J Bras Pneumol. 2023;49(2):e20230040
https://dx.doi.org/10.36416/1806-3756/e20230040

Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis. Official document of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association)

Rodrigo Abensur Athanazio[1], Suzana Erico Tanni[8], Juliana Ferreira[1], Paulo de Tarso Roth Dalcin[3,4], Marcelo B de Fuccio[5], Concetta Esposito[6], Mariane Gonçalves Martynychen Canan[7], Liana Sousa Coelho[8], Mônica de Cássia Firmida[9], Marina Buarque de Almeida[2], Paulo José Cauduro Marostica[10], Luciana de Freitas Velloso Monte[11,12], Edna Lúcia Souza[13], Leonardo Araujo Pinto[14], Samia Zahi Rached[1], Verônica Stasiak Bednarczuk de Oliveira[7,15], Carlos Antonio Riedi[7], Luiz Vicente Ribeiro Ferreira da Silva Filho[2]

References cited in this supplemental material follow the numbering of the list of references cited in the main article. References cited only in this supplemental material are cited here with numbering subsequent to the list of references in the main text.

Question S1. Detailed description of the findings.

For this question, the outcomes categorized as critical by the committee were mortality, adverse effects, and quality of life. Outcomes such as pulmonary function (FEV_1), BMI variation, and exacerbations were also evaluated and were categorized as important.

Regarding mortality, the effect of the treatment could not be estimated, because there were no deaths in any of the randomized clinical trials (RCTs) evaluated[12,32,35-37,39,47,48] or in the placebo groups of any of the observational studies evaluated.[28-31,34,38,40-46,49-54]

All of the studies used the Cystic Fibrosis Questionnaire-Revised (CFQ-R) in the respiratory symptoms domain[167] to assess quality of life. Pooled effect measures showed better quality for patients who were being treated with ivacaftor, in the RCTs (relative risk [RR] =6.46; 95% CI: 2.29-10.64) and in the observational studies (RR = 10.23; 95% CI: 5.08-15.38).

There was a higher occurrence of adverse events with the use of ivacaftor, with an RR of 1.46 (95% CI: 1.21-1.77) in the RCTs. However, serious adverse events that led to treatment discontinuation were rare, which supports the good safety profile of the drug.

For the outcomes categorized as important, the analysis of the studies allowed us to infer an improvement in pulmonary function (FEV_1) with the use of ivacaftor on the order of 8.52% (95% CI: 4.05-13.00) in the RCTs and 6.71% (95% CI: 5.49-7.93) in the observational studies. The treatment was associated with a reduction in the rate of exacerbations, with an RR of 0.66 (95% CI: 0.48-0.91) in the RCTs and 0.67 (95% CI: 0.63-0.70) in the observational studies.

In a real-life study published in 2020, Volkova et al.[55] evaluated disease progression in patients treated with ivacaftor for 5 years. The authors evaluated patients enrolled in cystic fibrosis (CF) registries in the US and UK, which maintain a high degree of data integrity. They analyzed 635 cases versus 1,875 controls in the US registry and 247 cases versus 1,230 controls in the UK registry. The authors also observed that, at the end of the 5-year follow-up period, the ivacaftor group patients had better lung function and a better nutritional status, as well as a lower frequency of exacerbations and hospitalizations, in comparison with their baseline values and the values obtained for the standard therapy without ivacaftor (control) group. Although the UK registry included fewer patients, the outcomes were similar. In addition, there were trends toward improvement in other relevant outcomes, such as a lower frequency of CF-related diabetes and a lower prevalence of chronic

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Unidade de Pneumologia, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil
3. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
4. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre – HCPA – Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
5. Hospital Júlia Kubitschek, Fundação Hospitalar do Estado de Minas Gerais – FHEMIG – Belo Horizonte (MG) Brasil.
6. Hospital Nereu Ramos, Florianópolis (SC) Brasil.
7. Hospital de Clínicas, Universidade Federal do Paraná, Curitiba (PR) Brasil.
8. Faculdade de Medicina de Botucatu, Universidade Estadual Paulista Julio de Mesquita Filho – UNESP – Botucatu (SP) Brasil.
9. Universidade do Estado do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
10. Unidade de Pneumologia Infantil, Hospital de Clínicas de Porto Alegre – HCPA – Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
11. Hospital da Criança de Brasília José Alencar, Brasília (DF) Brasil.
12. Universidade Católica de Brasília, Brasília (DF) Brasil.
13. Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador (BA) Brasil.
14. Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
15. Unidos Pela Vida – Instituto Brasileiro de Atenção à Fibrose Cística, Curitiba (PR) Brasil.

infection with *Pseudomonas aeruginosa*. Such findings in a real-life study[55] indicate that the modulator ivacaftor is indicated for the treatment of CF patients who carry the eligible genetic variants.

Question S2. Detailed description of the findings.

The outcomes categorized as critical by the committee were mortality, adverse effects, and quality of life. Outcomes such as pulmonary function (FEV_1), BMI variation, and exacerbations were also evaluated and considered important.

As for mortality, it was not possible to estimate the effect of treatment. In the 2 RCTs [12,57] there were no deaths in the intervention groups (a total of 840 patients). In the evaluation of the observational studies (1,407 subjects included), only 6 deaths occurred.

All studies used the CFQ-R in the respiratory symptoms domain to assess quality of life.[12,56-69] By using the data from the studies, it was possible to perform a meta-analysis. The pooled effect measure for the RCTs (RR = 2.5; 95% CI: 0.1-5.1) was similar to that obtained for the observational studies (RR = 3.82; 95% CI: 2.28-5.36), showing that the score for the CFQ-R respiratory symptoms domain was higher among the patients who were being treated with lumacaftor+ivacaftor. Despite the numerical improvement observed in quality of life, the result did not reach the necessary clinical significance of 4 points established in the score.

In all of the studies included, the proportion of patients reporting adverse events was described. The frequency of adverse events ranged from 59.4% to 96.5% in the treatment groups. The most commonly reported events were respiratory manifestations of mild to moderate severity, including dyspnea, chest tightness or discomfort, and bronchospasm. It is noteworthy that comparisons using appropriate statistical tests were not presented. The studies converged to a good safety profile regarding the use of lumacaftor+ivacaftor, although the quality of evidence was very low.

Two RCTs [12,57] evaluated the annual exacerbation rate and found it to be lower in the treatment group (RR = 0.65; 95% CI: 0.55-0.75), although the quality of evidence was very low. It was not possible to estimate the effect on exacerbation prevention in observational studies because of the lack of control groups. With regard to BMI, the use of lumacaftor+ivacaftor was found to provide a slight improvement in this index, in the RCTs (gain of 0.26 kg/m^2; 95% CI: 0.17-0.35) and in the observational studies (gain of 0.36 kg/m^2; 95% CI: 0.03-0.69).

The pooled effect measure for lung function showed an increase in FEV_1 of 2.98% (95% CI: 2.31-3.64) in the 2 RCTs,[12,57] and the results found were considered consistent. In the observational studies evaluated, the increase found was 2.17% (95% CI: 0.92-3.41), although the quality of evidence was very low.

Question S3. Detailed description of the findings.

For this question, the outcomes categorized as critical by the committee were mortality, adverse effects, and quality of life. Outcomes such as pulmonary function (FEV_1), BMI variation, and exacerbations were also evaluated and were categorized as important.

There were 4 RCTs that reported data on mortality.[14,15,74,75] None of those studies, involving a collective total of 452 patients in the control groups and 573 patients in the tezacaftor+ivacaftor groups, identified fatal events.

Four studies assessed quality of life using the CFQ-R.[13,14,70,72] One observational study[72] showed an increase of 3.4 points (95% CI: 1.4-5.5). The meta-analysis carried out with results from 3 other studies[13,14,70] showed an increase of 6.02 points (95% CI: 1.40-10.64), although the quality of evidence was very low.

Adverse effects were assessed and compiled. There was no statistically significant difference between the groups treated with tezacaftor+ivacaftor and the control groups, with a rate ratio of 1.07 (95% CI: 0.93-1.22).

Lung function was assessed using FEV_1, and the pooled effect measure showed an increase of 3.84% (95% CI: 2.23-5.45). The results found were considered consistent.

Two studies evaluated the annual exacerbation rate and found a lower rate in the intervention group.[13,14] However, the pooled analysis of the data did not show a statistically significant difference (RR = 0.68; 95% CI: 0.47-1.01). Regarding BMI, there is little evidence regarding the effect of tezacaftor+ivacaftor, and no differences were identified in relation to the control group in the studies evaluated.[13,70,72]

Question S4. Detailed description of the findings.

For this question, the critical outcomes analyzed were mortality, adverse events, and time free from infection with *P. aeruginosa*. The outcomes of microorganism eradication and pulmonary function, both categorized as important, were also analyzed. For the important outcomes of BMI and exacerbations, no studies were identified that would allow the effect that the treatment has on those outcomes to be evaluated.

Regarding the critical outcome of mortality, it was possible to select for analysis only one observational study,[86] in which the patients were followed for 56 days. In that study, there were no deaths in either group: that of patients receiving tobramycin for 28 days; and that of patients receiving tobramycin for 56 days. The quality of evidence was considered very low.

For the critical outcome of adverse events, an RR of 1.76 (95% CI: 1.14-2.74) was obtained for the eradication treatment, compared with placebo, in only 1 of the RCTs analyzed,[89] with very low quality of evidence.

One observational study[86] was selected to evaluate the critical outcome of time free from infection with *P. aeruginosa* with the eradication treatment, over a follow-up period of 6 months. The authors found that the time free from such infection was 23.75 months (95% CI: 12.50-34.40). It is noteworthy that the quality of evidence was very low.

With regard to the important outcome of eradication of *P. aeruginosa*, we analyzed only one RCT,[91] which demonstrated an RR of 1.43 (95% CI: 0.88-2.36), favoring treatment over placebo, with very low quality of evidence.

In the evaluation of the important outcome of lung function, 10 studies were selected, of which 7 were observational studies[76-80,82,87] and 3 were RCTs.[81,84,89] However, because of the heterogeneity of the measures used in the studies and the lack of comparison with placebo groups in the RCTs, only 4 observational studies were submitted to meta-analysis. A mean increase in FEV_1 of 5.81% of the predicted value (range, 2.02-9.60) was obtained in the treated group, with very low quality of evidence.[81-83]

Question S5. Detailed description of the findings.

For this question, the outcomes categorized as critical by the committee were mortality, adverse effects, and quality of life. Outcomes such as pulmonary function (FEV_1), BMI variation, and exacerbations were also evaluated and were categorized as important.

Regarding the outcome of mortality, the result of the analysis of 6 RCTs showed a benefit in the treatment group compared with the placebo group (0.1% vs. 1.1%), with a protective effect (RR = 0.11; 95% CI: 0.01-0.85).[94,96,104,116,112,115]

Fifteen studies included in this review assessed the critical outcome of adverse events. Despite a large number of individuals studied, there was heterogeneity and inconsistency in several aspects, which made the analysis difficult. The adverse events most commonly reported were coughing, wheezing, hemoptysis, and throat irritation. There were 977 events among 777 patients (a rate of 125.7%) in the intervention group and 737 events among 575 patients (a rate of 128.2%) in the placebo group, with no statistical difference (RR = 0.98; 95% CI: 0.89-1.09).[95-97,99,101,102,104-106,111-114,116]

Three studies, all classified as RCTs, evaluated the quality of life of patients.[97,106,113] Two of those studies[97,106] assessed the scores on the respiratory symptoms domain of the CFQ-R, and only 1[113] assessed the total CFQ-R scores. All three studies showed that quality of life was more improved in the treatment group (mean increase of 6.4 points; range, 3.2-9.6) than in the placebo group.

Regarding the risk of exacerbations, the articles that evaluated the treatment with inhaled antimicrobials for chronic infection with *P. aeruginosa* obtained conflicting results, making it impossible to clearly state whether there was a benefit from the treatment in terms of a reduction in the number of pulmonary exacerbations. The analysis showed no statistically significant difference.[100,101,103,110,117]

For the assessment of lung function, some studies have shown improvement in FEV_1 and FVC in the group treated with inhaled tobramycin or colistimethate when compared with controls.[111,112,117] In the present review, we identified a benefit of the treatment, with mean values that were 2.24% higher (95% CI: 0.17-4.30) in the RCTs[94-100,104-108,110-116,118] and 2.25% higher (95% CI: 2.89-7,39) in the observational studies.[101-103,109,117] It should be noted, however, that there was great heterogeneity and inconsistency of findings among the studies.

Only 1 study,[111] with an observational design, evaluated the impact that treatment for chronic infection had on BMI, and that study showed no significant differences.

Question S6. Detailed description of the findings.

For this question, the outcomes categorized as critical by the committee were mortality, adverse effects, and quality of life. Outcomes such as pulmonary function (FEV_1), BMI variation, and exacerbations were also evaluated and were categorized as important.

All of the studies evaluated the rate of success in eradicating methicillin-resistant *Staphylococcus aureus*.[120-127] In the two RCTs evaluated,[123,126] with follow-up periods of 28 days and 6 months, respectively, methicillin-resistant *S. aureus* was eradicated successfully (OR = 3.12; 95% CI: 1.7-5.7). It was not possible to evaluate two other critical outcomes: mortality and adverse events. As for the quality of life outcome, the results were not significant.

Three studies evaluated exacerbations[121,123,124] but did not report consistent results regarding differences with the control groups. Only 1 study did not assess lung function.[121] In the 2 RCTs that evaluated the gain in FEV_1,[123,126] an absolute gain of 5.8% of the predicted value (95% CI: 1.02-10.62) was observed.

Question S7. Detailed description of the findings.

For this question, the outcomes categorized as critical by the committee were mortality, adverse effects, and quality of life. Outcomes such as pulmonary function (FEV_1), BMI variation, and exacerbations were also evaluated and were categorized as important.

For the outcomes of mortality[17,149] and adverse effects,[17,143,146,149] no significant differences were observed with the use of dornase alfa. When assessing quality of life, an observational study of 152 patients reported a mean increase in the CFQ-R score of 7.38 points (95% CI: 4.24-10.52), although that study did not evaluate a control group (very low quality of evidence). In the only RCT analyzed,[155] no significant difference in quality of life was demonstrated with the use of dornase alfa.

Treatment with dornase alfa resulted in an improvement in FEV_1 (% of the predicted value) in 9 RCTs, which collectively analyzed 2,509 patients and showed a mean improvement in FEV_1 of 5% (95% CI: 1.65-8.35) [17,131-134,141,152-154] and in 12 observational studies,[136-139,143,146-148,150,156,157,161] which collectively analyzed 5,303 patients and showed a mean improvement in FEV_1 of 4.89% (95% CI: 1.42-8.35), although the quality of evidence was very low. A significant reduction in exacerbations (RR = 0.73; 95% CI: 0.54-0.91) was also identified in 2 RCTs,[17,152] with high quality of evidence. No significant differences were observed regarding BMI.

Question S8. Detailed description of the findings.

For this question, the outcomes categorized as critical by the committee were mortality, the eradication rate, adverse effects, and quality of life. Outcomes such as pulmonary function (FEV_1), BMI variation, and exacerbations were also evaluated and were categorized as important.

It was not possible to estimate the effect that eradication therapy had on mortality or on the eradication rate.

In the clinical trial by Tullis et al.[165] the number of adverse events, especially bronchospasm, was found to higher in the group treated with inhaled aztreonam than in the placebo group.

Eradication therapy for *Burkholderia cepacia complex* was not found to have any effect on the outcomes categorized as important (exacerbations, BMI, lung function, and quality of life).

REFERENCES

167. Quittner AL, Sawicki GS, McMullen A, Rasouliyan L, Pasta DJ, Yegin A, et al. Psychometric evaluation of the Cystic Fibrosis Questionnaire-Revised in a national sample. Qual Life Res. 2012;21(7):1267-1278. doi:10.1007/s11136-011-0036-z

Table S1A. GRADE analysis of ivacaftor compared with placebo in cystic fibrosis patients with class III (gating) or class IV (conduction) mutations regarding mortality, quality of life, and adverse events.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivacaftor	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
7	observational study	severe[a]	not severe	severe[b,c]	severe[d]	none	16/2008 (0.8%)		not estimable		⨁◯◯◯ Very low	CRITICAL
Mortality												
2	randomized clinical trials	severe[e]	not severe	severe[b,c]	severe[a]	none	0/109 (0.0%)	0/104 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Quality of life												
7	randomized clinical trials	very severe[e]	not severe	severe[b,c]	severe[a]	none	273	258	-	mean 6.46 higher (from 2.29 more to 10.64 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life												
6	observational study	severe	not severe	severe[b,c]	severe[a]	none	351	150	-	mean 10.23 higher (from 5.08 more to 15.38 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
6	randomized clinical trials	very severe[e]	not severe	severe[b]	severe[a]	none	303/236	174/198	RR 1.46 (1.21 to 1.77)	0 more per event in patient(s) (from 0 more to 1 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
7	observational study	very severe[a]	not severe	severe[b]	severe[a]	none	611/357 (171.1%)		not estimable		⨁◯◯◯ Very low	CRITICAL

RR: risk ratio

Explanations

a. Insufficient sample size
b. Differences between standard of care treatments
c. Different populations
d. Large confidence interval
e. No description of blind allocation, randomization, or outcomes

J Bras Pneumol. 2023;49(2):e20230040

Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis. Official document of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association)

Table S1B. GRADE analysis of ivacaftor compared with placebo in cystic fibrosis patients with class III (gating) or class IV (conduction) mutations regarding FEV_1, exacerbations, and BMI.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Relative (95% CI)	Absolute (95% CI)	Indirectness	Relative (95% CI)	Other considerations	Ivacaftor	Placebo	Relative (95% CI)	Absolute (95% CI)		
Lung function: FEV_1 of predicted												
4	randomized clinical trials	very severe[e]	severe[f]	severe[b,c]	severe[d]	none	193	188	-	mean 8.52% more (from 4.05 more to 13 more)	⨁◯◯◯ Very low	IMPORTANT
Lung function: FEV_1 of predicted												
19	observational study	very severe[c]	severe[f]	severe[b,c]	severe[d]	none	1378	3553	-	mean 6.71% more (from 5.49 more to 7.93 more)	⨁◯◯◯ Very low	IMPORTANT
Exacerbation												
2	randomized clinical trials	very severe[e]	not severe	severe[b]	severe[a]	none	39/117 (33.3%)	57/113 (50.4%)	RR 0.66 (0.48 to 0.91)	172 fewer per 1.000 (from 262 fewer to 45 fewer)	⨁◯◯◯ Very low	IMPORTANT
Exacerbation												
8	observational study	very severe[c]	not severe	severe[b]	severe[a]	none	556/886 (62.8%)	3808/4040 (94.3%)	RR 0.67 (0.63 to 0.70)	311 fewer per 1.000 (from 349 fewer to 283 fewer)	⨁◯◯◯ Very low	IMPORTANT
BMI variation												
3	randomized clinical trials	very severe[e]	not severe	severe[b,c]	severe[d]	none	142	143	-	mean 0.99 kg/m^2 higher (from 0.55 higher to 1.42 higher)	⨁◯◯◯ Very low	IMPORTANT
BMI variation												
14	observational study	severe[b,c]	severe[f]	severe[b,c]	not severe	none	1378	3553	-	mean 0.81 kg/m^2 higher (from 0.59 higher to 1.03 higher)	⨁◯◯◯ Very low	IMPORTANT

RR: risk ratio

Explanations

a. Insufficient sample size
b. Differences between standard of care treatments
c. Different populations
d. Large confidence interval
e. No description of blind allocation, randomization, or outcomes
f. Heterogeneity

Table S2A. GRADE analysis of lumacaftor+ivacaftor compared with placebo in cystic fibrosis patients homozygous for the *F508del* mutation regarding mortality, quality of life, and adverse events.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lumacaftor + ivacaftor	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomized clinical trials	not severe	severe[a]	severe[b]	severe[c]	none	0/840 (0.0%)	0/472 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Mortality												
4	observational study	severe[d]	severe[a]	severe[b]	severe[c]	none	6/1407 (0.4%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL
Adverse events												
2	randomized clinical trials	not severe	severe[a]	severe[b]	severe[c]	none	805/840	453/472	**RR 1.03** (0.90 to 1.16)		⨁◯◯◯ Very low	CRITICAL
Adverse events												
4	observational study	severe[d]	severe[a]	severe[b]	severe[c]	none	230/969 (23.7%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL
Quality of life												
1	randomized clinical trials	not severe	not severe	severe[b]	severe[c]	none	817	929	-	mean **2.5 higher** (from 0.1 fewer to 5.1 higher)	⨁⨁◯◯ Low	CRITICAL
Quality of life												
4	observational study	severe[d]	severe[a]	severe[b]	severe[c]	none	659	0	-	mean **3.82 higher** (from 2.28 higher to 5.36 higher)	⨁◯◯◯ Very low	CRITICAL

RR: risk ratio

Explanations

a. Insufficient sample size
b. Differences between standard of care treatments
c. Different populations
d. Large confidence interval
e. No description of blind allocation, randomization, or outcomes
f. Heterogeneity

Table S2B. GRADE analysis of lumacaftor+ivacaftor compared with placebo in cystic fibrosis patients homozygous for the *F508del* mutation regarding FEV_1, exacerbations, and BMI.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lumacaftor + ivacaftor	Placebo	Relative (95% CI)	Absolute (95% CI)		
Exacerbation												
2	randomized clinical trials	not severe	severe[a]	severe[b]	severe[c]	none	344/840 (41.0%)	368/472 (78.0%)	RR 0.65 (0.55 to 0.75)	273 fewer per 1.000 (from 351 fewer to 195 fewer)	⨁◯◯◯ Very low	IMPORTANT
Exacerbation												
5	observational study	severe[d]	severe[a]	severe[b]	severe[c]	none	91/194 (46.9%)	0/0	not estimable		⨁◯◯◯ Very low	IMPORTANT
Lung function: FEV_1												
2	randomized clinical trials	not severe	severe[a]	not severe	not severe	none	817	929	-	mean 2.98 higher (from 2.31 higher to 3.64 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Lung function: FEV_1												
8	observational study	severe[d]	severe[a]	severe[b]	severe[c]	Highly suspected publication bias[e]	1790	0	-	mean 2.17 higher (from 0.92 higher to 3.41 higher)	⨁◯◯◯ Very low	IMPORTANT
BMI variation												
1	randomized clinical trials	not severe	not severe	severe[b]	not severe	none	817	929	-	mean 0.26 higher (from 0.17 higher to 0.35 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
BMI variation												
5	observational study	severe[d]	severe[a]	severe[b]	severe[c]	none	1724	0	-	mean 0.36 higher (from 0.03 higher to 0.69 higher)	⨁◯◯◯ Very low	IMPORTANT

RR: risk ratio

Explanations

a. Heterogeneity
b. Different populations, different treatments
c. Insufficient sample size
d. Retrospective studies, no sample size calculation
e. Funnel plot

Table S3. GRADE analysis of tezacaftor+ivacaftor compared with placebo in cystic fibrosis patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations regarding mortality, adverse events, quality of life FEV_1, exacerbations, and BMI.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tezacaftor + ivacaftor	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomized clinical trials	severe[a]	not severe	not severe	severe[b]	none	0/573 (0.0%)	0/452 (0.0%)	not estimable		⨁⨁◯◯ Low	CRITICAL
Adverse events												
4	randomized clinical trials	severe[a]	not severe	not severe	severe[b]	none	401/452	477/573	**RR 1.07** (0.93 to 1.22)		⨁⨁◯◯ Low	CRITICAL
Quality of life												
3	randomized clinical trials	severe[a]	severe[c]	not severe	severe[d]	highly suspected publication bias[e]	466	422	-	mean **6.02 higher** (from 1.4 higher to 10.64 higher)	⨁◯◯◯ Very low	CRITICAL
Lung function: FEV_1												
3	randomized clinical trials	severe[a]	severe[c]	not severe	not severe	highly suspected publication bias[e]	484	447	-	mean **3.84% higher** (from 2.23 higher to 5.45 higher)	⨁◯◯◯ Very low	IMPORTANT
Exacerbation												
3	randomized clinical trials	severe[a]	not severe	severe[f]	severe[b]	none	96/518 (18.5%)	147/452 (32.5%)	**RR 0.68** (0.47 to 1.01)		⨁◯◯◯ Very low	IMPORTANT
BMI variation												
2	randomized clinical trials	severe[a]	severe[c]	severe[f]	severe	none	305	266	-	mean **0.025 kg/m² fewer** (from 0.08 fewer to 0.03 higher)	⨁◯◯◯ Very low	IMPORTANT

RR: risk ratio

Explanations

a. No sample size, intention-to-treat
b. Insufficient sample size
c. Heterogeneity
d. Large confidence interval
e. Funnel plot
f. Different populations

Table S4. GRADE analysis of the use of antimicrobials compared with placebo for the eradication of *Pseudomonas aeruginosa* infection in individuals with cystic fibrosis regarding mortality, adverse events, time free from the infection, eradication of the infection, lung function, and exacerbations.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antimicrobials	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 56 days)												
1	observational study	severe[a]	not severe	severe[a]	severe[b]	none	0/88 (0.0%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL
Adverse events												
1	randomized clinical trials	severe[a]	severe[c]	severe[a]	severe	none	22/26 (84.6%)	12/25 (48.0%)	**RR 1.76** (1.14 to 2.74)	**36 higher per 100** (from 7 higher to 84 higher)	⨁◯◯◯ Very low	CRITICAL
Time free from *P. aeruginosa* infection (follow-up: 6 months)												
1	observational study	severe[b]	not severe	severe[b]	severe[d]	none	24	0	-	MD **23.75% points higher** (from 12.5 higher to 34.4 higher)	⨁◯◯◯ Very low	CRITICAL
***P. aeruginosa* eradication**												
1	randomized clinical trials	severe	not severe	severe[a]	severe[d]	none	10/11 (90.9%)	7/11 (63.6%)	**RR 1.43** (0.88 to 2.36)	**27 more per 100** (from 8 fewer to 87 higher)	⨁◯◯◯ Very low	CRITICAL
***P. aeruginosa* eradication**												
6	observational study	severe[c]	severe[c]	severe[a]	severe[d]	none	400/590 (67.8%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL
Lung function (% of predicted)												
4	observational study	very severe[e]	severe[c]	severe	severe[d]	none	356	357	-	MD **5.81% higher** (from 2.02 higher to 9.6 higher)	⨁◯◯◯ Very low	IMPORTANT
Exacerbation												
0	randomized clinical trials	N/A	N/A	N/A	N/A	N/A			Not estimable			IMPORTANT

MD: mean difference; RR: risk ratio

Explanations

a. Open, not placebo-controlled study
b. Only one study
c. Heterogeneity
d. Insufficient number of patients
e. Retrospective studies

Table S5. GRADE analysis of the use of inhaled antimicrobials compared with placebo in patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* infection regarding mortality, adverse events, quality of life, exacerbations, and FEV_1.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled antimicrobials	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
6	randomized clinical trials	very severe[a]	severe[b]	severe[c]	severe[d]	none	1/883 (0.1%)	7/648 (1.1%)	**RR 0.11** (0.01 to 0.85)	**10 fewer per 1.000** (from 11 fewer to 2 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
6	randomized clinical trials	severe[d]	severe	not severe	severe[d]	none	977/777 (125.7%)	737/575 (128.2%)	**RR 0.98** (0.89 to 1.09)	**26 fewer per 1.000** (from 141 fewer to 115 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life												
3	randomized clinical trials	severe[e]	severe[b]	severe[c]	severe[d]	none	287	261	-	mean **6.4 points higher** (from 3.2 higher to 9.6 higher)	⨁◯◯◯ Very low	CRITICAL
Exacerbation												
6	randomized clinical trials	severe[a]	severe[b]	not severe	severe[d]	none	111/481 (23.1%)	150/688 (21.8%)	**RR 1.05** (0.85 to 1.30)	**11 higher per 1.000** (from 33 fewer to 65 more)	⨁◯◯◯ Very low	IMPORTANT
Lung function variation: FEV_1												
20	randomized clinical trials	very severe[a,f]	severe[b]	severe[c]	severe[d]	highly suspected publication bias[g]	1258	983	-	mean **2.24 % pints higher** (from 0.17 higher to 4.3 higher)	⨁◯◯◯ Very low	IMPORTANT
Lung function variation: FEV_1 % of predicted												
4	observational study	severe[h]	severe[b]	severe[c]	severe[d]	highly suspected publication bias[g]	389	637	-	mean **2.25% higher** (from 2.89 fewer to 7.39 higher)	⨁◯◯◯ Very low	IMPORTANT

RR: risk ratio

Explanations

a. Lack of randomization, blind allocation, unblinded outcome evaluators
b. Heterogeneity
c. Different Interventions with antimicrobials
d. Small samples
e. No sample size
f. Protocol analysis in some studies
g. Funnel plot
h. Open, patient selection

Table S6A. GRADE analysis of antimicrobial eradication treatment compared with placebo in patients with cystic fibrosis and methicillin-resistant *Staphylococcus aureus* (MRSA) colonization of the airways regarding mortality, MRSA eradication, and adverse events.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antimicrobial eradication treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	observational study	severe[a]	severe	severe[b]	severe[c]	none	0/36 (0.0%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL
MRSA eradication (follow-up: from 28 days to 6 months)												
2	randomized clinical trials	very severe[d]	not severe	not severe	severe[c]	none	30/51 (58.8%)	10/53 (18.9%)	RR 3.12 (1.70 to 5.70)	400 higher per 1.000 (from 132 higher to 887 higher)	⨁◯◯◯ Very low	CRITICAL
MRSA eradication												
6	observational study	very severe[a,e]	severe	severe[b]	severe[c]	none	88/130 (67.7%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL
Severe adverse events												
2	randomized clinical trials	very severe[d]	not severe	not severe	severe[c]	none	3/51 (5.9%)	1/53 (1.9%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Adverse events												
1	observational study	severe	severe	severe[b]	severe[c]	none	1/37 (2.7%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL

RR: risk ratio

Explanations

a. Population selection
b. Different antimicrobials
c. Insufficient number of patients
d. Open study, unblinded outcome evaluators, no intention-to-treat analysis
e. Retrospective studies

Table S6B. GRADE analysis of antimicrobial eradication treatment compared with placebo in patients with cystic fibrosis and methicillin-resistant *Staphylococcus aureus* (MRSA) colonization of the airways regarding quality of life, exacerbations, and FEV_1 in % of predicted values.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antimicrobial eradication treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of life												
1	randomized clinical trials	severe[f]	not severe	not severe	severe[c]	none	24	21	-	MD 0.26 fewer (from 11.5 fewer to 10.99 higher)	⨁⨁◯◯ Low	IMPORTANT
Exacerbation												
2	observational study	very severe[a]	very severe[b]	severe[b]	very severe[c,g]	none	0/43 (0.0%)	0/0	not estimable		⨁◯◯◯ Very low	IMPORTANT
Exacerbation												
1	randomized clinical trials	very severe[d]	not severe	not severe	severe[c]	none	29	32	-	MD 0.15 events higher (from 0.53 fewer to 0.83 higher)	⨁◯◯◯ Very low	IMPORTANT
Lung function: FEV_1 in % of predicted (follow-up period: from 28 days to 6 months)												
2	randomized clinical trials	very severe[d]	not severe	not severe	severe[c]	none	34	28	-	MD 5.8% higher (from 1.02 higher to 10.62 higher)	⨁◯◯◯ Very low	IMPORTANT
Lung function: FEV_1 in % of predicted												
1	observational study	severe[e]	severe	severe	severe[c]	none	4	5	-	MD 5.6% higher (from 12.52 fewer to 23.71 higher)	⨁◯◯◯ Very low	IMPORTANT

MD: mean difference; RR: risk ratio

Explanations

a. Population selection
b. Different antimicrobials
c. Insufficient number of patients
d. Open study, unblinded outcome evaluators, no intention-to-treat analysis
e. Retrospective studies
f. No intention-to-treat analysis
g. Technically inadequate evaluation of outcome

Table S7A. GRADE analysis of dornase alfa compared with placebo in patients with cystic fibrosis ≥ 6 years of age regarding mortality, adverse events, and quality of life.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	randomized clinical trials	severe[a]	severe[b]	not severe	severe[c]	none	10/604 (1.7%)	7/484 (1.4%)	RR 1.14 (0.44 to 2.99)	2 higher per 1.000 (from 8 fewer to 29 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
3	randomized clinical trials	severe[a,d]	severe[b]	not severe	severe[c]	none	222/639 (34.7%)	174/519 (33.5%)	RR 1.04 (0.88 to 1.22)	13 higher per 1.000 (from 40 fewer to 74 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
1	observational study	very severe[e]	not severe[b]	severe	severe[f]	none	600/760 (78.9%)	0/0	not estimable		⨁◯◯◯ Very low	CRITICAL
Quality of life												
1	randomized clinical trials	severe[a]	not severe	not severe	severe[c,f]	none	9	8	-	MD 3.82 points fewer (from 17.25 fewer to 9.61 higher)	⨁⨁◯◯ Low	CRITICAL
Quality of life measured with CFQ-R (follow-up: 12 months)												
1	observational study	severe[e]	not severe	not severe	severe[c,f]	none	152	0	-	MD 7.38 points higher (from 4.24 higher to 10.52 higher)	⨁◯◯◯ Very low	CRITICAL

MD: mean difference; RR: risk ratio

Explanations

a. Sample size not calculated for outcome
b. Heterogeneity
c. Large confidence interval
d. No randomization description
e. Open study, patient selection, confounding variables, outcome measurements
f. Insufficient sample size

Table S7B. GRADE analysis of dornase alfa compared with placebo in patients with cystic fibrosis ≥ 6 years of age regarding FEV_1 in % of predicted, exacerbations, and BMI.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dornase alfa	Placebo	Relative (95% CI)	Absolute (95% CI)		
Lung function: FEV_1												
9	randomized clinical trials	severe[a]	severe[b]	not severe	severe[c]	highly suspected publication bias	1661	848	-	mean 5 percentage points higher (from 1.65 higher to 8.35 higher)	⨁◯◯◯ Very low	IMPORTANT
Lung function												
16	observational study	very severe[d]	severe[b]	not severe	severe[c]	strong association	5303	0	-	mean 4.89% higher (from 1.42 higher to 8.35 higher)	⨁◯◯◯ Very low	IMPORTANT
Exacerbation												
2	randomized clinical trials	not severe	not severe	not severe	not severe	none	222/1122 (19.8%)	290/1112 (26.1%)	RR 0.73 (0.54 to 0.91)	70 fewer per 1.000 (from 120 fewer to 23 fewer)	⨁⨁⨁⨁ Alta	IMPORTANT
Exacerbation												
2	observational study	severe[d]	severe[b]	not severe	severe[e]	none	434/1126 (38.5%)	0/0	Not estimable		⨁◯◯◯ Very low	IMPORTANT
BMI												
1	randomized clinical trials	severe[a]	not severe	not severe	severe[e]	none	239	235	-	mean 0.2 z-score higher (from 2.36 fewer to 1.96 higher)	⨁⨁◯◯ Low	IMPORTANT
BMI												
1	observational study	severe[d]	severe[f]	not severe	severe[e]	none	82	0	-	mean 0.1 z-score higher (from 0.54 fewer to 0.34 higher)	⨁◯◯◯ Very low	IMPORTANT

RR: risk ratio

Explanations

a. Sample size not calculated for outcome
b. Heterogeneity
c. Large confidence interval
d. Open study, patient selection, confounding variables, outcome measurements
e. Insufficient sample size
f. Only one study

Table S8A. GRADE analysis of antimicrobial eradication treatment compared with placebo in patients with cystic fibrosis and colonization by *Burkholderia cepacia* complex regarding colonization eradication and adverse events.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antimicrobial eradication treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
B. cepacia complex eradication												
2	observational study	severe[a]	not severe	severe[b]	severe[c]	none	6/18 (33.3%)	1/14 (7.1%)	not estimable		⨁◯◯◯ Very low	CRITICAL
Adverse events												
1	randomized clinical trials	severe[d]	not severe	severe[b]	severe[c]	none	10/48 (20.8%)	3/52 (5.8%)	RR 3.61 (1.06 to 12.34)	151 higher per 1.000 (from 3 higher to 654 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events												
1	observational study	severe[a]	not severe	severe[b]	severe[c]	none	1/12 (8.3%)	0/10 (0.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL

RR: risk ratio

Explanations

a. Population selection

b. Different spectrum antimicrobials

c. Insufficient number of patients

d. Randomization and allocation

Table S8B. GRADE analysis of antimicrobial eradication treatment compared with placebo in patients with cystic fibrosis and colonization by *Burkholderia cepacia* complex regarding exacerbations, BMI, quality of life, and FEV_1.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antimicrobial eradication treatment	Placebo	Relative (95% CI)	Absolute (95% CI)		
Exacerbation												
1	randomized clinical trials	severe[d]	not severe	severe[b]	severe[c]	none	17/48 (35.4%)	21/52 (40.4%)	RR 0.88 (0.53 to 1.45)	48 fewer per 1.000 (from 190 fewer to 182 higher)	⨁◯◯◯ Very low	IMPORTANT
BMI (follow-up: 12 months)												
1	randomized clinical trials	severe[d]	not severe	severe	severe	none	48	52	-	mean 0.14 kg/m² higher (from 0.29 fewer to 0.56 higher)	⨁◯◯◯ Very low	IMPORTANT
BMI (follow-up: 12 months)												
1	observational study	severe[b]	not severe	severe[b]	severe[c]	none	6	4	-	mean 1.6 kg/m² higher (from 0.5 higher to 2.7 higher)	⨁◯◯◯ Very low	IMPORTANT
Quality of life (follow-up: 12 months)												
1	randomized clinical trials	severe[d]	not severe	severe[b]	severe[c]	none	48	52	-	0.18 higher (from 4.43 fewer to 4.78 higher)	⨁◯◯◯ Very low	IMPORTANT
Lung function – FEV_1 (follow-up: 12 months)												
1	randomized clinical trials	severe[d]	not severe	severe[b]	severe[c]	none	48	52	-	0.91 higher (from 3.24 fewer to 5.06 higher)	⨁◯◯◯ Very low	IMPORTANT
Lung function - FEV_1 in % of predicted (follow-up: 12 months)												
2	observational study	severe[a]	not severe	severe[b]	severe[c]	none	18	4	-	MD 0.82% higher (from 9.49 fewer to 11.12 higher)	⨁◯◯◯ Very low	IMPORTANT

MD: mean difference; RR: risk ratio

Explanations

a. Population selection
b. Different spectrum antimicrobials
c. Insufficient number of patients
d. Randomization and allocation

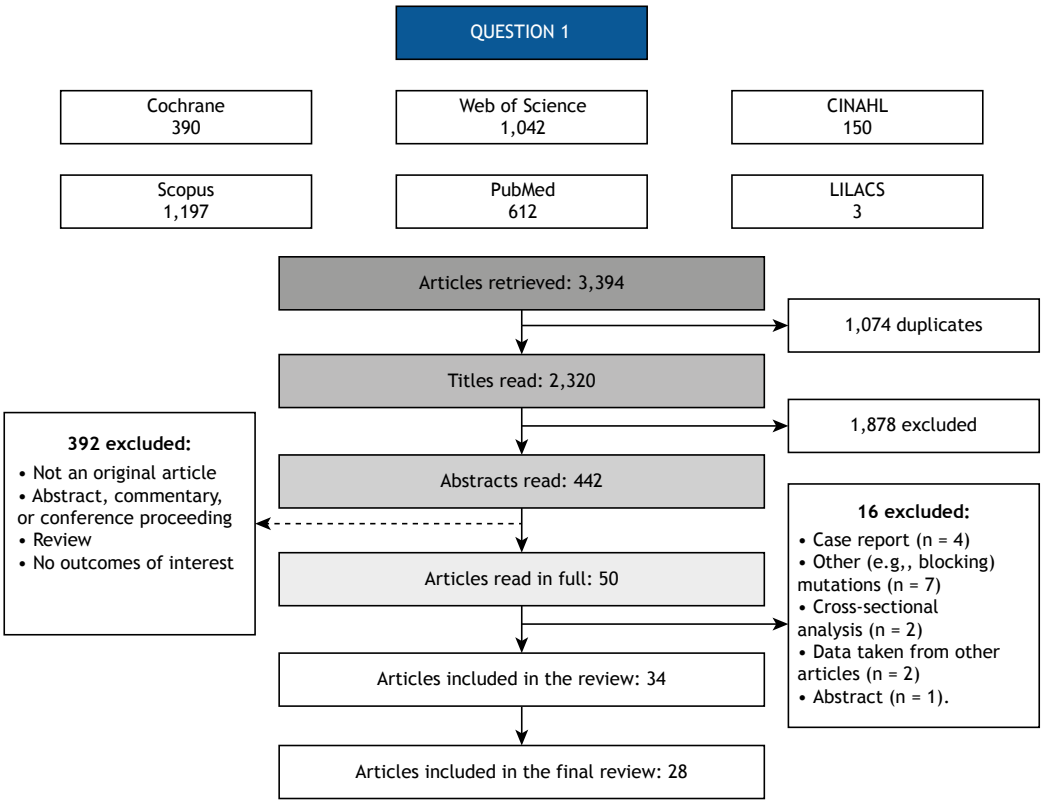

Figura S1. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 1.

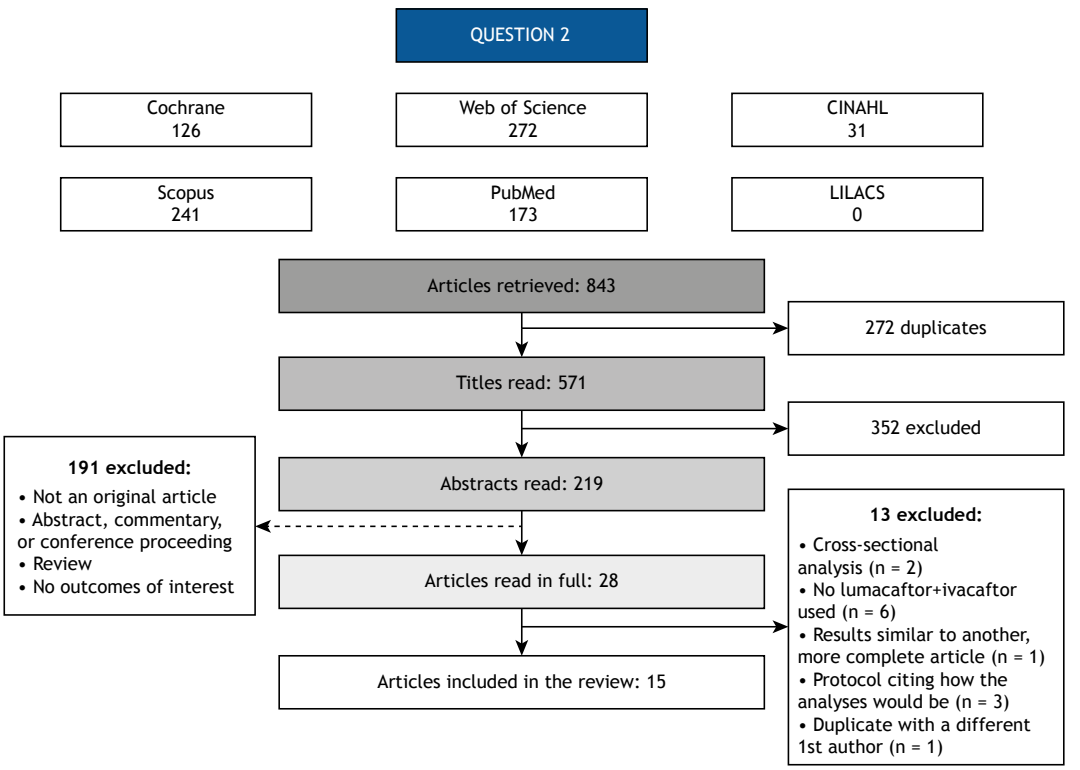

Figura S2. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 2.

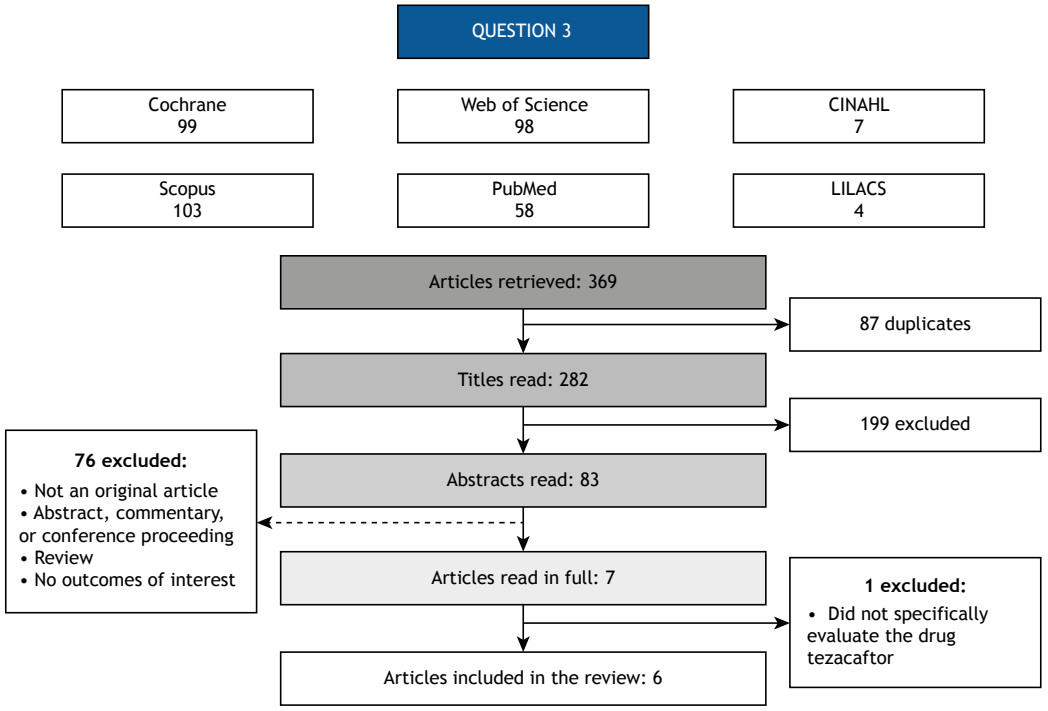

Figura S3. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 3.

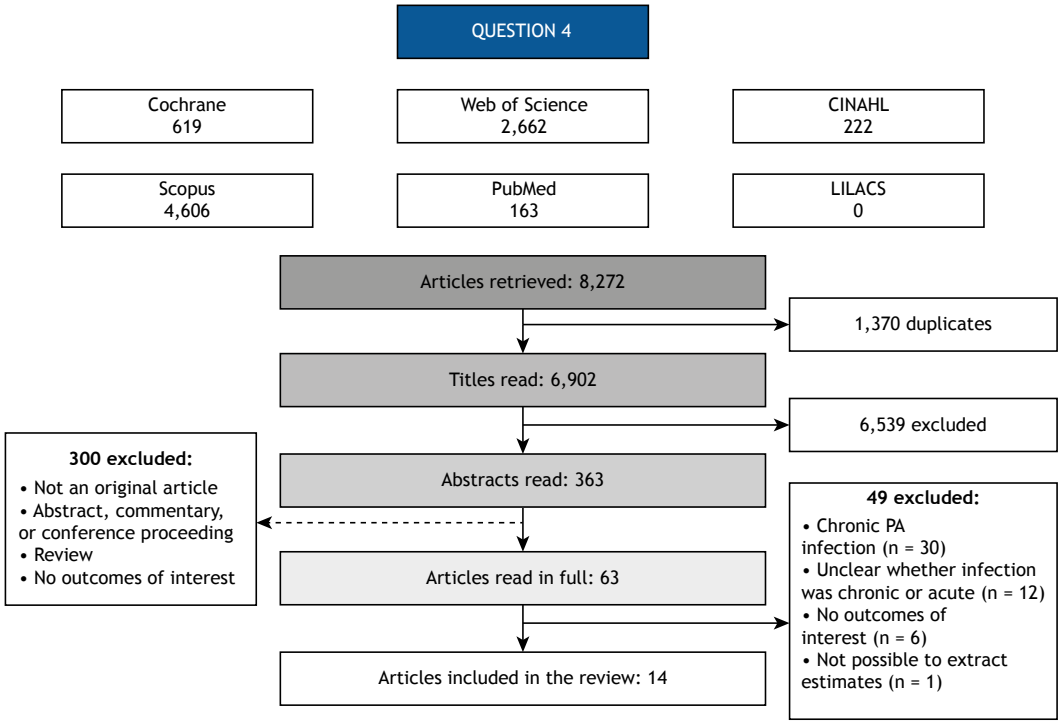

Figura S4. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 4. PA: *Pseudomonas aeruginosa*.

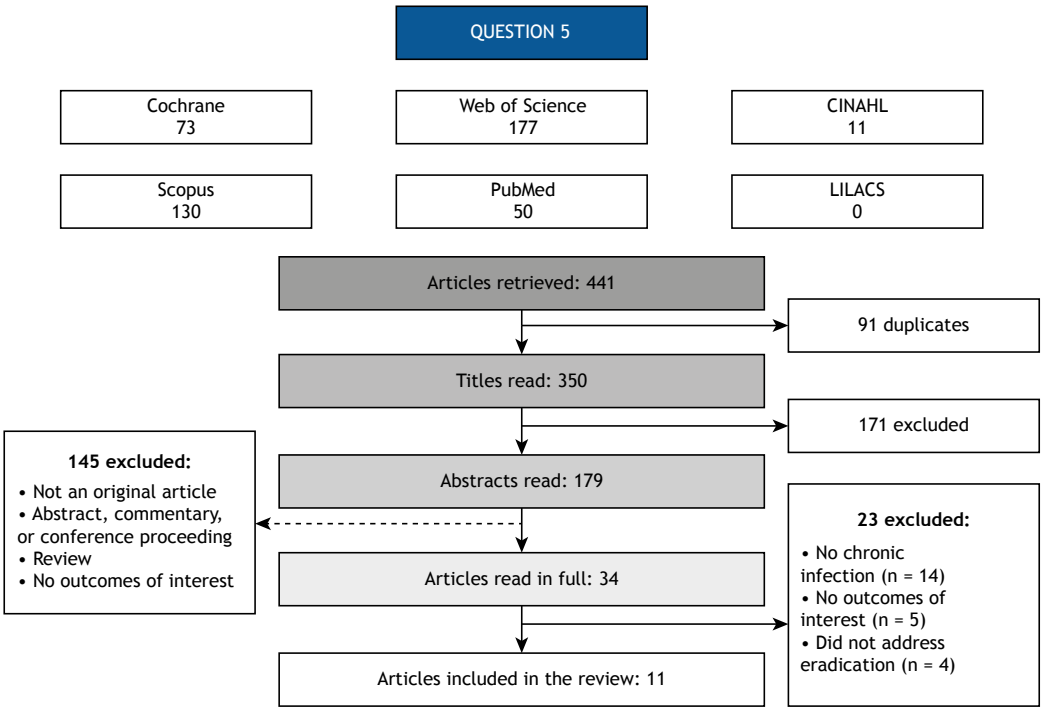

Figura S5. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 5.

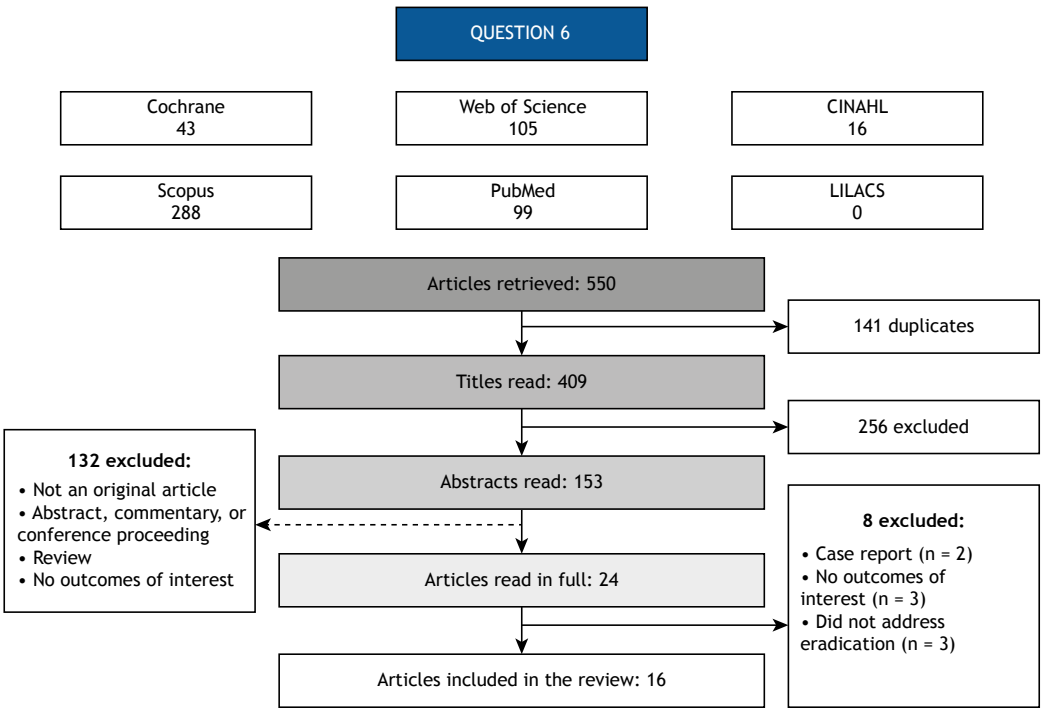

Figura S6. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 6.

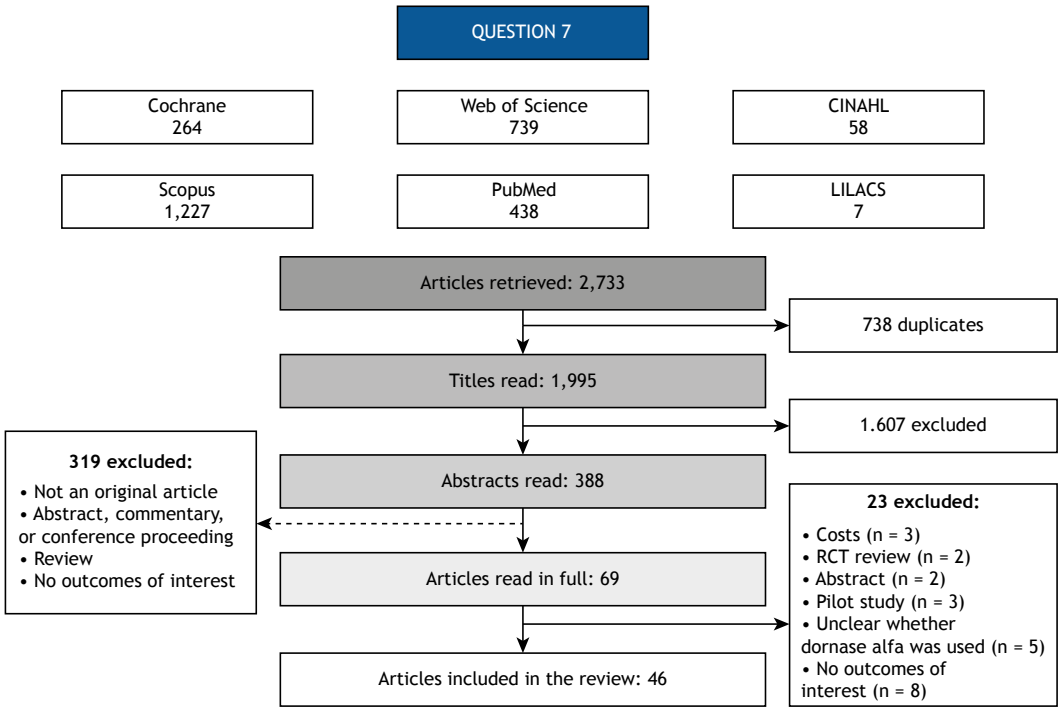

Figura S7. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 7. ECR: estudo clínico randomizado.

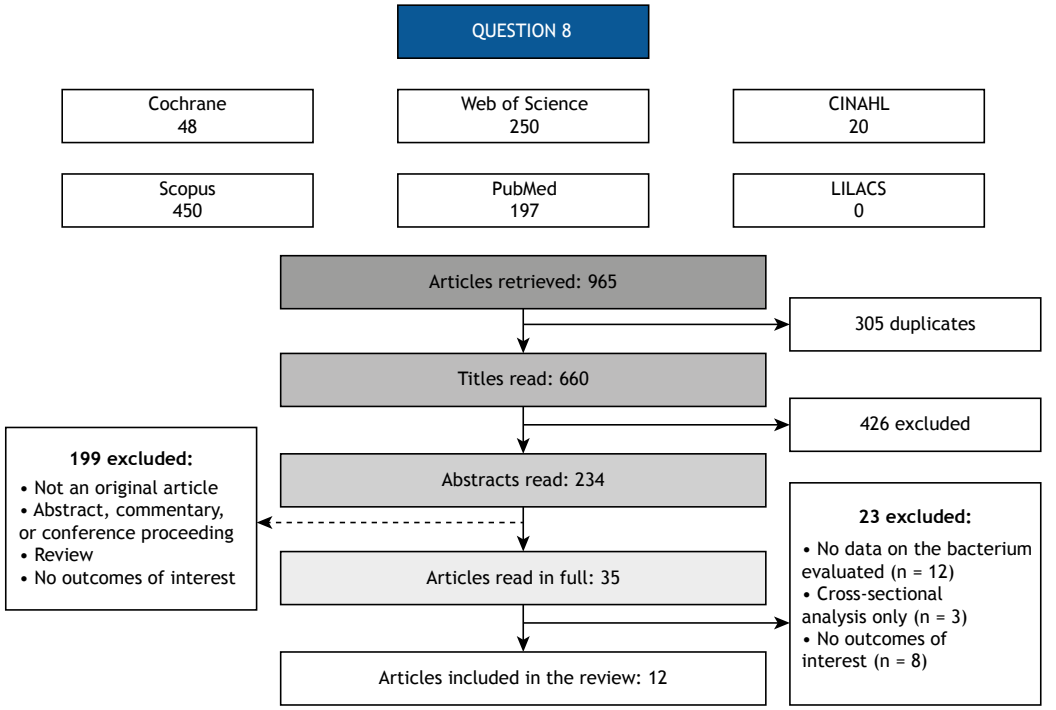

Figura S8. Fluxograma ilustrando todas as etapas na seleção de estudos para responder a pergunta 8.

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates.

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
1) Should we recommend treatment with ivacaftor in CF patients with class III (gating) or class IV (conduction) mutations in the *CFTR* gene?	1. Cochrane (“Fibrosis, Cystic” OR “Cystic Fibrosis” OR “Mucoviscidosis” OR “CFTR”) AND (“Ivacaftor” OR “Kalydeco” OR “VX-770” OR “CFTR potentiator”) in All Text TOTAL: 390 2. CINAHL (“Fibrosis, Cystic” OR “Cystic Fibrosis” OR “Mucoviscidosis” OR “CFTR”) AND (“Ivacaftor” OR “Kalydeco” OR “VX-770” OR “CFTR potentiator”) TOTAL: 150 3. Web of Science (“Fibrosis, Cystic” OR “Cystic Fibrosis” OR “Mucoviscidosis” OR “CFTR”) AND (“Ivacaftor” OR “Kalydeco” OR “VX-770” OR “CFTR potentiator”) TOTAL: 1.042 4. PubMed (“Fibrosis, Cystic” [All Fields] OR “Cystic Fibrosis” [All Fields] OR (“cystic fibrosis” [MeSH Terms] OR (“cystic” [All Fields] AND “fibrosis” [All Fields] “Fibrosis, Cystic” [All Fields]) OR “cystic fibrosis” [All Fields] OR “mucoviscidosis” [All Fields] OR “CFTR” [All Fields]) AND (“Ivacaftor” [All Fields] OR “Kalydeco” [All Fields] OR “VX-770” [All Fields] OR “CFTR potentiator” [All Fields]) TOTAL: 612 5. Scopus TITLE-ABS-KEY (“Fibrosis, Cystic” OR “Cystic Fibrosis” OR mucoviscidosis OR “CFTR”) AND (ivacaftor OR ntibiot OR vx-770 OR “CFTR potentiator”) TOTAL: 1197 6. Lilacs tw: (“fibrose, cística” OR “fibrose cística” OR mucoviscidose OR CFTR) AND (“Ivacaftor” OR “Kalydeco” OR “VX-770” OR “CFTR potentiator”) AND (db: “LILACS”) TOTAL: 3	3,394	2,320

Continue...▶

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates. (Continued...)

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
2) Should we recommend treatment with lumacaftor+ivacaftor in CF patients homozygous for the *F508del* mutation?	1. Cochrane ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("Lumacaftor" OR "Orkambi" OR "VX-809" OR "CFTR corrector" OR "lumacafor/ivacaftor") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") in All Text TOTAL: 126 2. CINAHL ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR CFTR) AND ("Lumacaftor" OR "Orkambi" OR "VX-809" OR "CFTR corrector" OR "lumacafor/ivacaftor") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") TOTAL: 31 3. Web of Science ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("Lumacaftor" OR "Orkambi" OR "VX-809" OR "CFTR corrector" OR "lumacafor/ivacaftor") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") TOTAL: 272 4. PubMed ("Fibrosis, Cystic" [All Fields] OR "Cystic Fibrosis" [All Fields] OR "CFTR" [All Fields] OR "cystic fibrosis" [MeSH Terms] OR ("cystic" [All Fields] AND "fibrosis" [All Fields]) OR "cystic fibrosis" [All Fields] OR "mucoviscidosis" [All Fields]) AND ("Lumacaftor" [All Fields] OR "Orkambi" [All Fields] OR "VX-809" [All Fields] OR "CFTR corrector" [All Fields] OR "lumacafor/ivacaftor" [All Fields]) AND ("F508del-CFTR" [All Fields] OR "Phe508del" OR "F508del" [All Fields]) TOTAL: 173 5. Scopus TITLE-ABS-KEY ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR mucoviscidosis OR CFTR) AND ("Lumacaftor" OR "Orkambi" OR "VX-809" OR "CFTR corrector" OR "lumacafor/ivacaftor") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") TOTAL: 241 6. Lilacs ("Fibrose Cística" OR Mucoviscidose OR CFTR) AND ("Lumacaftor" OR "Orkambi" OR "VX-809" OR "CFTR corrector" OR "lumacafor/ivacaftor") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") TOTAL: 0	843	571

Continue...▶

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates. (Continued...)

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
3) Should we recommend treatment with tezacaftor+ivacaftor in CF patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations?	1. Cochrane ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR Mucoviscidosis OR CFTR) AND ("Tezacaftor" OR "Symdeko" OR " VX-661" OR "CFTR corrector") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") in All Text TOTAL: 99 2. CINAHL ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR CFTR) AND ("Tezacaftor" OR "Symdeko" OR " VX-661" "CFTR corrector") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") TOTAL: 7 3. Web of Science ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR CFTR) AND ("Tezacaftor" OR "Symdeko" OR " VX-661" OR "CFTR corrector") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") TOTAL: 98 4. PubMed ("Fibrosis, Cystic" [All Fields] OR "Cystic Fibrosis" [All Fields] OR "CFTR" [All Fields] OR ("cystic fibrosis" [MeSH Terms] OR ("cystic" [All Fields] AND "fibrosis" [All Fields]) OR "cystic fibrosis" [All Fields] OR "mucoviscidosis" [All Fields]) AND ("Tezacaftor" [All Fields] OR "Symdeko" [All Fields] OR "VX-661" [All Fields] OR "CFTR corrector" [All Fields]) AND ("F508del-CFTR" [All Fields] OR "Phe508del" OR "F508del" [All Fields]) TOTAL: 58 5. Scopus TITLE-ABS-KEY ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR Mucoviscidosis OR "CFTR") AND ("Tezacaftor" OR "Symdeko" OR " VX-661" OR "CFTR corrector") AND ("F508del-CFTR" OR "Phe508del" OR "F508del") TOTAL: 103 6. Lilacs tw: ("fibrosis, cystic" OR "cystic fibrosis" OR mucoviscidosis OR "CFTR") AND ("Tezacaftor" OR "Symdeko" OR " VX-661" OR "CFTR corrector" OR "F508del-CFTR" OR "Phe508del" OR "F508del") AND (db: "LILACS") TOTAL: 4	369	282

Continue...▶

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates. (Continued...)

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
4) Should we recommend eradicating *P. aeruginosa* infection in individuals with CF?	1. Cochrane ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR CFTR) AND ("antimicrobials" OR "antibiotic" OR "colistin" OR "colomycin" OR "colistimethate" OR "Tobramycin" OR "aztreonam") AND ("infection" OR "eradication" OR "treatment" OR "colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") in All Text TOTAL: 619 2. CINAHL ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobials" OR "antibiotic" OR "colistin" OR "colomycin" OR "colistimethate" OR "Tobramycin" OR "aztreonam") AND ("infection" OR "eradication" OR "treatment" OR "colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") TOTAL: 222 3. Web of Science ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobials" OR "antibiotic" OR "colistin" OR "colomycin" OR "colistimethate" OR "Tobramycin" OR "aztreonam") AND ("infection" OR "eradication" OR "treatment" OR "colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") TOTAL: 2.662 4. PubMed ("Fibrosis, Cystic" [All Fields] OR "Cystic Fibrosis" [All Fields] OR "CFTR" [All fields] ("cystic fibrosis" [MeSH Terms] OR ("cystic" [All Fields] AND "fibrosis" [All Fields]) OR "cystic fibrosis" [All Fields] OR "mucoviscidosis" [All Fields]) AND ("antimicrobials" [All Fields] OR "antibiotic" [All Fields] OR "colistin" [All Fields] OR "colomycin" [All Fields] OR "colistimethate" [All Fields] OR "Tobramycin" [All Fields] OR "aztreonam" [All Fields]) AND ("infection" [All Fields] OR "eradication" [All Fields] OR "treatment" [All fields] "colonization" [All Fields]) AND ("Pseudomonas" [All fields] OR "Pseudomonadaceae" [All Fields]) TOTAL: 163 5. Scopus TITLE-ABS-KEY ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR mucoviscidosis OR CFTR) AND ("antimicrobials" OR "antibiotic" OR "colistin" OR "colomycin" OR "colistimethate" OR "Tobramycin" OR "aztreonam") AND ("infection" OR "treatment" OR "eradication" OR "colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") TOTAL: 4.606 6. Lilacs tw: ("fibrosis, cystic" OR "cystic fibrosis" OR mucoviscidosis OR CFTR) AND ("antimicrobials" OR "antibiotic" OR "colistin" OR "colomycin" OR "colistimethate" OR "Tobramycin" OR "aztreonam") AND ("infection" OR "eradication" OR "treatment" OR "colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") AND (db: "LILACS") TOTAL: 0	8,272	6,902

Continue...▶

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates. (Continued...)

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
5) Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection?	1. Cochrane ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("inhaled antibiotic" OR "inhaled antimicrobials" OR "Aerosol antibiotics" OR "Inhaled colistin" OR "Inhaled colomycin" OR "Inhaled colistimethate" OR "Inhaled Tobramycin" OR "Inhaled aztreonam" OR "Inhaled levofloxacin" OR "Inhaled gentamycin" OR "Inhaled amikacin") AND ("chronic infection" OR "colonization" OR "chronic colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") in All Text TOTAL: 73 2. CINAHL ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("inhaled antibiotic" OR "inhaled antimicrobials" OR "Aerosol antibiotics" OR "Inhaled colistin" OR "Inhaled colomycin" OR "Inhaled colistimethate" OR "Inhaled Tobramycin" OR "Inhaled aztreonam" OR "Inhaled levofloxacin" OR "Inhaled gentamycin" OR "Inhaled amikacin") AND ("chronic infection" OR "colonization" OR "chronic colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") TOTAL: 11 3. Web of Science ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("inhaled antibiotic" OR "inhaled antimicrobials"OR "Aerosol antibiotics" OR "Inhaled colistin" OR "Inhaled colomycin" OR "Inhaled colistimethate" OR "Inhaled Tobramycin" OR "Inhaled aztreonam" OR "Inhaled levofloxacin" OR "Inhaled gentamycin" OR "Inhaled amikacin") AND ("chronic infection" OR "colonization" OR "chronic colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") TOTAL: 177 4. PubMed ("Fibrosis, Cystic" [All Fields] OR "Cystic Fibrosis" [All Fields] OR "CFTR" OR ("cystic fibrosis" [MeSH Terms] OR ("cystic" [All Fields] AND "fibrosis" [All Fields]) OR "cystic fibrosis" [All Fields] OR "mucoviscidosis" [All Fields]) AND ("inhaled antibiotic" [All Fields] OR "inhaled antimicrobials" [All Fields] OR "Aerosol antibiotics" [All Fields] OR "Inhaled colistin" [All Fields] OR "Inhaled colomycin" [All Fields] OR "Inhaled colistimethate" [All Fields] OR "Inhaled Tobramycin" [All Fields] OR "Inhaled aztreonam" [All Fields] OR "Inhaled levofloxacin" [All Fields] OR "Inhaled gentamycin" [All Fields] OR "Inhaled amikacin" [All Fields]) AND ("chronic infection" [All Fields] OR "colonization" [All Fields] OR "chronic colonization" [All Fields]) AND ("Pseudomonas" [All Fields] OR "Pseudomonadaceae" [All Fields]) TOTAL: 50 5. Scopus TITLE-ABS-KEY ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR mucoviscidosis OR "CFTR") AND ("inhaled antibiotic" OR "inhaled antimicrobials" OR "Aerosol antibiotics" OR "Inhaled colistin" OR "Inhaled colomycin" OR "Inhaled colistimethate" OR "Inhaled Tobramycin" OR "Inhaled aztreonam" OR "Inhaled levofloxacin" OR "Inhaled gentamycin" OR "Inhaled amikacin") AND ("chronic infection" OR "colonization" OR "chronic colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") TOTAL: 130 6. Lilacs tw: ("fibrosis, cystic" OR "cystic fibrosis" OR mucoviscidosis OR "CFTR") AND ("inhaled antibiotic" OR "inhaled antimicrobials" OR "aerosol antibiotics" OR "Inhaled colistin" OR "Inhaled colomycin" OR "Inhaled colistimethate" OR "Inhaled Tobramycin" OR "Inhaled aztreonam" OR "Inhaled levofloxacin" OR "Inhaled gentamycin" OR "Inhaled amikacin") AND ("infection" OR "colonization" OR "chronic colonization") AND ("Pseudomonas" OR "Pseudomonadaceae") AND (db: "LILACS") TOTAL: 0	441	350

Continue...▶

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates. (Continued...)

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
6) Should we recommend antimicrobial eradication treatment in CF patients with MRSA colonization of the airways?	1. Cochrane ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Rifampicin" OR "Sulfamethoxazole + Trimethoprim" OR "Co-trimaxazole" OR "Linezolid" OR "Vancomycin" OR "Clindamycin") AND ("Methicillin Resistant Staphylococcus aureus" OR "Staphylococcus aureus methicillin resistant" OR "S aureus methicillin resistant" OR "MRSA") AND ("Eradication" OR "Treatment") in All Text TOTAL: 43 2. CINAHL ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Rifampicin" OR "Sulfamethoxazole + Trimethoprim" OR "Co-trimaxazole" OR "Linezolid" OR "Vancomycin" OR "Clindamycin") AND ("Methicillin Resistant Staphylococcus aureus" OR "Staphylococcus aureus methicillin resistant" OR "S aureus methicillin resistant" OR "MRSA") AND ("Eradication" OR "Treatment") TOTAL: 16 3. Web of Science ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Rifampicin" OR "Sulfamethoxazole + Trimethoprim" OR "Co-trimaxazole" OR "Linezolid" OR "Vancomycin" OR "Clindamycin") AND ("Methicillin Resistant Staphylococcus aureus" OR "Staphylococcus aureus methicillin resistant" OR "S aureus methicillin resistant" OR "MRSA") AND ("Eradication" OR "Treatment") TOTAL: 105 4. PubMed ("Fibrosis, Cystic" [All Fields] OR "Cystic Fibrosis" [All Fields] OR ("cystic fibrosis" [MeSH Terms] OR ("cystic" [All Fields] AND "fibrosis" [All Fields]) OR "cystic fibrosis" [All Fields] OR "mucoviscidosis" [All Fields] OR "CFTR" [All Fields]) AND ("antimicrobial" [All Fields] OR "antibiotic" [All Fields] OR "Rifampicin" [All Fields] OR "Sulfamethoxazole + Trimethoprim" [All Fields] OR "Co-trimaxazole" [All Fields] OR "Linezolid" [All Fields] OR "Vancomycin" [All Fields] OR "Clindamycin" [All Fields]) AND ("Methicillin Resistant Staphylococcus aureus" [All Fields] OR "Staphylococcus aureus methicillin resistant" [All Fields] OR "S aureus methicillin resistant" [All Fields] OR "MRSA" [All Fields]) AND ("Eradication" [All Fields] OR "Treatment" [All Fields]) TOTAL: 99 5. Scopus TITLE-ABS-KEY ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Rifampicin" OR "Sulfamethoxazole + Trimethoprim" OR "Co-trimaxazole" OR "Linezolid" OR "Vancomycin" OR "Clindamycin") AND ("Methicillin Resistant Staphylococcus aureus" OR "Staphylococcus aureus methicillin resistant" OR "S aureus methicillin resistant" OR "MRSA") AND ("Eradication" OR "Treatment") TOTAL: 288 6. Lilacs ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR" OR "Fibrose cística" OR "Mucoviscidose") AND ("antimicrobial" OR "antibiotic" OR " ntibiotic" OR "Rifampicin" OR "Sulfamethoxazole + Trimethoprim" OR "Co-trimaxazole" OR "Linezolid" OR "Vancomycin" OR "Clindamycin") AND ("Methicillin Resistant Staphylococcus aureus" OR "Staphylococcus aureus methicillin resistant" OR "S aureus methicillin resistant" OR "MRSA") AND ("erradicação" OR "erradicar" OR "eradication" OR "treatment" OR "tratamento") TOTAL: 0	550	409

Continue...▶

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates. (Continued...)

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
7) Should we recommend nebulized dornase alfa for CF patients ≥ 6 years of age?	1. Cochrane ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("dornase alfa" OR "pulmozyme" OR "Dnase") in All Text TOTAL: 264 2. CINAHL ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("dornase alfa" OR "pulmozyme" OR "Dnase") TOTAL: 58 3. Web of Science ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("dornase alfa" OR "pulmozyme" OR "Dnase") TOTAL: 739 4. PubMed ("Fibrosis, Cystic" [All Fields] OR "Cystic Fibrosis" [All Fields] OR ("cystic fibrosis" [MeSH Terms] OR ("cystic" [All Fields] AND "fibrosis" [All Fields]) OR "cystic fibrosis" [All Fields] OR "mucoviscidosis" [All Fields] OR "CFTR" [All Fields]) AND ("dornase alfa" [All Fields] OR "pulmozyme" [All Fields] OR "Dnase" [All Fields]) TOTAL: 438 5. Scopus TITLE-ABS-KEY ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "mucoviscidosis" OR "CFTR") AND ("dornase alfa" OR "pulmozyme" OR "Dnase") TOTAL: 1.227 6. Lilacs tw: ("fibrosis, cystic" OR "cystic fibrosis" OR "mucoviscidosis" OR "CFTR" OR "Fibrose cística" OR "mucoviscidose") AND ("dornase alfa" OR "pulmozyme" OR "Dnase") AND (db: "LILACS") TOTAL: 7	2,733	1,995

Continue...▶

Chart S1. Final syntax, search strategies, total number of articles retrieved in each database, and total number of articles after removal of duplicates. (Continued...)

Question	Syntax (after suggestions)	Total retrieved	Total without duplicates
8) Should we recommend antimicrobial eradication treatment in CF patients with airway colonization by *Burkholderia cepacia* complex strains?	1. Cochrane ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Tobramycin" OR "Minocycline" OR "Doxycycline" OR "Ceftazidime" OR "Meropenem" OR "Sulfamethoxazole + Trimethoprim" OR "co-Trimoxazole") AND ("Eradication" OR "Treatment") AND ("burkholderia" OR "Burkholderiaceae") in All Text TOTAL: 48 2. CINAHL ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Tobramycin" OR "Minocycline" OR "Doxycycline" OR "Ceftazidime" OR "Meropenem" OR "Sulfamethoxazole + Trimethoprim" OR "co-Trimoxazole") AND ("Eradication" OR "Treatment") AND ("burkholderia" OR "Burkholderiaceae") TOTAL: 20 3. Web of Science ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Tobramycin" OR "Minocycline" OR "Doxycycline" OR "Ceftazidime" OR "Meropenem" OR "Sulfamethoxazole + Trimethoprim" OR "co-Trimoxazole") AND ("Eradication" OR "Treatment") AND ("burkholderia" OR "Burkholderiaceae") TOTAL: 250 4. PubMed ("Fibrosis, Cystic" [All Fields] OR "Cystic Fibrosis" [All Fields] OR ("cystic fibrosis" [MeSH Terms] OR ("cystic" [All Fields] AND "fibrosis" [All Fields]) OR "cystic fibrosis" [All Fields] OR "mucoviscidosis" [All Fields] OR "CFTR" [All Fields]) AND ("antimicrobial" [All Fields] OR "antibiotic" [All Fields] OR "Tobramycin" [All Fields] OR "Minocycline" [All Fields] OR "Doxycycline" [All Fields] OR "Ceftazidime" [All Fields] OR "Meropenem" [All Fields] OR "Sulfamethoxazole + Trimethoprim" [All Fields] OR "co-Trimoxazole" [All Fields]) AND ("Eradication" [All Fields] OR "Treatment" [All Fields]) AND ("burkholderia" [All Fields] OR "Burkholderiaceae" [All Fields]) TOTAL: 197 5. Scopus TITLE-ABS-KEY ("Fibrosis, cystic" OR "Cystic Fibrosis" OR "mucoviscidosis" OR "CFTR") AND ("antimicrobial" OR "antibiotic" OR "Tobramycin" OR "Minocycline" OR "Doxycycline" OR "Ceftazidime" OR "Meropenem" OR "Sulfamethoxazole + Trimethoprim" OR "co-Trimoxazole") AND ("Eradication" OR "Treatment") AND ("burkholderia" OR "Burkholderiaceae") TOTAL: 450 6. LILACS ("Fibrosis, Cystic" OR "Cystic Fibrosis" OR "Mucoviscidosis" OR "mucoviscidose" OR "CFTR" OR "Fibrose cística) AND ("antimicrobial" OR "antibiotic" OR "antibiótico" OR "antimicrobiano" OR "Tobramycin" OR "Minocycline" OR "Doxycycline" OR "Ceftazidime" OR "Meropenem" OR "Sulfamethoxazole + Trimethoprim" OR "co-Trimoxazole") AND ("Eradication" OR "erradicação" OR "erradicar" OR "Treatment" OR "Tratamento") AND ("burkholderia" OR "Burkholderiaceae") TOTAL: 0	965	660

CF: cystic fibrosis; CINAHL: Cumulative Index to Nursing and Allied Health Literature; e MRSA: *Staphylococcus aureus* methicillin resistant (*S. aureus resistente a meticilina*).

Chart S2. Study design and outcomes evaluated in each study selected for question 1.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events
Abou Alaiwa [28]	2018	Observational	✓	✗	✗	✗	✗	✗	✗
Accurso [29]	2010	RCT	✓	✗	✗	✓	✗	✗	✓
Barry [30]	2014	Observational	✓	✓	✓	✗	✓	✓	✓
Bessonova [31]	2018	Observational	✓	✗	✓	✗	✓	✓	✗
Borowitz [32]	2016	RCT	✗	✓	✗	✗	✗	✗	✗
Davies [33]	2013	RCT	✓	✓	✗	✓	✗	✓	✓
De Boeck [34]	2014	RCT	✓	✓	✓	✓	✗	✗	✓
Donaldson [35]	2018	Observational	✓	✓	✗	✓	✗	✗	✗
Edgeworth [36]	2017	RCT	✓	✓	✗	✓	✗	✗	✓
Gomez-Pastrana [37]	2019	Observational	✓	✓	✗	✗	✗	✗	✓
Guerra [38]	2017	Observational	✓	✓	✗	✗	✗	✗	✗
Guimbellot [39]	2019	Observational	✓	✓	✓	✓	✗	✗	✗
Harris [40]	2019	Observational	✓	✗	✗	✗	✗	✗	✗
Hebestreit [41]	2013	Observational	✓	✗	✗	✗	✗	✓	✓
Hubert [42]	2018	Observational	✓	✓	✓	✗	✗	✓	✓
McKone [43]	2014	Observational	✓	✓	✓	✓	✗	✓	✓
Moss [44]	2015	RCT	✓	✓	✓	✓	✗	✗	✓
Quittner [45]	2015	RCT	✗	✗	✗	✓	✗	✗	✗
Ramsey [11]	2011	RCT	✓	✗	✓	✓	✗	✓	✓
Ronan [46]	2018	Observational	✓	✓	✗	✓	✗	✗	✗
Rosenfeld [47]	2018	Observational	✗	✓	✗	✗	✗	✓	✓
Rowe [48]	2018	Observational	✓	✓	✓	✓	✗	✗	✗
Salvatore [49]	2019	Observational	✓	✓	✓	✗	✗	✓	✓
Sheikh [50]	2015a	Observational	✓	✓	✓	✗	✗	✗	✗
Shiekh [51]	2015b	Observational	✗	✗	✓	✗	✗	✗	✗
Stallings [52]	2018	Observational	✓	✓	✗	✗	✗	✗	✗
Taylor-Cousar [53]	2016	Observational	✓	✓	✓	✗	✗	✓	✓
van de Peppel [54]	2018	Observational	✓	✓	✗	✗	✗	✗	✗

RCT: randomized clinical trial. Included (✓); Not included (✗)

Chart S3. Study design and outcomes evaluated in each study selected for question 2.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events
Burgel[58]	2019	Cohort	✓	✓	✓	✗	✗	✗	✓
Diab-Caceres[59]	2018	Cohort	✓	✓	✓	✗	✗	✗	✓
Graeber[60]	2018	Cohort	✓	✓	✗	✗	✗	✗	✗
Hubert[61]	2017	Cohort	✓	✓	✗	✗	✓	✓	✓
Jennings[62]	2017	Cohort	✓	✗	✗	✗	✗	✗	✓
Konstan[56]	2017	Cohort	✓	✓	✓	✓	✗	✗	✗
Masson[63]	2019	Cohort	✓	✓	✓	✗	✗	✗	✗
McNamara[64]	2019	Cohort	✗	✓	✗	✗	✗	✗	✗
Milla[65]	2017	Cohort	✓	✓	✗	✓	✗	✗	✓
Murer[66]	2018	Cohort	✓	✓	✓	✓	✗	✗	✗
Ratjen[57]	2017	RCT	✓	✓	✗	✓	✗	✗	✓
Taylor-Cousar[67]	2018	Cohort	✓	✓	✓	✓	✗	✗	✓
Tessell[68]	2019	Cohort	✗	✗	✓	✗	✗	✗	✗
Wainwright[12]	2015	RCT	✓	✓	✓	✓	✗	✗	✓
Wark[69]	2019	Cohort	✓	✗	✗	✗	✗	✗	✓

RCT: randomized clinical trial. Included (✓); Not included (✗)

Chart S4. Study design and outcomes evaluated in each study selected for question 3.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events
Davies[70]	2021	RCT	✓	✓	✗	✓	✗	✓	✓
Donaldson[71]	2018	RCT	✓	✗	✗	✗	✗	✓	✓
Rowe[14]	2017	RCT	✓	✗	✓	✓	✗	✓	✗
Taylor-Cousar[13]	2017	RCT	✓	✓	✓	✓	✗	✓	✗
Walker[72]	2019	Observational	✓	✓	✗	✓	✗	✗	✗

RCT: randomized clinical trial. Included (✓); Not included (✗)

Chart S5. Study design and outcomes evaluated in each study selected for question 4.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events	Eradication
Blanchard[75]	2017	Observational	✗	✗	✗	✗	✗	✗	✗	✓
Claude[76]	2019	Observational	✓	✓	✗	✗	✗	✗	✗	✗
Cohen-Cymberknoh[77]	2016	Observational	✓	✓	✗	✗	✗	✗	✗	✗
Emiralioglu[78]	2016	Observational	✓	✗	✗	✗	✗	✗	✗	✗
Frederiksen[79]	1997	Observational	✓	✗	✗	✗	✗	✗	✗	✗
Giugno[80]	2010	Observational	✓	✗	✗	✗	✗	✗	✗	✗
Hewer[81]	2020	RCT	✓	✓	✗	✗	✗	✗	✗	✓
Kenny[82]	2014	Observational	✓	✗	✗	✗	✗	✗	✗	✗
Mayer-Hamblett[83]	2015	Observational	✗	✗	✓	✗	✗	✗	✗	✓
Proesmans[84]	2013	RCT	✓	✗	✗	✗	✗	✗	✗	✗
Ratjen[85]	2019	RCT	✗	✗	✗	✗	✗	✗	✓	✗
Ratjen[86]	2010	Observational	✗	✗	✗	✗	✗	✓	✗	✓
Taccetti[87]	2005	Observational	✓	✗	✗	✗	✗	✗	✗	✗
Taccetti[88]	2012	RCT	✗	✗	✓	✗	✗	✗	✗	✓
Treggiari[89]	2011	RCT	✓	✗	✓	✗	✗	✗	✗	✗
Valerius[90]	1991	RCT	✗	✗	✗	✗	✗	✗	✗	✓
Wiesemann[91]	1998	RCT	✗	✗	✗	✗	✗	✗	✗	✓

RCT: randomized clinical trial. Included (✓); Not included (✗)

Chart S6. Study design and outcomes evaluated in each study selected for question 5.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events
Assael[95]	2013	RCT	✓	✗	✗	✗	✗	✗	✓
Chuchalin[96]	2007	RCT	✓	✗	✓	✗	✗	✓	✓
Flume[94]	2016	RCT	✓	✗	✓	✗	✗	✓	✓
Geller[97]	2011	RCT	✓	✗	✓	✓	✗	✗	✓
Hodson[98]	1981	RCT	✓	✗	✓	✗	✗	✗	✗
Hodson[99]	2002	RCT	✓	✗	✗	✗	✗	✗	✓
Jensen[100]	1987	RCT	✓	✗	✓	✗	✗	✗	✗
Konstan[101]	2011a	Observational	✓	✗	✗	✗	✗	✗	✓
Konstan[102]	2011b	Observational	✓	✗	✗	✗	✗	✗	✓
Kun[103]	1984	Observational	✓	✗	✗	✗	✗	✗	✗
Lenoir[104]	2007	RCT	✓	✗	✓	✗	✗	✓	✓
MacLusky[105]	1989	RCT	✓	✗	✗	✗	✗	✗	✓
McCoy[106]	2008	RCT	✓	✗	✓	✓	✗	✓	✓
Moss[107]	2001	RCT	✓	✗	✗	✗	✗	✗	✗
Murphy[108]	2004	RCT	✓	✗	✓	✗	✗	✗	✗
Nasr[109]	2010	Observational	✓	✗	✗	✗	✗	✗	✗
Nikolaizik[110]	2008	RCT	✓	✗	✗	✗	✗	✗	✗
Quintana-Gallego[111]	2014	RCT	✓	✓	✓	✗	✗	✗	✓
Ramsey[112]	1999	RCT	✓	✗	✓	✗	✗	✓	✓
Retsch-Bogart[113]	2009	RCT	✓	✗	✗	✓	✗	✓	✓
Schuster[114]	2013	RCT	✓	✗	✗	✗	✗	✗	✓
Stead[115]	1987	RCT	✓	✗	✗	✗	✗	✗	✗
Stuart Elborn[116]	2015	RCT	✓	✗	✗	✗	✗	✗	✓
Toukan[117]	2018	Observational	✓	✗	✗	✗	✗	✗	✗
Westerman[118]	2004	RCT	✓	✗	✗	✗	✗	✗	✗

RCT: randomized clinical trial. Included (✓); Not included (✗)

Chart S7. Study design and outcomes evaluated in each study selected for question 6.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events	Eradication
Dolce[123]	2019	RCT	✓	✓	✓	✗	✗	✗	✗	✓
Garske[124]	2014	Observational	✓	✓	✓	✗	✗	✗	✗	✓
Hall[120]	2015	Observational	✓	✓	✗	✗	✗	✗	✗	✓
Kappler[125]	2016	Observational	✓	✓	✗	✗	✗	✗	✓	✓
Muhlebach[126]	2017	RCT	✓	✗	✗	✓	✗	✗	✓	✓
Solis[127]	2003	Observational	✓	✗	✗	✗	✗	✗	✗	✓
Vallières[121]	2016	Observational	✗	✗	✓	✗	✗	✓	✗	✓
Vanderhelst[122]	2015	Observational	✓	✓	✗	✗	✗	✗	✗	✓

RCT: randomized clinical trial. Included (✓); Not included (✗)

Chart S8. Study design and outcomes evaluated in each study selected for question 7.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events
Amim[131]	2011	RCT	✓	✗	✗	✓	✗	✗	✗
Bakker[132]	2011	RCT	✓	✗	✗	✗	✗	✗	✗
Barker[133]	2004	RCT	✓	✗	✗	✗	✗	✗	✗
Ballmann[134]	2002	RCT	✓	✗	✗	✗	✗	✗	✗
Bollert[135]	1999	RCT	✓	✗	✗	✗	✗	✗	✗
Bonestro[136]	2010	Observational	✓	✗	✓	✗	✗	✗	✗
Cobos[137]	2000	Observational	✓	✗	✗	✗	✗	✗	✗
Davies[138]	1997	Observational	✓	✗	✗	✗	✗	✗	✗
Derelle[139]	1998	Observational	✓	✗	✗	✗	✗	✗	✗
Fiel[140]	1995	RCT	✓	✗	✗	✗	✗	✗	✗
Frederiksen[141]	2006	RCT	✓	✗	✗	✗	✗	✗	✗
Fuchs[17]	1994	RCT	✓	✗	✓	✗	✗	✓	✓
Furuya([114)2	2001	RCT	✓	✗	✗	✗	✗	✗	✗
Harms[143]	1998	Observational	✓	✗	✓	✗	✗	✗	✓
Heijerman[144]	1995	RCT	✓	✗	✗	✗	✗	✗	✗
Hodson[145]	1995	RCT	✓	✗	✗	✗	✗	✗	✗
Hodson[146]	2003	Observational	✓	✗	✓	✗	✗	✗	✓
Johnson[147]	1999	Observational	✓	✗	✗	✗	✗	✗	✗
Konstan[148]	2011	Observational	✓	✗	✗	✗	✗	✗	✗
McCoy[149]	1996	RCT	✓	✗	✗	✗	✗	✓	✓
Milla[150]	1998	Observational	✓	✗	✗	✗	✗	✗	✗
Minasian[151]	2010	RCT	✓	✗	✗	✗	✗	✗	✗
Quan[152]	2001	RCT	✓	✓	✓	✗	✗	✗	✗
Robinson[153]	2000	RCT	✓	✗	✗	✗	✗	✗	✗
Robinson[154]	2005	RCT	✓	✗	✗	✗	✗	✗	✗
Rozov[155]	2010	Observational	✗	✗	✗	✓	✗	✗	✗
Rozov[156]	2013	Observational	✓	✗	✓	✓	✗	✗	✗
Shah[157]	2001	Observational	✓	✗	✓	✗	✗	✗	✗
Shah[158]	1995	Observational	✓	✗	✗	✗	✗	✗	✗
Shah[159]	1996	RCT	✓	✗	✗	✗	✗	✗	✗
Suri[160]	2001	RCT	✓	✗	✗	✗	✗	✗	✗
Wizla-Deram[161]	1998	Observational	✓	✓	✗	✗	✗	✗	✗

RCT: randomized clinical trial. Included (✓); Not included (✗)

Chart S9. Study design and outcomes evaluated in each study selected for question 8.

First author	Year	Design	Lung function	BMI	Exacerbation	Quality of life	Transplant	Mortality	Adverse events
Garcia[23]	2018	Observational	✓	✓	✗	✗	✗	✗	✗
Tullis[165]	2014	RCT	✓	✓	✗	✓	✗	✗	✗
Uluer[166]	2013	Observational	✓	✗	✗	✗	✗	✗	✗

RCT: randomized clinical trial. Included (✓); Not included (✗)