GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Squeeze It! Blood Pressure Reading by Cuff Size

Squeeze It! Blood Pressure Reading by Cuff Size

Effects of Cuff Size on the Accuracy of Blood Pressure Readings: The Cuff Size (SZ) Randomized Crossover Trial

Ishigami J, Charleston J, Miller ER 3rd, Matsushita K, Appel LJ, Brady TM. Effects of Cuff Size on the Accuracy of Blood Pressure Readings: The Cuff (SZ) Randomized Crossover Trial. *JAMA Intern Med.* 2023;183(10):1061-1068. doi:10.1001/jamainternmed.2023.3264

KEY TAKEAWAY: There are statistically significant differences in mean blood pressure (BP) when individuals are placed in an inappropriately sized BP cuff; BP is higher in those placed in a smaller cuff size, and lower when placed in a larger cuff size.

STUDY DESIGN: Community, randomized crossover trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to non-blinding of patients)

BRIEF BACKGROUND INFORMATION: Studies on previous BP cuff sizing describe higher or lower readings due to cuff inadequacies with auscultation. Cuff size differences have not been rigorously studied with automatic BP devices. This study aims to investigate incorrect cuffing with automated BP devices in a controlled study design and replicating an outpatient setting.

PATIENTS: Adults

INTERVENTION: BP reading with different-sized cuffs

CONTROL: Appropriately sized cuff

PRIMARY OUTCOME: Difference in mean BP

Secondary Outcome: Quantified BP difference per size BP cuff, the magnitude of difference when off by one or two sizes

METHODS (BRIEF DESCRIPTION):

- Patients over 18 years old were recruited from the Baltimore community at various public locations who met the criteria of BP cuff size small, regular, large, or extra-large.
- Patients with hypertension were included.
- Patients were excluded if evidence of an overlying rash, gauze dressings, casts, edema, paralysis, tubes, open wounds, or arteriovenous shunts on both arms, pregnant, or arm circumference >55 cm.
- The mean age was 54 years old, mean BMI of 28.8, with 34% male, 68% Black, 51% with pre-existing hypertension, and 20% with diabetes.
- The participants were randomized to the order of BP cuff application (appropriate, too small, too large) and underwent four sets of triplicate BP measurements, the first three of which were randomized and the last with appropriate size.
- Appropriate BP cuff size was determined by measurement and manufacturer labeling.
- Blood pressures were obtained between 9:00 am and 6:00 pm using an oscillometric device on the right arm after the patient had emptied their bladder and walked for two minutes with two minutes of rest between BP measurements.
- The primary outcome measured was the difference in mean systolic BP and diastolic BP from the regular cuff compared with the appropriate cuff.
- The secondary outcomes included the difference in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) using the too-small or large cuff compared to the appropriate size.

INTERVENTION (# IN THE GROUP): 195

COMPARISON (# IN THE GROUP):

- Small BP cuff: 35
- Regular BP cuff: 54
- Large BP cuff: 66
- Extra-large BP cuff: 40

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- Patients for whom a small BP cuff was appropriate had lower BP measurements as compared to when a regular cuff was used; 1 size too large (mean difference [MD] –3.6 mmHg; 95% CI, –5.6 to –1.7).
- Patients for whom a large BP cuff was appropriate had a higher BP measurement as compared to when a regular cuff was used; 1 size too small (MD 4.8 mmHg; 95% CI, 3.0–6.6).

Secondary Outcome –

- Patients with two size differences (overcuffing) had greater differences in BP than those with one size difference:
  - One size difference: Extra large cuff size (appropriate) vs large cuff size (MD 9.6 mmHg; 95% CI, 7.3–12)

- Two size differences: Extra large cuff size (appropriate) vs regular cuff (MD 20 mmHg; 95% CI, 16–23).

LIMITATIONS:

- The study sample size was limited.
- The arm circumferences studied may not reflect the general population and may limit applicability across the BMI spectrum.
- This investigation excluded individuals with open wounds/shunts and likely comorbid diseases which could introduce bias.
- The investigation did not include patient-oriented outcomes such as medication changes, cardiovascular events, or adverse events such as falls.

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Discontinuing Infliximab: An Unwelcome Return for Crohn's Patients

Discontinuation of Infliximab Therapy in Patients with Crohn's Disease

Buhl S, Steenholdt C, Brynskov J, et al. Discontinuation of Infliximab Therapy in Patients with Crohn's Disease. *NEJM Evid*. 2022;1(8):EVIDoa2200061. doi:10.1056/EVIDoa2200061

KEY TAKEAWAY: Patients with Crohn's disease in remission who discontinue infliximab therapy are at significantly increased risk of relapse within one year.

STUDY DESIGN: Multicenter, randomized, double-blind, placebo-controlled withdrawal study

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Infliximab and other TNF-alpha inhibitors have significantly improved control of Crohn's disease and have helped patients maintain remission by stabilizing and healing the intestinal mucosa. Crohn's is a chronic condition and many patients require lifelong biologic treatment. Given concerns regarding the cost and adverse effects of these biologics when taken chronically, people are weighing the risks of relapse when this treatment is discontinued.

PATIENTS: Patients with Crohn's disease and remission with infliximab

INTERVENTION: Continuing infliximab maintenance therapy

CONTROL: Discontinuing infliximab maintenance therapy (placebo infusion)

PRIMARY OUTCOME: Time to relapse

Secondary Outcome: Time to loss of remission, proportion of patients maintaining clinical and endoscopic remission, proportion of patients who relapsed

METHODS (BRIEF DESCRIPTION):

- Patients with luminal Crohn's disease who were treated with infliximab maintenance therapy for a minimum of one year were included.
- Patients must have had stable infliximab dosing for at least three months before the inclusion visit.
- Patients were randomly assigned to either continue their current infliximab maintenance therapy or to discontinue their infliximab.
    - The discontinuation group received a matched placebo infusion.
    - Each group received an infusion every eight weeks (5mg/kg of infliximab or placebo infusion) for a total of 48 weeks.
- Time to relapse was defined as a Crohn's disease activity index (CDAI) of at least 150 with an increase of at least 70 CDAI points above the baseline over two consecutive weeks.
- Time of relapse was defined as the second CDAI assessment that confirmed active disease (>150).
- Relapse was defined as CDAI of at least 150 with an increase of at least 100 points above baseline over two consecutive weeks.

INTERVENTION (# IN THE GROUP): 59

COMPARISON (# IN THE GROUP): 56

FOLLOW-UP PERIOD: 48 weeks

RESULTS:

Primary Outcome –

- Infliximab discontinuation reduced the time to relapse compared to infliximab continuation (hazard ratio [HR] 0.08; 95% CI, 0.035–0.19).
- Infliximab continuation led to 100% survival without relapse while Infliximab discontinuation led to 51% survival without relapse.

Secondary Outcome –

- Infliximab discontinuation increased the number of patients lost to remission (24 patients) compared to infliximab continuation (2 patients) (CDAI >150).
- Infliximab discontinuation reduced the time to loss to remission compared to infliximab continuation (HR 0.025; 95% CI, 0.003–0.19).
- At the end of the study, a significantly greater proportion of patients who continued infliximab remained in remission (98%) compared to patients who discontinued therapy (47%).

LIMITATIONS:

- Initially, at the start of the study, CDAI scores were considered sufficient to evaluate disease activity, but by the end of the study, CDAI scores and endoscopy were needed to evaluate disease activity more accurately.
- The patients in the study had different subtypes of Crohn's disease and included patients with and without previous surgeries.

- The measured duration of remission (past the required duration for inclusion) was different for the patients in the study.
- The inclusion period was extended, and they only obtained 93% of the sample size that they planned to enroll in the study.

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Is Manual Therapy of the Diaphragm Effective for People with Obstructive Lung Diseases? A Systematic Review

Tsimouris D, Arvanitidis M, Moutzouri M, et al. Is manual therapy of the diaphragm effective for people with obstructive lung diseases? A systematic review. *Respir Med Res.* 2023;83:101002. doi:10.1016/j.resmer.2023.101002

KEY TAKEAWAY: Manual therapy was effective at increasing diaphragm excursion, chest expansion, and exercise capacity, but it remains unclear if this provides a therapeutic benefit in patients with chronic obstructive pulmonary disease (COPD) or asthma.

STUDY DESIGN: Systematic review and meta-analysis of two trials (N=39)

LEVEL OF EVIDENCE: STEP 2 (downgraded due to limited evidence and non-randomized studies included)

BRIEF BACKGROUND INFORMATION: Dysfunction of the diaphragm amongst individuals with obstructive lung disease is common and manual therapy techniques may improve distress. This unique study investigates the impact of manual therapy on flexibility and strength of the diaphragm and its potential role in enhancing respiratory function. This study is important to improve overall quality of life for individuals with obstructive lung disease.

PATIENTS: Adults with COPD or asthma

INTERVENTION: Manual therapy of the diaphragm

CONTROL: Usual care

PRIMARY OUTCOME: Diaphragm excursion, chest expansion, exercise capacity

METHODS (BRIEF DESCRIPTION):

- Patients were adults ≥18 years old with COPD or asthma that was mild, moderate, or severe in severity.
- Eligible studies were those that compared:
  - Manual therapy to no treatment
  - Manual therapy to usual care (breathing retraining, inspiratory muscle training, exercise alone, stretching exercises)
  - Manual therapy to light manual interventions (gentle massage)
  - A combination of these interventions
- Two studies were selected:
  - Study one only reviewed diaphragm excursion (DE), exercise capacity (EC), maximum respiratory pressures (MRP), abdominal and chest wall kinematics (ACWK).
    - 19 patients with COPD were selected.
    - Diaphragmatic mobility, exercise capacity, maximal respiratory pressures, and optoelectronic plethysmography in both groups were measured over six sessions and at the end.
    - The experimental group applied manual diaphragmatic release techniques.
    - The control group applied sham techniques.
  - Study two only reviewed DE and chest expansion (CE).
    - 20 patients with COPD were selected.
    - Diaphragmatic excursion via ultrasonography, and chest expansion via an inch tape were measured.
    - 10 participants were in each group and they completed two sets of 10 breaths.
- Usual care included gentle massage, breathing retraining, inspiratory muscle training, exercise alone, stretching exercises, or sham techniques.

INTERVENTION (# IN THE GROUP):

- Study one: 10
- Study two: 10

COMPARISON (# IN THE GROUP):

- Study one: 9
- Study two: 10

FOLLOW-UP PERIOD:

- Study one: Two weeks
- Study two: Three hours

RESULTS:

Primary Outcome –

- Manual therapy interventions were effective in improving the following in patients with COPD:
  - Diaphragm excursion at session six (6 mm; 95% CI, 2–9)
  - Chest expansion:
    - Diaphragmatic stretching technique
      - 4^{th} intercostal space (difference of 0.76±0.71; *P*=.001)

        - Xiphoid process (difference of 0.62±0.64; *P=.001)*
    - Manual diaphragm release technique
        - 4th intercostal space (difference of 0.82±0.06; *P=.002)*
        - Xiphoid process (difference of 0.72±0.88; *P=.002*)
- Exercise capacity (22 m; 95% CI, 11–32)

LIMITATIONS:

- There is insufficient evidence to substantiate the use of manual therapy in treating asthmatic patients given there is low data to conclude this.
- Limited population who were not all comparable with a low sample size.
- These were studies that only included direct hands-on manual therapy.
- There was low-quality evidence and lack of an dyspnea assessment.
- Differences in study design between the two studies chosen were present.
- The duration of follow-up in the trials examined might not have been insufficient.
- More extensive trials might be necessary to ascertain if manual therapy of the diaphragm improves the quality of life for patients with obstructive lung disease.
- Barriers to implementing the interventions include limited attendance and lack of participants.

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Testosterone for Gender-Affirming Care: High Hemoglobin is Hardly a Concern

Erythrocytosis in Gender-Affirming Care with Testosterone

Porat AT, Ellwood M, Rodina M, Dianat S. Erythrocytosis in Gender-Affirming Care With Testosterone. *Ann Fam Med.* 2023;21(5):403-407. doi:10.1370/afm.3018

KEY TAKEAWAY: Injectable testosterone cypionate for gender-affirming hormone treatment (GAHT) is rarely associated with severe erythrocytosis at 20 months.

STUDY DESIGN: Descriptive fixed cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Use of testosterone therapy has been associated with an increase in hemoglobin (Hgb) and/or hematocrit (Hct). Studies have demonstrated a correlation between erythrocytosis and arterial/venous thromboses, though causation has not been supported. Despite this, GAHT guidelines recommend monitoring baseline and serial Hgb and/or Hct every three months for the first year after starting testosterone therapy. This study enumerated the incidence of erythrocytosis associated with GAHT.

PATIENTS: Participants ≥16 years old receiving GAHT

INTERVENTION: Injectable testosterone cypionate

CONTROL: Baseline Hct

PRIMARY OUTCOME: Cumulative incidence of erythrocytosis at 20 months

METHODS (BRIEF DESCRIPTION):

- Participants who received testosterone for GAHT and received regular Hct monitoring at any Virginia League for Planned Parenthood-affiliated site were included in the study.
- Individuals already taking testosterone before the study, did not have baseline Hct values, or those with gaps >1 month in hormone therapy were excluded.
- Demographic characteristics:
  - Median age 21 years old
  - 61% White, 12% African American, 1.8% Asian, 0.01% Native Hawaiian or other Pacific Islander, 24% preferred not to answer
- Median testosterone dose: 80 mg/wk
  - Dose range: 40–120 mg/wk
- Formulation: Injectable 279, gel 3
- The cumulative incidence of erythrocytosis was evaluated with Hct at three-month intervals up to 32 months.
  - Hct >50: Lowest threshold definition for erythrocytosis
  - Hct >54: Severe erythrocytosis

INTERVENTION (# IN THE GROUP): 282

COMPARISON (# IN THE GROUP): 71 at 20 months

FOLLOW-UP PERIOD: 32 months

RESULTS:

Primary Outcome –

- Cumulative incidence at 20 months:
  - Hct >50 = 15%
  - Hct >52= 1.0%
  - Hct >54= 0.6%

LIMITATIONS:

- The study had a 75% loss to follow-up at 20 months and only three participants remained at the end of the study (32 months).
- The injection route (intramuscular vs subcutaneous) was not documented.
- The study could not be certain that it captured all cases of thromboembolism.
- The study could not compare the prevalence of smoking in the overall population with the subset who developed erythrocytosis as smoking is a known risk factor for erythrocytosis.

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