Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-009 Tezacaftor/Ivacaftor

Stand: März 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Tezacaftor / 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-481 Ivacaftor (Beschluss am 20.02.2020)* - *D-480 Ivacaftor (Beschluss am 20.02.2020)* - *D-479 Ivacaftor (Beschluss am 20.02.2020)* - *D-478 Ivacaftor (Beschluss am 20.02.2020)* - *D-477 Ivacaftor (Beschluss am 20.02.2020)* - *D-476 Ivacaftor (Beschluss am 20.02.2020)* - *D-431 Ivacaftor (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 (nAGW; 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:	
Ivacaftor/ Tezacaftor R07AX31 Symkevi®	Ivacaftor/Tezacaftor wird angewendet als Kombinationsbehandlung mit Ivacaftor 150 mg Tabletten zur Behandlung der zystischen Fibrose (CF) bei Patienten ab 12 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. (FI Stand: 02/2019)
CFTR-Modulatoren	
Ivacaftor R07AX02 Kalydeco®	Kalydeco-Tabletten werden angewendet zur Behandlung von Patienten mit zystischer Fibrose (CF, Mukoviszidose) ab 6 Jahren mit einem Körpergewicht von mindestens 25 kg, die eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549Noder S549R. Kalydeco-Tabletten werden außerdem angewendet zur Behandlung von Patienten mit zystischer Fibrose (CF) ab 18 Jahren, bei denen eine R117H-Mutation im CFTR-Gen vorliegt. Kalydeco-Tabletten werden ferner angewendet im Rahmen einer Kombinationsbehandlung mit Tezacaftor 100 mg/Ivacaftor 150 mg-Tabletten zur Behandlung von Patienten mit zystischer Fibrose ab 12 Jahren, die homozygot für die F508del-Mutation sind oder heterozygot für die F508del-Mutation und eine der folgenden Mutationen im CFTR-Gen aufweisen: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10kbC→T. (FI Stand: 04/2019)
Lumacaftor/ Ivacaftor R07AX30 Orkambi®	Lumacaftor/Ivacaftor ist angezeigt zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten ab 12 Jahren, die homozygot für die F508del-Mutation im CFTR-Gen sind. (FI Stand: 01/2019)
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. (FI Ceftazidim Kabi Stand: 08/2015)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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. (FI Stand: 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. (FI Ciprobay® Stand: 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. (FI Quinsair® Stand: 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. (FI ColistiFlex® Stand: 08/2017)
Meropenem 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. (FI Stand: 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. (FI Bramitob® Stand: 03/2019)
Sekretolytische Therapie	
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. (FI Stand: 04/2017)
Mannitol R05CB16 Bronchitol®	Mannitol wird angewendet zur Behandlung der zystischen Fibrose (Mukoviszidose) bei Erwachsenen ab 18 Jahren zusätzlich zum besten Therapiestandard. (FI Stand: 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. (FI Stand: 08/2006)

Quellen: AMIS-Datenbank, Fachinformationen Stand: 10/2019

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-009 (Tezacaftor und Ivacaftor)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	25. Februar 2020

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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

Indikation für die Synopse: Zystische Fibrose (CF, Mukoviszidose)
Hinweis zur Synopse: Systematische Übersichtsarbeiten zur Physiotherapie und Ernährungstherapie wurden nicht eingeschlossen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation zystische Fibrose durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.10.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 535 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 25 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

G-BA, 2020 [3].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AMRL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ivacaftor (Überschreitung 50 Mio. € Grenze: zystische Fibrose, Kombinationsbehandlung mit Tezacaftor/Ivacaftor bei Patienten ab 12 Jahren (homozygot bzgl. F508del)). Vom 20. Februar 2020.

Anwendungsgebiet

Anwendungsgebiet (laut Zulassung vom 10. Oktober 2018): Kalydeco-Tabletten werden ferner angewendet im Rahmen einer Kombinationsbehandlung mit Tezacaftor 100 mg/Ivacaftor 150 mg-Tabletten zur Behandlung von Patienten mit zystischer Fibrose ab 12 Jahren, die homozygot für die F508del-Mutation sind.

Zweckmäßige Vergleichstherapie

- Patienten ab 12 Jahren mit zystischer Fibrose, die homozygot für die F508del-Mutation sind: Lumacaftor/Ivacaftor

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ivacaftor in Kombination mit Tezacaftor/Ivacaftor gegenüber Lumacaftor/Ivacaftor:

- Ein Zusatznutzen ist nicht belegt.

G-BA, 2020 [4].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AMRL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ivacaftor (Überschreitung 50 Mio. € Grenze: Zystische Fibrose, Patienten ab 6 Jahren mit G551D-Mutation). Vom 20. Februar 2020.

Anwendungsgebiet

„Kalydeco-Tabletten werden angewendet zur Behandlung von Patienten mit zystischer Fibrose (CF, Mukoviszidose) ab 6 Jahren mit einem Körpergewicht von mindestens 25 kg, die eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R (siehe Abschnitte 4.4 und 5.1).“

Der vorliegende Beschluss bezieht sich ausschließlich auf das Anwendungsgebiet der zystischen Fibrose bei Patienten ab 6 Jahren mit einem Körpergewicht von mindestens 25 kg, bei denen die Gating-Mutation G551D im CFTR-Gen vorliegt.

Zweckmäßige Vergleichstherapie

a) Patienten mit zystischer Fibrose mit einer G511D-Mutation im CFTR-Gen im Alter von 6 bis 11 Jahren:

- Best-Supportive-Care

  Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der Heilmittel-RL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

b) Patienten mit zystischer Fibrose mit einer G511D-Mutation im CFTR-Gen ab 12 Jahren:

- Best-Supportive-Care

  Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der Heilmittel-RL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

Fazit / Ausmaß des Zusatznutzens

a) Patienten mit zystischer Fibrose mit einer G511D-Mutation im CFTR-Gen im Alter von 6 bis 11 Jahren:

- Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen

b) Patienten mit zystischer Fibrose mit einer G511D-Mutation im CFTR-Gen ab 12 Jahren:

- Anhaltspunkt für einen beträchtlichen Zusatznutzen

G-BA, 2020 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AMRL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ivacaftor (Überschreitung 50 Mio. € Grenze: Zystische Fibrose, Patienten ab 6 Jahren, diverse Gating-Mutationen). Vom 20. Februar 2020.

Anwendungsgebiet

„Kalydeco-Tabletten werden angewendet zur Behandlung von Patienten mit zystischer Fibrose (CF, Mukoviszidose) ab 6 Jahren mit einem Körpergewicht von mindestens 25 kg, die eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R (siehe Abschnitte 4.4 und 5.1)."

Der vorliegende Beschluss bezieht sich ausschließlich auf das Anwendungsgebiet der zystischen Fibrose bei Patienten ab 6 Jahren mit einem Körpergewicht von mindestens 25 kg, bei denen eine der folgenden Gating-Mutationen im CFTR-Gen vorliegt: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R (nicht G551D-Mutation).

Zweckmäßige Vergleichstherapie

Patienten mit zystischer Fibrose ab 6 Jahren, die eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R:

- Best-Supportive-Care

Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der Heilmittel-RL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

G-BA, 2020 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ivacaftor (Neubewertung eines Orphan-Drugs nach Überschreitung der 50 Mio. Euro Grenze: Patienten mit CF ab 18 Jahren, R117H-Mutation). Vom 20. Februar 2020.

Anwendungsgebiet

Kalydeco wird angewendet zur Behandlung von Patienten mit zystischer Fibrose (CF) ab 18 Jahren, bei denen eine R117H-Mutation im CFTR-Gen vorliegt (siehe Abschnitt 4.4 und 5.1).

Zweckmäßige Vergleichstherapie

Patienten mit zystischer Fibrose ab 18 Jahren, bei denen eine R117H-Mutation im CFTR- Gen vorliegt Zweckmäßige Vergleichstherapie:

- Best-Supportive-Care

  Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i.S. der HeilmittelRL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2020 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AMRL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ivacaftor (Überschreitung 50 Mio. € Grenze: Zystische Fibrose, Patienten von 2–5 Jahren). Vom 20. Februar 2020.

Anwendungsgebiet

Ivacaftor wird angewendet zur Behandlung von Kindern mit zystischer Fibrose (CF, Mukoviszidose) ab 12 Monaten mit einem Körpergewicht zwischen 7 kg und weniger als 25 kg, die eine der folgenden Gating-Mutationen (Klasse III) im CFTRGen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R.

Der vorliegende Beschluss bezieht sich ausschließlich auf das Anwendungsgebiet Kinder mit zystischer Fibrose im Alter von 2 bis 5 Jahren, die eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R

Zweckmäßige Vergleichstherapie

Kinder mit zystischer Fibrose im Alter von 2 bis 5 Jahren, die eine der folgenden GatingMutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R:

- Best-Supportive-Care

Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der HeilmittelRL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

G-BA, 2020 [1].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AMRL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ivacaftor (neues Anwendungsgebiet: Zystische Fibrose, Patienten 12 - < 24 Monate). Vom 20. Februar 2020.

Anwendungsgebiet

Ivacaftor wird angewendet zur Behandlung von Kindern mit zystischer Fibrose (CF, Mukoviszidose) ab 12 Monaten mit einem Körpergewicht zwischen 7 kg und weniger als 25 kg, die eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N oder S549R.

Der vorliegende Beschluss bezieht sich ausschließlich auf das neu zugelassene Anwendungsgebiet vom 30. November 2019, d.h. auf Kinder mit zystischer Fibrose im Alter von 12 bis < 24 Monaten, die eine der folgenden Gating-Mutationen (Klasse III) im CFTRGen aufweisen: G551D, G1244E, G1349D, G178R, G5515, S1251N, S1255P, S549N oder S549R.

Zweckmäßige Vergleichstherapie

Kinder mit zystischer Fibrose im Alter von 12 bis < 24 Monaten, die eine der folgenden Gating-Mutationen (Klasse III) im CFTR-Gen aufweisen: G551D, G1244E, G1349D, G178R, G5515, S1251N, S1255P, S549N oder S549R:

- Best-Supportive-Care

Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der HeilmittelRL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen

G-BA, 2020 [2].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AMRL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ivacaftor (Überschreitung 50 Mio. € Grenze: zystische Fibrose, Kombinationsbehandlung mit Tezacaftor/Ivacaftor bei Patienten ab 12 Jahren (heterozygot bzgl. F508del)). Vom 20. Februar 2020.

Anwendungsgebiet

Kalydeco-Tabletten werden ferner angewendet im Rahmen einer Kombinationsbehandlung mit Tezacaftor 100 mg/Ivacaftor 150 mg-Tabletten zur Behandlung von Patienten mit zystischer Fibrose ab 12 Jahren, die heterozygot für die F508del-Mutation sind und eine der folgenden Mutationen im CFTR-Gen aufweisen: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10kbC→T.

Zweckmäßige Vergleichstherapie

Patienten ab 12 Jahren mit zystischer Fibrose, die heterozygot für die F508del-Mutation sind und eine der folgenden Mutationen im CFTR-Gen aufweisen: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10kbC→T.

- Best-Supportive-Care

  Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der Heilmittel-RL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [8].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Lumacaftor/Ivacaftor (neues Anwendungsgebiet: zystische Fibrose, Patienten 2–5 Jahre), vom 15. August 2019.

Anwendungsgebiet

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.

Hinweis: Der vorliegende Beschluss bezieht sich ausschließlich auf das neu zugelassene Anwendungsgebiet vom 15. Januar 2019, d.h. auf Kinder von 2 bis 5 Jahren mit zystischer Fibrose, die homozygot für die F508del-Mutation im CFTR-Gen sind.

Zweckmäßige Vergleichstherapie

Patienten im Alter von 2 bis 5 Jahren mit zystischer Fibrose, die homozygot für die F508del-Mutation sind:

- Best-Supportive-Care.

Als Best-Supportive-Care (BSC) wird diejenige Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der Heilmittel-RL), unter Ausschöpfung aller möglicher diätetischer Maßnahmen) gewährleistet.

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Lumacaftor/Ivacaftor gegenüber Best-Supportive-Care:

- Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen.

G-BA, 2019 [14].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Mai 2019 - Tezacaftor/Ivacaftor.

Anwendungsgebiet

Symkevi® wird angewendet als Kombinationsbehandlung mit Ivacaftor 150 mg Tabletten zur Behandlung der zystischen Fibrose (CF) bei Patienten ab 12 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.

Zweckmäßige Vergleichstherapie

Tezacaftor/Ivacaftor ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 11 1. Halbs. SGB V gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) das Ausmaß des Zusatznutzens für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht. Diese Quantifizierung des Zusatznutzens erfolgt am Maßstab der im 5. Kapitel § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien.

Fazit / Ausmaß des Zusatznutzens

a) Patienten ab 12 Jahren mit zystischer Fibrose, die homozygot für die F508del-Mutation sind.

- Ausmaß des Zusatznutzens: beträchtlicher Zusatznutzen

b) Patienten ab 12 Jahren mit zystischer Fibrose, die heterozygot für die F508del-Mutation sind und eine der folgenden Mutationen im CFTR-Gen aufweisen: P67L, R117C, L206W, R352Q,

A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G und 3849+10kbC→T.

- Ausmaß des Zusatznutzens: geringer Zusatznutzen

G-BA, 2018 [12].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. August 2018 - Lumacaftor/Ivacaftor (neues Anwendungsgebiet: zystische Fibrose, Patienten ab 6 Jahren).

Anwendungsgebiet

Orkambi ist angezeigt zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten ab 6 Jahren, die homozygot für die F508del-Mutation im CFTR-Gen sind.

Zweckmäßige Vergleichstherapie

Bestmögliche symptomatische Therapie (BST) (insbesondere Antibiotika bei pulmonalen Infektionen, Mukolytika, Pankreasenzyme bei Pankreasinsuffizienz, Physiotherapie (i. S. der Heilmittel-RL)), unter Ausschöpfung aller möglicher diätetischer Maßnahmen.

Ausmaß des Zusatznutzens

Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen

G-BA, 2016 [13].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Juni 2016 - Lumacaftor/Ivacaftor

Anwendungsgebiet

Orkambi ist angezeigt zur Behandlung der zystischen Fibrose (CF, Mukoviszidose) bei Patienten ab 12 Jahren, die homozygot für die F508del-Mutation im CFTR-Gen sind

Vergleichstherapie

Best supportive care (BSC)

Ausmaß des Zusatznutzens

Hinweis für einen beträchtlichen Zusatznutzen

G-BA, 2018 [9].

Richtlinie des Gemeinsamen Bundesausschusses Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung (Heilmittel-Richtlinie/HeilM-RL): zuletzt geändert am 21. September 2017; veröffentlicht im Bundesanzeiger BAnz AT 23.11.2017 B1, in Kraft getreten am 1. Januar 2018.

H. Ernährungstherapie

§ 42 Grundlagen

(1) Ernährungstherapie im Sinne dieser Richtlinie ist ein verordnungsfähiges Heilmittel, das sich auf die ernährungstherapeutische Behandlung seltener angeborener Stoffwechselerkrankungen oder Mukoviszidose (Cystische Fibrose − CF) richtet, wenn sie als medizinische Maßnahme (gegebenenfalls in Kombination mit anderen Maßnahmen) zwingend erforderlich ist, da ansonsten schwere geistige oder körperliche Beeinträchtigungen oder Tod drohen. Die Ernährungstherapie nach Satz 1 ist Teil des ärztlichen Behandlungsplans und umfasst insbesondere die Beratung zur Auswahl und Zubereitung natürlicher Nahrungsmittel und zu krankheitsspezifischen Diäten sowie die Erstellung und Ergänzung eines Ernährungsplans.

G-BA, 2018 [10].

Richtlinie des Gemeinsamen Bundesausschusses Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung (Heilmittel-Richtlinie/HeilM-RL): zuletzt geändert am 21. September 2017; veröffentlicht im Bundesanzeiger BAnz AT 23.11.2017 B1, in Kraft getreten am 1. Januar 2018; zweiter Teil Zuordnung der Heilmittel zu Indikationen.

2 Mukoviszidose

Indikation			Heilmittelverordnung im Regelfall	
Diagnosengruppe	**Funktionelle/strukturelle Schädigung**	**Ziel der Ernährungstherapie**	**Heilmittel**	**Verordnungsmengen je Diagnose ---------- weitere Hinweise**
CF **Mukoviszidose (Cystische Fibrose)**	- kompensierter normaler Ernährungszustand - Gedeihstörung oder Gewichtsverlust - drohende Gedeihstörung oder drohender Gewichtsverlust - Gedeihstörung oder Gewichtsverlust im Zusammenhang mit sonstigen Organmanifestationen/ -Komplikationen • Pankreas • Leber und Gallenwege • Organtransplantation	- Erhalt des Normalgewichts - Vermeidung eines Gewichtsverlustes - Stabilisierung des Ernährungszustandes	**Ernährungstherapie**	**Erst-VO und Folge-VO:** • je nach Bedarf für maximal 12 Wochen **Frequenzempfehlung:** • nach Bedarf In der Ernährungstherapie sind keine behandlungsfreien Intervalle gemäß § 7 Absatz 5 Satz 1 der Richtlinie zu berücksichtigen.

G-BA, 2019 [11].

Richtlinie des Gemeinsamen Bundesausschusses über die ambulante spezialfachärztliche Versorgung nach § 116b SGB V; zuletzt geändert am 22. März 2019
(Ergänzung Buchstabe b (Mukoviszidose) mit Beschluss vom 15. Dezember 2016)

2 Behandlungsumfang (jeweils in alphabetischer Reihenfolge)

Zur Diagnostik und Behandlung werden im Allgemeinen folgende Leistungen erbracht:

Diagnostik

− Allergiediagnostik (z. B. Intracutantest)

− Allgemeine Herzfunktionsdiagnostik (z. B. EKG) und spezielle Herzfunktionsdiagnostik (z. B. Echokardiographie, Belastungs-EKG)

− Anamnese

− Bildgebende Diagnostik (z. B. Sonographie, Röntgenuntersuchung, CT, MRT, Osteodensitometrie)

− Endoskopie des Gastrointestinaltraktes (z. B. ERCP), des Respirationstraktes (z. B. Bronchoskopie, bronchoalveoläre Lavage) und der Nasennebenhöhlen

− Makroskopische und mikroskopische Untersuchung bei einer Patientin und bei einem Patienten entnommenen Materials

− Histologische und zytologische Untersuchungen von Geweben und Sekreten

− HNO-ärztliche Funktionsuntersuchung (z. B. Audiometrie)

− Humangenetische Untersuchungen

− Körperliche Untersuchung

− Laboruntersuchungen (z. B. Sputumuntersuchung auf Erreger und Resistenz)

− Pulmonale Funktionsdiagnostik

− Schweißtest

− Tuberkulintest

Behandlung

− Ausstellen, z. B. von Bescheinigungen, Anträgen, Berichten

− Behandlungsplanung, -durchführung und -kontrolle

− Behandlung in Notfallsituationen

− Behandlung von Therapienebenwirkungen, Komplikationen und akuten unerwünschten Behandlungsfolgen

− Einleitung der Rehabilitation

− Medikamentöse Therapien inklusive Inhalations- und Infusionstherapie

− Perkutane endoskopische Gastrostomie (PEG)

− Physikalische Therapie

− Psychotherapeutische Beratung und Betreuung

− Therapeutische Punktionen und Drainagen

Beratung

− zu Diagnostik und Behandlung

− zu Ernährung

− zu Hilfsmitteln inklusive Anleitung zum Gebrauch

− zu humangenetischen Fragestellungen

− zu Medikamentengabe und Nebenwirkungen

− zu psychosozialen Beratungs- und Betreuungsangeboten

− zu Rehabilitationsangeboten

− zu Sexualität und Familienplanung

− zu sozialen Beratungsangeboten

− zu vorhandenen Selbsthilfeangeboten

− zu Verhalten in Notfallsituationen; die Information kann z. B. mittels eines Notfallausweises erfolgen

− zur Prävention von Infektionen und zur Besiedlung mit pathogenen Keimen (z. B. PSAE, MRSA, Cepacia-Komplex; Aspergillen)

3.2 Cochrane Reviews

Yang C et al., 2018 [25].

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:

- primäre EP:
  - Changes in lung function from baseline
    - forced expiratory volume at one second (FEV1)
    - forced vital capacity (FVC)
    - lung clearance index (LCI)
    - forced expiratory volume at 0.5 seconds (FEV0.5)
  - Change from baseline in quality of life (QoL)
  - Mean number of exacerbations
- Sekundäre EP:
  - 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
  - Change in weight from baseline
  - Number of adverse events such as alteration in voice, haemoptysis, bronchospasm
  - Cost (including indirect costs of therapy)

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: 23 April 2018.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

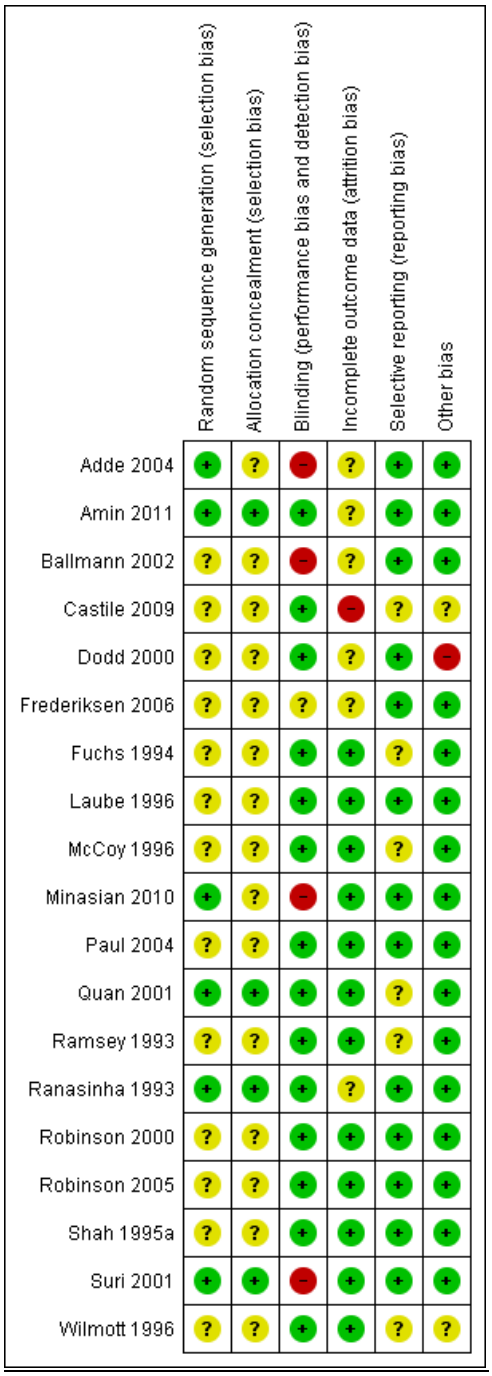
- 19 RCTs (2565 participants)

Charakteristika der Population:

- Four trials included adults only
- Four trials included children only, including one trial in infants (mean (SD) age of 42 (32) weeks)
- All trials except for one included participants with stable lung disease;
- Severity of lung disease varied across the trials (2 trials: severe, 9 trials: mild and/or moderate)

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.



<u>Studienergebnisse:</u>

<u>Dornase alfa vs placebo or no treatment</u>

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.

Dornase alfa vs hypertonic saline

Dornase alfa compared with hypertonic saline for cystic fibrosis

Patient or population: Children with cystic fibrosis
Settings: Outpatients
Intervention: Dornase alfa (once daily)
Comparison: Hypertonic saline

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Hypertonic Saline	Dornase alfa				
Mean relative percentage in FEV_1 (L) at 3 months	See comment	See comment	**MD** 8.00 (2.00 to 14.00)	up to 43[1,2] (1 cross-over study) (see comment)	⊕⊕○○ **low**[3,4]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design
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 Mannitol	Corresponding risk Dornase Alfa				
Mean absolute change in FEV1 (L) at 3 months	See comment	See comment	**MD** 0.02 (-0.11 to 0.16)	up to 23[1] (1 cross-over study)	⊕⊕○○ **low**[2,3]	Positive MD indicates an advantage for dornase alfa. Participants received both interventions in cross-over design
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 [18].

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:

- primäre EP:
  - Health-related quality of life
  - Lung function
  - Adverse events
- Sekundäre EP:
  - Pulmonary exacerbations
  - Time off school or work
  - Need for additional non-routine antibiotics
  - Hospitalisations
  - Assessment of symptoms

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

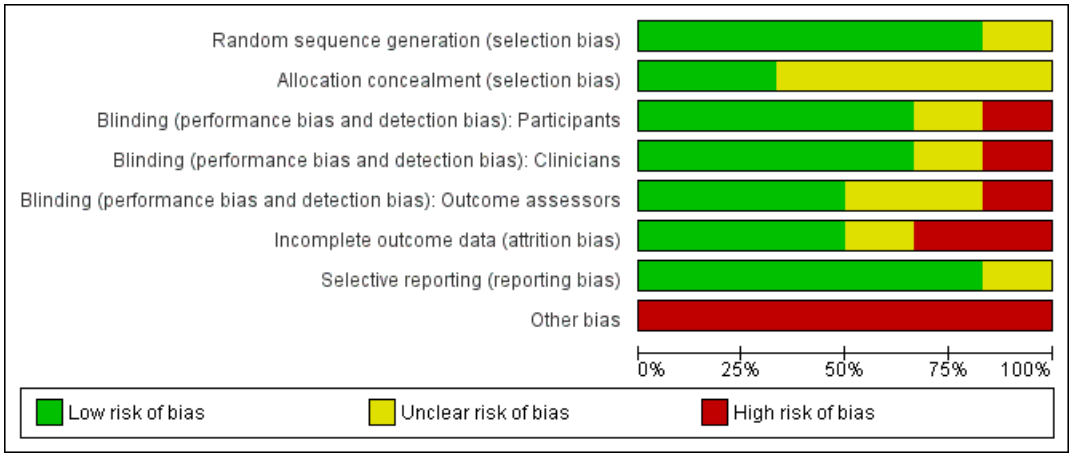
Anzahl eingeschlossener Studien:

- 6 RCTs

Charakteristika der Population:

- Alter: 6-55 Jahre

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%

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

- 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

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 [22].

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

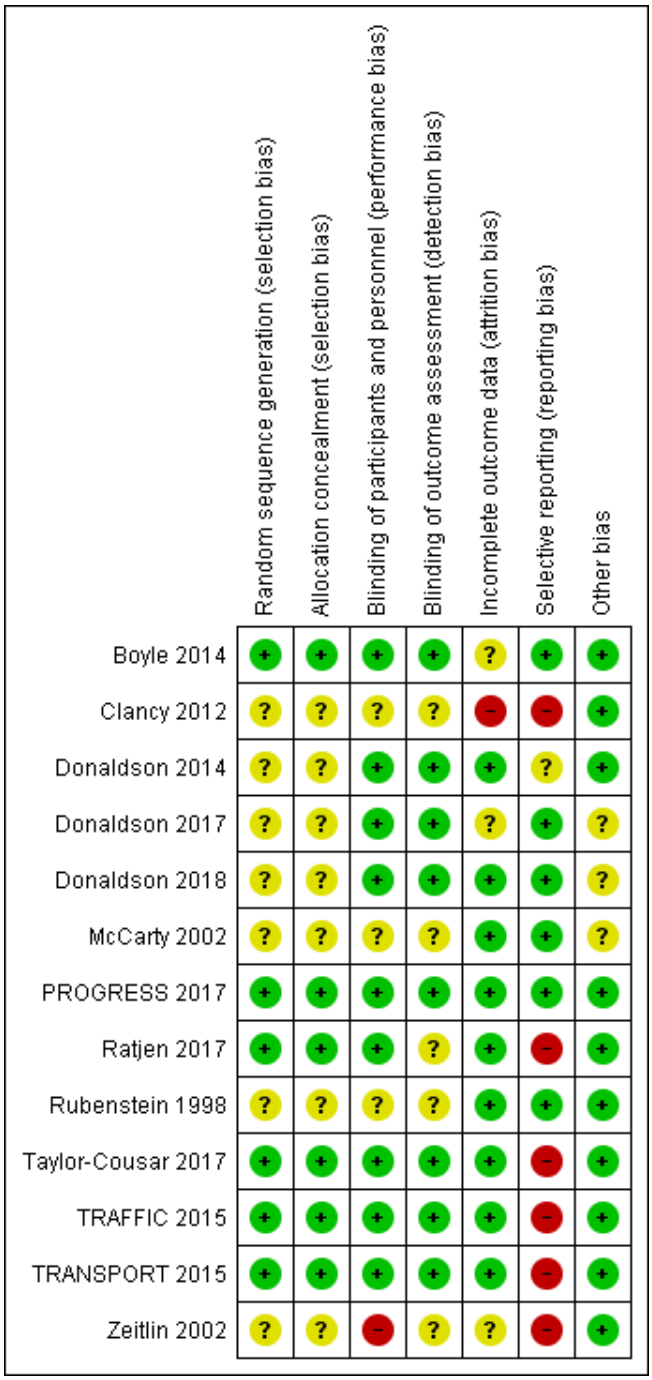
Anzahl eingeschlossener Studien:

- 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).

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:

- o Mild AE: most commonly reported side effect was cough with no significant difference
- o 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
- o 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
  - o 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.

Wark P et al., 2018 [23].

Nebulised hypertonic saline for cystic fibrosis

Fragestellung

To investigate efficacy and tolerability of treatment with nebulised hypertonic saline on people with CF compared to placebo and or other treatments that enhance mucociliary clearance.

Methodik

Population:

- People of all ages and of both sexes with CF diagnosed clinically or by sweat and genetic testing, including all degrees of disease severity.

Intervention:

- Nebulised hypertonic saline (defined as any concentration of saline greater than or equal to 3% delivered via a mask or mouthpiece with a nebuliser pump)

Komparator:

- placebo or usual treatment or any other mucus-mobilising treatments (including, but not limited to, physical airway clearance techniques and medications which demonstrate improved mucus clearance e.g. rhDNase).

Endpunkte:

- primäre Endpunkte:
  - Survival
  - Physiological measures of lung function
- sekundäre Endpunkte:
  - Measures of sputum clearance
  - Measures of exercise capacity
  - Quality of life (QoL)
  - Adverse effects
  - Pulmonary exacerbations

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: 8 August 2018.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

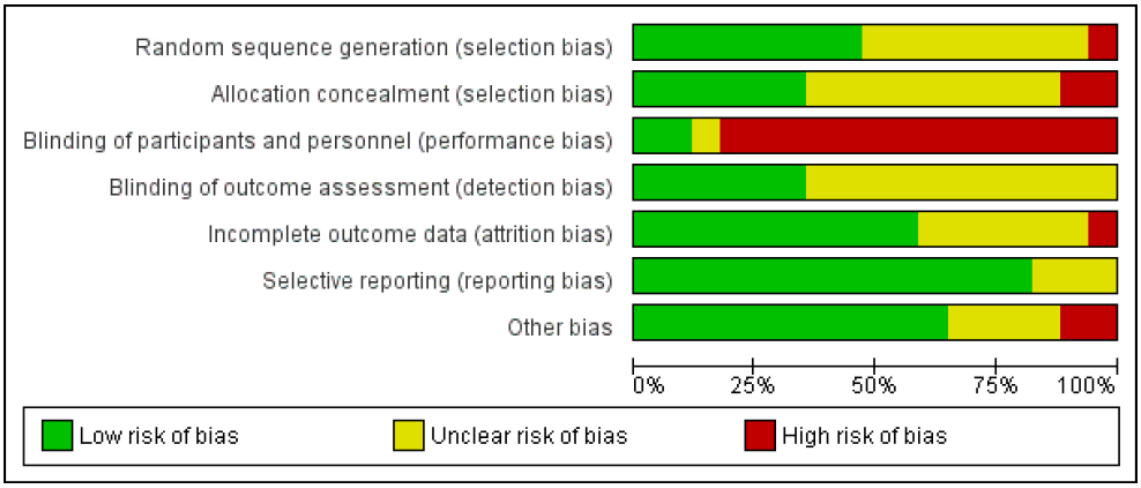
- 17 trials (966 participants)

Charakteristika der Population:

- age of participants ranged from four months to 63 years
- Most studies only recruited participants over the age of five or six years
- Three trials stated they tested for tolerance to hypertonic saline

Qualität der Studien:

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Studienergebnisse:

Hypertonic saline 3% to 7% versus isotonic saline in stable lung disease

Hypertonic saline 3% to 7% versus isotonic saline for cystic fibrosis (stable lung disease)						
Patient or population: adults and children with cystic fibrosis (stable lung disease) **Settings:** outpatients **Intervention:** hypertonic saline 3% to 7% **Comparison:** isotonic saline						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (trials)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Isotonic saline	**Hypertonic saline 3% to 7%**				
Mortality	Outcome not reported.		NA	NA	NA	

FEV_1 (% predicted) change from baseline, short term Follow-up: 4 weeks	The mean change in FEV_1 (% predicted) ranged from -1.42 to 2.8 in the isotonic saline groups	The mean change in FEV_1 (% predicted) was 3.44 higher (0.67 higher to 6.21 higher) in the hypertonic saline group	NA	225 (3 trials)[1]	⊕○○○ **very low**[2,4,5,6]	
FEV_1 (% predicted) change from baseline, long term Follow-up: 48 weeks	The mean change in FEV_1 (% predicted) was 2.44 in the isotonic saline group.	The mean change in FEV_1 (% predicted) was 2.31 higher (2.72 lower to 7.34 higher) in the hypertonic saline group	NA	134 (1 trial)	⊕⊕○○ **low**[2,3]	The included trial also measured change in FEV_1 (% predicted) at: 12 weeks, MD 4.10 (95% CI -0.08 to 8.28); 24 weeks, MD 5.37 (95% CI 1.03 to 9.71); and 36 weeks, MD 3.63 (95% CI -1.56 to 8.82)
Pulmonary exacerbations Follow-up: up to 48 weeks	One trial showed that there were fewer exacerbations per year requiring intravenous antibiotic therapy in the hypertonic saline group than in the isotonic saline group and that the interval during which participants remained free of exacerbations was also significantly longer in the hypertonic saline group The second trial found no significant differences in the mean number of exacerbations per year There was no difference reported in hospitalisation rates between the hypertonic saline group and the controls		NA	415 (2 trials)	⊕⊕○○ **low**[2,8]	
Adverse events Follow up: up to 48 weeks	There were no significant difference between treatment groups in adverse events including cough, chest tightness, pharyngitis, haemoptysis, sinusitis, sneezing, tonsillitis and vomiting		NA	589 (6 trials)[9]	⊕○○○ **very low**[2,4,5]	

*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).
CI: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **LCI**: lung clearance index; **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. 1 trial (n = 19) was of a cross-over design.
2. Downgraded once due to applicability: results apply only to those who can tolerate hypertonic saline.
3. Downgraded once due to imprecision; small sample size which did not achieve the targeted sample size generated by the power calculation.
4. Downgraded once due to risk of bias: high risk of detection bias as participants could discern the taste of the intervention and also limited information about trial methods.
5. Downgraded once due to imprecision: cross-over trials analysed as a parallel trials (due to available data) which is likely to over-estimate the within study variability and increase imprecision.
6. Downgraded once due to inconsistency: substantial heterogeneity (I^2 = 67%) which may have originated from different age groups recruited in the trials or different baseline levels of lung function.
7. Downgraded once due to applicability: results apply only to those who can tolerate hypertonic saline and the trial only included children aged 6 to 18 years, so results may not apply to adults.
8. Downgraded once due to risk of bias: one trial was at high risk of detection bias as participants could discern the taste of the intervention.
9. 4 trials (n = 104) were of a cross-over design.

- Measures of exercise capacity
  - One study demonstrated a significant improvement in exercise tolerance (MD 0.88 (95% CI 0.19 to 1.57) and week 2, MD 1.01 (95% CI 0.18 to 1.84))
- Measures of QoL and symptom scores
  - CFQ-R domain for parents or participants was assessed in three trials and this demonstrated no statistically significant improvement in the hypertonic saline group, MD 1.62 (95% CI -1.69 to 4.92)

- Two trials assessed symptom improvement after short-term treatment using simple VAS and found an improvement in feelings of better chest clearance, exercise tolerance and quality of sleep.
- In the long-term trials (48 weeks), Elkins showed treatment may improve some aspects of QoL in adults but not in children, while Rosenfeld showed no improvement in parent-reported QoL scores.

Hypertonic saline compared with rhDNase with for cystic fibrosis

Hypertonic saline compared with rhDNase with for cystic fibrosis

Patient or population: adults and children with cystic fibrosis
Settings: outpatients
Intervention: hypertonic saline (daily)
Comparison: rhDNase (daily)[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	rhDNase	Hypertonic saline				
FEV_1 (% predicted) change from baseline, long term Follow-up: 3 months	The mean change from baseline in FEV_1 (% predicted) was 8% higher (2% higher to 14% higher) in the hypertonic saline group compared to the daily rhDNase group.[2]		NA	47 (1 trial)	⊕○○○ **very low**[2,6,7]	Trial had a cross-over design. An additional cross-over trial of 18 participants found no difference between treatments in FEV_1 after 10 weeks (no data presented).
Pulmonary exacerbations Follow-up: NA	15 episodes occurring during treatment with hypertonic saline and 18 with daily rhDNase, there was no statistical difference between treatments (see comment)		NA	47 (1 trial)	⊕○○○ **very low**[2,6,7]	Trial had a cross-over design. Number of episodes reported rather than the number of participants with exacerbations (leading to a unit of analysis issue) so data not entered into the analysis
Adverse events Follow up: 3 months	Increased cough was reported in 13 participants using hypertonic saline and 17 on daily rhDNase. There were similar rates of other adverse events between treatment arms (see comment)		NA	47 (1 trial)	⊕○○○ **very low**[2,6,7]	Trial had a cross-over design, so data not entered into analysis

*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).
CI: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **LCI**: lung clearance index; **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. An alternate day rhDNase group was also included in one of the trials (Suri 2001), but to allow a comparison across the trials, only results from the rhDNase daily group are presented in the tables.
2. Data analysed as MD between treatment groups via generic inverse variance due to cross-over design of the trial, therefore an estimate of the assumed risk is not available.
3. Downgraded once due to risk of bias: high risk of detection bias as participants could discern the taste of the intervention and limited information was provided about the methodological design of the trial.
4. Downgraded once due to applicability: results apply only to those who can tolerate hypertonic saline.

- One trial reported at 12 weeks on the change in exercise tolerance, dyspnoea, oxygen saturation during exercise and symptom score and found no differences between those treated with rhDNase and hypertonic saline.

Hypertonic saline compared with mannitol for cystic fibrosis

Hypertonic saline compared with mannitol for cystic fibrosis						
Patient or population: adults and children with cystic fibrosis **Settings:** outpatients **Intervention:** hypertonic saline **Comparison:** mannitol						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (trials)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Mannitol	**Hypertonic saline**				
Pulmonary exacerbations	Outcome not reported.		NA	NA	NA	
Adverse events Follow up: up to 95 minutes	See comment.		NA	12 (1 trial)	⊕○○○ **very low**[1,2,4]	Trial had cross-over design. Mannitol was considered to be a more 'irritating' treatment than other treatments (4-armed trial); no specific data given

*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).
CI: confidence interval; **FEV_1**: forced expiratory volume in 1 second; **LCI**: lung clearance index; **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 risk of bias: high risk of detection bias as participants could discern the taste of the intervention and no washout period was used.
2. Downgraded once due to applicability: results apply only to those who can tolerate hypertonic saline and the trial included only participants over the age of 16 so results may not apply to younger children.
3. Downgraded once due to applicability: the outcome measured only at very short-term time-points (minutes after intervention), which are not of clinical relevance to this review.
4. Downgraded once due to imprecision: no numerical data provided and small sample size.

- no difference between groups in symptoms (cough)

Fazit der Autoren

Regular use of nebulised hypertonic saline by adults and children over the age of 12 years with CF results in an improvement in lung function after four weeks (very low-quality evidence from three trials), but this was not sustained at 48 weeks (low-quality evidence from one trial). The review did show that nebulised hypertonic saline reduced the frequency of pulmonary exacerbations (although we found insufficient evidence for this outcome in children under six years of age) and may have a small effect on improvement in quality of life in adults.

Evidence from one small cross-over trial in children indicates that rhDNase may lead to better lung function at three months; qualifying this we highlight that while the study did demonstrate that the improvement in FEV1 was greater with daily rHDNase, there were no differences seen in any of the secondary outcomes.

In the majority of trials hypertonic saline was used after pre-treatment with bronchodilators and as an adjunct to chest physiotherapy; in both cases this may be important to ensure its efficacy. When delivered following a bronchodilator, hypertonic saline is an inexpensive and safe therapy for people with CF.

Smith S et al., 2018 [20].

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

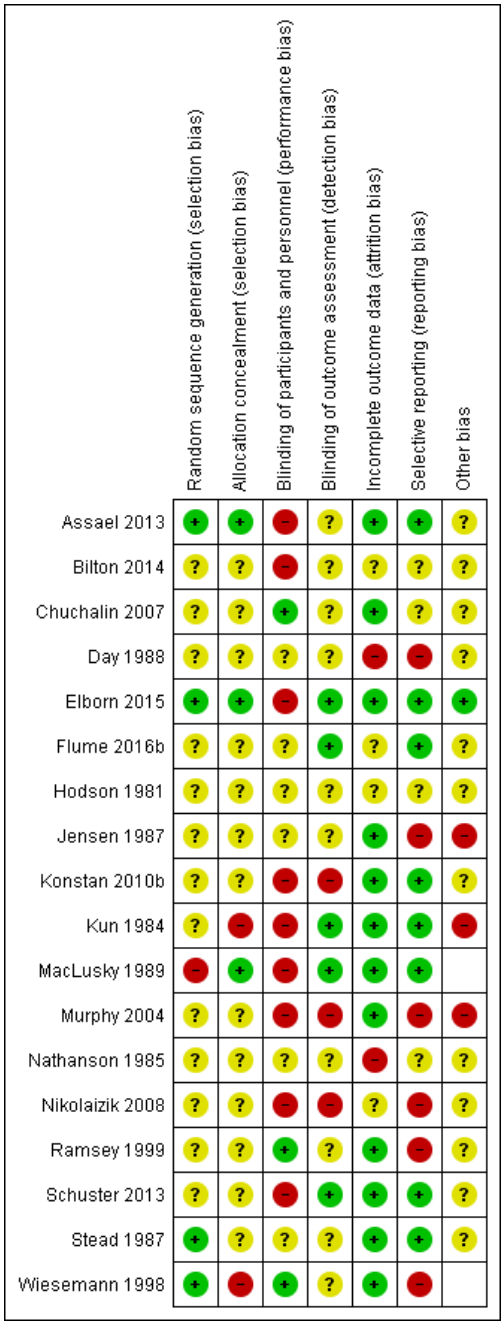
Anzahl eingeschlossener Studien:

- 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 TIS	Corresponding risk 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.

Somaraju UR et al., 2016 [21].

Pancreatic enzyme replacement therapy for people with cystic fibrosis.

Fragestellung

To evaluate the efficacy and safety of pancreatic enzyme replacement therapy in children and adults with cystic fibrosis and to compare the efficacy and safety of different formulations of this therapy and their appropriateness in different age groups. Also, to compare the effects of pancreatic enzyme replacement therapy in cystic fibrosis according to different diagnostic subgroups (e.g. different ages at introduction of therapy and different categories of pancreatic function).

Methodik

Population:

- People of any age with CF, either diagnosed clinically and confirmed with sweat test, or by genetic testing or by newborn screening.

Intervention:

- Any dose of PERT and in any formulation, in either home or hospital setting, for a period of not less than four weeks commenced either at diagnosis of cystic fibrosis, at the onset of symptoms or at confirmation of abnormal pancreatic function.

Komparator:

- placebo or other PERT preparations

Endpunkte:

- primäre Endpunkte:
  - Changes in nutritional status
- sekundäre Endpunkte:
  - Bowel symptoms,
  - Days in hospital,
  - QoL,
  - Number of times vitamin deficiency diagnosed,
  - Adverse events,
  - Fecal fat excretion (FFE),
  - Lung disease

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: July 2016.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- One parallel trial and 12 cross-over trials of children and adults with cystic fibrosis were included in the review.

Qualität der Studien:

- The included trials had mostly an unclear risk of bias from the randomisation process as the details of this were not given; they also mostly had a high risk of attrition bias and reporting bias.
- *Hinweis* → We could not combine data from all the trials as they compared different formulations. Findings from individual studies provided insufficient evidence to determine the size and precision of the effects of different formulations. Ten studies reported information on the review's primary outcome (nutritional status); however, we were only able to combine data from two small cross-over studies (n = 41).

Studienergebnisse:

- The estimated gain in body weight was imprecise, 0.32 kg (95% confidence interval -0.03 to 0.67; P = 0.07).
- Combined data from the same studies gave statistically significant results favouring enteric-coated microspheres over enteric-coated tablets for our secondary outcomes stool frequency, mean difference -0.58 (95% confidence interval -0.85 to -0.30; P < 0.0001); proportion of days with abdominal pain, mean difference -7.96% (95% confidence interval -12.97 to -2.94; P = 0.002); and fecal fat excretion, mean difference -11.79 g (95% confidence interval -17.42 to -6.15; P < 0.0001).
- Data from another single small cross-over study also favoured enteric-coated microspheres over non-enteric-coated tablets with adjuvant cimetidine in terms of stool frequency, mean difference -0.70 (95% confidence interval -0.90 to -0.50; P < 0.00001).

Fazit der Autoren

There is limited evidence of benefit from enteric-coated microspheres when compared to non-enteric coated pancreatic enzyme preparations up to one month. In the only comparison where we could combine any data, the fact that these were cross-over studies is likely to underestimate the level of inconsistency between the results of the studies due to over-inflation of confidence intervals from the individual studies. There is no evidence on the long-term effectiveness and risks associated with pancreatic enzyme replacement therapy. There is also no evidence on the relative dosages of enzymes needed for people with different levels of severity of pancreatic insufficiency, optimum time to start treatment and variations based on differences in meals and meal sizes. There is a need for a properly designed study that can answer these questions.

3.3 Systematische Reviews

Habib AR et al., 2019 [15].

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.

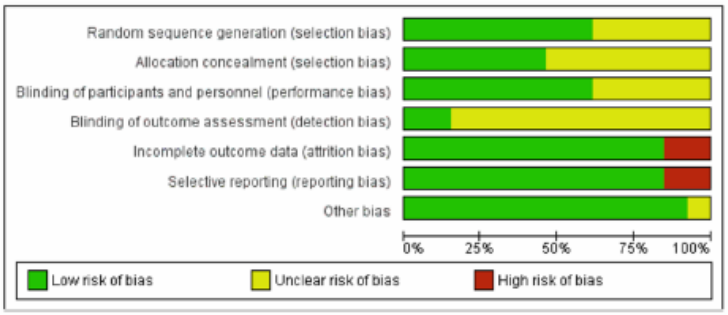


Figure 2. Risk of Bias Summary for Included Studies. Selective outcome reporting was noted for Kerem *et al.*[18] as the study authors did not report in their full text publication all outcomes listed in their study protocol including antibiotic use and hospitalization due to CF-related symptoms, disruption to school or work due to CF-related symptoms, and pharmacokinetics. Similarly, Ramsey *et al.*[20] did not report on all CFQ-R domain items or tertiary outcomes pre-defined in their clinical trial protocol including EQ-5D, oxygen saturation, and outpatient sick visits to the clinic or hospital for CF-related complications. Ratjen *et al.*[19] did not report data on exacerbations (time to first, number) and the Treatment Satisfaction Questionnaire despite these being listed as secondary endpoints in the publication. Wainwright *et al.*[17] did not report data on the EQ-5D or Treatment Satisfaction Questionnaire despite it being listed in their trial protocol.

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.

Anmerkung/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.

Wu HX et al., 2019 [24].

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:

- Primary outcomes: ppFEV1, the CFQ-R respiratory domain score, and BMI.
- Secondary outcomes: adverse events (AEs) and the proportion of discontinued treatments due to 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.

3.4 Leitlinien

Ren CL et al., 2018 [19].

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

Table 4. Summary of recommendations for patient, intervention, comparator, and outcomes question 3 (ivacaftor/lumacaftor for patients with cystic fibrosis with two copies of F508del)

Subgroup No.	Age (*Yr*)	$PPFEV_1$ (%)	Certainty	Recommendation
21	0–5	N/A	N/A	No recommendation
22	6–11	<40	Very low	Conditional for
23	6–11	40–90	Very low	Conditional for
24	6–11	>90	Very low	Conditional for
25	12–17	<40	Moderate	Strong for
26	12–17	40–90	Moderate	Strong for
27	12–17	>90	Low	Conditional for
28	18+	<40	Moderate	Strong for
29	18+	40–90	Moderate	Strong for
30	18+	>90	Low	Conditional for

Definition of abbreviations: N/A = not applicable; $PPFEV_1$ = percent predicted forced expiratory volume in 1 second.

National Institute for Health and Care Excellence (NICE), 2017 [17].

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

Grundlage der Leitlinie

- 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 Meta-analysen 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

Empfehlung

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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Lahiri T et al., 2016 [16].

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

Bronchodilators

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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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2019) am 22.10.2019

#	Suchfrage
1	MeSH descriptor: [Cystic Fibrosis] explode all trees
2	("cystic fibrosis" OR mucoviscidosis):ti
3	#1 OR #2
4	#3 with Cochrane Library publication date from Oct 2014 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 22.10.2018

#	Suchfrage
1	cystic fibrosis[MeSH Terms]
2	cystic fibrosis[Title/Abstract]
3	mucoviscidosis[Title/Abstract]
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 studies[pt] OR validation studies[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 (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 ("2014/10/01"[PDAT] : "3000"[PDAT])

Leitlinien in Medline (PubMed) am 22.10.2019

#	Suchfrage
#1	cystic fibrosis[MeSH Terms]
#2	cystic fibrosis[Title/Abstract]
#3	mucoviscidosis[Title/Abstract]
#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 ("2014/10/01"[PDAT] : "3000"[PDAT])

Referenzen

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