

NSAIDS: Is there a catch?



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Prudence suggests antibiotics should remain first-line even for uncomplicated UTIs

CLINICAL SCENARIO

Lorraine, a 21-year-old university student, presented with typical symptoms of uncomplicated cystitis.

I recalled an online discussion about the surprising (to me) concept that non-steroidal anti-inflammatory drugs (NSAIDs) could be used rather than antibiotics. What is the evidence for this therapy?

CLINICAL QUESTION

What is the effect of oral NSAIDs on symptoms and cure of uncomplicated urinary tract infections (UTIs) compared with antibiotics?

Step 1: The Cochrane Library

There are several systematic reviews of antibiotics as treatment for UTIs,¹ but none on the use of NSAIDs.

Step 2: TripDatabase

I conducted a search using the TripDatabase PICO search tool (Participant: "UTI", Intervention: "NSAID", Comparator: "antibiotics", Outcomes: blank).

The first and only relevant result was an evidence synopsis in BestBETs that found only one small pilot study published in 2010.²

Step 3: PUBMED

Next I conducted a search in PubMed to identify any newer and larger studies. I identified one randomised trial by the authors of the 2010 study, published in the

BMJ in 2015. Let's look at this study by Gágyor and colleagues in more detail.³

CRITICAL APPRAISAL

I will use the randomised controlled trial appraisal sheet from the Centre for Evidence Based Medicine.⁴

PICO

Participants: who was studied?

Women aged between 18 and 65 attending general practice clinics in northern Germany with symptoms suggestive of a UTI (dysuria ± frequency/urgency ± lower abdominal pain) were approached for inclusion in the study.

Exclusions included: signs of upper UTI (fever, loin tenderness), pregnancy, renal disease, UTI within the last two weeks, urinary catheterisation, current NSAID use, and current antibiotic use.

Out of 1184 assessed for eligibility, 494 were randomised and 446 completed the study. The mean age of the participants was 37. Almost all the participants had dysuria and frequency/urgency as symptoms, and just more than half had had symptoms for up to two days. About 75% had a positive urine culture, with *E. coli* the most common isolate.

Intervention: what was the exposure?

3 × ibuprofen 400mg daily, for three days, with 1 × sachet placebo granules.

Comparator: what was the control/alternative?

1 × fosfomycin 3g sachet, with 3 × placebo tablets for three days.

Women in both groups were advised to consult their GP again if symptoms persisted or worsened, and antibiotic treatment could be initiated at the GP's discretion.

Outcomes: what was measured?

Primary outcome:

- Total number of courses of antibiotics on days 0-28;
- Burden of symptoms on days 0-7 (measured as area under the curve of the sums of daily symptom scores).

INTERNAL VALIDITY: ARE THE TRIAL RESULTS VALID?

Randomised patient assignment?

Yes. The randomisation process was computer generated.

INTENTION TO TREAT ANALYSIS

In randomised trials, noncompliance (to the study protocol) and missing outcomes (eg, participant drop outs) can lead to exaggerated estimates of treatment effects. One way to address this is for the data to be analysed according to the "intention-to-treat" principle – to include all participants who were randomised in the study.⁵

Stat Facts

Groups similar at the start?

Yes. The groups were largely similar (see Table 1, p. 4).³

Groups treated equally apart from assigned treatment?

Yes. The protocol was well designed.

All patients accounted for?

Yes. There were a small number (< 10%) of participants who did not complete the study, and the analysis was conducted on an intention-to-treat basis (see Stat Facts).

Measures objective? Or patients and clinicians kept blinded?

Yes/Probably. Self-reported symptom measures of UTI are somewhat subjective,



but there is no evidence that the participants or clinicians not kept blinded.

What were the results?

Primary outcomes:

- The ibuprofen group used less antibiotics than the fosfomycin group:
 - incidence rate reduction: 66.5% (95% CI 58.8% to 74.4%, $p < 0.001$);
- The ibuprofen as compared to the fosfomycin group experienced more symptoms:
 - area under the curve ratio: 140.5% (95% CI 125.4% to 157.3%).

Other outcomes:

- All secondary outcomes related to symptoms favoured the fosfomycin group;

- There were more cases of pyelonephritis in the ibuprofen group (4 vs 1) though this was not statistically significant

DISCUSSION AND CONCLUSION

The earlier pilot study suggested ibuprofen might be non-inferior to antibiotics for uncomplicated UTIs² – an interesting finding that challenges the assumption that antibiotics are necessary, and perhaps a reminder that in the pre-antibiotic era, UTIs were ultimately self-limiting.

This well-conducted and better-powered study demonstrates that most women who received ibuprofen had resolution of their UTI.

However, this was at the cost of worse symptoms for a longer duration. There is, furthermore, a suggestion that there is an increased risk for severe outcomes, such as pyelonephritis.

If we take the position that the patient-meaningful outcome is symptom burden and cure, rather than necessarily antibiotic avoidance, then ibuprofen is most likely inferior to antibiotics.

NSAIDs should not be recommended as a first line treatment for uncomplicated UTIs, though they might have a role in individuals who refuse antibiotic therapy.

Lorraine received an empirical course of trimethoprim and recovered without issue. ■

References at medobs.com.au