GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

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What's in this week's issue?

Week of March 15 - 19, 2021

SPOTLIGHT: Antibiotics only for treatment of appendicitis?

- Initiation of Renal-Replacement Therapy in Acute Kidney Injury
- Reconsider Antibiotic Necessity: Prolonged Use Tied to Increased Risk of Cardiovascular Disease in Older Women
- Do anticoagulants and NSAIDs affect the results of fecal immunochemical tests?
- Stillbirth May Be Associated with Maternal Renal Disease

Antibiotics only for treatment of appendicitis?

A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis

Flum DR, Davidson GH, Monsell, SE, et al. A randomized trial comparing antibiotics with appendectomy for appendicitis. *NEJM*. 2020; 383(20)197–1919.

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KEY TAKEAWAY: Antibiotics alone were non-inferior to appendectomy in the treatment of acute uncomplicated appendicitis based on health status at 30 days. However, 29% required appendectomy by 90 days and experience more complications.

STUDY DESIGN: Non-blinded randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Appendectomy is the most common treatment for appendicitis accounting for 95% of all US patients. Emerging evidence demonstrates treating uncomplicated appendicitis with antibiotics may be an alternative to appendectomy.

PATIENTS: Adults over 18 years of age in US emergency departments with confirmed appendicitis on imaging

INTERVENTION: 10 day course of antibiotics

CONTROL: Appendectomy

OUTCOME: 30-day health status assessment on the European Quality of Life-5 Dimensions (EQ-5Q) questionnaire

Secondary outcomes: self-reported symptom resolution (pain, fever, tenderness), serious adverse events, National Surgical Quality Improvement Program (NSQIP) defined complications, and appendectomy in the antibiotics group

METHODS (BRIEF DESCRIPTION):

- Treatment group received intravenous antibiotics for 24 hours with transition to oral for 10-day total course
- Excluded: septic shock, diffuse peritonitis, recurrent appendicitis, walled-off abscess, free air, evidence of neoplasm, and evidence of severe phlegmon on imaging
- Patients contacted at 24 hours after discharge and surveyed by telephone, mail, or email at 1, 2, and 4 weeks, quarterly for a year then annually to measure for both primary and secondary outcomes.

INTERVENTION (# IN THE GROUP): 776

COMPARISON (# IN THE GROUP): 776

FOLLOW UP PERIOD: 90 days, including 30 and 90 day surveys

RESULTS:

Primary Outcome:

- The mean 30-day EQ-5D score was 0.92 ± 0.13 in the antibiotics group vs 0.91 ± 0.13 in the appendectomy group (mean difference 0.01 points; 95% CI, -0.001 to 0.03). This met the predefined threshold for noninferiority of antibiotics to appendectomy.

Secondary Outcomes:

- In the antibiotic group, 41% of patients underwent surgery by 90 days if appendicolith was present and 25% of patients underwent surgery by 90 days if absent.
- NSQIP defined complications: 8.1 per 100 participants in antibiotic group, vs. 3.5 per 100 participants in surgery group. (Rate ratio 2.2; 95% CI, 1.3-3.9). Higher rate in antibiotic group was attributed to appendicolith-related complications.

LIMITATIONS:

- Trial was unblinded
- No standardization or protocol for pain-control, hospitalization, or antibiotic regimen
- Follow-up only 90 days, significantly limiting monitoring for reoccurrence and complications

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Initiation of Renal-Replacement Therapy in Acute Kidney Injury

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. *N Engl J Med*. 2020; 383(3):240–251.

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KEY TAKEAWAY: In critically ill patients with acute kidney injury (AKI), earlier initiation of renal-replacement therapy (RRT) showed no significant benefit regarding mortality at 90 days and was associated with a higher risk of adverse events when compared to the standard approach.

STUDY DESIGN: Multinational, randomized, open-label, controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients who are critically ill frequently develop AKI and may require subsequent RRT. Optimal timing of initiation of RRT in this setting has yet to be identified in prior studies.

PATIENTS: 18 years or older admitted to an ICU with AKI (serum creatinine ≥1.13 mg/dl in females or ≥1.47 mg/dl in males)

INTERVENTION: Accelerated-strategy RRT

CONTROL: Standard-strategy RRT

OUTCOME: Measured at 90 days

Primary outcome: death from any cause

Secondary outcomes: dependence on RRT; composite of death or dependence on RRT; occurrence of adverse events including death, dependence on RRT, or sustained reduction in kidney function (eGFR <75% baseline value)

METHODS (BRIEF DESCRIPTION):

- Study occurred at 168 hospitals in 15 countries
- Eligible patients were randomly assigned to either an accelerated- or standard-strategy group:
    - Accelerated-strategy: RRT initiated within 12 hours of meeting eligibility criteria
    - Standard-strategy: RRT discouraged unless conventional indications developed, or AKI persisted for more than 72 hours
- Excluded if: emergency indications, previous RTT, advanced chronic kidney disease, and rare causes of AKI

INTERVENTION (# IN THE GROUP): 1465 (1418 received RRT)

COMPARISON (# IN THE GROUP): 1462 (903 received RRT)

FOLLOW UP PERIOD: 90 days after randomization

RESULTS:

Primary Outcome: There was no significant difference in the primary outcome of death at 90 days between the accelerated-strategy and standard-strategy groups (43.9% vs. 43.7%, Relative Risk [RR] 1.0; 95% CI, 0.93–1.09).

Secondary Outcomes:

- RRT dependence at 90 days was significantly greater in the accelerated-strategy group compared to the standard-strategy group (10.4% vs. 6.0%, RR 1.7; 95% CI, 1.2–2.4).
- No significant differences were found between groups in secondary outcomes of the composite of death, RRT dependence, major adverse kidney events at 90 days, death in the ICU at 28 days, or length of hospitalization.

Adverse Events:

- 23% in the accelerated-strategy group vs. 16.5% in the standard-strategy group (RR 1.4; 95% CI, 1.2–1.6)

LIMITATIONS:

- Risk of selection bias in that individual clinicians were permitted to determine patient eligibility
- Risk of treatment bias in relying on clinician discretion to initiate therapy in the standard-strategy group
- Adverse events reported more frequently in accelerated-strategy group due to potential for pre-specified focus on reporting events

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Reconsidering Antibiotic Necessity: Prolonged Use Tied to Increased Risk of Cardiovascular Disease in Older Women

Duration and life-stage of antibiotic use and risk of cardiovascular events in women

Heianza Y, Zheng Y, Ma W, et al. Duration and life-stage of antibiotic use and risk of cardiovascular events in women. *European Heart Journal*. 2019; 40: 3838–3845.

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KEY TAKEAWAY: Longer duration of exposure to antibiotics in middle and older adulthood may be related to increased risk of future cardiovascular disease (CVD) among elderly women.

STUDY DESIGN: 8-year prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Antibiotics are often prescribed inappropriately in outpatient encounters, which raises concern for potential adverse effects. Recent data associate antibiotic use to negative alteration of gut microbiota, prolongation of QT interval, deadly cardiac rhythms, and stimulation of macrophage activity, which can induce inflammation, atherosclerosis, and subsequent CVD.

PATIENTS: Registered nurse females aged >60 years, free of CVD or cancer

INTERVENTION: Antibiotic exposure in young adulthood (age 20–39), middle-adulthood (age 40–59), and late-adulthood (age ≥ 60 years)

CONTROL: Women who did not use antibiotics

OUTCOME: Developing CVD (fatal and non-fatal MI or fatal and non-fatal stroke)

METHODS (BRIEF DESCRIPTION):

- Based on self-administered questionnaire, participants were divided into four groups based on duration of their antibiotic exposure (none, <15 days, 15 days – 2 months, ≥2 months) during 3 life stages: young-adulthood (age 20–39 years), middle-adulthood (age 40–59 years), and late adulthood (age ≥ 60 years).
- More than 2 months of antibiotic use was defined as long term.

INTERVENTION (# IN THE GROUP): 29,609

COMPARISON (# IN THE GROUP): 6,820

FOLLOW UP PERIOD: 7.6 years

RESULTS:

- 1,056 women developed CVD.
- Long term antibiotic use (>2 months) in late or middle adulthood was associated with significantly higher risk of CVD compared to those who did not use antibiotics during these life stages:
  - Late-adulthood (Hazard ratio [HR] 1.3; 95% CI, 1.0–1.7)
  - Middle-adulthood (HR 1.4; 95% CI, 1.0–1.9)
  - Antibiotic use of any duration during young-adulthood was not associated with a significantly increased risk of CVD.

LIMITATIONS:

- The study population did not include males.
- The information on antibiotic use was self-reported and those women who used more antibiotics may have been sicker.
- Information on specific types of antibiotics was not given.
- True causal relationship cannot be determined from this study.

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Do anticoagulants and NSAIDs affect the results of fecal immunochemical tests?

Effect of anticoagulants and NSAIDs on accuracy of faecal immunochemical tests (FITs) in colorectal cancer screening: a systematic review and meta-analysis

Nieuwenburg SA, Vuik FE, Kruip MJ, Kuipers EJ, Spaander MC. Effect of anticoagulants and NSAIDs on accuracy of faecal immunochemical tests (FITs) in colorectal cancer screening: a systematic review and meta-analysis. *Gut.* 2019; 68(5): 866–872.

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KEY TAKEAWAY: Anti-coagulants and NSAIDs do not impact the positive-predictive value (PPV) of fecal immunochemical tests (FITs).

STUDY DESIGN: Meta-analysis of 8 studies including 7 cohort and 1 case-control

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: With FITs being more commonly used for colorectal screening, there is concern oral anticoagulants and NSAIDs may impact the PPV of FITs. Oral anticoagulants could decrease the PPV of FITs by causing bleeding from benign lesions or increase the PPV by increasing the likelihood for cancerous lesions to bleed.

PATIENTS: Patients greater than 40 years of age at average risk of colorectal cancer with positive FIT

INTERVENTION: Use of oral anti-coagulants (OACs) and NSAIDs

CONTROL: Non-users of OACs and NSAIDs

OUTCOME: PPV for advanced neoplasia and colorectal cancer, FIT positivity rate, sensitivity and specificity of FIT tests

METHODS (BRIEF DESCRIPTION): Comprehensive search for studies which include the following:

- FIT results of participants at average risk for colorectal cancer
- Users and non-users of OACs or NSAIDs
- Follow-up colonoscopy if FIT was positive

INTERVENTION (# IN THE GROUP): 633

COMPARISON (# IN THE GROUP): 2,930

FOLLOW UP PERIOD: Trial end-point at time of follow-up colonoscopy after positive FIT test

RESULTS: Use of OACs had no significant impact on the PPV of FIT tests for advanced neoplasia (adenomas >10 mm, villous histology, or high-grade dysplasia) or colorectal cancer (malignant cells observed beyond the muscularis mucosa) (7 trials; N=3,563; RR 1; 95% CI, 0.85–1.17; *P*=.75).

- Non-users: PPV=40% (95% CI, 39%–42%)
- Users: PPV=37.6% (95% CI, 34%–41%)

Use of NSAIDs/aspirin had no significant impact on the PPV of FIT test for adenoma and colorectal cancer (6 trials; N=2,901; RR 1.1; 95% CI, 0.87–1.17; *P*=.59)

- Non-users: PPV=39% (95% CI, 38%–41%)
- Users: PPV=38% (95% CI, 34%–42%)

LIMITATIONS:

- Variable hemoglobin cut-off points to define a positive test which could have influence the PPV of an adenoma or colorectal cancer from the FIT test.
- Length of NSAID/OAC use not evaluated for impact on outcome.

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Stillbirth May Be Associated with Maternal Renal Disease

Stillbirth is associated with increased risk of long-term maternal renal disease: a nationwide cohort study
Barrett PM, McCarthy FP, Evans M, et al. Stillbirth is associated with increased risk of long-term maternal renal disease: a nationwide cohort study.
Am J Obstet Gynecol 2020; 223:427.e1–14.
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KEY TAKEAWAY: Women who have experienced stillbirth may be at an increased risk of developing chronic kidney disease.
STUDY DESIGN: Retrospective population-based cohort study
LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: There are many factors that lead to the development of CKD and ESRD that are routinely screened. However, this study attempts to make a connection between stillbirth and maternal renal disease while controlling for known risk factors.
PATIENTS: Pregnant women
INTERVENTION: Women who experienced a stillbirth
CONTROL: Women who experienced a live birth
OUTCOME: Occurrence of chronic kidney disease or end-stage renal disease

METHODS (BRIEF DESCRIPTION): Population based study using data from Swedish national medical registries.

- Patient population: Cohort of pregnancies registered in Sweden
- Exclusions were made based on known risk factors for CKD, including known renal disease, diabetes, hypertension, cardiovascular disease, lupus, systemic sclerosis, coagulopathy, and hemoglobinopathy.
- Data was retrospectively analyzed using survival analysis.
- The outcome of CKD or ESRD were defined by recorded diagnoses in the national registries.

INTERVENTION (# IN THE GROUP): 13,032 (0.7%)
COMPARISON (# IN THE GROUP): 1,928,025 (99.3%)

FOLLOW UP PERIOD: January 1, 1973 – December 31, 2012

RESULTS:

- The cohort consisted of a total of 1,942,057 women followed over 42,313,758 person-years.
- The overall incidence of stillbirth was 3.5/1,000 deliveries
- 18,017 women developed CKD and 1,283 women developed ESRD
- There was an increased risk of CKD and ESRD in women who experienced stillbirth versus live births
  - CKD: HR 1.6 (95% CI 1.4–1.8)
  - ESRD: HR 3.5 (95% CI 2.5–5.0)

LIMITATIONS:

- Inability to measure more than one stillbirth
- Lack of knowledge of the underlying causes of stillbirth
- The definition of stillbirth changed in the middle of the study timeframe
- Possible missed cases of CKD or ESRD due to charting or diagnosis errors
- Missing data on BMI, smoking, and gestational diabetes

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