GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of April 12 - 16, 2021

SPOTLIGHT: COPD is better with three

- Does routine use of GI bleed prophylaxis really reduce mortality in critically ill patients?
- New Antibiotic (Zoliflodacin) for Treatment of Urogenital Gonorrhea
- Is Sweet Pee the Missing Key?

COPD is better with three

GEMs
GOOD EVIDENCE MATTERS
SPOTLIGHT

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. N Engl J Med 2018;378:1671-80.

KEY TAKEAWAY: Triple inhaler therapy is superior to either dual inhaler therapy options in the treatment of COPD.

STUDY DESIGN: Phase 3, randomized, double blind, parallel-group, multicenter trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: COPD affects over 16 million Americans, and it is the third leading cause of death in the US. COPD associated costs per year are approximately 50 billion dollars, with COPD-related hospitalizations accounting for 70% of these costs. Strains on the health care system and patients are clear; thus, it is important to understand how to effectively control the disease and prevent hospitalizations.

PATIENTS: Patients ≥ 40 years old with COPD.

INTERVENTION: Once daily triple therapy (inhaled glucocorticoid + LAMA + LABA; Fluticasone 100µ + umeclidinium 62.5µ + vilanterol 25µg)

CONTROL: Once daily dual therapy of Inhaled glucocorticoid + LABA (Fluticasone 100µg + vilanterol 25µg) or LAMA + LABA (umeclidinum 62.5µg + vilanterol 25µg)

OUTCOME:

- Primary: annual rate of moderate or severe exacerbations during treatment
- Secondary: Trough FEV1, change in the St. George's Respiratory Questionnaire (SGRQ), and the time to the first moderate or severe COPD exacerbation during treatment.

METHODS (BRIEF DESCRIPTION):

- Patients were included if they had a COPD Assessment Test (CAT)score ≥ 10 who, in the last year, had FEV1 <50% predicted and history of ≥ 1 moderate or severe exacerbation; or FEV1 50-80% predicted and ≥ 2 exacerbations; or 1 severe exacerbation.
- Patients were from 37 countries seen between June 2014 and July 2017.
- Each patient randomly received a once daily dry powder inhaler that contained either triple therapy (glucocorticoid + LAMA + LABA) or one of two dual therapies (glucocorticoid + LABA or LAMA+LABA)
- Patients continued home regimen for 2 weeks prior to randomization
- Baseline chest x-rays were obtained upon trial entry
- Medications were delivered via Ellipta inhaler
- All patients completed St. George's Respiratory Questionnaire (SGRQ) and spirometry studies for secondary outcomes

INTERVENTION (# IN THE GROUP): 4,151 triple therapy

COMPARISON (# IN THE GROUP): 4,134 dual therapy (glucocorticoid + LABA); 2,070 dual therapy (LABA + LAMA)

FOLLOW UP PERIOD: 52 weeks

RESULTS:

PRIMARY

- Patients treated with once daily triple therapy inhaler had lower rates of moderate or severe COPD exacerbation per year compared to either dual inhaler in glucocorticoid + LABA group (0.91/year vs 1.07/year seen; RR: 0.85; 95% CI, 0.8-0.9, 15% difference) and LAMA-LABA group (0.91/year vs 1.21/year; RR 0.75; 95% CI, 0.7-0.81, 25% difference)

SECONDARY

- Triple therapy resulted in improved trough FEV1 in glucocorticoid + LABA group [mean change from baseline, 97ml; 95% CI, 85 to 100] and in LAMA-LABA (mean change from baseline, 54ml; 95% CI, 39 to 69).
- Decreased number of hospitalizations due to severe exacerbations in LAMA + LABA group (RR 0.66; 95% CI, 0.56-0.78).
- Increased health-related quality of life compared to either dual therapy in glucocorticoid + LABA group (OR: 1.4; 95% CI, 1.3 - 1.6) and in LAMA-LABA (OR 1.4, 95% CI, 1.3 - 1.6).

LIMITATIONS:

- Abrupt discontinuation of inhaled corticosteroid (prior to start of the clinical trial) in those assigned to LAMA-LABA group may have contributed to the higher rate of exacerbations compared to those assigned to the inhaled glucocorticoid groups.

- All-cause mortality in the glucocorticoid groups was decreased, contrary to prior research.
- The definition of an exacerbation was determined by the clinical investigators, which could introduce bias.

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Does routine use of GI bleed prophylaxis really reduce mortality in critically ill patients?

Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis

Wang Y, Ye Z, Ge L, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis. BMJ. 2020 Jan 6;368:l6744.

KEY TAKEAWAY: Compared to placebo, proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) decreases risk of clinically important gastrointestinal (GI) bleeding in critically ill patients, but they had no effect on mortality, length of ICU and/or hospital stay, *Clostridium difficile* (*C. diff*) infections, or duration of mechanical ventilation.

STUDY DESIGN: Meta-analysis of 72 RCTs; N= 12,660

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: GI bleeding prophylaxis is commonly used in critically ill ICU patients. But there have been concerns regarding the efficacy and potential harms associated with use of GI bleeding prophylaxis.

PATIENTS: Critically ill, adult patients

INTERVENTION: PPIs, H2RAs or sucralfate

CONTROL: Placebo, no prophylaxis, or vs. one another

OUTCOME: Mortality, clinically important GI bleeding, pneumonia, C. diff infection, length of ICU and hospital stay, duration of mechanical ventilation

METHODS (BRIEF DESCRIPTION):

- Comprehensive literature search for RCTs comparing the benefits and safety of GI bleeding prophylaxis with PPIs, H2RAs, or sucralfate compared to placebo, no prophylaxis, or one another in critically ill adult patients
- Patients were assigned to four categories based on risk of clinically important GI bleeding for comparison in analysis of GI bleeding:
    - Low risk: (<2%) Critically ill patients with either no risk factors or potential risk factors of acute hepatic failure, use of steroids/immunosuppression, use of anticoagulants; cancer; male gender
    - Moderate risk: (2-4%) Mechanical ventilation with enteral nutrition; shock; sepsis; acute kidney injury
    - High risk: (>4-8%) Coagulopathy
    - Highest risk: (>8%) Mechanical ventilation without enteral nutrition; Chronic liver disease
- Clinically important gastrointestinal bleeding defined as evidence of upper gastrointestinal bleeding with any of the following:
    - significant hemodynamic changes
    - transfusion of more than two units of blood
    - significant decrease in hemoglobin level
    - evidence of bleeding on upper GI endoscopy
    - need for surgery to control bleeding

INTERVENTION (# IN THE GROUP):

- PPI (N=3564)
- H2RA (N=3669)
- Sucralfate (N=1896)

COMPARISON (# IN THE GROUP): Placebo or no prophylaxis (N=3531)

FOLLOW UP PERIOD: Unreported in most trials

RESULTS:

GI BLEEDING

PPIs and H2RAs each decreased risk of clinically important GI bleeding in critically ill patients in the high and highest risk group compared with placebo or no prophylaxis:

- PPIs (8 trials; N=4317; OR 0.61, 95% CI, 0.42-0.99)
- H2RAs (14 trials; N=1242; OR 0.55, 95% CI, 0.33-0.88)

No significant difference in risk of bleeding comparing PPIs vs H2RAs as prophylaxis:

- PPIs vs H2RAs: (5 trials ; N=1010; OR 0.66, 95% CI, 0.33-1.2)

PNEUMONIA

Risk of pneumonia may be increased with PPIs and H2RAs but was not statistically significant:

- PPIs (6 trials; N= 3974; OR 1.4, 95% CI, 1.0-2.1)
- H2RAs (11 trials; N= 1159; OR 1.3, 95% CI, 0.99-1.9)

MORTALITY

Compared to placebo mortality was not improved with either PPIs or H2RAs

- PPIs vs placebo/no prophylaxis: (9 trials; N= 4194; OR 1.1, 95% CI, 0.90-1.3)
- H2RAs vs placebo/no prophylaxis: (16 trials; N=2576; OR 0.96, 95% CI, 0.88-1.2)

LIMITATIONS:

- Most studies did not report duration of follow-up.
- Some studies reported larger effects with H2RAs than PPIs while others with PPIs than H2RAs.
- Enteral nutrition may itself provide protection against GI bleeding and reduce the effect of prophylaxis on bleeding.

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New Antibiotic (Zoliflodacin) for Treatment of Urogenital Gonorrhea

Single-Dose Zoliflodacin (EETX0914) for Treatment of Urogenital Gonorrhea

Taylor SN, Marrazzo J, Batteiger BE, et al. Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea. N Engl J Med. 2018; 379(19):1835–1845

KEY TAKEAWAY: Single dose Zoliflodacin 3g is as efficacious as Ceftriaxone 500mg for the treatment of uncomplicated urogenital gonorrhea.
STUDY DESIGN: Randomized control trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Antibiotic resistance is a growing worldwide public health concern, threatening the effectiveness of current standard treatments for infectious diseases. The rise of antibiotic-resistant *Neisseria gonorrhea* (*N. gonorrhoeae*) has driven developers to create new alternative therapies.

PATIENTS: Men and woman age 18–55 with signs and symptoms of uncomplicated urogenital gonorrhea, untreated urogenital gonorrhea, or sexual contact 14 days prior with a person who had gonorrhea
INTERVENTION: Oral Zoliflodacin 2g or 3g
CONTROL: IM Ceftriaxone 500mg
OUTCOME:

- Primary: Microbiological cure rate of urogenital gonorrhea
- Secondary: Microbiologic cure rate of pharyngeal or rectal gonorrhea

METHODS (BRIEF DESCRIPTION):

- Random assignment in a 70:70:40 ratio to be given oral Zoliflodacin 2g, oral Zoliflodacin 3g, or IM Ceftriaxone 500mg
- Urethral, cervical, pharyngeal, and rectal cultures taken prior to treatment
- Samples cultured for gonorrhea and Nucleic Acid Amplification Tests (NAAT)
- On test of cure day (day 6) and safety visits (day 31), repeat cultures and swabs for NAAT from all previous sites
- The proportion of participants with microbiologic cure from each treatment group were recorded

INTERVENTION (# IN THE GROUP): 57 oral Zoliflodacin 2g; 56 oral Zoliflodacin 3g

COMPARISON (# IN THE GROUP): 28 IM Ceftriaxone 500mg

FOLLOW UP PERIOD: Follow up period: 31 +/- 2 days

RESULTS:
Primary Outcome (Microbiologic Cure of Urogenital Gonorrhea):

- Per protocol group:
  - IM Ceftriaxone 500mg was more efficacious than oral Zoliflodacin 2g, but not significantly more effective than Zoliflodacin 3g.
  - Oral Zoliflodacin 2g: 98% (95% CI 89%–100%)
  - Oral Zoliflodacin 3g: 100% (95% CI 92%–100%)
  - IM Ceftriaxone 500mg: 100% (95% CI 84%–100%)
- Micro ITT group:
  - IM Ceftriaxone 500mg was more efficacious than both oral Zoliflodacin 2g and 3g.
  - Oral Zoliflodacin 2g: 96% (95% CI 88%–100%)
  - Oral Zoliflodacin 3g: 96% (95% CI 88%–100%)
  - IM Ceftriaxone 500mg: 100% (95% CI 88%–100%)

Secondary Outcomes:

- Microbiological cure of **pharyngeal gonorrhea** in **per protocol group**
  - IM Ceftriaxone 500 mg is more efficacious in treating pharyngeal gonorrhea vs Zoliflodacin 2g or 3g.
  - Oral Zoliflodacin 2g: 67% (95% CI 22%–96%)
  - Oral Zoliflodacin 3g: 78% (95% CI 40%–97%)
  - IM Ceftriaxone 500mg: 100% (95% CI 40%–100%)
- Microbiological cure **rectal gonorrhea** in **per protocol group**
  - IM Ceftriaxone 500 mg, oral Zoliflodacin 2g, and Zoliflodacin 3g were similarly effective in treating rectal gonorrhea.
  - Oral Zoliflodacin 2 g – 100% (95% CI 40%–100%)
  - Oral Zoliflodacin 3 g – 100% (95% CI 54%–100%)

- IM Ceftriaxone 500 mg – 100% (95% CI 29%–100%)

Safety/Adverse Events

- 44 participants reported adverse events, most commonly gastrointestinal and self-limiting related to treatment therapy.
  - Oral Zoliflodacin 2 g: 12 events
  - Oral Zoliflodacin 3g: 16 events
  - IM Ceftriaxone 500mg: 16 events

LIMITATIONS:

- Female sample size was only 7.2% of initial trial size
- Small sample sizes for rectal and pharyngeal test groups

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Is Sweet Pee The Missing Key?

D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis

Lenger SM, Bradley MS, Thomas DA, Bertolet MH, Lowder JL, Sutcliffe S. D-mannose vs other agents for recurrent urinary tract infection prevention in adult women: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2020; 223(2):265.e1-265.

KEY TAKEAWAY: D-mannose was better than placebo at preventing recurrent urinary tract infection, but not statistically different from prophylactic antibiotics.
STUDY DESIGN: Meta-analysis of 3 studies; N =399Systematic review of 8 studies; N = 653
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Recurrent UTIs (rUTI), 2 UTI episodes in 6 months, or 3 UTI episodes in 12 months, have traditionally been treated with antibiotics, which are associated with potential adverse effects including allergic reactions, nausea, diarrhea, and candidiasis. Up to half of women who report a physician-diagnosed UTI will experience a recurrent UTI within one year. This study investigates the use of D-mannose for rUTI prevention as an alternative to traditionally-used antibiotics.

PATIENTS: Women ≥18 years old with a current acute UTI and a history of recurrent urinary tract infection
INTERVENTION: D-mannose containing products
CONTROL: Either antibiotic prophylactic (Bactrim/Nitrofuantoin) or placebo
OUTCOME: UTI recurrence rate

METHODS (BRIEF DESCRIPTION):
A comprehensive literature review of meta-analyses (1 RCT, 1 randomized cross over trial, and 1 prospective cohort) and systematic reviews (2 RCTs, 1 randomized cross over trial, 4 prospective cohort, and 1 retrospective cohort) for women being treated in an outpatient setting for rUTI that included one study arm using D-mannose for prophylaxis in women ≥18 years.

INTERVENTION (# IN THE GROUP): Oral D-mannose ranging in dose from 420mg – 2g (N=317)
COMPARISON (# IN THE GROUP): Nitrofurantoin 50 mg daily (N=103); Bactrim DS BID (N=30); Placebo (N=275)

FOLLOW UP PERIOD: Greater than 6 months

RESULTS:
- Use of D-mannose was statistically significant in lowering risk of rUTI compared to placebo. (2 trials; N=248; RR 0.23; 95% CI; 0.1-0.44)
- There was no significant difference between D-Mannose and prophylactic antibiotics in lowering the risk of rUTI (2 trials; N=326; RR 0.44; 95% CI; 0.12-1.25).

LIMITATIONS:
This review had a small number of studies, varied dosings and dosing intervals, overall small sample size, and included studies in English language only.

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