Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-257-z Ivacaftor/Tezacaftor/Elexacaftor

Stand: November 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Ivacaftor/Tezacaftor/Elexacaftor in Kombination mit Ivacaftor zur Behandlung der zystischen Fibrose (CF); Alter 2 bis < 6 Jahre	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Ggf. Ernährungsbezogene Maßnahmen, Unterstützung der Atemfunktion, Physiotherapie (i. S. der Heilmittel-RL)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Änderung der Arzneimittel-Richtlinie, Anlage XII: Beschlüsse über die Nutzenbewertung von neuen Arzneimitteln nach § 35a SGB V - D-793/D-794/D-795/D-796/D-797 Ivacaftor (nAWG; Beschluss 04.08.2022) - D-773/D-774/D-775/D-776/D-777 Ivacaftor/Tezacaftor/Elexacaftor (nAWG; Beschluss 04.08.2022) - D-733 Lumacaftor/Ivacaftor (Neubewertung nach Fristablauf; Beschluss am 18.03.2022) - D-690/D-688/D-686 Ivacaftor (nAWG; Beschluss 19.11.2021) - D-689/D-687/D-685 Ivacaftor/Tezacaftor/Elexacaftor (nAWG; Beschluss 19.11.2021) - D-623/D-624/D-619/D-605 Ivacaftor (nAWG; Beschluss 20.05.2021) - D-608/D-609 Tezacaftor/Ivacaftor (nAWG; Beschluss 20.05.2021) - D-586/587 Ivacaftor (nAWG; Beschluss 18.02.2021) - D-584/D-585 Ivacaftor/Tezacaftor/Elexacaftor (Beschluss 18.02.2021) - D-555 Ivacaftor (nAWG; Beschluss 17.12.2020) - D-552/D-553 Tezacaftor/Ivacaftor (Neubewertung nach Überschreitung 50 Mio. € Grenze; Beschluss 17.12.2020) - D-500 Ivacaftor (nAWG; Beschluss am 04.06.2020) - D-476 bis D-481 Ivacaftor (nAWG; Beschluss am 20.02.2020) - D-431 Ivacaftor (nAWG; Beschluss am 20.02.2020) - D-432 Lumacaftor/Ivacaftor (Beschluss am 15.08.2019) - D-408 Tezacaftor/Ivacaftor (Beschluss vom 16.05.2019) - D-339 Lumacaftor/Ivacaftor (nAWG; Beschluss vom 02.08.2018) - D-204 Lumacaftor/Ivacaftor (Beschluss vom 02.06.2016) - D-200 Ivacaftor (nAWG; Beschluss vom 02.06.2016)

	- D-133 Ivacaftor (nAWG; Beschluss vom 19.02.2015) - D-034 Ivacaftor (Beschluss vom 07.02.2013)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Tezacaftor/ Ivacaftor/ Elexacaftor R07AX32 Kaftrio®	<u>Neues Anwendungsgebiet laut positive opinion:</u> "Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients **aged 2 to less than 6 years** who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene." <u>Bereits zugelassenes Anwendungsgebiet</u>: Kaftrio wird angewendet als Kombinationsbehandlung mit Ivacaftor zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten **ab 6 Jahren**, die mindestens eine F508del-Mutation im CFTR-Gen (Cystic Fibrosis Transmembrane Conductance Regulator) aufweisen (siehe Abschnitt 5.1). *[Stand FI Kaftrio Tabletten: 06/2023]*
Ivacaftor R07AX02 Kalydeco®	<u>Neues Anwendungsgebiet laut positive opinion:</u> "In a combination regimen with ivacaftor/tezacaftor/elexacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one F508del mutation in the CFTR gene." <u>Bereits zugelassenes Anwendungsgebiet</u>: Kalydeco-Granulat wird angewendet zur Behandlung von Säuglingen **ab 4 Monaten**, Kleinkindern und Kindern mit einem Körpergewicht zwischen 5 kg und weniger als 25 kg mit zystischer Fibrose (CF, Mukoviszidose), die eine R117H-CFTR-Mutation oder eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R (siehe Abschnitte 4.4 und 5.1). *[Stand FI Kalydeco Granulat: 04/2022]* Kalydeco-Tabletten werden angewendet:

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
	• als Monotherapie zur Behandlung von Erwachsenen, Jugendlichen und Kindern **ab 6 Jahren** mit einem Körpergewicht von mindestens 25 kg mit zystischer Fibrose (CF, Mukoviszidose), die eine *R117H-CFTR*-Mutation oder eine der folgenden Gating-Mutationen (Klasse III) im Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*)-Gen aufweisen: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* oder *S549R* (siehe Abschnitte 4.4 und 5.1). • im Rahmen einer Kombinationsbehandlung mit Tezacaftor/Ivacaftor-Tabletten zur Behandlung von Erwachsenen, Jugendlichen und Kindern ab 6 Jahren mit zystischer Fibrose (CF), die homozygot für die *F508del*-Mutation sind oder heterozygot für die *F508del*- Mutation und eine der folgenden Mutationen im *CFTR*Gen aufweisen: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G* und *3849+10kbC→T*. • im Rahmen einer Kombinationsbehandlung mit Ivacaftor/Tezacaftor/Elexacaftor-Tabletten zur Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit zystischer Fibrose (CF), die mindestens eine *F508del*-Mutation im *CFTR*-Gen haben (siehe Abschnitt5.1). *[Stand FI Kalydeco Tabletten: 01/2022]*
CFTR-Modulatoren	
Lumacaftor/ Ivacaftor R07AX30 Orkambi	Orkambi-Tabletten sind angezeigt zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten **ab 6 Jahren**, die homozygot für die F508del-Mutation im CFTR-Gen sind (siehe Abschnitte 4.2, 4.4 und 5.1). *[Stand FI: 07/2023]* Orkambi Granulat ist angezeigt zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten **ab 1 Jahr**, die homozygot für die F508del-Mutation im CFTR-Gen sind (siehe Abschnitte 4.2, 4.4 und 5.1) *[Stand FI: 07/2023]*
Tezacaftor/ Ivacaftor R07AX31 Symkevi	Symkevi wird angewendet als Kombinationsbehandlung mit Ivacaftor-Tabletten zur Behandlung der zystischen Fibrose (CF) bei Patienten **ab 6 Jahren**, die homozygot für die F508del-Mutation sind oder heterozygot für die F508del-Mutation und eine der folgenden Mutationen im CFTR-Gen (Cystic Fibrosis Transmembrane Conductance Regulator) aufweisen: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10kbC→T. *[Stand FI: 05/2022]*
Antibiotika	
Ceftazidim J01DD02 Generisch	Ceftazidim wird angewendet bei Erwachsenen und **Kindern inklusive Neugeborenen (von Geburt an)** bei Infektionen die untenstehend aufgelistet sind: - Bronchopulmonale Infektionen bei zystischer Fibrose […] Bei der Wahl von Ceftazidim sollte sein antibakterielles Spektrum berücksichtigt werden, welches hauptsächlich auf aerobe Gramnegative Bakterien limitiert ist. Ceftazidim sollte gemeinsam mit anderen antibakteriellen Substanzen angewendet werden, wenn die mögliche Bandbreite der verursachenden

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
	Bakterien nicht vom Wirkspektrum von Ceftazidim abgedeckt wird. Offizielle Richtlinien zum angemessenen Gebrauch von antibakteriellen Arzneimitteln sollten berücksichtigt werden. *[Stand FI Ceftazidim Kabi: 10/2020]*
Aztreonam J01DF01 Cayston	Aztreonam wird angewendet zur suppressiven Behandlung chronischer Lungeninfektionen durch Pseudomonas aeruginosa bei Patienten mit Mukoviszidose (zystischer Fibrose, CF) **ab einem Alter von 6 Jahren**. Offizielle Empfehlungen zur angemessenen Anwendung von Antibiotika sind zu berücksichtigen. *[Stand FI: 02/2023]*
Ciprofloxacin J01MA02 Generisch	Ciprofloxacin ist indiziert für die Behandlung der folgenden Infektionen. Vor Beginn der Behandlung müssen die vorliegenden Informationen zu Resistenzen gegenüber Ciprofloxacin besonders berücksichtigt werden. Offizielle Empfehlungen zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden. Erwachsene: Untere Atemwegsinfektionen verursacht durch Gramnegative Bakterien: - Bronchopulmonale Infektionen bei zystischer Fibrose oder bei Bronchiektasien **Kinder und Jugendliche:** Durch Pseudomonas aeruginosa verursachte bronchopulmonale Infektionen bei zystischer Fibrose Die Behandlung sollte nur von einem in der Behandlung von zystischer Fibrose und/oder von schweren Infektionen bei Kindern und Jugendlichen erfahrenen Arzt initiiert werden. *[Stand FI Ciprobay: 12/2020]*
Levofloxacin J01MA12 Generisch	Levofloxacin ist zur Behandlung von chronischen Infektionen der Lunge durch Pseudomonas aeruginosa **bei erwachsenen Patienten** mit zystischer Fibrose (cystic fibrosis [CF], Mukoviszidose) angezeigt. Offizielle Empfehlungen zur angemessenen Anwendung von Antibiotika sind zu berücksichtigen. *[Stand FI Quinsair: 08/2021]*
Colistimethat J01XB01 Generisch	ColistiFlex ist **bei erwachsenen Patienten und Kindern** mit zystischer Fibrose zur Behandlung chronischer pulmonaler Infekte indiziert, die durch Pseudomonas aeruginosa verursacht werden. Die offiziellen Richtlinien zur sachgemäßen Anwendung von Antibiotika sind zu beachten. *[Stand FI ColistiFlex: 04/2023]*
Meronem J01D H02 Meronem	Meronem ist angezeigt zur Behandlung der folgenden Infektionen bei Erwachsenen und Kindern **ab einem Alter von 3 Monaten**: - Bronchopulmonale Infektionen bei zystischer Fibrose […] Für den angemessenen Gebrauch von Antibiotika sollten die offiziellen Leitlinien beachtet werden. *[Stand FI: 11/2022]*
Tobramycin J01GB01 Generisch	Zur Behandlung chronischer Infektionen der Lunge mit Pseudomonas aeruginosa bei Patienten mit Mukoviszidose **ab einem Alter von 6 Jahren**. Bramitob ist für die inhalative Anwendung bestimmt und nicht für eine parenterale Anwendung geeignet. Die offiziellen Richtlinien zur sachgemäßen Anwendung von Antibiotika sind zu beachten. Die Therapie sollte von einem Arzt mit Erfahrung in der Behandlung von Mukoviszidose eingeleitet werden. *[Stand FI Bramitob®: 01/2022]*
Sekretolytische Therapie	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Dornase alfa R05CB13 Pulmozyme	Dornase alfa ist angezeigt zur Behandlung der cystischen Fibrose (Mukoviszidose) bei Patienten, die **älter als 5 Jahre** sind und deren forcierte Vitalkapazität (FVC) mehr als 40 % des Normalwertes beträgt. *[Stand FI: 04/2017]*
Mannitol R05CB16 Bronchitol	Mannitol wird angewendet zur Behandlung der zystischen Fibrose (Mukoviszidose) bei Erwachsenen **ab 18 Jahren** zusätzlich zum besten Therapiestandard. *[Stand FI: 03/2021]*

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-257-z (Ivacaftor/Tezacaftor/Elexacaftor und Ivacaftor)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. November 2023

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse Event (Unerwünschtes Ereignis)
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CF	cystic fibrosis (zystische Fibrose)
CFQ-R	Cystic Fibrosis Questionnaire Revised (CFQ-R)
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
EP	Endpunkt
FEV1	Forced expiratory volume at one second
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LCI	lung clearance index
LFT	liver function tests
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PEx	Pulmonary exacerbations
ppFEV1	percent-predicted forced expiratory volume in one second
QoL	Quality of Life
rhDNase	recombinant human deoxyribonuclease I (Dornase alfa)
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Treatment of cystic fibrosis (CF) in patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Mukoviszidose* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 06.10.2023 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 662 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 9 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Holland P et al., 2021 [3].

Single versus combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis.

Fragestellung

To assess the effectiveness of single compared to combination intravenous anti-pseudomonal antibiotic therapy for treating people with CF.

Methodik

Population:

- Children and adults with defined CF, diagnosed clinically and by sweat or genetic testing, with all degrees of disease severity

Intervention/Komparator:

- Trials of any single IV anti-pseudomonal antibiotic compared to a combination of the same IV anti-pseudomonal antibiotic plus one or more other IV anti-pseudomonal antibiotics (drug A versus drug A plus drug B)

Endpunkte:

- spirometric lung function, Sputum bacteriology, Adverse effects, Quality of life (QoL), nutritional status, Additional treatment required, Duration of hospitalization, Time to next course of IV antibiotics, Changes in inflammatory markers (in sputum or blood)

Recherche/Suchzeitraum:

- Most recent search of the Group's Trials Register: 07 October 2020

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 59 trials, of which we included eight trials (356 participants) comparing a single anti-pseudomonal agent to a combination of the same antibiotic and one other

Charakteristika der Population:

- There was a wide variation in the individual antibiotics used in each trial
- In total, the trials included seven comparisons of a beta-lactam antibiotic (penicillin-related or third generation cephalosporin) with a beta-lactam-aminoglycoside combination and three comparisons of an aminoglycoside with a beta-lactam-aminoglycoside combination.
- All trials either stated that they included both adults and children, or did not state the age range. No trial looked at the effects of single versus combination antibiotic therapy in children alone. One trial included 17 children, but included three children twice, giving a total of 20 treatment courses (McCarty 1988).

Qualität der Studien:

- Six of the included trials were published between 1977 and 1988; these were singlecentre trials with flaws in the randomisation process and small sample size. Overall, the methodological quality was poor and the certainty of the evidence ranged from low to moderate.

Studienergebnisse:

- The review did not find any differences between monotherapy and combination therapy in either the short term or in the long term for the outcomes of different lung function measures, bacteriological outcome measures, need for additional treatment, adverse effects, quality of life or symptom scores.

Fazit der Autoren

- The results of this review, regarding the benefits and risks of single versus combination anti-pseudomonal antibiotic therapy in terms of lung function and clinical outcome in people with cystic fibrosis (CF), are inconclusive. In particular, side effects of treatment have not been investigated to a sufficient level, and therefore it is not possible to conclude from this review that either treatment choice is preferable or safer compared to the other. All the trials included in the review looked at different antibiotics, both as a single antipseudomonal agent and in combination therapy and therefore the drug(s) of choice remains uncertain.

Kommentare zum Review

- There was considerable heterogeneity amongst the trials, leading to difficulties in performing the review and interpreting the results. These results should be interpreted cautiously.
- Due to the small number of trials, it was not possible to examine for effects of trial quality, type of antibiotic or treatment regimen using sensitivity and subgroup analyses.

Nevitt SJ et al., 2020 [4].

Inhaled mannitol for cystic fibrosis

Fragestellung

To assess whether inhaled dry powder mannitol is well tolerated, whether it improves the quality of life and respiratory function in people with cystic fibrosis and which adverse events are associated with the treatment

Methodik

Population:

- Adults and children with CF

Intervention:

- orally inhaled dry powder mannitol (either alone or with another agent)

Komparator:

- active inhaled comparators (for example, hypertonic saline or dornase alfa) or with no treatment

Endpunkte:

- QoL, lung function, AEs, Exacerbations, hospitalisations, etc.

Recherche/Suchzeitraum:

- Date of last search: 12 December 2019.

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

Ergebnisse

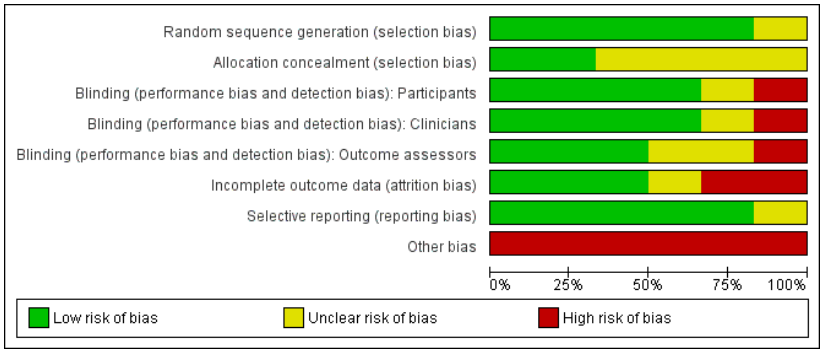
Anzahl eingeschlossener Studien:

- 6 RCTs

Charakteristika der Population:

- Alter: 6-55 Jahre
- In three studies the mean age was late teens or early 20s (Aitken 2012; Bilton 2011; Jaques 2008) and in three studies the mean age was between 12 and 14 years (de Boeck 2017; Middleton 2015; Minasian 2010).

Qualität der Studien:



The main issues influencing the quality of the evidence within this review were that all six studies included in the review were sponsored by the manufacturer of mannitol (Pharmaxis); some study authors declared financial interests.

Studienergebnisse:

Summary of findings 1. Summary of findings - 400 mg inhaled mannitol compared with 50 mg inhaled mannitol for cystic fibrosis

400 mg inhaled mannitol compared with 50 mg inhaled mannitol for CF

Patient or population: adults, children and young people with CF

Settings: outpatients

Intervention: 400 mg inhaled mannitol

Comparison: 50 mg (sub-therapeutic) inhaled mannitol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk 50 mg inhaled mannitol	Corresponding risk 400 mg inhaled mannitol				
HRQoL - all domains (change from baseline) Scale: age-appropriate versions of the CFQ-R questionnaire Follow-up: up to 6 months	There were no consistent statistically significant differences between treatment groups in changes from baseline for any domains of the CFQ-R at any of the time points for which data were available.		NA	324 - 507 participants (variable by domains) *2 studies*	⊕⊕⊝⊝ **low[1,2]**	
Lung function: FEV_1 mL (change from baseline) Follow-up: up to 6 months, repeated measures	The mean change from baseline in FEV_1 mL ranged across the 50 mg mannitol groups from 26.0 to 32.5.	The mean change from baseline in FEV_1 mL in the 400 mg mannitol groups was on average 86.5 higher (95% CI 45.2 to 127.9 higher).	NA	600 participants *2 studies*	⊕⊕⊕⊝ **moderate[1]**	Data provided by mannitol manufacturer Pharmaxis were analysed via a MMRM analysis.
Lung function: FEV_1 % predicted (change from baseline) Follow-up: up to 6 months, repeated measures	The mean change from baseline in FEV_1 % predicted ranged across the 50 mg mannitol groups from 0.62 to 1.63.	The mean change from baseline in FEV_1 % predicted in the 400 mg mannitol groups was on average 3.89 higher (95% CI 1.69 to 6.08 higher).	NA	600 participants *2 studies*	⊕⊕⊕⊝ **moderate[1]**	Data provided by mannitol manufacturer Pharmaxis were analysed via a MMRM analysis.
Lung function: FVC mL (change from baseline) Follow-up: up to 6 months, repeated measures	The mean change from baseline in FVC mL ranged across the 50 mg mannitol groups from 15.9 to 47.5.	The mean change from baseline in FVC mL in the 400 mg mannitol groups was on average 102.2 higher (95% CI 48.4 to 155.9 higher).	NA	600 participants *2 studies*	⊕⊕⊕⊝ **moderate[1]**	Data provided by mannitol manufacturer Pharmaxis were analysed via a MMRM analysis.
Lung function: FEF_{25-75} mL/s (change from baseline) Follow-up: up to 6 months, repeated measures	The mean change from baseline in FEF_{25-75} mL/s ranged across the 50 mg mannitol groups from 10.87 to 46.7.	The mean change from baseline in FEF_{25-75} mL/s in the 400 mg mannitol groups was on average 42.67 higher (95% CI -28.07 lower to 113.42 higher).	NA	600 participants *2 studies*	⊕⊕⊕⊝ **moderate[1]**	Data provided by mannitol manufacturer Pharmaxis were analysed via a MMRM analysis.
Adverse events relating to treatment Scale: mild, moderate, severe and total Follow-up: up to 6 months	The most commonly adverse events reported were cough and haemoptysis (in 5% and 2% of participants respectively).	The most commonly adverse events reported were cough and haemoptysis (in 10% and 5% of participants respectively).	See comment	600 participants *2 studies*	⊕⊕⊕⊝ **moderate[1]**	We found no statistically significant differences in rates of adverse events related to treatment (of all severities) between treatment groups.

*For lung function outcomes, the basis for the **assumed risk** is the range of mean values in the control group and the **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

For Health related Quality of Life and Adverse events, the basis of the **assumed risk** and the **corresponding risk** is described in the comments

CF: cystic fibrosis;**CFQ-R:** Cystic Fibrosis Questionnaire-Revised version, **CI:** confidence interval; **FEF_{25-75}**: mid-expiratory flow; **FEV_1**: forced expiratory volume at one second; **FVC**: forced vital capacity; **HRQoL**: health-related quality of life; **MMRM**: mixed model repeated measures; **NA:** not applicable.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. Evidence downgraded due to indirectness: the participant population included only those with CF who passed the tolerance test and not all potential participants with CF.
2. Evidence downgraded due to indirectness: the CFQ-R tool used in the studies was not designed to assess mucolytics. Also, pooling of the age-appropriate tools may not be valid so results should be interpreted with caution.

- Pulmonary exacerbations: statistically significant benefit with 400 mg mannitol compared to 50mg mannitol, pooled RR 0.71 (95% CI 0.51 to 0.98, P = 0.04), but the CIs are wide due to the low numbers of events, which shows that the average effect of 400 mg mannitol may reduce the exacerbation risk by as much as 49% or by as little as only 2%

Summary of findings 2. Summary of findings - Inhaled mannitol compared with control (non-respirable mannitol) for cystic fibrosis

Inhaled mannitol compared with control (non-respirable mannitol) for CF

Patient or population: adults, children and young people with CF

Settings: outpatients

Intervention: inhaled mannitol

Comparison: non-respirable mannitol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Non-respirable mannitol	Corresponding risk Inhaled mannitol				
HRQoL - all domains (change from baseline) Scale: age-appropriate versions of the CFQ-R questionnaire Follow-up: 2 weeks	At the end of the study there were no significant differences between mannitol and control for the respiratory, health, physical and vitality domains.		NA	39[1] *1 cross-over study*	⊕⊝⊝⊝ **very low**[1,2,3]	
Lung function: FEV_1 mL (absolute change from baseline) Follow-up: 2 weeks	A statistically significant improvement on mannitol compared to control was observed.		NA	39[1] *1 study*	⊕⊕⊝⊝ **low**[1,2]	
Lung function: FEV_1 % predicted (change from baseline) Follow-up: 2 weeks to 8 weeks	One study showed a statistically significant improvement in absolute change from baseline on mannitol compared to control at 2 weeks. The second study showed statistically significant improvement in both absolute and relative change from baseline on mannitol compared to control at 8 weeks.		NA.	126[1] *2 cross-over studies*	⊕⊕⊝⊝ **low**[1,2]	
Lung function: FVC mL or % predicted (change from baseline) Follow-up: 2 weeks to 8 weeks	No statistically significant differences in absolute or relative change from baseline in FVC (mL or % predicted) were found in either study.		NA	126[1] *2 cross-over studies*	⊕⊕⊝⊝ **low**[1,2]	
Lung function: FEF_{25-75} mL/s or % predicted (change from baseline) Follow-up: 2 weeks to 8 weeks	One study showed a statistically significant improvement in absolute change from baseline in FEF_{25-75} (mL/S) on mannitol compared to control at 2 weeks. The other study showed statistically significant improvement in both absolute and relative change from baseline in in FEF_{25-75} (% predicted) on mannitol compared to control at 8 weeks.		NA	126[1] *2 cross-over studies*	⊕⊕⊝⊝ **low**[1,2]	
Adverse events relating to treatment Scale: mild, moderate, severe and total Follow-up: 2 weeks to 8 weeks	The most commonly reported adverse events in both groups in the two studies were cough, haemoptysis, headache, nasopharyngitis and lung infections.		NA	123-125[4] *2 cross-over studies*	⊕⊕⊝⊝ **low**[1,2]	Frequencies of adverse events according to severity and association to treatment only were reported, a statistical comparison was not made in either study.

*The basis of the **assumed risk** and the **corresponding risk** is described in the comments. The study authors adjusted for the cross-over design of the study via a mixed model of analysis of variance when analysing and presenting results, however the format of the presented data does not allow us to perform analyses in this review. Published results from the study paper are presented

CF: cystic fibrosis;**CFQ-R**: Cystic Fibrosis Questionnaire-Revised version; **CI**: confidence interval; **FEF_{25-75}**: mid-expiratory flow; **FEV_1**: forced expiratory volume at one second; **FVC**: forced vital capacity; **HRQoL**: health-related quality of life; **NA:** not applicable.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In one of the studies it was stated that 39 participants were randomised, unclear how many were evaluated for each outcome. In the other study, the study may have been underpowered and imputation of missing data may have introduced bias (evidence downgraded due to risk of bias of incomplete outcome data).
2. Evidence downgraded due to indirectness: the participant population included only those with CF who passed the tolerance test and not all potential participants with CF.
3. Evidence downgraded due to indirectness: the CFQ-R tool used in the studies was not designed to assess mucolytics. Also, pooling of the age-appropriate tools may not be valid so results should be interpreted with caution.
4. One of the studies, adverse event data available for 38 and 36 participants in the mannitol and control groups respectively.

Summary of findings 4. Summary of findings - Inhaled mannitol compared with dornase alfa for cystic fibrosis

Inhaled mannitol compared with dornase alfa for CF

Patient or population: children and young people with CF

Settings: outpatients

Intervention: inhaled mannitol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dornase alfa	Inhaled mannitol				
HRQoL - all domains (change from baseline) Scale: age-appropriate versions of the CFQ-R questionnaire Follow-up: up to 3 months	No significant differences were found between treatment groups for any domains of the CFQ-R.		NA	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low[1,2,3]**	
Lung function: FEV_1 mL (percentage change from baseline) Follow-up: up to 3 months	The mean (SD) absolute change from baseline in the dornase alfa group was 84 (273) mL.	The mean (SD) absolute change from baseline in the mannitol group was -1 (279) mL.	**MD 2.80%** (95% CI: -4.80% to 10.40%).	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low[1,2]**	Only the relative effect of percentage change from baseline could be analysed*.
Lung function: FEV_1 % predicted Follow-up: NA	Outcome not reported.				NA	
Lung function: FVC mL (percentage change from baseline) Follow-up: up to 3 months	The mean (SD) absolute change from baseline in the dornase alfa group was 7 (415) mL.	The mean (SD) absolute change from baseline in the mannitol group was -58 (361) mL.	**MD 0.14%** (95% CI: -0.02% to 0.30%).	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low[1,2]**	Only the relative effect of percentage change from baseline could be analysed*.
Lung function: FEF_{25-75} mL/s (percentage change from baseline) Follow-up: up to 3 months	The mean (SD) absolute change from baseline in the dornase alfa group was 173 (310) mL/s.	The mean (SD) absolute change from baseline in the mannitol group was 55 (282) mL/s.	**MD -0.01%** (95% CI: -0.23 to 0.21%).	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low[1,2]**	Only the relative effect of percentage change from baseline could be analysed*.
Adverse events relating to treatment Scale: mild, moderate, severe and total Follow-up: up to 3 months	CF exacerbation was the most commonly reported adverse event (5% of participants).	Cough and CF exacerbation were the most commonly reported adverse events (22% and 17% of participants respectively).	See comment.	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low[1,2]**	Frequencies of adverse events according to severity only were reported, a statistical comparison was not made.

*The basis of the **assumed risk** and the **corresponding risk** is described in the comments. For lung function outcomes, absolute data was not presented in a format which could be analysed due to the cross-over design of the study, therefore only analyses of percentage change from baseline were included in this review

CF: cystic fibrosis;**CFQ-R**: Cystic Fibrosis Questionnaire-Revised version, **CI**: confidence interval; **FEF_{25-75}**: mid-expiratory flow; **FEV_1**: forced expiratory volume at one second; **FVC**: forced vital capacity; **HRQoL**: health-related quality of life; **MD**: mean difference; **NA:** not applicable; **SD**: standard deviation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. Stated that 28 participants were randomised, unclear how many participants dropped out and how many were evaluated for each outcome (evidence downgraded due to incomplete outcome data). Evidence also downgraded due to imprecision, study is known to be underpowered.
2. Evidence downgraded due to indirectness: the participant population included only those with CF who passed the tolerance test and not all potential participants with CF.
3. Evidence downgraded due to indirectness: the CFQ-R tool used in the studies was not designed to assess mucolytics. Also, pooling of the age-appropriate tools may not be valid so results should be interpreted with caution.

Summary of findings 5. Summary of findings - Inhaled mannitol plus dornase alfa compared with dornase alfa for cystic fibrosis

Inhaled mannitol plus dornase alfa compared with dornase alfa for CF

Patient or population: children and young people with cystic fibrosis

Settings: outpatients

Intervention: inhaled mannitol plus dornase alfa

Comparison: dornase alfa

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dornase alfa	Inhaled mannitol plus dornase alfa				
HRQoL - all domains (change from baseline) Scale: age-appropriate versions of the CFQ-R questionnaire Follow-up: up to 3 months	No significant differences were found between treatment groups for any domains of the CFQ-R.		NA	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low**[1,2,3]	
Lung function: FEV_1 mL (percentage change from baseline) Follow-up: up to 3 months	The mean (SD) absolute change from baseline in the dornase alfa group was 84 (273) mL.	The mean (SD) absolute change from baseline in the mannitol group was -31 (306) mL.	**MD -4.30%** (95% CI: -14.10% to 5.50%).	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low**[1,2]	Only the relative effect of percentage change from baseline could be analysed*.
Lung function: FEV_1 % predicted Follow-up: NA	Outcome not reported.				NA	
Lung function: FVC mL (percentage change from baseline) Follow-up: up to 3 months	The mean (SD) absolute change from baseline in the dornase alfa group was 7 (415) mL.	The mean (SD) absolute change from baseline in the mannitol group was -103 (394) mL.	**MD -0.07%** (95% CI: -0.30% to 0.16%).	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low**[1,2]	Only the relative effect of percentage change from baseline could be analysed*.
Lung function: FEF_{25-75} mL/s (percentage change from baseline) Follow-up: up to 3 months	The mean (SD) absolute change from baseline in the dornase alfa group was 173 (310) mL/s.	The mean absolute change from baseline in the mannitol group was 68 (489) mL/s.	**MD -0.03%** (95% CI: -0.18 to 0.24%).	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low**[1,2]	Only the relative effect of percentage change from baseline could be analysed*.
Adverse events relating to treatment Scale: mild, moderate, severe and total Follow-up: up to 3 months	CF exacerbation was the most commonly reported adverse event (5% of participants).	Cough and CF exacerbation were the most commonly reported adverse events (9% and 30% of participants respectively).	See comment.	up to 23[1] *1 cross-over study*	⊕⊖⊖⊖ **very low**[1,2]	Frequencies of adverse events according to severity only were reported, a statistical comparison was not made.

*The basis of the **assumed risk** and the **corresponding risk** is described in the comments. For lung function outcomes, absolute data was not presented in a format which could be analysed due to the cross-over design of the study, therefore only analyses of percentage change from baseline were included in this review

CF: cystic fibrosis;**CFQ-R**: Cystic Fibrosis Questionnaire-Revised version, **CI**: confidence interval; **FEF_{25-75}**: mid-expiratory flow; **FEV_1**: forced expiratory volume at one second; **FVC**: forced vital capacity; **HRQoL**: health-related quality of life; **MD**: mean difference; **NA:** not applicable; **SD**: standard deviation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1 Stated that 28 participants were randomised, unclear how many participants dropped out and how many were evaluated for each outcome (evidence downgraded due to incomplete outcome data). Evidence also downgraded due to imprecision, study is known to be underpowered.
2. Evidence downgraded due to indirectness: the participant population included only those with CF who passed the tolerance test and not all potential participants with CF.
3. Evidence downgraded due to indirectness: the CFQ-R tool used in the studies was not designed to assess mucolytics. Also, pooling of the age-appropriate tools may not be valid so results should be interpreted with caution.

Fazit der Autoren

In this review, we were able to combine results from two large, well powered studies comparing 400 mg twice-daily inhaled mannitol to low-dose, sub-therapeutic (50 mg inhaled mannitol) in people with cystic fibrosis (CF) (Aitken 2012; Bilton 2011). Pooled evidence from these studies demonstrates moderate quality evidence of efficacy for 400 mg mannitol in terms of improved lung function (forced expiratory volume at one second (FEV1)), both mL and % predicted) at two, four and six months. This efficacy is shown in adults and both dornase alfa users and non-users.

We found no clear evidence in this review of an association between health-related quality of life (HRQoL) and the use of inhaled mannitol. We also found no consistent evidence of the association between inhaled mannitol and adverse effects.

When compared to non-respirable mannitol as a control treatment in four small studies of short duration, this review provides only low- to very low-quality evidence regarding differences in HRQoL, lung function and adverse events associated with treatment.

However, results of this review do not provide a definitive argument for the universal use of mannitol in all people with cystic fibrosis (CF). This review provides limited information regarding the effectiveness of inhaled mannitol in different severities of CF. Stakeholders need to be aware of this evidence base when assessing the use of inhaled mannitol for CF.

Kommentare zum Review

- Keine klaren Subruppenanalysen für das im AWG genannte Alter

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Skilton, M. et al., 2019 [5].

Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis.

Fragestellung

Methodik To evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with CF.

Population:

- children or adults with CF

Intervention/Komparator:

- CFTR potentiators to placebo or another intervention

Endpunkte:

- Survival, QoL, FEV1, adverse events, hospitalisation, nutrition, growth, etc.

Recherche/Suchzeitraum:

- Last search: 21 November 2018.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- five RCTs (447 participants with different mutations) lasting from 28 days to 48 weeks, all assessing the CFTR potentiator ivacaftor.

Charakteristika der Population:

- All 447 participants in the included trials had a confirmed diagnosis of CF. The F508del trial examined the effect of ivacaftor on people homozygous for the F508del mutation (class II mutation) (DISCOVER 2011). In the three G551D trials (class III mutation), participants were required to possess at least one G551D-CFTR allele (Accurso 2010; ENVISION 2013; STRIVE 2011). The R117H trial required participants to have at least one R117H-CFTR allele (KONDUCT 2015).
- Two trials recruited recruited participants aged 12 years and older (DISCOVER 2011; STRIVE 2011); participants in the F508del trial had a mean age of 25.5 years (DISCOVER 2011) and participants in the adult G551D trial had a mean age of 23.2 years (STRIVE 2011). The phase 2 G551D trial recruited participants aged 18 years and over and participants had a median 21 age of years (Accurso 2010). The paediatric phase 3 G551D trial enrolled participants aged 6 to 11 years of age and participants had a mean age of 8.9 years (ENVISION 2013). The R117H trial recruited those over 6 years of age and participants had a mean age of 31 years (KONDUCT 2015).

Qualität der Studien:

- The quality of the evidence was moderate to low, mainly due to risk of bias (incomplete outcome data and selective reporting) and imprecision of results, particularly where few individuals experienced adverse events. Trial design was generally well-documented. All trials were industry-sponsored and supported by other non-pharmaceutical funding bodies.

Studienergebnisse:

- F508del (class II) (140 participants)
  - One 16-week trial reported no deaths, or changes in quality of life (QoL) or lung function (either relative or absolute change in forced expiratory volume in one second (FEV1) (moderate-quality evidence). Pulmonary exacerbations and cough were the most reported adverse events in ivacaftor and placebo groups, but there was no difference between groups (low-quality evidence); there was also no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Number of days until the first exacerbation was not reported, but there was no difference between groups in how many participants developed pulmonary exacerbations. There was also no difference in weight. Sweat chloride concentration decreased, mean difference (MD) -2.90 mmol/L (95% confidence interval (CI) -5.60 to -0.20).
- **G551D (class III) (238 participants)**
  - The 28-day phase 2 trial (19 participants) and two 48-week phase 3 trials (adult trial (167 adults), paediatric trial (52 children)) reported no deaths. QoL scores (respiratory domain) were higher with ivacaftor in the adult trial at 24 weeks, MD 8.10 (95% CI 4.77 to 11.43) and 48 weeks, MD 8.60 (95% CI 5.27 to 11.93 (moderate-quality evidence). The adult trial reported a higher relative change in FEV1 with ivacaftor at 24 weeks, MD 16.90% (95% CI 13.60 to 20.20) and 48 weeks, MD 16.80% (95% CI 13.50 to 20.10); the paediatric trial reported this at 24 weeks, MD 17.4% ($P < 0.0001$)) (moderate-quality evidence). These trials demonstrated absolute improvements in FEV1 (% predicted) at 24 weeks, MD 10.80% (95% CI 8.91 to 12.69)

and 48 weeks, MD 10.44% (95% CI 8.56 to 12.32). The phase 3 trials reported increased cough, odds ratio (OR) 0.57 (95% CI 0.33 to 1.00) and episodes of decreased pulmonary function, OR 0.29 (95% CI 0.10 to 0.82) in the placebo group; ivacaftor led to increased dizziness in adults, OR 10.55 (95% CI 1.32 to 84.47). There was no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Fewer participants taking ivacaftor developed serious pulmonary exacerbations; adults taking ivacaftor developed fewer exacerbations (serious or not), OR 0.54 (95% CI 0.29 to 1.01). A higher proportion of participants were exacerbation-free at 24 weeks with ivacaftor (moderate-quality evidence). Ivacaftor led to a greater absolute change from baseline in FEV1 (% predicted) at 24 weeks, MD 10.80% (95% CI 8.91 to 12.69) and 48 weeks, MD 10.44% (95% CI 8.56 to 12.32); weight also increased at 24 weeks, MD 2.37 kg (95% CI 1.68 to 3.06) and 48 weeks, MD 2.75 kg (95% CI 1.74 to 3.75). Sweat chloride concentration decreased at 24 weeks, MD -48.98 mmol/L (95% CI -52.07 to -45.89) and 48 weeks, MD -49.03 mmol/L (95% CI -52.11 to -45.94).

- **R117H (class IV) (69 participants)**
  - One 24-week trial reported no deaths. QoL scores (respiratory domain) were higher with ivacaftor at 24 weeks, MD 8.40 (95% CI 2.17 to 14.63), but no relative changes in lung function were reported (moderate-quality evidence). Pulmonary exacerbations and cough were the most reported adverse events in both groups, but there was no difference between groups; there was no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Number of days until the first exacerbation was not reported, but there was no difference between groups in how many participants developed pulmonary exacerbations. No changes in absolute change in FEV1 or weight were reported. Sweat chloride concentration decreased, MD -24.00 mmol/L (CI 95% -24.69 to -23.31).

Fazit der Autoren

The F508del trial demonstrated no evidence to support the use of ivacaftor in those with the F508del mutation (DISCOVER 2011). The two G551D phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes at 24 and 48 weeks in children (over six years of age) and adults with cystic fibrosis (CF) and the G551D mutation (ENVISION 2013; STRIVE 2011). The R117H trial demonstrated an improvement in the respiratory domain of the CFQ-R but no improvement in respiratory function (KONDUCT 2015). These trials were judged to have a moderate risk of bias.

Kommentare zum Review

- Keine klaren Subruppenanalysen für das im AWG genannte Alter

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Southern KW et al., 2020 [7].

Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis

Fragestellung

To evaluate the effects of CFTR correctors on clinically important outcomes, both benefits and harms, in children and adults with CF and class II CFTR mutations (most commonly F508del).

Methodik

Population:

- children or adults with CF, as confirmed either by the presence of two disease-causing mutations, or by a combination of positive sweat test and recognised clinical features of CF.
- participants with any level of disease severity.
- Participants should have at least one class II mutation.

Intervention:

- CFTR corrector (defined as a drug, which aims to increase the amount of CFTR expressed at the epithelial cell apical membrane, by reducing or preventing degradation of CFTR by normal intracellular mechanisms. The main mutation targeted by this approach is F508del.)
- CFTR correctors alongside another class of drug that also aims to improve CFTR function (e.g. potentiators).

Komparator:

- placebo or another intervention

Endpunkte:

- primäre Endpunkte:
  - Survival, Quality of life (QoL), Physiological measures of lung function
- sekundäre Endpunkte:
  - Adverse effects, Extra courses of antibiotics, BMI

Recherche/Suchzeitraum:

- Most recent search: 14 October 2020.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

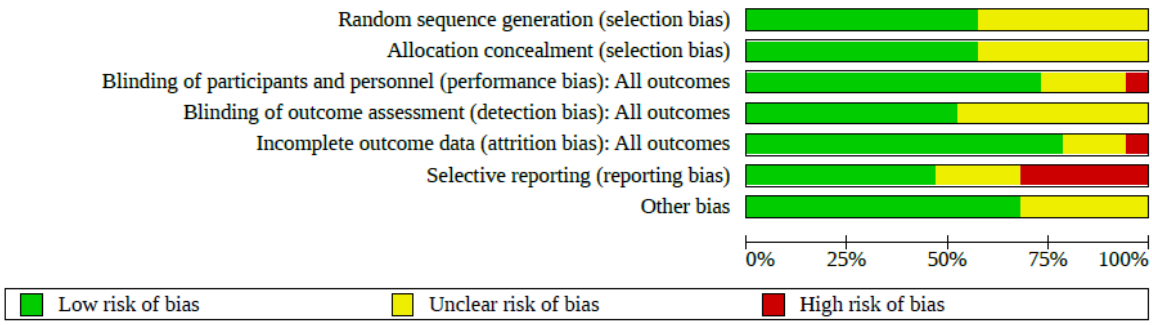
Ergebnisse

Anzahl eingeschlossener Studien:

- There were 19 studies (97 references) which met the eligibility criteria for inclusion in this review

Qualität der Studien:

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

Summary of findings 1. Summary of findings - monotherapy: lumacaftor compared to placebo for cystic fibrosis

Lumacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Lumacaftor				
Survival Follow-up: 14 to 28 days	No deaths reported.	No deaths reported.	NA	147 (2 studies)	⊕⊕⊝⊝ **low**[a]	
Quality of life - total score Follow-up: 14 to 28 days	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 14 to 28 days	There was a significant decrease in the CFQ-R respiratory domain in the 50 mg lumacaftor group compared to placebo. No differences were found in the other dose groups (25 mg, 100 mg, 200 mg) compared to placebo.		NA	85 (1 study)	⊕⊕⊝⊝ **low**[a]	A higher score indicates a better outcome.
FEV_1 % predicted: relative change from baseline Follow-up: 14 to 28 days	Outcome not reported.				NA	
FEV_1 % predicted: absolute change from baseline Follow-up: 14 to 28 days	The mean change from baseline was 1.7% predicted.	The mean change from baseline was 1.90% predicted lower (4.13 lower to 0.33 higher).	NA	61 (1 study)	⊕⊕⊕⊝ **moderate**[b]	
Adverse events Follow-up: 14 to 28 days	There were no significant differences between groups in terms of participants experiencing any specific adverse event. In 1 of the studies, 1 participant from each of the lumacaftor arms - 1 participant in each of the discontinued the study drug due to respiratory adverse effects. No participants discontinued from the placebo group.		NA	115 (2 studies)	⊕⊝⊝⊝ **very low**[a,b,c]	
Time to first pulmonary exacerbation Follow-up: 14 to 28 days	Outcome not reported (see comment).				NA	Time to first pulmonary exacerbation was not reported. There was no significant difference between groups in the number of participants experiencing pulmonary exacerbations.

*The basis for the **assumed risk** is the mean placebo group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval, **EQ-5D-3L**: 5-Dimension-3 Level, **FEV_1**: forced expiratory volume at one second; **MD**: mean difference.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a Downgraded twice due to risk of bias: in one study, data were selectively reported and often presentation of data did not allow for inclusion in analysis. There are also incomplete outcome data in the study with participants unaccounted for in analysis.
b Downgraded once due to indirectness: design of the study means that monotherapy treatment was measured for only 14 days before a combination therapy phase was started.
c Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide.

Summary of findings 3. Summary of findings - dual therapy: lumacaftor plus ivacaftor (once daily) compared with placebo for cystic fibrosis (short term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (600 mg once daily or 400 mg once daily) plus ivacaftor (250 mg twice daily)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk Lumacaftor plus ivacaftor				
Survival Follow-up: 6 months	No deaths reported.	No deaths reported.	NA	1108 (2 studies)	⊕⊕⊕⊕ **high**	
Quality of life - (EuroQol) EQ-5D-3L Index Score (total score): absolute change from baseline Follow-up: 6 months	The mean absolute change from baseline ranged from 0.0006 to 0.0017 points.	The mean absolute change from baseline was 0.00 points higher (0.01 lower to 0.01 higher).	NA	1061 (2 studies)	⊕⊕⊕⊖ **moderate**[a]	A higher score indicates a better outcome.
Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 6 months	The mean absolute change from baseline ranged from 1.1 to 2.81 points.	The mean absolute change from baseline was 2.62 points higher (0.64 higher to 4.59).	NA	1076 (2 studies)	⊕⊕⊕⊖ **moderate**[a]	A higher score indicates a better outcome. There was also a significant difference between groups at 28 days, MD 3.70 points (95% CI 1.81 to 5.58).
FEV_1 % predicted: relative change from baseline Follow-up: 6 months	The mean relative change from baseline ranged from -0.34% to 0%.	The mean relative change from baseline was 5.21% higher (3.61% higher to 6.80% higher).	NA	1072 (2 studies)	⊕⊕⊕⊕ **high**	
FEV_1 % predicted: absolute change from baseline Follow-up: 6 months	The mean absolute change from baseline ranged from -0.44 to -0.15% predicted.	The mean absolute change from baseline was 3.07% predicted higher (2.17 higher to 3.97 higher).	NA	1072 (2 studies)	⊕⊕⊕⊖ **moderate**[a]	There was also a significant difference between groups at 28 days, MD 2.37% predicted (95% CI 1.52 to 3.22).
Adverse events Follow-up: 6 months	Cough was significantly more common in the placebo group compared to the lumacaftor-ivacaftor group. Dyspnoea was significantly more common in the lumacaftor-ivacaftor group compared to the placebo group.		NA	1108 (2 studies)	⊕⊕⊕⊕ **high**	

	There were no significant differences between groups in terms of number of participants experiencing adverse events, serious adverse events or other adverse events. Long-term open-label follow-up data of the 2 studies showed a significant increase in early transient shortness of breath. In participants allocated a 400 mg twice-daily dose, there was a significant rise in blood pressure.				
Time to first pulmonary exacerbation Follow-up: 6 months	Time to first pulmonary exacerbation was significantly longer in both in the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily and the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily groups	NA	1108 (2 studies)	⊕⊕⊕⊖ **moderate**[a]	Presentation of data did not allow an analysis of the lumacaftor doses pooled.

*The basis for the **assumed risk** is the mean placebo group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **EQ-5D-3L**: 5-Dimension-3 Level; **EuroQol**: Euro Quality of Life Scale; **FEV_1**: forced expiratory volume at one second; **MD**: mean difference.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a Downgraded once due to risk of bias from selective reporting: data contributing to analyses were extrapolated from published graphs or estimated. We have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update and this judgement will be reconsidered.

Summary of findings 4. Summary of findings - dual therapy: lumacaftor plus ivacaftor (twice daily) compared with placebo for cystic fibrosis (short term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Survival Follow-up: 24 weeks	No deaths reported.	No deaths reported.	NA	204 (1 study)	⊕⊕⊕⊖ **moderate**[a]	
Quality of life - total score Follow-up: 24 weeks	Outcome not reported.				NA	A higher score indicates a better outcome.

Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 24 weeks	See comment.	The mean change in the CFQ-R respiratory domain was 2.50 points higher in the lumacaftor-ivacaftor group compared to the placebo group, ranging from 0.10 lower to 5.10 higher.	NA	204 (1 study)	⊕⊕⊙⊙ **low**[a,b]	A higher score indicates a better outcome. Data were analysed via a MMRM. Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24.
FEV_1 % predicted: relative change from baseline Follow-up: 24 weeks	Outcome not reported.				NA	Relative change from baseline in FEV_1 was listed in the methods of the study but no numerical results were presented. if numerical data becomes available at a later date, it will be included in an update of this review.
FEV_1 % predicted: absolute change from baseline Follow-up: 24 weeks	See comment.	The mean change in FEV_1 % predicted was 2.40 higher in the lumacaftor-ivacaftor group compared to the placebo group, ranging from 0.40 higher to 4.40 higher.	NA	204 (1 study)	⊕⊕⊙⊙ **low**[a,b]	Data were analysed via a MMRM. Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24.
Adverse events Follow-up: 24 weeks	There was no significant difference between the groups in terms of productive cough, nasal congestion, oropharyngeal pain, upper abdominal pain, rhinorrhoea, increased sputum, cough, pyrexia, headache, upper respiratory tract infection, abdominal pain, nausea, vomiting, fatigue and respiratory events (such as wheezing, dyspnoea, asthma and chest discomfort).		NA	204 (1 study)	⊕⊕⊙⊙ **low**[b,c]	
Time to first pulmonary exacerbation Follow-up: 24 weeks	Outcome not reported.				NA	Time to first pulmonary exacerbation was listed in the methods of the study but no numerical results were presented. If numerical data become available at a later date, they will be included in an update of this review.

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **MMRM**: mixed model for repeated measures; **NA**: not applicable.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a Downgraded once due to indirectness: children aged 6 - 11 years were recruited in this study, therefore, results are not applicable to other age groups.
b Downgraded once due to risk of bias from selective reporting: limited data available which is adjusted for all visits. Further graphical data were available in the publication but could not be accurately extracted. We have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update and this judgement will be reconsidered
c Downgraded once due to imprecision; few events occurred therefore CIs for occurrence of specific events are very wide.

Summary of findings 5. Summary of findings - dual therapy: lumacaftor plus ivacaftor compared with placebo for cystic fibrosis (immediate term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (200 mg) plus ivacaftor (150 mg or 250 mg twice daily)[a]

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants	Quality of the evidence	Comments

	Assumed risk	Corresponding risk		(studies)	(GRADE)	
	Placebo	Lumacaftor plus ivacaftor[a]				
Survival Follow-up: 21 days[1]	No deaths reported.	No deaths reported.	NA	62 (1 study)	⊕⊕⊕⊖ **moderate[b]**	
Quality of life: total score Follow-up: 21 days[1]	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life: respiratory domain Follow-up: 21 days[1]	Outcome not reported.				NA	A higher score indicates a better outcome.
FEV_1 % predicted: relative change from baseline Follow-up: 21 days[1]	Outcome not reported.				NA	
FEV_1 % predicted: absolute change from baseline Follow-up: 21 days[1]	The mean change from baseline was 0.3.	The mean change from baseline was 1.57% predicted higher (-2.13 lower to 5.27 higher).	NA	59 (1 study)	⊕⊕⊕⊖ **moderate[b]**	
Adverse events Follow-up: 21 days[1]	There were no significant differences between groups in terms of participants experiencing: cough, oropharyngeal pain, nasal congestion, dizziness, a prolonged prothrombin time, and upper respiratory tract infection.		NA	61 (1 study)	⊕⊕⊖⊖ **low[b,c]**	
Time to first pulmonary exacerbation Follow-up: 21 days [1]	Outcome not reported (see comment).				NA	Time to first pulmonary exacerbation was not reported. There was no significant difference between groups in the number of participants experiencing pulmonary exacerbations.

*The basis for the **assumed risk** is the mean placebo group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **FEV_1**: forced expiratory volume at 1 second.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a The design of the study was 14 days of lumacaftor monotherapy (200 mg once daily) then a dose of ivacaftor (150 mg or 250 mg once daily) was added on for 7 days of combination therapy. Results presented in this table are from the combination treatment period only.
b Downgraded once due to indirectness: design of the study means that combination treatment was measured for only 7 days and prior lumacaftor monotherapy phase (see footnote 1) may have influenced results of the combination phase.
c Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide.

Summary of findings 6. Summary of findings - dual therapy: tezacaftor plus ivacaftor compared with placebo or ivacaftor alone for cystic fibrosis

Tezacaftor plus ivacaftor compared with placebo or ivacaftor alone for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: tezacaftor (100 mg daily) plus ivacaftor (150 mg twice daily)

Comparison: placebo (i.e. tezacaftor placebo) or ivacaftor (150 mg twice daily)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or ivacaftor alone	Tezacaftor plus ivacaftor				
Survival Follow-up: up to 24 weeks	No deaths reported.	No deaths reported.	NA	522 (2 studies)	⊕⊕⊕⊖ **moderate[a,b]**	
Quality of life: total score	Outcome not reported.				NA	A higher score indicates a better outcome.

Follow-up: NA						
Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: up to 24 weeks	See comment.	The mean absolute change from baseline in CFQ-R respiratory domain score in the tezacaftor-ivacaftor group was 5.10 points higher (3.20 higher to 7.00 higher) than the placebo group (result from 1 study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊖ **moderate**[a,b]	A higher score indicates a better outcome Difference in absolute change from baseline calculated by least-squares regression, hence assumed risk not presented. The mean absolute change from baseline in CFQ-R respiratory domain score in the tezacaftor plus ivacaftor group was also significantly higher than the placebo group at 4 weeks: MD 5.10 (95% CI 2.99 to 7.21) The second study (n = 18) showed that the treatment effect of tezacaftor-ivacaftor versus placebo was 6.81 points of CFQ-R respiratory domain (P = 0.2451) up to day 28.
FEV_1 % predicted: relative change from baseline Follow-up: up to 24 weeks	See comment.	The mean relative change from baseline in FEV_1 % predicted in the tezacaftor-ivacaftor group was 6.80% higher (5.30% higher to 8.30% higher) than the placebo group (result from 1 study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊖ **moderate**[a,b]	Difference in relative change from baseline calculated by least-squares regression, hence assumed risk not presented. The second study (n = 18) showed no significant difference between groups in mean relative change from baseline in FEV_1 % predicted MD 3.72 (95% CI -7.77 to 15.21).
FEV_1 % predicted: absolute change from baseline Follow-up: up to 24 weeks	See comment	The mean absolute change from baseline in FEV_1 % predicted in the tezacaftor plus ivacaftor group was 4.00 % predicted higher (3.10 higher to 4.90 higher) than the placebo group (result from one study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊖ **moderate**[a,b]	Difference in absolute change from baseline calculated by least-squares regression, hence assumed risk not presented. The mean absolute change from baseline in FEV_1 % predicted in the tezacaftor-ivacaftor group was also significantly higher than the placebo group at 4 weeks, MD 3.59 (95% CI 2.40 to 4.78), 2 studies, n = 528, I^2 =0%.
Adverse events: most commonly occurring events (occurring in at least 10% of participants) Follow-up: up to 24 weeks	The most commonly occurring adverse events in both groups were cough and pulmonary exacerbation. There were no significant differences between groups (99% confidence intervals) in the number of participants experiencing cough, pulmonary exacerbation, headache, nasal congestion or nasopharyngitis, increased sputum, haemoptysis, pyrexia, oropharyngeal pain, nausea or fatigue.		NA	527 (2 studies)	⊕⊕⊕⊖ **moderate**[a,b]	
Time to first pulmonary exacerbation Follow-up: up to 24 weeks	The hazard ratio for pulmonary exacerbation in the tezacaftor plus–ivacaftor group, as compared with the placebo group was 0.64 (95% CI 0.46 to 0.89).		NA	504 (1 study)	⊕⊕⊕⊖ **moderate**[a,b]	A hazard ratio below 1 favours the tezacaftor-ivacaftor group.

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **MD**: mean difference; **NA**: not applicable.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a Downgraded once due to indirectness: 1 study recruited individuals over the age of 12 (Taylor-Cousar 2017) and 1 study recruited individuals over the age of 18 with one F508del mutation and one G551D mutation (Donaldson 2018). Therefore, results are not applicable to children under the age of 12 and some results are not applicable to individuals homozygous for F508del.
b One study has some unclear details related to methodological design and had unbalanced treatment group sizes and baseline characteristics (Donaldson 2018). However, this study contributed a small proportion of the evidence of this comparison (n = 18, 3% of evidence) compared to the second study in the comparison (n = 509, 97% of evidence, overall low risk of bias) (Taylor-Cousar 2017). Therefore, no downgrading is made due to potential risks of bias in the smaller study.

Anmerkung/Fazit der Autoren

There is no evidence to support monotherapy with a corrector for people with cystic fibrosis (pwCF) who have two F508del variants (F508del/F508del).

There is some evidence to support dual therapies (lumacaftor-ivacaftor and tezacaftor-ivacaftor) for pwCF with the genotype F508del/F508del. There are still no data to assess

the effectiveness of tezacaftor-ivacaftor in children. There are no new data on these compounds to alter the conclusions presented in the previous version of this review (Southern 2018).

Combined data from Phase 3 studies of dual therapy with both lumacaftor and tezacaftor combined with ivacaftor demonstrate small but consistent improvements in key clinical outcomes. The size and quality of evidence from the studies gives us confidence in the validity of these results. Overall the drugs were well-tolerated, but important adverse effects were reported, in particular with the lumacaftor-ivacaftor combination. Adverse events noted with lumacaftor-ivacaftor were not recorded in the tezacaftor-ivacaftor studies and this combination appears to have a more acceptable safety profile.

In children younger than 12 years of age, there are no data to assess tezacaftor-ivacaftor. In a study of lumacaftor-ivacaftor in children aged 6 to 11 years, there was some evidence of clinical efficacy (decreasing lung clearance index (LCI) value), but the clinical relevance of these changes is not clear. The reports of increased adverse events for lumacaftor-ivacaftor in this age group and in older pwCF should be taken into account when considering this intervention for this age group until further data or an alternative agent (e.g. tezacaftor-ivacaftor) are available.

Kommentare zum Review

- Keine klaren Subruppenanalysen für das im AWG genannte Alter

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Yang C et al., 2020 [9].

Dornase alfa for cystic fibrosis.

Fragestellung

To determine whether the use of dornase alfa in cystic fibrosis is associated with improved mortality and morbidity compared to placebo or other medications that improve airway clearance, and to identify any adverse events associated with its use.

Methodik

Population:

- Children and adults, of any age, with CF

Intervention:

- Dornase alfa

Komparator:

- placebo or other medications that are adjuncts to airway clearance (typically hyperosmotic agents such as hypertonic saline or mannitol)

Endpunkte:

- Lung function, QoL, exacerbation, number of deaths, number of days treatment with intravenous (IV) antibiotics, number of days treatment with oral antibiotics, number of days in hospital due to respiratory exacerbations, weight, AEs

Recherche/Suchzeitraum:

- Date of the most recent search of the Group's register: 12 October 2020.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 19 RCTs (2565 participants)

Charakteristika der Population:

- Four trials included adults only. Four trials included children only; one trial enrolled children aged six to 10 years, two trials enrolled participants aged six to 18 years and the remaining trial recruited infants with a mean (SD) age of 42 (32) weeks. Seven trials included mixed adult and paediatric populations. One trial included participants aged one year and over, four trials included participants aged five years or older, one trial included participants aged seven years or older and a further trial included participants aged eight years or older.

Qualität der Studien:

- Most trials were judged to have a low risk of performance, detection, reporting and attrition bias. Many of the included trials did not have enough information in the publication to determine if there was a risk of selection bias.

Studienergebnisse:

Summary of findings 1. Dornase alfa versus placebo or no dornase alfa treatment

Dornase alfa compared with placebo or no dornase alfa treatment for cystic fibrosis

Patient or population: Adults and children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa

Comparison: Placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no dornase alfa treatment	Dornase alfa				
Relative mean percentage change in FEV_1 (% predicted) at 3 months	The relative mean percentage change in FEV_1 (% predicted) was **2.10**	The relative mean percentage change in FEV_1 (% predicted) was **7.30 higher** (4.04 higher to 10.56 higher)	NA	320 (1 study)[1]	⊕⊕⊕⊖ **moderate**[2]	
Relative mean percentage change in FEV_1 (% predicted) at 6 months	The relative mean percentage change in FEV_1 (% predicted) was **0.00**	The relative mean percentage change in FEV_1 (% predicted) was **5.80 higher** (3.99 higher to 7.61 higher)	NA	647 (1 study)[1]	⊕⊕⊕⊕ **high**[3]	Result presented from once-daily dornase alfa group. Significant benefit for dornase alfa also present in twice-daily dornase alfa group
Relative mean percentage change in FVC (% predicted) at 3 months	The relative mean percentage change in FVC (% predicted) was **7.30**	The relative mean percentage change in FVC (% predicted) was **5.10 higher** (1.23 higher to 8.97 higher)	NA	318 (1 study)[4]	⊕⊕⊕⊖ **moderate**[2]	

Relative mean percentage change in FVC (% predicted) at 6 months	See comment	See comment	**MD** 3.80 (2.62 to 4.98)	647 (1 study)[1]	⊕⊕⊕⊕ **high**[3]	Mean difference between groups only presented. Result presented from once-daily dornase alfa group. Significant benefit for dornase alfa also present in twice-daily dornase alfa group
Change in quality of life - CFQ-R respiratory at 1 month	See comment	See comment	**MD** 0.84 (-10.74 to 12.42)	19 (1 cross-over study)[5]	⊕⊕⊝⊝ **low**[6,7]	Positive MD indicates an advantage for dornase alfa daily. Participants received both interventions in cross-over design.
Change in quality of life - CFQ-R respiratory (parent) at 1 month	See comment	See comment	**MD** 9.78 (-2.58 to 22.14)	19 (1 cross-over study)[5]	⊕⊕⊝⊝ **low**[6,7]	Positive MD indicates an advantage for dornase alfa daily. Participants received both interventions in cross-over design.
Number of people experiencing exacerbations at up to 2 years	**252 per 1000**	**196 per 1000** (156 to 242)	**RR 0.78** (0.62 to 0.96)	1157 (3 studies)[8]	⊕⊕⊕⊝ **moderate**[9]	RR <1 indicates an advantage for dornase alfa.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Assumed and corresponding risk not calculated for quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study
CI: confidence interval; **RR:** risk ratio **MD:** mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Additionally four trials included in analysis at one month showed a significant advantage to dornase alfa over placebo or no dornase alfa treatment (Laube 1996; Ramsey 1993; Ranasinha 1993; Shah 1995a). Three studies not included in pooled analysis showed no difference between groups in relative FEV_1(L) (Robinson 2000) and relative FEV_1 (% predicted) (Wilmott 1996) or absolute FEV_1 (% predicted) (Amin 2011) at one month. At one year, one study showed a significant advantage to dornase alfa over placebo or no dornase alfa treatment (Frederiksen 2006) and one study showed no difference between treatments (Robinson 2005). At one year, one study showed a significant advantage to dornase alfa over placebo or no dornase alfa treatment (Quan 2001) and at three years, one study showed no significant difference between treatments (Paul 2004).
2. Downgraded due to indirectness: participants in McCoy 1996 had severe lung disease (FVC below 40%).
3. No evidence of imprecision, inconsistency, indirectness, publication bias or serious risk of bias.

Summary of findings 3. Dornase alfa versus hypertonic saline

Dornase alfa compared with hypertonic saline for cystic fibrosis

Patient or population: Children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa (once daily)

Comparison: Hypertonic saline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Hypertonic Saline	Dornase alfa				
Mean relative percentage in FEV_1 (L) at 3 months	See comment	See comment	**MD** 8.00 (2.00 to 14.00)	up to 43[1,2] (1 cross-over study) (see comment)	⊕⊕⊖⊖ **low**[3,4]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean relative percentage in FVC (L) at 3 months	See comment	See comment	**MD** 0.08, (-0.02 to 0.18)	up to 43[1,2] (1 cross-over study)	⊕⊕⊖⊖ **low**[3,4]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean relative percentage in quality of life score at 3 months	See comment	See comment	**MD** 0.03, (-0.01 to 0.07)	up to 43[1,2] (1 cross-over study)	⊕⊕⊖⊖ **low**[3,4]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Number of pulmonary exacerbations at 3 months	15 exacerbations	17 exacerbations	NA (see comment)	up to 43[1,2] (1 cross-over study)	⊕⊕⊖⊖ **low**[3,4]	No difference was found in the number of pulmonary exacerbations (no statistical comparison made)

*Assumed and corresponding risk not calculated lung function and quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study.
CI: confidence interval; **MD**: mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the cross-over trial, 43 participants completed the dornase alfa arm and 40 completed the hypertonic saline arm (Suri 2001).
2. Two additional cross-over trials compared dornase alfa and hypertonic saline, no significant differences were found between the treatments for % change in FEV_1 and other primary outcomes of the review were not recorded in these trials (Adde 2004; Ballmann 2002).
3. Downgraded once for lack of applicability: Suri included children only so results are not applicable to adults (Suri 2001).
4. Downgraded once for high risk of bias due to lack of blinding.

Summary of findings 4. Dornase alfa versus mannitol

Dornase alfa compared with mannitol for cystic fibrosis

Patient or population: Children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa

Comparison: Mannitol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Mannitol	Corresponding risk Dornase Alfa				
Mean absolute change in FEV1 (L) at 3 months	See comment	See comment	**MD** 0.02 (-0.11 to 0.16)	up to 23[1] (1 cross-over study)	⊕⊕⊖⊖ **low**[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean absolute change in FVC (L) at 3 months	See comment	See comment	**MD** -0.02, (-0.23 to 0.19)	up to 23[1] (1 cross-over study)	⊕⊕⊖⊖ **low**[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Change in quality of life - CFQ-R at 3 months	See comment	See comment	**MD** 10.61 (0.27 to 20.95)	up to 23[1] (1 cross-over study)	⊕⊕⊖⊖ **low**[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Number of people experiencing exacerbations - at 3 months	**130 per 1000**	**143 per 1000** (33 to 631)	**RR 1.10** (0.25 to 4.84)	up to 23[1] (1 cross-over study)	⊕⊕⊖⊖ **low**[2,3]	RR <1 indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.

*Assumed and corresponding risk not calculated for lung function and quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study.
CFQ-R: Cystic Fibrosis Questionnaire - Revised; **CI**: confidence interval; **MD**: mean difference; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the cross-over trial, 21 participants completed the dornase alfa arm and 23 participants completed the mannitol arm (Minasian 2010).
2. Downgraded once for lack of applicability: Minasian included children only so results are not applicable to adults (Minasian 2010).
3. Downgraded once for high risk of bias due to lack of blinding.

Summary of findings 5. Dornase alfa versus dornase alfa and mannitol

Dornase alfa compared with dornase alfa and mannitol for cystic fibrosis

Patient or population: Children with cystic fibrosis

Settings: Outpatients

Intervention: Dornase alfa

Comparison: Dornase alfa and Mannitol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Dornase alfa and mannitol	Corresponding risk Dornase alfa				
Mean absolute change in FEV_1 (L) at 3 months	See comment	See comment	**MD** 0.10 (-0.06 to 0.25)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ **low**[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Mean absolute change in FVC (L) at 3 months	See comment	See comment	**MD** 0.13 (-0.11 to 0.37)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ **low**[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Change in quality of life - CFQ-R at 3 months	See comment	See comment	**MD** 10.61 (0.27 to 20.95)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ **low**[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.
Number of people experiencing exacerbations at 3 months	**261 per 1000**	**143 per 1000** (41 to 501)	**RR 0.55** (0.16 to 1.92)	up to 23[1] (1 cross-over study)	⊕⊕⊝⊝ **low**[2,3]	RR <1 indicates an advantage for dornase alfa. Participants received both interventions in cross-over design.

*Assumed and corresponding risk not calculated lung function and quality of life. Relative effect and 95% CI presented is adjusted for the cross-over design of the study.
CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. In the crossover trial, 21 participants completed the dornase alfa arm and 23 participants completed the dornase alfa plus mannitol arm (Minasian 2010).
2. Downgraded once for lack of applicability: Minasian included children only so results are not applicable to adults (Minasian 2010).
3. Downgraded once for high risk of bias due to lack of blinding.

Fazit der Autoren

Therapy with dornase alfa is associated with an improvement in lung function in short-term trials as well as longer trials lasting up to two years. Although there was no significant difference between groups in a trial lasting three years, lung function was not the primary outcome within this trial which was therefore not powered to detect differences in lung function. There was a reduction in the risk of infective exacerbations using a once-daily regimen, risk ratio (RR) 0.78 (95% confidence interval (CI) 0.62 to 0.96). Not all people with cystic fibrosis (CF) increase their lung function with dornase alfa, but the effects on lung function are seen in within one month; therefore, if dornase alfa is started for this indication, a one month trial should detect improvements in lung function. It should be noted that improvements in lung function did not predict which individuals experienced a decrease in exacerbations with dornase alfa in the single trial that examined this (Quan

2001); thus, a longer trial may be needed to assess this outcome in people with CF. The effect of dornase alfa on mortality is inconclusive due to trials of short duration.

Dornase alfa is a well-tolerated therapy with only voice alteration and rash being reported with increased frequency in groups treated with dornase alfa.

Data from comparative trials of dornase alfa and hyperosmolar agents, suggests that dornase alfa is superior to hypertonic saline in improving lung function, but there was no reported difference in the time to or frequency of pulmonary exacerbations. However, the longest trial to assess this was three months in duration, which is likely not long enough to detect differences in pulmonary exacerbations. There was no differences detected between dornase alfa and mannitol; and in the first trial to assess a combination of dornase with a hyperosmolar agent compared to either agent alone, there was no improvements noted with the combination of medications.

Kommentare zum Review

- Keine klaren Subruppenanalysen für das im AWG genannte Alter

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Smith S et al, 2022 [6].

Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis

Fragestellung

To evaluate the effects of long-term inhaled antibiotic therapy in people with CF on clinical outcomes (lung function, frequency of exacerbations and nutrition), QoL and adverse events (including drug-sensitivity reactions and survival).

Methodik

Population:

- People with CF diagnosed by clinical features associated with an abnormal sweat electrolyte test or mutations of the CFTR gene or both. All ages and all levels of severity of respiratory disease were included.

Intervention und Komparator:

- Any inhaled antibiotic (all doses and methods of inhalation) with activity against P aeruginosa given for at least three months compared to an inhaled placebo or no placebo, i.e. usual treatment (where this did not include any oral or intravenous antibiotic therapy during the trial), or another inhaled anti-pseudomonal antibiotic. Trials in which an antibiotic was tested at two or more doses are also eligible.

Endpunkte:

- Lung function, Exacerbation of respiratory infection, Nutrition, QoL, Survival, Antibiotic resistance in P aeruginosa or other organisms, Adverse events

Recherche/Suchzeitraum:

- Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 28 June 2022.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- In total, 18 trials (115 citations) with 3042 participants were included in the review

Qualität der Studien:

Studienergebnisse:

Summary of findings 1. Summary of findings: anti-pseudomonal antibiotics versus placebo

Anti-pseudomonal antibiotics compared with placebo for long-term therapy in CF

Patient population: adults and children with CF and *P aeruginosa*

Settings: outpatients

Intervention: inhaled anti-pseudomonal antibiotics

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Inhaled anti-pseudomonal antibiotics				
FEV_1 (% predicted) Follow-up: at 3 months and up to 36 months	4 trials found a significant improvement in FEV_1 with inhaled antibiotics compared to placebo, although no data were available for 3 of these. 1 trial reported that the rate of decline in FEV_1 favoured antibiotics. The remaining 6 trials showed no significant difference between inhaled antibiotics and placebo.		NA	1130 (11)	⊕⊕⊝⊝ **low**[a]	The included trials all measured FEV_1 but in different ways and for different lengths of time. It was not possible to combine the trials in a meta-analysis.
FVC (% predicted) Follow-up: at 3 months and up to 36 months	5 of the 10 trials found significant changes in FVC at the end of the trial period, favouring inhaled antibiotics when compared to placebo. 1 trial found no significant difference in absolute values of FVC % predicted between inhaled antibiotics and control but found that mean change in FVC % predicted was significantly different (favouring antibiotics). 1 trial found a combination of gentamycin and carbenicillin versus placebo to be significantly different and favouring antibiotics yet ceftazidime versus placebo was not significantly different. 3 trials found no significant difference between antibiotics and placebo with regard to FVC % predicted.		NA	1097 (10)	⊕⊕⊝⊝ **low**[a]	FVC was measured differently across the trials.
Pulmonary exacerbations: frequency of one or more hospital admissions Follow-up: over 3 months and up to 12 months	**397 per 1000**	**262 per 1000** (187 to 369 per 1000)	**RR 0.66** (0.47 to 0.93)	946 (3)	⊕⊕⊝⊝ **low**[a]	
Quality of life: lost school or working days Follow-up: over 3 months and up to 12 months	The mean number of lost school or working days in the control group was 10 days.	The mean number of lost school or working days in the inhaled antibiotic group was 5.3 days lower (8.59 lower to 2.01 lower).	NA	245 (1)	⊕⊕⊝⊝ **low**[b,c]	
Survival: number of deaths Follow-up: over 3 months and up to 12 months	**17 per 1000**	**3 per 1000** (1 to 19 per 1000)	**RR 0.17** (0.03 to 1.09)	767 (2)	⊕⊕⊝⊝ **low**[b,c]	
Antibiotic resistance: frequency of tobramycin-resistant *P aeruginosa*	**105 per 1000**	**205 per 1000** (90 to 464 per 1000)	**RR 1.95** (0.86 to 4.42)	672 (2)	⊕⊕⊕⊝ **moderate**[b]	

Follow-up: at end of trial (12 months)					
Adverse events Follow-up: at the end of the trial (84 days to 33 months)	There were no significant differences between inhaled antibiotics and placebo for auditory impairment, pneumothorax, haemoptysis. Tinnitus and voice alteration were significantly more common in the inhaled antibiotics groups.	NA	1014 (6)	⊕⊝⊝⊝ **very low**[a,c]	Rate of auditory impairment reported in 5 trials for 996 participants. Rate of pneumothorax reported in 3 trials for 558 participants. Rate of haemoptysis reported in 1 trial for 520 participants. Rate of tinnitus reported in 1 trial for 520 participants. Rate of voice alteration reported in 2 trials for 701 participants.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CF: cystic fibrosis; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RR**: risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to most trials included in the comparison being at unclear or high risk of bias. 3 trials were at high or unclear risk of bias across all domains. All the 11 trials were at high or unclear risk of bias for randomisation or allocation concealment (or both) and also blinding of participants or outcome assessors (or both).
[b]Downgraded once because of unclear risk of bias across some domains (randomisation or allocation concealment (or both) and blinding of participants or outcome assessment (or both)) of the included trials.
[c]Downgraded once due to imprecision due to low event rates.

Summary of findings 2. Summary of findings: colistimethate dry powder for inhalation (Colobreathe®) versus tobramycin for inhalation solution

Colistimethate dry powder (Colobreathe®) compared with TISfor long-term therapy in CF

Patient population: children and adults with CF and *P aeruginosa* infection

Settings: outpatients

Intervention: colistimethate dry powder for inhalation (1 1.6625 MU capsule twice daily for 24 weeks)

Comparison: TIS (3 cycles of 28 days of TIS (300 mg/5 mL) twice daily followed by a 28-day off period)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS	Colistimethate dry powder for inhalation (Colobreathe®)				
FEV_1 (% predicted): mean change from baseline Follow-up: 24 weeks	Adjusted mean difference between the groups (ITT population LOCF) for the change in FEV_1 % predicted, MD -0.98% (95% CI-2.74% to 0.86%). There was no significant difference between the 2 groups for this outcome.		NA	374 (1)	⊕⊕⊝⊝ **low**[a,b]	The data were not normally distributed and were analysed using log-transformation analysis. We have reported the results directly from the paper.
FVC (% predicted): mean change from baseline Follow-up: 24 weeks	There was no significant difference between groups for FVC % predicted in the ITT population (LOCF), MD 0.01 L (95% CI -0.09 to 0.10).		NA	374 (1)	⊕⊕⊝⊝ **low**[a,b]	The data were not normally distributed and were analysed using log-transformation analysis. We have reported the results directly from the paper.
Pulmonary exacerbations: number of pulmonary exacerbations Follow-up: 24 weeks	**262 per 1000**	**312 per 1000** (225 to 430 per 1000)	**RR 1.19** (0.86 to 1.64)	374 (1)	⊕⊕⊕⊝ **moderate**[a]	

Quality of life: adjusted mean change in CFQ-R score at the end of treatment Follow-up: 24 weeks	The adjusted mean changes at the end of the trial favoured the Colobreathe® group in terms of treatment burden (P = 0.091). This difference was significant at Week 4 (P < 0.001).		NA	374 (1)	⊕⊕⊖⊖ **low**[a,c]	The trial was not powered to detect differences in overall quality of life. Results reported directly from paper.
Survival: number of deaths Follow-up: over 3 months and up to 12 months	**10 per 1000**	**2 per 1000** (0 to 43 per 1000)	**RR 0.21** (0.01 to 4.32)	374 (1)	⊕⊕⊖⊖ **low**[a,d]	
Antibiotic resistance: change in mean MIC_{50} and MIC_{90} at the end of the trial Follow-up: 24 weeks	The mean MIC_{50} (breakpoint of ≥ 8 mg/L) changed in the TIS group by 0.5 compared to 0.0 in the Colobreathe® group. The mean MIC_{90} (breakpoint of ≥ 8 mg/L) changed in the both groups by 4.0.		NA	374 (1)	⊕⊕⊖⊖ **low**[a,c]	
Adverse events: number of treatment related adverse events Follow-up: 24 weeks	**466 per 1000**	**820 per 1000** (699 to 969 per 1000)	**RR 1.76** (1.50 to 2.08)	379 (1)	⊕⊕⊖⊖ **low**[a,d]	Treatment-related adverse events were significantly lower in the TIS group than the Colobreathe® group P < 0.0001.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CF: cystic fibrosis; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **ITT**: intention-to-treat; **LOCF**: last observation carried forward; **MIC**: minimum inhibitory concentration; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RR**: risk ratio; **TIS**: tobramycin for inhalation solution.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to an unclear or high risk of bias across 4 out of the 7 domains, particularly randomisation, allocation concealment and participant blinding.
[b]Downgraded once due to LOCF analysis increasing risk of bias.
[c]Downgraded once for imprecision; the trial was underpowered to detect differences in overall quality of life.
[d]Downgraded once for imprecision due to low event rates.

Summary of findings 3. Summary of findings: Inhaled TOBI® (IV preparation) versus tobramycin for inhalation solution

Inhaled TOBI® (IV preparation) compared with TIS for long-term therapy in CF

Patient population: adults and children with CF and *P aeruginosa*

Settings: outpatients

Intervention: inhaled tobramycin (TOBI®) (IV preparation) continuous twice-daily 80 mg

Comparison: TIS intermittent (4-weekly on-off cycles) twice-daily 300 mg/5 mL

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS intermittent	Inhaled tobramycin (IV preparation) continuous				
FEV_1 (% predicted): change from baseline Follow-up: the end of the first treatment phase (12 weeks)	The change from baseline in FEV_1 % predicted was on average 1.07% less in the TIS group than in the inhaled tobramycin (IV preparation) group, values ranged from 11.20% less to 9.06% higher.		NA	32 (1)	⊕⊖⊖⊖ **very low**[a,b]	Trial investigators provided individual participant data for lung function and we have analysed the first-period data ourselves using the generic inverse variance method in RevMan.
FVC (% predicted): change from baseline	The change from baseline in FVC % predicted was on average 0.01% more in the TIS group than in the inhaled tobramycin (IV preparation) group, values ranged from 9.48% less to 9.50% higher.		NA	32 (1)	⊕⊖⊖⊖ **very low**[a,b]	Trial investigators provided individual participant data for lung function and we have analysed the first-period data ourselves using the generic inverse variance method in RevMan.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CF: cystic fibrosis; **CI:** confidence interval; **FEV_1:** forced expiratory volume at 1 second; **FVC**: forced vital capacity; **IV**: intravenous; **NA**: not applicable; ***P aeruginosa***: *Pseudomonas aeruginosa;* **TIS**: tobramycin for inhalation solution.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Summary of findings 4. Summary of findings: tobramycin for inhalation powder versus tobramycin for inhalation solution

TIP compared with TIS for long-term therapy in CF

Patient population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: TIP twice-daily 4 capsules (total of 112 mg) (3 cycles (28 days on-drug, 28 days off-drug))

Comparison: TIS twice-daily 300 mg/5 mL

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS	TIP				
FEV_1 (% predicted): relative change from baseline Follow-up: 24 weeks	The MD between the 2 groups was 1.10 (95% CI -2.33 to 4.53) favouring TIS, but not significantly.		NA	517 (1)	⊕⊕⊕⊖ **moderate**[a]	TIP was found to be non-inferior to TIS.
FVC Follow-up: NA	Outcome not reported.				NA	
Pulmonary exacerbations: number of participants experiencing pulmonary exacerbation Follow-up: 24 weeks	**301 per 1000**	**337 per 1000** (259 to 436 per 1000)	**RR 1.12** (0.86 to 1.45)	517 (1)	⊕⊕⊕⊖ **moderate**[a]	
Quality of life	Outcome not reported.				NA	

Follow-up: NA						
Survival: number of deaths Follow-up: 24 weeks	Not calculable as there were no deaths in the TIS group. There were 3 deaths in the TIP group.		**RR4.76** (0.25 to 91.62)	517 (1)	⊕⊕⊖⊖ **low**[a,b]	
Antibiotic resistance: mean change from baseline in *P aeruginosa* sputum density Follow-up: 24 weeks	Mucoid and non-mucoid *P aeruginosa* sputum densities showed a decrease from baseline in both groups at all time points. Mean change was -1.6 versus -0.92 log_{10} CFU/g for mucoid phenotype and -1.77 versus -0.73 log_{10} CFU/g for non-mucoid phenotype.		NA	517 (1)	⊕⊕⊕⊖ **moderate**[a]	
Adverse events: number of any adverse event reported Follow-up: 24 weeks	**842 per 1000**	**901 per 1000** (842 to 968 per 1000)	**RR 1.07** (1.00 to 1.15)	517 (1)	⊕⊕⊕⊖ **moderate**[a]	A range of adverse events were reported but the only adverse events which were significantly different between the 2 groups were *favouring TIS* • cough: RR 1.56 (95% CI 1.23 to 1.96) • hoarseness: 3.56 (95% CI 1.71 to 7.43).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CF: cystic fibrosis; **CFU**: colony forming units; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RR**: risk ratio; **TIP**: tobramycin inhalation powder **TIS**: tobramycin for inhalation solution.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias within the trial. This was an open-label trial and so was at high risk of bias for blinding and had an unclear risk for randomisation and allocation concealment.
[b]Downgraded once for imprecision due to low event rates.

Summary of findings 5. Summary of findings: aztreonam lysine for inhalation versus tobramycin for inhalation solution

AZLI compared with TIS for long-term therapy in CF

Patient population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: AZLI 75 mg 3 times daily

Comparison: TIS 300 mg twice-daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS	AZLI				
FEV_1 (% predicted): mean relative change from baseline averaged across 3 cycles Follow-up: 24 weeks	The MD between groups was -3.40 (95% CI -6.63 to -0.17), favouring AZLI.		NA	268 (1)	⊕⊕⊕⊖ **moderate**[a]	
FVC Follow-up: NA	Outcome not reported.				NA	
Pulmonary exacerbations: need for additional antibiotics	**576 per 1000**	**380 per 1000** (294 to 495 per 1000)	**RR 0.66** (0.51 to 0.86)	268 (1)	⊕⊕⊕⊖ **moderate**[a]	

Follow-up: 24 weeks						
Quality of life: mean change from baseline in CFQ-R respiratory symptom scale averaged across 3 cycles Follow-up: 24 weeks	The mean (SD) change in CFQ-R score was 2.2 (17.7) in the TIS group.	The mean change in CFQ-R score in the AZLI group was 4.10 points higher (0.06 points lower to 8.26 points higher).	NA	268 (1)	⊕⊕⊕⊖ **moderate**[a]	
Survival Follow-up: 24 weeks	See comments.			268 (1)	⊕⊕⊖⊖ **low**[a,b]	2 participants died during the trial, but neither were related to treatment and the treatment group was not specified.
Antibiotic resistance: change from baseline in *P aeruginosa* CFU/g of sputum at week 24 Follow-up: 24 weeks	The mean (SD) change in log_{10} CFU/g was -0.32 (1.87) in the TIS group.	The mean change in log_{10} CFU/g in the AZLI group was 0.23 lower (0.76 lower to 0.3 log_{10} CFU/g higher).	NA	268 (1)	⊕⊕⊕⊖ **moderate**[a]	
Adverse events: number of treatment-related adverse events Follow-up: 24 weeks	**129 per 1000**	**228 per 1000** (133 to 392 per 1000)	**RR 1.77** (1.03 to 3.04)	268 (1)	⊕⊕⊕⊖ **moderate**[a]	Whilst treatment-related events were significantly more likely in the AZLI-treated group P < 0.04), the difference in serious adverse events (also more likely in the AZLI group) did not quite reach significance. No significant difference was reported for any other reported adverse event.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
AZLI: aztreonam lysine for inhalation; **CFQ-R**: cystic fibrosis questionnaire - revised; **CF**: cystic fibrosis; **CFU**: colony forming units; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable; ***P aeruginosa***: *Pseudomonas aeruginosa*;**RR**: risk ratio; **SD**: standard deviation; **TIS**: tobramycin for inhalation solution.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias within the trial. The trial was open-label with the treatments given at a different frequency and so obvious to participants. There was also an unclear risk attributed to blinding of outcome assessment.
[b]Downgraded once due to imprecision from low event rates.

Summary of findings 6. Summary of findings: amikacin liposome inhalation suspension (ALIS) versus tobramycin for inhalation solution

ALIS compared with TIS for long-term therapy in CF

Patient or population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: ALIS 590 mg once daily with eFlow® nebuliser

Comparison: TIS 300 mg twice daily via PARI LC® PLUS nebuliser

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS	ALIS				
FEV_1: LS mean FEV_1 (L) Follow-up: 168 days	The difference in LS mean FEV_1 (L) adjusted for treatment and randomisation strata, at the end of treatment was MD −1.31% (95% CI, −4.95 to 2.34; P = 0.48).		NA	262 (1)	⊕⊕⊕⊖ **moderate**[a]	This analysis was carried out on the per-protocol data. The lower CI was above -5% indicating non-inferiority of ALIS to TIS.
FVC Follow-up: NA	Outcome not reported.				NA	
Pulmonary exacerbations: frequency of pulmonary exacerbations	There were more participants in the ALIS group experiencing an exacerbation than in		NA	294 (1)	⊕⊕⊕⊖ **moderate**[a]	The study also reported on hospitalisations and found that there was no

Follow-up: 168 days	pared to 51.4% in the TIS group, P = 0.02).					difference, RR 0.82 (95% CI 0.50 to 1.33). Time to first exacerbation was also shorter in the ALIS group, HR 1.51 (95% CI 1.07 to 2.13) P = 0.03.
Quality of life: change in CFQ-R domain scores (mean CFQ-R score) Follow-up: 168 days	There was no difference in change in CFQ-R scores between groups at the end of the study across any domain.		NA	294 (1)	⊕⊕⊕⊖ **moderate**[a]	
Survival Follow-up: NA	Outcome not reported.				NA	No deaths were reported in either group for the duration of the study (Bilton 2020).
Antibiotic resistance: change from baseline in *P aeruginosa* CFU/g of sputum density Follow-up: 168 days	LS mean difference was no different between groups at the end of the study P = 0.13		NA	259 (1)	⊕⊕⊕⊖ **moderate**[a]	The authors also report that mean *P aeruginosa* sputum densities were below baseline level at day 168 in both the ALIS group and the TIS group (Bilton 2020).
Adverse events: number of participants experiencing any TEAE Follow-up: 168 days	**788 per 1000**	**1000 per 1000** (638 to 1000 per 1000)	**RR 1.47** (0.81 to 2.66)	294 (1)	⊕⊕⊕⊖ **moderate**[a]	There were no differences between groups by severity of TEAE.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ALIS: amikacin liposome inhalation solution; **CFU** colony forming units; **CF**: cystic fibrosis; **CFQ-R**: cystic fibrosis questionnaire - revised; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **HR**: hazard ratio; **LS**: least squares; **MD**: mean difference; **NA**: not applicable; ***P aeruginosa***: *Pseudomonas aeruginosa;* **RR**: risk ratio; **TEAE**: treatment-related adverse event; **TIS**: tobramycin for inhalation solution.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias within the trial being unclear or high across all domains, largely due to the trial being open label with unclear process for generation of sequence and allocation concealment.

Summary of findings 7. Summary of findings: levofloxacin for inhalation solution versus tobramycin for inhalation solution

LIS compared with TIS for long-term therapy in CF

Patient population: adults and children aged over 12 with CF and *P aeruginosa*

Settings: outpatients

Intervention: LIS (Aeroquin™, MP376, APT-1026) 240 mg (2.4 mL of 100 mg per mL solution) twice daily

Comparison: TIS 300 mg/5 mL twice daily

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk TIS	Corresponding risk LIS				
FEV_1 (% predicted): relative mean change from baseline Follow-up: 6 months	The mean (SD) change in % predicted FEV_1 was -1.5 (14.8) in the TIS group.	The mean change in % predicted FEV_1 in the LIS group was 0.30 higher (3.02 lower to 3.62 higher).	NA	282 (1)	⊕⊕⊕⊕ **high**	
FVC(% predicted): relative mean change from baseline Follow-up: 6 months	The mean (SD) change in FVC % predicted was -1.3 (12.8) in the TIS group.	The mean change in FVC % predicted in the LIS group was 0.60 higher (2.23 lower to 3.43 higher).	NA	282 (1)	⊕⊕⊕⊕ **high**	
Pulmonary exacerbations:	**280 per 1000**	**173 per 1000** (112 to 274 per 1000)	**RR 0.62** (0.40 to 0.98)	282 (1)	⊕⊕⊕⊕ **high**	

number of hospitalisations due to respiratory exacerbations Follow-up: 6 months					
Quality of life: change from baseline in CFQ-R Follow-up: 6 months	The trial reported that scores in the respiratory domain of the CFQ-R were similar in the 2 groups at baseline, increased in the LIS group and decreased in the TIS group at day 28 and were similar again by the end of the trial.		NA	282 (1)	⊕⊕⊙⊙ **low**[a,b]	No data could be entered into analysis.
Survival Follow-up: NA	Outcome not reported.				NA	
Antibiotic resistance: mean change in *P aeruginosa* sputum density (log_{10} CFU/g) Follow-up: 6 months	The mean (SD) sputum density in the TIS group was -0.25 (1.76) log_{10} CFU/g.	The mean sputum density in the LIS group was 0.12 higher (0.31 log_{10} CFU/g lower to 0.55 log_{10} CFU/g higher).	NA	282 (1)	⊕⊕⊕⊕ **high**	
Adverse events: number of treatment-related adverse events Follow-up: 6 months	Significantly fewer participants in the LIS group reported epistaxis, RR 0.2 (95% CI 0.04 to 1.00), general malaise, RR 0.1 (95% CI 0.01 to 0.83) and increased blood glucose, RR 0.28 (95% CI 0.08 to 0.94). Significantly more participants in the LIS group reported dysgeusia, RR 46.25 (95% CI 2.88 to 742). No other differences were noted.		NA	282 (1)	⊕⊕⊕⊕ **high**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CF: cystic fibrosis; **CFU**: colony forming units; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **LIS**: levofloxacin for inhalation solution; **NA**: not applicable; ***P aeruginosa***: *Pseudomonas aeruginosa*;**RR**: risk ratio; **TIS**: tobramycin for inhalation solution.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to indirectness. Quality of life was measured by the CFQ-R score but no data were provided, just a summary. It is unclear which participants were included in this outcome.
[b]Downgraded once due to publication bias as the results were not presented in full for this outcome.

Summary of findings 8. Summary of findings: continuous cycles alternating aztreonam lysine for inhalation with tobramycin for inhalation solution versus continuous cycles alternating placebo with tobramycin for inhalation solution

Continuous AZLI/TIScompared with continuous placebo/TIS (i.e. intermittent TIS) for long-term therapy in CF

Patient population: children and adults with CF and *P aeruginosa*

Settings: outpatients

Intervention: continuous alternating cycles of AZLI (75 mg (diluted in 0.17% NaCL) 3 times-daily) and TIS (300 mg/5 mL twice-daily)

Comparison: alternating cycles of placebo (lactose monohydrate and sodium chloride reconstituted with the same diluent used for AZLI 3 times daily) and TIS (300 mg/5 mL twice-daily)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TIS/placebo	AZLI/TIS				
FEV_1 (% predicted): mean change from baseline (average values across the end of the 3 treatment cycles) Follow-up: 6 months (24 weeks)	The change from baseline in FEV_1 % predicted was on average 1.33% more in the AZLI/TIS group than in the in the TIS/placebo group, values ranged from 0.51% lower to 3.17% higher.		NA	90 (1)	⊕⊕⊙⊙ **low**[a,b]	
FVC	Outcome not reported.				NA	

Follow-up: NA						
Pulmonary exacerbations: rate of PDEs per participant year Follow-up: 24 weeks	**489 per 1000**	**347 per 1000** (210 to 577 per 1000)	**RR 0.71** (0.43 to 1.18)	90 (1)	⊕⊕⊙⊙ **low**[a,b]	The rate of PDEs was lower in the AZLI/TIS group (1.31 PDEs per participant year) than in the placebo/TIS group (1.76 PDEs per participant year). The difference between the groups was not reported to be significant (P = 0.25, RR 0.74 (95% CI 0.45 to 1.24)).
Quality of life: CFQ-R respiratory symptom scores averaged from weeks 4, 12 and 20 Follow-up: 24 weeks	Scores improved by a mean (SE) 1.00 (1.74) in the AZLI/tobramycin group, they worsened by a mean (SE) -2.06 (1.63) in the placebo/TIS group. The difference between the groups was not found to be significant, MD 3.06 (95% CI -1.61 to 7.73).		NA	90 (1)	⊕⊕⊙⊙ **low**[a,b]	
Survival Follow-up: NA	Outcome not reported.				NA	
Antibiotic resistance: mean change from baseline in *Paeruginosa* sputum density (CFU/g) Follow-up: 24 weeks	Adjusted mean changes from baseline sputum *Paeruginosa* density after each course of AZLI/placebo or TIS during the comparative phase were small (0.36 to -0.55 $\log_{10}$ CFU/g) and differences between treatment groups were not statistically significant.		NA	87 (1)	⊕⊕⊙⊙ **low**[a,b]	Results reported narratively from the paper.
Adverse events: any adverse event in the comparative phase Follow-up: 24 weeks	**978 per 1000**	**949 per 1000** (880 to 1000)	**RR 0.97** (0.90 to 1.05)	88 (1)	⊕⊕⊙⊙ **low**[a,b]	A range of adverse events were reported but the only adverse events which were significantly different between the 2 groups were: *favouring continuous treatment* • dyspnoea: RR 0.59 (95% CI 0.35 to 1.01); • decrease in exercise tolerance: RR 0.27 (95% CI 0.08 to 0.90); • decreased appetite: RR 0.34 (95% CI 0.14 to 0.85) *favouring intermittent treatment* • nasal congestion: RR 3.01 (95% CI 1.04 to 8.74).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AZLI: inhaled aztreonam lysine; **CF**: cystic fibrosis;**CFQ-R**: cystic fibrosis questionnaire - revised; **CFU**: colony forming units; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **NA**: not applicable; **PDE**: protocol-defined exacerbation; ***P aeruginosa***: *Pseudomonas aeruginosa*; **RR**: risk ratio; **SE**: standard error; **TIS**: tobramycin for inhalation solution.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once due to risk of bias being unclear across 5 of the domains around randomisation, allocation concealment, blinding of participants and incomplete outcome data.
[b]Downgraded once due to imprecision as trial enrolment was limited and the trial was underpowered.

Anmerkung/Fazit der Autoren

The practise of prescribing inhaled antibiotics for many years to suppress chronic infection in people with cystic fibrosis (CF) is widespread. At present, the most commonly-used drugs are tobramycin and colistin (Colobreathe®). Other emerging treatments are aztreonam, ciprofloxacin, levofloxacin, amikacin and combined fosfomycin-tobramycin. This review is restricted to randomised trials designed to test the benefit of these drugs for periods of three months or more. The review found limited evidence that inhaled antibiotic treatment of chronic infection with Pseudomonas aeruginosa (P aeruginosa) is of some benefit in

terms of improvement in lung function and reduction in exacerbations of respiratory infection for up to 33 months (the duration of the longest trial). In addition, there do not seem to be severe or frequent adverse effects. The best evidence is for the use of tobramycin which was studied in 12 trials. However, the findings of this review raise some issues to consider when prescribing this treatment long-term.

1. There is a lack of evidence of benefit in terms of survival, quality of life or nutritional outcomes.

2. The level of benefit is uncertain as some trials are small and prone to error. We have included several larger trials, but heterogeneity in measurement and reporting of outcomes is such that very little pooled analysis was possible.

3. The major evidence for benefit is for use for up to six months, hence uncertainty about any longer-term benefit remains;

4. There is no adequate evidence from randomised controlled trials to support the use of colistin.

Kommentare zum Review

- Keine klaren Subruppenanalysen zu Kindern/Erwachsenen.

3.2 Systematische Reviews

Wu HX et al., 2019 [8].

Efficacy and Safety of CFTR Corrector and Potentiator Combination Therapy in Patients with Cystic Fibrosis for the F508del-CFTR Homozygous Mutation: A Systematic Review and Meta-analysis.

Fragestellung

to assess the efficacy and safety of CFTR corrector and potentiator combination therapy on ppFEV1, BMI and CFQ-R respiratory domain score in CF patients with the F508del-CFTR homozygous mutation.

Methodik

Population:

- CF patients with the F508del-CFTR mutation

Intervention/Komparator:

- CFTR corrector and potentiator combination therapy vs. Placebo

Endpunkte:

- ppFEV1, the CFQ-R respiratory domain score, BMI, AEs

Recherche/Suchzeitraum:

- Web of Science, Cochrane Central Register of Controlled Trials, Medline, and Embase to October 26, 2018

Qualitätsbewertung der Studien:

- Cochrane Approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Five RCTs, including a total of 1637 participants with the F508del-CFTR homozygous mutation
- 1035 were allocated to receive combination therapy, while 582 were administered placebo

Qualität der Studien:

- All RCTs were at low risk of bias. No study was excluded for low quality (GRADE).

Studienergebnisse:

- Primary analysis revealed that combination therapy increased ppFEV1 (MD 2.38, 1.62–3.15,
- P\0.00001), improved CFQ-R respiratory domain score (MD2.59, 0.96–4.22, P = 0.002) and BMI (MD 0.21, 0.03–0.39, P = 0.02) in CF patients with the F508del-CFTR mutation.
- In secondary analysis, combination therapy had no impact on the number of participants reporting AEs (OR 0.88, 0.58–1.33, P = 0.53), but increased the proportion of discontinued treatments due to AEs (OR 2.71, 1.3–5.63, P = 0.008).

Anmerkung/Fazit der Autoren

This study shows that CFTR corrector and potentiator combination therapy has an acceptable safety profile and shows improvement in lung function, nutritional status and clinical score in CF subjects homozygous for F508del. It also indicates the combination therapy potential as a novel, effective regimen for CF with F508del homozygous mutation.

Kommentar zum Review

- Keine Subgruppenanalysen nach Alter

3.3 Leitlinien

AWMF, 2020 [2].

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

S3-Leitlinie: Mukoviszidose bei Kindern in den ersten beiden Lebensjahren, Diagnostik und Therapie.

Zielsetzung/Fragestellung

Damit die Vorteile des neu eingeführten Neugeborenen-Screenings durch die frühere Diagnose und den früheren Therapiebeginn für die Patienten tatsächlich in Lebenszeit und – qualität umgesetzt werden können und um die Versorgung von Kindern mit Mukoviszidose in den ersten beiden Lebensjahren zu optimieren, soll mit dieser Leitlinie eine Orientierungshilfe für die sinnvolle und notwendige Diagnostik und Behandlung zur Verfügung gestellt werden.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- systematische Literaturrecherchen in der MEDLINE und der Cochrane Library: 2017

LoE/GoR

Evidenzlevel	Therapiestudien (auch Beobachtungsstudien)	Diagnostikstudien
1a	Systematischer Review von RCTs	Systematischer Review von Level 1 Diagnostikstudien
1b	Einzelne RCTs	Kohortenstudien mit guten Referenzstandards zur Validierung eines diagnostischen Tests
2a	Systematischer Review von Kohortenstudien	Systematischer Review von Level 2 Diagnostikstudien
2b	Einzelne Kohortenstudien	Explorative Kohortenstudien mit guten Referenzstandards
3a	Systematische Reviews von Fallkontrollstudien	Systematische Reviews von Level 3 Diagnostikstudien
3b	Einzelne Fallkontrollstudien	Nicht konsekutiv durchgeführte Studie oder Studie ohne konsistent angewandte Referenzstandards
4	Fallserien; Grundlagenarbeiten	Fallkontrollstudien mit schlechtem oder nicht-unabhängigem Referenzstandard
5	Expertenmeinung, (nicht systematischer) Review	Expertenmeinung

Bei methodischen Mängeln oder hohem Verzerrungsrisiko wurde dem Evidenzlevel ein „-“ beigefügt.

Empfehlungsgrad	Definition
A	Starke Empfehlung (soll)
B	Empfehlung (sollte)
0	Empfehlung offen (kann)

Empfehlungen

Wann und wie sollte mit der Therapie begonnen werden?

- Physiotherapie soll zeitnah nach Diagnosestellung begonnen werden. [Empfehlungsgrad: A]
- Bestandteile der Therapie sollten die Sekretmobilisation, die Förderung körperlicher Aktivität und die Schulung der Inhalationstherapie sein, insbesondere die Anleitung der Sorgeberechtigten in die selbständige Durchführung. [Empfehlungsgrad: B]
- Die physiotherapeutischen Behandlungen sollen von Physiotherapeuten durchgeführt werden, die eine Zusatzqualifikation in atemtherapeutischen Techniken erworben haben, z.B. in Deutschland „Grundkurs Physiotherapie bei chronischen Lungenerkrankungen und Mukoviszidose“. [Empfehlungsgrad: A]
- Eine Inhalation mit atemwegserweiternden Medikamenten (z.B. Salbutamol) kann vor der Physiotherapie durchgeführt werden. [Empfehlungsgrad: 0]
- Inhalation mit Dornase alfa kann durchgeführt werden. [Empfehlungsgrad 0]
- Eine Inhalation von hypertoner Kochsalzlösung soll durchgeführt werden. [Empfehlungsgrad A]
- Beta-2-Mimetika sollten vorher angewendet werden, wenn es klinische Hinweise auf eine Bronchialobstruktion gibt. [Empfehlungsgrad B]
- Inhalationen mit kurzwirksamen ß2-Sympathomimetika können durchgeführt werden. [Empfehlungsgrad: 0]
- Bei Erstnachweis von S. aureus (Penicllin- oder Methicillin-sensibel oder Methicillin-resistenter S. aureus; PSSA, MSSA oder MRSA) soll eine antibiotische Therapie mit gegen S. aureus empfohlenen, sensibel getesteten Antibiotika erfolgen. [Empfehlungsgrad A]
- Bei wiederholtem Nachweis von S. aureus (PSSA, MSSA oder MRSA) soll nur bei pulmonaler Exazerbation antibiotisch behandelt werden. [Empfehlungsgrad A]
- Eine antibiotische Dauerprophylaxe soll nicht durchgeführt werden [Empfehlungsgrad A]
- Bei Erstnachweis von H. influenzae soll eine antibiotische Therapie mit gegen H. influenzae gerichteten Antibiotika durchgeführt werden. [Empfehlungsgrad A]
- Bei Erregern wie S. maltophilia und A. xylosoxidans sollte eine antibiotische Therapie mit gegen die entsprechenden Erreger gerichteten Antibiotika durchgeführt werden. [Empfehlungsgrad B]
- Bei wiederholtem Nachweis dieser Erreger soll bei pulmonaler Exazerbation antibiotisch behandelt werden. [Empfehlungsgrad A]
- Eine prophylaktische antibiotische Therapie, um eine Kolonisation mit diesen gramnegativen Erregern zu verhindern, sollte nicht durchgeführt werden. [Empfehlungsgrad B]
- Bei erstem Nachweis von Pseudomonas aeruginosa soll eine frühe Eradikation mittels Tobramycin inhalativ für 4 Wochen ODER mittels Ciprofloxacin p.o kombiniert mit Colistin inhalativ über 3 Wochen erfolgen. Für den Fall, dass eine Inhalation nicht möglich ist, sollte eine intravenöse Kombinationstherapie als Möglichkeit in Betracht

gezogen werden (Übernommen aus S3 – Leitlinie „Lungenerkrankung bei Mukoviszidose“, Modul 1) [Empfehlungsgrad: A]

- Bei Patienten mit chronischer Pseudomonas aeruginosa-Infektion soll eine inhalative antibiotische Suppressionstherapie durchgeführt werden (Übernommen aus S3 – Leitlinie „Lungenerkrankung bei Mukoviszidose“, Modul 2) [Empfehlungsgrad: A]
- Eine generelle Therapie der Lungenerkrankung bei Mukoviszidose sollte weder mit inhalativen noch mit oralem NAC erfolgen. [Empfehlungsgrad B]
- Eine Nasenspülung mit physiologischer Kochsalzlösung sollte regelmäßig durchgeführt werden. [Empfehlungsgrad B]
- Wegen des unklaren Sicherheitsprofils und der Notwendigkeit von Spiegelbestimmungen sollte eine Langzeittherapie mit Ibuprofen nicht durchgeführt werden. [Empfehlungsgrad B]
- Eine Langzeittherapie mit Montelukast soll bei einer alleinigen Indikation Mukoviszidose nicht durchgeführt werden. [Empfehlungsgrad A]
- Eine Langzeittherapie mit inhalativen Steroiden soll wegen fehlender Wirksamkeit und wegen möglicher Nebenwirkungen bei einer alleinigen Indikation Mukoviszidose nicht durchgeführt werden. [Empfehlungsgrad A]
- Eine Langzeitbehandlung mit oralen Steroiden soll wegen der damit verbundenen Nebenwirkungen bei einer alleinigen Indikation Mukoviszidose nicht durchgeführt werden. [Empfehlungsgrad A]

Mutationsspezifische Therapien (CFTR-Modulatoren)

Das bessere Verständnis der Biologie und Funktion des CFTR Proteins hat in den letzten Jahren zur Zulassung mutationsspezifische Therapien für Kinder über zwei Jahren u.a.

für Patienten mit homozygoter F508del-Mutation und Gatingmutationen geführt [5]. Eine mutationsspezifische Therapie bei Kindern in den ersten Lebensjahren ist mit der Hoffnung verbunden, die frühe Lungenerkrankung und die exokrine Pankreasfunktion zu verbessern. Dem stehen offene Fragen nach Sicherheit, Wirksamkeit und altersadaptierter Dosierung und Applikationsform gegenüber. Für Kinder in den ersten beiden Lebensjahren Altersgruppe liegen nur Studienergebnisse für Ivacaftor vor.

Ivacaftor: Für Kinder zwischen 12 und 24 Monaten mit mindestens einer Gating Mutation (G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, oder G1349D) und einem Gewicht von mindestens sieben kg liegt eine offene, nicht randomisierte Studie mit 19 Studienteilnehmern und einer Studiendauer von 24 Wochen (ARRIVAL, [243], Evidenzlevel 2b) vor. Als wichtigste Nebenwirkung fand sich ein Transaminasenanstieg >5xULN in 11,1% (2/18). Der mittlere Abfall der Chloridkonzentration im Schweiß nach 24 Wochen lag bei – 73,5 mmol/l. Es wurde ein Anstieg der faekalen Pankreaselastase im Stuhl bei sechs von neun Patienten von < 50µg/g Stuhl auf ≥ 200µg/g Stuhl und ein Abfall erhöhter Trypsin, Lipase und Amylasewerte im Serum berichtet. Die Studienergebnisse haben zu einer Zulassung durch die European Medicines Agency im November 2018 geführt.

Empfehlung: Kinder im Alter zwischen 12-24 Monaten mit mindestens einer Gating Mutation (G551D, G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, oder G1349D) und einem Gewicht von mindestens 7 kg sollten Ivacaftor als mutationsspezifische Therapien erhalten. [Empfehlungsgrad B]

AWMF, 2022 [1].

„Lungenerkrankung bei Mukoviszidose“: Pseudomonas aeruginosa

Zielsetzung/Fragestellung

Die vorliegende Leitlinie soll zur weiteren Optimierung der Versorgung von Patient:innen mit Mukoviszidose beitragen, i.e. Verbesserung der Lebensqualität von Patient:innen mit Mukoviszidose durch ein späteres Einsetzen der chronischen PA-Infektion und weniger Exazerbationen bei einem möglichst minimierten Therapieregime.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.
- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Der Suchzeitraum war vom 20.3.2014-18.3.2019 und in einer Update-Recherche bis zum 11.5.2020.

LoE

- Bei Therapiestudien erhielten systematische Reviews von randomisierten klinischen Studien bzw. einzelne RCTs den Evidenzlevel 1, Systematische Reviews von prospektiven Studien bzw. einzelne prospektive Kohortenstudien den Evidenzlevel 2, systematische Reviews von retrospektiven Studien bzw. retrospektive Studien (z.B. Registerauswertungen) den Evidenzlevel 3 usw.

GoR

- A Starke Empfehlung (soll)
- B Empfehlung (sollte)
- 0 Empfehlung offen (kann)

Empfehlungen

05 Eradikationstherapie

05.1 Welche antibiotischen Behandlungsmöglichkeiten werden für Patient:innen mit erstem PA-Nachweis in den unteren Atemwegen empfohlen (für die oberen Atemwege s. Kapitel 11)

Empfehlungen

Eine Eradikation **soll** durchgeführt werden. Die Eradikationstherapie soll nicht später als 4 Wochen nach einem PA-Erstnachweis beginnen.

Empfehlungsgrad A
(Konsensstärke: starker Konsens)

Die Eradikation **kann** mittels Tobramycin inhalativ für 4 Wochen

ODER mittels Ciprofloxacin p.o. über 3 Wochen kombiniert mit Colistin inhalativ über 3 Monate durchgeführt werden.

Empfehlungsgrad 0
(Konsensstärke: Konsens)

Eine intravenöse Therapie kann erwogen werden.

Empfehlungsgrad: 0
(Konsensstärke: Konsens)

Falls eine Inhalation nicht möglich ist, **soll** eine intravenöse Kombinationstherapie durchgeführt werden. Zu Dosierungen und Therapiedauer der einzelnen Antibiotika s. Tabelle 5.1.
Empfehlungsgrad: A
(Konsensstärke: Konsens)

Zusammenfassung: Die Durchführung einer Therapie zur Eradikation von P. aeruginosa ist besser als keine Therapie ([85-89] Evidenzlevel 1). Bisher wurden verschiedene Strategien zur Eradikation von P. aeruginosa beschrieben. Diese unterscheiden sich in der Wahl der Antibiotika, der Dosis und Dauer der Therapie. Die Medikamente wurden inhalativ, oral oder intravenös oder in verschiedenen Kombinationen verwendet. Die jeweiligen Eradikationsraten variieren in Abhängigkeit vom Nachbeobachtungszeitraum. In den bislang verfügbaren Studien konnte keine Überlegenheit eines Eradikationsschemas gezeigt werden ([86] Evidenzelevel 1). Für die Kombinationstherapie mit Ciprofloxacin und Colistin gibt es Hinweise, dass bei wiederholtem P. aeruginosa Nachweis eine Therapie über 3 Monate (dänisches Schema) wirksamer ist als eine über 3 Wochen ([101, 102] Evidenzlevel 2).

- Für die Inhalationstherapie mit Tobramycin wurde gezeigt, dass die Inhalation über 56 Tage keinen Vorteil gegenüber einer Dauer von 28 Tagen bringt ([91], Evidenzlevel 1).
- Die zusätzliche Gabe von Ciprofloxacin zu einer Tobramycin-Inhalation führte zu keiner Verbesserung der Eradikationsrate ([93] Evidenzlevel 1).
- Die intravenöse Gabe von Ceftazidim und Tobramycin führt im Vergleich zur oralen Gabe von Ciprofloxacin über 12 Wochen zu keiner besseren Eradikationsrate ([97] Evidenzlevel 1).
- Es gibt insgesamt nur eine schwache Evidenz über die Wirksamkeit intravenöser Therapien bei Erstnachweis ([97] Evidenzlevel 1; [98];[99] Evidenzlevel 2).

05.2 Sind zur Eradikationstherapie intravenöse, orale und inhalative Antibiotika beziehungsweise deren Kombination gleichermaßen wirksam? Bei welchen Patient:innen sollte primär intravenös therapiert werden?

Empfehlungen

Bei Patient:innen mit pulmonaler Exazerbation im Rahmen des ersten *P.*-

aeruginosa-Nachweises **soll** primär eine intravenöse Therapie durchgeführt werden.

Empfehlungsgrad A
(Konsensstärke: starker Konsens)

Anschließend zum besseren Erfolg der Eradikation kann eine Therapie mit Tobramycin inhalativ (4 Wochen) oder Colistin inhalativ (3 Monate) und Ciprofloxacin p.o. (3 Wochen) durchgeführt werden.

Empfehlungsgrad: 0
(Konsensstärke: Konsens)

05.3 Bei welchen Patient:innen sollte bei Erstnachweis einer PA-Infektion eine sequentielle Kombinationstherapie aus einem intravenösen Antibiotikum und einem inhalativen Antibiotikum erfolgen?

Empfehlung:

Es gibt keine Patient:innengruppe, bei der eine sequentielle Kombinationstherapie durchgeführt werden sollte.

Bei Patient:innen mit pulmonaler Exazerbation **kann** im Rahmen des *P.-aeruginosa*-Erstnachweises eine sequentielle Kombination aus einem intravenösen und einem inhalativen Antibiotikum verabreicht werden.

Empfehlungsgrad: 0
(Konsensstärke: Konsens)

05.6 Spielt das Alter der Patient:innen eine Rolle für das Therapieregime? Welche Dosierung sollte eingesetzt werden, welche Dosisintervalle sind sinnvoll?

Empfehlungen

Eine antibiotische Therapie **soll** hinsichtlich Dosierung und Dosierungsintervall laut Fachinformation durchgeführt werden.

Empfehlungsgrad: A
(Konsensstärke: Konsens)

Bei Säuglingen und kleinen Kindern **kann** eine inhalative Antibiotikatherapie über eine Maske erfolgen.

Empfehlungsgrad: 0
(Konsensstärke: Konsens)

Zu Beginn der Eradikationstherapie **soll** die Inhalationstechnik überprüft werden.

Empfehlungsgrad: A
(Konsensstärke: Konsens)

Ist eine Inhalation nicht möglich bzw. kann eine korrekte Inhalationstechnik nicht sichergestellt werden, **soll** eine intravenöse Antibiotikatherapie erfolgen.

Empfehlungsgrad: A
(Konsensstärke: Konsens)

06 Inhalative Suppressionstherapie

06.1 Welche Indikation gibt es für die inhalative Suppressionstherapie?

Empfehlung

Eine inhalative Suppressionstherapie **soll** bei Patient:innen mit chronischer *Pseudomonas aeruginosa*-Infektion durchgeführt werden.

Empfehlungsgrad: A
(Konsensstärke: starker Konsens)

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2023) am 05.10.2023

#	Suchfrage
1	[mh "cystic fibrosis"]
2	("cystic fibrosis"):ti,ab,kw
3	Mucoviscidos*s:ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Oct 2018 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 05.10.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"Cystic fibrosis" [mh]
2	Cystic fibrosis[tiab]
3	Mucoviscidos*[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR

#	Suchfrage
	proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
6	(#5) AND ("2018/10/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 05.10.2023

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"Cystic fibrosis" [mh]
2	Cystic fibrosis[tiab]
3	Mucoviscidos*[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR* recommendation*[ti])
6	(#5) AND ("2018/10/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 06.10.2023

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), Gesellschaft für Pädiatrische Pneumologie (GPP).** Lungenerkrankung bei Mukoviszidose: Pseudomonas aeruginosa; S3-Leitlinie, Langfasung [online]. AWMF-Registernummer 026-022. Redaktionelle Änderungen am 07.02.23. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2022. [Zugriff: 06.10.2023]. URL: https://register.awmf.org/assets/guidelines/026-022l_S3_Lungenerkrankung-bei-Mukoviszidose-Pseudomonas-aeruginosa__2023-02_02.pdf.
2. **Gesellschaft für Pädiatrische Pneumologie (GPP), Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ).** Mukoviszidose bei Kindern in den ersten beiden Lebensjahren, Diagnostik und Therapie; S3-Leitlinie, Langfasung [online]. AWMF-Registernummer 026-024. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2020. [Zugriff: 06.10.2023]. URL: https://register.awmf.org/assets/guidelines/026-024l_S3_Mukoviszidose-Kinder-in-den-ersten-beiden-Lebensjahren-Diagnostik-Therapie_2020-03_1_01.pdf.
3. **Holland P, Jahnke N.** Single versus combination intravenous anti-pseudomonal antibiotic therapy for people with cystic fibrosis. Cochrane Database of Systematic Reviews [online]. 2021(6):Cd002007. URL: http://dx.doi.org/10.1002/14651858.CD002007.pub5.
4. **Nevitt SJ, Thornton J, Murray CS, Dwyer T.** Inhaled mannitol for cystic fibrosis. Cochrane Database of Systematic Reviews [online]. 2020(5):Cd008649. URL: http://dx.doi.org/10.1002/14651858.CD008649.pub4.
5. **Skilton M, Krishan A, Patel S, Sinha IP, Southern KW.** Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. Cochrane Database of Systematic Reviews [online]. 2019(1):Cd009841. URL: http://dx.doi.org/10.1002/14651858.CD009841.pub3.
6. **Smith S, Rowbotham NJ.** Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. Cochrane Database of Systematic Reviews [online]. 2022(11):Cd001021. URL: http://dx.doi.org/10.1002/14651858.CD001021.pub4.
7. **Southern KW, Murphy J, Sinha IP, Nevitt SJ.** Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). Cochrane Database of Systematic Reviews [online]. 2020(12):Cd010966. URL: http://dx.doi.org/10.1002/14651858.CD010966.pub3.
8. **Wu HX, Zhu M, Xiong XF, Wei J, Zhuo KQ, Cheng DY.** Efficacy and safety of CFTR corrector and potentiator combination therapy in patients with cystic fibrosis for the F508del-CFTR homozygous mutation: a systematic review and meta-analysis. Adv Ther 2019;36(2):451-461.
9. **Yang C, Montgomery M.** Dornase alfa for cystic fibrosis. Cochrane Database of Systematic Reviews [online]. 2021(3):Cd001127. URL: http://dx.doi.org/10.1002/14651858.CD001127.pub5.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2023-B-257-z

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Datum der Erstellung	3. November 2023

Indikation
„[…]for the treatment of cystic fibrosis (CF) in patients aged 2 to less than 6 years who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene“
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Die Mukoviszidose ist eine chronisch-progrediente, genetisch determinierte Erkrankung. Durch verschiedene Mutationen im „cystic fibrosis transmembrane conductance regulator (CFTR)“-Gen kommt es zu einer Fehlfunktion des CFTR-Proteins, einem Salzkanal. Dies führt zu Veränderungen des Chloridtransportes in verschiedenen Zelltypen und zu einer progredienten Funktionseinschränkung in multiplen Organen. Vor allem betroffen sind obere und untere Atemwege, Leber und Gallenwege, Pankreas, Darm, Geschlechtsorgane und Schweißdrüsen. Die hieraus resultierenden Probleme für den individuellen Patienten sind unterschiedlich stark ausgeprägt, sodass die rein symptomatische Therapie sich bislang in ihrer Intensität an dem aktuellen Gesundheitszustand des jeweiligen Kindes orientiert. Entsprechend der S2-Leitlinie zur Diagnostik und Therapie der CF in den ersten beiden Lebensjahren (1) gibt es Therapieempfehlungen, die für alle Kinder mit CF gelten und die mit entsprechender Literatur in der vorgenannten Leitlinie übersichtlich dargestellt und zusammengefasst sind. Kurz zusammengefasst gehören dazu: Enzymersatztherapie und Substitution fettlöslicher Vitamine, ggf. Therapie eines Diabetes mellitus, hochkalorische Ernährung, Sekretolyse mittels Inhalation und Atemtherapie sowie antibiotische Therapie bei Infektionen. Damit hat sich die Lebenserwartung in den letzten Jahren deutlich verbessert, nichtsdestotrotz ist sie ohne kausale Therapeutika wie CFTR-Modulatoren weiter gegenüber der Normalbevölkerung eingeschränkt. In den vergangenen Jahren ist nun diese neue Medikamentenklasse der CFTR-Modulatoren entwickelt worden, die CFTR-mutationsabhängig eine Verbesserung der CFTR-Funktion bewirken. Damit können die durch Fehlfunktion ausgelösten Symptome verbessert und chronische Schäden verringert werden. Aktuell stehen im Vorschulalter folgende CFTR-modulierende Therapien zur Verfügung: - Ivacaftor (Kalydeco) ab dem Alter von 4 Monaten bei Kindern mit mind. einer der folgenden Mutationen: R117H oder eine der folgenden Gating-Mutationen G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R. - Lumacaftor / Ivacaftor (Orkambi) ab dem Alter von 1 Jahr bei Kindern, die homozygot für die Mutation F508del (F/F) sind. Ein möglichst frühes Eingreifen in das Fortschreiten dieser schweren Erkrankung macht medizinisch außerordentlich Sinn, um strukturelle Schäden in den verschiedenen betroffenen Organen zu verhindern. Dies zeigt sich auch an der Tatsache, dass eine initial schlechtere Lungenfunktion im Kindesalter ein wichtiger Prädiktor für einen schlechteren Krankheitsverlauf im weiteren Leben darstellt (6, 7). Best-supportive-care bei CF beinhaltet bisher ausschließlich symptomatische Therapieansätze, die den Krankheitsprogress schlechter adressieren als kausale Therapieansätze, z.B. in Form der CFTR-Modulatoren, die den Basisdefekt der CF behandeln (8). Aus diesem Grund ist es wahrscheinlicher, dass CFTR-Modulatoren eher als symptomatische Therapieansätze geeignet sind, den Krankheitsverlauf nachhaltig zu verändern. So zeigt sich bereits bei 2-5jährigen Kindern mit

CF, F/F, eine Verbesserung im LCI2,5 unter kausaler Therapie mit der CFTR-Modulatorkombination LUM/IVA. Zudem zeigte sich eine höhere Wahrscheinlichkeit einer Befundverbesserung im Lungen-MRT unter der Therapie mit Lumacaftor/Ivacaftor bei den 2-5jährigen Kindern (10) im Vergleich zur Placebo-Gruppe, die lediglich mit der Standardtherapie behandelt wurde. Darüber hinaus ist anzumerken, dass der Anteil der Patienten mit mind. einer pulmonalen Exazerbation in der VX16-809-121-Placebogruppe bei 62,5% und in der LUM/IVA-Gruppe bei 42,9% lag. Obwohl dieser Unterschied formal nicht signifikant ist, weist er einen sehr eindeutigen Trend auf und ist höchst patientenrelevant, da er eine Reduktion von 30% feststellt, wodurch u.a. die Lebensqualität der Patienten deutlich verbessert wird.

Es ist zu erwarten, dass durch die Therapie des CF-Basisdefekts Morbidität und Mortalität der Betroffenen effektiver reduziert werden können, aber auch krankheitsrelevante ökonomische Kosten beeinflusst werden können. So werden z.B. die momentan in der CF-Therapie zentralen inhalativen Antibiotika, die einen beträchtlichen Kostenfaktor darstellen, erst bei Patienten benötigt, die eine chronische Besiedlung mit typischen Bakterien aufzeigen. Diese chronische Besiedlung wird durch strukturelle Schäden der Lunge begünstigt, so dass frühe Therapien, die strukturelle Lungenschädigungen verhindern oder verlangsamen können, geeignet sein können, eine Pathogenbesiedlung und damit die Notwendigkeit dieser kostenintensiven Therapeutika hinauszuzögern oder bei ausreichend frühzeitigem Beginn gar ganz zu verhindern.

In diesem Zusammenhang verweisen wir außerdem auf das Ziel des 2016 flächendeckend in Deutschland eingeführten CF-Neugeborenenscreenings (9). Durch das CF-NGS, das die Diagnosestellung des überwiegenden Teils der CF-Patienten in den ersten 8 Wochen des Lebens ermöglichen soll, soll sichergestellt werden, dass die Patienten Zugang zu den empfohlenen CF-typischen Therapien erhalten, damit durch eine frühzeitige, möglichst effektive Therapie, Morbidität, Mortalität und krankheitsbedingte Folgekosten reduziert werden können. Diese neuen Therapeutika sollten daher allen Kindern ab einem möglichst frühen Alter zur Verfügung stehen. Die Daten bei älteren CF-Patienten zur Verbesserung der CFTR-Funktion weisen darauf hin, dass das Ansprechen auf die Dreifach-CFTR-modulierende Therapie mit Elexacaftor / Tezacaftor / Ivacaftor (Kalydeco) größer ist als auf eine Zweifach-CFTR-modulierende Therapie (Tezacaftor / Ivacaftor oder Lumacaftor / Ivacaftor) (11). Es gibt biologisch keinen Grund, warum dies nicht auch bei Kindern im Vorschulalter der Fall sein sollte, sodass der frühe Einsatz der Dreifach-CFTR-modulierenden Therapie bei 2-5jährigen Kindern ein deutlich höheres therapeutisches und v.a. auch präventives Potential bietet als (im Falle der F/F-Kinder) die Zweifach-CFTR-modulierende Therapie. Zudem gibt es erste Daten, die darauf hindeuten, dass das Therapieansprechen auf die Triplekombination gerade jüngerer Kinder im Vergleich zu Jugendlichen und Erwachsenen eher besser ist (12). Für alle Kinder mit nur einem F508del-Allel und ohne eines der für eine Ivacaftor-Monotherapie-qualifizierenden Allele gibt es bisher keine CFTR-modulierende Therapie, hier ist die Dreifach-CFTR-modulierende Therapie die erste kausale Therapieoption.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Die Entscheidung für eine symptomatische Therapie aller Kinder orientiert sich an den individuellen Beschwerden und Auffälligkeiten der klinischen Parameter wir Lungenfunktion sowie laborchemischen und strukturellen Veränderungen (s.u.). Für die Therapie mit CFTR Modulatoren müssen entsprechende Mutationen vorliegen (s.o.).

Es liegen Daten zum Verlauf der Erkrankung von Kindern mit CF in den ersten Lebensjahren aus longitudinalen Beobachtungsstudien vor, die den Verlauf der frühen CF-Lungenerkrankung bei Kindern im Vorschulalter unter best-supportive-care (symptomatischer Therapie) mit Gasauswaschverfahren (multiple-breath washout, MBW) zur Erhebung des LCI2,5 und Magnetresonanztomografie (MRT) der Lunge untersucht haben. den Verlauf der frühen CF-Lungenerkrankung bei Kindern im Vorschulalter unter best-supportive-care (symptomatischer

Therapie) mit Gasauswaschverfahren (multiple-breath washout, MBW) zur Erhebung des LCI2,5 und Magnetresonanztomografie (MRT) der Lunge untersucht haben.
Hierbei zeigt sich in der Untersuchung von Stanojevic et al. an 2-5jährigen Kindern mit CF, dass diese bei regelmäßigen Untersuchungen mittels MBW über ein Jahr stets höhere (=schlechtere) LCI2,5-Werte hatten als gesunde Gleichaltrige (2). Im Mittel lagen die LCI2,5-Werte bei den Kindern mit CF, welche mit best-supportive-care behandelt wurden, zu jedem Untersuchungszeitpunkt im pathologischen Bereich und zeigten zudem eine Verschlechterung über die Zeit (2). Die LCI2,5-Werte der gesunden Vorschulkinder waren zu jedem Zeitpunkt im Normalbereich und zeigten keine Änderung über das Jahr der Beobachtung (2). Dies unterstreicht, dass die funktionelle Einschränkung im Rahmen der CF-Lungenerkrankung auch schon im Vorschulalter nachweisbar und progredient ist und der LCI2,5 hierfür ein geeigneter Endpunkt ist, um lungenkranke von lungengesunden Vorschulkindern zu unterscheiden.
Darüber hinaus haben Stahl et al. kürzlich gezeigt, dass die CF-Lungenerkrankung in der hier betrachteten Altersgruppe mittels MRT nachweisbar und über die ersten vier Lebensjahre unter best-supportive-care progredient ist (3). Hierbei sind die morphologischen und funktionellen Veränderungen, die mittels MRT erkennbar werden, bei Kindern nach klinischer Diagnosestellung der CF stärker ausgeprägt als bei solchen, welche über das CF-Neugeborenenscreening (CF-NGS) identifiziert wurden (3). Betrachtet man jedoch die Rate der jährlichen Verschlechterung über die ersten Lebensjahre, so ist diese bei den Kindern, die über das CF-NGS identifiziert wurden, vergleichbar zu denen mit klinischer Diagnosestellung, was dafürspricht, dass effektivere Therapieoptionen als die symptomatischen Behandlungen notwendig sind, um das Voranschreiten der CF-Lungenerkrankung zu reduzieren oder gänzlich zu verhindern (3). Diese Untersuchung bestätigt, dass es schon früh im Leben der CF-Patienten pulmonale Veränderungen gibt, die bei gesunden Gleichaltrigen nicht auftreten, und dass diese mittels MRT festgestellt werden können (4,5).
Diese Beobachtung führt zu unserer Empfehlung, eine kausale Therapie mit CFTR-Modulatoren so früh wie möglich zusätzlich zur Standardtherapie zu empfehlen. So ist eine Normalisierung der Lebenserwartung der Betroffenen und Reduktion von Folgekosten im Gesundheitswesen realistisch.

Referenzliste:

1. Hammermann J, Claßen M, Schmidt S, Bend J, Ballmann M, Baumann I, Bremer W, Ellemunter H, Felbor U, Hahn G, Heuer H-E, Hogardt M, Junge S, Kahl BC, Koitschev A, Laaß M, Loff S, Mentzel H-J, Palm B, Pfannenstiel C, Regamey N, Renner S, Rietschel E, Schmitt-Grohe S, Sitter H, Smrekar U, Sommerburg O, Staab D, Weber A-K, Weigand C, Zerlik J, Nährlich L. S3-Leitlinie: Mukoviszidose bei Kindern in den ersten beiden Lebensjahren, Diagnostik und Therapie. *awmf* 2020;AWMF-Registernummer 026 – 024.
2. Stanojevic S, Davis SD, Retsch-Bogart G, Webster H, Davis M, Johnson RC, Jensen R, Pizarro ME, Kane M, Clem CC, Schornick L, Subbarao P, Ratjen FA. Progression of Lung Disease in Preschool Patients with Cystic Fibrosis. *Am J Respir Crit Care Med* 2017;195:1216-1225.
3. Stahl M, Steinke E, Graeber SY, Joachim C, Seitz C, Kauczor HU, Eichinger M, Hammerling S, Sommerburg O, Wielputz MO, Mall MA. Magnetic Resonance Imaging Detects Progression of Lung Disease and Impact of Newborn Screening in Preschool Children with Cystic Fibrosis. *Am J Respir Crit Care Med* 2021; Epub ahead of print.
4. Stahl M, Graeber SY, Joachim C, Barth S, Ricklefs I, Diekmann G, Kopp MV, Naehrlich L, Mall MA. Three-center feasibility of lung clearance index in infants and preschool children with cystic fibrosis and other lung diseases. *J Cyst Fibros* 2018;17:249-255.
5. Wielputz MO, von Stackelberg O, Stahl M, Jobst BJ, Eichinger M, Puderbach MU, Nahrlich L, Barth S, Schneider C, Kopp MV, Ricklefs I, Buchholz M, Tummler B, Dopfer C, Vogel-Claussen J, Kauczor HU, Mall MA. Multicentre standardisation of chest MRI as radiation-free outcome measure of lung disease in young children with cystic fibrosis. *J Cyst Fibros* 2018;17:518-527.
6. Hardaker KM, Panda H, Hulme K, Wong A, Coward E, Cooper P, Fitzgerald DA, Pandit C, Towns S, Selvadurai H, Robinson PD. Abnormal preschool Lung Clearance Index (LCI) reflects clinical status and predicts lower spirometry later in childhood in cystic fibrosis. *J Cyst Fibros* 2019;18:721-727.

7. van Horck M, van de Kant K, Winkens B, Wesseling G, Gulmans V, Hendriks H, van der Grinten C, Jobsis Q, Dompeling E. Risk factors for lung disease progression in children with cystic fibrosis. *Eur Respir J* 2018;51.
8. Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, Sermet-Gaudelus I, Southern KW, Barben J, Flume PA, Hodkova P, Kashirskaya N, Kirszenbaum MN, Madge S, Oxley H, Plant B, Schwarzenberg SJ, Smyth AR, Taccetti G, Wagner TOF, Wolfe SP, Drevinek P. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018;17:153-178.
9. Pressemitteilung des G-BA: Screening auf Mukoviszidose für Neugeborene beschlossen (20 Aug 2015) https://www.g-ba.de/institution/presse/pressemitteilungen/585/.
10. Stahl M, Roehmel J, Eichinger M, Doellinger F, Naehrlich L, Kopp MV, Dittrich AM, Lee C, Sommerburg O, Tian S, Xu T, Wu P, Joshi A, Ray P, Duncan ME, Wielputz MO, Mall MA. Effects of Lumacaftor/Ivacaftor on Cystic Fibrosis Disease Progression in Children 2 through 5 Years of Age Homozygous for F508del-CFTR: A Phase 2 Placebo-controlled Clinical Trial. *Ann Am Thorac Soc* 2023.
11. Graeber SY, Renz DM, Stahl M, Pallenberg ST, Sommerburg O, Naehrlich L, Berges J, Dohna M, Ringshausen FC, Doellinger F, Vitzthum C, Röhmel J, Allomba C, Hämmerling S, Barth S, Rückes-Nilges C, Wielpütz MO, Hansen G, Vogel-Claussen J, Tümmler B, Mall MA, Dittrich AM. Effects of Elexacaftor/Tezacaftor/Ivacaftor Therapy on Lung Clearance Index and Magnetic Resonance Imaging in Patients with Cystic Fibrosis and One or Two *F508del* Alleles. Am J Respir Crit Care Med. 2022 Aug 1;206(3):311-320. doi: 10.1164/rccm.202201-0219OC. PMID: 35536314.
12. Schütz K, Pallenberg ST, Kontsendorn J, DeLuca D, Sukdolak C, Minso R, Büttner T, Wetzke M, Dopfer C, Sauer-Heilborn A, Ringshausen FC, Junge S, Tümmler B, Hansen G, Dittrich AM. Spirometric and anthropometric improvements in response to elexacaftor/tezacaftor/ivacaftor depending on age and lung disease severity. Front Pharmacol. 2023 Jul 4;14:1171544. doi: 10.3389/fphar.2023.1171544. PMID: 37469865; PMCID: PMC10352657.