

# Efficacy and safety of different therapies of non-steroidal anti-inflammatory drugs against antibiotic monotherapy in the treatment of uncomplicated lower urinary tract infection: A systematic review

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## Abstract

This systematic review aimed to evaluate the efficacy of different non-steroidal anti-inflammatory drugs therapy (monotherapy or combined with antibiotics) against antibiotics monotherapy to understand the possible role of non-steroidal anti-inflammatory drugs in managing uncomplicated urinary tract infections and reduce overall antibiotic prescription. We searched four databases: PubMed, EMBASE, Scopus, and Cochrane CENTRAL. We included randomized controlled trials, which had included non-pregnant females above 18 years, published from 2010 to 2020 AD in the English language. We assessed risk of bias (ROB) using COCHRANE ROB version 2.0. We synthesized the conclusion from low ROB studies. Among five included studies, four studies compared non-steroidal anti-inflammatory drugs monotherapy against antibiotics monotherapy, and one study compared non-steroidal anti-inflammatory drugs + antibiotic therapy against antibiotic monotherapy. All studies with low ROB showed significantly higher events of symptom resolution by day 7 with antibiotic monotherapy compared to non-steroidal anti-inflammatory drugs monotherapy. Overall, adverse events were not significantly different in two of three low risk of bias studies; however, one study reported significantly higher adverse effects with non-steroidal anti-inflammatory drugs. Non-urinary tract infection–related adverse events were more common than urinary tract infections–related adverse events in both non-steroidal anti-inflammatory drugs and antibiotic groups. Urinary tract infection–related adverse events were higher in the non-steroidal anti-inflammatory drugs group compared to antibiotics. For every 20–60 participants treated, one would develop pyelonephritis additionally in non-steroidal anti-inflammatory drugs compared to antibiotics. Antibiotics were superior to non-steroidal anti-inflammatory drugs for treating uncomplicated lower urinary tract infections. However, further studies regarding the characteristics of patients likely to develop pyelonephritis on non-steroidal anti-inflammatory drugs monotherapy, and the effectiveness and safety of a combination of non-steroidal anti-inflammatory drugs and antibiotics therapy are essential to reduce the burden of antibiotics and their associated problems.

## Keywords

Antibiotics, cystitis, non-steroidal anti-inflammatory drugs, systematic review, urinary tract infection

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## Introduction

Urinary tract infection (UTI) is a collective term that indicates the infection of any part of the urinary tract such as the urethra, bladder, ureters, and kidney.<sup>1</sup> More than 150 million people are infected by UTIs every year worldwide.<sup>2</sup> It is more prevalent in women than men with a ratio of 8:1.<sup>3</sup> UTI accounts for nearly one-fourth of all infections in women.<sup>2</sup> Similarly, it is estimated that more than half of the women develop UTI at least once in their life.<sup>4</sup>

UTIs are clinically categorized into two types: complicated and uncomplicated. Complicated UTIs involve factors associated with urinary tract obstructions or abnormalities, renal failure, neurologically linked urinary retention, renal transplantation, pregnancy, immunosuppression, male sex, and foreign body presence (catheter, indwelling, calculi, etc.).<sup>5</sup> Uncomplicated infections affect those women who are healthy and have no urinary and neurological abnormalities.<sup>6</sup>

The prevalence of uncomplicated UTI is estimated to be 11% in female.<sup>7</sup> It commonly occurs in sexually active ages, mostly between 18 to 39 years.<sup>7</sup> The most common cause of uncomplicated UTI is a gram-negative *Escherichia coli* (*E. coli*) bacteria, which is estimated to be present in 85% of all cases; while rest of infections are mostly supposed to be caused by *Staphylococcus saprophyticus*, *Klebsiella*, and *Proteus* species.<sup>8</sup> Therefore, antimicrobials are commonly used for the management of uncomplicated UTI. Infectious Diseases Society of America (IDSA) has recommended antimicrobials such as a single dose of fosfomycin, 3 days of trimethoprim–sulfamethoxazole (TMP–SMX) or nitrofurantoin, 5 days of pivmecillinam for its management.<sup>8</sup>

However, an uncomplicated UTI is often self-limiting. Studies have shown that 25%–42% of untreated women became free from symptoms in 1 week, and 31%–41% had no growth of uropathogenic organisms within a week.<sup>9–11</sup> Therapeutic guidelines of Australia reported that half of the non-pregnant women aged less than 65 years were free from symptoms within a week without any antibiotics.<sup>12</sup> The median time to resolve the infection has been reported to be 3 days with antibiotics and 5 days without antibiotics therapy.<sup>13</sup> Furthermore, only about 0.4% to 2.6% of untreated uncomplicated UTIs have been reported to develop acute uncomplicated pyelonephritis.<sup>14</sup> Therefore, the main objective is to relieve the symptoms such as dysuria, urgency, or suprapubic pain.

The increasing use of antibiotics has been reported to cause an increase in antimicrobial resistance and adverse effects associated with it.<sup>15,16</sup> Thus, antibiotics are often advised for limited use in self-limiting bacterial diseases such as acute otitis media, respiratory tract infections, sinusitis, and traveler's diarrhea, although the symptoms may be prolonged with the symptomatic treatment.<sup>17–22</sup> A similar approach of antibiotic-sparing strategies such as symptomatic treatment can be considered for uncomplicated UTIs; for an instance, the use of non-steroidal

anti-inflammatory drugs (NSAIDs) for the symptomatic relief of uncomplicated UTIs.

A previous systematic review comparing NSAIDs monotherapy against antibiotics monotherapy showed that antibiotics were superior to NSAIDs in terms of symptom resolution by day 3 and prevention of pyelonephritis.<sup>23</sup> However, no systematic review evaluating the differences between different NSAID therapies (monotherapy or combined with antibiotics) against antibiotics monotherapy in terms of symptom resolution by day 7 (the time period when almost half of the uncomplicated lower UTIs self-resolve)<sup>12</sup> had been done till the date of the start of this review. Furthermore, emerging evidence shows that NSAIDs increase the therapeutic activity of antibiotics against bacteria causing UTI.<sup>24</sup> Therefore, the aim of this systematic review was to evaluate the efficacy of different NSAIDs therapies (monotherapy or combined with antibiotics) against antibiotics monotherapy (the usual practice) to understand the possible role of NSAIDs in managing uncomplicated UTIs and reducing overall antibiotic prescription.

## Methods

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (see supplementary file).<sup>25</sup> The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020193989) on 21 August 2020.

### Eligibility criteria

We included randomized control trials (RCTs) comparing NSAIDs monotherapy or NSAIDs with antibiotics against antibiotic monotherapy, and fulfilling the following criteria: (1) study recruited adult non-pregnant females over 18 years of age and (2) reported at least one of our primary or additional outcome.

Studies were excluded if (1) population included pregnant women, men, or if they had flank pain, fever, or features of upper UTI; (2) full texts could not be retrieved; (3) case reports or series; and (4) not available in the English language.

### Search strategy and data sources

Two authors (SG and RS) conducted a systematic literature search. The search was conducted in PubMed, EMBASE, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL). We used the following search terms: “lower urinary tract infection,” “UTI,” “cystitis,” “urethritis,” “Uncomplicated,” “NSAIDs,” “ibuprofen,” “flurbiprofen,” “diclofenac,” “aceclofenac,” “nimesulide,” “antibiotic,” “fosfomycin,” “pivmecillinam,” “nitrofurantoin,” “bactrim,” “cotrimoxazole,” “mecillinam,” “fluoroquinolones,”

“ciprofloxacin,” “norfloxacin.” The search results were limited to human studies, English language, and from 2010 to 2020 AD. The search strategy for each database is available in supplementary file.

### Study selection

Results from the search strategy were collected in EndNoteX7 and duplicates were removed. Two authors (MMA and RS) independently screened the titles and abstract based on eligibility criteria. Then, the two authors (MKC and VC) independently performed the full-text screening. Any differences between the screening authors were resolved by a third author (BRA). Details of excluded studies from full-text screening are given in supplementary file.

### Data collection and extraction

An excel spreadsheet including study year, design, duration of the study, inclusion criteria, population information (gender and age), urine analysis, results of included population, details regarding interventions and control, and primary and secondary outcomes were used for data extraction. Two authors independently extracted all the data (YAE and MMA) except primary and secondary outcomes of the study, which were extracted by SG and verified by RS. The data for intention to treat analysis were used. The corresponding authors were contacted via email in case of incomplete or unclear data.

### Quality assessment

Quality assessment was evaluated by two authors (SG and MMA) using the COCHRANE risk of bias (ROB) tool for randomized trials (ROB-2) version 2.0.<sup>26</sup> Any differences that arose during the quality assessment were first discussed among the two authors (SG and MMA), and if not resolved, a third author (MRG) broke the tie.

### Outcome measures

We chose the following outcomes.

#### Primary outcome

1. Resolution of clinical symptoms by day 7. The measure of effect was relative risk (RR) ratio.
2. Adverse events including complications over a month follow-up. The measure of effect was RR ratio.

#### Secondary outcomes

1. Weighted mean difference in total courses of antibiotics within a month.
2. Mean or median duration (MD) from therapy till complete resolution of symptoms.

### Statistical analysis

A meta-analysis was not done owing to the concerns regarding different groups of antibiotics used across the included studies, different ROB, and different scales for composite score of symptoms. The antimicrobial resistance varies according to the types of antibiotics. For instance, a meta-analysis reported the highest antimicrobial resistance to tetracyclines (69.1%) followed by sulphonamides (59.3%), quinolones (49.4%), and beta-lactams (36.9%).<sup>27</sup> Therefore, we have summarized the evidence of the included studies rather than calculating a composite score. The finding of studies having a low ROB from our quality assessment was considered for a summary. Risk ratio for complete resolution of symptoms by day 7 and adverse events by day 30 were calculated. Mean difference was used to compare NSAIDs and antibiotics (ABs) groups in terms of total antibiotics course required within a month. A forest plot was used to show the distribution of effect measures of different outcomes across the included studies using Stata version 14.2.

## Results

### Description of search result and study details

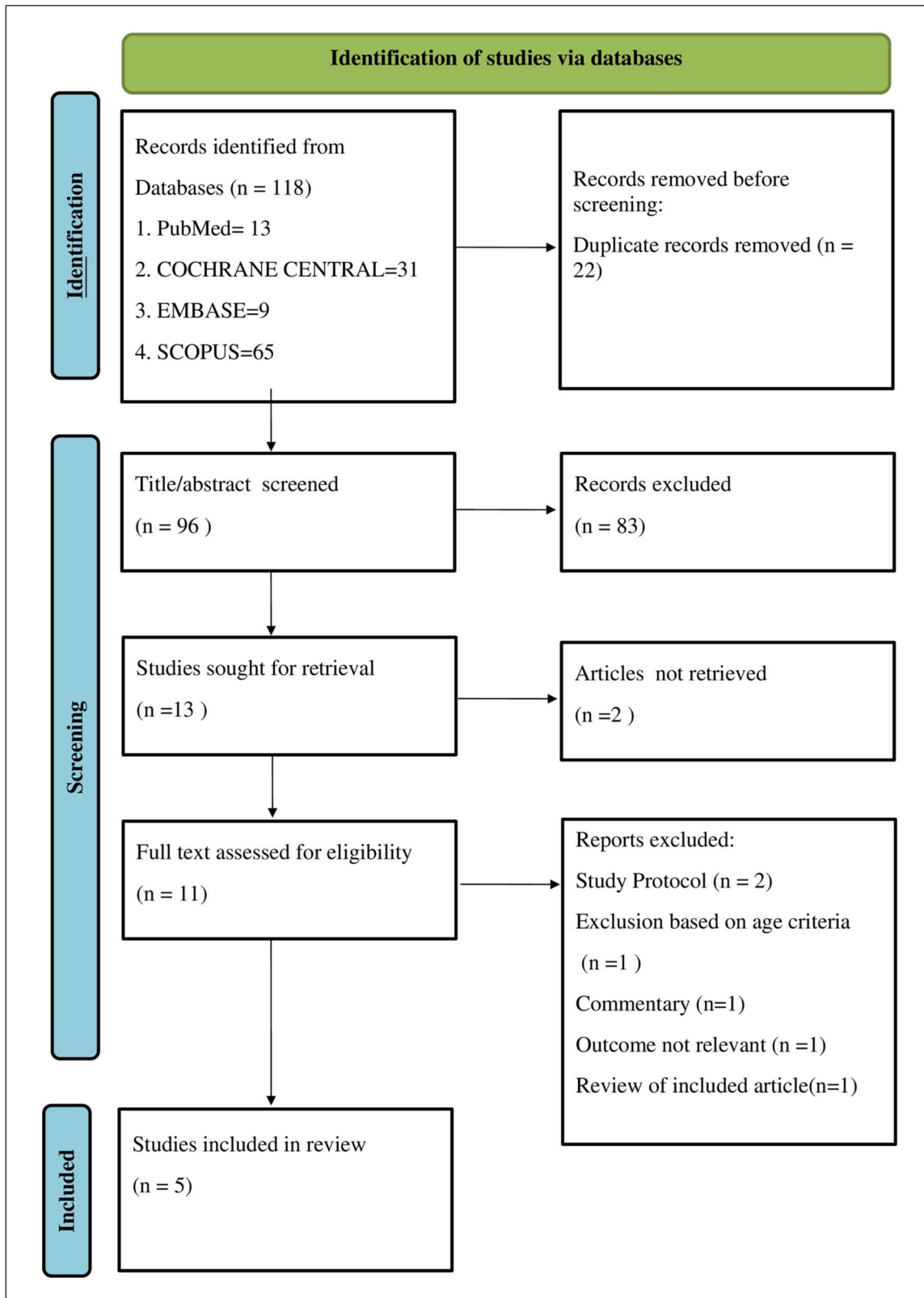
The systematic search resulted in 118 studies; among them, 22 were removed as duplicates. A total of 96 studies were taken for initial title/abstract screening. A total of 13 articles were eligible for the full-text assessment. Two articles could not be retrieved and six articles were excluded for the following reasons: study protocol (n=2), age below 18 years (n=1), commentary (n=1), review (n=1), and study with no relevant outcome (n=1). Finally, five studies were selected for the systematic review. The PRISMA flowchart is shown in Figure 1.

### Risk of Bias

Among five included studies, three studies<sup>28-30</sup> were found to have a low ROB, one study<sup>31</sup> was found to have a high ROB, and one study<sup>32</sup> had some concern for ROB (Table 1).

### Characteristics of included studies, participants, and intervention

Four included studies were double-blinded randomized trials<sup>28-30,32</sup> while one study was an open-labeled randomized trial.<sup>31</sup> Among five studies, two were pilot studies conducted among only 79 participants (40 NSAIDs and 39 antibiotics),<sup>32</sup> and 55 participants (28 combined NSAIDs and antibiotics therapy, and 27 antibiotics monotherapy).<sup>31</sup> In terms of continent, four studies<sup>28-30,32</sup> were conducted among the participants of European countries and one study<sup>31</sup> in Asia. Bleidorn et al.<sup>32</sup> and Gágyor et al.<sup>28</sup> were conducted in Germany by the support of the German Ministry. Vik et al.<sup>29</sup>



**Figure 1.** PRISMA flowchart of included studies.

**Table 1.** Risk of bias assessment of included studies.

Study name	Study design	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Bleidorn et al. <sup>32</sup>	Double-blind, randomized controlled trial	+	+	+	+	?	?
Vik et al. <sup>29</sup>	Double-blind, randomized, parallel group, multicentre non-inferiority trial	+	+	+	+	+	+
Gágyor et al. <sup>28</sup>	Double-blind, randomized controlled drug trial	+	+	+	+	+	+
Kronenberg et al. <sup>30</sup>	Double-blinded randomized controlled trial	+	+	+	+	+	+
Ko K et al. <sup>31</sup>	Prospective, open-labeled and randomized control pilot study	+	?	+	-	?	-

and Kronenberg et al.<sup>30</sup> were funded by the organization of their respective countries. However, Ko K et al.<sup>31</sup> did not declare the funding resources. All five studies were conducted between 2007 and 2016 AD (Table 2).

All five studies were carried out in adult women aged more than 18 years.<sup>28–32</sup> The maximum upper age limit was 60, 65, and 70 years in three studies,<sup>28–30</sup> whereas two studies did not mention the upper age limit.<sup>31,32</sup> Dysuria and urinary frequency were the common inclusion criteria for sample selection in all five studies (Table 2).<sup>28–32</sup>

In total, 1264 patients were included in the study. Among them, 615 patients belonged to the NSAIDs group, 27 belonged to NSAIDs + ABs (antibiotics) group, and 622 belonged to the ABs monotherapy group. Ibuprofen was used as NSAIDs in three studies,<sup>28–32</sup> and diclofenac and aceclofenac in two other studies.<sup>30,31</sup> On the contrary, five different ABs were used in five different studies.<sup>28–32</sup> Unlike other studies, Kronenberg et al.<sup>30</sup> used fosfomycin as a rescue antibiotic for patients that were not cured by NSAIDs. In all the studies,<sup>28–32</sup> for intervention and comparator groups, the medications were administered for 3 days (Table 2).

### Outcome measures of included studies

The outcomes of each study can be seen in Table 3.

Regarding our primary outcomes, four studies<sup>28–30,32</sup> clearly mentioned the scale used for symptom assessment. Vik et al.,<sup>29</sup> Bleidorn et al.,<sup>32</sup> and Kronenberg et al.<sup>30</sup> used a Likert-type scale. Bleidorn et al.<sup>32</sup> and Gágyor et al.<sup>28</sup> used daily symptom sum scores including dysuria, frequency/urgency of micturition, and low abdominal pain, each on a five-point scale (0 as no symptoms at all while 4 as frequent symptoms). The study by Vik et al.<sup>29</sup> used a daily symptom

sum score, where each of the symptoms (dysuria, urinary urgency, and urinary frequency) were scored on a scale from 0 to 6; 0 being normal and 6 being the worst. Similarly, Kronenberg et al.<sup>30</sup> also used UTI symptoms (dysuria, frequency, urgency, abdominal pain while micturating, loin, or back pain/tenderness), each scored from 0 to 6, with a maximum score of 30. Complete resolution of symptoms was defined as a composite score of 0. However, Ko K et al.<sup>31</sup> used a numerical pain score method as pain reduction was the major outcome of their study. Symptom resolution in this study was defined as a pain scale below one point. For the adverse effect, Kronenberg et al.<sup>30</sup> and Bleidorn et al.<sup>32</sup> mentioned that they used a telephone inquiry and verbally asked about the recording of adverse events that participants experienced for up to a month. Similarly, Vik et al.<sup>29</sup> and Gágyor et al.<sup>28</sup> mentioned that the participants were followed up via a telephone call by a research nurse/doctor. The quantitative data for our primary and secondary outcomes are given in Table 4.

For our secondary outcome, only one study (Gágyor et al.<sup>28</sup>) reported total antibiotics required in days 0–28 for UTIs and other conditions such as acute bronchitis, otitis, and so on.

### NSAIDs monotherapy versus antibiotics monotherapy

**Clinical resolution of symptoms by day 7.** Figure 2 presents the clinical resolution of symptoms by day 7 in four included studies. Here, we have summarized the evidence from the studies with a low ROB.

Kronenberg et al.<sup>30</sup> reported higher events of symptom resolution with norfloxacin as compared to diclofenac (logRR = -0.15, 95% confidence interval (CI): -0.26 to

**Table 2.** Characteristics of included studies, participants, and interventions.

Study	Duration of study	Recruitment and study setting	Inclusion criteria	Gender, age (years)	Intervention	Comparator
Low risk of bias						
Gágyor et al. <sup>28</sup>	February 2012 to February 2014	494 patients from 42 general practices in northern Germany	Typical symptoms such as dysuria and/or frequency/urgency of micturition, with or without lower abdominal pain	Females, 18–65	Ibuprofen 400 mg TID for 3 days to 248 patients	Fosfomycin 3 gm OD for 3 days to 246 patients
Vik et al. <sup>29</sup>	11 April 2013 to 22 April 2016	383 patients from the accident and emergency outpatient clinics (AEOCs) in Oslo and Bergen, Norway, and 14 general practices of Denmark and Sweden (7 from each)	Dysuria combined with either increased urinary frequency or urinary urgency or both, with or without visible hematuria	Females, 18–60	Ibuprofen 600 mg TID for 3 days to 194 patients	Pivmecillinam 200 mg TID for 3 days to 189 patients
Kronenberg et al. <sup>30</sup>	7 February 2012 to 3 December 2014	253 women from 17 general practices of Switzerland	One or more symptoms or signs of dysuria, frequency, macrohaematuria, cloudy or smelly urine, or positive urine dipstick test for nitrite or leukocytes or both	Females, 18–70	Diclofenac 75 mg BID for 3 days to 133 patients	Norfloxacin 400 mg BID for 3 days to 120 patients
Some concern						
Bleidorn et al. <sup>32</sup>	July 2007 to April 2008	79 patients from 29 German general practices	Typical symptoms (dysuria and/or frequency)	Females, more than 18	Ibuprofen 400 mg TID for 3 days to 40 patients	Ciprofloxacin 250 mg BID for 3 days to 39 patients
High risk of bias						
Ko K et al. <sup>31</sup>	August 2014 to July 2015	55 Korean patients	More than two symptoms, including urination frequency, dysuria, urgency, and lower abdominal discomfort.	Females, more than 18	Cefpodoxime 100 mg BID + aceclofenac 100 mg BID for 3 days to 28 patients	Cefpodoxime 100 mg BID for 3 days to 27 patients

TID: thrice a day; OD: once a day; BID: twice a day.

−0.51, 253 participants, one study; low ROB). Gágyor et al.<sup>28</sup> also reported similar effects when the fosfomycin-treated group was compared to the ibuprofen-treated group (logRR=−0.49, 95% CI: −0.78 to −0.20, 459 participants, one study; low ROB). Similarly, a beneficial effect was seen with pivmecillinam compared to ibuprofen-treated patients in a study by Vik et al.<sup>29</sup> (logRR=−0.37, 95% CI: −0.49 to −0.29, 359 participants, one study; low ROB).

**Adverse events in a month follow-up.** All adverse events from three studies with a low ROB are summarized as follows: Gágyor et al.<sup>28</sup> (logRR=−0.12, 95% CI: −0.45 to 0.21, 484 participants) and Vik et al.<sup>29</sup> (logRR=0.13, 95% CI: −0.25 to 0.50, 359 participants) did not show a significant difference in overall adverse events in NSAIDs-treated group compared

to antibiotics-treated group. However, Kronenberg et al.<sup>30</sup>, a comparatively smaller study with a low ROB, had shown a significantly higher risk of having adverse events with NSAIDs as compared to antibiotics (Figure 3).

Non-UTI adverse events were more common than UTI-related adverse events in both NSAIDs and ABs groups. UTI-related adverse events were more common in the NSAIDs arm compared to antibiotics in all three low ROB studies. Non-UTI-related adverse events were present in 12.78%, 17.43%, and 17.68% of NSAIDs-treated group in the studies by Kronenberg et al.,<sup>30</sup> Gágyor et al.,<sup>28</sup> and Vik et al.,<sup>29</sup> respectively. However, it was 1%, 23.40%, and 21.30%, respectively in the studies by Kronenberg et al.,<sup>30</sup> Gágyor et al.,<sup>28</sup> and Vik et al.<sup>29</sup> in the antibiotics-treated group (Table 5).

**Table 3.** Outcome measures of included studies.

Study	Primary outcome		Secondary outcomes
	Outcome name	Finding or outcome	Outcome name
Bleidorn et al. <sup>32</sup>	Symptom resolution by day 4	A slight higher proportion of ibuprofen group patients showed symptoms resolution by day 4	Burden of symptoms on days 4 and 7 Symptom resolution on day 7 Frequency of relapses until day 28 Incidence of adverse events
Gágyor et al. <sup>28</sup>	Total ABs courses 0–28 days (for UTI or other conditions) Burden of symptoms on days 0–7	Antibiotics consumption is lower in the ibuprofen group but the resolution of overall symptoms is greater in the ABs group on days 0–7 in the AUC curve	Numbers of adverse events Relapse rate up to day 28 and within 6 and 12 months Women without symptoms on days 4 and 7 Symptoms load until days 4 and 7 Activity impairment
Vik et al. <sup>29</sup>	Proportion of patients cured by day 4	A higher proportion of ABs group patients were cured by day 4	Duration of symptoms and patients' symptom load for specific symptoms Proportion of patients: With positive second urine culture In need of a medical consultation within 4 weeks of follow-up Who received antibiotics treatment during 4 weeks follow-up
Kronenberg et al. <sup>30</sup>	Symptom resolution on day 3	A comparatively higher proportion of patients in ABs group showed symptom resolution	Use of any ABs up to 30 days, resolution of symptoms on day 7 Complete absence of symptoms on days 3 and 7 Use of fosfomycin up to day 3 Negative urinary culture result on day 10 Re-consultations up to day 30 Mean composite symptom score on days 3, 7, and 30 Time until complete resolution of symptoms, adverse events
Ko K et al. <sup>31</sup>	Differences in pain reduction between the two groups by the third day	No difference was observed in the magnitude of the pain scale reduction in both groups	Rate of symptom improvement on day 7 Prevalence of antibiotic resistance

UTI: urinary tract infection; ABs: antibiotics; AUC: area under curve.

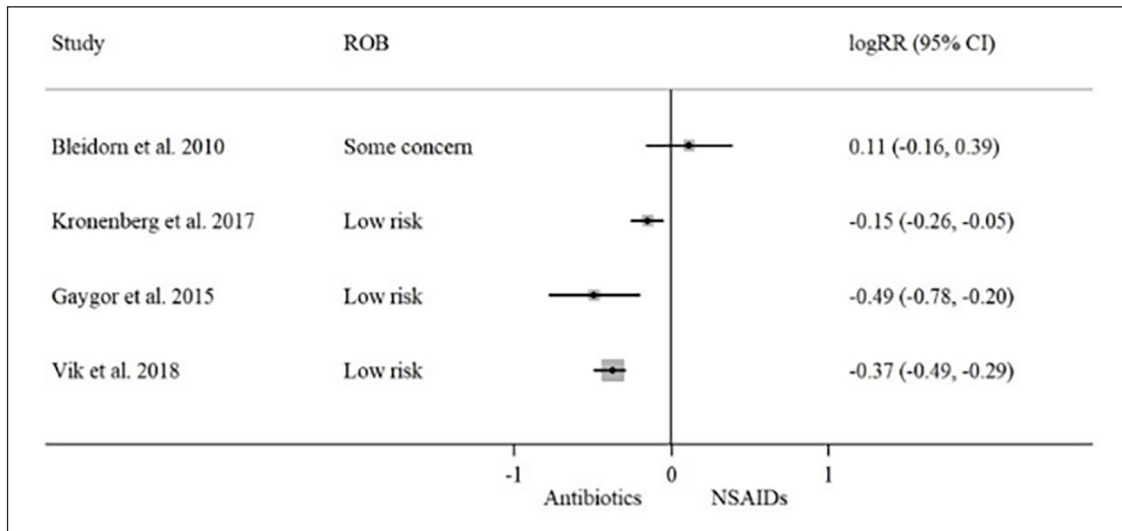
**Table 4.** Outcome data of each study (events and total).

Study	Clinical resolution of symptoms by day 7				Patients with adverse events by a month			
	Intervention		Comparator		Intervention		Comparator	
	N (%)	T	N (%)	T	N (%)	T	N (%)	T
NSAIDs monotherapy versus antibiotics monotherapy								
Bleidorn et al. <sup>32</sup>	30 (77)	39	26 (68)	38	28 (72)	39	29 (76)	38
Kronenberg et al. <sup>30</sup>	44 (33)	133	65 (54)	120	41 (31)	133	21 (18)	120
Gaygor et al. <sup>28</sup>	163 (70)	232	186 (82)	227	51 (21)	241	58 (24)	243
Vik et al. <sup>29</sup>	114 (63)	181	162 (91)	178	45 (25)	181	39 (22)	178
NSAIDs + antibiotics versus antibiotics monotherapy								
Ko K et al. <sup>31</sup>	24 (86)	28	18 (67)	27	4 (14)	28	0 (0)	27

N: number of participants with events; NSAIDs: non-steroidal anti-inflammatory drugs; T: total participants in each arm.

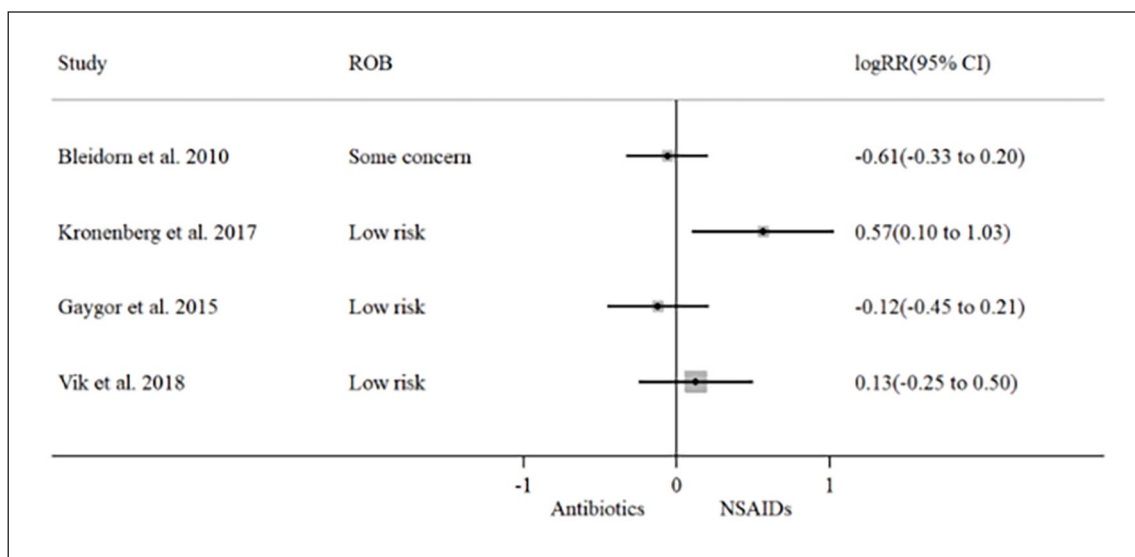
A close emphasis revealed that 3.80%, 2.07%, and 4.50% of NSAIDs-treated patients developed pyelonephritis in the studies by Kronenberg et al.<sup>30</sup> (risk difference=0.05, 95% CI: 0.01–0.08), Gágyor et al.<sup>28</sup> (risk

difference=0.02, 95% CI: –0.00 to 0.04), Vik et al.<sup>29</sup> (risk difference=0.04, 95% CI: 0.01–0.07), respectively. The number needed to harm in terms of pyelonephritis when treated with NSAIDs was 20, 60, and 25 according to Kronenberg



**Figure 2.** Comparison of relative risk of symptom resolution by day 7 for participants treated with NSAIDs monotherapy versus antibiotics monotherapy.

NSAIDs: non-steroidal anti-inflammatory drugs.



**Figure 3.** Comparison of relative risk of adverse events in a month of follow-up for participants treated with NSAIDs monotherapy versus antibiotics monotherapy.

NSAIDs: non-steroidal anti-inflammatory drugs.

et al.,<sup>30</sup> Gágyor et al.,<sup>28</sup> and Vik et al.,<sup>29</sup> respectively. The use of secondary antibiotic use for persistent or worsening UTI symptoms was significantly higher with NSAIDs compared to antibiotics in the studies by Gágyor et al.<sup>28</sup> (RR=2.52, 95% CI: 1.72–3.70), Kronenberg et al.<sup>30</sup> (RR=3.66, 95% CI: 2.33–5.76), and Vik et al.<sup>29</sup> (RR=4.53, 95% CI: 2.85–7.22).

In terms of recurrence, Kronenberg et al.<sup>30</sup> had a non-significant difference between the two groups (logRR=0.12, 95% CI: -1.17 to 1.41,  $p=0.85$ ). Similarly, it was not significant in the study by Gágyor et al.<sup>28</sup> too (logRR=-0.22, 95% CI: -0.70 to 0.25,  $p=0.36$ ).

**Total antibiotics course.** Only Gágyor et al.<sup>28</sup> reported this outcome, where a significant reduction in the total antibiotic course was reported during the treatment of uncomplicated UTI and follow-up (MD=-64.7, 95% CI: -70.7 to -58.7,  $p<0.001$ , 484 participants, 1 study; low ROB).

**MD from therapy till complete resolution of symptoms.** Gágyor et al.<sup>28</sup> reported a mean of 5.60 and 4.60 days in the ibuprofen and fosfomycin group respectively (MD=0.98, 95% CI=0.59–1.08). Similarly, Kronenberg et al.<sup>30</sup> reported a median of 4 days in the diclofenac group and 2 days in the



**Table 5.** Details of UTI and non-UTI-related adverse events in a month follow-up.

Study	UTI-related				Non-UTI-related			
	NSAIDs		Antibiotics		NSAIDs		Antibiotics	
	N (%)	Total	N (%)	Total	N (%)	Total	N (%)	Total
Bleidorn et al. <sup>32</sup>	10 (25.64)	39	8 (21.05)	38	19 (48.72)	39	20 (52.63)	38
Kronenberg et al. <sup>30</sup>	26 (19.55)	133	10 (8.33)	120	17 (12.78)	133	12 (10)	120
Gágyor et al. <sup>28</sup>	8 (3.32)	241	1 (0.41)	243	42 (17.43)	241	57 (23.46)	243
Vik et al. <sup>29</sup>	12 (6.63)	181	0 (0)	178	32 (17.68)	181	38 (21.35)	178

UTI: urinary tract infection; N: number of participants with the event; NSAIDs: non-steroidal anti-inflammatory drugs.

**Table 6.** Outcome measures of combination therapy of NSAIDs and antibiotics versus monotherapy of antibiotics.

Outcomes	Results
Clinical resolution of symptoms by day 7	LogRR=0.25, 95% CI: -0.06 to 0.56 suggesting no significant difference
Adverse events	LogRR=2.16, 95% CI: -0.7131 to 5.04

NSAIDs: non-steroidal anti-inflammatory drugs; RR: relative risk; CI: confidence interval.

norfloxacin group. Vik et al.<sup>29</sup> reported a median symptom duration of 6 days in the ibuprofen group as compared to 3 days in pivmecillinam.

*NSAIDs and antibiotics combination therapy versus antibiotics monotherapy.* Only one study by Ko K et al.<sup>31</sup> in 2017 was found. It was labeled to be at high ROB; hence, a summary of evidence has not been done. However, the outcome measures of this study have been presented in Table 6.

## Discussion

In this systematic review, we evaluated five RCTs comparing different therapies of NSAIDs against antibiotics for the treatment of uncomplicated lower UTI. To the authors' best knowledge, this is the first systematic review to include both NSAIDs monotherapy and combined therapy (NSAIDs with antibiotics) in a comparison with antibiotics monotherapy for evaluation of clinical efficacy by day 7 and adverse events over a month follow-up.

Among the five included studies, four studies<sup>28–30,32</sup> compared NSAIDs monotherapy against antibiotics monotherapy, while one study<sup>31</sup> compared combined NSAIDs and antibiotics against antibiotics monotherapy. Of the four studies comparing NSAIDs monotherapy (585 participants) against antibiotics monotherapy (563 participants), three studies<sup>28–30</sup> with a low ROB showed antibiotics to be superior for the resolution of symptoms by day 7. A similar result for symptom resolution on days 3 or 4 of post-randomization was obtained from a recent systematic review.<sup>23</sup> On the other hand, 33%–77% of the participants assigned to the NSAIDs

arm had symptom resolution by day 7 without any antibiotics in our study.<sup>28–30,32</sup> The same set of studies showed that 39%–58% of the NSAIDs-treated group had symptom resolution by days 3 or 4 without antibiotics. This is probably due to the clinical symptoms-based inclusion criteria used by all of the included studies.<sup>28–32</sup> The gold standard for the diagnosis of UTI is the detection of pathogen along with typical clinical features.<sup>33</sup> Hence, an error rate of approximately 33% has been observed when a diagnosis of UTI was made alone by clinical criteria.<sup>33</sup> In our review also, approximately 14%–67% of participants in NSAIDs arm were culture negative at baseline.<sup>28–32</sup> In culture-negative participants, a comparable efficacy with no significant difference between NSAIDs and antibiotics for symptom resolution by day 7 or 6 is evident from the studies done by Gágyor et al.<sup>28</sup> and Vik et al.,<sup>29</sup> respectively. Therefore, this could be one of the reasons why a large proportion of participants had a resolution of symptoms when treated with NSAIDs only. On the contrary, a significantly higher burden of symptoms in the NSAIDs group as compared to antibiotics was observed in urine culture-positive participants in both the studies.<sup>28,29</sup> In addition, antibiotics did not show any significant difference in symptom burden between the urine culture-positive and negative participants in the study by Gágyor et al.<sup>28</sup> In all studies with low ROB, use of secondary antibiotics for persistent or degrading symptoms was significantly higher in NSAIDs arm compared to antibiotics. These explain why the antibiotics were significantly superior to NSAIDs in terms of symptom resolution. However, the authors cannot deny the evidence that NSAIDs resulted in a complete resolution of symptoms by day 7 in 33%–77% of participants assigned to NSAIDs,<sup>28–30,32</sup> which happens to be more than what would be expected if NSAIDs were to work only in culture-negative participants (which is 14%–67% of participants assigned to NSAIDs arm).<sup>28–32</sup> Hence, the authors believe that finding populations in which NSAIDs can be used safely in uncomplicated lower UTI could be useful.

UTI-related complications were comparatively higher with NSAIDs than antibiotics, while non-UTI-related adverse events were relatively more in the ABs group than NSAIDs from our study. For every 20 to 60 treated people, one would develop pyelonephritis in NSAIDs-treated group

compared to antibiotics monotherapy group.<sup>28–30</sup> This was similar to the result of a systematic review, which showed that 22 to 62 people would be needed to treat with antibiotics to avoid one case of pyelonephritis.<sup>23</sup> The rate of pyelonephritis was 2%–4.50% in the NSAIDs-treated group in the included studies, which was higher than 0.15% of ABs group and 0.40%–2.60% of placebo reported in a previous meta-analysis of RCTs.<sup>14</sup> This could be because of the relative small time period of included studies in the previous meta-analysis, which is discussed as one of the limitations of the study.<sup>14</sup> These findings suggest that antibiotics are comparatively useful in reducing urinary complications.

Although pyelonephritis rates are higher in NSAIDs than antibiotics-treated group, identifying the patients who have higher chances of developing pyelonephritis could help to reduce the burden of antibiotics use. This approach requires close monitoring of the patient's situation. Kronenberg et al.<sup>30</sup> did not find any baseline character to predict possible pyelonephritis; however, women developing pyelonephritis had a positive correlation with C-reactive protein values more than 10 mg/L, indicating the possible requirement to treat with antibiotics. Similarly, in the study by Gágyor et al.,<sup>28</sup> women developing pyelonephritis had a higher initial symptom score (7.5) than the mean symptom severity score (6 out of a total of 12). Further research is required to identify the characters of patients who would develop pyelonephritis to make NSAIDs a potential strategy to reduce usage of antibiotics in the treatment of uncomplicated lower UTI.

Only one study reported the total antibiotic required for the complete resolution of symptoms.<sup>28</sup> It reported a significant reduction in the total antibiotic course while using NSAIDs as first treatment approach and antibiotics as an additional approach for persistent, worsening, or recurrent symptoms. This was evident in both positive-culture and negative-culture participants. Our review also showed a longer MD of symptoms with NSAIDs use as compared to antibiotics. Hence, NSAIDs might be capable of reducing the total antibiotics prescription at the cost of prolongation of symptoms and concerning adverse events.

Emerging evidence shows that NSAIDs increase the therapeutic activity of antibiotics against bacteria causing UTI.<sup>24</sup> This led us to evaluate the efficacy of combined therapy of NSAIDs and antibiotics against antibiotics monotherapy for the treatment of UTI. One such study included in our systematic review had no significant difference between the two groups on day 7.<sup>31</sup> However, it revealed a faster resolution of symptoms with combined approach of therapy as compared to antibiotics monotherapy.<sup>31</sup> More such RCTs could give further insight as to whether concurrent therapy of NSAIDs with antibiotics is beneficial as compared to antibiotics monotherapy in terms of faster resolution of symptoms.

This review has several strengths, including a comprehensive literature search on multiple databases, a published protocol, and comparison of different therapies of NSAIDs against antibiotics. However, it has got several limitations.

We could not perform a synthesis or a meta-analysis because of clinical heterogeneity in intervention and comparator arm (different groups of antibiotics used), different ROB, and different scores of clinical symptoms used across the studies. Furthermore, the included studies had participants mostly from Europe. Antimicrobial resistance also depends on the region and microbial organisms. For instance, the resistance rate to ciprofloxacin for *E. coli* and *Klebsiella pneumoniae* varied from 8.4% to 92.9% and 4.1% to 79.4%, respectively, in countries reporting to the Global Antimicrobial Resistance and Use Surveillance System.<sup>34</sup> A meta-analysis of further studies with representative samples from different regions of the world and specific antibiotics could help us generate better evidence. Second, we were limited in comparison of combined therapy of NSAIDs and antibiotics against antibiotics monotherapy due to a paucity of studies. Third, only five articles were included, which could potentially lead to missing the rare outcomes. Fourth, this article provides data for a month follow-up, and hence, long-term outcome of NSAIDs versus antibiotic therapy could not be discussed. Fifth, a sample size calculation or power analysis was not performed for this study.

In summary, our review demonstrates the inferiority of NSAIDs to antibiotics in the treatment of uncomplicated lower UTI. Furthermore, it highlights the need of research to identify the effectiveness of combination therapy of NSAIDs and antibiotics, and characteristics of patients who are likely to develop pyelonephritis on NSAIDs monotherapy during the treatment of uncomplicated UTI.

## Conclusion

This review highlights the effectiveness of antibiotics compared to NSAIDs in the treatment of uncomplicated lower UTIs. However, the study determined the need of further research regarding the characteristics of patients that could help in predicting the development of pyelonephritis, and the effectiveness and safety of combined therapy of NSAIDs with antibiotics to pin the possible role of NSAIDs in reducing antibiotics prescription.

## Author contributions

All the authors were involved in developing the concept and design of study. S.G. and R.S. were involved in literature search. R.S., M.K.C., M.M.A., B.R.A., and V.C. were involved in literature selection. S.G. and B.R.A. were involved in risk of bias assessment. Y.A.E., M.M.A., S.G., and R.S. were involved in data extraction and verification. S.G., R.S., B.R.A., M.R.G., M.M.A., and M.K.C. were involved in drafting of the article. S.G. and R.S. were involved in critical revision of the article. All the authors approved the final version of the article.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Supplemental material

Supplemental material for this article is available online.

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