Original Article

Comparative efficacy and safety of inhaled antibiotics in managing chronic *Pseudomonas aeruginosa* infection in patients with cystic fibrosis and bronchiectasis: a systematic review and network meta-analysis

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Background: An expanding array of inhaled antibiotic therapies can be effective for the treatment of chronic *Pseudomonas aeruginosa* (*P. aeruginosa*) infection in patients with cystic fibrosis (CF) and non-CF bronchiectasis (NCFB). Nonetheless, there is a paucity of direct studies comparing the curative effects of these regimens. This network meta-analysis (NMA) aimed to assess the efficacy and safety of different inhaled antibiotic therapies for the relative short-term (4 weeks) and long-term (≥4 months) management of chronic *P. aeruginosa* infection in patients with CF and NCFB, respectively.

Methods: We searched PubMed, Web of Science, Embase, and Cochrane Library database as at 25th February, 2024. Randomized controlled trials (RCTs) involving inhaled antibiotic therapies for treatment of CF or NCFB were thoroughly screened. We conducted this NMA within a Bayesian framework. The surface under the cumulative ranking curve (SUCRA) was calculated to estimate relative effects of interventions per outcome.

Results: A total of 39 RCTs were included, involving 18 inhaled antibiotic treatment regimens and 7,486 participants. The primary outcomes assessed were microbiological efficacy and tolerability. According to SUCRA results, for patients with CF, tobramycin inhalation powder (TIP) had the best profile regarding microbiological efficacy at both short-term and long-term follow-up (SUCRA, 94.5%; 90.5%). Colistin for inhalation (SUCRA, 84.0%) and tobramycin inhalation solution (TIS; SUCRA, 75.7%) had the best tolerability profile at short-term and long-term follow-up, respectively. For patients with NCFB, TIP (SUCRA, 84.2%) and gentamicin injectable solution (GM) for inhalation (SUCRA, 92.2%) had the best profile regarding microbiological efficacy at short-term and long-term follow-up, respectively. Ciprofloxacin inhalation powder had the best tolerability profile at both short-term and long-term follow-up (SUCRA, 66.4%; 85.6%).

Conclusions: The present study suggests that inhalation of TIS and GM are deemed exhibiting favorable profile across various outcomes for treating chronic *P. aeruginosa* infection in patients with CF and NCFB, respectively. Further large-scale and higher-quality studies are needed to support the conclusion.

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Keywords: Inhaled antibiotics; *Pseudomonas aeruginosa* (*P. aeruginosa*); cystic fibrosis (CF); bronchiectasis; network meta-analysis (NMA)

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Introduction

Bronchiectasis is a chronic respiratory disease characterized by irreversible and abnormal airway dilatation that significantly impacts patient well-being (1). The development of bronchiectasis has been associated with various factors, including lower respiratory tract infections, immune deficiencies, and inherited disorders such as primary ciliary dyskinesia and cystic fibrosis (CF) (2,3). Among those factors, CF, although thoroughly studied, is a less common cause (4). CF is a multisystem disorder with a high prevalence in Caucasian populations, which mainly affects gastrointestinal tract and respiratory system. In advanced stages, CF is often accompanied by respiratory failure, drastically reducing life expectancy (5). On the other hand, bronchiectasis caused by factors other than CF is collectively known as non-CF bronchiectasis (NCFB). Clinical manifestations vary among patients, with cough, sputum, and lethargy being the most common but nonspecific symptoms (6). This poses challenges in timely clinical diagnosis, leading to a concerning number of undiagnosed or misdiagnosed NCFB cases (1).

The fundamental pathological processes of lung disease in CF and NCFB align with the vicious circle hypothesis. This hypothesis suggests that airway infection, mucus obstruction, impaired mucociliary clearance, and inflammation synergistically contribute to an escalating cascade reaction that perpetuates disease progression and lung injury (7,8). Lung infections in patients with CF and NCFB are complex, often involving the coexistence of multiple pathogens. Among these pathogens, *Pseudomonas aeruginosa* (*P. aeruginosa*) is the most prevalent in sputum cultures and of major concern (9), affecting up to 50% of adult patients with CF (5) and 20% to 40% of adult patients with NCFB (10,11). Furthermore, chronic *P. aeruginosa* infection has frequently been reported as a strong predictor of unfavorable prognosis, highly correlated with worse lung function, frequent exacerbations, and premature mortality (12,13). Consequently, multinational guidelines and consensuses recommend long-term antimicrobial therapy for patients with CF and *P. aeruginosa* infection, but also for NCFB in patients with *P. aeruginosa* infection and ≥3 exacerbations per year (1,14-17).

Specific to respiratory infectious diseases, inhaled antibiotic therapy assumes a critical role in long-term suppression treatment due to its unique route of administration. Inhaled antibiotics offer advantages such as precise targeting, rapid onset of action, high local concentration, fewer systemic adverse reactions, and a low risk of drug resistance. Tobramycin, colistin, aztreonam lysine, levofloxacin, and amikacin liposome are widely recognized as the most commonly used anti-pseudomonal inhalation agents. Additionally, inhalation of ciprofloxacin, gentamicin, and azithromycin have shown promising results

Highlight box

Key findings
- Inhalation of tobramycin inhalation solution and gentamicin may be the best choice in long-term management of cystic fibrosis (CF) and non-CF bronchiectasis (NCFB) with *Pseudomonas aeruginosa* infection, respectively.
- Differences in clinical characteristics, etiologies, treatment strategies, and intrapulmonary microenvironments may contribute to the significant differences in clinical response to inhaled antibiotic therapy in patients with CF and NCFB.

What is known and what is new?
- Multinational guidelines and consensuses have recommended a list of inhaled antibiotic treatment regimens for CF and NCFB. Nonetheless, there is a paucity of direct studies comparing the curative effects of these regimens.
- This study compared and ranked the efficacy and safety of various inhaled antibiotic regimens through network meta-analysis. And the factors contributing to marked differences in clinical response between inhaled antibiotics-treated patients with CF and NCFB were discussed.

What is the implication, and what should change now?
- Based on the current evidence, our findings may better inform clinical decisions for CF and NCFB treatment, particularly in countries with limited local resources and capabilities.
- Further large-scale and higher-quality studies are needed to support the conclusion.

as alternative treatment options (18,19).

Given the expanding array of inhaled antibiotics, the search for optimal treatment regimens becomes crucial to guide clinical practice. Nonetheless, there is a paucity of direct studies comparing the efficacy and safety of these inhaled antibiotic regimens in either CF or NCFB. Thus, we conducted a network meta-analysis (NMA) to fill this gap and provide valuable insights for clinical decisions. Our objective was to systematically evaluate the efficacy and safety of different inhaled antibiotic therapies and identify the most effective ones for relative short-term (4 weeks) and long-term management (≥4 months) of chronic *P. aeruginosa* infection in patients with CF and NCFB, respectively. We present this article in accordance with the PRISMA-NMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1525/rc) (20).

Methods

The protocol of this study was registered in the international prospective register of systematic reviews (PROSPERO) under the registration code of CRD42024581515.

Literature search

A systematic literature search was conducted in PubMed, Web of Science, Embase (via Ovid), and the Cochrane Library from the inception of each database till 25th February, 2024. The primary search terms were as follows: ("Cystic Fibrosis" OR "Bronchiectasis" OR "Pseudomonas aeruginosa") AND "Inhalation" AND "Anti-Bacterial Agents" AND "Randomized controlled trial". No restrictions regarding date, language, publication status, or year were applied. Further details of search strategy are shown in Table S1. Additional searches were performed by reviewing the ClinicalTrials.gov registry and the reference lists of included publications. Two investigators (Y.C. and Z.L.) independently conducted searches for potentially eligible studies, and any discrepancies were resolved by a senior investigator (J.Z.).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) study design: randomized controlled trials (RCTs); (II) population: patients over 6 years of age with *P. aeruginosa* infection and CF, confirmed by sweat test or gene analysis, or adult patients (≥18 years) with *P. aeruginosa* infection and NCFB, confirmed by computed tomography or bronchography; (III) intervention: use of inhaled antibiotic therapies for a minimum of 4 weeks; and (IV) outcome: inclusion of the primary and/or secondary outcome indicators.

The exclusion criteria were as follows: (I) meta-analyses, reviews, guidelines, letters, case reports, conference abstracts, or protocols; (II) studies with incomplete or non-extractable data; (III) studies of patients with a pulmonary exacerbation at screening; and (IV) studies of patients with their first or early Pseudomonas infection.

In the case of studies published multiple times (e.g., preliminary reports), only the edition with the most informative and complete data was included.

Data extraction

Two investigators (Y.C. and Z.D.) independently extracted the following data from included studies into a pre-designed Excel spreadsheet: (I) study characteristics: first author, publication year, registration number, design, period, enrollment country; (II) patient characteristics: age, sex, respiratory comorbidities, disease severity, treatment regimen; and (III) outcomes: number of patients with each outcome and denominator for dichotomous outcomes, mean and standard deviation (SD) for continuous outcomes. Any discrepancies that arose in this course were resolved through discussion with the senior investigator (J.Z.).

Outcomes of interest

Outcomes of interest included: (I) primary outcomes: microbiological efficacy (measured as change in *P. aeruginosa* sputum density) and tolerability [measured as discontinuation due to adverse events (AEs)]; and (II) secondary outcomes: change in forced expiratory volume in the first second as a percentage of predicted value (FEV_1% predicted), frequency of pulmonary exacerbation per patient-year, change in respiratory symptom scores [using CF questionnaire revised respiratory symptom score (CFQR-RSS) (21,22) or quality-of-life bronchiectasis respiratory symptom score (QoL-B-RSS) (23,24)], and safety (measured as drug-related AEs). The detailed outcome definitions are shown in Table S2.

We evaluated efficacy, tolerability, and safety in terms of short-term (4 weeks) and long-term (≥4 months) outcomes. For the analysis of short-term outcomes, we collected

outcome data at 4 weeks of treatment. For the long-term analysis, we used the longest timepoint after 4 months of treatment.

Quality assessment and certainty of evidence

Two investigators (Y.C. and S.L.) independently assessed the quality of included studies using the Cochrane risk of bias 2.0 tool, and evaluated the certainty of evidence for each comparison using the Confidence in Network Meta-Analysis (CINeMA) tool. Any disagreements were resolved by the corresponding author (L.W.).

Statistical analysis

The NMA was conducted within a Bayesian framework when sufficient outcome data were reported. For dichotomous outcomes, we calculated the pooled odds ratio (OR) with a 95% confidence interval (95% CI), and for continuous outcomes, we estimated the pooled mean difference (MD) with a 95% CI. Convergence was monitored using trace and density plot, as well as Brooks-Gelman-Rubin analysis. The degree of heterogeneity was assessed with the I^2 statistic test. The node-splitting test was utilized for each network loop to determine if there were any inconsistencies between direct and indirect effects. Comparison-adjusted funnel plots were performed for NMA with at least 10 studies to intuitively assess publication bias. Additionally, the surface under the cumulative ranking curve (SUCRA) was calculated to estimate the ranking probability of treatments for the target outcomes.

All analyses were conducted using the gemtc package of R software (Version 4.3.1, RStudio) with the Markov Chain Monte Carlo engine JAGS (Version 4.3.1), and the netmeta package of STATA software (Version 17.0).

Results

Search results

Out of the 2,671 records initially retrieved from electronic databases, 33 publications (*Table 1*) involving 37 eligible RCTs were included in the main analysis as of 25th February, 2024, following a systematic screening process. Four manuscripts (49-52) described two independent trials each. Two additional RCTs (TR02-107, NCT00775138; PROMIS-I, NCT03093974) were identified through a search of the ClinicalTrials.gov registry, and unpublished data from these trials were obtained. Including these two trials allowed us to incorporate a total of 39 eligible RCTs with 7,486 patients (*Figure 1*, Table S3).

Study characteristics

The detailed characteristics of all studies are displayed in *Table 1* and Table S4. There were 18 inhaled antibiotic treatment regimens involving 12 antibacterial preparations: tobramycin inhalation solution (TIS), tobramycin inhalation powder (TIP), aztreonam lysine for inhalation (AZLI), levofloxacin inhalation solution (LIS), amikacin liposome inhalation suspension (ALIS), fosfomycin/tobramycin for inhalation (FTI), colistin for inhalation (Col), colistin dry powder for inhalation (Col_DPI), dual-release ciprofloxacin for inhalation (DRCFI), ciprofloxacin dry powder for inhalation (Cip_DPI), gentamicin injectable solution (GM), and azithromycin tablet (AZM).

We extracted the subgroup data of patients with CF and NCFB, respectively. As a result, 21 RCTs were conducted in populations with CF, predominantly male patients (53.9%) with a mean age (SD) of 23.8 (10.9) years. Of these, 8 (38.1%) trials were head-to-head studies with TIS as the comparator. The remaining 18 RCTs were conducted in patients with NCFB, predominantly female (64.4%) with a mean age (SD) of 62.2 (14.1) years. All trials were placebo-controlled.

NMA results for patients with CF

The network plots for eligible comparisons for primary outcomes are shown in *Figure 2*. The results of the NMA for primary outcomes are shown in *Figures 3*,*4*. And *Figure 5* shows the forest plots for primary outcomes. Additional information for secondary outcomes is listed in Figures S1-S4. SUCRA values of each outcome are shown in Tables S5,S6.

Primary outcomes

Microbiological efficacy: change in P. aeruginosa sputum density

At 4 weeks, 16 RCTs reported the microbiological outcome, involving 11 antibacterial regimens and a total of 3,117 patients (*Figure 2A*). TIP, AZLI (75 mg, t.i.d.), TIS, ALIS, Col, LIS, and FTI following a 28-day run-in course of AZLI (75 mg, t.i.d.) were more efficacious than placebo regarding change in bacterial load, with MD ranging from −0.84 to −1.76 (all moderate certainty of evidence).

Table 1 Characteristics of included studies

Author, year (study group)	Study design	Intervention/comparator	No. of patients	Male (%)	Age (years), mean (SD)	Baseline FEV_1% predicted	Treatment schedule	Duration (weeks)	Outcome
Inhaled antibiotic therapies for treating patients with CF and pseudomonas aeruginosa chronic bronchial infection									
Nichols *et al.*, 2022 (TEACH) (25)	RDBPCT	Oral AZM (500 mg, t.i.w.) + TIS/TIP (300 mg/112 mg, b.i.d.)	61	32 (52.5)	26.1 (9.9)	70.7 (18.2)	28 days of treatment	6	①③⑤
		TIS/TIP (300 mg/112 mg, b.i.d.)	54	28 (51.9)	26.5 (9.7)	69.6 (21.1)			
Bilton *et al.*, 2020 (CLEAR-108) (26)	Phase III, open-label, RCT	ALIS (590 mg, q.d.)	148	79 (53.4)	22.8 (10.2)	64.5 (21.5)	3 cycles of 28 days on/off treatment	24	①②③⑤⑥
		TIS (300 mg, b.i.d.)	146	76 (52.1)	22.0 (10.0)	61.9 (22.0)			
Flume *et al.*, 2016 (27)	Phase III, RDBPCT	AZLI (75 mg, t.i.d.) alternating with TIS (300 mg, b.i.d.)	42	18 (42.9)	28.5 (12.1)	49.9 (17.7)	Continuous alternating treatment scheme	24	②⑥
		TIS (300 mg, b.i.d.)	46	19 (41.3)	28.3 (10.8)	50.1 (15.3)	3 cycles of 28 days on/off treatment		
Flume *et al.*, 2016 (28)	Phase III, RDBPCT	LIS (240 mg, b.i.d.)	219	114 (52.1)	29.4 (10.3)	NR	28 days of treatment	8	①②③
		Placebo	110	63 (57.3)	28.8 (10.9)	NR			
Elborn *et al.*, 2015 (29)	Phase III, open-label, RCT	LIS (240 mg, b.i.d.)	182	103 (54.5)	28.1 (8.96)	54.8 (17.0)	3 cycles of 28 days on/off treatment	24	①②③⑤
		Placebo	90	56 (60.2)	28.8 (10.9)	53.2 (15.7)			
Dorkin *et al.*, 2015 (30)	Phase IIB, RDBPCT	Cip_DPI (32.5 mg, b.i.d.)	93	44 (47.3)	27.7 (NR)	55.0 (11.9)	28 days of treatment	8	①②③⑤⑥
		Placebo	65	39 (60.0)	31.7 (NR)	54.8 (13.0)			
Assael *et al.*, 2013 (31)	Open-label, RCT	AZLI (75 mg, t.i.d.)	136	68 (50.0)	25.8 (9.1)	52.3 (15.6)	3 cycles of 28 days on/off treatment	24	①②③⑤⑥
		TIS (300 mg, b.i.d.)	132	66 (50.0)	25.1 (9.0)	52.2 (14.6)			
Schuster *et al.*, 2013 (Freedom) (32)	Phase III, open-label, RCT	Col_DPI (1.6625 MU, b.i.d.)	186	103 (56.3)	21.3 (9.72)	NR	Continuous treatment	24	②③⑤
		TIS (300 mg, b.i.d.)	192	101 (52.9)	20.9 (9.30)	NR	3 cycles of 28 days on/off treatment		
Clancy *et al.*, 2013 (33)	Phase II, RDBPCT	ALIS (560 mg, q.d.)	36	21 (58.3)	23.0 (12.6)	66.4 (17.4)	28 days of treatment	8	①
		Placebo	36	16 (44.4)	20.3 (7.7)	67.9 (19.4)			
Galeva *et al.*, 2013 (EDIT) (34)	Phase III, RDBPCT	TIP (112 mg, b.i.d.)	30	9 (30.0)	12.9 (4.3)	61.8 (17.5)	28 days of treatment	8	①②③⑥
		Placebo	32	13 (40.5)	12.9 (4.7)	63.1 (18.7)			
Trapnell *et al.*, 2012 (35)	RDBPCT	FTI (80/20 mg, b.i.d.) following AZLI (75 mg, t.i.d.)	38	21 (55.0)	35 (10.9)	50.0 (13.4)	28 days of treatment	8	①②③⑤⑥
		Placebo	40	27 (68.0)	31 (8.8)	48.0 (13.6)			
Wainwright *et al.*, 2011 (AIR-CF4) (36)	RDBPCT	AZLI (75 mg, t.i.d.)	76	46 (60.5)	19.5 (9.1)	95.5 (12.7)	28 days of treatment	8	①②③⑤
		Placebo	81	44 (54.3)	18.9 (9.1)	94.7 (12.9)			
Geller *et al.*, 2011 (37)	RDBPCT	LIS (240 mg, b.i.d.)	39	25 (64.1)	29.2 (10.0)	48.8 (15.2)	28 days of treatment	8	①②③⑤
		Placebo	37	19 (51.4)	30.1 (9.9)	25.0 (64.1)			
Konstan *et al.*, 2010 (EVOLVE) (38)	RDBPCT	TIP (112 mg, b.i.d.)	46	19 (41.3)	13.4 (4.42)	54.7 (18.9)	28 days of treatment	8	②③
		Placebo	49	23 (46.9)	13.2 (3.91)	58.5 (20.0)			
Konstan *et al.*, 2011 (EAGER) (39)	Open-label, RCT	TIP (112 mg, b.i.d.)	308	171 (55.5)	26 (11.4)	53.0 (14.2)	3 cycles of 28 days on/off treatment	24	①②③
		TIS (300 mg, b.i.d.)	209	115 (55.0)	25 (10.2)	53.0 (15.9)			

Table 1 (*continued*)

Table 1 (*continued*)

Author, year (study group)	Study design	Intervention/comparator	No. of patients	Male (%)	Age (years), mean (SD)	Baseline FEV_1% predicted	Treatment schedule	Duration (weeks)	Outcome
Retsch-Bogart *et al.*, 2009 (AIR-CF1) (40)	RDBPCT	AZLI (75 mg, t.i.d.)	80	48 (60.0)	27.4 (11.8)	54.4 (13.4)	28 days of treatment	6	①②⑤
		Placebo	84	45 (53.6)	31.7 (15.8)	54.8 (14.0)			
McCoy *et al.*, 2008 (AIR-CF2) (41)	RDBPCT	AZLI (75 mg, b.i.d.) following TIS (300 mg, b.i.d.)	69	38 (55.1)	26.5 (10.0)	56.3 (14.8)	28 days of treatment	12	①②③⑤
		AZLI (75 mg, t.i.d.) following TIS (300 mg, b.i.d.)	66	38 (57.6)	24.1 (10.8)	55.4 (16.3)			
		Placebo	76	45 (59.2)	27.9 (13.8)	53.9 (15.3)			
Chuchalin *et al.*, 2007 (42)	RDBPCT	TIS (300 mg, b.i.d.)	162	89 (55.3)	14.8 (5.7)	60.7 (14.8)	3 cycles of 28 days on/off treatment	24	③⑥
		Placebo	84	46 (54.8)	14.7 (6.6)	63.6 (15.0)			
Lenoir *et al.*, 2007 (43)	RDBPCT	TIS (300 mg, b.i.d.)	29	15 (51.7)	11.0 (5.0)	57.7 (14.1)	28 days of treatment	8	②⑥
		Placebo	30	17 (56.7)	14.2 (5.5)	59.8 (14.6)			
Hodson *et al.*, 2002 (44)	RDBPCT	Col (80 mg, b.i.d.)	53	20 (37.7)	21.3 (9.6)	55.4 (22.9)	28 days of treatment	8	①②③
		TIS (300 mg, b.i.d.)	62	32 (51.6)	20.1 (9.4)	59.4 (22.6)			
Ramsey *et al.*, 1999 (45)	RDBPCT	TIS (300 mg, b.i.d.)	258	149 (58.0)	20.8 (9.5)	49.9 (15.5)	3 cycles of 28 days on/off treatment	24	①③
		Placebo	262	132 (50.0)	20.6 (10.0)	51.2 (16.8)			
Inhaled antibiotic therapies for treating patients with NCFB and pseudomonas aeruginosa chronic bronchial infection									
Guan *et al.*, 2023 (TORNASOL) (46)	Phase III, RDBPCT	TIS (300 mg, b.i.d.)	167	58 (34.7)	53.0 (13.0)	60.9 (21.5)	2 cycles of 28 days on/off treatment	16	①②④⑤⑥
		Placebo	172	60 (34.9)	54.0 (12.0)	63.6 (22.5)			
Terpstra *et al.*, 2022 (BATTLE) (47)	RDBPCT	TIS (300 mg, q.d.)	26	13 (50.0)	67.9 (6.6)	65.9 (24.9)	Continuous treatment	52	②⑤
		Placebo	26	9 (34.6)	64.1 (14.0)	70.5 (24.0)			
Loebinger *et al.*, 2021 (iBEST) (48)	Phase II, RDBPCT	TIP (112 mg, b.i.d.)	15	5 (33.3)	64.3 (17.9)	62.4 (26.3)	Continuous treatment	24	①②④⑤
			14	7 (50.0)	62.4 (16.7)	58.7 (22.4)	2 cycles of 28 days on/off treatment		
		Placebo	21	8 (38.1)	69.1 (13.2)	54.7 (16.6)	Continuous/intermittent treatment		
Haworth *et al.*, 2019 (ORBIT-3) (49)	Phase III, RDBPCT	DRCFI (135/54 mg, q.d.)	206	72 (35.0)	63.3 (13.5)	62·6 (22.2)	6 cycles of 28 days on/off treatment	48	①②④⑤⑥
Haworth *et al.*, 2019 (ORBIT-4) (49)		Placebo	98	35 (36.0)	64.2 (12.6)	59.8 (20.8)			
De Soyza *et al.*, 2018 (RESPIRE-1) (50)	Phase III, RDBPCT	Cip_DPI (32.5 mg, b.i.d.)	137	49 (35.8)	65.2 (13.5)	59.4 (16.7)	12 cycles of 14 days on/off treatment	56	②④⑤⑥
		Placebo	138	24 (35.3)	65.0. (12.9)	57.4 (15.5)			
		Cip_DPI (32.5 mg, b.i.d.)	141	40 (28.2)	64.2 (12.1)	59.5 (15.1)	6 cycles of 28 days on/off treatment		
		Placebo	138	18 (25.7)	64.0 (13.5)	61.7 (16.7)			
Aksamit *et al.*, 2018 (RESPIRE-2) (51)	Phase III, RDBPCT	Cip_DPI (32.5 mg, b.i.d.)	176	80 (45.5)	60.4 (13.7)	54.3 (17.3)	12 cycles of 14 days on/off treatment	56	②④⑤⑥
		Placebo	88	26 (29.5)	60.4 (15.0)	56.4 (18.8)			
		Cip_DPI (32.5 mg, b.i.d.)	171	79 (46.2)	60.4 (13.7)	56.4 (18.8)	6 cycles of 28 days on/off treatment		
		Placebo	86	34 (39.5)	60.6 (13.7)	56.2 (18.2)			

Table 1 (*continued*)

Table 1 (*continued*)

Author, year (study group)	Study design	Intervention/comparator	No. of patients	Male (%)	Age (years), mean (SD)	Baseline FEV_1% predicted	Treatment schedule	Duration (weeks)	Outcome
Barker *et al.*, 2014 (AIR-BX1) (52)	Phase III, RDBPCT	AZLI (75 mg, t.i.d.)	134	50 (47.0)	64.2 (12.9)	60.4 (22.6)	2 cycles of 28 days on/off treatment	24	①②④⑤
		Placebo	132	34 (27.0)	64.9 (12.1)	64.5 (18.7)			
Barker *et al.*, 2014 (AIR-BX2) (52)		AZLI (75 mg, t.i.d.)	136	47 (35.0)	63.3 (14.2)	63.8 (19.5)			
		Placebo	138	37 (27.0)	62.7 (13.3)	63.4 (21.6)			
Haworth *et al.*, 2014 (53)	RDBPCT	Col (1 MU, b.i.d.)	73	27 (37.0)	58.3 (15.3)	55.9 (24.3)	Continuous treatment	26	①②
		Placebo	71	34 (48.0)	60.3 (15.8)	57.6 (24.9)			
Serisier *et al.*, 2013 (ORBIT-2) (54)	Phase II, RDBPCT	DRCFI (150/60 mg, q.d.)	20	10 (50.0)	70.0 (5.6)	60.7 (24.1)	2 cycles of 28 days on/off treatment	24	①②
		Placebo	22	9 (40.9)	59.5 (13.2)	53.1 (22.7)			
Wilson *et al.*, 2013 (55)	Phase II, RDBPCT	Cip_DPI (32.5 mg, b.i.d.)	60	21 (35.0)	64.7 (11.8)	57.2 (13.7)	28 days of treatment	12	①
		Placebo	64	21 (32.8)	61.4 (11.9)	54.6 (14.8)			
Murray *et al.*, 2011 (56)	Single-blind, RCT	GM (80 mg, b.i.d.)	27	9 (33.3)	58.0 (10.4)	72.9 (15.7)	Continuous treatment	60	①②④
		Placebo	30	15 (50.0)	64.0 (9.63)	63.4 (25.9)			
Barker *et al.*, 2000 (57)	Phase II, RDBPCT	TIS (300 mg, q.d.)	37	14 (37.8)	66.6 (13.0)	56.2 (21.2)	28 days of treatment	6	①
		Placebo	37	15 (40.5)	63.2 (13.5)	53.3 (22.1)			
TR02-107 (NCT00775138)	RCT	ALIS (560 mg, q.d.)	19	8 (42.1)	58.5 (16.0)	64.5 (20.7)	28 days of treatment	8	①
		Placebo	19	4 (44.4)	52.3 (11.1)	62.6 (15.7)			
PROMIS-I (NCT03093974)	Phase III, RDBPCT	Col (1 MU, b.i.d.)	176	53 (29.9)	64.2 (14.8)	NR	Continuous treatment	48	④
		Placebo	197	71 (35.5)	64.3 (13.0)	NR			

①: change in P. aeruginosa sputum density; ②: discontinuation due to adverse events; ③: change in FEV1% predicted; ④: frequency of pulmonary exacerbation per patient-year; ⑤: change in respiratory symptom scores; ⑥: drug-related adverse events. ALIS, amikacin liposome inhalation suspension; AZLI, aztreonam lysine for inhalation solution; AZM, azithromycin tablet; CF, cystic fibrosis; Cip, ciprofloxacin; Col, colistin for inhalation; DPI, dry powder for inhalation; DRCFI, dual release ciprofloxacin for inhalation; FEV1, forced expiratory volume in the first second; FTI, fosfomycin/tobramycin for inhalation; GM, gentamicin injectable solution; LIS, levofloxacin inhalation solution; NCFB, non-cystic fibrosis bronchiectasis; NR, data not reported; RCT, randomized controlled trial; RDBPCT, randomized, double-blinded, placebo-controlled trial; SD, standard deviation; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

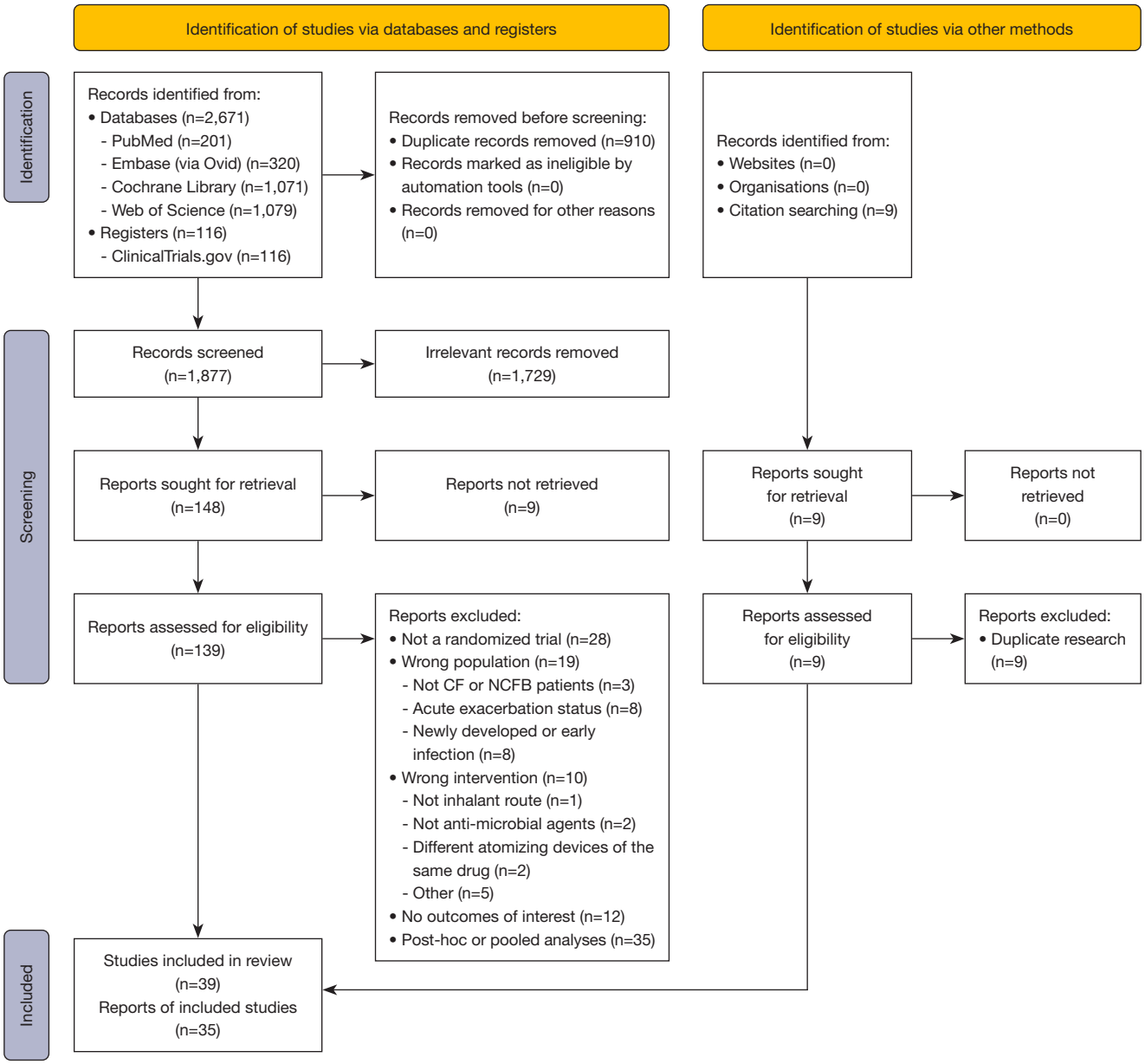


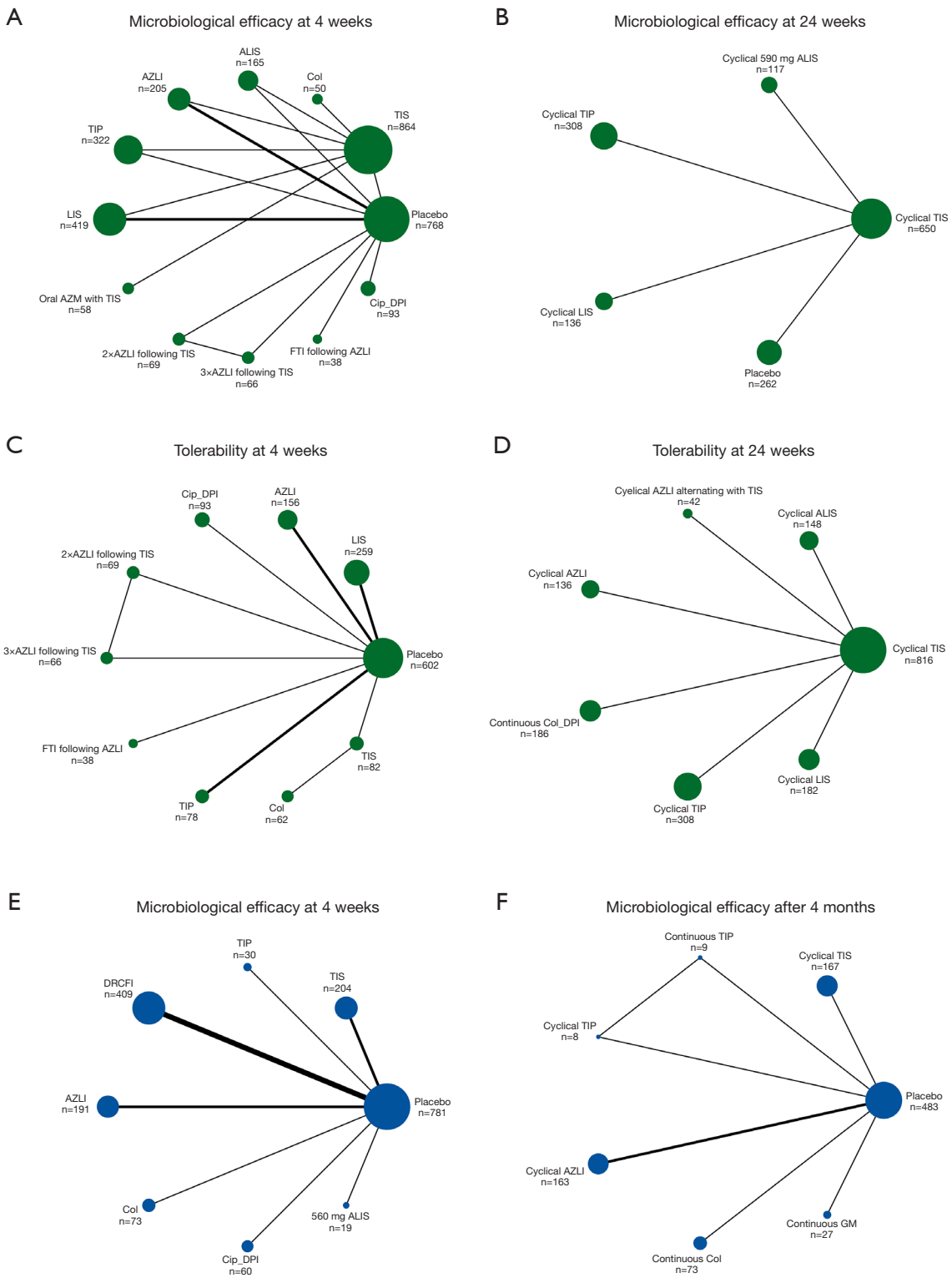
Figure 1 Flow diagram for study screen and selection. CF, cystic fibrosis; NCFB, non-cystic fibrosis bronchiectasis.

TIP was more efficacious than LIS, AZLI (75 mg, b.i.d.) following a 28-day run-in course of TIS, AZLI (75 mg, t.i.d.) following TIS, and oral AZM combining with TIS, with MD ranging from −0.92 to −1.25 (all moderate certainty). Additionally, TIS was more efficacious than oral AZM with TIS (MD =−0.79; 95% CI: −1.57 to −0.01; moderate certainty). Further SUCRA results revealed that TIP was most likely to be the best treatment in terms of reduction in *P. aeruginosa* sputum density (SUCRA, 94.5%).

At 24 weeks, four RCTs reported the microbiological outcome, involving four antibacterial regimens and a total of 1,473 patients (*Figure 2B*). No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that TIP (intermittent scheme) was most likely to be the best treatment in terms of reduction in *P. aeruginosa* sputum density (SUCRA, 90.5%).

Tolerability: discontinuation due to AEs

At 4 weeks, 11 RCTs reported the tolerability outcome,



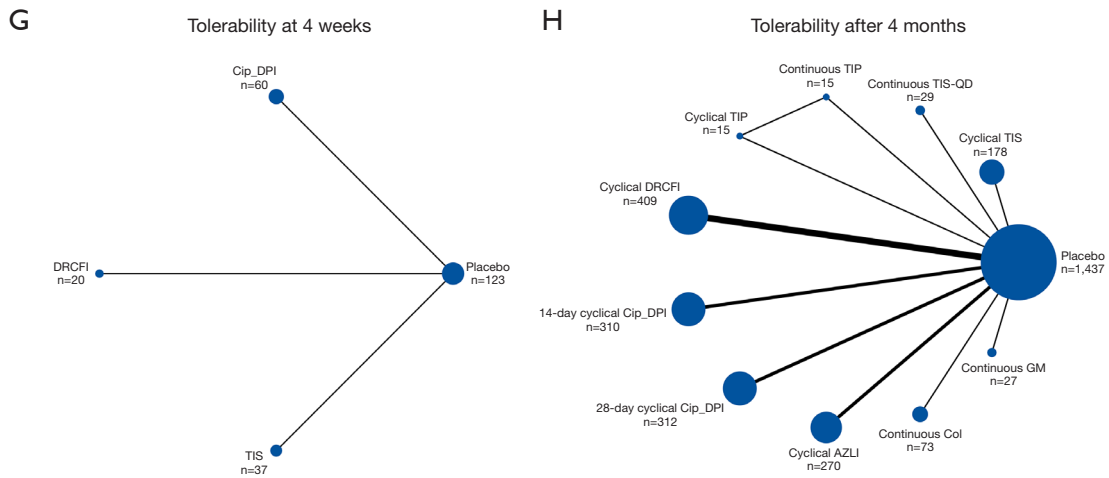


Figure 2 Network plots of direct comparisons in patients with CF for microbiological efficacy at 4 weeks (A) and at 24 weeks (B), tolerability at 4 weeks (C) and at 24 weeks (D), and in patients with NCFB for microbiological efficacy at 4 weeks (E) and after 4 months (F), tolerability at 4 weeks (G) and after 4 months (H). The thickness of the lines is in proportion to the number of trials per comparison. The size of the nodes is in proportion to the number of randomized participants. CF, cystic fibrosis; NCFB, non-cystic fibrosis bronchiectasis; ALIS, amikacin liposome inhalation suspension; AZLI, aztreonam lysine for inhalation solution; AZM, azithromycin tablet; Cip, ciprofloxacin; Col, colistin for inhalation; DPI, dry powder for inhalation; DRCFI, dual-release ciprofloxacin for inhalation; FTI, fosfomycin/tobramycin for inhalation; GM, gentamicin injectable solution; LIS, levofloxacin inhalation solution; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

involving nine antibacterial regimens and a total of 1,505 patients (*Figure 2C*). No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that Col was most likely to have the best tolerability profile (SUCRA, 84.0%).

At 24 weeks, six RCTs reported the tolerability outcome, involving seven antibacterial regimens and a total of 1,818 patients (*Figure 2D*). No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that TIS (intermittent scheme) was most likely to have the best tolerability profile (SUCRA, 75.7%).

Secondary outcomes

Change in FEV1% predicted

At 4 weeks, 15 RCTs reported spirometry results as FEV_1% predicted, involving 10 antibacterial regimens and a total of 2,985 patients. No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that AZLI (75 mg, t.i.d.) was most likely to be the best treatment in terms of improvement in FEV_1% predicted, followed by TIP (SUCRA, 68.5% and 68.3%, respectively).

At 24 weeks, seven RCTs reported spirometry results as FEV_1% predicted, involving six antibacterial regimens and a total of 2,491 patients. No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that AZLI (75 mg, t.i.d.) was most likely to be the best treatment in terms of improvement in FEV_1% predicted (SUCRA, 80.2%).

Change in respiratory symptom scores

At 4 weeks, 10 RCTs reported respiratory symptom scores using CFQR-RSS, involving nine antibacterial regimens and a total of 1,776 patients. No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that AZLI (75 mg, t.i.d.) was most likely to be the best treatment in terms of improvement in CFQR-RSS (SUCRA, 68.8%).

At 24 weeks, three RCTs reported respiratory symptom scores using CFQR-RSS, involving four antibacterial regimens and a total of 940 patients. No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that ALIS was most likely to be the best treatment in terms of improvement in CFQR-RSS (SUCRA, 83.3%).

Safety: drug-related AEs

At 4 weeks, four RCTs reported the safety outcome, involving four antibacterial regimens and a total of 357 patients. No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that TIS was associated with the lowest incidence of drug-

Figure 3 Network meta-analysis for primary outcomes at 4 weeks and at 24 weeks in patients with CF. Comparisons should be read from left to right. Microbiological efficacy and tolerability estimates are located at the intersection between the column-defining treatment and the row-defining treatment. For microbiological efficacy, data are in mean difference (95% CI), and data above 0 favour the column-defining treatment. For tolerability, data are odds ratio (95% CI), and data above 1 favour the column-defining treatment. Significant results are in bold. The certainty of the evidence (according to CINeMA) was incorporated in this figure. ⊕⊕⊕◯: moderate certainty of evidence; ⊕⊕◯◯: low certainty of evidence; ⊕◯◯◯: very low certainty of evidence. ALIS, amikacin liposome inhalation suspension; AZLI, aztreonam lysine for inhalation solution; AZM, azithromycin tablet; CF, cystic fibrosis; CI, confidence interval; CINeMA, Confidence in Network Meta-Analysis; Cip, ciprofloxacin; Col, colistin for inhalation; DPI, dry powder for inhalation; FTI, fosfomycin/tobramycin for inhalation; LIS, levofloxacin inhalation solution; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

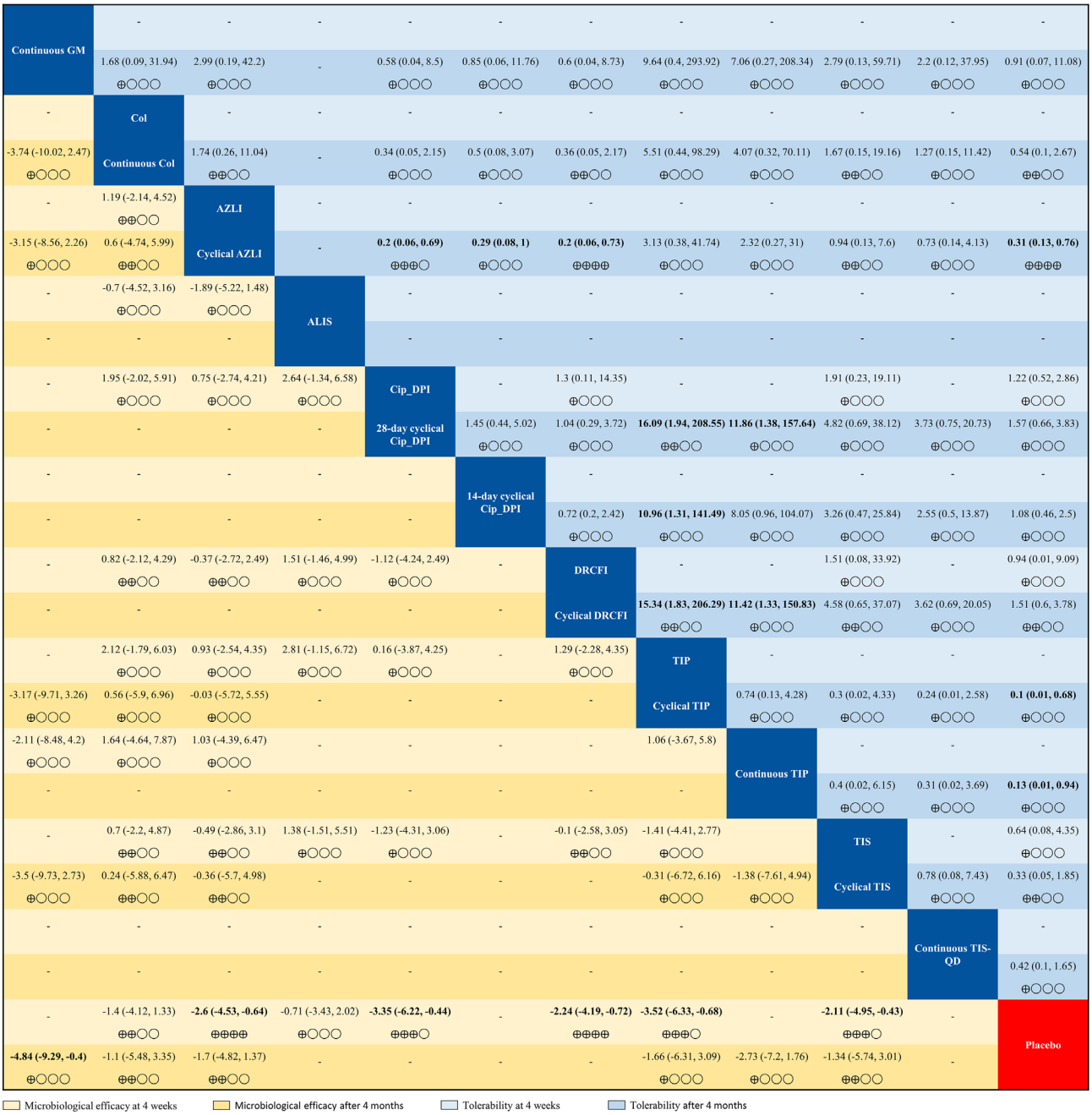


Figure 4 Network meta-analysis for primary outcomes at 4 weeks and after 4 months in patients with NCFB. Comparisons should be read from left to right. Microbiological efficacy and tolerability estimates are located at the intersection between the column-defining treatment and the row-defining treatment. For microbiological efficacy, data are in mean difference (95% CI), and data above 0 favour the column-defining treatment. For tolerability, data are odds ratio (95% CI), and data above 1 favour the column-defining treatment. Significant results are in bold. The certainty of the evidence (according to CINeMA) was incorporated in this figure. ⊕⊕⊕⊕: high certainty of evidence; ⊕⊕⊕◯: moderate certainty of evidence; ⊕⊕◯◯: low certainty of evidence; ⊕◯◯◯: very low certainty of evidence. ALIS, amikacin liposome inhalation suspension; AZLI, aztreonam lysine for inhalation solution; CI, confidence interval; CINeMA, Confidence in Network Meta-Analysis; Cip, ciprofloxacin; Col, colistin for inhalation; DPI, dry powder for inhalation; DRCFI, dual-release ciprofloxacin for inhalation; GM, gentamicin injectable solution; LIS, levofloxacin inhalation solution; NCFB, non-cystic fibrosis bronchiectasis; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

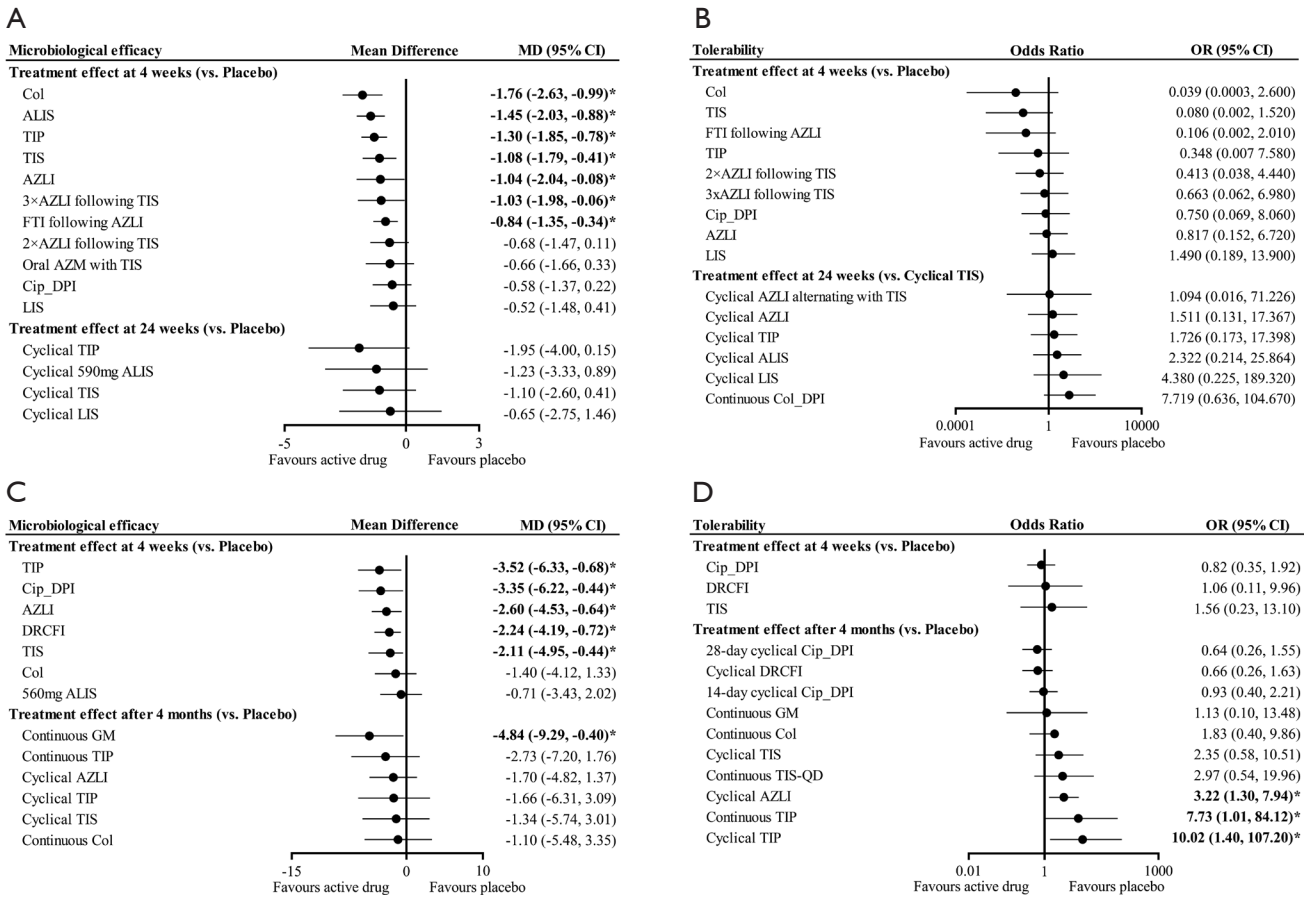


Figure 5 Forest plots of network meta-analysis in patients with CF for microbiological efficacy (A) and tolerability (B) and in patients with NCFB for microbiological efficacy (C) and tolerability (D). Significant results are in bold. *, P<0.05. ALIS, amikacin liposome inhalation suspension; AZLI, aztreonam lysine for inhalation solution; AZM, azithromycin tablet; CF, cystic fibrosis; CI, confidence interval; Cip, ciprofloxacin; Col, colistin for inhalation; DPI, dry powder for inhalation; DRCFI, dual release ciprofloxacin for inhalation; FTI, fosfomycin/tobramycin for inhalation; GM, gentamicin injectable solution; LIS, levofloxacin inhalation solution; MD, mean difference; NCFB, non-cystic fibrosis bronchiectasis; OR, odds ratio; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

related AEs (SUCRA, 90.8%).

At 24 weeks, five RCTs reported the safety outcome, involving five antibacterial regimens and a total of 1,276 patients. No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that TIS (intermittent scheme) was associated with the lowest incidence of drug-related AEs (SUCRA, 73.6%).

NMA results for patients with NCFB

Primary outcomes

Microbiological efficacy: change in P. aeruginosa sputum density

At 4 weeks, 11 RCTs reported the microbiological outcome, involving seven antibacterial regimens and a total of 1,767 patients (*Figure 2E*). TIP, Cip_DPI, AZLI (75 mg, t.i.d.), DRCFI, and TIS were more efficacious than placebo, with MD ranging from –2.11 to –3.52 (all moderate or high certainty). Further SUCRA results revealed that TIP was most likely to be the best treatment in terms of reduction in *P. aeruginosa* sputum density (SUCRA, 84.2%).

After 4 months of follow-up, six RCTs reported the microbiological outcome, involving six antibacterial regimens and a total of 930 patients (*Figure 2F*). GM was more efficacious than placebo (MD =–4.84; 95% CI: –9.29 to –0.4; very low certainty). Further SUCRA results revealed that GM was most likely to be the best treatment in terms of reduction in *P. aeruginosa* sputum density

(SUCRA, 92.2%).

Tolerability: discontinuation due to AEs

At 4 weeks, three RCTs reported the tolerability outcome, involving three antibacterial regimens and a total of 240 patients (*Figure 2G*). No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that Cip_DPI was most likely to have the best tolerability profile (SUCRA, 66.4%).

After 4 months of follow-up, 14 RCTs reported the tolerability outcome, involving 10 antibacterial regimens and a total of 3,075 patients (*Figure 2H*). TIP (intermittent scheme), TIP (continuous scheme) and AZLI (75 mg, t.i.d.) caused fewer discontinuations due to AEs than DRCFI, Cip_DPI (28-day intermittent scheme), and placebo (P<0.05). Additionally, TIP (intermittent scheme) and AZLI (75 mg, t.i.d.) caused fewer discontinuations than Cip_DPI (14-day intermittent scheme) (P<0.05). Further SUCRA results revealed that Cip_DPI (28-day intermittent scheme) was most likely to have the best tolerability profile (SUCRA, 85.6%).

Secondary outcomes

Frequency of pulmonary exacerbation per patient-year

Only one and two RCTs reported the spirometry results measured as FEV_1% predicted at short-term and long-term timepoints, respectively. Due to insufficient data, it was not possible to assess the change in FEV_1% predicted. Consequently, the outcome of frequency of pulmonary exacerbation per patient-year was included as a supplementary measure. Only long-term treatment effects were analyzed since it is necessary to have a sufficiently long follow-up time to capture an adequate number of events.

After 4 months of follow-up, 12 RCTs reported the exacerbation outcome, involving nine antibacterial regimens and a total of 2,799 patients. GM significantly reduced the frequency of exacerbations compared to AZLI, Col, Cip_DPI, TIS (intermittent scheme), and placebo, with MD ranging from –1.12 to –1.65 (all very low or low certainty). Further SUCRA results revealed that GM was associated with the lowest risk of exacerbation (SUCRA, 97.8%).

Change in respiratory symptom scores

At 4 weeks, four RCTs reported respiratory symptom scores using QoL-B-RSS, involving three antibacterial regimens and a total of 928 patients. No marked differences were noted between interventions (P>0.05). Further SUCRA results revealed that TIS was most likely to be the best treatment in terms of improvement in QoL-B-RSS (SUCRA, 90.6%).

After 4 months of follow-up, nine RCTs reported respiratory symptom scores using QoL-B-RSS, involving eight antibacterial regimens and a total of 1,857 patients. TIS (intermittent scheme) significantly improved respiratory symptoms compared to placebo (MD =6.69; 95% CI: 0.12 to 13.24; low certainty). Further SUCRA results revealed that TIS (intermittent scheme) was most likely to be the best treatment in terms of improvement in QoL-B-RSS (SUCRA, 86.5%).

Safety: drug-related AEs

No trial included in the analysis reported the incidence of drug-related AEs at 4 weeks, making it impossible to assess the short-term safety outcome.

After 4 months of follow-up, seven RCTs reported the safety outcome, involving four antibacterial regimens and a total of 2,165 patients. There was a significant increase in drug-related AEs with TIS (intermittent scheme) compared to Cip_DPI (28-day intermittent scheme; OR =4.17, 95% CI: 1 to 16.67; very low certainty) and placebo (OR =3.54, 95% CI: 1.11 to 11.91; low certainty). Further SUCRA results revealed that Cip_DPI (28-day intermittent scheme) was associated with the lowest incidence of drug-related AEs (SUCRA, 74.7%).

Quality assessment, consistency assessments, publication bias and certainty of evidence

A summary of the quality of included studies indicated that 21 (56.8%), 16 (40.5%), and 1 (2.7%). Studies were classified as having low, moderate, and high overall risk of bias, respectively (Figure S5). Two trials were unpublished, and their quality could not be fully evaluated. No evidence of significant inconsistency and publication bias were reported in the node splitting test and funnel plots, respectively (Figures S6-S8). The certainty of evidence, as measured with CINeMA, varied from high to very low (26 comparisons scored high or moderate). Full details on CINeMA are shown in Appendix 1.

Discussion

The present Bayesian NMA provides a comprehensive evaluation of the benefits and harms of different inhaled antibiotic therapies for the short-term (4 weeks) and long-term (≥4 months) management of chronic *P. aeruginosa* infection in patients with CF and NCFB, respectively.

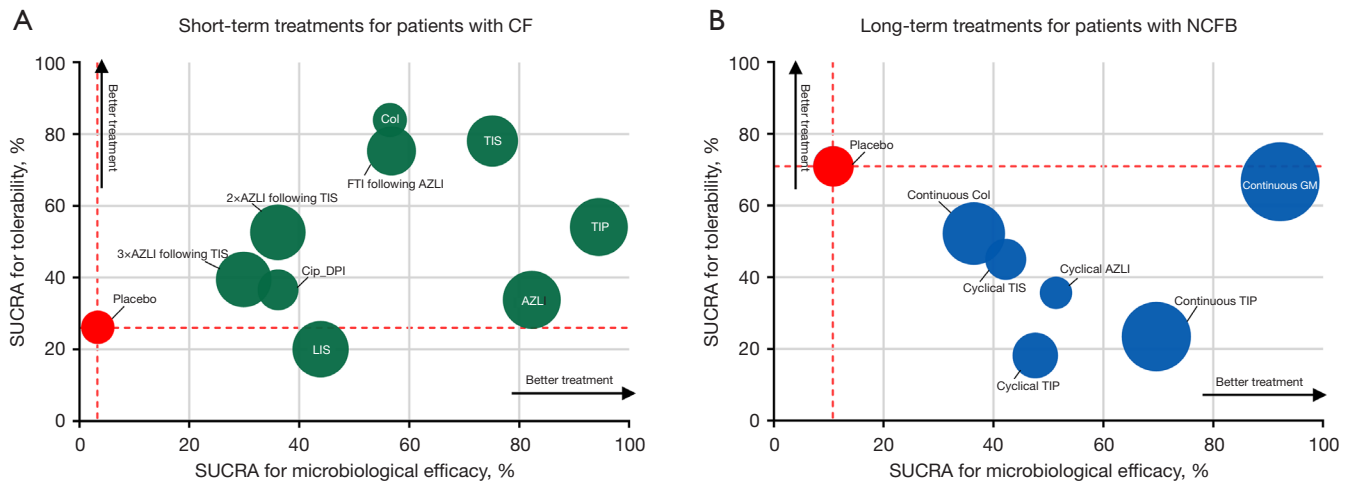


Figure 6 Clustered ranking plots based on SUCRA. (A) Clustered ranking plot of short-term treatment outcomes for patients with CF. The plot shows SUCRA values of nine antimicrobial treatments and placebo, commonly included in the analyses of the following outcomes: microbiological efficacy, tolerability and change in FEV_1% predicted. (B) Clustered ranking plot of long-term treatment outcomes for patients with NCFB. The plot shows SUCRA values of six antimicrobial treatments and placebo, commonly included in the analyses of the following outcomes: microbiological efficacy, tolerability and frequency of pulmonary exacerbation per patient-year. Treatments with better microbiological efficacy and tolerability are in the upper-right corner of the graph. In addition, the larger bubble size reflects the greater clinical benefits. AZLI, aztreonam lysine for inhalation solution; CF, cystic fibrosis; Cip, ciprofloxacin; Col, colistin for inhalation; DPI, dry powder for inhalation; FEV_1, forced expiratory volume in the first second; FTI, fosfomycin/tobramycin for inhalation; GM, gentamicin injectable solution; NCFB, non-cystic fibrosis bronchiectasis; SUCRA, surface under the cumulative ranking curve; TIP, tobramycin inhalation powder; TIS, tobramycin inhalation solution.

For patients over 6 years old with CF and P. aeruginosa infection, inhalation of TIS is the best treatment

According to the clustered ranking plot, both TIS and TIP had a better profile in terms of microbiological efficacy, tolerability, and improvement in FEV_1% predicted when compared to other treatments (*Figure 6A*). TIS, the first inhaled antibiotic available in liquid form for nebulization since 1997, has been extensively studied for use in CF. Subsequently, a new dry-powder formulation of tobramycin, known as TIP, was developed to enhance drug delivery efficiency and shorten administration time (58). TIP is delivered via the portable T-326 Inhaler and has become a more convenient alternative for patients with CF in comparison to TIS. A controlled clinical study (39) has demonstrated that TIP possesses a safety and efficacy profile comparable to that of TIS. However, it is important to note that the powder formulation may lead to an increased incidence of coughing, dyspnea and dysphonia due to heightened irritation of the throat and airways. Patients with a history of reactive airway disease, asthma, or bronchospasm are advised to use a short-acting bronchodilator prior to administration of TIP. AZLI is indicated for the improvement of respiratory symptoms in patients with CF and *P. aeruginosa* infection. Our study also confirmed its superiority in terms of respiratory symptom improvement and change in FEV_1% predicted. In a study conducted by McCoy *et al.* (41), AZLI significantly improved respiratory symptoms and pulmonary function in patients with CF who had received intensive therapy based on TIS. However, our findings indicate that AZLI is associated with a lower ranking in terms of tolerability. AZLI-treated patients discontinued treatment prematurely mainly due to cough and dyspnea, with most discontinuations occurring during the first course of treatment. Additionally, despite the routine use of short-acting bronchodilators prior to AZLI administration, bronchospasm still occurred in 3% of patients (40,41). In overall consideration, TIS appears to be the optimal choices for the treatment of chronic *P. aeruginosa* infection in patients with CF.

For adult patients with NCFB and P. aeruginosa infection, inhalation of GM is the best treatment

GM had the best profile in terms of microbiological efficacy and frequency of pulmonary exacerbation per patient-year, and was well tolerated (*Figure 6B*). However, it is important to note that the data relating to GM-based regimens in our study were derived from only one small-sample RCT (56), so caution must be exercised when interpreting the results. On the other hand, novel formulations of ciprofloxacin, specifically the top three regimens with the best tolerability profile, showed promising results in our study. For instance, DRCFI (drug with a specific formulation of ciprofloxacin) benefits from an innovative dual-release liposome formulation (49). This formulation allows for gradual release of the drug from the liposome, thereby reducing direct contact between the drug and the lung epithelium, resulting in decreased airway irritation. The other antibacterial regimens ranked lower than placebo in terms of tolerability. Additionally, two regimens, based on TIP and AZLI respectively, led to more frequent treatment discontinuation due to AEs compared to placebo. Furthermore, intermittent inhalation of TIS was associated with an increased risk of drug-related AEs when compared to placebo. This finding was predominantly based on a clinical trial conducted by Guan *et al.* in 2023 (46), which reported that most AEs were mild to moderate and resolved during the "off" phase. Only two cases experienced discontinuation due to drug-related AEs in the TIS group, and these effects, including blurred vision and dizziness, resolved rapidly without causing any lasting complications after immediate discontinuation of TIS. It is possible that these events are related to vestibular nerve dysfunction caused by TIS. In overall consideration, GM appears to be the optimal choice for the treatment of chronic *P. aeruginosa* infection in patients with NCFB.

Factors contributing to significant differences in clinical response between inhaled antibiotics-treated patients with CF and NCFB

Our study indicates that whereas inhaled antibiotic therapy is beneficial for patients with CF, its effectiveness in NCFB is limited, with a marked reduction in bacterial load but minimal clinical improvement and relatively poor tolerability. Three key factors may account for the observed differences between CF and NCFB: (I) clinical characteristics: the clinical profiles of patients with CF and NCFB differ substantially. Patients with NCFB tend to be older and often present with multiple respiratory comorbidities (59,60). Approximately 42% of individuals with bronchiectasis have comorbid asthma, and 36% have chronic obstructive pulmonary disease (61). These factors may contribute to more extensive and severe lung tissue damage in patients with NCFB, making it difficult to achieve improvements in lung function. Additionally, the high heterogeneity in clinical manifestations among patients with NCFB may lead to variable clinical outcomes. (II) Etiologies and therapeutic strategies: CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, resulting in defective or absent CFTR protein function. Precision treatments, including small molecule modulator therapy and gene therapy, have shown significant benefits for patients with CF (62). Ivacaftor was the first CFTR modulator by targeting the underlying cause of CF. A 5-year prospective study (63) showed a lower prevalence of *P. aeruginosa* among ivacaftor-treated patients than among untreated comparators. In contrast, NCFB has a multifactorial etiology, involving bronchial infections or obstruction, immune deficiency, genetic factors, and systemic diseases such as rheumatoid arthritis and gastroesophageal reflux. Most etiologies underlying NCFB lack specific treatments, and current management primarily involves symptomatic treatments like airway clearance to alleviate symptoms and improve quality of life (59). (III) Intrapulmonary microenvironments: advances in molecular techniques have expanded our understanding of the intrapulmonary microenvironments in CF and NCFB, revealing significant differences in their composition and progression. These complex microbial ecologies include major pathogens and a wide array of unexplored microbiomes, which may influence disease progression and treatment efficacy (64-66). This may partly explain the limited response to current inhaled antibiotic therapies that primarily target *P. aeruginosa*.

Strengths and limitations

This study included 39 unique RCTs related to inhaled antibiotic therapies for treating chronic *P. aeruginosa* infection in patients with CF or NCFB. The funnel plots did not suggest publication bias, and the CINeMA approach was used to assess the certainty of evidence, reflecting the methodological rigor of our study. Compared with previous studies (67,68), our analyses expanded the evaluation dimensions to include microbiological and clinical effectiveness, tolerability, and safety, thus providing a more

comprehensive evaluation of intervention effects. This approach aims to inform the clinical selection of optimal inhaled antibiotic regimens for CF and NCFB.

We should acknowledge several limitations as well. Many comparisons were graded as very low to low certainty of evidence, primarily due to imprecision issues. Additionally, there was significant variability in the measures of lung function and exacerbation among trials, making it challenging to combine results from multiple studies. Furthermore, about one-third of the trials had relatively small sample sizes (sample size <100), and comparisons between many active treatments relied on indirect evidence, which may have affected the reliability of the results. Finally, only English-language literature was retrieved, potentially limiting the generalizability of the findings.

Conclusions

Current evidence suggests that inhalation of TIS may be the best treatment for chronic *P. aeruginosa* infection in patients with CF, whereas inhalation of GM may be optimal for chronic *P. aeruginosa* infection in patients with NCFB. Differences in clinical characteristics, etiologies, treatment strategies, and intrapulmonary microenvironments may contribute to the significant differences in clinical response to inhaled antibiotic therapy in patients with CF and NCFB. These results may guide shared decision-making among patients, caregivers, clinicians, and policymakers.

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None.

Footnote

Reporting Checklist: The authors have completed the PRISMA-NMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1525/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1525/prf

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1525/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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