV insertion:
    - Informational Group: 1.4 vs 0.09; *P*=.001
    - Cartoon Group: 1.4 vs 0.3; *P*=.001
    - Control Group: 1.4 vs 4.1; *P*=.001
  - Mean fear scores before vs after IV insertion:
    - Informational Group: 1.8 vs 0.05; *P*=.001
    - Cartoon Group: 1.8 vs 0.32; *P*=.001
    - Control Group: 1.8 vs 3.4; *P*=.001

LIMITATIONS:

- Not a double blind study
- Data entered by unblinded nurse who performed the IV insertion.
- Parents aware of study and may have anticipated results.
- Intra-class correlation highest in control group, possible bias.
- Clinical trial protocols not registered.

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Does Liraglutide Effectively Treat Obesity in Adolescents?

A randomized, controlled trial of Liraglutide for adolescents with obesity

Kelly AS, Auerbach P, Barrientos-Perez M, et al. A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. *N Engl J Med*. 2020; 382(22):2117–2128. doi:10.1056/NEJMoa1916038

KEY TAKEAWAY: For adolescents with obesity, Liraglutide plus lifestyle therapy led to a greater reduction in the BMI when compared to placebo plus lifestyle therapy but with increased gastrointestinal adverse effects.
STUDY DESIGN: Multi-site, randomized, double-blind, placebo controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pediatric obesity is a growing problem in the United States and places children and adolescents at risk for developing serious comorbid conditions later on in life. Beyond lifestyle modifications, the use of medications to address obesity have been shown to reduce comorbid risk. Liraglutide, a GLP-1 analogue, has resulted in meaningful weight loss in adults with obesity, but has not been approved by the FDA for use in children. As a safe drug with a minimal side effect profile, more studies are beginning to look at its utility to address the growing issue of pediatric obesity in this country and around the world.

PATIENTS: Obese adolescents with a poor response to lifestyle therapy alone
INTERVENTION: Liraglutide
CONTROL: Placebo
OUTCOME: Change in BMI
Secondary Outcomes: Changes in body weight, waist circumference, waist to hip ratio, glucose metabolism, blood pressure, and quality of life

METHODS (BRIEF DESCRIPTION):

- Participants: Male and female adolescents (12–17 years old) with a BMI >30 or ≥ 95th percentile
- Treatment:
  - 12 weeks of weight loss and nutrition counseling before randomization to treatment or placebo group
  - Treatment group: daily subcutaneous injection of 3 mg Liraglutide for 56 weeks
  - Placebo group: daily subcutaneous injection of 3 mL placebo solution
- The number of standard deviations away from the population mean (age and sex matched) BMI was recorded at baseline.
  - The change in this baseline score was compared across groups at week 56.
- Outcomes analyzed using the intention to treat principle to preserve randomization.

INTERVENTION (# IN THE GROUP): 125
COMPARISON (# IN THE GROUP): 126

FOLLOW UP PERIOD: 94 weeks

RESULTS:

- Liraglutide treatment resulted in a larger change in BMI compared to placebo (–1.4 vs 0.19 respectively; absolute change –1.6; 95% CI, –2.5 to –0.69).
- Liraglutide treatment resulted in greater improvements in waist circumference compared to placebo (–4.4 cm vs –1.4 cm respectively; mean change –2.9 cm; 95% CI, –5.2 to –0.63).
- There was no difference between Liraglutide and placebo in the following secondary outcomes: glycated hemoglobin, fasting plasma glucose, systolic blood pressure, cholesterol, triglycerides, fasting insulin, fasting C-peptide, beta cell function, insulin resistance, high sensitivity C-reactive protein, or quality of life
- Liraglutide treatment compared to placebo resulted in significantly more adverse events in the following areas:
  - Adverse events leading to treatment termination (10.4% vs 0% respectively; *P*<.001)
  - Gastrointestinal adverse events (65% vs 37% respectively; *P*=.001)

LIMITATIONS:

- Confidence intervals were not adjusted for multiplicity in treatment analysis so the results cannot be used to defer definitive treatment effects.
- Smaller sample size compared to similar pediatric phase 3 trials for same drug
- Trial designed, sponsored, and overseen by representatives of the drug manufacturer.
- Overwhelming majority of participants in both treatment and placebo group identify as non-

Hispanic White (84% in treatment group and 91% in placebo group) which may limit generalizability.

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Osteopathic Treatment May Improve Physiologic Stress Response in Premature Babies

Effects of osteopathic treatment versus static touch on heart rate and oxygen saturation in premature babies: a randomized controlled trial

Manzotti A, Cerritelli F, Lombardi E, et al. Effects of osteopathic treatment versus static touch on heart rate and oxygen saturation in premature babies: A randomized controlled trial. *Complement Ther Clin Pract*. 2020; 39:101116. doi:10.1016/j.ctcp.2020.101116

KEY TAKEAWAY: Osteopathic treatment slightly decreases heart rate and slightly increases SpO_2 in healthy preterm newborns.
STUDY DESIGN: Single-site, double blind randomized trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Previous studies have showed that OMT can improve length of stay in preterm newborns, however the data behind this has not yet been studied. Human touch alone is known to improve stress responses across age groups. The specific mechanics of osteopathic treatment which alters the autonomic nervous system may be of added benefit.

PATIENTS: Healthy, preterm infants in the NICU born between 28 and 37 weeks
INTERVENTION: 10 minutes of osteopathic manipulation
CONTROL: 10 minutes of static touch
OUTCOME: Physiologic stress response measured by heart rate (primary outcome) and SpO_2 (secondary outcome)

METHODS (BRIEF DESCRIPTION):

- Patients: Otherwise healthy preterm infants born between 28 and 37 weeks at Buzzi hospital in Milan, Italy
- Patients were randomized by computer software into a control group and an intervention group.
- NICU staff and the statistical analyst were blinded.
- Control group: 10 minutes of constant static touch on the dorsum
- Intervention group: 10 minutes of indirect craniosacral manipulation treatment
- Both the intervention and control group patients were monitored for 5 minutes before in an incubator and then for another 5 minutes after.
- Outcomes were measured by comparing heart rate and SpO_2 before treatment versus after treatment.

INTERVENTION (# IN THE GROUP): 50
COMPARISON (# IN THE GROUP): 46

FOLLOW UP PERIOD: 4 months

RESULTS:
Primary Outcome:

- Heart rate after OMT was significantly decreased (mean –1.2 bpm; $P<.01$). The change in heart rate after static touch was not significant.

Secondary Outcome:

- SpO_2 after OMT was significantly increased (mean 0.3%; $P<.05$). The change in SpO_2 after static touch was not significant.

LIMITATIONS:

- Small sample size
- Single-site
- Unable to blind providers performing the intervention
- Long-term outcomes not assessed

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