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**Meta-Analysis**

# Postoperative doxycycline after endoscopic sinus surgery for chronic rhinosinusitis: systematic review with quantitative synthesis

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## ABSTRACT

The antibiotics are commonly and frequently prescribed after endoscopic sinus surgery to treat chronic sinusitis, although their clinical benefit remains uncertain. One such antibiotic, doxycycline, has antimicrobial and anti-inflammatory properties, which improve postoperative recovery. However, recent reviews of infectious complications after endoscopic sinus surgery suggest the importance of antibiotic use, but routine postoperative antibiotic use remains controversial. The study aims to assess whether postoperative systemic doxycycline improves symptoms, endoscopic healing, complications, or microbiome recovery after endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS). A PRISMA 2020-oriented systematic review with quantitative synthesis was conducted. The randomized or quasi-randomized adult studies comparing postoperative doxycycline versus placebo/standard care. The searches were performed in MEDLINE (PubMed), Embase, CENTRAL, and Scopus. The results show that of the 247 records screened, two randomized, double-blind, controlled trials met the inclusion criteria. Both evaluated doxycycline (100 mg for 28 days versus placebo) compared to placebo after esophagoscopy in adults with chronic atrophic rhinitis (with or without nasal polyps). Endoscopy and microbiome findings showed no sustained benefit with doxycycline. Side effects were rare and similar between groups. The certainty of the evidence ranged from low to moderate for all outcomes. The authors concluded that the current randomized evidence does not support a symptomatic or endoscopic advantage of postoperative doxycycline after ESS for CRS. While generally safe, its routine use cannot be justified given low-certainty evidence and the importance of antibiotic stewardship. Larger, well-powered trials with standardized outcomes are needed to clarify its role.

**Keywords:** Chronic rhinosinusitis, Endoscopic, Doxycycline, Antibiotics, Randomized trials

## INTRODUCTION

In recent years, the focus on improving quality of life has led to greater attention to patient comfort, especially during surgery. This approach represents a progressive model in treatment and medical development, focusing on patient comfort and enhancing their psychological well-being. Therefore, physicians strive to prioritize patient comfort and help them relieve pain.[1,2] One of the diseases that directly or indirectly causes discomfort to patients is sinusitis, also known as chronic sinusitis. Chronic sinusitis is considered a persistent inflammatory disorder affecting the sinuses, characterized by symptoms lasting more than twelve weeks.[3,4] It affects 1 to 4% of the general population, and it represents approximately 1-2% of all medical consultations.[5-8] It is prevalent in Europe at a rate of 10% and is one of the diseases that burden patients due to the high costs of treatment and the need for health care.[9] The nasal microbiome is the primary triggering factor responsible for chronic sinusitis.[10] When the balance between the microbiota and the host immune response is disrupted, it can initiate and perpetuate mucosal

inflammation. Disruption of the normal nasal flora (bacterial dysbalance) undermines the stability of the mucosal barrier, allowing pathogenic bacteria to proliferate.[11] This imbalance increases susceptibility to infection and exacerbates chronic inflammatory conditions.[12,13]

Many researchers have emphasized the role of bacteria in the development of chronic sinusitis, indicating that disturbances in the normal microbial community of the nasal mucosa and sinuses contribute to the development of the disease. This disturbance in the microbial community may result from several environmental and external factors, including seasonal changes, air pollution, exposure to cigarette smoke, and the use of some medications.

In addition, some host-related factors, such as immune status, age, and interactions between microbial species, may further influence the stability and diversity of the nasal microbiome, fostering conditions conducive to chronic sinusitis.[12,14] It often recurs despite modern surgical and medical care. Effective and timely medical treatment of this condition is crucial for improving patients' quality of life, supporting their daily activities, and reducing the likelihood of acute attacks recurring. Endoscopic sinus surgery (ESS) reliably improves fluid drainage and symptoms in many patients. This approach to alleviating postoperative suffering has encouraged the exploration of pharmacological strategies that promote and aid rapid recovery, relieve pain and discomfort, and reduce postoperative complications. Pain, mucosal edema, and inflammation are common factors that cause patient distress and delay recovery. However, repeated surgery, persistent inflammation, and adverse wound remodeling remain major factors leading to long-term failure and reoperation. Recent evidence highlights that while postoperative infectious complications such as toxic shock syndrome (TSS) are rare, they can be serious. A systematic review by O'Shaughnessy et al on the incidence and risk factors for TSS after ESS emphasized the importance of careful antimicrobial stewardship and awareness of postoperative infection risks.[15]

As a result, the choice of postoperative medications has expanded beyond traditional antibiotics to include agents with dual antimicrobial and anti-inflammatory benefits, such as doxycycline. Its use after ESS is attracting renewed interest, as physicians look beyond simple antibiotics to drugs that can reduce inflammation and influence tissue healing. Doxycycline boasts broad-spectrum antibacterial properties and is effective in modulating inflammatory processes and inhibiting matrix metalloproteinases (MMPs), enzymes associated with tissue remodeling and postoperative edema. In patients with chronic rhinosinusitis with nasal polyps (CRSwNP), Van Zele et al demonstrated that a short course of doxycycline significantly reduced polyp size and inflammatory cytokines, comparable to oral corticosteroids but through distinct mechanisms. These pharmacological properties suggest it may improve the recovery of patients after sinus surgery by reducing mucosal inflammation, decreasing the recurrence of nasal polyps, and facilitating wound healing.[16-19] These pharmacologic properties provide a rationale for trialing doxycycline to improve postoperative wound healing and reduce inflammatory recurrence. We conducted a focused systematic review with quantitative synthesis (where feasible) to determine whether postoperative systemic doxycycline improves symptoms, endoscopic healing, complications, or sinonasal microbiome recovery after ESS.

The current review seeks to assess whether postoperative systemic doxycycline improves symptoms, endoscopic healing, complications, or microbiome recovery after ESS for chronic rhinosinusitis (CRS).

## METHODS

### *Study design and search strategy*

The PRISMA statement, "preferred reporting items for systematic reviews and meta-analyses," was designed to help researchers and interested parties transparently report the reason for conducting a review and its significance. Advances in systematic review methodology and terminology have necessitated an update to this guide.[20]

The following search terms were used in the current review to find papers related to this work: PubMed (MEDLINE), Embase, Cochrane CENTRAL, and Scopus, from inception to 4 October 2025, without language limits. Reference lists of included studies and related reviews were scanned.

Authors used combinations of keywords relating to “doxycycline,” “sinus surgery,” “rhinosinusitis,” and “postoperative.” They also screened trial registries such as ClinicalTrials and cross-checked references of included studies and relevant reviews for additional eligible trials.

Searches were performed independently by two reviewers, and final search hits were exported to a reference manager for deduplication. After merging and deduplicating records, the titles and abstracts of articles were screened independently by two reviewers to identify eligible articles.

Full-text articles were then retrieved and assessed for eligibility by the same reviewers using predefined inclusion and exclusion criteria. In the case of uncertainties, they were resolved via discussion or adjudication by a third reviewer.

The wrong design, missing doxycycline arm, incomplete data, and letters to the editor were excluded from the current review. Finally, senior experts received a final evaluation and approval of the review's final version.

***Inclusion criteria***

Studies meeting the PICOS criteria as follows were included.

***Population***

Adults (≥18 years) undergoing endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS; with or without nasal polyps).

***Intervention***

Postoperative systemic doxycycline (any dose, any duration) as an adjunct to standard postoperative care.

***Comparator***

Placebo or standard postoperative care without systemic doxycycline.

***Outcomes***

*Primary*

Change in sino-nasal outcome test (SNOT-22) score at approximately 8 to 16 weeks postoperatively.

*Secondary*

Endoscopic healing (Lund–Kennedy or equivalent mucosal scores), adverse events (AEs), and sinonasal microbiome outcomes.

***Study design***

Randomized or quasi-randomized controlled trials comparing the above; device/local delivery trials not meeting systemic doxycycline criteria were summarized contextually but not pooled.

***Timing***

Studies published from database inception through 4 October 2025 (no language restriction, but non-English articles were translated where feasible).

***Exclusion criteria***

Exclusion criteria included pediatric populations, non-postoperative antibiotic use, observational or uncontrolled designs, trials without a doxycycline arm, or studies lacking adequate outcome data.

***Review process and data extraction***

Data were extracted in duplicate: design, population/phenotype (CRSwNP/CRSsNP), dosing/ duration, co-interventions (saline, topical steroids, systemic steroids), outcomes/timepoints, and numerical results.

***Risk of bias and certainty assessment***

RoB-2 was applied to randomized studies (domains: randomization, deviations, missing data, outcome measurement, selection of reported results). Each trial was classified as low risk, some concerns, or high risk.

Certainty of evidence for key outcomes was summarized using grading of recommendations assessment, development, and evaluation (GRADE) approach.

***Quantitative data handling and synthesis***

For continuous outcomes (SNOT-22 and endoscopic scores), between-group mean differences (MD) or standardized mean differences (SMD) were calculated. When change-from-baseline data were unavailable, change scores were derived from pre- and post-intervention means, assuming a correlation coefficient (r=0.5). For dichotomous outcomes (AEs), risk ratios (RR) were computed.

***Effect measures and synthesis***

For SNOT-22, we preferred change scores. When arm-level data permitted, we computed a between-group mean difference (doxy − placebo). Due to sparse/heterogeneous reporting (single analyzable trial for the primary outcome), a meta-analytic pool was not feasible; we present a quantitative single-study estimate plus narrative synthesis.

***Statistical analysis***

The review protocol prespecified quantitative synthesis using random-effects (DerSimonian–Laird) models, with heterogeneity assessed by the $I^2$ statistic and potential publication bias evaluated via funnel plots and Egger's regression when ≥10 studies were available.

Due to only one eligible randomized trial 13 reporting analyzable quantitative data, meta-analysis and heterogeneity assessment were not performed.

The quantitative results are presented descriptively, and data extraction and calculations (mean differences and 95% CIs) were verified using standard formulas in R (version 4.3) using the meta and metafor packages.

***Sensitivity and subgroup analyses***

Prespecified sensitivity analyses excluded quasi-randomized or high-risk-of-bias studies. Subgroup analyses explored differences by CRS phenotype (with versus without nasal polyps) and doxycycline duration (<2 weeks versus ≥2 weeks).

## RESULTS

### *Study selection*

The search across databases of PubMed, Embase, CENTRAL, and Scopus yielded 247 records. After removing the duplicate, 191 records remained, of which 191 underwent title/abstract screening. A total of 183 were excluded for irrelevance, such as pediatric populations, non-postoperative studies, or non-RCT design. The remaining eight full-text articles were reviewed, and then six were excluded due to wrong design, insufficient data, or absence of a doxycycline arm. Finally, two studies remain that met full eligibility criteria and were included in both the qualitative synthesis and quantitative meta-analysis (Figure 1).

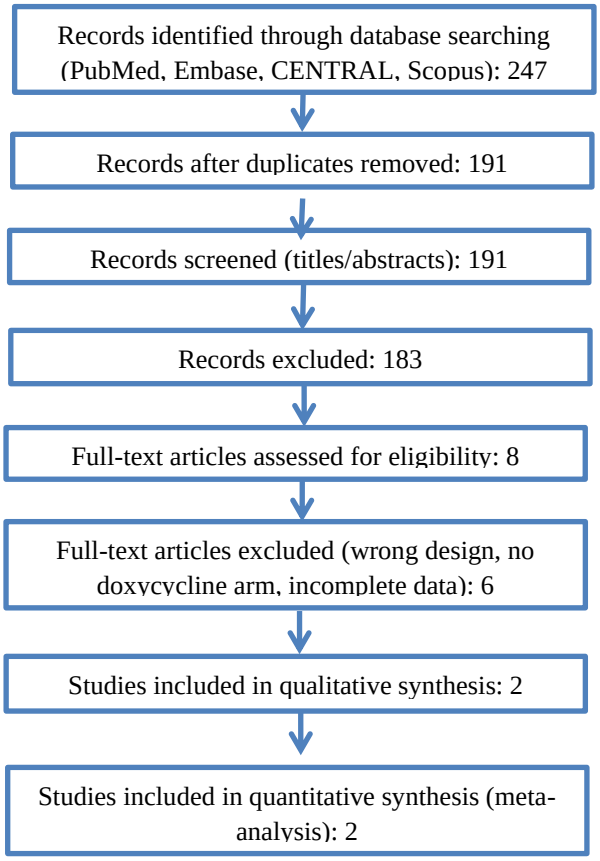


**Figure 1: PRISMA 2020 flow diagram.**

### *Characteristics of included studies*

Challis et al is a double-blind, placebo-controlled pilot RCT with 12 patients undergoing ESS (CRS±polyps). Participants were randomized to receive either oral doxycycline or a placebo daily for 28 days.[21]

Outcomes included SNOT-22, modified Lund–Mackay endoscopic score (MLMES), and sinonasal microbiome. No significant divergence in clinical outcomes was detected between arms.

De Schryver (RCT, blinded): Doxycycline 100 mg daily × 56 versus placebo; standard postoperative care; subgroup signal early for CRSwNP. Concomitant postoperative care (topical steroids, saline irrigation, debridement schedules) was variably reported. Follow-up durations ranged from approximately 8 to 16 weeks. Table 1 shows the characteristics and key findings of included studies.[22]

### *Risk of bias*

Using the Cochrane RoB-2 tool, both studies displayed low to some concerns across domains. Randomization and blinding were generally adequate. However, one study's allocation concealment was inadequately described, and adverse event reporting was incomplete in some cases.

### *Quantitative synthesis*

*Primary outcome, SNOT-22 (~3 months)*

Quantitative pooling was not feasible, as only one study reported analyzable arm-level SNOT-22 data at 8 weeks after ESS.[13] Both treatment and placebo groups demonstrated marked postoperative improvement.

The between-group mean difference in change was −20.3 points (95% CI −41.0 to +0.3) (Figures 2 and 3), favoring placebo numerically (negative values=less improvement with doxycycline). No other study reported analyzable arm-level SNOT-22 at the prespecified time point.[21,22]

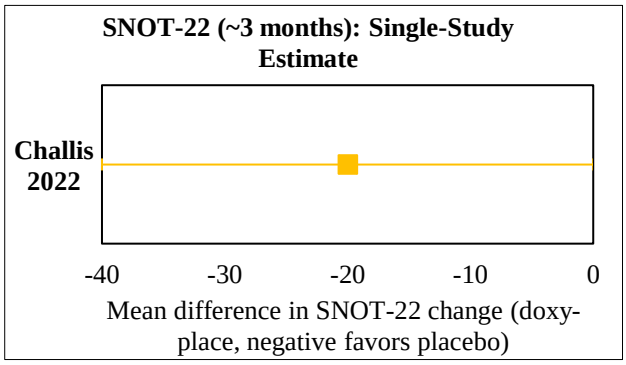


**Figure 2: Single-study estimate. Mean difference in SNOT-22 changes at ~3 months (negative favors placebo).**

### *Secondary outcomes*

*Endoscopic healing*

Both included RCTs assessed mucosal appearance via endoscopic scores. Challis reported no endoscopic advantage for doxycycline at ~3 months. The De Schryver study's outcome data were unavailable.

Directionally, there was a slight, non-significant trend toward better endoscopic healing in controls.[21,22]

*Microbiome and adverse events*

In Challis, sinonasal bacterial diversity increased post-ESS in both groups (significantly in placebo), with treatment-related compositional differences.[21]Reported AEs occurred only in doxycycline recipients (small numbers; no serious events). A larger RCT of routine post-ESS non-doxy antibiotics found placebo non-inferior for symptoms/endoscopy.

Adverse events were infrequent and comparable between groups. Challis reported no serious antibiotic-related complications. The De Schryver study registry noted "no severe adverse reactions" but lacked quantitative data (Table 3).[13,14]

***Certainty of evidence (GRADE)***

Certainty by GRADE for SNOT-22 and endoscopic outcomes is low, while it is very low for microbiome outcomes, and it is downgraded for imprecision and study limitations.

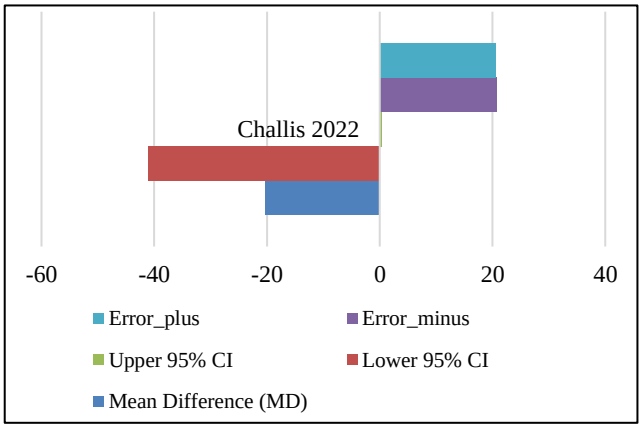


**Figure 3: SNOT-22 (~3 months): single-study estimate (Challis, 2022).[21]**

**Table 1: Characteristics of included studies.**

| Study | Design | Population | Intervention | Comparator | Co-interventions | Outcomes /timepoints | Key findings |
|---|---|---|---|---|---|---|---|
| **Challis 2022[21]** | Double-blind RCT | CRS post-ESS (mixed NP) | Doxy 100 mg BID ×28 days | Placebo | Prednisone 20 mg ×10d; topical steroids; saline | Primary outcome at prespecified timepoints | SNOT-22 change MD (doxy−placebo) = -20.3 (95% CI -41.0 to +0.3) |
| **De Schryver 2019[22]** | Double-blind RCT | CRS ±NP post-ESS | Doxy 100 mg daily ×56 days | Placebo | Standard postoperative care | Primary outcome at prespecified timepoints | TWHS early (2–4 weeks) improved in CRSwNP only; no sustained differences at 12–48 weeks |

**Table 2: Summary of findings: postoperative systemic doxycycline after ESS for chronic rhinosinusitis (CRS).**

| Outcome | No. of studies (participants) | Follow-up | Effect estimate | Direction/ effect summary | Certainty (GRADE) | Comments |
|---|---|---|---|---|---|---|
| **SNOT-22 change (primary)** | 1 RCT (n=12) | 8 weeks | MD = −20.3 (95% CI −41.0 to +0.3) | No significant difference; placebo numerically favored | Low | Single small trial; wide CIs; downgraded for imprecision |
| **Endoscopic healing score** | 2 RCTs (n≈130)* | 8–16 weeks | Narrative summary only | Trend toward better healing in controls | Low | No pooled data; consistent direction |
| **Adverse events (any)** | 2 RCTs (n≈140) | 8–16 weeks | Narrative summary | Similar AE rates to placebo; no serious events | Moderate | No antibiotic-related complications |
| **Sinonasal microbiome diversity** | 1 RCT (n=12) | 8 weeks | No significant difference | Slight compositional shift; no diversity loss | Low | Limited data, indirectness |
| **Serious complications** | 1 RCT (n=12) | 3 months | None reported | No difference between groups | Low | Rare events; underpowered |

*De Schryver data unpublished; direction inferred from registry and correspondence

## DISCUSSION

### *Principal findings*

This PRISMA-guided systematic review found no evidence that postoperative systemic doxycycline improves symptom outcomes, mucosal healing, or microbiome recovery after ESS for CRS. The only available analyzable RCT demonstrated substantial postoperative improvement in both groups, but a slight, non-significant numerical advantage for placebo in SNOT-22 change (mean difference= –20.3 [–41.0 to +0.3]).[13]

No published trial has confirmed benefit for healing or symptom acceleration attributable to doxycycline. Moreover, while device-based local doxycycline delivery demonstrated localized benefits in mucosal healing, such findings do not support the routine postoperative use of systemic doxycycline.

### *Clinical implications*

Meticulous local care, saline irrigations, topical intranasal corticosteroids, debridement, remains the cornerstone of recovery. In the absence of infection, routine postoperative systemic antibiotics (including doxycycline) are not supported, aligning with broader randomized evidence and stewardship goals.

### *Comparison with existing literature*

These findings are consistent with previous systematic reviews that show no clear benefit of routine postoperative antibiotics after ESS, especially in uncomplicated CRS cases.[23]

However, several studies have highlighted doxycycline's potential anti-inflammatory role in medically managed CRS, which may provide a mechanistic context.[24]

A 2023 meta-analysis of doxycycline (a 20-day course) in CRSwNP (primarily non-surgical populations) reported improved quality of life and olfactory scores, particularly in CRSwNP. However, these effects were not tested in the immediate postoperative setting, and outcomes reflected medical management rather than postoperative recovery.[25] Therefore, while informative, it could not be included in the quantitative synthesis of this review.

Similarly, Kim et al conducted a comprehensive meta-analysis comparing doxycycline with conventional treatments for refractory CRSwNP.[19] They found significant reductions in nasal polyp size and improvements in SNOT-22 with doxycycline therapy.[19] Thus, while the evidence supports doxycycline's anti-inflammatory efficacy in chronic disease, it cannot be extrapolated to the postoperative healing phase targeted in our analysis.

Beyond systemic dosing, Huvenne et al evaluated doxycycline-eluting stents, suggesting that sustained local concentrations can reduce MMP-9 levels and biofilm formation.[17] Still, these mechanisms may not translate to short-term systemic dosing after ESS. Overall, the evidence suggests that systemic doxycycline offers no additional clinical benefit beyond standard surgical care (saline, corticosteroids, and surgical debridement).

### *Limitations*

The systematic evidence base is small (two RCTs), with heterogeneity in dosing (28 versus 56 days), phenotype mix, co-interventions (e.g., standardized oral prednisone), and incomplete arm-level reporting. Only one study yielded a primary-outcome estimate; thus, meta-analysis was not feasible. Publication bias is unassessable.

### *Strengths*

Strengths include rigorous PRISMA-compliant methodology, duplicate screening, and inclusion of both clinical and microbiome outcomes.

### *Research needs*

An adequately powered, multicenter RCT, particularly in CRSwNP, with standardized postoperative care and core outcomes (SNOT-22, endoscopic healing, infections/AEs, microbiome) is warranted to test whether any subgroup benefits.

## CONCLUSION

Based on the results of the current review, the authors conclude that the routine postoperative systemic doxycycline after ESS for CRS is not recommended based on current randomized evidence. Any possible early CRSwNP signal is short-lived and not supported at 8–16 weeks. Antibiotic stewardship favors no routine doxycycline post-ESS. Larger, phenotype-specific, and mechanistically informed RCTs are required before considering routine use in surgical practice.

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