GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of March 1 - 5, 2021

SPOTLIGHT: Putting a Cap on CAP - Using a CDR to Rule Out Community-Acquired Pneumonia

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Putting a Cap on CAP: Using a CDR to Rule out Community-Acquired Pneumonia

Signs and symptoms that rule out community-acquired pneumonia in outpatient adults: a systematic review and meta-analysis

Marchello CS, Ebell MH, Dale AP, Harvill ET, Shen Y, Whalen CC. Signs and symptoms that rule out community-acquired pneumonia in outpatient adults: a systematic review and meta-analysis. *J Am Board Fam Med*. 2019; 32:234–247.

KEY TAKEAWAY: Normal vital signs and lung exam can be used to rule out CAP in the outpatient setting.
STUDY DESIGN: Meta-analysis of 12 studies; N=10254
LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Community acquired pneumonia (CAP) is a leading cause of hospitalization and death in the United States. CXR is recommended for diagnosing CAP, when a patient presents with suspicious signs and symptoms, but is not ideal for excluding CAP due to cost and unnecessary radiation exposure. There have not been any systematic reviews of clinical decision rules to help rule out CAP in the outpatient setting.
PATIENTS: Adults and adolescents (ages 15 and up) in an outpatient setting (emergency department, urgent care, primary care, or outpatient clinic)
INTERVENTION: CDR to diagnose, predict or rule out CAP
CONTROL: CXR or CT
OUTCOME: CAP

METHODS (BRIEF DESCRIPTION): Comprehensive literature review of articles that used a CDR (3-10 elements) to diagnose, predict, or rule out CAP in the outpatient setting and also used a CXR or CT for all patients as the primary reference standard. More than half of the studies were performed in the United States; the rest involved studies from Norway, The Netherlands, Denmark, Chile, Switzerland, Iran, and one study that included 12 different European countries.

INTERVENTION (# IN THE GROUP): CDR of normal vital signs (normal temp, normal HR, normal RR) plus normal pulmonary exam (no crackles, no decreased breath sounds) to rule out CAP (N=2173). Other CDRs that were found to be less predictive involved elements such as oxygen saturation, myalgias, sore throat, sputum, CRP.

COMPARISON (# IN THE GROUP): CXR or CT to confirm absence of CAP (N=2173)

FOLLOW UP PERIOD: N/A

RESULTS:

- CDR of normal vital signs plus normal pulmonary exam rules out CAP (3 studies; N=1865; LR- 0.10; 95% CI, 0.07– 0.13). When assuming a low prevalence of CAP (4%), this CDR reduces the likelihood of CAP to 0.4%.
- CDR of normal vital signs rules out CAP (4 studies; N=2173; LR- 0.24; 95% CI, 0.17–0.34).

LIMITATIONS: All but 2 of the studies included are greater than 30 years old – must be validated with current population. A bias assessment indicated that half of the studies had a moderate risk of bias.

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How Low Can You Go? Oral Ibuprofen Dosing for Acute Pain in Adults

Comparison of Oral Ibuprofen at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial

Motov S, Masoudi A, Drapkin J, et al. Comparison of Oral Ibuprofen at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial. *Ann Emrg Med*. 2019 Oct; 74(4):530–537.

KEY TAKEAWAY: Oral ibuprofen at doses of 400mg, 600mg, and 800mg, showed similar efficacy in short-term reduction of acute pain in adults.

STUDY DESIGN: Single-center, randomized, double-blind trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Ibuprofen is commonly dosed beyond 400mg in anticipation of greater analgesic effect. However, there are varying thoughts on the analgesic ceiling of ibuprofen. For example, literature of dental/oral surgery suggests the optimal ibuprofen dose is 400mg.

PATIENTS: Adults age 18 years and older presenting to an ED with acute pain

INTERVENTION: Single dose oral ibuprofen 400mg

CONTROL: Single doses of oral ibuprofen, 600mg or 800mg

OUTCOME: Primary: mean pain scores (scale of 0-10) at 60 minutes.
Secondary: difference in mean pain score within each group, rate of adverse events, need for rescue analgesia.

METHODS (BRIEF DESCRIPTION): 225 adult patients in a 711-bed urban community teaching hospital who presented to the ED with acute pain and without peptic ulcer disease, GI bleeding, renal or hepatic insufficiency, NSAID allergies, altered mental status, opioid use at least 4 hours prior to presentation, pregnancy and breast feeding were randomly placed into three treatment groups by programming software. The majority of diagnoses in each group consisted of musculoskeletal pain (400 mg-61.3%, 600 mg-56.8%, 800 mg- 55.4%). Other diagnoses included cutaneous pain, dental pain, headaches, abdominal pain, chest pain, flank pain and genitourinary pain. Providers, patients, and investigators were all blinded. Patients reported their level of pain prior to intervention. Pain scores were reassessed after 60 minutes.

INTERVENTION (# IN THE GROUP): 400 mg group (n=75)

COMPARISON (# IN THE GROUP): 600 mg group (n=75); 800 mg group (n=75)

FOLLOW UP PERIOD: 60 minutes

RESULTS:

- Clinically meaningful differences were not observed in the mean pain score between the groups at 60 minutes.
- Difference in mean pain scores:
  - 400mg and 600mg groups at 60 minutes = -0.14 (95% Confidence Interval (CI) -0.67–0.39)
  - 400mg and 800mg groups at 60 minutes = 0.14 (95% CI 0.65–0.37)
  - 600mg and 800mg groups at 60 minutes = 0.00 (CI -0.47–0.47)
- Reductions in pain scores within each group before and after intervention were similar.
- No adverse effects reported in any group.
- Four patients in 400mg group, one in 600mg group, and four in 800mg group required rescue analgesics at 60 minutes.

LIMITATIONS:

- Possible selection bias due to sample selection only occurring during investigator's shifts.
- Small sample size and short duration prove inadequate to assess safety of the interventions since no follow up occurred past 60 minutes.

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Does Lack of Improvement at Week 6 of Antidepressant Therapy Warrant Change?

Predicting antidepressant response by monitoring early improvement of individual symptoms of depression: individual patient data meta-analysis
de Vries YA, Roest AM, Bos EH, et al. Predicting antidepressant response by monitoring early improvement of individual symptoms of depression: individual patient data meta-analysis. *Br J Psychiatry*. 2019; 214(1):4–10.

KEY TAKEAWAY: Response and remission rates in patients with MDD on SSRI/SNRI therapy increase between 6 and 12 weeks of therapy.
STUDY DESIGN: Secondary analysis of a meta-analysis consisting of 30 randomized placebo or active comparator controlled double blind trials
LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Often times, if patients are not responding to medication within a short time frame physicians are quick to assume a positive repose to therapy is unlikely. However, patients may still elicit a positive response to medication over a longer period of time.
PATIENTS: Patients with moderate to severe Major Depression Disorder (MDD) according to the Hamilton Rating Scale for Depression (HSRD)
INTERVENTION: SSRI/SNRI therapy
CONTROL: Placebo
OUTCOME: Primary outcome was response rate at week 6. Secondary outcome was remission at week 6 and response and remission rate for patients at week 12.

METHODS (BRIEF DESCRIPTION):
- Individual patient data was collected from 30 trials consisting of 2,184 placebo-treated and 6058 medically treated patients.
- Outcomes were measured by Hamilton Rating Scale for Depression.
- HRSD is a questionnaire that determines the severity of 17 symptoms of depression each scored from 0 to 4. Score ranges from 0-7 is considered normal, or in remission, while a score of 20 or higher is considered moderate to severe disease.
- Patients had HRSD scores taken at baseline, week 2, and week 6 or week 12.
- Patient demographics consisted of patients clinically diagnosed with MDD with a mean HRSD score of 21.6.
- Response was set to be >50% reduction in HRSD score.
- Remission was set to be <7 points on HRSD score.
- The primary outcome was set as >50% reduction in HRSD score at week 6.
- The secondary outcome was remission at week 6 or response and remission at week 12.

INTERVENTION (# IN THE GROUP): 6,058
COMPARISON (# IN THE GROUP): 2,184

FOLLOW UP PERIOD: 6 and 12 weeks

RESULTS: At week 6, 51% of treated patients responded (32% remitted) compared to placebo at week 6 which, exhibited a 38% response rate and a 22% remission rate. At week 12, 68% responded and 49% remitted in the treatment group. In the placebo group at week 12, 53% responded and 34% remitted.

LIMITATIONS:
- Did not take dosing schedules into account
- Did not report any significant data (p-values or confidence intervals) to support their data

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Getting to the POINT of Dual Antiplatelet Therapy for Ischemic CVA and TIA

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA Lowers Risk of Major Ischemic Events
Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med*. 2018; 379(3):215–225

KEY TAKEAWAY: Patients who received aspirin and clopidogrel for minor ischemic stroke or high-risk TIA had a lower risk of major ischemic stroke but a higher risk of major hemorrhage after 90 days compared to those on aspirin monotherapy.
STUDY DESIGN: Randomized, Double-Blind, Placebo-Controlled Trial, Multi-site
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The CHANCE trial, a large Random Controlled Trial, in a Chinese population in 2013 demonstrated reduced recurrence of ischemic stroke with the use of aspirin and clopidogrel in the first 90 days following a minor ischemic stroke or TIA. The POINT trial was created to test this on an international scale.
PATIENTS: Adults at least 18 years old with National Institute of Health Stroke Scale ≤3 or high-risk TIA score of ≥4 on $ABCD^2$ scale
INTERVENTION: Aspirin plus clopidogrel
CONTROL: Aspirin plus placebo
OUTCOME: Major hemorrhage and ischemic stroke, MI, or death from vascular causes
Secondary: death from any cause, minor hemorrhage, and other bleeding subcategories

METHODS (BRIEF DESCRIPTION): Enrollment represented North America, Europe, Australia and New Zealand with 82.8% from the US. Each participant was randomly assigned to receive either aspirin (50-325 mg daily) plus clopidogrel (600 mg on first day and 75 mg daily thereafter) or aspirin alone for 90 days and monitored for primary and secondary outcomes.

INTERVENTION (# IN THE GROUP): 2432
COMPARISON (# IN THE GROUP): 2449

FOLLOW UP PERIOD: 90 days

RESULTS:
- Primary outcomes:
  - Composite of major ischemic stroke, MI, or ischemia related death was lower in clopidogrel and aspirin group vs. aspirin alone (5% vs 6.5%; HR 0.7; 95% CI 0.59–0.95; NNT=67)
  - Major hemorrhage risk increased in clopidogrel and aspirin group (0.9% vs 0.4%; HR 2.3; 95% CI 1.10–4.87; NNH=200)
- Secondary outcomes:
  - Ischemic stroke was decreased in clopidogrel and aspirin group (4.6% vs 6.3%; HR 0.7; 95% CI 0.56–0.92; NNT=59)
  - Major hemorrhage other than intracranial hemorrhage increased in clopidogrel and aspirin group (0.7% vs 0.3%; HR 2.5; 95% CI 1.01–5.90, NNH=250)
  - Minor hemorrhage increased in clopidogrel and aspirin group (1.6% vs 0.5%; HR 3.1; 95% CI 1.67–5.83; NNH=91)
  - There was no significant difference in rates of MI, ischemia-related death, MI, death from ischemic vascular causes, or death from any cause.

LIMITATIONS:
- Net enrollment was decreased as 29% of patients stopped treatment early (mostly due to clinician preference and safety concerns), thereby limiting the power of the study
- Event rates were lower than expected, further weakening the power of the study
- The clopidogrel dose was different in this trial, limiting ability to compare to CHANCE trial outcomes

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Hypothyroidism: Are there differences in successful treatment between levothyroxine and desiccated thyroid?

Thyroid Stimulating Hormone Stability in Patients Prescribed Synthetic or Desiccated Thyroid Products: A Retrospective Study

Kuye R, Riggs C, King J, et al. Thyroid Stimulating Hormone Stability in Patients Prescribed Synthetic or Desiccated Thyroid Products: A Retrospective Study. *Ann Fam Med*. 2020 Sep; 18(5):452–454.

KEY TAKEAWAY: TSH values are similar in both patients treated with desiccated thyroid and levothyroxine.

STUDY DESIGN: Retrospective matched cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Hypothyroidism is treated with both synthetic (levothyroxine) and biologic (desiccated thyroid) thyroid replacement therapies. While levothyroxine is more widely used, some physicians prefer desiccated thyroid. A few small trials show improved symptom control and quality of life with desiccated thyroid. However, there are limited data comparing the impact of levothyroxine and desiccated thyroid on TSH over an extended period.

PATIENTS: Adults > 18 years with hypothyroidism

INTERVENTION: Levothyroxine or desiccated thyroid product

CONTROL: N/A

OUTCOME: TSH

Secondary: visit-to-visit TSH variability, percent of patients with euthyroid TSH values throughout the entire follow-up period, and number of TSH values

METHODS (BRIEF DESCRIPTION):

- 870 patients at Kaiser Permanente Colorado aged >=18 years, between 1/1/2005 and 12/31/2015
- Compared the frequency of euthyroid TSH levels (0.320-5.5000 uIU/mL) in patients treated with levothyroxine and those treated with desiccated thyroid
- Patients split into two equal sized groups (435 patients)
- Patients were matched 1:1 in both groups based on age (mean 63.4 years), sex (90.1% female in each group), and race/ethnicity (83.4% non-Hispanic white, 1.1% non-Hispanic black, 5.1% Hispanic, 10.3% other)
- Patients were excluded if they received more than one thyroid therapy, or if they had the following comorbid conditions: panhypopituitarism, post-radio-iodine therapy, history of thyroid cancer, pregnancy, Graves' disease, or Hashimoto's thyroiditis
- Patients prescribed levothyroxine who met inclusion criteria were matched 1:1 on age, sex, and race/ethnicity to patients prescribed desiccated thyroid
- Earliest thyroid product prescription was identified, and then the second thyroid product dispensed at least one year later was identified, with the latter date being the index date
- TSH values, the number of TSH values collected, TSH value variability, and percent of patients with euthyroid TSH values were measured for 3 years after the index date

INTERVENTION (# IN THE GROUP): 435

COMPARISON (# IN THE GROUP): 435

FOLLOW UP PERIOD: 3 years

RESULTS:

- Primary outcome: There were no differences In the percent of euthyroid TSH values between the desiccated (79.3%) and the levothyroxine (79.1%) groups, P = 0.905
- Secondary outcomes:
  - There was less variability in TSH measurements in patients treated with levothyroxine (1.25) than in those treated with desiccated thyroid (1.44), P = 0.015
  - There was no difference in the number of patients with euthyroid TSH values between the two groups (60%, P = 0.951)
  - The median number of TSH laboratory values obtained for patients treated with levothyroxine (4) was not statistically different than the median number of laboratory values obtained for patients treated with desiccated thyroid (3), P = 0.573

LIMITATIONS:

- Baseline TSH was statistically different between the two groups
- Inability to account for adherence, differences in prescriber practice between agents, or concurrent medications that could have affected TSH
- Subjective outcomes of hypothyroid management were unable to be measured

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