

Safety and Efficacy of Nitazoxanide-Based Regimen for the Eradication of *Helicobacter pylori* Infection: A Systematic Review and Meta-Analysis

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Abstract

Background: *Helicobacter pylori* (HP) is the most common cause of gastritis worldwide. Clarithromycin-based triple therapy or bismuth-based quadruple therapy is usually considered the first-line treatment, however with around 30% failure rate for both regimens. Drug resistance of clarithromycin and metronidazole is a growing concern in some parts of the world. Therefore, there is a need for effective eradication regimen for HP. Nitazoxanide, a bactericidal thiazolide antibiotic, has been shown to be effective in HP infection. We conducted a systematic review and meta-analysis to evaluate the efficacy of nitazoxanide-based regimen for the eradication of HP.

Methods: We have searched PubMed, Embase, Ovid Medline and Cochrane library database from inception to December 9, 2020 to identify studies that utilized nitazoxanide in the treatment regimen for HP eradication. Our primary outcome was pooled eradication rate of HP.

Results: Thirteen studies including 1,028 patients met our inclusion criteria and were analyzed in a meta-analysis. HP eradication was successful in 867 patients with a pooled eradication rate of 86% (95% confidence interval (CI): 79-90%) with 84% heterogeneity. A subgroup analysis that included 230 patients who failed other prior

eradication regimens revealed a pooled eradication rate of 85% (95% CI: 69-94%) without heterogeneity. In a subgroup analysis, highest eradication rates were achieved with levofloxacin, doxycycline, nitazoxanide and proton pump inhibitor with a pooled eradication rate of 92% (88-95%).

Conclusion: Nitazoxanide-based regimen is safe and effective in the eradication of HP infection. It is also successful as a salvage therapy in patients who have failed prior treatments.

Keywords: Nitazoxanide; *Helicobacter pylori*; Eradication regimen; Meta-analysis

Introduction

Helicobacter pylori (HP), a gram-negative bacillus, is a potent bacterial colonizer of human gastric mucosa with an estimated 50% of the world's population chronically infected [1]. Chronic infection due to HP can subsequently lead to the development of certain gastrointestinal (GI) complications, such as chronic gastritis, peptic ulcer disease and gastric malignancies such as gastric adenocarcinoma and mucosal-associated lymphoid tissue (MALT) lymphomas. The eradication of HP plays a crucial role in reducing the incidence of these complications [2-4]. The increasing prevalence of antibiotic resistance has decreased eradication rates (ERs) with current first-line guideline recommended strategies that include standard triple therapy (proton pump inhibitor (PPI), clarithromycin, and amoxicillin or metronidazole) or bismuth-based quadruple therapy (PPI or H₂ receptor antagonists, bismuth, metronidazole and tetracycline) [5-7]. More recently, sequential therapy of these treatment options has also been introduced [8]. Specifically, recent studies have reported resistant rates to clarithromycin ranging from 18% in Europe to as high as 50% in Asia. Resistance to metronidazole, similarly, has been reported to range between 30% and 40% in developed and as high as 80% in developing nations across the globe [5, 7, 9]. Such overwhelming antibiotic resistance has warranted a critical need for alternative therapeutic options.

Over the last decade, nitazoxanide (NTZ), a broad-spectrum thiazolide antibiotic that is characteristically similar to

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metronidazole, has emerged as a potential treatment of HP [10]. Presently, NTZ, a compound with anti-bacterial, anti-viral and anti-parasitic activity, is the first-line therapy for treatment of *Cryptosporidium parvum* and *Giardia lamblia* [11]. Recently, studies have shown effective eradication of HP with treatments including NTZ. Here, we aimed to evaluate the efficacy and safety of treatment strategies that incorporate NTZ for HP infection treatment.

Materials and Methods

Search strategy

We have searched PubMed, Embase, Ovid Medline and Cochrane library database from inception to December 9, 2020 to identify studies which utilized NTZ in the treatment regimen for HP eradication. A manual search was also performed through the bibliographies of the retrieved publications to increase the yield of possibly relevant studies. Two investigators independently conducted the systematic literature review. Observational studies or randomized controlled trials (RCTs) that evaluated NTZ as part of eradication regimen for HP were eligible for inclusion in the meta-analysis. The sample size of a study did not restrict its inclusion in the meta-analysis. When possible, we only included patients who completed the full length of therapy and were tested for eradication on follow-up. Our primary outcome was pooled ER of HP. We also performed a subgroup analysis to evaluate ER of NTZ-based regimen in patients who failed prior treatment. This study was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [12]. Quality assessment of the observational studies was performed by using Newcastle-Ottawa quality assessment scale and Jadad score was utilized to assess the quality of RCT. Quality assessment did not affect the eligibility of the studies in the meta-analysis. Institutional review board approval and ethical compliance were not needed given this is a meta-analysis.

Data extraction

A structured data collection form was used to extract the following data from each study: the title of the study, publication year, name of the first author, country where the study was performed, number of participants, characteristics of the participants, eradication regimen, ER, dose of NTZ used and adverse events. To ensure accuracy, data extraction was independently performed by two investigators (UI and KFH) and was reviewed by the third investigator (HUS). Any disagreement was resolved by mutual agreement.

Statistical analysis

Incidence rates (IRs) and confidence intervals (CIs) were initially calculated for the primary outcome (ER) from included

studies. The pooled IR is considered statistically significant if 95% CI did not contain 1. Forest plots were then made using pooled estimates and measure of variability of each included study. Publication bias was evaluated by funnel plot diagram. Variability between included studies was assessed by heterogeneity tests using I^2 statistic. All analyses were conducted using RStudio (Version 1.0.136; Boston, MA) using the “Meta” and “Metafor” package.

Results

Initial search revealed 172 articles. After removal of duplicates, editorials and case reports 20 articles underwent full review. Out of 20 articles, 13 studies including 1,028 patients met our inclusion criteria and were analyzed in a meta-analysis as summarized in Table 1 [13-25]. Figure 1 elaborates the systematic review process of our meta-analysis. There were eight observational studies and five randomized clinical trials. All the randomized trials are fair quality. Among observational studies, seven were of good quality and one was of fair quality. Table 1 elaborates complete eradication regimen, dosage of NTZ and patient population included in each study.

Out of 1,028 patients, HP eradication was successful in 867 patients with a pooled ER of 86% (95% CI: 79-90%) with 84% heterogeneity (Fig. 2). We also performed a subgroup analysis including 230 patients who have failed other prior eradication regimens and revealed a pooled ER of 85% (95% CI: 69-94%) without heterogeneity. No serious adverse events were reported in the studies. Table 1 reports minor adverse events reported in each study. In a subgroup analysis, highest ERs were achieved with levofloxacin, doxycycline, NTZ and PPI with a pooled ER of 92% (88-95%) (Fig. 3). There was no publication bias as evaluated by funnel plot diagram (Fig. 4).

Discussion

The increasing resistance to antibiotics poses an important challenge with regards to the treatment of HP. Specifically, a previous meta-analysis of over 53,000 patients demonstrated a cure rate of less than 80% for guideline recommended first-line therapy [26, 27]. Furthermore, the number of patients who are treatment refractory continues to rise, with evidence suggesting that at least 10% of patients infected with HP will fail both first- and second-line regimens [28]. For these reasons, there is a growing need to find other suitable treatment modalities such as those that include NTZ.

In this systematic review and meta-analysis, we demonstrated that HP eradication with regimens containing NTZ is an effective and safe strategy. HP pooled ERs with NTZ regimens equated to 83% (95% CI: 76-90%) without heterogeneity ($P = 0.17$). Furthermore, subgroup analysis of 230 patients with failed eradication of HP revealed a pooled ER of 80% (95% CI: 66-94%) without heterogeneity ($P = 0.39$). Treatment regimens that included levofloxacin, doxycycline, NTZ and PPIs were the most effective, achieving the highest HP pooled ER of 92% (82-100%). With regards to safety, no serious adverse

Table 1. Baseline Characteristics of the Included Studies

Authors, year of publication and country	Study design and sample size	Patient population/prior treatments	Eradication regimen	Dose of NTZ and duration	ER and criteria for eradication	Adverse events
Megraud et al, 1998, Egypt [16]	Open phase II dose ranging pilot study	Previously untreated dyspeptic patients diagnosed with HP	NTZ + omeprazole 20 mg/day	500 mg BID for 14 days; 500 mg TID for 7 days; or 1,000 mg BID for 7 days.	ER was 65% in 500 mg BID for 14 days group, 58% in 500 mg TID for 7 days group and 83% in 1 g BID group. Patients were included if HP was positive in two of the following: histology, culture and serology. Same tests were repeated (except for serology) 4 weeks after treatment to confirm eradication. Urea breath test was also performed after treatment.	Minor adverse events were reported in 15 patients.
Sanjujo et al, 1999, Mexico [25]	Open prospective, longitudinal study	Previously untreated	NTZ + BS + LP 30 mg BID	500 - 1,000 mg in three different regimens	ER was 41.37% in NTZ 1 g + BS 240 mg + PPI for 7 days group, 75% in NTZ 500 + BS 120 mg + PPI for 14 days group and 83% in NTZ 1,000 + BS 240 mg and PPI for 14 days group. Eradication was confirmed with negative urea breath test 6 weeks after treatment.	No serious adverse events were reported.
Campitelli et al, 2008, Argentina [22]	Open label study	Previously untreated	NTZ + LP + amoxicillin for 7 days	500 mg BID	ER was 90%. Eradication was confirmed with negative urea breath test 6 - 8 weeks after treatment.	No major adverse events were reported.
Basu et al, 2008, USA [23]	Open label prospective study	Failed prior treatment regimen	Levofloxacin, esomeprazole, NTZ and doxycycline for 10 days	500 mg BID	ER was 100% in per protocol analysis (90% in intention to treat analysis). Eradication was confirmed with negative stool antigen test in 2 weeks after treatment.	Nausea and bloating were reported in two patients. Non-specific itching was reported in one patient.
Stuppy, 2009, USA [18]	RCS	Previously untreated	Sucralfate + NTZ for 14 days	1,000 mg BID	ER was 73%. Eradication was confirmed with negative salivary HP antibodies 1 to 6 months after the end of therapy.	Yellowing of urine and GI discomfort were reported in few patients
Stuppy, 2010, USA [19]	RCS	39 previously untreated; 11 failed prior treatment	Sucralfate + NTZ for 14 days	1,000 mg BID	ER was 84%. Eradication was confirmed with negative salivary HP antibodies 1 - 6 months after the end of therapy.	Yellowing of urine and GI discomfort were reported in few patients.
Basu et al, 2011, USA [14]	Randomized open label trial	Previously untreated	Levofloxacin, omeprazole, NTZ and doxycycline for 7 days or 10 days	500 mg BID	ER was 93.6% in per protocol analysis (89.4% in intention to treat analysis). Eradication was confirmed with negative stool antigen test in 4 weeks after treatment.	Minor adverse events (headache, abdominal pain, nausea, diarrhea, etc.)

Table 1. Baseline Characteristics of the Included Studies - (continued)

Authors, year of publication and country	Study design and sample size	Patient population/prior treatments	Eradication regimen	Dose of NTZ and duration	ER and criteria for eradication	Adverse events
Basu et al, 2013, USA [21]	Randomized open label clinical pilot study	Failed prior treatment regimens	Rifabutin + NTZ + omeprazole + doxycycline (ROAD) or macrodantin + NTZ + doxycycline + omeprazole (MOAD)	500 mg BID	ER was 65.7% overall (72% in ROAD group and 52% in MOAD group).	Minor adverse events like nausea, vomiting, diarrhea and headache.
Ramos-Soriano and Black, 2015, USA [15]	RCS	Previously untreated pediatric population	NTZ for 3 days + azithromycin and cefixime or any third-generation cephalosporin for 7 - 10 days + PPI for 30 days	Mean dose of 327.5 mg BID	ER was 89.2%. Eradication was confirmed with negative urea breath test with resolution of symptoms within 4 months of treatment.	10% patients had minor adverse events like nausea, vomiting and abdominal cramping.
Abd-Elisalam et al, 2016, Egypt [13]	Open label study	Failed clarithromycin-based regimen in the past	Levofloxacin, omeprazole, NTZ and doxycycline for 14 days	500 mg BID	88.3% in per protocol analysis (83% in intention to treat analysis). Eradication was confirmed with negative stool antigen test in 6 weeks after treatment.	Minor adverse events (headache, abdominal pain, nausea, diarrhea etc.) were noted in 21 patients.
Shehata et al, 2017, Egypt [17]	RCT	Previously untreated patients	Clarithromycin + NTZ and omeprazole for 14 days	500 mg BID	ER was 94.6%. Eradication was confirmed with negative stool antigen test in 6 weeks after treatment.	Abdominal pain, nausea, constipation and dizziness
Waheeb et al, 2018, Egypt [24]	RCT	25 previously untreated patients and 22 patients failed treatment in the past.	Clarithromycin + NTZ + amoxicillin and omeprazole for 14 days	500 mg BID	85% (92% in previously untreated and 77.3% in patients who failed prior treatment). Eradication was confirmed with negative stool antigen test in 6 weeks after treatment.	Minor adverse events like nausea and vomiting were reported in few patients.
Basu et al, 2010, USA [20]	RCT	Previously untreated patients	Levofloxacin, omeprazole, NTZ and doxycycline for 7 days or dexlansoprazole + moxifloxacin + amoxicillin + doxycycline + NTZ for 4 days	500 mg BID	82% eradication in intention to treat analysis. Eradication was confirmed with negative stool antigen test 30 days after treatment.	Minor rash, dizziness, diarrhea and palpitations

HP: *Helicobacter pylori*; BID: twice a day; TID: three times a day; BS: bismuth subcitrate; LP: lansoprazole; PPI: proton pump inhibitor; GI: gastrointestinal; NTZ: nitazoxanide; RCT: randomized controlled trial; ER: eradication rate.

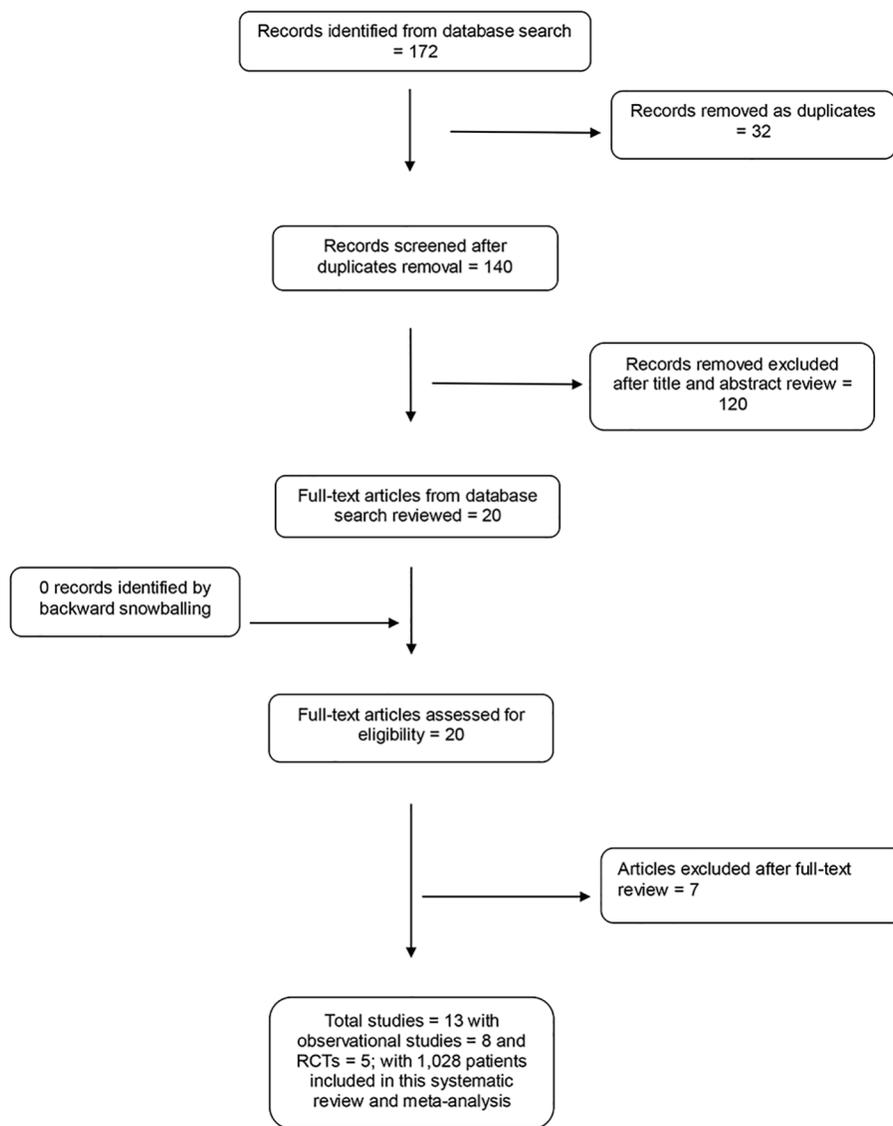


Figure 1. PRISMA flow diagram.

events were reported.

NTZ is a thiazolide antibiotic that exerts its bactericidal activity via mechanisms that prevent anaerobic energy metabolism via the inhibition of pyruvate oxidoreductase enzyme [29]. Although characteristically similar to metronidazole, NTZ differs due to its anti-vacuolating toxin activity that prevents against the formation of antimicrobial resistance. These findings are supported by in vitro studies that demonstrate NTZ to be a potent agent against metronidazole-resistant strains [16, 30]. These characteristics of NTZ may explain the success of NTZ containing regimens as both first-line and against multidrug-resistant HP strains. The success rates of NTZ regimens are as high as 80%, as shown in this meta-analysis, against multidrug-resistant HP strains, and may point to a synergistic interaction between NTZ and other antibiotics.

Treatment regimens that included levofloxacin, doxycycline, NTZ and PPIs achieved an ER of 92%, which achieves

a grade B or good rating as per Graham’s reporting scale [31]. Such successful ERs may be due to the activity of levofloxacin on DNA gyrase, allowing it to interfere with bacterial DNA replication [32]. Another important factor is the use of doxycycline, a tetracycline analog. Doxycycline inhibits bacterial protein synthesis in order to exert its bacteriostatic effects. Studies have shown little or no resistance to doxycycline and support the use of doxycycline as a rescue therapy in the treatment of HP [33-35].

Presently, PPIs form the backbone of any treatment regimen against HP. PPIs alter gastric acidity, thereby disrupting the optimal environment for HP replication. Omeprazole and esomeprazole were the primary PPIs utilized in the studies included in this meta-analysis.

In terms of safety, clinical studies with NTZ have shown successful use with no significant adverse events at total daily doses ranging from 1,000 to 2,000 mg as well as 500 mg

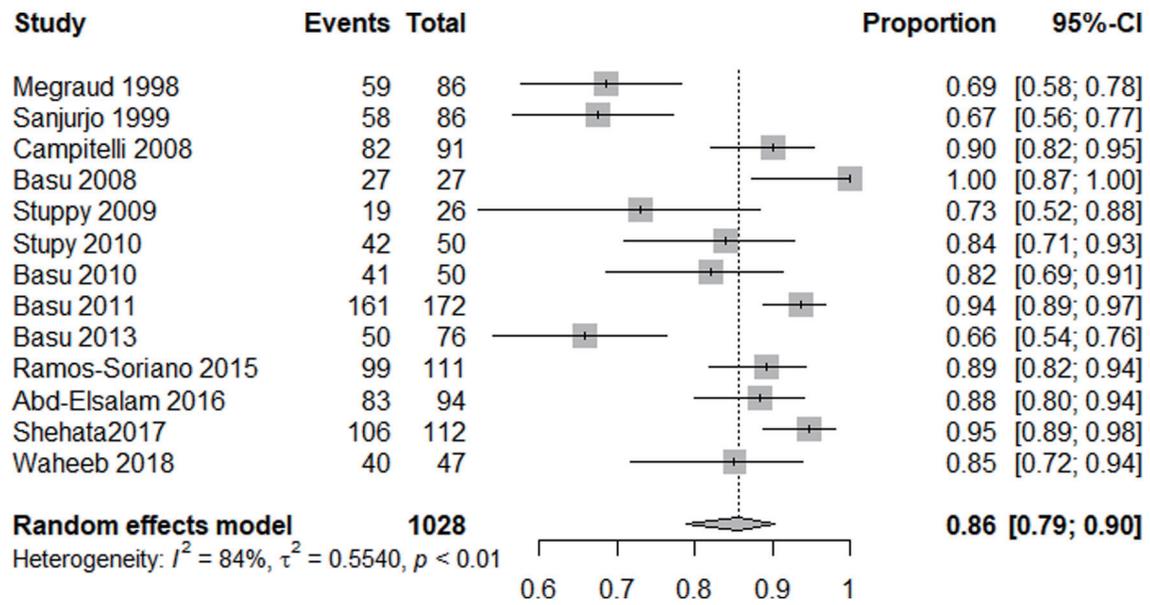


Figure 2. Pooled eradication rate.

when used in combination with other antibiotics [5, 14, 19]. Our meta-analysis supported these findings with no reported serious adverse events occurring in the included studies. Minor adverse events such as abdominal pain, headache, nausea, change in urinary color and diarrhea were reported in these studies. These findings suggest that NTZ containing therapies are a safe alternative and that lower doses of 500 mg might suffice in the treatment of HP.

The systematic review process for the meta-analysis was comprehensive and we included all available studies to date. We recognize, however, that there are certain limitations of this meta-analysis, and thus, the results should be interpreted with caution. Considerations that may have influenced the pooled ERs include the duration of treatment, which varied from 4 to 14 days, dosage variability as well as the region in which the studies were performed. Our meta-analysis included studies from North America, South America and Africa with no studies from Asia. HP infection is a global health dilemma with varying patterns depending on geographic location, and thus our results may not represent findings in places such as Asia.

In conclusion, this meta-analysis indicates that NTZ-

based regimens are safe and effective in the eradication of HP infection. Additionally, these regimens can also play a role as rescue therapies in patients with multidrug-resistant infections who have failed first- or second-line treatments. The specific combination of levofloxacin, doxycycline, NTZ and PPIs may be a reasonable therapeutic option based on antimicrobial susceptibility testing. Although these findings are promising, further research in the form of larger randomized controlled studies are required to delineate the most effective NTZ-based regimens for the eradication of HP.

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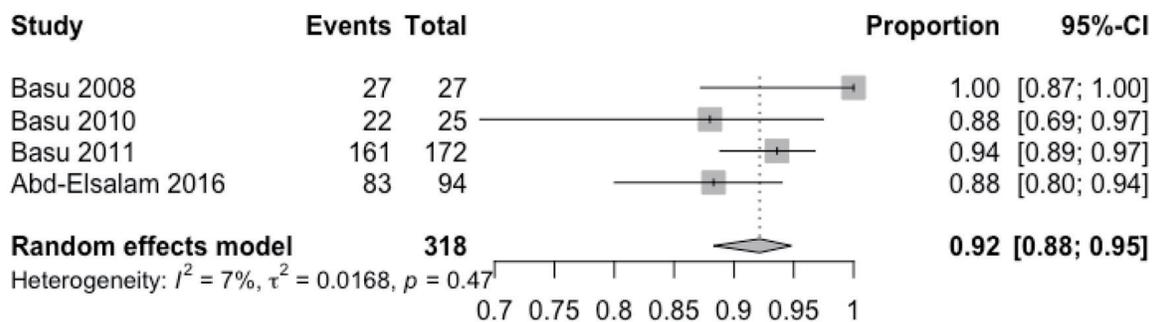


Figure 3. Pooled eradication rate of levofloxacin, doxycycline, nitazoxanide and proton pump inhibitor therapy.

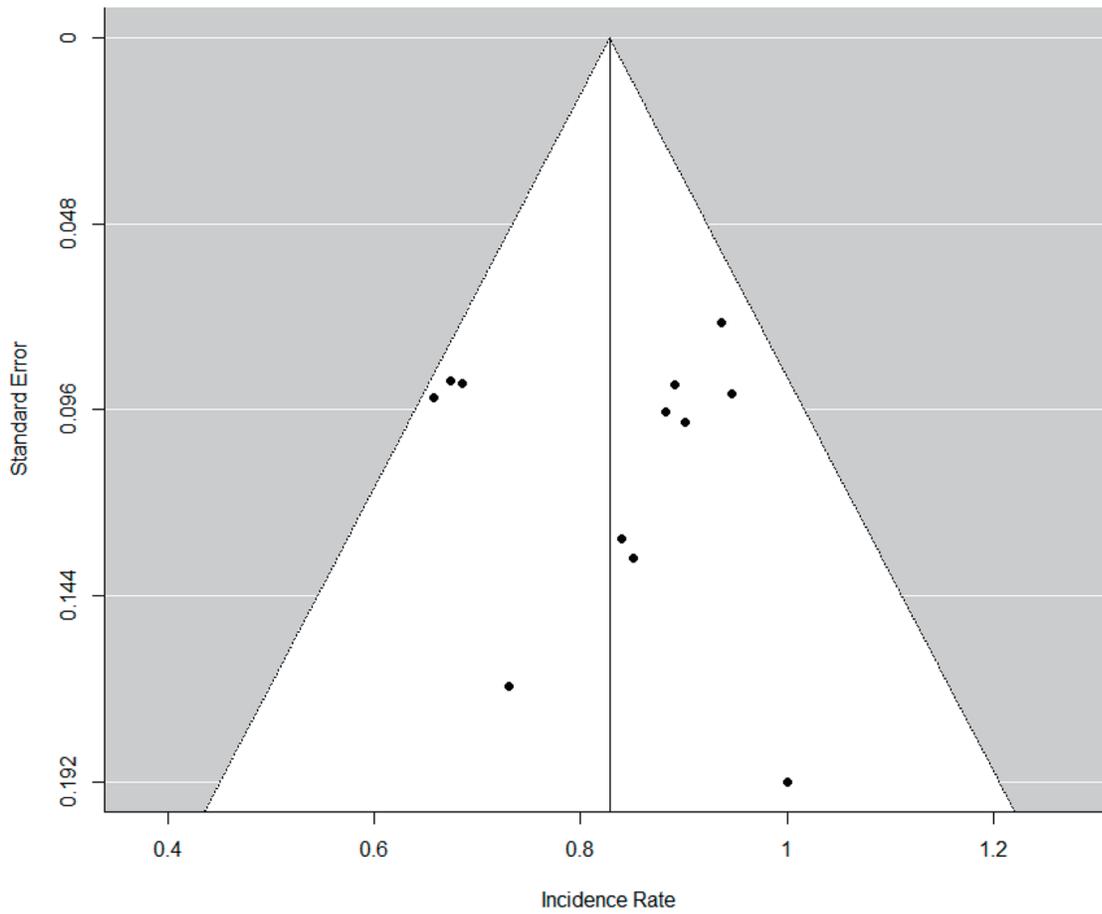


Figure 4. Funnel plot for publication bias.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Umair Iqbal: data abstraction, writing manuscript, quality assessment and statistical analysis. Harshit S. Khara: manuscript writing and supervising the research project. Yirui Hu: synthesis of results and statistical analysis. Hafiz Umair Siddiqui: literature search and manuscript writing. Hafsa Anwar: literature

search and manuscript writing. Khwaja F. Haq: search strategy. Marika Bergenstock: literature search and quality assessment. Daud Akhtar: manuscript writing. Matthew J. Shellenberger: reviewing and supervising the project.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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