A network meta-analysis of the efficacy of inhaled antibiotics for chronic Pseudomonas infections in cystic fibrosis

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Abstract

Background: Various inhaled antibiotics are currently used for treating chronic Pseudomonas aeruginosa lung infection in cystic fibrosis (CF) patients, however their relative efficacies are unclear. We compared the efficacy of the inhaled antibiotics tobramycin (TIP, TIS-T, TIS-B), colistimethate sodium (colistin) and aztreonam lysine for inhalation (AZLI) based on data from randomised controlled trials.

Methods: In the base case, efficacies of antibiotics were compared using a network meta-analysis of seven trials including change from baseline in forced expiratory volume in 1 second (FEV1) % predicted, P. aeruginosa sputum density and acute exacerbations.

Results: The tobramycin preparations, AZLI and colistin, showed comparable improvements in efficacy in terms of FEV1% predicted at 4 weeks; the difference in % change from baseline (95%CrI) for TIP was compared to TIS-T (-0.55, -3.5;2.4), TIS-B (-0.64, -7.1;5.7), AZLI (3.64, -1.0;8.3) and colistin (5.77, -1.2;12.8).

Conclusion: We conclude that all studied antibiotics have comparable efficacies for the treatment of chronic P. aeruginosa lung infection in CF.

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Keywords: Cystic fibrosis; Pseudomonas aeruginosa; Inhaled antibiotics; Tobramycin; Network metaanalysis

1. Introduction

Cystic fibrosis (CF) is the most common fatal inherited disease among Caucasians, affecting approximately 80,000 individuals in Europe and North America [1]. CF is characterised by chronic lung infections with opportunist pathogens [2] due to the consequences of mutations in the CF transmembrane conductance regulator (CFTR) gene [3] which compromise innate immune functions [4]. Respiratory infections with P. aeruginosa are recognised as having the largest impact on morbidity and mortality. Improved antibiotic strategies against respiratory tract infections are considered the main reason for the increased life expectancy in CF patients in the last decades. Particularly, early eradication antibiotic therapy has successfully eradicated P. aeruginosa from CF airways for considerable time periods and delayed onset of chronic infection in many European CF centres in the last two decades [5]. However, once established, chronic P. aeruginosa infections are difficult to treat with antibiotics and the pathogen is virtually never eradicated due to biofilm formation [5]. Therefore, clinical trials of antibiotics for chronic P. aeruginosa lung infection in individuals with CF use endpoints such as relative increase in lung function and reduction of P. aeruginosa sputum density or acute exacerbations rather than pathogen eradication. However, while there are a number of antibiotics available which have been used in the past to treat individuals with CF with chronic P. aeruginosa infections, there is a paucity of data comparing the efficacy and safety of these treatments to each other which would guide the CF clinician.
We compared the efficacy and safety of inhaled antibiotics tobramycin, colistimethate sodium and aztreonam lysine, using a network meta-analysis (NMA). In the absence of head to head trials against all comparators, NMA methods allow assessment of relative efficacy in a structured and objective way [6,7]. We assessed the endpoints; % change from baseline (CFB) in forced expiratory volume in 1 second (FEV₁) % predicted, CFB of P. aeruginosa sputum density and exacerbations. Previously, a Cochrane review [18] was conducted on inhaled antibiotics for CF. However, a meta-analysis was at that time, not conducted judging study designs and reporting of results too variable.

2. Methods

2.1. Antibiotic formulations

The following approved antibiotic formulations for inhalation were compared in this study: (i) tobramycin inhalation powder capsule (TIP), containing 112 mg tobramycin BID (TOBI Podhaler®), (ii) tobramycin inhalation solution (TIS-T), containing 300 mg/5 ml tobramycin BID (TOBI®), (iii) tobramycin inhalation solution (TIS-B), containing 300 mg/4 ml tobramycin BID (Bramitob®), (iv) colistimethate sodium (colistin), containing 80 mg/3 ml colistimethate sodium BID (Colomycin®, Promixin®), and (v) aztreonam lysine inhalation solution (AZLI), containing 75 mg aztreonam lysine TID (Cayston®).

2.2. Identification and selection of studies

A systematic literature review was conducted for English language publications in Medline, Medline in Process, Embase and the Cochrane Library. Search terms included free-text and thesaurus terms for cystic fibrosis, Pseudomonas, the interventions of interest and randomised controlled study design. The search was conducted on October 2010 and two publications of the two TIP trials were added in January 2011. Conference data from 2009 and 2010 were screened in BIOSIS and from the European CF Conference, North American CF Conference, European Respiratory Society and American Thoracic Society. Two reviewers independently screened first the abstracts, then selected full papers against the following predefined inclusion criteria: (1) population: CF patients aged 6 years or older with chronic P. aeruginosa infection; (2) interventions: inhaled tobramycin, colistin, AZLI, amikacin or ciprofloxacin; (3) comparisons: interventions above (at licensed dose) to each other or placebo; (4) outcomes: percent CFB in FEV₁ % predicted at 4 weeks and 20 weeks, CFB in P. aeruginosa sputum density (measured by Log₁₀ CFUs) at 4 weeks and 20 weeks, percent of patients with use of additional anti-P. aeruginosa antibiotics (intravenous, oral or inhaled) and percent of patients with at least one hospitalisation for acute respiratory events within 24 weeks; and (5) study design: randomised controlled trials in full publications or from conferences (if sufficient data were presented).

2.3. Data extraction and validity assessment

For included studies, data were extracted on study design, population, interventions, and outcomes described above. In cases where CFBs of FEV₁ % predicted were not reported, data were calculated from reported data, or else extracted from figures using Digitizit software version 1.5.8 (Share-it!, Cologne, Germany). The standard error of the difference in percent CFB was extracted where reported, or calculated (e.g. based on 95% confidence interval or standard deviation). If there were insufficient data for the calculations, an average standard deviation was calculated from included studies in each analysis and combined with study-specific sample sizes to estimate the study-specific standard error.

2.4. Network meta-analysis (NMA)

Bayesian NMA models were applied with non-informative priors [6–8] to simultaneously synthesize the results of included studies and compare the efficacy and safety of antibiotics. The outcome was the relative treatment effect of each intervention versus placebo, and of TIP versus other comparators with a probability of being the better treatment. Both fixed and random effects models were evaluated. Fixed effects models assume one true treatment effect, while random effects models allow for different true treatment effects across studies, thus take account of heterogeneity in relative treatment effects. The choice between a fixed or random effects model for reported outcomes was based on model fit criteria (Deviance Information Criteria (DIC)) which penalise greater model complexity [8].

The NMA can synthesise a network of randomised controlled trials (RCTs) and allow inferences about comparisons that have not been studied in a head-to-head fashion. Even when direct evidence is available for some treatments, combining this with indirect comparisons in a NMA may yield a more refined and precise estimate for the relative treatment effect [6,7]. Data on the following outcomes were analysed from RCTs that were connected via common comparators; changes in (i) FEV₁ % predicted, (ii) P. aeruginosa sputum density and (iii) exacerbations (i.e. assessed by respiratory hospitalisations or need for additional anti-P. aeruginosa antibiotic use). Separate analyses for each outcome included models for all available study data, various subgroups of studies and/or inclusion of one of the following study-level covariates [9] for possible effect modifiers that could bias results: mean baseline age or mean baseline FEV₁ % predicted and mean percent of patients with prior exposure to study drug. WinBUGS 1.4.1 statistical software was used for the analyses [10].

3. Results

3.1. Study identification

The literature search identified 413 abstracts. Of these, 39 full papers were included for full-text screening from which 11 potentially relevant trials were assessed for the NMA (Fig. 1). Eight were placebo-controlled trials and three compared two active drugs (Tables 1 and 2). The base case analysis included a network of 7 trials (Fig. 2).
3.2. Study and patient characteristics

All studies were published after 2006, except for studies by Jensen [11], Ramsey [12] and Hodson [13] (Table 1). With the exclusion of Jensen [11], the remaining studies were considered a homogenous group regarding study publication date. Five studies included a younger population (mean baseline age between 11 and 16 years), and six studies included an older population (mean baseline age between 20 and 32 years). Mean baseline FEV1% predicted was between 49.9 and 63.6 (i.e. moderate impairment (GOLD 2008)) in all studies except Nasr [15] (mean baseline FEV1% predicted N80%) and Jensen [11] (mean baseline FEV1% predicted N70%) where patients were considered to have mild impairment. The Lenoir study [16] included a mixture of chronically- and intermittently-infected CF patients with P. aeruginosa infection; 24.1% and 16.7% of patients in the TIS-B and placebo arms, respectively, had a first or intermittent P. aeruginosa infection. Regarding prior exposure to study (active) drug, six studies had primarily treatment naïve populations (i.e. the majority of patients had never been exposed to the active drug) and two studies had primarily exposed populations (i.e. most patients had previously used the active drug). In the Nasr [15] and Jensen [11] studies exposure status was unknown, and in the Oermann study [17], one arm was exposed and one arm naïve to the study drugs. Patients who are maintained (previously exposed) on a nebulised antibiotic treatment appear to reach a plateau in FEV1% predicted after some time and do not show a great improvement if at all.

Table 1

Study characteristics of 11 identified inhaled antibiotic studies in patients with CF.

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of RCT</th>
<th>Duration (weeks)</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[23]</td>
<td>*DB, PC, MC</td>
<td>24: 3 cycles**</td>
<td>TIP 122 mg BID vs. PLA</td>
</tr>
<tr>
<td>[22]</td>
<td>OL, MC</td>
<td>24</td>
<td>TIP 112 mg BID vs. PLA</td>
</tr>
<tr>
<td>[12]</td>
<td>DB, PC, MC</td>
<td>24: 3 cycles</td>
<td>TIS-T 300 mg BID vs PLA</td>
</tr>
<tr>
<td>[15]</td>
<td>DB, PC (pilot)</td>
<td>24: 3 cycles</td>
<td>TIS-T 300 mg/5 mL BID vs PLA</td>
</tr>
<tr>
<td>[13]</td>
<td>OL, MC</td>
<td>4</td>
<td>TIS-T 300 mg/5 mL BID vs Colistimethate sodium (colistin) 80 mg/3 mL BID vs PLA</td>
</tr>
<tr>
<td>[11]</td>
<td>DB, PC</td>
<td>13</td>
<td>Colistimethate sodium (colistin) 1 MU/ml BID vs PLA</td>
</tr>
<tr>
<td>[16]</td>
<td>DB, PC, MC, PG</td>
<td>8: 1 cycle</td>
<td>TIS-B 300 mg/4 mL BID vs PLA</td>
</tr>
<tr>
<td>[21]</td>
<td>DB, PC, MC, PG</td>
<td>24: 3 cycles</td>
<td>TIS-B 300 mg/4 mL BID vs PLA</td>
</tr>
<tr>
<td>[24]</td>
<td>DB, PC, MC</td>
<td>4 + 8 follow up</td>
<td>AZLI 75 mg BID or TID vs PLA BID or TID</td>
</tr>
<tr>
<td>[25]</td>
<td>DB, PC, MC</td>
<td>4</td>
<td>AZLI 75 mg TID or PLA TID vs PLA TID</td>
</tr>
<tr>
<td>[17]</td>
<td>OL, PC, MC</td>
<td>24: 3 cycles</td>
<td>AZLI 75 mg TID vs PLA TID</td>
</tr>
</tbody>
</table>

*Double blind (DB), placebo-controlled (PC), multi-centre (MC), open-label (OL), parallel-group (PG), placebo (PLA), tobramycin inhalation powder capsule (TIP), tobramycin inhalation solution 300 mg/5 mL (TIS-T), tobramycin inhalation solution 300 mg/4 mL (TIS-B), colistimethate sodium (colistin), aztreonam lysine for inhalation (AZLI), twice a day (BID), three times a day (TID).* **Cycle=4 weeks on/4 weeks off.

Fig. 1. Study selection flow diagram. *Oermann data was only available in a poster.
Improvements in FEV₁% predicted are therefore expected to be largest in patients who are naïve to the antibiotic. The population in each study arm was classified as naïve or exposed to the active ingredient tested, and within each trial there was consistency in exposure status. The Oermann data [17], however, could not be included in the analysis as the study arm populations differed regarding naïve/exposed status.

### 3.3. Base case results using % CFB in FEV₁% predicted at 4 weeks

The base case NMA combined individual study results from 7 of the 11 trials assessing % CFB in FEV₁% predicted (Table 3). The Lenoir study [16] was excluded because not all patients were chronically-infected with *P. aeruginosa* [5]. The Oermann study [17] was excluded because the study arm populations differed regarding naïve/exposed status. The studies of Nasr [15] and Jensen [11], where patients had mild FEV₁ impairment, were excluded. Among the 7 included studies, there was variation in mean age (2 studies < 18 y vs. 5 studies > 18 y) and exposure status (2 studies exposed vs. 5 studies naïve to the study drug). As such, the base case included a covariate for exposure.

TIP and TIS-T were more efficacious than placebo in improving % CFB in FEV₁% predicted (Table 4). For TIS-B, AZLI and colistin, the point estimates suggested improvement in % CFB in FEV₁% predicted over placebo, although there was a fair degree of uncertainty around the point estimates. Regarding the treatment effect of TIP, point estimates suggested that TIP was superior to colistin and AZLI and was comparable to TIS-T and TIS-B; the level of uncertainty around point estimates, however, suggested a comparable efficacy of all treatments. TIS-T and TIS-B, as well as AZLI and colistin seem to offer a comparable efficacy.

### 3.4. Scenario analysis results

Several scenario analyses were run with or without a covariate for baseline age, exposure or baseline FEV₁, and in naïve or exposed subgroups or in different age subgroups: (1) The ‘No EXP covariate’ scenario included all 7 studies without a covariate for exposure; (2) The naïve subgroup included the 5 studies with no prior exposure to active drug; (3) The exposed subgroup included the 2 studies with previously exposed populations; (4) Scenario mild FEV₁ included the Nasr [15] and Jensen [11] studies with baseline FEV₁% predicted >70% and a covariate for baseline FEV₁; (5) ‘All ages — cov AGE’ scenario included all 7 studies with a covariate for age rather than for exposure status; and (6) The subgroups for age either included the 2 studies with a mean age < 18 years, or 3 studies with mean age > 18 years.

The effects of each intervention versus placebo were fairly consistent across each scenario compared to the base case (Fig. 3). The largest effects were seen for inhaled tobramycin (TIP, TIS-T and TIS-B), followed by AZLI and colistin (Fig. 4). The base case with no covariate scenario resulted in less uncertainty around results. It was not possible to compare the age subgroups, due to differences in comparators included in these subgroups, except for TIP; the effect of TIP versus placebo was higher in the subgroup with mean age < 18 years compared to > 18 years. Due to the lack of data, it was not possible to assess whether this difference was driven by the age differences or the naïve/exposed status differences.
3.5. Scenarios on impact of exposure status (Scenarios 1–3)

The naïve subgroup did not allow a comparison to colistin and produced slightly greater differences in efficacy than the base case results, which is in line with the larger %CFB in FEV_{1}\% predicted observed in these studies compared to the exposed status studies. The comparison of TIP to colistin was possible via the indirect route TIP–TIS-T/TIS-T–colistin. Given the lack of comparators in the exposed subgroup, it was difficult to compare it to naïve subgroups. There was, however, a consistent trend across all scenario analyses in the effect of TIP relative to alternatives; with the largest benefits compared to placebo, colistin and AZLI, and with comparable benefits to TIS-T and TIS-B (Fig. 4).

3.6. Scenario on impact of baseline FEV_{1}\% predicted (Scenario 4)

A consistent trend to the base case was observed across all FEV_{1} analyses for the effect of TIP relative to alternatives. As Nasr [15] and Jensen [11] studies were small (≤40 patients) these had less weighting in the network, and therefore a minor impact on results.

3.7. Scenarios on impact of mean baseline age (Scenarios 5 and 6)

Compared to the base case analysis, adding a covariate for age rather than exposure produced similar results but greater uncertainty. The subgroup with mean age<18 years included all naïve patients, and only allowed a comparison between TIP and TIS-B. The subgroup with mean age>18 years included a mix of naïve and exposed status studies but did not include TIS-B in the network. Therefore comparisons between

the <18 year and >18 year populations were limited by lack of data. Overall, a consistent trend to the base case was observed across all scenario analyses for the effect of TIP relative to alternatives.

3.8. Other endpoints

There were insufficient data to produce reliable results for % CFB in FEV_{1}\% predicted at 20 weeks, P. aeruginosa sputum density at 20 weeks, respiratory hospitalisation and anti-P. aeruginosa antibiotic use at 24 weeks. Only 3 studies reported these outcomes, with differences across studies, i.e., mix of naïve/exposed status and age groups, and limited comparisons possible. Regarding P. aeruginosa sputum density at 4 weeks; 7 studies reported this outcome and comparisons were possible between TIP, TIS-T, TIS-B, colistin and AZLI. For this outcome, TIP was expected to have better outcomes than placebo, and comparable outcomes to other active treatments. As this analysis included the same studies as for FEV_{1} at 4 weeks, there was variability across the studies due to age and exposure (Fig. 5). This resulted in a lot of uncertainty around results, and the limited data available made it difficult to draw conclusions. Subgroup analyses were limited because they did not allow comparisons to all treatments of interest, and the inclusion of a covariate to address the underlying variability increased the uncertainty of the results.

4. Discussion

CF is a rare disease with few pivotal studies of inhaled antibiotics, and limited data on direct comparisons of currently available treatment options. NMA helps overcome the lack of head to head trials against all comparators. NMA is a valid accepted method to assess relative efficacy and provides

### Table 3

Percent change from baseline in FEV_{1}\% predicted in cystic fibrosis patients treated with different antibiotics from data reported in trials and relative treatment effects.

<table>
<thead>
<tr>
<th>Source</th>
<th>Mean age</th>
<th>Exposure</th>
<th>% CFB (SE)</th>
<th>Difference in % CFB (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>TIS-T</td>
</tr>
<tr>
<td>[23]</td>
<td>&lt;18 y</td>
<td>Naive</td>
<td>0.68 (2.81)</td>
<td>13.97 (2.81)</td>
</tr>
<tr>
<td>[22]</td>
<td>&gt;18 y</td>
<td>Exposed</td>
<td>3.60 (1.03)</td>
<td>2.80 (1.20)</td>
</tr>
<tr>
<td>[12]</td>
<td>&gt;18 y</td>
<td>Naive</td>
<td>0.07 (1.02)</td>
<td>11.85 (1.53)</td>
</tr>
<tr>
<td>[15]</td>
<td>&lt;18 y</td>
<td>Unknown</td>
<td>0.90 (1.14)</td>
<td>1.36 (1.24)</td>
</tr>
<tr>
<td>[13]</td>
<td>&gt;18 y</td>
<td>Exposed</td>
<td>6.70 (2.14)</td>
<td>0.37 (1.41)</td>
</tr>
<tr>
<td>[16]</td>
<td>&lt;18 y</td>
<td>Naive</td>
<td>4.23 (3.65)</td>
<td>27.92 (3.46)</td>
</tr>
<tr>
<td>[21]</td>
<td>&lt;18 y</td>
<td>Naive</td>
<td>0.77 (2.03)</td>
<td>12.9 (1.46)</td>
</tr>
<tr>
<td>[24]</td>
<td>&gt;18 y</td>
<td>Naive</td>
<td>-2.00 (1.00)</td>
<td>4.50 (1.00)</td>
</tr>
<tr>
<td>[25]</td>
<td>&gt;18 y</td>
<td>Naive</td>
<td>-2.44 (1.33)</td>
<td>8.03 (1.33)</td>
</tr>
<tr>
<td>[17]</td>
<td>&gt;18 y</td>
<td>Naive and exposed</td>
<td>0.55 (1.42)</td>
<td>8.35 (1.42)</td>
</tr>
</tbody>
</table>

Excluded studies: [15] had mild FEV_{1} impairment, [11] had mild FEV_{1} impairment and old study, [17] had inconsistency due to naïve and exposed status, and [16] included a non-chronic Pa infected population. Calculated data in italics (from mean CFB data or mean FEV_{1} at 4 weeks and baseline FEV_{1}, SE from SD and sample size).

Tobramycin inhalation powder capsule (TIP), tobramycin inhalation solution 300 mg/5 ml (TIS-T), tobramycin inhalation solution 300 mg/4 ml (TIS-B), colistimethate sodium (colistin), aztreonam lysine for inhalation (AZLI), percent change from baseline (%CFB), standard error (SE), P. aeruginosa (Pa), forced expiratory volume in 1 second percentage (FEV_{1}%).

a Randomised and treated population with no imputation of missing data.
b Per protocol population.
c Randomised and treated population with imputation using LOCF.
d Randomised and treated population, unknown imputation status.
relevant information for healthcare decisions [7]. However, NMA is limited by the quality of the data included. As randomisation only holds within a trial but not across trials, it is possible to have bias in indirect comparisons. In this study, we made every effort to avoid bias by ensuring only comparable trials, i.e. similar populations and study designs, were combined. To further control for potential bias, we included the following covariates to control effect modifiers in our models: 1) exposure status; 2) baseline FEV1% predicted; and 3) age.

Five antibiotics were presented in 11 trials, with a large amount of heterogeneity across studies (e.g. naïve/exposed status, mild/moderate FEV1% predicted, age differences, publication date) which hampered the analyses and resulted in relatively low precision of the estimates. Controlling for both potential effect modifiers (mean age and previous exposure to the study drug) was not possible simultaneously in this small dataset. Therefore scenarios on exposure were not able to control for age differences, and vice versa. Despite these drawbacks, the analyses, based on point estimates, suggested that all treatments provided an improvement compared to placebo, and that tobramycin formulations provided an improvement over AZLI or colistin. However, credible limits were too large to make this statistically significant. The difference in % CFB for TIP compared to placebo, colistin and AZLI can be considered clinically meaningful, using a cut-off of 3.5% CFB in FEV1% predicted. Our results are comparable to the conclusions of a previous Cochrane review [18].

Table 4
Network meta-analysis results: Difference in % CFB in FEV1% predicted at 4 weeks in Cystic Fibrosis patients treated with different antibiotics.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TIS-T (0.67, 26.29)</th>
<th>TIS-B (-0.27, 27.3)</th>
<th>AZLI (-5.82, 6.06)</th>
<th>Colistin (-5.82, 6.06)</th>
<th>TIP (0.18, 25.73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>13.47</td>
<td>13.55</td>
<td>9.28</td>
<td>12.92</td>
<td></td>
</tr>
<tr>
<td>TIS-T</td>
<td>0</td>
<td>(0.67, 26.29)</td>
<td>(-0.27, 27.3)</td>
<td>(-5.82, 6.06)</td>
<td>(-3.76, 22.14)</td>
<td></td>
</tr>
<tr>
<td>TIS-B</td>
<td>13.55</td>
<td>0.09</td>
<td>(-5.82, 6.06)</td>
<td>9.68</td>
<td>-0.27</td>
<td></td>
</tr>
<tr>
<td>AZLI</td>
<td>9.28</td>
<td>-4.19</td>
<td>-9.68</td>
<td>-15.11</td>
<td>-0.27</td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>12.92</td>
<td>0</td>
<td>-6.40</td>
<td>-9.58</td>
<td>-0.27</td>
<td></td>
</tr>
<tr>
<td>TIP</td>
<td>12.92</td>
<td>-0.55</td>
<td>-0.64</td>
<td>3.64</td>
<td>-0.64</td>
<td></td>
</tr>
</tbody>
</table>

Tobramycin inhalation powder capsule (TIP), tobramycin inhalation solution 300 mg/5 ml (TIS-T), tobramycin inhalation solution 300 mg/4 ml (TIS-B), colistimethate sodium (colistin), aztreonam lysine for inhalation (AZLI), percent change from baseline (%CFB), forced expiratory volume in 1 second percentage (FEV1%), credible limit (CrL).

Fig. 3. Overview of network meta-analysis scenario results for change in lung function of different antibiotics versus placebo. Exposed subgroup network did not include placebo. Fixed effects model (FEM), random effects model (REM), exposure status (EXP), forced expiratory volume (FEV), covariate (Cov), percent change from baseline (%CFB), forced expiratory volume in 1 second percentage (FEV1%), tobramycin inhalation powder capsule (TIP), tobramycin inhalation solution 300 mg/5 ml (TIS-T), tobramycin inhalation solution 300 mg/4 ml (TIS-B), colistimethate sodium (colistin), aztreonam lysine for inhalation (AZLI).
Fig. 4. Overview of network meta-analysis scenario results for change in lung function of TIP versus alternative antibiotics. Fixed effects model (FEM), Random effects model (REM), exposure status (EXP), forced expiratory volume (FEV), covariate (Cov), percent change from baseline (%CFB), forced expiratory volume in 1 second percentage (FEV1%), tobramycin inhalation powder capsule (TIP), tobramycin inhalation solution 300 mg/5 ml (TIS-T), tobramycin inhalation solution 300 mg/4 ml (TIS-B), colistimethate sodium (colistin), aztreonam lysine for inhalation (AZLI).

Fig. 5. Overview of network meta-analysis scenario results for change in sputum density of TIP versus alternative antibiotics. Fixed effects model (FEM), random effects model (REM), exposure status (EXP), forced expiratory volume (FEV), covariate (Cov), percent change from baseline (%CFB), forced expiratory volume in 1 second percentage (FEV1%), tobramycin inhalation powder capsule (TIP), tobramycin inhalation solution 300 mg/5 ml (TIS-T), tobramycin inhalation solution 300 mg/4 ml (TIS-B), colistimethate sodium (colistin), aztreonam lysine for inhalation (AZLI).
active drug, and therefore had a population who was naïve to the active drug. The head to head studies were conducted after approval of colistin and tobramycin, and therefore included a population that was already exposed to these drugs. From the data reported in trials, there was generally a larger gain in % CFB in FEV1% predicted for naïve populations than for data reported in trials, there was generally a larger gain in % population that was already exposed to these drugs. More recent trials, such as the Oermann study [17], are more likely to include exposed populations as the majority of chronically-infected patients are now regularly treated with inhaled tobramycin or colistin. The Oermann study [17], however, included one arm with prior exposure to the active drug (TIS-T) and one arm naïve to the active drug (AZLI). Therefore the study design presented an inconsistency in the network by not comparing ‘like with like’. Objective comparison between the treatments in this study was therefore challenging.

Future trials and comparisons will increasingly need to consider study design and population differences. Additional research is needed on potential effect modifiers to understand their impact on outcomes and their relative importance. One such example is chest computed tomography to characterize structural lung abnormalities at baseline [19,20]. Future studies should include a more homogenous population regarding age, baseline FEV1% predicted and inclusion of either chronically- or non-chronically-infected patients. The major study design difficulty is in controlling for exposure status as most patients today will have prior exposure to several antibiotics. This field needs clinicians and researchers to align the approach to study design, population selection and the most relevant comparative outcomes.

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