GEMs
GOOD EVIDENCE MATTERS

# GEMs of the Week

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## What's in this week's issue?

### Week of January 24 - 28, 2022

### SPOTLIGHT: Doxycycline Instead of Azithromycin for Rectal Chlamydia Infection?

- Is Extended-Release Metformin Superior to Immediate-Release Metformin?
- Ibuprofen and Hypertensive Disorders of Pregnancy: Can You Use It?

# Doxycycline Instead of Azithromycin for Rectal Chlamydia Infection?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

**Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis***

Lau A, Kong FYS, Fairley CK, et al. Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*. *N Engl J Med*. 2021 Jun 24; 384(25):2418–2427.



KEY TAKEAWAY: Treatment with Doxycycline 100 mg twice daily for seven days is statistically superior to Azithromycin 1 g as a one-time dose for asymptomatic rectal chlamydia infection in men who have sex with men.

STUDY DESIGN: Double-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Treatment guidelines for asymptomatic rectal chlamydia in males who have sex with males previously recommended either Doxycycline or Azithromycin. Recent observational data indicate that Doxycycline is likely the more effective treatment, however there is a lack of randomized control trials evaluating this finding in current literature.

PATIENTS: Men who have sex with men diagnosed with asymptomatic *Chlamydia trachomatis* on routine screening

INTERVENTION: Doxycycline 100 mg twice daily for seven days

CONTROL: Azithromycin 1 g once

OUTCOME: Cure of *Chlamydia trachomatis*
Secondary Outcome: Adverse events

METHODS (BRIEF DESCRIPTION):

- Patients: Males from five sexual health clinics in Australia positive for rectal chlamydia via NAAT testing who are at least 16 years old, had sexual contact with another male within the past year, and without evidence of coinfection, lymphogranuloma venereum, recent antibiotic use, or contraindication to trail drugs.
- Treatment: Doxycycline 100 mg twice daily for seven days or Azithromycin 1 g once
- Trial: Double-blind randomized trial with adverse events and adherence reported via daily text message survey for the seven days of treatment.
- Outcomes: Test of cure at four weeks via NAAT, genotyping, and genomic sequencing

INTERVENTION (# IN THE GROUP): 314

COMPARISON (# IN THE GROUP): 311

FOLLOW UP PERIOD: Four weeks

RESULTS:

Primary Outcome –

- Those treated with Doxycycline were more likely to see cure of infection compared to Azithromycin (97 % vs 76%; adjusted risk difference 20%; 95% CI, 15–25).

Secondary Outcome –

- Less participants in the Doxycycline group had adverse events compared to the Azithromycin group (34% vs 45%; risk difference –11%; 95% CI, –20 to –3.2).
  - Diarrhea occurred more commonly in the Azithromycin group compared to the Doxycycline group (40% vs 26%; risk difference –14; 95% CI, –21 to –7.8).

LIMITATIONS:

- Secondary outcomes of chlamydia reinfection and treatment failure were not monitored due to inability to complete mRNA testing during COVID-19 pandemic.
- Study limited to males who were asymptomatic without coinfections.
- HIV viral loads were not monitored.

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# Is Extended-Release Metformin Superior to Immediate-Release Metformin?

**Metformin Extended-Release versus Metformin Immediate-Release for Adults with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**

Abrilla AA, Pajes ANNI, Jimeno CA. Metformin extended-release versus metformin immediate-release for adults with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract.* 2021; 178:108824. doi:10.1016/j.diabres.2021.108824



KEY TAKEAWAY: Immediate-release metformin (MIR) slightly reduces mean HbA1c 0.09% more than extended-release metformin (MXR). Compared to MIR, MXR resulted in fewer episodes of dyspepsia, but there was no difference in diarrhea, nausea, vomiting, or abdominal pain.

STUDY DESIGN: Systematic review and meta-analysis of 9 RCTs (N=2,057)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Type 2 diabetes mellitus (T2DM) is a chronic disease affecting millions worldwide. Metformin is the preferred first-line medical treatment, but patients often have trouble tolerating MIR secondary to gastrointestinal side effects. MXR is marketed as a more tolerable and equipotent alternative to MIR; however, the efficacy and tolerability between MXR and MIR have not been compared.

PATIENTS: Adults with type 2 diabetes mellitus (T2DM)

INTERVENTION: MXR

CONTROL: Conventional MIR

OUTCOME: Mean HbA1c change from baseline (efficacy) and incidence of gastrointestinal (GI) symptoms (tolerability – abdominal discomfort or pain, diarrhea, dyspepsia, nausea, and vomiting)

METHODS (BRIEF DESCRIPTION):

- Database search for randomized controlled trials comparing equal dosing of MXR and MIR for at least 12 weeks in adults with T2DM.
- Databases included PubMed, Cochrane Library, ClinicalTrials.gov and others.
- Out of 814 studies, nine studies met eligibility criteria (equal doses of drugs, 18 years of age or older, no history of end organ damage, and >12 weeks of treatment).
- Evidence quality was assessed using GRADE approach.

INTERVENTION (# IN THE GROUP): 1,120

COMPARISON (# IN THE GROUP): 937

FOLLOW UP PERIOD: Median of 16 weeks, frequency varied

RESULTS:

- The MIR group experienced statistically significant more improvement in mean HbA1c compared to the MXR group (9 trials, N=2,057; mean difference 0.09%; 95% CI, 0.01% to 0.17% ).
- The MXR group experienced less incidences of dyspepsia than the MIR group (4 trials, N=1,265; RR 0.58; 95% CI, 0.34–0.98).
- No difference in other abdominal discomfort, pain, diarrhea, nausea, and vomiting.

LIMITATIONS:

- Some major databases were not included in the search.
- Short follow up (median follow up of 16 weeks).
- Only evaluated surrogate marker of HbA1c and did not assess complications of diabetes.
- A composite endpoint of GI adverse events would likely have been completely negative, but the studies divided GI adverse events into different groups, some of which are clinically similar (e.g., “abdominal discomfort or pain” and “dyspepsia”).
- Mainly Caucasian study population; may not be able to extrapolate to other populations.
- Different doses of MIR vs MXR in some of the studies.
- Uncertain bias: funding sources for included studies unknown.
- Lack of subject-level data; only had aggregate data from studies.

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# Ibuprofen and Hypertensive Disorders of Pregnancy: Can You Use It?

**Ibuprofen and Postpartum Blood Pressure in Women with Hypertensive Disorders of Pregnancy**

Penfield CA, McNulty JA, Oakes MC, Nageotte MP. Ibuprofen and postpartum blood pressure in women with hypertensive disorders of pregnancy. *Obstetrics & Gynecology*. 2019; 134(6):1219–1226. doi:10.1097/aog.0000000000003553



KEY TAKEAWAY: Using Ibuprofen in the postpartum period does not affect average blood pressure, pain control, overall satisfaction, length of hospital stay, or diuresis in women with a hypertensive disorder of pregnancy.

STUDY DESIGN: Double blind, randomized controlled clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: NSAIDs are common and highly effective medications used to treat pain, especially after cesarean delivery and vaginal birth. Use of these medications helps to decrease the use of opioids for pain control. However, it has been shown that NSAIDs raise the blood pressure of adults with a diagnosis of chronic hypertension. This study looks to see if NSAIDs also raise the blood pressure of women with hypertensive disorders or pregnancy, and therefore if they should be used with more caution in this group of patients.

PATIENTS: Adult women who have delivered at >24 weeks gestation with a hypertensive disorder of pregnancy in the post-partum period up to 10 days after delivery

INTERVENTION: Ibuprofen 600 mg orally every six hours

CONTROL: Tylenol 650 mg orally every six hours

OUTCOME: Mean arterial pressure

Secondary Outcomes: Additional needed pain medication, length of stay, post-partum diuresis, patient satisfaction

METHODS (BRIEF DESCRIPTION):

- Women who were >18 years old and delivered at >24 weeks with a hypertensive disorder of pregnancy before delivery were included in this study.
- Women with severe disease, chronic hypertension, post-partum hemorrhage, or contraindications to either study drug were excluded.
- After deliver, study subjects were randomly assigned to control (Tylenol 650 mg every 6 hours) or intervention group (Ibuprofen 600 mg every 6 hours) and dispensed blindly to patients with the pharmacy staff keeping track of which medication was dispensed to which patient.
- Hydrocodone 5 or 10 mg / Acetaminophen 325 mg every six hours was available for moderate to severe pain control and oxycodone or morphine was provided for beyond severe pain.
- Blood pressure measurements were taken at least every four hours.
- Pain scores were taken every 12 hours using standardized scales.
- A standardized satisfaction survey was given to patients before discharge to assess overall satisfaction.
- An outpatient follow-up appointment was scheduled within a week to ten days of discharge to follow up on blood pressure.

INTERVENTION (# IN THE GROUP): 31

COMPARISON (# IN THE GROUP): 30

FOLLOW UP PERIOD: Immediately post-partum through up to 10 days after discharge

RESULTS:

Primary Outcome –

- There was no difference in Mean Arterial Blood Pressure (MAP) between the Ibuprofen and Tylenol groups (93 mmHg vs 93 mmHg, *P*=.9).

Secondary Outcomes –

- There was no difference in need for breakthrough pain medications in the Ibuprofen and Tylenol groups (24% vs 30%, *P*=0.6).
- The Ibuprofen and Tylenol groups did not have different lengths of stay (48 hours vs 43 hours, *P*=.06) or different rate of post-partum diuresis (61% vs 77%, *P*=.2).
- Both the Ibuprofen and Tylenol groups reported they were “always” satisfied with the pain medications they received (73% vs 76%, *P*=.8).

LIMITATIONS:

- Small study that was under-powered.
- Low number of patients who returned for outpatient follow up of blood pressure after discharge from the hospital.
- Limited information on outcomes in women who underwent cesarean delivery since a small number of subjects delivered in this way.

- Limited information on outcomes in women with severe hypertension since these women were excluded from the study.

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