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Original Research

Inhaled tobramycin in non-cystic fibrosis bronchiectasis: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Non-cystic fibrosis bronchiectasis (NCFB) is often complicated by chronic Pseudomonas aeruginosa infection. Inhaled antibiotics, such as tobramycin, have been explored for their efficacy in managing these infections, but their efficacy and safety in NCFB remains uncertain.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the efficacy and safety of inhaled tobramycin in NCFB patients. PubMed, EMBASE, Cochrane Library, and ISI Web of Science databases were searched up to June 2024 using predefined keywords. Studies comparing inhaled tobramycin versus placebo were included if they reported outcomes related to P. aeruginosa eradication, sputum density, exacerbations, hospital admissions, and adverse events.

Results: Nine RCTs involving 772 patients met the inclusion criteria. Inhaled tobramycin significantly increased P. aeruginosa eradication rates compared to placebo ($I^2 = 22.0$ %, $P = 0.255$; RR 2.422, 95 % CI 1.570 to 3.738, $P < 0.001$). There was a marked reduction in hospital admissions ($I^2 = 27.9$ %, $P = 0.250$; WMD -0.523, 95 % CI -0.879 to −0.167, $P = 0.004$) but no significant difference in exacerbation rates ($I^2 = 31.9$ %, $P = 0.196$; RR 0.837, 95 % CI 0.519 to 1.349, $P = 0.464$). Adverse events leading to trial discontinuation were higher in the tobramycin group ($I^2 = 0.0$ %, $P = 0.634$; RR 1.968, 95 % CI 1.197 to 3.236, $P = 0.008$).

Conclusions: Inhaled tobramycin therapy demonstrated efficacy in eradicating P. aeruginosa and reducing hospital admissions in patients with NCFB. However, no significant impact on exacerbation rates was observed, and the higher incidence of adverse events necessitates careful consideration in clinical practice.

1. Introduction

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic lung condition characterized by abnormal and permanent dilation of the bronchi, leading to mucus accumulation and recurrent infections [1,2]. A common and serious complication in NCFB is chronic infection with Pseudomonas aeruginosa, a pathogen that exacerbates inflammation, accelerates lung function decline, and worsens prognosis [3–5]. Inhaled antibiotics have emerged as a targeted treatment for managing these infections. They deliver high local concentrations of the drug directly to the site of infection, reducing bacterial load and inflammation [6,7]. However, their efficacy is limited by factors such as antibiotic resistance, variability in drug deposition within the lungs, and potential side effects [8–10].

Tobramycin, an aminoglycoside with significant antipseudomonal properties, has been proven effective in treating chronic P. aeruginosa infections in cystic fibrosis (CF) patients [11]. Emerging evidence suggests potential benefits in non-cystic fibrosis bronchiectasis (NCFB), including reducing P. aeruginosa density in sputum and improving respiratory symptoms [12]. However, the current evidence for its use in NCFB remains limited [13]. An earlier meta-analysis by Sangiovanni et al. provided preliminary evidence supporting the use of inhaled tobramycin in NCFB [14]. However, the study included only a limited number of trials with small sample sizes, which may have contributed to variability in the findings. Given the growing body of evidence in recent years, we conducted this meta-analysis incorporating randomized controlled trials (RCTs) to further investigate the efficacy and safety of tobramycin in NCFB.

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2. Methods

2.1. Literature search

We systematically searched the PubMed, EMBASE, Cochrane Library, and ISI Web of Science databases from their inception to June 2024, without language restrictions, to identify all RCTs examining the efficacy and safety of inhaled tobramycin in patients with NCFB. Our search utilized "tobramycin" and "bronchiectasis" as keywords. The meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

2.2. Inclusion criteria

Studies were included based on the following criteria: (1) RCTs; (2) comparison of inhaled tobramycin versus placebo in assessing efficacy and safety for NCFB patients; and (3) reporting of at least one of the following outcomes: P. aeruginosa eradication, change in P. aeruginosa density in sputum, exacerbation frequency, hospital admissions, and adverse events. Reviews, conference papers, case reports, and overlapping trials were excluded.

2.3. Data extraction and quality assessment

Two authors independently screened each citation based on title, abstract, and full text. Eligible studies underwent data extraction using a structured form, capturing baseline characteristics (author's name, publication year, sample size, mean age, smoking history, lung function data, and follow-up duration) and outcomes (P. aeruginosa eradication, change in sputum P. aeruginosa density, exacerbation frequency, hospital admissions, and adverse events). The methodological quality and risk of bias of each trial was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials 2.0 (RoB 2.0) [16]. Any discrepancies in study selection or data extraction between the two authors were resolved through consensus or referred to a third investigator.

2.4. Statistical analysis

Statistical analyses were conducted using STATA version 12.0 with the metan function. Binary outcome data were presented as risk ratios (RR) with 95 % confidence intervals (CI), while continuous data were expressed as weighted mean differences (WMD) with corresponding 95 % CIs. Heterogeneity was assessed using I^2 statistics, and a random-effects (RE) model was employed regardless of heterogeneity, as recommended [17]. Sensitivity or subgroup analyses were planned in cases of significant heterogeneity among studies. Funnel plot asymmetry was evaluated using Begg's test [18]. The threshold for statistical significance was set at $P < 0.05$.

3. Results

3.1. Selected studies and baseline characteristics

Following our search strategy, we initially identified a total of 1003 citations. After removing duplicates, reviews, case reports, letters, conference abstracts, and articles unrelated to our topic, ten articles underwent full-text assessment. Among these, one was excluded for not meeting the criteria for RCTs [12]. Ultimately, nine RCTs involving 772 patients were included in our meta-analysis [19–27]. The study flow is detailed in Fig. 1, and baseline information from these trials is summarized in Table 1.

3.2. Quality assessment and risk of bias

The methodological quality and risk of bias of the included studies were evaluated using the RoB 2.0 tool [16], which includes the following five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Most studies were classified as low

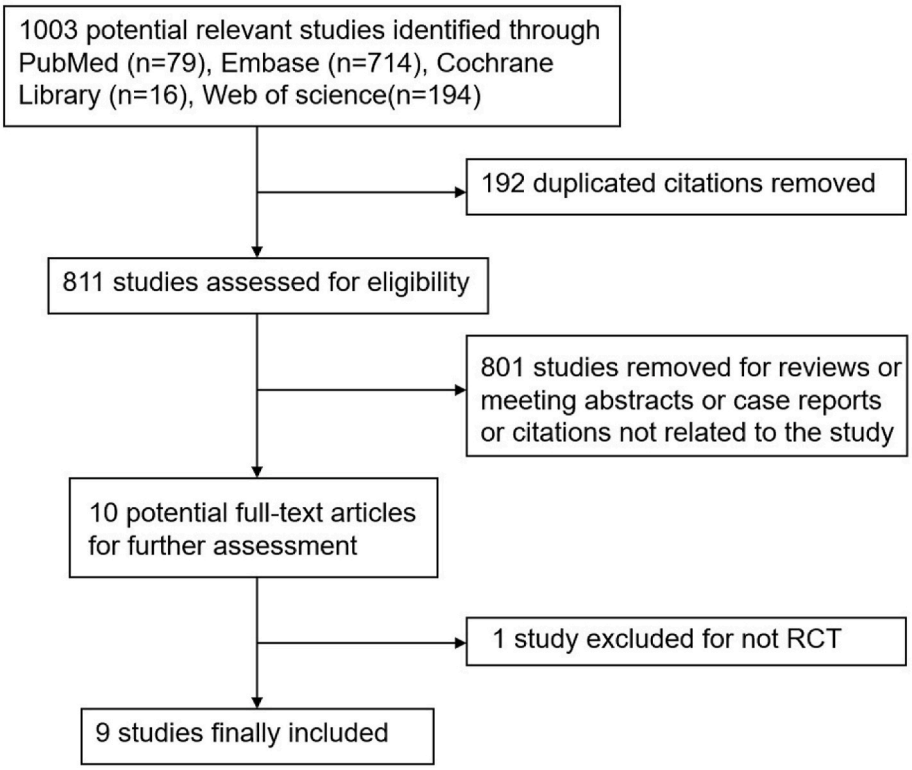

Fig. 1. Flow chart of study selection. RCT = randomized controlled trial.

Table 1
Characteristics of included studies.

Study	year	TG regimen	CG regimen	Treatment duration
Terpstra et al. [19]	2023	TIS (300 mg/5 mL) once daily	placebo (0.9 % saline, 5 mL) once daily	1 year
Guan et al. [20]	2023	TIS (300 mg/5 mL) twice daily	placebo (0.9 % saline, 5 mL) twice daily	TIS 28 days + placebo 28 days for two cycles
Terpstra et al. [21]	2022	TIS (300 mg/5 mL) once daily	placebo (0.9 % saline, 5 mL) once daily	1 year
Loebinger et al. [22]	2021	TIP 84 mg once daily or 140 mg once daily or 112 mg twice daily	placebo	TIP 28 days + placebo 28 days for two cycles or TIP continue for 112 days
Orriols et al. [23]	2015	TIS (300 mg) twice daily	placebo (0.9 % saline) twice daily	3 months
Bilton et al. [24]	2006	TIS (300 mg/5 mL) twice daily	placebo (quinine sulfate 1.25 mg/5 mL) twice daily	14 days
Drobnic et al. [25]	2005	TIS (300 mg/8 mL) twice daily	placebo (0.9 % saline, 8 mL) twice daily	6 months
Barker et al. [26]	2000	TIS (300 mg/5 mL) twice daily	placebo (quinine sulfate 1.25 mg/5 mL) twice daily	28 days
Orriols et al. [27]	1999	TIS (100 mg/8 mL) twice daily	symptomatic treatment	1 year

Study	Year	TG/ CG	Sample size, n	Age, mean (SD)	Females, n (%)	Never smoker, n (%)	FEV1 % predicted, mean (SD)	Use of steroids, n (%)	Follow-up
Terpstra et al. [19]	2023	TG	28	68.6 (7.2)	14 (50.0)	12 (42.9)	89.4 (18.3)	19 (67.9)	1 year
		CG	29	65.8 (14.3)	19 (65.5)	12 (41.4)	71.4 (23.7)	21 (72.4)	
Guan et al. [20]	2023	TG	167	53.0 (13.0)	109 (65.3)	144 (86.2)	60.9 (21.5)	9 (5.4)	16 weeks
		CG	172	54.0 (12.0)	112 (65.1)	152 (88.4)	63.6 (22.5)	6 (3.5)	
Terpstra et al. [21]	2022	TG	26	67.9 (6.6)	13 (50.0)	12 (46.2)	65.9 (24.9)	17 (65.4)	1 year
		CG	26	64.1 (14.0)	17 (65.4)	10 (38.5)	70.5 (24.0)	19 (73.1)	
Loebinger et al. [22]	2021	TG	86	NR	53 (61.6)	NR	NR	12 (14.0)	24 weeks
		CG	21	NR	13 (61.9)	NR	NR	1 (4.8)	
Orriols et al. [23]	2015	TG	16	69.4(2.1)	6 (37.5)	5 (31.3)	56.8 (21.3)	NR	15
		CG	19	70.1(1.9)	10 (52.6)	10 (52.6)	55.3 (30.3)	NR	months
Bilton et al. [24]	2006	TG	26	61.9 (11.4)	20 (76.9)	14 (51.9)	53.2 (19.7)	NR	6 weeks
		CG	27	63.7 (11.7)	18 (66.7)	18 (69.2)	51.4 (19.4)	NR	
Drobnic et al. [25]	2005	TG	20	NR	NR	NR	NR	NR	13
		CG	20	NR	NR	NR	NR	NR	months
Barker et al. [26]	2000	TG	37	66.6 (13.0)	23 (62)	13 (35.1)	56.2 (21.2)	20 (54.0)	8 weeks
		CG	37	63.2 (13.5)	22 (59)	21 (56.8)	53.3 (22.1)	21 (57.0)	
Orriols et al. [27]	1999	TG	7	62.0 (8.5)	1 (14.3)	NR	62.3 (19.9)	NR	1 year
		CG	8	61.4 (10.3)	4 (50.0)	NR	56.2 (21.4)	NR	

TG inhaled tobramycin group; *CG* control group; *TIS* tobramycin inhalation solution; *TIP* tobramycin inhalation powder.
TG inhaled tobramycin group; *CG* control group; *NR* not reported; *SD* standard deviation.

risk of bias (Fig. 2). The publication bias was calculated based on the endpoint of P. aeruginosa eradication (Fig. 3), with no significant bias being identified (Begg's test, P = 0.386).

3.3. Meta-analysis results

3.3.1. P. aeruginosa eradication

Eight RCTs [20–27] reported the eradication of P. aeruginosa. The eradication rate was 35.98 % (136/378) in the tobramycin group and 11.73 % (38/324) in the control group. The results showed that inhaled tobramycin therapy significantly increased the rate of P. aeruginosa eradication compared to the control group (I^2 = 22.0 %, P = 0.255; RR 2.422, 95 % CI 1.570 to 3.738, P < 0.001) (Fig. 4).

3.3.2. P. aeruginosa density in sputum

Three trials [20,24,26] involving 405 participants assessed the change in P. aeruginosa density in sputum. Due to substantial heterogeneity (I^2 = 95.6 %, P < 0.001) and the limited number of studies, a meta-analysis was not performed. However, all three studies observed that the reduction in P. aeruginosa density was more significant in the inhaled tobramycin group compared to the control group.

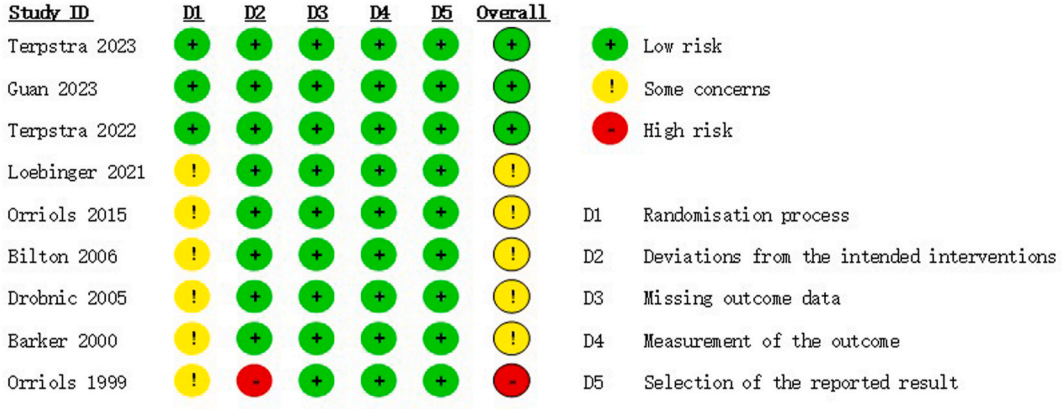

Fig. 2. Cochrane risk of bias tool for randomized controlled trials 2.0 (RoB 2.0) results for each individual trial.

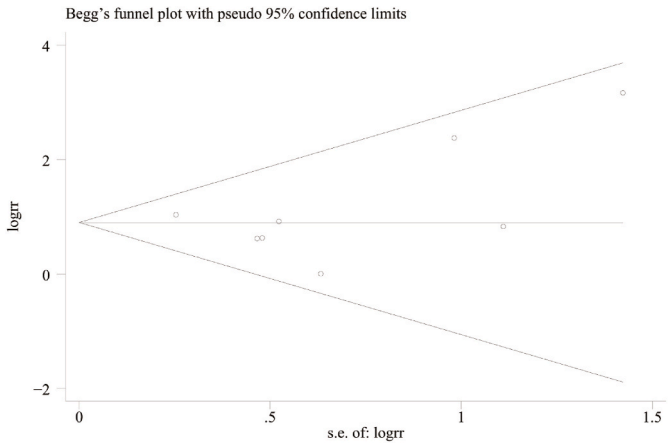

Fig. 3. Funnel Plot for P. aeruginosa eradication. RR = relative risk; TG = inhaled tobramycin group; CG = control group.

3.3.3. *Acute exacerbations*

Eight studies [20–27] reported on acute exacerbations, with two presenting results as means and standard deviations [23,25]. Consequently, six RCTs [20–22,24,26,27] involving 339 patients were included in the meta-analysis. The results showed no significant difference in the acute exacerbation rate between the inhaled tobramycin group and the control group. (I^2 = 31.9 %, P = 0.196; RR 0.837, 95 % CI 0.519 to 1.349, P = 0.464) (Fig. 5).

3.3.4. *Hospital admissions*

Three studies [23,25,27] reported on the outcome of hospital admissions. The results indicated that the number of admissions was significantly lower in the inhaled tobramycin group compared to the control group (I^2 = 27.9 %, P = 0.250; WMD -0.523, 95 % CI -0.879 to −0.167, P = 0.004) (Fig. 6).

3.3.5. *Adverse events leading to trial discontinuation*

Adverse events were common across all nine studies [19–27], with varying definitions. Therefore, a meta-analysis was conducted on adverse events leading to trial discontinuation. The results showed that adverse events were significantly higher in the inhaled tobramycin group compared to the control group (I^2 = 0.0 %, P = 0.634; RR 1.968, 95 % CI 1.197 to 3.236, P = 0.008) (Fig. 7).

4. Discussion

In this meta-analysis of RCTs investigating the efficacy and safety of inhaled tobramycin in NCFB, our findings reveal significant improvements in P. aeruginosa eradication rates with inhaled tobramycin compared to the control group. Additionally, there was a notable reduction in hospital admissions among patients treated with inhaled tobramycin. However, no significant differences were observed in acute exacerbation rates between the tobramycin and control groups. Adverse events leading to trial discontinuation were more frequent in the inhaled tobramycin group. These results suggest that while inhaled tobramycin effectively eradicates P. aeruginosa and reduces hospital admissions, it is associated with a higher risk of adverse events compared to control treatments.

P. aeruginosa is a predominant pathogen in NCFB, significantly contributing to disease progression and exacerbations [28,29]. Its ability to form biofilms and acquire resistance mechanisms further complicates treatment outcomes [30]. Tobramycin, an aminoglycoside antibiotic, is widely recognized for its potent bactericidal activity against P. aeruginosa. It exerts its effect by binding to bacterial ribosomes, thereby inhibiting protein synthesis and disrupting bacterial growth. Inhaled tobramycin represents a strategic advantage in managing chronic respiratory infections such as CF by delivering high concentrations of the drug directly to the lungs [31]. This localized approach not only enhances efficacy against P. aeruginosa but also minimizes systemic exposure, thus reducing the risk of systemic adverse effects associated with prolonged antibiotic use. However, despite the potential advantages supported by some clinical studies, the use of inhaled tobramycin in NCFB still lacks sufficient evidence due to potential side effects such as pulmonary irritation and ototoxicity.

Multiple studies have demonstrated that inhaled tobramycin significantly reduces P. aeruginosa density and improves clinical symptoms associated with bronchiectasis. However, previous reviews, such as the meta-analysis conducted by Sangiovanni et al. [14], included only 2–3

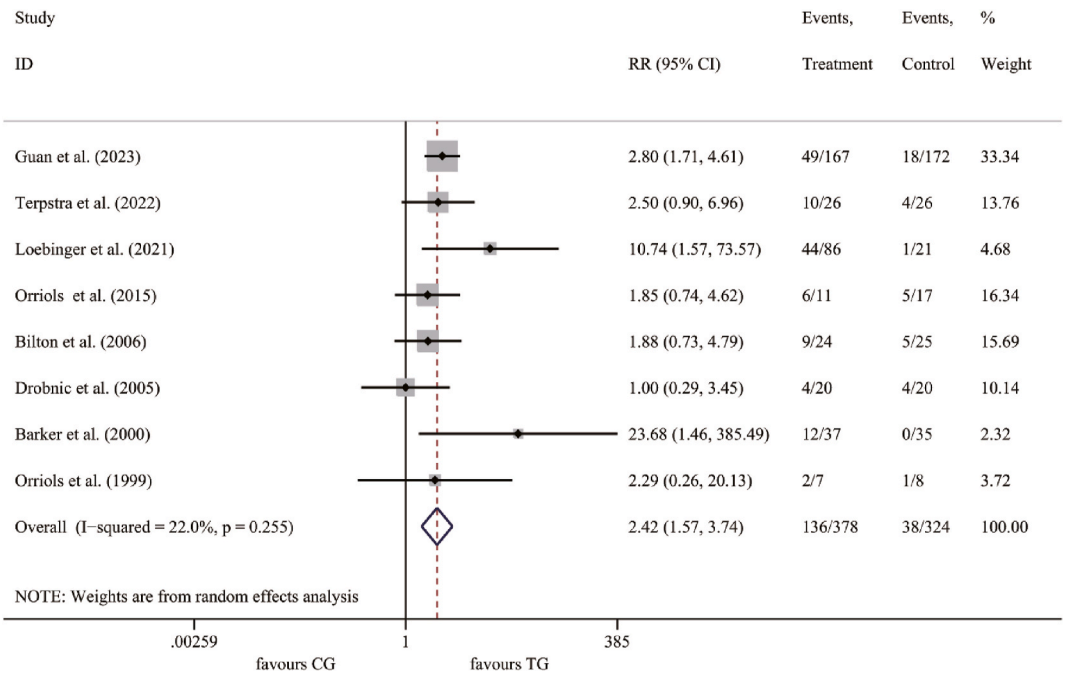

Fig. 4. Forest plot for P. aeruginosa eradication. RR = relative risk; TG = inhaled tobramycin group; CG = control group.

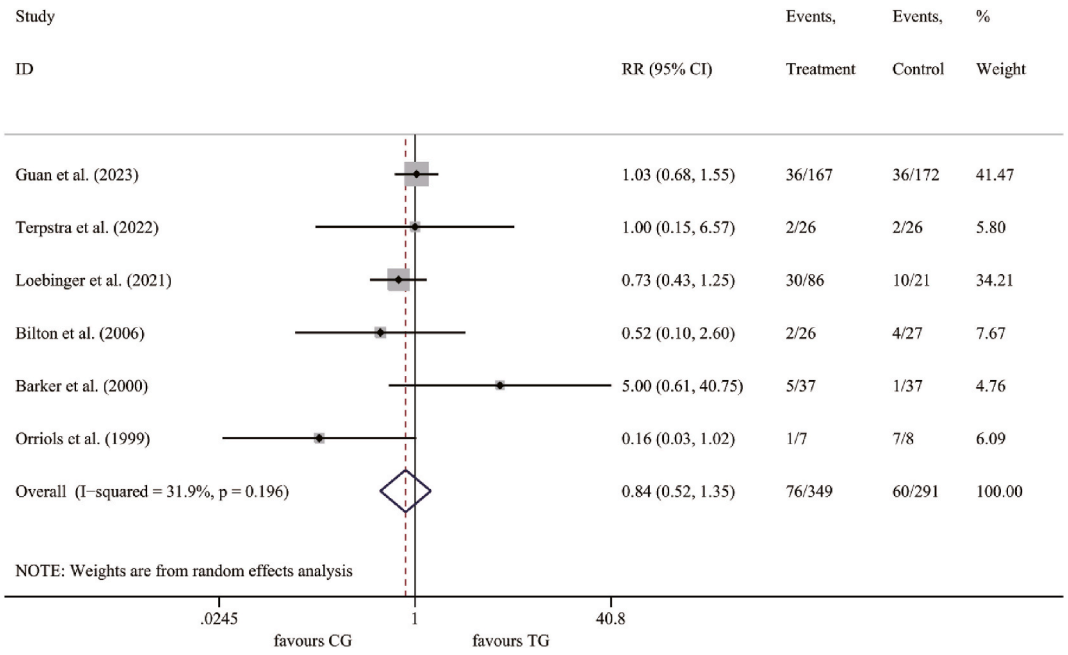

Fig. 5. Forest plot for acute exacerbations. RR = relative risk; TG = inhaled tobramycin group; CG = control group.

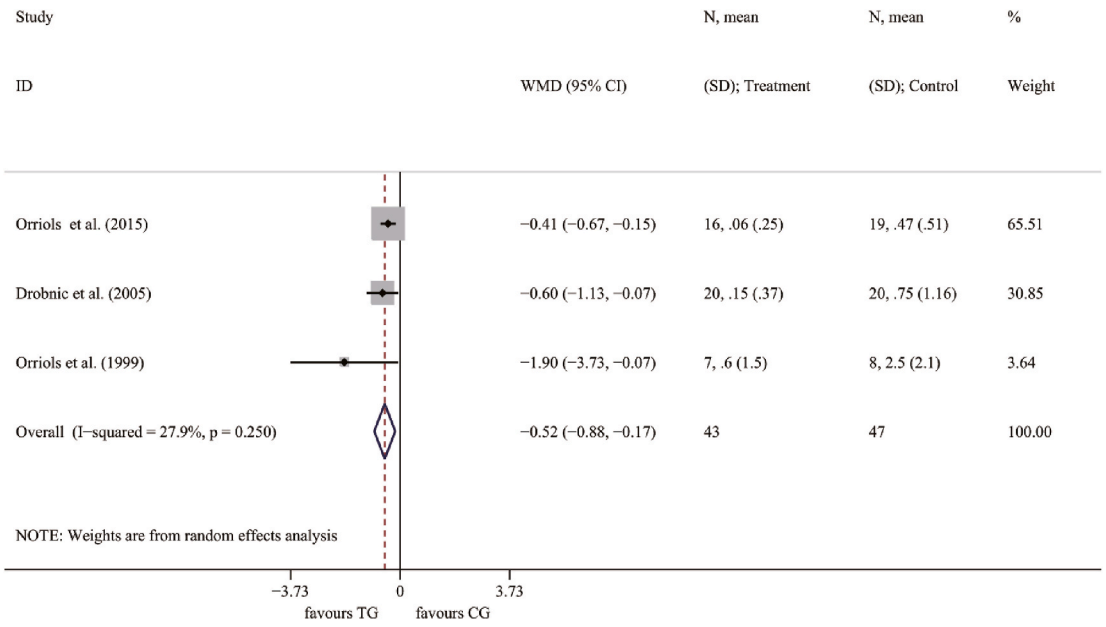

Fig. 6. Forest plot for hospital admissions. WMD = weighted mean difference; TG = inhaled tobramycin group; CG = control group.

studies with small sample sizes of fewer than 150 participants, leading to high heterogeneity and limiting the reliability of the conclusions. Given the diverse etiologies of NCFB, a larger patient population may be necessary to obtain more robust findings [32]. Our study included 9 RCTs with a total of 772 patients, providing the latest clinical evidence for the use of inhaled tobramycin in patients with NCFB. We observed a significant improvement in P. aeruginosa eradication in the inhaled tobramycin group. However, no notable difference in exacerbation rates was detected, possibly due to variations in baseline characteristics and definitions of exacerbation across studies. Despite this, the inhaled tobramycin group showed a significant reduction in severe hospitalizations, suggesting a potential benefit in preventing critical exacerbations requiring hospital care. Another consideration is the side effects of inhaled tobramycin. In previous studies, side effects were fairly common, generally mild to moderate, and most events were considered unrelated to the treatment by investigators [20]. However, in the present study, adverse events leading to trial discontinuation were significantly more frequent in the inhaled tobramycin group, emphasizing the importance of ongoing monitoring and patient education during tobramycin inhalation therapy.

Several limitations of the study should be noted. Firstly, while our study included nine RCTs with a total of 772 patients, the heterogeneity in baseline characteristics and definitions of exacerbation among the included trials may have influenced the results, particularly the non-significant difference in overall exacerbation rates. Secondly, while we acknowledge that variations in treatment duration, dosing frequency, formulation types (e.g., dry powder vs. solution), and inhalation devices could theoretically introduce heterogeneity, our pre-specified

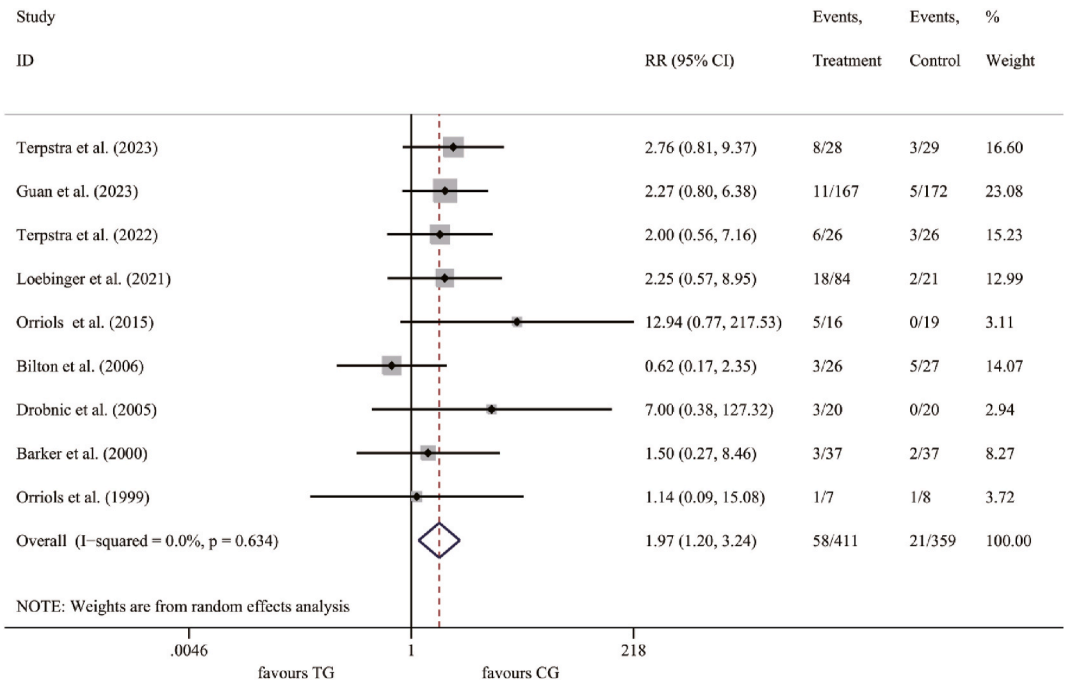

Fig. 7. Forest plot for adverse events leading to trial discontinuation. RR = relative risk; TG = inhaled tobramycin group; CG = control group.

heterogeneity analyses demonstrated acceptable consistency across studies for most outcomes. Nonetheless, the potential clinical implications of these protocol variations warrant careful consideration. Thirdly, the variability in adverse event reporting and definitions across studies poses a challenge, as it may have led to an underestimation or overestimation of the true incidence of adverse events associated with inhaled tobramycin. Future RCTs should adopt consistent adverse event reporting guidelines to facilitate more accurate meta-analyses and better inform clinical practice. Fourthly, due to the limited number of studies reported, we were unable to evaluate additional outcomes, such as quality of life (QoL). Considering that QoL is a critical outcome in the management of bronchiectasis, future trials should incorporate standardized QoL measures to more comprehensively assess the impact of treatment. Lastly, the lack of detailed patient-level data on other baseline characteristics, such as the severity of bronchiectasis, coexisting conditions, and previous treatments, limits our ability to perform more nuanced subgroup analyses, which could provide deeper insights into the patient populations that might benefit most from inhaled tobramycin therapy. Given these limitations, the findings should be interpreted with caution. Future studies enrolling larger, more homogeneous patient populations and employing standardized outcome measures are warranted. Moreover, meta-analyses or clinical trials that incorporate detailed subgroup evaluations are needed to identify patient populations that may derive the greatest benefit from inhaled tobramycin therapy.

5. Conclusion

Inhaled tobramycin therapy demonstrated efficacy in eradicating P. aeruginosa and reducing hospital admissions in patients with NCFB. However, no significant impact on exacerbation rates was observed, and the higher incidence of adverse events necessitates careful consideration in clinical practice. Given the study's limitations, further investigation is warranted to validate these findings.

CRediT authorship contribution statement

Zhaoshuang Zhong: Writing – original draft, Investigation, Conceptualization. **Chunyang Zhang:** Writing – original draft, Investigation, Conceptualization. **Long Zhao:** Methodology, Formal analysis. **Yan Zhao:** Methodology. **Shuyue Xia:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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