GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Does It Take Two for Rescue? Combination Therapy Compared to Traditional Monotherapy in Asthma Rescue

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Papi A, Chipps BE, Beasley R, et al. Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. *N Engl J Med*. 2022;386(22):2071-2083. doi:10.1056/NEJMoa2203163

KEY TAKEAWAY: Use of a high dose, combination Albuterol-Budesonide inhaler as rescue therapy reduces severe asthma exacerbation in patients with moderate-severe asthma when compared to albuterol alone.

STUDY DESIGN: Multinational, double blind, phase three, randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Short acting bronchodilators have long been the mainstay of rescue therapy in asthma. While patients feel symptomatic relief from airway dilation, the underlying inflammation remains untreated. This study evaluated the question of whether combination therapy targeting both the immediate symptoms and underlying inflammation results in a reduced likelihood of severe exacerbations.

PATIENTS: Asthma with at least one severe exacerbation in the last 12 months

INTERVENTION: Fixed low or high dose budesonide with albuterol rescue inhaler

CONTROL: Albuterol alone

PRIMARY OUTCOME: Severe asthma exacerbations

Secondary Outcomes: Annualized rates of severe asthma exacerbations, annualized total dose of systemic steroids, asthma quality of life

METHODS (BRIEF DESCRIPTION):

- 3,132 patients at least four years old were randomly assigned to one of three groups in a 1:1:1 ratio, albuterol (180 mcg), low dose budesonide-albuterol (80 mcg – 180 mcg), or high dose budesonide-albuterol (160 mcg – 180 mcg) with children under twelve excluded from the high dose group.
- Only the trial medication could be used as rescue medication for symptoms or before exercise; other medication including nebulizers were prohibited.
- The maximum daily dose was 12 inhalations/6 doses for all patients.
- Compliance with home controller medication and trial rescue medication was recorded by participants or guardians in an electronic diary, and patients were followed for a minimum of 24 weeks.
- Age-appropriate validated Asthma Quality of Life questionnaires (ACQ-5, AQLQ-12) were completed at baseline and week 24.
- The primary endpoint was a time to event analysis of the first incidence of severe asthma exacerbation.

INTERVENTION (# IN THE GROUP):

- High dose: 960
- Low dose: 975

COMPARISON (# IN THE GROUP): 956

FOLLOW UP PERIOD: 24 weeks

RESULTS:

Primary Outcomes (intention-to-treat analysis) –

- The risk of severe asthma exacerbation was lower in the high dose combination group compared to albuterol alone (HR 0.74; 95% CI, 0.62–0.89; NNT=13).
- There was no significant difference in risk of exacerbations in the low dose group when compared to albuterol alone (HR 0.84; 95% CI, 0.71–1.0).

Secondary Outcomes (intention-to-treat analysis) –

- High dose and low dose combination therapy reduced severe asthma exacerbations more than albuterol.
  - High dose vs Albuterol: rate ratio [RR] 0.75; 95% CI, 0.61–0.91
  - Low dose vs Albuterol: RR 0.81; 95% CI, 0.66–0.98
- There was no difference in annualized doses of systemic steroids between the groups.
- High dose combination therapy increased quality of life (ACQ-5) compared to albuterol (OR 1.2; 95% CI, 1.01–1.5).
  - There was no difference in quality of life (ACQ-5) between low dose combination therapy and albuterol.
- High dose combination increased quality of life (AQLQ-12) compared to albuterol (OR 1.3; 95% CI, 1.04–1.5).
  - There was no difference in quality of life (AQLQ-12) between low dose combination therapy and albuterol.
- Adverse events were similar among all three groups.

LIMITATIONS:

- Only 2.7% of the study population were children ranging from 4–12 years old, which is an underrepresentation of this important demographic.

- Lack of objective measure of patient response to treatment (such as inhaled NO as a measure of inflammation).
- Lack of a cost analysis.

Jared Stewart, MD
Northern Light Eastern Maine Medical Center FMR
Bangor, ME

Is the Pressure Worth the Pain? Why You Should Think Twice About Acetaminophen in Hypertensive Patients

Regular Acetaminophen Use and Blood Pressure in People with Hypertension: The PATH-BP Trial

MacIntyre IM, Turtle EJ, Farrah TE, et al. Regular Acetaminophen Use and Blood Pressure in People with Hypertension: The PATH-BP Trial. *Circulation*. 2022;145(6):416-423. doi:10.1161/CIRCULATIONAHA.121.056015

KEY TAKEAWAY: Among people with hypertension, acetaminophen increased both systolic and diastolic blood pressure. Providers should consider the risk of increased blood pressure while prescribing long-term acetaminophen use.

STUDY DESIGN: Double-blind, placebo-controlled, crossover study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Other than its known risks of hepatic toxicity associated with overdose, acetaminophen has traditionally been perceived as a safer alternative to chronic NSAID use in the management of chronic pain. Recent studies on the safety of long-term acetaminophen use at therapeutic doses have shown conflicting results, but observational studies have suggested that acetaminophen use increases blood pressure (BP).

PATIENTS: Adults with treated or untreated hypertension

INTERVENTION: Acetaminophen

CONTROL: Placebo

PRIMARY OUTCOME: Systolic ambulatory BP

Secondary Outcomes: Diastolic ambulatory BP, systolic 24-hour BP, diastolic 24-hour BP, clinic measured BP

METHODS (BRIEF DESCRIPTION):

- Inclusion criteria:
  - At least 18 years old and hypertensive
  - Either:
    - Treated for hypertension with average daytime ambulatory BP of <150/95 mmHg on stable doses of at least one antihypertensive medication
    - Untreated for hypertension with average daytime ambulatory BP ≥135/85 mmHg but <150/95 mmHg.
- Exclusion criteria: History of ischemic heart disease, heart failure, cerebrovascular disease, liver impairment, chronic kidney disease stage III–V, or suicidal ideation; weight less than 55 kg; regular use of acetaminophen, NSAIDs, corticosteroids, or oral anticoagulants
- Study participants were recruited from local ambulatory BP clinics, general practices, and Scottish Health Research Register.
- 204 local participants were screened, and 110 White patients were randomized with a drop out rate of less than 10%, resulting in 103 total participants included in the analysis.
- Patients were randomly assigned to receive either 1 g acetaminophen four times a day or matching placebo for two weeks.
  - Then, patients had a two-week washout period and participants were then crossed over to the other treatment arm for an additional two weeks of treatment (total of 6 weeks).
- BP was measured either in clinic or via a 24-hour ambulatory BP monitor (ABPM) over four visits during each arm of the study.

INTERVENTION (# IN THE GROUP): 53

COMPARISON (# IN THE GROUP): 50

FOLLOW UP PERIOD: None documented

RESULTS:

Primary Outcome –

- Acetaminophen increased mean daytime systolic ambulatory BP, regardless of existing antihypertensive use, by 4.7 mmHg compared to placebo (95% CI, 2.9–6.6).

Secondary Outcomes –

- Acetaminophen resulted in the following compared to placebo:
  - 1.6 mmHg increase in mean daytime diastolic BP (95% CI, 0.5–2.7).
  - 4.2 mmHg increase in mean 24-hour systolic BP (95% CI, 2.4–6.0).
  - 1.4 mmHg increase in mean 24-hour diastolic BP (95% CI, 0.3–2.5).
  - 4.6 mmHg increase in measured clinic systolic BP (95% CI, 2.4–6.7).
  - 1.6 mmHg increase in measured clinic systolic BP (95% CI, 0.1–3.0).

LIMITATIONS:

- The impacts of extended acetaminophen use on BP is unclear, as the length of the trial was short.
- The study utilized a standard maximum dose of

therapeutic acetaminophen, so a dose-dependent response cannot be observed.
- The study population was not stratified by age cohort, so it is unclear if there are different BP responses based on age.
- Generalizability is limited as patients were all of Caucasian descent in Europe and all had existing hypertension.
- Pain increases blood pressures; therefore, it would be useful to compare acetaminophen's effect on BP compared to other analgesic options.

Rhona Ke, MD
Advocate Illinois Masonic Medical Center
Chicago, IL

Are Platelet-Rich Plasma Injection and Conventional Physical Therapy Effective Treatments for Adhesive Capsulitis?

Comparison of Ultrasound-Guided Platelet-Rich Plasma Injection and Conventional Physical Therapy for Management of Adhesive Capsulitis: A Randomized Trial

Thu AC, Kwak SG, Shein WN, Htun M, Htwe TTH, Chang MC. Comparison of ultrasound-guided platelet-rich plasma injection and conventional physical therapy for management of adhesive capsulitis: a randomized trial. *J Int Med Res*. 2020 Dec;48(12):300060520976032. doi: 10.1177/0300060520976032. PMID: 33296615; PMCID: PMC7731701.

KEY TAKEAWAY: Both PRP injections and conventional physiotherapy improve pain, upper limb function, and ROM at six weeks. PRP injections may reduce the acetaminophen consumption compared to conventional physiotherapy.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Adhesive capsulitis (AC) of the shoulder is a common clinical condition that affects 2–5% of the population. There is no definitive treatment for AC and physicians use oral pain relievers, corticosteroid injections, and conventional physiotherapy (CPT) with mixed results. This study compared the effectiveness of platelet-rich plasma (PRP) injections and CPT.

PATIENTS: Adhesive capsulitis with shoulder pain and limited range of motion (ROM)

INTERVENTION: PRP injection

CONTROL: Conventional physiotherapy

PRIMARY OUTCOME: Pain level, ROM, upper limb function, acetaminophen consumption

METHODS (BRIEF DESCRIPTION):

- 64 patients from an outpatient pain clinic were included based on the following inclusion criteria:
  - 20–65 years old
  - Onset of pain less than three months ago
  - Shoulder pain with movement of shoulder joint
  - Limited passive range of shoulder motion
  - Visual analog scale (VAS) >50 for shoulder pain
- Exclusion criteria: Bilateral AC, glenohumeral joint injection within last six months, history of shoulder dislocation or surgery
- The patients were randomly allocated into two groups.
  - One group received an ultrasound-guided injection of 4 mL of PRP (obtained from the patient) mixed with 1 mL of 2% lidocaine into the affected glenohumeral joint.
  - The other group received CPT in the form of 15 minutes of short-wave diathermy and 30 minutes of exercise therapy, conducted in three sessions per week for six weeks.
- Therapeutic effectiveness was measured before and at one, three, and six weeks after initiation of PRP and CPT.
- Outcomes were measured using the VAS for shoulder pain, passive ROM of the shoulder, and the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire for disability of the upper limbs, scored 0–100 with higher scores indicating greater disability.
- There was one investigator of treatment outcomes, and this investigator was blinded to the group allocation and did not participate in the treatments.

INTERVENTION (# IN THE GROUP): 32

COMPARISON (# IN THE GROUP): 32

FOLLOW UP PERIOD: 6 weeks after therapy initiation

RESULTS:

- Both groups had improved pain, upper limb function, and ROM at six weeks; however, between group statistical significance was not provided.
- Shoulder pain decreased from baseline to six weeks in both groups.
  - Conventional physiotherapy: 83 vs 31, respectively ($P<.001$)
  - PRP injection: 83 vs 28, respectively ($P<.001$)
- Disability of the upper limbs decreased from baseline to six weeks in both groups.
  - Conventional physiotherapy: 54 vs 20, respectively ($P<.001$)
  - PRP injection: 53 vs 14, respectively ($P<.001$)
- Conventional physiotherapy improved ROM at six weeks compared to baseline.
  - ROM-flexion: 102 vs 142, respectively ($P<.001$)
  - ROM-abduction: 90 vs 130, respectively ($P<.001$)
  - ROM-external rotation: 53 vs 78, respectively ($P<.001$)
- PRP injections improved ROM at six weeks compared to baseline.
  - ROM-flexion: 105 vs 146, respectively ($P<.001$)
  - ROM-abduction: 93 vs 132, respectively ($P<.001$)
  - ROM-external rotation: 56 vs 81, respectively ($P<.001$)
- PRP injections resulted in the consumption of less

acetaminophen compared to conventional physiotherapy (2.7 vs 7.7 participants; *P*=.002).

LIMITATIONS:

- This was a small trial with relatively short follow up.
- There were no between group differences with p-values or 95% CIs reported.

Peter Hartung, DO
LewisGale Medical Center FMRP
Salem, VA

Persistent Throat Symptoms: Punt the PPIs

Use of Proton Pump Inhibitors to Treat Persistent Throat Symptoms: Multicenter, Double Blind, Randomized, Placebo Controlled Trial

O'Hara J, Stocken DD, Watson GC, et al. Use of proton pump inhibitors to treat persistent throat symptoms: Multicentre, double blind, randomised, placebo controlled trial. *BMJ*. 2021:m4903. doi:10.1136/bmj.m4903

KEY TAKEAWAY: There is no evidence of symptomatic benefit from PPI treatment in patients with persistent throat symptoms.

STUDY DESIGN: Multicenter, double-blinded, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Persistent throat symptoms are a common concern in primary care. GERD medications, such as proton pump inhibitors, are commonly used, but current evidence does not support this.

PATIENTS: Adults with >6 weeks persistent throat symptoms

INTERVENTION: 30 mg PO lansoprazole BID

CONTROL: Placebo

PRIMARY OUTCOME: Symptom severity

METHODS (BRIEF DESCRIPTION):

- Participants were adults (mean 52 years old) newly referred to one of eight hospital UK ENT clinics with greater than six weeks of throat symptoms (hoarseness, throat pain, globus sensation, throat clearing, postnasal secretions, cough or choking sensation).
- Exclusion criteria: Score of <10 on items 1–8 of RSI questionnaire, those with endoscopic evidence of disease, those who had PPIs within the last four weeks.
- Participants were randomized 1:1 to 30 mg lansoprazole BID for 16 weeks or placebo.
- Participants and research team staff were blinded to treatment allocation throughout the trial.
- Randomization stratified by clinic and baseline symptoms based off severity index score on preassessment RSI questionnaire items 1–8.
- Primary outcome was total RSI score at 16 weeks. RSI is scaled 0–45, higher numbers indicate more severe symptoms. Secondary outcomes included RSI-HB score (scaled 0–40, higher numbers indicate more severe symptoms), comprehensive reflux symptom score (CReSS, scaled 0–170, higher numbers indicate more severe symptoms), LPR-HRQL (43 item laryngopharyngeal health related quality of life tool and utility of baseline laryngeal mucosal changes).

INTERVENTION (# IN THE GROUP): 172

COMPARISON (# IN THE GROUP): 174

FOLLOW UP PERIOD: 16 weeks

RESULTS:

Primary Outcome –

- Symptom severity did not differ between the lansoprazole and placebo groups (between group difference 1.9 points; 95% CI, –0.3 to 4.2).

Secondary Outcomes –

- Lansoprazole and placebo treatment did not significantly affect the following outcomes:
  - Symptom severity measured by RSI-HB (between group difference 2.4 points; 0.0–4.8)
  - Symptom severity measured by CReSS (between group difference 4.2 points; 95% CI, –3.2 to 12)
  - Laryngopharyngeal health related quality of life (between group difference 3.4 points; 95% CI, –2.4 to 9.2)

LIMITATIONS:

- Large drop-out rate among the research groups
- Compliance issues among research groups leading to underpowered analysis
- Measure for GERD is based off self-reported score

Andrew Jones, CPT, MD
Dwight D. Eisenhower Army Medical Center FMRP
Fort Gordan, GA

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