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: 2021-B-399-z/400-z Ivacaftor/Tezacaftor/Elexacaftor in Kombination mit Ivacaftor

Stand: Januar 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Ivacaftor/Tezacaftor/Elexacaftor in Kombination mit Ivacaftor zur Behandlung der zystischen Fibrose (CF)	
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-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. € Grenz; 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 is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged **6** years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene" (<u>Bereits zugelassen:</u> Kaftrio wird angewendet als Kombinationsbehandlung mit Ivacaftor 150 mg Tabletten zur Behandlung der zystischen Fibrose (CF) bei Patienten ab 12 Jahren, die mindestens eine *F508del*-Mutation im *CFTR*-Gen (*Cystic Fibrosis Transmembrane Conductance Regulator*) aufweisen)
Ivacaftor R07AX02 Kalydeco®	<u>Neues Anwendungsgebiet laut positive opinion:</u> "Kalydeco tablets are indicated in a combination regimen with ivacaftor /tezacaftor /elexacaftor tablets for the treatment of adults**,** adolescents **and children** aged **6** years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene" (<u>Bereits zugelassen</u>: Kalydeco-Tabletten werden angewendet: • 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

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
	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). 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, Mukovis-zidose), 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
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: 01/2019] Orkambi Granulat ist angezeigt zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Kindern ab 2 Jahren, die homozygot für die F508del-Mutation im CFTR-Gen sind (siehe Abschnitte 4.2, 4.4 und 5.1) [Stand FI: 05/2020]
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: 11/2020]
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 Bakterien nicht vom Wirkspektrum von Ceftazidim abgedeckt wird. Offizielle Richtlinien zum angemessenen Gebrauch von antibakteriellen Arzneimitteln sollten berücksichtigt werden. [Stand FI Ceftazidim Kabi: 08/2015]

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
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: 04/2019]
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®: 01/2019]
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®: 02/2019]
Colistimethat J01XB01 Generisch	ColistiFlex ist bei erwachsenen Patienten und Kindern mit zystischer Fibrose zur Behandlung chronischer pulmonaler Infekte indiziert, die durch Pseudomonas aeruginosa verursacht warden. Die offiziellen Richtlinien zur sachgemäßen Anwendung von Antibiotika sind zu beachten. [Stand FI ColistiFlex®: 08/2017]
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: 08/2019]
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®: 03/2019]
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: 04/2019]
Carbocistein R05CB03 Transbronchin® Kapseln	Zur begleitenden Behandlung bei akuten und chronischen bronchopulmonalen Erkrankungen, die mit einer Störung von Schleimbildung und Schleimtransport einhergehen. Aus FI 4.2. Dosierung nur für Erwachsene und Jugendliche ab dem 13. Lebensjahr. [Stand FI: 08/2006]

Quellen: AMIce-Datenbank, Fachinformationen Stand: 01/2022

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-399z & B-400z (Ivacaftor & Ivacaftor/Tezacaftor/Elexacaftor)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	17. Dezember 2021

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

Zur Behandlung der zystischen Fibrose (CF) bei Patienten im Alter zwischen 6 – 12 Jahren, welche mindestens eine F508del-Mutation im CFTR-Gen aufweisen.

Hinweise zur Synopse:
Übersichtsarbeiten zu Physiotherapie und Ernährungstherapie wurden nicht eingeschlossen.

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 *zystische Fibrose* 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), MEDLINE (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.

Die Erstrecherche wurde am 15.10.2020 abgeschlossen, die folgende am 26.11.2021. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. 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 720 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 15 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Holland, P. & Jahnke, 2021 [5].

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:

- The Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register, comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. Most recent search of the Group's Trials Register: 07 October 2020
- Also searched online trials registries on 16 November 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.

Skilton, M. et al., 2019 [10].

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:

- The Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books.
- Also searched the reference lists of relevant articles, reviews and online clinical trial registries. 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.

Smith, S. et al., 2018 [11].

Inhaled antibiotics for pulmonary exacerbations in cystic fibrosis.

Fragestellung

To determine if treatment of pulmonary exacerbations with inhaled antibiotics in people with cystic fibrosis improves their quality of life, reduces time off school or work and improves their long-term survival.

Methodik

Population:

- Children and adults with CF who are diagnosed with having a pulmonary exacerbation

Intervention/Komparator:

- any inhaled antibiotic

Endpunkte:

- QoL, Lung function (spirometry), Need for hospital admission, Need for additional antibiotics, Time to next pulmonary exacerbation, Weight, Adverse effects, etc.

Recherche/Suchzeitraum:

- Cochrane Cystic Fibrosis Group's Cystic Fibrosis Trials Register. Date of the last search: 03 October 2018.
- ClinicalTrials.gov, the Australia and New Zealand Clinical Trials Registry and WHO ICTRP for relevant trials. Date of last search: 09 October 2018.

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

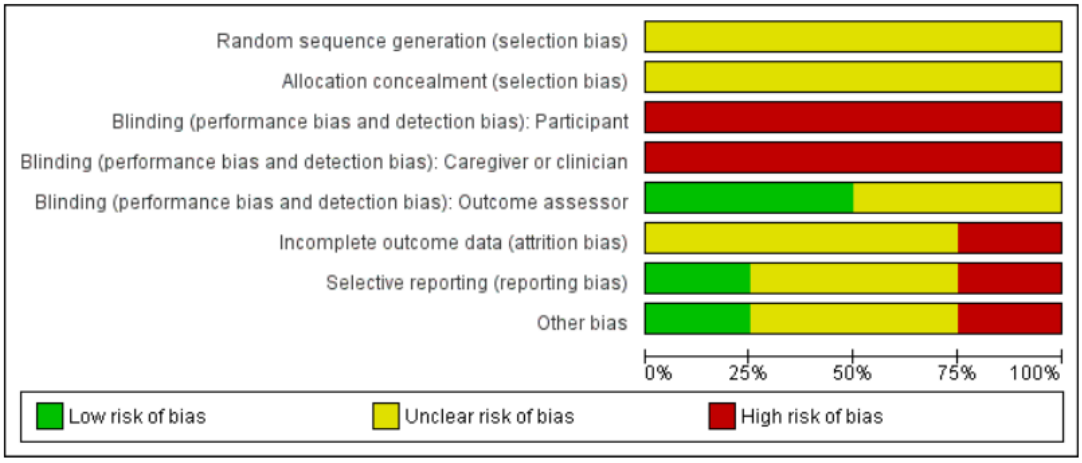
Ergebnisse

Anzahl eingeschlossener Studien & Charakteristika der Population:

- Four trials with 167 participants are included in the review. Two trials (77 participants) compared inhaled antibiotics alone to intravenous antibiotics alone and two trials (90 participants) compared a combination of inhaled and intravenous antibiotics to intravenous antibiotics alone. In all trials the inhaled antibiotics were compared to the same antibiotics given intravenously. The numbers of participants in each trial ranged from 18 to 62.

Qualität der Studien:

- Risk of bias was difficult to assess in most trials, but for all trials we judged there to be a high risk from lack of blinding and an unclear risk with regards to randomisation. Results were not fully reported and only limited data were available for analysis.



Studienergebnisse:

- Inhaled antibiotics alone versus intravenous antibiotics alone
  - Only one trial (n = 18) reported a perceived improvement in lifestyle (quality of life) in both groups (very low-quality of evidence).
  - Two trials measured lung function, but there was no difference reported between treatment groups (very low-quality evidence).
  - One trial (n = 18) reported no difference in the need for additional antibiotics and the second trial (n = 59) reported on the time to next exacerbation. In neither case was a difference between treatments identified (both very low-quality evidence).
  - The single trial (n = 18) measuring adverse events and sputum microbiology did not observe any in either treatment group for either outcome (very low-quality evidence).
- Inhaled antibiotics plus intravenous antibiotics versus intravenous antibiotics alone
  - Two trials measured lung function, but found no difference between groups in forced expiratory volume in one second (one trial, n = 28, very low-quality evidence) or vital capacity (one trial, n = 62).
  - Neither trial reported on the need for additional antibiotics or the time to the next exacerbation; however, one trial (n = 28) reported on hospital admissions and found no difference between groups.
  - Two trials reported no difference between groups in adverse events (very low-quality evidence) and one trial (n = 62) reported no difference in the emergence of antibiotic-resistant organisms (very low-quality evidence).

Fazit der Autoren

There is little useful high-level evidence to judge the effectiveness of inhaled antibiotics for the treatment of pulmonary exacerbations in people with cystic fibrosis. The included trials were not sufficiently powered to achieve their goals. Hence, we are unable to demonstrate whether one treatment was superior to the other or not. Further research is needed to establish whether inhaled tobramycin may be used as an alternative to intravenous tobramycin for some pulmonary exacerbations.

Kommentare zum Review

- Sowohl Kinder als auch Erwachsene in den Studien. Keine separaten Analysen.

Yang C et al., 2018 [15].

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, 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:

- Group's Cystic Fibrosis Trials Register (compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective hand searching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis.), trials database Clinicaltrials.gov and the International Clinical Trials Registry Platform
- Date of the most recent search of the Group's register: 23 April 2018.

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:
Dornase alfa vs placebo or no 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
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.

6. Downgraded once for lack of applicability: Amin included children only so results are not applicable to adults (Amin 2011).
7. Downgraded once for imprecision: wide confidence intervals around the effect size due to limited sample size of the trial.
8. Additionally, one study reported an age-adjusted RR of having more than one respiratory exacerbation, but these data were not included in the pooled analysis (McCoy 1996). No significant difference was found between dornase alfa and control.
9. Downgraded once as data from one cross-over trial was analysed as parallel data (Amin 2011), which is a conservative approach.

- Mortality: RR = 1.70 (95% CI 0.70 to 4.14) with 12 deaths in the dornase alfa group and seven deaths in the control group.
- Dornase alfa improved lung function in trials of up to one month duration compared to placebo, mean difference (MD) in forced expiratory volume at one second (FEV1) per cent (%) predicted 9.51% (95% confidence interval (CI) 0.67 to 18.35).
- FEV1 was significantly better in the dornase alfa group in trials ranging from three months to two years.
- Dornase alfa also decreased the number of participants experiencing pulmonary exacerbations
- Quality of life improved in some trials and was unchanged in others.
- Dornase alfa was well-tolerated and other than voice alteration, RR 1.69 (95% CI 1.2 to 2.39), and rash, RR 2.4 (95% CI 1.16 to 4.99), side effects were not more common than in the control group.

<u>Dornase alfa vs hypertonic saline</u>

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 Hypertonic Saline	Corresponding risk 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
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.

- Trials of one month or less did not find a significant difference in FEV1 between hypertonic saline (HS) and dornase alfa (Adde 2004; Ballmann 2002); whereas a three-month trial reported an improvement with dornase compared to HS, MD 8.00%(95%CI 2.00% to 14.00%) (Suri 2001).
- Mortality: There were no deaths reported in any of the trials.

Dornase alfa vs 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	Corresponding risk				
	Mannitol	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
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.

- Mortality: There were no deaths reported in any of the trials.
- The trial comparing dornase alfa and mannitol (dornase alfa n =21, mannitol n = 23) did not report a significant difference between the two interventions for FEV1 (low-quality evidence).

Dornase alfa vs 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	Corresponding risk				
	Dornase alfa and mannitol	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
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.

- Mortality: The trial did not measure this outcome.
- There was no difference between the two groups in either FEV1, or FVC.

Fazit der Autoren

There is evidence to show that, compared with placebo, therapy with dornase alfa improves lung function in people with cystic fibrosis in trials lasting from one month to two years. There was a decrease in pulmonary exacerbations in trials of six months or longer. Voice alteration and rash appear to be the only adverse events reported with increased frequency in randomised controlled trials. There is not enough evidence to firmly conclude if dornase alfa is superior to other hyperosmolar agents in improving lung function.

Nevitt SJ et al., 2018 [8].

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, Kung function, AEs, Exacerbations, hospitalisations, etc.

Recherche/Suchzeitraum:

- Relevant trials were identified from the Group's Cystic Fibrosis Trials Register (compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of theCochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis.), trials database Clinicaltrials.gov and the International Clinical Trials Registry Platform
- Date of the most recent search of the Group's register: 28 September 2017.

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

Ergebnisse

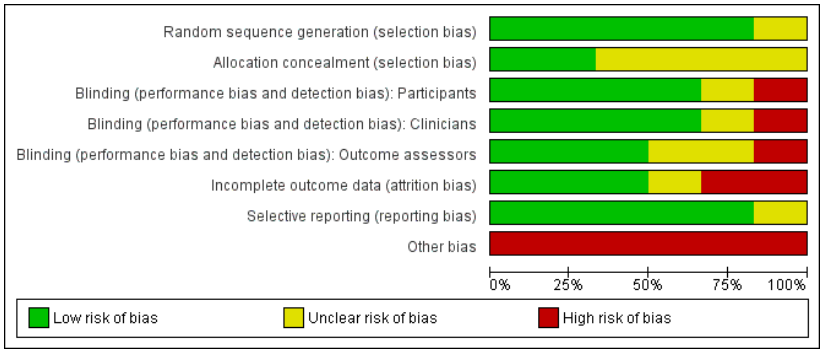
Anzahl eingeschlossener Studien:

- 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:

Mannitol compared with control (sub-therapeutic mannitol) - parallel studies of individuals with 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	Corresponding risk				
	50 mg inhaled mannitol	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
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%

Mannitol versus control - cross-over studies of individuals with cystic fibrosis (2 studies, n=134)

- HRQoL: no significant differences between mannitol and control for the respiratory, health, physical and vitality domains (very low-quality evidence).
- Pulmonary exacerbations: 1 study: less frequently in the 400 mg mannitol group (11.5%) compared to the control arm (16.1%)
- The most commonly reported adverse events in both groups in the two studies were cough, haemoptysis, headache, nasopharyngitis and lung infections. Frequencies of adverse events according to severity and association to treatment only were reported, a statistical comparison was not made in either study.

Mannitol versus dornase alfa - cross-over study of individuals with cystic fibrosis (1 study, n=28)

Inhaled mannitol compared with dornase alfa for CF

Patient or population: children and young people with CF
Settings: outpatients
Intervention: inhaled mannitol
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				
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*
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.

- Pulmonary exacerbations: no significant difference

Mannitol plus dornase alfa compared with dornase alfa - cross-over study of individuals with 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*
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.

- Pulmonary exacerbations: no significant difference

Subgroup analysis – age:

- Lung function

Table 2. Mannitol versus control - subgroup analysis by age (lung function)

Outcome	Time point	Adults (n = 317)			Children (n = 258)			P value for test of subgroup differences
		MD	95% CI	P value	MD	95% CI	P value	
FEV_1 (mL)	up to 2 months	89.3	38.96 to 139.64	0.001	50.24	-7.82 to 108.30	0.09	0.32
	up to 4 months	87.83	29.08 to 146.58	0.003	25.89	-40.72 to 92.50	0.45	0.17
	up to 6 months	123.12	56.43 to 189.81	0.0001	62.52	-11.65 to 136.69	0.09	0.23
FEV_1 (% predicted)	up to 2 months	3.72	0.82 to 6.64	0.012	2.64	-0.73 to 6.02	0.13	0.63
	up to 4 months	4.23	0.98 to 7.48	0.01	1.34	-2.42 to 5.10	0.49	0.25
	up to 6 months	5.74	2.36 to 9.13	0.001	3.03	-0.78 to 6.84	0.12	0.30
FVC (mL)	up to 2 months	101.66	35.15 to 168.16	0.003	69	-5.0 to 142.99	0.07	0.52
	up to 4 months	111.82	36.75 to 186.89	0.004	46.16	-35.53 to 127.84	0.27	0.25
	up to 6 months	158.44	74.87 to 242.01	0.001	71.21	-19.1 to 161.51	0.12	0.17
FEF_{25-75} (mL/s)	up to 2 months	95.09	0.56 to 189.63	0.05	15.44	-95.62 to 126.51	0.79	0.28
	up to 4 months	108.42	10.23 to 206.63	0.03	-53.07	-165.97 to 59.84	0.36	0.03
	up to 6 months	59.27	-55.59 to 174.12	0.31	31.29	-96.72 to 159.30	0.63	0.75
Exacerbations	up to 6 months	0.76	0.52 to 1.13	0.18	0.62	0.35 to 1.09	0.10	0.55

CI: confidence interval; **FEF_{25-75}**: mid-expiratory flow; **FEV_1**: forced expiratory volume at one second; **FVC**: forced vital capacity; **MD**: mean difference; **RR**: risk ratio.
MD and 95% CI for measures of lung function is change from baseline pooled across two studies (Aitken 2012; Bilton 2011).
RR and 95% CI represents the proportion of participants experiencing pulmonary exacerbations pooled across two studies (Aitken 2012; Bilton 2011).
* Intention-to-treat population analysed for lung function outcomes, all randomised participants were included for the outcome of pulmonary exacerbations: adults (n = 341) and children (n = 259).

- Adverse events

Adverse event	Adults (n = 341)		Children (n = 259)		P value for test of subgroup differences
	RR	99% CI	RR	99% CI	
Cough	2.05	0.75 to 5.57	2.03	0.48 to 8.67	0.99
Haemoptysis	1.83	0.46 to 7.28	5.48	0.36 to 82.41	0.35
Pharyngolaryngeal pain	2.18	0.35 to 13.47	1.77	0.26 to 11.92	0.84
Throat irritation	0.97	0.09 to 10.24	2.05	0.11 to 39.42	0.61
Productive cough	0.65	0.08 to 5.16	3.48	0.07 to 183.99	0.33
Wheezing	0.32	0.04 to 3.00	1.13	0.08 to 15.79	0.35
Asthma	0.13	0.00 to 7.11	3.36	0.06 to 175.87	0.14
Bronchospasm	3.35	0.06 to 177.81	NA		NA
Condition aggravated	1.30	0.33 to 5.17	1.73	0.21 to 14.32	0.77
Chest discomfort	1.08	0.17 to 6.89	1.13	0.08 to 15.79	0.97
Chest pain	NA		0.13	0.00 to 7.03	NA
Vomiting	0.67	0.05 to 8.52	2.73	0.16 to 47.76	0.34
Post-tussive vomiting	4.39	0.09 to 210.79	2.73	0.16 to 47.76	0.80
Headache	3.90	0.25 to 61.93	1.70	0.20 to 14.30	0.54
Decreased appetite	3.35	0.06 to 177.81	NA		NA
Infections and infestations	0.43	0.08 to 2.21	0.69	0.12 to 4.07	0.61
Musculosketal and connective tissue disorders	3.24	0.20 to 53.67	0.68	0.05 to 8.93	0.29
Skin and subcutaneous disorders	1.31	0.15 to 11.79	2.05	0.11 to 39.42	0.75

CI: confidence interval; **NA:** not estimable (no events reported in the subgroup); **RR**: risk ratio.
RR and 99% CI represents the proportion of participants experiencing pulmonary exacerbations pooled across two studies (Aitken 2012; Bilton 2011) (except asthma, bronchospasm, chest pain and decreased appetite reported in Bilton 2011 only).

Fazit der Autoren

There is moderate-quality evidence to show that treatment with mannitol over a six-month period is associated with an improvement in some measures of lung function in people with cystic fibrosis compared to control. There is low to very low-quality evidence suggesting no difference in quality of life for participants taking mannitol compared to control. This review provides very low-quality evidence suggesting no difference in lung function or quality of life comparing mannitol to dornase alfa alone and to mannitol plus dornase alfa. The clinical implications from this review suggest that mannitol could be considered as a treatment in cystic fibrosis; but further research is required in order to establish who may benefit most and whether this benefit is sustained in the longer term. Furthermore, studies comparing its efficacy against other (established) mucolytic therapies need to be undertaken before it can be considered for mainstream practice.

Southern KW et al., 2018 [13].

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:

- Relevant trials were identified from the Group's Cystic Fibrosis Trials Register (compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective hand searching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis.), trials database Clinicaltrials.gov and the International Clinical Trials Registry Platform
- Date of the most recent search of the Group's register: 24 February 2018.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

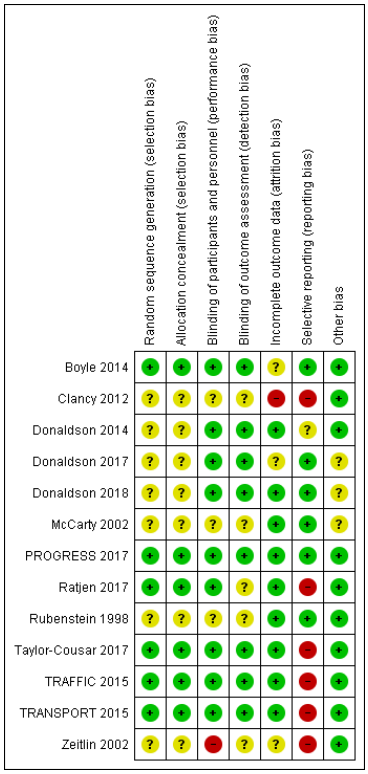
Anzahl eingeschlossener Studien:

- 13 studies in total
- 10 studies included in meta-analysis
- Two studies compared 4PBA (4-Phenylbutyrate) to placebo – Ergebnisse zu diesem Vergleich wurden nicht extrahiert
- One study compared escalating doses of CPX to placebo - – Ergebnisse zu diesem Vergleich wurden nicht extrahiert
- One study compared sequential ascending doses of N6022 to placebo - Ergebnisse zu diesem Vergleich wurden nicht extrahiert
- One study (n = 26) compared cavosonstat 200 mg (twice daily) to placebo - Ergebnisse zu diesem Vergleich wurden nicht extrahiert
- One included study compared lumacaftor monotherapy to placebo (n = 17) for 28 days ((Clancy 2012).
- Five studies evaluated lumacaftor-ivacaftor combination therapy - Ergebnisse zu diesem Vergleich wurden nicht extrahiert
- Two studies have evaluated tezacaftor-ivacaftor combination therapy (Donaldson 2018; Taylor-Cousar 2017).

Charakteristika der Population:

- A Phase 2 study included a dose-escalation arm, a comparison of various doses of tezacaftor-ivacaftor in people homozygous for F508del, and a comparison of tezacaftor-ivacaftor against ivacaftor alone in people with one F508del mutation and one G551D mutation (Donaldson 2018).
- One study recruited children between the ages of 6 to 11 years (Ratjen 2017), five studies recruited adolescents and adults (PROGRESS 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015) and the remaining 13 studies recruited only adults.

Qualität der Studien:



Studienergebnisse:

Lumacaftor vs placebo

- Survival: no death reported
- QoL:
  - Immediate term (up to and including one month): significantly lower CFQ-R scores in some domains
- Adverse effects:
  - Mild AE: most commonly reported side effect was cough with no significant difference
  - Moderate AE (therapy is discontinued, and the adverse effect ceases): no statistically significant differences in terms of any lumacaftor dose compared to placebo in the number of adverse events requiring study drug discontinuation up to day 28
  - Severe AE (life-threatening or debilitating, or which persists even after treatment is discontinued): In the Clancy study, adverse effects in eight participants were considered severe: fatigue (n = 1); sinus congestion (n = 1); musculoskeletal discomfort (n = 1); cough (n = 2); and pulmonary exacerbation (n = 3). It is not stated which arm these participants were randomised to. Four out of 89 participants (5%) - one participant from each of the lumacaftor arms - discontinued the study drug due to respiratory adverse effects. No participants discontinued from the placebo group (Clancy 2012).
- Extra courses of antibiotics
  - no statistically significant difference in the frequency of participants who developed pulmonary exacerbations between those in the lumacaftor groups and the placebo group, OR 1.50 (99% CI 0.16 to 14.31) and OR 2.72 (99%CI 0.05 to 156.17)

Tezacaftor plus Ivacaftor compared with placebo or ivacaftor alone

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**[1,2]	
Quality of life: total score Follow-up: NA	Outcome not reported.				NA	A higher score indicates a better outcome.
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**[1,2]	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 statistically 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**[1,2]	Difference in relative change from baseline calculated by least-squares regression, hence assumed risk not presented The second study (n = 18) showed no statistically significant difference between groups in mean relative change from baseline in FEV_1 % predicted MD 3.72 (95% CI -7.77 to 15.21).

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 statistically 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**[1,2]	
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**[1,2]	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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **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.

1. 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.
2. 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 insufficient evidence that monotherapy with correctors has clinically important effects in people with CF who have two copies of the F508del mutation.
Combination therapies (lumacaftor-ivacaftor and tezacaftor-ivacaftor) each result in similarly small improvements in clinical outcomes in people with CF; specifically improvements quality of life (moderate-quality evidence), in respiratory function (high-quality evidence) and lower pulmonary exacerbation rates (moderate-quality evidence). Lumacaftor-ivacaftor is associated with an increase in early transient shortness of breath and longer-term increases in blood pressure (high-quality evidence). These adverse effects were not observed for tezacaftor-ivacaftor. Tezacaftor-ivacaftor has a better safety profile, although data are not available for children younger than 12 years. In this age group, lumacaftor-ivacaftor had an important impact on respiratory function with no apparent immediate safety concerns, but this should be balanced against the increase in blood pressure and shortness of breath seen in longer-term data in adults when considering this combination for use in young people with CF.

Kommentare zum Review

- Mutationsstatus in einigen der eingeschlossenen Studien ist nicht F508del homozygot. Keine klaren Subruppenanalysen zu Kindern/Erwachsenen.

Smith S et al., 2018 [12].

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

Fragestellung

To evaluate the effects long-term inhaled antibiotic therapy in people with cystic fibrosis on clinical outcomes (lung function, frequency of exacerbations and nutrition), quality of life 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:

- Any inhaled antibiotic (all doses and methods of inhalation) with activity against P aeruginosa given for at least three months

Komparator:

- 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

Endpunkte:

- primäre Endpunkte:
  - Physiological measures of lung function
  - Exacerbation of respiratory infection
- sekundäre Endpunkte:
  - Nutrition
  - Quality of life (QoL)
  - Adverse effects
  - Survival
  - Antibiotic resistance in P aeruginosa or other organisms

Recherche/Suchzeitraum:

- Relevant trials were identified from the Group's Cystic Fibrosis Trials Register (compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective hand searching of two journals - Pediatric Pulmonology and the Journal of Cystic Fibrosis.), trials database Clinicaltrials.gov and the International Clinical Trials Registry Platform
- Date of the most recent search of the Group's register: 13 February 2018.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

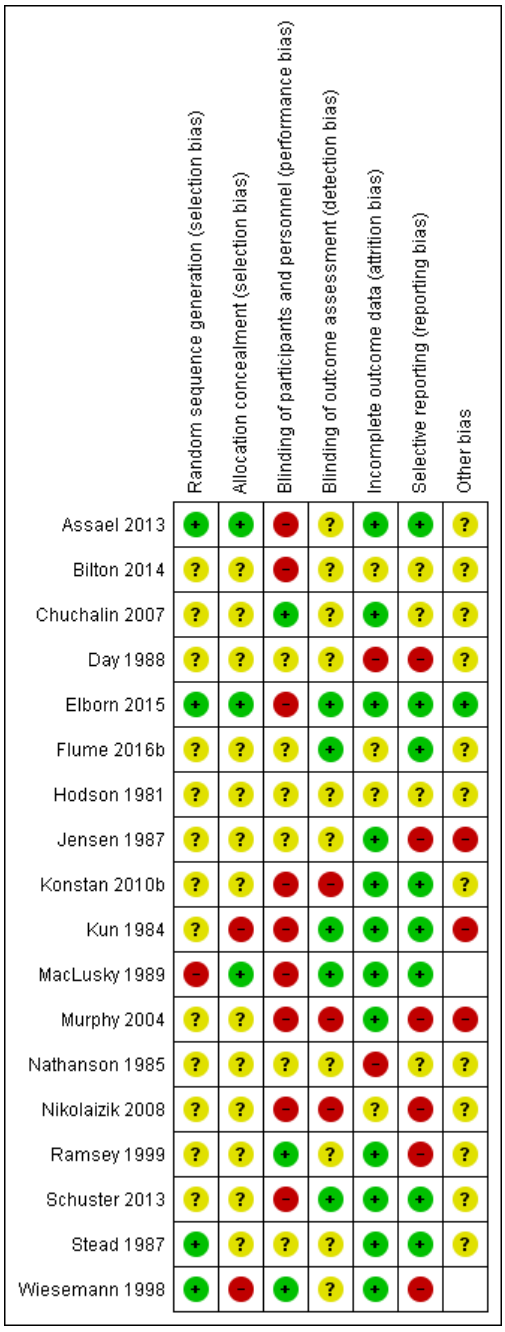
Anzahl eingeschlossener Studien:

- 18 trials

Charakteristika der Population:

- Participants were both children and adults

Qualität der Studien:



Studienergebnisse:
Colistimethat vs Tobramycin

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

Patient population: children and adults with CF and *P aeruginosa* infection
Settings: outpatients
Intervention: colistimethate dry powder for inhalation (one 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)	No of participants (studies)	Quality of the 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**[1,2]	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**[1]	
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**[1,3]	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**[1,4]	
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**[1,3]	
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**[1,4]	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).
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 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. Downgraded once due to an unclear or high risk of bias across four out of the seven domains, particularly randomisation, allocation concealment and participant blinding.
2. Downgraded once due to LOCF analysis increasing risk of bias
3. Downgraded once for imprecision; the trial was underpowered to detect differences in overall quality of life.
4. Downgraded once for imprecision due to low event rates.

Tobramycin vs Aztreonam

TIS compared with AZLI 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)	No of participants (studies)	Quality of the 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**[1]	
Pulmonary exacerbations: need for additional antibiotics. Follow-up: 24 weeks	**576 per 1000**	**380 per 1000** (294 to 495 per 1000)	**RR 0.66** (0.51 to 0.86)	268 (1)	⊕⊕⊕○ **moderate**[1]	
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**[1]	
Survival Follow-up: 24 weeks	See comments.			268 (1)	⊕⊕○○ **low**[1,2]	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**[1]	
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**[1]	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; **CFU**: colony forming units; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **MD**: mean difference; **P aeruginosa**: *Pseudomonas aeruginosa*; **RR**: risk ratio; **SD**: standard deviation; **TIS**: tobramycin for inhalation solution.

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. 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.
2. Downgraded once due to imprecision from low event rates.

Levofloxacin vs. Tobramycin

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)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk TIS	Corresponding risk LIS				
FEV_1 (% predicted): relative mean change from baseline Follow-up: six 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**	
Pulmonary exacerbations: number of hospitalisations due to respiratory exacerbations Follow-up: six months	**280 per 1000**	**173 per 1000** (112 to 274 per 1000)	**RR 0.62** (0.40 to 0.98)	282 (1)	⊕⊕⊕⊕ **high**	
Quality of life: change from baseline in CFQ-R	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**[1,2]	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: six 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	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).
CFU: colony forming units; **CI**: confidence interval; **FEV_1**: forced expiratory volume at 1 second; **FVC**: forced vital capacity; **LIS**: levofloxacin for inhalation solution; **P aeruginosa**: *Pseudomonas aeruginosa*; **RR**: risk ratio; **TIS**: tobramycin for inhalation solution.

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

Fazit der Autoren

Inhaled anti-pseudomonal antibiotic treatment probably improves lung function and reduces exacerbation rate, but pooled estimates of the level of benefit were very limited. The best evidence is for inhaled tobramycin. More evidence from trials measuring similar outcomes in the same way is needed to determine a better measure of benefit. Longer-term trials are needed to look at the effect of inhaled antibiotics on quality of life, survival and nutritional outcomes.

Kommentar zum Review:

- Keine Subgruppenanalsen zu Kindern/Erwachsenen.

3.2 Systematische Reviews

Habib AR et al., 2019 [1].

A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis.

Fragestellung

to evaluate the impact of CFTR modulators on lung function and other clinically important outcomes including pulmonary exacerbations, hospitalizations, respiratory symptoms, nutritional status, and adverse events in individuals with CF.

Methodik

Population:

- patients with CF

Intervention:

- CFTR modulators (e.g. potentiators, correctors, translational read-through agents)

Komparator:

- Placebo

Endpunkte:

- Primary outcome: Change in percent-predicted forced expiratory volume in one second (ppFEV1)
- Secondary efficacy outcomes: pulmonary exacerbations (PEx), hospitalization due to PEx, respiratory symptoms (i.e., Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory domain), and nutritional status (i.e., body mass index and weight).
- Adverse events, serious adverse events (including deaths) leading to treatment discontinuation, and the prevalence of elevated liver function tests (LFTs)

Recherche/Suchzeitraum:

- From January 1, 2005 to March 31, 2018. Online databases searched included: MEDLINE, EMBASE, ACP Journal Club, Cochrane Central Register for Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Cochrane Methodology Register (CMR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), and NHS Economic Evaluation Database (NHSEED).

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- eight phase 3 and six phase 2 studies

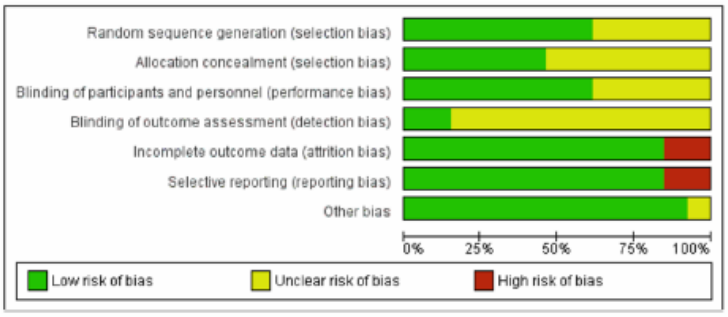
Charakteristika der Population:

Generic name	Genotypes investigated	Type of CFTR Modulator	No. of Studies
Ataluren	Nonsense mutation ≥ 1 allele	Translational readthrough agent – promotes ribosomal readthrough of premature termination codons to enable the production of full-length, functional CFTR	1
Ivacaftor (IVA)	F508del homozygous; F508del heterozygous G551D ≥ 1 allele; R117H ≥ 1 allele	CFTR "potentiator" – increases CFTR channel open probability (i.e., the fraction of time that the channel remains open)	5
Lumacaftor (LUM)	F508del homozygous	CFTR "corrector" – corrects CFTR misprocessing to increase the amount of cell surface-localized protein	2
Lumacaftor-ivacaftor (LUM-IVA)	F508del homozygous; F508del heterozygous	Combination CFTR corrector and potentiator	5
Tezacaftor (TEZ)	F508del homozygous	CFTR "corrector" – corrects CFTR misprocessing to increase the amount of cell surface-localized protein	1
Tezacaftor-ivacaftor (TEZ-IVA)	F508del homozygous; F508del/G551D	Combination CFTR corrector and potentiator	2

Table 1. CFTR Modulators Investigated in Phase 2 and 3 Clinical Trials. Abbreviations: CFTR = cystic fibrosis transmembrane conductance regulator.

Qualität der Studien:

- Most studies were considered 'low risk' for selection, performance, and attrition bias.



Studienergebnisse:

- Primary outcome (ppFEV1):
  - Of all the CFTR modulators examined to date, individuals with a G551D mutation treated with IVA experienced the largest improvement in ppFEV1 compared to placebo (n = 2 studies; n = 213; weighted absolute mean difference 10.8, 95% CI: 9.0–12.7) with no heterogeneity (I2 = 0%) in results between studies.
  - For F508del homozygous individuals 12 years and older, ppFEV1 significantly improved with LUM-IVA and TEZ-IVA compared to placebo. The effect size was similar for TEZ-IVA (n = 2 studies; n = 535; weighted absolute mean difference 4.0, 95% CI: 3.2–4.8) and higher dose LUM-IVA (n = 3 studies; n = 755; weighted absolute mean difference 3.4, 95% CI: 2.4–4.4).
  - For individuals 6–11 years, there was a mild increase in ppFEV1 for LUM-IVA compared to placebo (n = 1 study; n = 204; absolute mean difference 2.4, 95% CI: 0.4–4.4)19. No significant treatment effect was observed with IVA or TEZ alone, and there was a trend toward worsening in ppFEV1 for F508del homozygous individuals treated with higher doses of LUM (Fig. 3A).
  - For F508del heterozygous individuals, there was no significant improvement in ppFEV1 on LUM or LUM-IVA. In a small study involving individuals with F508del/G551D, TEZ-IVA did not lead to a significant improvement in ppFEV1 compared to IVA alone.

- For individuals with the R117H mutation on at least one allele, IVA did not lead to an overall improvement in ppFEV1 compared to placebo, but there was a significant improvement in a pre-defined subgroup analysis restricted to adults (n = 50; absolute mean difference 5.0, 95% CI 1.2–8.8).
- For individuals with a nonsense mutation on at least one allele, ataluren did not result in a significant relative improvement in ppFEV1 compared to placebo.

- Secondary outcomes
  - Pulmonary exacerbations (PEx): Of all the CFTR modulators examined, individuals (≥12 years old) with a G551D mutation receiving IVA derived the greatest reduction in PEx risk compared to placebo (n = 1 study; n = 161; OR 0.39, 95% CI: 0.21–0.74). LUM-IVA and TEZ-IVA also significantly reduced the risk of PEx compared to placebo in F508del homozygous individuals (≥12 years old) but the risk reduction was less than that observed with IVA in G551D. In comparison to placebo, no significant reduction in PEx risk was observed for F508del homozygous individuals or individuals with the R117H mutation on at least one allele receiving IVA, nor for individuals with a nonsense mutation receiving ataluren.
  - Pulmonary exacerbations (PEx) requiring hospitalization: LUM-IVA reduced the risk of PEx requiring hospitalization in F508del homozygous individuals. TEZ-IVA also significantly reduced the rate of PEx leading to hospitalization compared to placebo (n = 1 study; n = 504; rate ratio 0.53, 95% CI 0.34–0.82) but a risk ratio could not be calculated. Individuals with the G551D mutation on at least one allele treated with IVA also experienced a reduction in the risk of PEx requiring hospitalization but this was not statistically significant.
  - CFQ-R respiratory domain: Compared to placebo, CFQ-R Respiratory domain scores improved to a similar extent for IVA treated individuals (≥6 years old) with the G551D mutation on at least one allele (n = 3 studies; n = 236; weighted absolute mean difference: 7.2, 95% CI: 3.3–11.1), IVA treated individuals ≥18 years old with at least one R117H mutation (n = 1 study; n = 69; absolute mean difference: 8.4, 95% CI: 2.2–14.6), and for LUM-IVA treated F508del heterozygous individuals ≥18 years old (n = 1 study; n = 125; absolute mean difference: 6.5, 95% CI 1.4–11.6).
  - CFQ-R Respiratory domain scores also significantly improved with TEZ-IVA and LUM-IVA in F508del homozygous individuals (≥12 years old) but the mean difference did not exceed the minimal clinically important difference (MCID) for LUM-IVA. Furthermore, there was no significant improvement in CFQ-R Respiratory domain scores for patients 6–11 years old on LUM-IVA compared to placebo.
  - There was worsening of the CFQ-R Respiratory domain score for F508del homozygous and heterozygous individuals (≥18 years old) on LUM alone. In a small phase 2 study involving individuals with F508del/G551D, TEZ-IVA did not lead to significant improvement in the CFQ-R Respiratory domain compared to IVA alone. For individuals with a nonsense mutation on at least one allele, ataluren did not modify CFQ-R Respiratory domain score compared to placebo.
  - Nutritional outcomes (BMI and weight): For individuals with at least one G551D mutation (≥6 years old), significant improvements in weight were observed on IVA compared to placebo (n = 2 studies; n = 213; weighted absolute mean difference: 2.8 kg, 95% CI: 1.8–3.8). For F508del homozygous individuals (≥12 years old), a clinically modest but statistically significant increase in BMI was observed for both doses of LUM-IVA compared to placebo; however, no significant treatment effect was seen in individuals 6–11 years on LUM-IVA. TEZ-IVA did not lead to improvement in BMI compared to placebo in individuals 12 years and older. For F508del heterozygous individuals (≥18 years old), LUM-IVA did not result in significant improvement in

weight or BMI compared to placebo26. There were no significant improvements in BMI compared to placebo among IVA treated individuals with an R117H mutation or ataluren treated individuals with a nonsense mutation (data not shown).

- Adverse event reporting: CFTR modulators were generally well tolerated compared to placebo. For studies involving F508del homozygous and heterozygous individuals, those assigned to LUM had increased dyspnea and “abnormal respiration” compared to placebo. F508del homozygous and heterozygous subjects assigned to LUM and LUM-IVA also had more respiratory-related adverse events leading treatment discontinuation compared to placebo. For the one study involving individuals with a nonsense mutation, subjects receiving ataluren had increased incidence of acute kidney injury compared to placebo (15% vs. <1%) resulting in higher rates of treatment discontinuation.
- The prevalence of LFT abnormalities was generally similar between treatment and placebo, however there were a few exceptions. A greater proportion of G551D patients had severe ALT elevations (>8x ULN) on IVA compared to placebo (3.6% vs 0%). Milder elevations in AST (2–3X ULN) were observed for G551D patients on IVA and ALT or AST (>3X ULN) in F508del homozygous children aged 6–11 on LUM-IVA compared to placebo.

Fazit der Autoren

In conclusion, based on randomized placebo-controlled parallel design trials, CFTR potentiation with IVA in individuals with a G551D mutation is safe, and results in robust clinical benefits compared to placebo and to date is superior to the effects observed with CFTR modulators in other CF genotypes. The effects of TEZ-IVA and LUM-IVA in F508del homozygous individuals are comparable with respect to the magnitude of change in ppFEV1 and PEx risk reduction but TEZ-IVA is safer and leads to greater improvement in respiratory symptoms.

Kommentar zum Review

- Keine Subgruppenanalysen nach Alter

Wu HX et al., 2019 [14].

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

Hammermann, J. et al., 2020 [4] & [3] & [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]

Ren CL et al., 2018 [9].

Cystic Fibrosis Foundation clinical practice guidelines endorsed by the American Thoracic Society

Cystic Fibrosis Foundation Pulmonary Guidelines: Use of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy in Patients with Cystic Fibrosis.

Fragestellung

Develop evidence-based guidelines for CFTR modulator therapy in patients with CF.

Methodik

Grundlage der Leitlinie

- Repräsentatives Leitliniengremium: independent, multidisciplinary group of individuals with expertise and experience in CF care, and included pediatric pulmonologists, adult pulmonologists, a pharmacist, a nurse practitioner, and a respiratory therapist, an adult CF patient, a parent of a child with CF
- bei Vorliegen eines Interessenkonfliktes keine Teilnahme in Leitliniengremium
- systematische Literatursuche anhand von PICO-Fragen
- Nutzung des GRADE Evidence-to-Decision Framework zur Ableitung der Empfehlungen
- Konsensusprozess nicht beschrieben

Recherche/Suchzeitraum:

- A systematic review of peer-reviewed literature published from database inception through April 2016 was conducted in Ovid, EMBASE, PubMed, Cochrane Library Scopus, and Google Scholar. We repeated the search in September 2017 and found no relevant new citations.

LoE/GoR

- GRADE-System

Table 1. Interpretation of the strength of grading of recommendations, assessment, development, and evaluation recommendations

Implications	Strong Recommendation	Conditional Recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Sonstige methodische Hinweise

- Keine Gültigkeit bzw. Updateprozess beschrieben

Empfehlung

Question 2: Should IVA versus No CFTR Modulator Treatment Be Used for Individuals with a CF Diagnosis Due to the R117H Mutation?

- Recommendation 11. The committee suggests against IVA therapy for individuals aged 0–5 years and with a CF diagnosis due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

  Remarks: this recommendation placed high value on the substantial expected costs of therapy and potential side effects against lack of potential for improvement in patient-important outcomes, such as lung function in age range that cannot be easily stratified by lung function. The data considered for this recommendation were comprised of individuals aged 6–11 years, which contained few individuals with compromised lung function and with possible overrepresentation of individuals with limited disease penetrance. Parents and providers may be more likely to use this medication in situations where more severe or more rapidly progressive disease, assessed by other criteria, is present.

  Recommendation 12. The committee suggests IVA for individuals aged 6–11 years with PPFEV1 less than 40% with a diagnosis of CF due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

  Remarks: the overall consensus of the group was that patients, parents, and providers would be more likely to use this medication in situations where more severe or more rapidly progressive disease is present, especially where patients are demonstrating declining lung function while being adherent to usual care.
- Recommendation 13. The committee suggests IVA treatment for individuals aged 6–11 years with PPFEV1 40%–90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, very low certainty in the evidence).

  Remarks: as previously here, patients, parents, and providers would be more likely to use this medication in situations where younger patients are already demonstrating reduced lung function.
- Recommendation 14. The committee suggests that IVA not be used for individuals aged 6–11 years with PPFEV1 greater than 90% with a diagnosis of CF due to the R117H mutation (conditional recommendation, low certainty in the evidence).

  Remarks: the panel believed that this group most closely matched the data from Moss and colleagues (33), which demonstrated a fall in PPFEV1, and patients, parents, and providers would be less likely to use this medication in individuals with possibly limited disease penetrance. (…)

Question 3: Should IVA/LUM Combination Drug versus No CFTR Modulator Treatment Be Used in Individuals with Two Copies of the F508del Mutation?

- Recommendation 21. The committee makes no recommendation for or against IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 0–5 years.

  Remarks: the committee chose not to make a recommendation for or against IVA/ LUM combination therapy for this age group, because there is no formulation of this drug that is clinically available.
- Recommendation 22. The committee suggests IVA/LUM combination therapy for individuals with a diagnosis of CF and two copies of the F508del mutation who are aged 6–11 years with PPFEV1 less than 40%. (conditional recommendation, very low certainty in the evidence).

Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is balancing the potential benefits for this population versus well-documented intolerance of IVA/ LUM in patients with poor lung function. Additional considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.

- Recommendation 23. The committee suggests IVA/LUM combination therapy for individuals aged 6–11 years with a diagnosis of CF and two copies of the F508del mutation with PPFEV1 40%–90% (conditional recommendation, very low certainty in the evidence).

  Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. These considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.
- Recommendation 24. The committee suggests IVA/LUM combination therapy for individuals aged 6–11 years with a diagnosis of CF and two copies of the F508del mutation with PPFEV1 greater than 90% (conditional recommendation, very low certainty in the evidence).

  Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is whether or not patients with normal lung function will benefit from treatment through prevention of deterioration rather than improvement in PPFEV1. Other considerations include possible drug–drug interactions, insurance coverage, and cost to the patient.
- Recommendation 25. The committee suggests IVA/LUM combination therapy for individuals aged 12–17 years with a diagnosis of CF and two copies of the F508del mutation with PPFEV1 less than 40% (strong recommendation, moderate certainty in the evidence). Remarks: decisions on whether or not to prescribe IVA/LUM may vary based on several factors. One factor is balancing the potential benefits for this population versus well-documented intolerance of IVA/ LUM in patients with poor lung function. (…)

National Institute for Health and Care Excellence (NICE), 2017 [7].

Cystic Fibrosis: diagnosis and management.

Fragestellung

By making robust recommendations based on the available evidence and best practice in cystic fibrosis care, this guideline will help improve care for this highly complex condition.

Methodik

<u>Grundlage der Leitlinie</u>

- Multidisziplinäres Leitliniengremium (healthcare professionals and researchers as well as lay members)
- Darlegung von Interessenkonflikten und kompletter bzw. teilweiser Ausschluss bei Vorliegen eines Interessenkonfliktes
- Systematische Suche und Qualitätsbewertung, wenn möglich Erstellung von Metaanalysen und GRADE-Profilen
- Recommendations were drafted on the basis of the group's interpretation of the available evidence, taking into account the balance of benefits, harms and costs

between different courses of action. This was either done formally, in an economic model, or informally.

- When clinical and economic evidence was of poor quality, conflicting or absent, the group drafted recommendations based on their expert opinion.
- Konsensusprozess nicht beschrieben
- Update geplant, keine Angabe konkreter Zeiträume

Recherche/Suchzeitraum:

- Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions from January 2015 to September 2016 and partly updated in January 2017. All searches were conducted in MEDLINE, Embase and The Cochrane Library.

LoE

- GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	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	Any estimate of effect is very uncertain.

GoR

- the word 'offer' was used for strong recommendations and 'consider' for weak recommendations

Recommendations

Pulmonary monitoring, assessment and management

Mucoactive agents

Consideration of clinical benefits and harms

The committee discussed whether a mucoactive or mucolytic agent should be prescribed to everyone who has cystic fibrosis. However, taking into account the potential adverse effects, as well as the inconvenience and the cost of treatment, it was agreed not to recommend it to everyone. Instead, the committee agreed that it should be offered to people with cystic fibrosis who have clinical evidence of lung disease based on radiological imaging or lung function testing.
The committee reviewed the evidence comparing dornase alfa to placebo, which shows significant differences in FEV1 in favour of dornase alfa at 1, 3, 6 and 24 month follow-ups, but also a lack of significant differences in FEV1 in people with severe lung disease at 1 month follow-up.
The committee discussed the evidence comparing nebulised sodium chloride with control (0.9%) or low-concentration (< 3%). After reviewing the conflicting evidence comparing 7% sodium chloride to 0.9% sodium chloride, the committee relied on their expertise and experience to recommend hypertonic sodium chloride instead of isotonic sodium chloride. The committee also reviewed the evidence comparing 7% sodium chloride to 3% sodium chloride. A moderate quality RCT found a clinically significant improvement in FEV1 in the group of participants receiving 7% sodium chloride compared to those who were receiving 3% sodium chloride at 2 and 4 week follow-ups. It was discussed whether a specific concentration of hypertonic sodium chloride should be specified in the recommendations. The committee concluded that it was appropriate not to mention a specific concentration because the highest concentration tolerable for the individual patient should be used (to maximum 7%).

The committee reviewed the evidence comparing acetylcysteine to placebo. Very low to moderate quality evidence showed no clinically significant differences in FEV1 between acetylcysteine and placebo at 4, 12 and 24 week follow-ups. Likewise, low quality evidence showed no differences in need for additional intravenous antibiotics for pulmonary exacerbation at 24 week follow-up. No clinically significant differences were found in inflammatory markers or quality of life either. The committee also noted that acetylcysteine was not commonly used in clinical practice because of the unpleasant smell and taste. Moreover, acetylcysteine needs to be taken up to 4 times a day, so overall it is less tolerable and more burdensome than other mucoactive agents. Based on this, the committee agreed not to make a recommendation in favour of acetylcysteine.
The committee was aware of the NICE TA266 that provides guidance on the use of mannitol dry powder for inhalation for the treatment of cystic fibrosis in adults. Therefore data on mannitol was stratified by age to allow the committee to consider the evidence on children and young people separately from the evidence on adults. The committee discussed the recommendations from NICE TA266 and agreed that mannitol could be recommended as an option in adults who cannot use dornase alfa because of ineligibility, intolerance or inadequate response, and in those whose lung function is rapidly declining (FEV1 decline greater than 2% annually) for whom other osmotic agents are not considered appropriate. They agreed that people currently receiving mannitol whose cystic fibrosis does not meet the cited criteria should be able to continue treatment until they, and their clinician, consider it appropriate to stop. Therefore, the committee adopted these recommendations from NICE TA266.
The committee discussed the use of mannitol in children and young people. Overall the evidence did not show mannitol to have significant clinical benefit nor harm. The committee noted that mannitol is rarely used in clinical practice in children and young people. They were aware of issues of poor tolerability and difficulties with the inhaler device in children and young people. The committee agreed that mannitol may be an option for children and young people when rhDNase and hypertonic sodium chloride have failed or are not tolerated and so made a recommendation to this effect.
The committee reviewed the evidence comparing nebulised dornase alfa to hypertonic sodium chloride, which showed significant differences in FEV1 in favour of dornase alfa at 3 month follow-up but not at 3 week follow-up. The evidence was low or very low quality. Due to the limited evidence, the committee relied on their expertise and experience to guide their decision as to whether dornase alfa or hypertonic sodium chloride should be the first-line treatment. On balance, they agreed that dornase alfa was more effective and tolerable, and insufficient evidence was presented to change currently accepted practice. Therefore, the committee recommended dornase alfa as first choice treatment and hypertonic sodium chloride as second choice treatment.
The committee recommended using hypertonic sodium chloride (alone or in combination with dornase alfa) if there is an inadequate response to dornase alfa, based on clinical assessment or lung function testing. The committee noted that treatment should be tailored to the individual, taking into account their previous experience of mucoactive agents and any previously demonstrated efficacy.
The committee discussed whether separate recommendations on dornase alfa and hypertonic sodium chloride were needed for different age groups. However, they concluded that the choice of mucoactive agent would not differ based on age group in current practice and noted that some studies did not present data disaggregated by age subgroups.
No evidence was found for children under 5 years in the evidence review. The committee noted that dornase alfa is not licensed for this age group, however, it is current practice to prescribe dornase alfa to children under 5.

Recommendations:

- Offer a mucoactive agent to people with cystic fibrosis who have clinical evidence of lung disease.
- Offer rhDNase (dornase alfa; recombinant human deoxyribonuclease) as the first choice of mucoactive agent.
- If clinical evaluation or lung function testing indicates an inadequate response to rhDNase, consider both rhDNase and hypertonic sodium chloride or hypertonic sodium chloride alone.
- Consider mannitol dry powder for inhalation for children and young people who cannot use rhDNase and hypertonic sodium chloride because of ineligibility, intolerance or inadequate response.
- Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:

- who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and
- whose lung function is rapidly declining (forced expiratory volume in 1 second [FEV1] decline greater than 2% annually) and
- for whom other osmotic agents are not considered appropriate.

Immunomodulatory agents

Consideration of clinical benefits and harms

The committee discussed the results of the evidence and their experience in clinical practice.
The committee discussed the NMA results that found azithromycin had the best probability of reducing exacerbations and one of the worst for improving lung function. Based on their clinical experience, the committee agreed azithromycin can reduce exacerbations, but may not necessarily improve lung function. They highlighted, however, that there is no evidence that supports a direct link between lung function and clinical exacerbations and the critical outcome is to reduce the number of pulmonary exacerbations. They noted azithromycin does not have such a problematic interaction profile compared to other alternative immunomodulatory agents. They also noted azithromycin is usually offered as first-line in current practice and they agreed to recommend it to people who are suffering a clinical deterioration (as assessed by lung function) and to those who present recurrent pulmonary exacerbations. They suggested that due to its pharmacokinetic profile, it can be administered 3 times per week, rather than daily. The committee discussed the duration of treatment as, in practice, it tends to be used for longer than the duration in studies. It was agreed that treatment should be reviewed periodically to assess response.
The committee agreed that oral corticosteroids can be considered if clinical deterioration continues despite treatment with azithromycin, where all other treatments have been maximised.
The committee noted there was less evidence on fluticasone than the other treatments in the NMA. It was tested in only 12 patients suggesting that more research on fluticasone is needed to increase the confidence in the results. They noted that in practice, fluticasone does not improve lung function to the extent the NMA inferred. In the absence of evidence-base and empirical evidence to support its use, they agreed to not recommend the use of inhaled corticosteroids.
The committee also noted the lack of evidence for omalizumab and that this is limited to case reports.
The committee acknowledged ibuprofen showed a beneficial effect in terms of lung function and nutritional status. However, they were reluctant to recommend it widely due to the high dose and therapeutic drug monitoring required (which is not universally available), its adverse effects profile and potential interaction with other drugs. Although the studies did not show significant adverse events for ibuprofen, they emphasised longer follow-up trials are needed to assess this. Moreover, none of the studies reported on renal function, which is known to be negatively affected by long-term ibuprofen use.
The committee noted ibuprofen is not currently routinely used in clinical practice for the management of cystic fibrosis in the UK. Nevertheless, they agreed not to write a “do not do” recommendation, as they acknowledged ibuprofen may be suitable for some people (for example when azithromycin is not deemed appropriate).
The committee agreed it is important to assess tolerability and adverse effects in addition to efficacy when making decisions about treatment.

Recommendations

- For people with cystic fibrosis and deteriorating lung function or repeated pulmonary exacerbations, offer long-term treatment with azithromycin at an immunomodulatory dose.
- For people who have continued deterioration in lung function, or continuing pulmonary exacerbations while receiving long-term treatment with azithromycin, stop azithromycin and consider oral corticosteroids.
- Do not offer inhaled corticosteroids as an immunomodulatory treatment for cystic fibrosis.

Nutritional Interventions

Consideration of clinical benefits and harms

People with cystic fibrosis often suffer from undernutrition due to faecal fat loss, increased energy requirements caused by chronic infections and malabsorption due to pancreatic insufficiency. It is well established that nutrition is important for lung function and overall health, therefore, different nutritional interventions to improve the nutritional status and growth of people with cystic fibrosis should be considered. Because nutrition is such an important component of overall health and a considerable problem among people with cystic fibrosis, the committee agreed that dietitians should be an integral part of the multidisciplinary team caring for the person with cystic fibrosis and review the patient regularly. This should be from an individualised basis considering a myriad of factors, including current diet, salt and water intake, bowel habit in relation to pancreatic enzyme use as well as family circumstances and needs and capabilities before recommending any nutritional intervention.

If there are nutrition concerns, the committee recommended, based on their clinical experience and expertise, to encourage people to increase portion size and eat high-energy foods in order to increase calorie intake and counterbalance increased energy requirements and malabsorption.

The committee noted that the available evidence showed that oral calorie supplements are not effective in improving nutrition or growth in people in cystic fibrosis. Therefore, the committee agreed not to recommend them as a routine intervention for the general population of people with cystic fibrosis. They discussed whether to recommend them if there are nutrition concerns. They noted that out of 3 studies on oral nutritional supplements, the population in 2 studies (Hanning 1993 and Kalnins 2005) was small (between 15 and 20 participants) and did not represent the population that dietitians would actually consider offering nutrition interventions to because inclusion criteria were either unclear (Hanning 1993) or used relatively high thresholds for weight (Kalnins 2005) to define the study populations. Only one study (Poustie 2006, 102 participants) showed no effectiveness of oral nutritional supplements in a population defined by inclusion criteria that were similar to the thresholds for additional nutritional support outlined in the CF Trust consensus document on nutritional management of cystic fibrosis. The committee agreed that supplements, if effective, would be preferable, from a patient's perspective, to enteral tube feeding, which is an invasive technique, or to appetite stimulant drugs which may be associated with adverse effects. Therefore, based on their clinical experience and expertise, they agreed that oral nutritional supplements should be considered on a trial basis for people requiring additional nutrition who had not responded to dietary advice before considering more invasive interventions.

The committee noted that the evidence showed enteral tube feeding to be effective in improving nutrition and growth in people with cystic fibrosis. The committee agreed that the capacity and the capabilities of the person and family should always be carefully considered before embarking on this.

The committee looked at appetite stimulants as an alternative to enteral tube feeding. The committee noted that evidence on megestrol acetate and cyproheptadine hydrochloride shows that they can improve nutritional status and growth. However, the committee noted that the evidence was based on studies with small sample size and discussed whether appetite stimulants can have adverse effects such as hyperglycaemia and adrenal insufficiency. There was no evidence available on adverse effects of cyproheptadine hydrochloride and limited evidence available on adverse effects of megestrol acetate, which was limited to either 3 or 6 months follow-up. This evidence showed no clinically significant difference in constipation at 6 months and no difference in fasting blood glucose levels at 3 months (clinical significance could not be calculated) between participants receiving megestrol acetate and those receiving placebo. According to the evidence, some participants had decreased morning cortisol levels after receiving megestrol acetate, however, in one study with 3 months follow-up values in the control group were not reported, while in the other study with 6 months follow-up there was no clinically significant difference with the control group, and values increased after the intervention group stopped receiving megestrol acetate. The committee discussed that although many people with cystic fibrosis considering appetite stimulants might already have diabetes, and in their clinical experience, adrenal insufficiency is not very often observed, they agreed to recommend them only in adults, short-term (for example up to 3 months) and after all other options had been fully explored. Moreover, possible adverse effects should be explained so that an informed decision can be made. The committee discussed whether the appetite stimulants for which the evidence was reviewed (megestrol acetate and cyproheptadine hydrochloride) should be named in the recommendations. However, they agreed not to endorse these specifically because of the limitations of the evidence. The decision about these treatments should be based on the whole clinical picture as well as the patient's preferences and capabilities.

The committee agreed that oral calorie supplements, enteral feeding and appetite stimulants should be closely monitored and discontinued if there are no positive outcomes.

Recommendations

- The cystic fibrosis specialist dietitian should offer advice on the benefits of optimal nutrition, and at the annual assessment, review the person's:
  - total nutritional intake, including energy intake (calories)
  - estimated nutritional needs
  - pancreatic enzyme replacement therapy, if appropriate.
- Encourage people to increase calorie intake by increasing portion size and eating high-energy foods, if there is concern about their nutrition (including weight loss and inadequate weight gain).
- If increased portion size and high-energy foods are not effective, consider a trial of oral nutritional supplements.
- If attempts to increase calorie intake are not effective, consider:
  - supplementation with enteral tube feeding, or
  - for adults, a short-term trial of an appetite stimulant (for example up to 3 months).

Exocrine pancreatic insufficiency

Consideration of clinical benefits and harms

The committee agreed that the use of PERT is well-established in clinical practice as it is known that PERT treatment is useful in overcoming enzyme deficiency in people with cystic fibrosis. However, they noted there is uncertainty regarding the optimal doses of enzymes needed.
Based on this, the committee agreed to recommend to offer PERT to people with cystic fibrosis with pancreatic insufficiency and that the dose should be adjusted for each person in order to minimise symptoms of malabsorption.
The committee agreed that evidence regarding the effectiveness of PERT dose and acid suppression in relation to resolution of malabsorption symptoms, improvement in weight and improvement in patient satisfaction or health-related quality of life was very limited and of very low quality or completely lacking. They noted that the normal clinical approach to determining individual need was an empirical one, for instance titrating the PERT dose in terms of units of lipase against the amount of fat being ingested. A standard dose, related to age in children, was usually given and adjustment then made based on the clinical response in terms of trying to achieve a normal bowel habit and the resolution of any malabsorption symptoms. They recommended that, in people with confirmed pancreatic exocrine insufficiency, the dose was titrated against symptoms and regularly reviewed. High enzyme concentration products would aid treatment optimisation where there was a higher dose requirement.

Recommendations

- Test for exocrine pancreatic insufficiency in people with cystic fibrosis, using a non-invasive technique such as stool elastase estimation. If the test result is normal, repeat it if symptoms or signs suggesting malabsorption occur.
- Offer oral pancreatic enzyme replacement therapy to people with exocrine pancreatic insufficiency. Adjust the dose as needed to minimise any symptoms or signs of malabsorption.
- Consider an acid suppression agent (for example an H2 receptor antagonist or a proton pump inhibitor) for people who have persistent symptoms or signs of malabsorption despite optimal pancreatic enzyme replacement therapy.

Referenzen aus Leitlinien

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Poustie, V. J., Russell, J. E., Watling, R. M., Ashby, D., Smyth, R. L., Calico Trial Collaborative Group, Oral protein energy supplements for children with cystic fibrosis: CALICO multicentre randomised controlled trial, BMJ, 332, 632-6, 2006

Lahiri T et al., 2016 [6].

Cystic Fibrosis Foundation

Clinical Practice Guidelines from the Cystic Fibrosis Foundation for Preschoolers With Cystic Fibrosis

Fragestellung

To develop comprehensive evidence-based and consensus recommendations for the care of preschool children, ages 2 to 5 years, with CF. This document includes recommendations in the following areas: routine surveillance for pulmonary disease, therapeutics, and nutritional and gastrointestinal care.

Methodik

Grundlage der Leitlinie

- multidisziplinäres Leitliniengremium: 16 CF pediatric experts and parents
- Interessenkonflikte sind dargelegt, Umgang damit unklar
- Entwicklung von PICO-Fragen, Suche in Medline und Handsuche
- Entwicklung von Empfehlungen auf Basis der Evidenz, bei fehlender Evidenz Nutzung von Evidenz von älteren Kindern und klinischer Erfahrung
- Konsensusprozess anhand eines Online Surveys, 80% Zustimmung waren für die Annahme der Empfehlung notwendig, mindestens 87,5 % wurden bei allen Empfehlungen erreicht

Recherche/Suchzeitraum:

- Suche in Medline in 2014 (keine exakte Angabe)

LoE

- nicht bewertet

GoR

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Sonstige methodische Hinweise

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz zur pädiatrischen Population, wird die LL jedoch ergänzend dargestellt.

Empfehlungen

Topic	Recommendation Statement	Grade or Consensus	Previous Guideline(s)
Therapeutics: Exacerbations	16. For children with CF, ages 2 through 5 y, the CF Foundation recommends the use of oral, inhaled, and/or intravenous antibiotics to treat pulmonary exacerbations.	Consensus Recommendation	
Therapeutics: Airway Clearance	17. For children with CF, ages 2 through 5 y, the CF Foundation recommends the use of daily airway clearance to improve lung function and reduce exacerbations.	Consensus Recommendation	Cystic Fibrosis Foundation Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009) Consensus Recommendation Certainty: Low Benefit: Moderate Cystic Fibrosis Pulmonary Guidelines: Airway Clearance Therapies (2009) Grade B, Certainty Fair, Benefit: Moderate
Therapeutics: Airway Clearance	18. For children with CF, ages 2 through 5 y, the CF Foundation recommends increasing frequency and/or duration of airway clearance treatments for children diagnosed with pulmonary exacerbations.	Consensus Recommendation	Cystic Fibrosis Pulmonary Guidelines: Airway Clearance Therapies (2009) Grade B
Therapeutics: Bronchodilators	19. For children with CF, ages 2 through 5 y, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled bronchodilators to improve lung function and quality of life or reduce exacerbations.	Grade: I; Certainty: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013), Grade: I, Certainty: Low
Therapeutics: Hypertonic saline	20. For children with CF, ages 2 through 5 y, the CF Foundations recommends that hypertonic saline be selectively offered to patients based on individual circumstances.	Grade C; Certainty: Moderate; Benefit: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013) Grade: B, Certainty: Moderate, Benefit: Moderate
Therapeutics: Dornase alfa	21. For children with CF, ages 2 through 5 y, the CF Foundation recommends that dornase alfa be selectively offered to patients based on individual circumstances.	Grade C; Certainty: Moderate; Benefit: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013) Moderate to severe disease: Grade: A, Certainty: High, Benefit: Substantial. Mild disease: Grade: B. Certainty: High, Benefit: Moderate Cystic Fibrosis Foundation Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009) In symptomatic infants: Consensus Recommendation, Certainty: Low, Benefit: Moderate

Therapeutics: Inhaled Corticosteroids	22. For children with CF, ages 2 through 5 y, and without asthma or recurrent wheezing, the CF Foundation recommends against the routine use of inhaled corticosteroids to reduce exacerbations, airway inflammation, or improve lung function or quality of life.	Grade: D; Certainty: High; Benefit: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013) Grade: D, Certainty: High, Benefit: Zero. Cystic Fibrosis Foundation Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009) Consensus Recommendation, Certainty: Low, Benefit: Zero/Negative
Therapeutics: Corticosteroids	23. For children with CF, ages 2 through 5 y, and without allergic bronchopulmonary aspergillosis, the CF Foundation recommends against the chronic use of systemic corticosteroids to reduce exacerbations, or improve lung function, or quality of life.	Grade: D; Certainty: High; Benefit: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013) Grade: D, Certainty: High, Benefit: Negative
Therapeutics: Ibuprofen	24. For children with CF, ages 2 through 5 y, the CF Foundation concludes that there is insufficient evidence to recommend for or against chronic high-dose ibuprofen use to slow rate of decline of FEV_1, reduce exacerbations and hospitalizations, or improve quality of life.	Grade: I; Certainty: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013), Grade B, Certainty: Moderate, Benefit: Moderate
Therapeutics: Leukotriene Modifiers	25. For children with CF, ages 2 through 5 y, the CF Foundation concludes that the evidence is insufficient to recommend for or against the routine chronic use of leukotriene modifiers to improve lung function or quality of life or reduce exacerbations	Grade: I; Certainty: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013), Grade: I, Certainty: Low
Therapeutics: Azithromycin	26. For children with CF, ages 2 through 5 y, the CF Foundation concludes that there is insufficient evidence to recommend for or against the chronic use of azithromycin.	Grade: I; Certainty: Low	Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013), Grade: C, Certainty: Moderate, Benefit: Small
Therapeutics: Ivacaftor	31. For children with CF, ages 2 through 5 y, the Preschool Guidelines Committee recommends the routine use of ivacaftor in those with specific gating mutations* and a consideration for those with a confirmed diagnosis of CF and a R117H mutation. *The mutations are G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, and S549R.	Consensus Recommendation	Chronic Medications (2013) Grade: A, Certainty: Substantial, Benefit: High
Nutrition, Behavior, and Gastrointestinal: Nutritional Risk	38. For children with CF, ages 2 through 5 y, and at nutritional risk, the CF Foundation recommends the use of oral nutrition supplements, in addition to usual dietary intake, to improve rate of weight gain.	Grade: B; Certainty: Moderate; Benefit: Moderate	Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review (2008) Grade: B
Nutrition, Behavior, and Gastrointestinal: Nutritional Risk	40. For children with CF, ages 2 through 5 y, at nutritional risk who do not respond to standard nutritional intervention and who have not responded to the evaluation and management plan of the multidisciplinary team, the CF Foundation recommends the use of enteral nutritional supplements via a feeding tube to improve the rate of weight gain. The concept of enteral feedings should be introduced early as a component of CF care.	Grade: B; Certainty: Moderate; Benefit: Moderate	
Nutrition, Behavior, and Gastrointestinal: Vitamins	41. For children with CF, ages 2 through 5 y, the CF Foundation recommends standard, age-appropriate non–fat-soluble vitamins and the recommended levels of vitamins A, D, E, and K by using a fat-soluble vitamin supplement formulated for children with CF and if indicated based on levels, additional supplementation of vitamins A, D, E, and K.	Consensus Recommendation	Cystic Fibrosis Foundation Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009) Consensus Recommendation Certainty: Low Benefit: Moderate
Nutrition, Behavior, and Gastrointestinal: PERT	45. For children with CF and PI, ages 2 through 5 y, the CF Foundation recommends that PERT be adjusted up to a dose of no greater than 2500 lipase units per kg per meal with a maximum daily dose of 10 000 lipase units/kg.	Consensus Recommendation	Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review (2008) Consensus Recommendation

<u>Bronchodilators</u>

No studies were found that address bronchodilator efficacy in the absence of asthma or bronchial hyperresponsiveness in CF; therefore, the evidence is insufficient to recommend for or against the chronic use of inhaled bronchodilators in preschoolers. However, viral-

triggered wheezing or asthma in preschoolers may respond to bronchodilator therapy. (Recommendation 19).

Hypertonic Saline

Several studies have demonstrated safety and tolerability of 7% hypertonic saline (HS) in infants and young children.[69–71] Unlike a study in older individuals with CF, [72] a randomized controlled trial of 344 children <5 years failed to show a reduction in the primary endpoint of pulmonary exacerbation rate.[73] However, in 2 small studies that were part of this larger trial, infant lung function and the LCI did demonstrate improvement in subjects receiving 7% HS.[73, 74] Given these findings, the CF Foundation recommends that HS be offered to patients based on individual circumstances, either for chronic use or during acute pulmonary exacerbation. Further studies may alter this recommendation. (Recommendation 20.)

Dornase Alfa

Routine use of dornase alfa is associated with reduced pulmonary exacerbations, improved lung function, and decreased rate of lung function decline among older children and adults with CF.[75–81] Dornase alfa has been shown to have positive effects on CT changes and LCI[82–84] and improved health-related quality-of-life scores in children >6 years.[85] Safety and tolerability of dornase alfa has been demonstrated in children ages 3 months to 5 years.[86, 87] Potential benefits include its effect on mucous plugging, air trapping, and lung health in CF that may result in delayed pulmonary disease progression. Based on moderate evidence that dornase alfa is safe and effective, and the potential benefit is at least small, the CF Foundation recommends that dornase alfa be offered to patients based on individual circumstances, either for chronic use or during acute pulmonary exacerbation. Further studies may alter this recommendation. (Recommendation 21)

Systemic and Inhaled Corticosteroids

With the exception of treatment of allergic bronchopulmonary aspergillosis, systemic corticosteroids are not recommended for routine use in children with CF, as potential harm outweighs any benefit. Inhaled corticosteroids are not recommended for management of CF lung disease, as no clear benefit has been identified.[2] (Recommendation 22–23)

Ibuprofen

High-dose ibuprofen is recommended for chronic use in individuals with CF older than 6 years with mild lung disease.[2] We found no prospective trials that support its use in children younger than 6 years and conclude there is insufficient evidence to recommend for or against its use in preschoolers with CF. (Recommendation 24).

Azithromycin

Routine use of azithromycin is recommended for individuals with CF >6 years with persistent P aeruginosa infection.[2] Azithromycin is safe, reduces lower airway inflammation and exacerbations, and improves lung function and weight gain in older children with mild CF lung disease.[88, 89] There are conflicting data regarding the potential for higher nontuberculous mycobacterial infection rates in individuals with CF on chronic azithromycin.[60,90–92] There is insufficient evidence to recommend for or against the chronic use of azithromycin in preschoolers with CF. (Recommendation 26)

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Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2021) am 26.11.2021

#	Suchfrage
1	[mh "cystic fibrosis"]
2	("cystic fibrosis" OR mucoviscidosis):ti
3	#1 OR #2
4	#3 with Cochrane Library publication date from Nov 2016 to Nov 2021

Systematic Reviews in Medline (PubMed) am 26.12.2021

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	cystic fibrosis[mh]
2	cystic fibrosis[tiab]
3	mucoviscidosis[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT

#	Suchfrage
	(letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	(#5) AND ("2016/11/01"[CDAT] : "3000"[CDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 26.11.2021

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	mucoviscidosis[tiab]
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2016/11/01"[CDAT] : "3000"[CDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 26.11.2021

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, 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

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

2021-B-399-z + 2021-B-400-z

Kontaktdaten

Dr. med. Jutta Hammermann für GPP

Indikation gemäß Beratungsantrag

„zur Behandlung der zystischen Fibrose (CF) bei Personen ≥ 6 bis < 12 Jahre, die mindestens eine F508del-Mutation im CFTR-Gen (Cystic Fibrosis Transmembrane Conductance Regulator) aufweisen."

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Der Behandlungsstandard bei Kindern mit Mukoviszidose und mindestens einer F508del-Mutation besteht aus allgemeinen präventiven und therapeutischen Maßnahmen, organspezifischen symptomorientierten Therapien und CFTR-Modulator-Therapien, entsprechend der Zulassung für die individuelle Mutationskombination. Zu den allgemeinen präventiven und therapeutischen Maßnahmen gehört die Empfehlung für besondere Hygienestandards bei Mukovsizidose zur Vermeidung chronischer Lungeninfektionen, die Ernährungstherapie mit Empfehlung zur hochkalorischen fett- und eiweißreichen, eher kohlenhydratarmen Ernährung gesteuert nach Wachstum und Gewichtszunahme, Salzzufuhr nach Bedarf, körperlicher Aktivität und Sport.

Organspezifisch gehören zur Basistherapie der Lungenerkrankung neben spezieller Physioatemtherapie, sekretolytische Inhalationen mit hypertoner Kochsalzlösung und nach Bedarf DNase, sowie bedarfsorientiert Inhalationen mit Bronchospasmolytika und je nach Keimstatus Therapie mit oralen und/oder inhalativen Antibiotika akut oder dauerhaft.

Besteht eine exokrine Pankreasinsuffizienz (80% der Patienten mit Mukoviszidose) muss eine fettadaptierte Lipase-Substitution erfolgen, sowie Substitution fettlöslicher Vitamine und Spurenelemente nach Bedarf.

Die Therapie der Lebererkrankung bei Mukoviszidose richtet sich ebenfalls nach der klinischen Manifestation und erfolgt mit Deoxyursocholsäure. Es muss auf eine ausreichende Flüssigkeitszufuhr geachtet werden, symptomorientierte Therapie von Darmmotilitätsstörungen und gastroösophagealem Reflux.

Die symptomatische Therapie sollte immer individuell angepasst je nach Symptomlast, körperlicher Entwicklung und Nachweis bakterieller Erreger erfolgen.

Neben der symptomatischen Therapie steht mit den CFTR-Modulatoren eine Therapie des Basisdefektes bei Mukoviszidose zur Verfügung. In der Altersklasse von 6 – 12 Jahren sind derzeit die CFTR Modulatoren Ivacaftor, die Kombination Ivacaftor/Lumacaftor und Ivacaftor/Tezacaftor zugelassen. Die Wahl des CFTR-Modulators zur Therapie ist abhängig von der vorliegenden CFTR-Mutations-Kombination. Ivacaftor ist zugelassen für Patienten mit sogenannten Gating-Mutationen (G551D, G1244E, G1349D, G178R G551S, S1251N, S1255P, S549N, S549R, R117H), auch in Kombination mit einer F508del-Mutation. Ivacaftor/Lumacaftor ist zugelassen für Patienten mit einer Homozygotie F508del. Ivacaftor/Tezacaftor ist zugelassen für Patienten mit einer Homozygotie F508del oder Compound-Heterozygotie F508del in Kombination mit folgenden Mutationen: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272 26A→G, 3849+10kbC→T. Durch den Einsatz von CFTR-Modulatoren wird je nach vorliegenden Mutationen in unterschiedlichem Ausmaß eine Verbesserung der CFTR-Funktion erreicht. Das führt ebenfalls in unterschiedlichem Ausmaß zu einer Verbesserung der Schweiß-Chloridwerte und der Lungenfunktions-Parameter, sowie zu einer Abnahme der pulmonalen Exazerbationsrate und Verbesserung der Gewichts- und Längenentwicklung. Durch den frühen Einsatz dieser Therapie-Optionen noch vor Vorliegen ausgeprägter klinischer Symptome kann der Krankheitsverlauf positiv beeinflusst werden. Welche

Modulator-Kombination bei Patienten mit einer Homozygotie F508del eingesetzt wird (Ivacaftor/Lumacaftor oder Ivacaftor/Tezacaftor), hängt von der individuellen Wirkung und den individuellen Nebenwirkungen ab. Ab 12 Jahren ist die Modulator-Triple-Kombination Ivacafor/Tezacaftor/Elexacaftor für Patienten mit mindestens einer F508del-Mutation zugelassen. In der Altersgruppe ab 12 Jahren konnten in den Studien noch deutlich potentere Effekte auf die CFTR-Funktion nachgewiesen werden, so dass eine Absenkung der Altersgrenze bezüglich der Zulassung auch hier wünschenswert ist, um allen Mukoviszidose-Patienten mit entsprechenden Mutations-Kombinationen dieses Medikament schon früh verfügbar machen zu können und dadurch sowohl den Verlauf der Lungenerkrankung und chronischer Veränderungen am Lungengewebe positiv zu beeinflussen, als auch die exokrine Pankreasrestfunktion länger zu erhalten und weitere Organ-Manifestationen zu verzögern oder sogar zu vermeiden.

In Deutschland erfolgt die Versorgung der meisten Patienten mit Mukoviszidose in spezialisierten Ambulanzen und Zentren. Die Gesellschaft für pädiatrische Pneumologie (GPP) und die Deutsche Gesellschaft für Pneumologie (DGP) hat gemeinsam mit dem Mukoviszidose-Institut unter dem Dach des Mukoviszidose e.V. ein Zertifizierungsverfahren für Mukoviszidose-Ambulanzen etabliert. Nach diesem Verfahren zertifizierte Ambulanzen zeichnen sich durch die Bereitstellung aller personellen Ressourcen, welche zu einem Behandler-Team für Mukoviszidose gehören (Ärzte, Physiotherapeuten, Ernährungsberater, psychosozialer Dienst, spezialisiertes Pflegepersonal), sowie notwendiger diagnostische Möglichkeiten, entsprechenden Hygienekonzepten, Therapie nach vorliegenden Empfehlungen, regelmäßiger Teilnahme an spezifischen Weiterbildungsmaßnahmen und Teilnahme am Deutschen Mukoviszidose-Register aus. Eine Karte aller zertifizierten (und auch nicht zertifizierten) CF-Ambulanzen ist im Internet über die Seite des Mukoviszidose e.V. (www.muko.info) abrufbar. Neben den internationalen Leitlinien wurden und werden deutschsprachige Leitlinien zur Diagnosestellung, Diagnostik und Therapie der Mukoviszidose erstellt, diese sind über die AWMF verfügbar. Neben der allgemeinen Auswertung von Registerdaten ist ein Benchmarking-Projekt über das Mukoviszidose-Institut etabliert um die Versorgungsqualität ständig zu vergleichen und zu optimieren.

Zu Therapiestandards speziell in der angefragten Altersklasse von 5-11 Jahren steht unter anderem folgende Literatur zur Verfügung (ohne Anspruch auf Vollständigkeit):

AWMF-Leitlinien (www.awmf.org):
S3-Leitlinie: Mukoviszidose bei Kindern in den ersten beiden Lebensjahren, Diagnostik und Therapie
AWMF-Registernummer 026 – 024
S2-Konsensus-Leitlinie: Diagnose der Mukoviszidose
AWMF-Registernummer 026-023
S3 – Leitlinie: Lungenerkrankung bei Mukoviszidose, Modul 1: Diagnostik und Therapie nach dem ersten Nachweis von Pseudomonas aeruginosa
AWMF-Registernummer 026 – 022
S3-Leitlinie: Lungenerkrankung bei Mukoviszidose, Modul 2: Diagnostik und Therapie bei der chronischen Infektion mit Pseudomonas aeruginosa
AWMF-Registernummer 026 - 018

European Cystic Fibrosis Society Standards of Care: Best Practice guidelines.
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Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Kriterien für unterschiedliche Behandlungsentscheidungen sind zum einen der sehr variable klinische Verlauf der Mukoviszidose. Dieser ergibt sich zum einen durch die unterschiedlichen Mutations-Kombinationen zum Anderen auch durch weitere genetische und klinische, sowie soziale Kontext-Faktoren. Die Behandlung muss immer individuell mit den Mukoviszidose-Patienten und ihren Familien abgestimmt werden, sie richtet sich nach der Wirkung aber auch den Nebenwirkungen der durchgeführten Therapien und nach der Therapie-Adherence. Für Patienten mit Mukoviszidose ist eine regelmäßige, mindestens 4x jährliche Verlaufskontrolle in einer spezialisierten Mukoviszidose-Ambulanz empfohlen. Kontrolliert werden klinischer Verlauf, Lungenfunktion, anthropometrische Daten, Keimstatus, Laborparameter, Ernährungsstatus, Bildgebung der Lunge und des Abdomens, soziale und psychische Faktoren. Speziell zur Verlaufskontrolle unter Modulator-Therapie eignen sich zusätzliche Schweißtest-Verlaufskontrollen. Alle diese Faktoren fließen dann in eine individuelle Therapie-Anpassung ein.

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