Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2012-B-050 Lumacaftor+Ivacaftor

Stand: November .2012

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Lumacaftor+Ivacaftor Zur Behandlung der zystischen Fibrose mit der F508del Mutation	
Kriterien gemäß 5. Kapitel § 6 VerfO	
1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Aztreonam, Ceftazidim, Ciprofloxacin, Colistimethat, Dornase alfa, Mannitol, Pankreatin, Tobramycin
2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Atemtherapie (entsprechend Heilmittel-Richtlinie)
3. Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	Richtlinie über die Verordnung von Heilmitteln in der vertragsärztlichen Versorgung
4. Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche
5. Bei mehreren Alternativen ist die wirtschaftlichere Therapie zu wählen, vorzugsweise eine Therapie, für die ein Festbetrag gilt.	nicht angezeigt
• […] vorzugsweise eine Therapie, […] die sich in der praktischen Anwendung bewährt hat.	nicht angezeigt

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Lumacaftor+Ivacaftor	*Angaben aus der Beratungsanforderung:* Zur Behandlung der zystischen Fibrose bei Patienten im Alter von 6 Jahren oder älter, die homozygot für die F508del-Mutation im CFTR-Gen sind
Pankreatin H04 Generisch	Störungen der exokrinen Pankreasfunktion, die mit einer Maldigestion einhergehen. Bei Mukoviszidose zur Unterstützung der ungenügenden Funktion der Bauchspeicheldrüse.
Ceftazidim J01DD02 Generisch	Schwere Infektionen, wenn diese durch Ceftazidim-empfindliche Erreger verursacht sind. Dosisangabe für „Patienten mit Mukoviszidose“ in Fachinformation
Tobramycin J01GB01 Generisch	Zur Behandlung von schweren Infektionen durch tobramycinempfindliche Bakterien, wenn weniger toxische antimikrobielle Wirkstoffe nicht wirksam sind. - Exazerbation von unteren Atemwegsinfektionen bei Patienten mit zystischer Fibrose
Ciprofloxacin J01MA02 Generisch	Untere Atemwegsinfektionen verursacht durch Gram-negative Bakterien – bronchopulmonale Infektionen bei zystischer Fibrose oder bei Bronchiektasen
Aztreonam J01XB01 Cayston	Cayston wird angewendet zur suppressiven Behandlung chronischer Lungeninfektionen durch Pseudomonas aeruginosa bei Patienten mit Mukoviszidose (zystischer Fibrose, CF) ab einem Alter von 6 Jahren.
Colistimethat J01XB01 Promixin	Promixin ist zur Inhalationsbehandlung bei Besiedelung und Infektionen der Lunge durch gegen Colistimethat-Natrium empfindliche Pseudomonas aeruginosa bei Patienten mit Mukoviszidose angezeigt.
Dornase alfa R05CB13 Pulmozyme	Pulmozyme 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.

Mannitol R05CB16 Bronchitol	Angaben aus dem SPC der EMA: Bronchitol wird angewendet zur Behandlung der zystischen Fibrose (Mukoviszidose) bei Erwachsenen ab 18 Jahren zusätzlich zum besten Therapiestandard.

Gemeinsamer Bundesausschuss

Synoptische Evidenzübersicht zur Ermittlung der zVT:

Inhalt

Indikation für die Recherche:

,,Behandlung der zystischen Fibrose bei Patienten (6 Jahre oder älter) die homozygot für die F508del-Mutation im CFTR-Gen sind. ‘‘

Berücksichtigte Wirkstoffe/Therapien:

Medikamentöse und nicht-medikamentöse Therapieoptionen.

Systematische Recherche:

Es wurde eine systematische Leitlinienrecherche nach Evidenz-basierten systematischen Leitlinien zur Indikation ***„zystische Fibrose“(CF)*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***29.10.2012*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken: MEDLINE (PubMed), AWMF, GIN, NGC, TRIP. Es wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab ***36*** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Davon wurden **6** Quellen eingeschlossen und in die synoptische Evidenz-Übersicht aufgenommen.

Cochrane Reviews

Erstautor Titel Quelle **Jahr** ggf. (assessed as up-to-date Jahr)	• -

Systematische Reviews

Erstautor Titel Quelle **Jahr**	• -

Primärstudien

Erstautor Titel Quelle **Jahr**	• -

Leitlinien

Stern et al. 2011: AWMF Leitlinie: Mukoviszidose (Cystische Fibrose): Ernährung und exokrine Pankreasinsuffizienz.	• **Therapie:** • Ernährung: Negative Energiebilanz und Ernährungsdefizite sind zentrale Probleme in der Behandlung der Mukoviszidose mit unmittelbarer prognostischer Bedeutung für Lebensqualität und Lebenserwartung (Hodson & Geddes, 3. Aufl. 2007; Reinhardt et al., 2001; Sens & Stern, 2010). Prävention der Mangelernährung und frühe Intervention bei Auftreten eines Defizits sind Grundlage des praktischen Vorgehens. • Ihr Evidenzgrad bleibt niedrig, der Wert der Ernährungstherapie ist dennoch unumstritten o Energiezufuhr: Basis der Ernährung bei Mukoviszidose ist eine fettreiche und ballaststoffreiche Nahrung, die bis zu 130 % der Empfehlungen für die Energiezufuhr der DACH-Referenzwerte enthält. Parenterale Ernährung wird nur für spezielle Indikationen empfohlen. o Physiotherapie und Sportprogramme unterstützen die Ernährungstherapie vor allem im Adoleszenten- und Erwachsenenalter. o Für die verschiedenen Altersgruppen werden je nach Schweregrad des Ernährungsdefizits verschiedene Schritte der Ernährungsintervention definiert (Tab. 2). An erster Stelle steht dabei die Prävention, und als erster praktischer Schritt erfolgt die Erhöhung der Energiezufuhr auf normalem Wege (Kaloriendichte), bevor Supplementnahrungen eingesetzt werden. Besondere Beachtung müssen die Patienten finden, die einen Kleinwuchs unterhalb der 3. Perzentile aufweisen. Die Maßnahmen reichen von der präventiven Beratung über verstärkte Ernährungsberatung, Einsatz von oralen Supplementen bis hin zum invasiven Ernährungssupport, zum Beispiel mittels PEG (perkutane endoskopische Gastrostomie). o Fettlösliche Vitamine: Fettlösliche Vitamine müssen bei CF bei pankreasinsuffizienten und ggf. auch bei pankreassuffizienten Patienten substituiert werden. Um eine ausreichende orale Bioverfügbarkeit zu gewährleisten, sollten die fettlöslichen Vitamine A, D, E

	und K bei Pankreasinsuffizienz zeitgleich mit der Pankreasenzymgabe substituiert werden. o Mineralien, Spurenelemente, weitere: Wie für die Vitaminsupplementierung erreichen die Empfehlungen für Mineralien und Spurenelemente lediglich einen niedrigen Evidenzgrad. So müssen Natrium und Chlorid bei Säuglingen in besonderer Situation zugesetzt werden (hohe Außentemperatur, Fieber, Tachypnoe, Schwitzen, Erbrechen, Durchfall). In allen Altersstufen muss Kochsalz bei Anstrengung im heißen Klima (Auslandsaufenthalte) ersetzt werden. Einschränkend muss hier erwähnt werden, dass bei einigen CF-Patienten die Natriumausscheidung beeinträchtigt sein kann. Kalzium muss bei verminderter Zufuhr durch die Nahrung zugeführt werden. Die Aufnahme ist ebenso wie beim Phosphat Vitamin D-abhängig. Magnesium muss bei schwerer Malabsorption und bei langzeitparenteraler Behandlung mit minoglykosiden ersetzt werden. Bei einigen CF Patienten unter 2 Jahren besteht ein Zinkmangel, der Ursache für eine anhaltende Steatorrhoe und für mäßiges Gedeihen sein kann. Eine Substitution mit 1 mg Zink/kg/d aufgeteilt auf mehrere Dosen für 6 Monate ist in solchen Fällen empfohlen. Für die Zufuhr essentieller Fettsäuren und langkettige, vielfach ungesättigter Fettsäuren gibt es derzeit keine generelle Empfehlung. •
Flume et al. 2007[Δ]: Cystic Fibrosis Pulmonary Guidelines Chronic Medications for Maintenance of Lung Health	• **Aerosolized Antibiotics:** • For patients with CF, 6 years of age and older, who have moderate to severe lung disease and with P. aeruginosa persistently present in cultures of the airways, the Cystic Fibrosis Foundation strongly recommends the chronic use of inhaled tobramycin to improve lung function and reduce exacerbations. (Level of evidence, good; net benefit, substantial; grade of recommendation, A). • For patients with CF, age 6 years and older who are asymptomatic or with mild lung disease, and with P. aeruginosa persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the chronic use of inhaled tobramycin to reduce exacerbations. (Level of evidence, fair; net benefit, moderate; grade of recommendation, B). • For patients with CF, age 6 years and older, with Pseudomonas aeruginosa persistently present in cultures of the airways, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing other chronically inhaled antibiotics (i.e. colistin, gentamicin, ceftazidime) to improve lung function and reduce exacerbations. (Level of evidence, poor; net benefit, small; grade of recommendation, I). • • **Recombinant Human DNase:** • For patients with CF, 6 years of age and older, with moderate to severe lung disease, the Cystic Fibrosis Foundation strongly recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations. *(Level of evidence, good; net benefit, substantial; grade of recommendation, A).* • For patients with CF, 6 years of age and older, and asymptomatic or with mild lung disease, the Cystic Fibrosis

	Foundation recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.*(Level of evidence, fair; net benefit, moderate; grade of recommendation, B).* **Hypertonic Saline:** • For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation recommends the chronic use of inhaled hypertonic saline to improve lung function and to reduce exacerbations. *(Level of evidence, fair; net benefit, moderate; grade of recommendation, B).* **Antiinflammatory Agents:** • For patients with CF, 6 years of age and older, and without asthma or ABPA, the Cystic Fibrosis Foundation recommends against the routine use of inhaled corticosteroids to improve lung function and to reduce exacerbations. *(Level of evidence, fair; net benefit, zero; grade of recommendation, D).* • For patients with CF, between 6 and 18 years of age, and without asthma or ABPA, the Cystic Fibrosis Foundation recommends against the chronic use of oral corticosteroids to improve lung function and to reduce exacerbations. *(Level of evidence, good; net benefit, negative; grade of recommendation, D).* • For patients with CF, 6 years of age and older, and with FEV1 greater than 60% predicted, the Cystic Fibrosis Foundation recommends the chronic use of oral ibuprofen to slow the loss of lung function. *(Level of evidence, fair; net benefit, moderate; grade of recommendation, B).* • For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing the chronic use of leukotriene (i.e., LTD4) modifiers to improve lung function and to reduce exacerbations. *(Level of evidence, poor; net benefit, zero; grade of recommendation, I).* • For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing the chronic use of cromolyn to improve lung function and to reduce exacerbations. *(Level of evidence, poor; net benefit, zero; grade of recommendation, I).* **Macrolide Antibiotics:** • For patients with CF, 6 years of age and older, and with Pseudomonas aeruginosa persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the chronic use of azithromycin to improve lung function and to reduce exacerbations *(Level of evidence, fair; net benefit, substantial; grade of recommendation, B).* **Antistaphylococcal Antibiotics:** • For patients with CF, the Cystic Fibrosis Foundation recommends against the prophylactic use of oral antistaphylococcal antibiotics to improve lung function and to reduce exacerbations *(Level of evidence, fair; net benefit,*

	negative; grade of recommendation, D). **Bronchodilators:** • For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation recommends the chronic use of inhaled b2-adrenergic receptor agonists to improve lung function. *(Level of evidence, good; net benefit, moderate; grade of recommendation, B).* • For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function. *(Level of evidence, poor; net benefit, small; grade of recommendation, I).* **N-acetylcysteine:** • For patients with CF, 6 years of age and older, the Cystic Fibrosis Foundation concludes that the evidence is insufficient to recommend for or against routinely providing for the chronic use of inhaled or oral N-acetylcysteine to improve lung function and to reduce exacerbations. *(Level of evidence, poor; net benefit, zero; grade of recommendation, I).* *<u>Hinweis: 'Key unanswered Questions'</u>* →How should the clinician prioritize these therapies? *'The committee recognizes that not all patients will benefit from each of these medications and many patients will benefit from using multiple therapies….' 'There are no studies that have evaluated when to introduce any of these medications; there is a great need for research in this area.'*
Flume et al. 2009▲: Cystic Fibrosis Pulmonary Guidelines Treatment of Pulmonary Exacerbations	• **Site of Treatment:** • The CF Foundation recommends against delivery of intravenous antibiotics in a nonhospital setting unless resources and support equivalent to the hospital setting can be assured for the treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation.) • • **Continuing Chronic Therapies for Maintenance of Lung Health:** • The CF Foundation concludes that there is insufficient evidence to recommend for or against continued use of inhaled antibiotics in patients treated with the same antibiotics intravenously for the treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation). • The CF Foundation recommends continuing chronic therapies for maintenance of lung health during treatment of an acute exacerbation of pulmonary disease. (Grade B recommendation). • The CF Foundation recommends that airway clearance therapy be increased as part of the treatment of an acute exacerbation of pulmonary disease. (Grade B recommendation). • • **Number of Antibiotics Used to Treat Pseudomonas aeruginosa:** • The CF Foundation concludes that there is insufficient evidence to recommend the use of a single antibiotic as being equivalent to the use of more than one antibiotic class for treatment of

	Pseudomonas infection during an acute exacerbation of pulmonary disease. (Grade I recommendation). • • **Dosing of Antibiotics:** • The CF Foundation recommends that once-daily dosing of aminoglycosides is preferable to 3-times daily dosing for treatment of an acute exacerbation of pulmonary disease. (Grade C recommendation). • The CF Foundation concludes that there is insufficient evidence to recommend the continuous infusion of b-lactam antibiotics for treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation). • • **Duration of Antibiotic Treatment:** • The CF Foundation concludes that there is insufficient evidence to recommend an optimal duration of antibiotic treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation). • • **Synergy Testing:** • The CF Foundation recommends against the use of synergy testing as part of the routine evaluation of the patient with an acute exacerbation of pulmonary disease and multidrug-resistant bacteria. (Grade D recommendation). • • **Corticosteroids:** • The CF Foundation concludes that there is insufficient evidence to recommend the routine use of corticosteroids in the treatment of an acute exacerbation of pulmonary disease. (Grade I recommendation).
Flume et al. 2009▲: Cystic Fibrosis Pulmonary Guidelines: Airway Clearance Therapies ACT).	• ACT is recommended for all patients with cystic fibrosis for clearance of sputum, maintenance of lung function, and improved quality of life. (Level of evidence, fair; net benefit, moderate; grade of recommendation, B). • In general, there is no ACT that has been demonstrated to be superior to others. (Level of evidence, fair; grade of recommendation, B). • For the individual, one form of ACT may be superior to the others. The prescription of ACT should be individualized based on factors such as age, patient preference, and adverse events, among others. (Level of evidence, fair; grade of recommendation, consensus recommendation, B). • Aerobic exercise is recommended for patients with cystic fibrosis as an adjunctive therapy for airway clearance and its additional benefits to overall health. (Level of evidence, fair; net benefit, moderate; grade of recommendation, B). •
UK 2011: ANTIBIOTIC TREATMENT FOR CYSTIC FIBROSIS: Report of the UK Cystic Fibrosis Trust Antibiotic Working Group.	• **<u>ORAL ANTIBIOTICS IN CYSTIC FIBROSIS</u>** • • **Recommendations for treatment of MSSA (meticillin-sensitive Staphylococcus aureus) in CF:** • Continuous, anti-staphylococcal antibiotic prophylaxis, with a narrow spectrum antibiotic such as flucloxacillin, may be used, from diagnosis until the age of 3 years, to reduce the incidence of infection with MSSA. The prophylactic dose used in previous clinical trials is 125 mg twice daily [A]. • If MSSA grows while the patient is receiving flucloxacillin, consider patient adherence and increase the flucloxacillin to

	100 mg/kg/day and add a second oral anti-staphylococcal antibiotic for two to four weeks (sodium fusidate, or rifampicin) (section 8.2). Check cultures after treatment. If clear, continue long-term prophylactic flucloxacillin [D]. For patients who are allergic or intolerant to penicillins then an alternative antibiotic should be used. The choice is determined by the antibiotic sensitivity pattern of the organism and the age of the patient (e.g. tetracyclines should be avoided in children under 12 years). • If cultures are still positive after 2 weeks of 2 antibiotics to which the organism is sensitive continue treatment for another 4 weeks. Culture every week if possible. If the patient is unwell and still growing MSSA, give a course of intravenous antibiotics (section 6.4.1). Two antibiotics, to which the organism is sensitive, should be used but in practice it may be easier to give one of these orally (e.g. fusidic acid or rifampicin) [D]. • If MSSA remains even after a course of IV antibiotics continue with long-term flucloxacillin (100 mg/kg/day) and also check patient's adherence to treatment. Treat with an additional antistaphylococcal antibiotic whenever there is any increase in the symptoms and signs and always try to include an anti-staphylococcal antibiotic with any subsequent IV courses of treatment [C]. • Broad spectrum cephalosporins should not be used as treatment for MSSA [B]. • Macrolides cannot be assumed to provide effective empirical treatment for MSSA because macrolide resistance is increasingly common [D]. • Whatever regular regimen is chosen, any upper or lower airway isolate of MSSA is treated with a course of a new anti-staphylococcal regimen for two to four weeks and a further respiratory specimen obtained at the end of treatment to ensure the organism has been eradicated [C]. • • **Recommendations for use of linezolid in CF:** • Linezolid should be reserved for treatment of refractory MRSA (2–4 week courses) [D]. • Monitoring should be as for the non-CF patient; there is no evidence to suggest that special precautions are necessary. Frequent monitoring of blood count is recommended for all patients at risk of thrombocytopaenia e.g., CF patients with splenomegaly [C]. • There is no advantage to intravenous therapy over oral therapy, and doses appropriate for the non-CF patient can be used [C]. • • **Recommendations for antibiotic use when H. influenzae is isolated:** • If H. influenzae is isolated from acute or routine respiratory tract cultures at any time, even if the patient is apparently asymptomatic, an appropriate antibiotic is given for two to four weeks [D]. Suggested antibiotics include co-amoxiclav, or doxycycline (patients over 12 years only). Macrolide resistance is common and macrolides are not particularly effective against H.influenzae, even if it appears sensitive in the laboratory. Resistance to amoxicillin is also common. • Cultures should be repeated after treatment. If the cultures are still positive but the patient is well, note sensitivities and give

	further 2–4 weeks of an oral antibiotic [D]. • If cultures are still positive after one month, the patient should be considered for a 2-week course of IV antibiotics [D]. • If new symptoms have not cleared, even though the culture is negative, or if the clinical condition worsens at any time, a course of IV antibiotics is indicated [D]. • If cultures remain positive despite intensive treatment or there are frequent recurrences of H. influenzae positive cultures after courses of treatment, a long-term anti-H. influenzae antibiotic should be considered, analogous to the use of anti-staphylococcal prophylaxis. Cephalosporins should not be used (above [D]). • • **Recommendations for the use of ciprofloxacin** • Ciprofloxacin may be prescribed as part of the eradication regimen, for periods of up to 3 months. This is usually combined with a nebulised antibiotic.[A]. • • **Recommendations for treatment of patients chronically infected with P. aeruginosa:** • A 2-week course of ciprofloxacin may be given to patients with CF who are chronically infected with P. aeruginosa at times of upper respiratory infections at the first sign of an increase in symptoms and signs of their chest infection [D]. • These patients will usually be taking a regular nebulised anti-pseudomonal antibiotic, which should be continued [D]. • • **Recommendations for use of oral chloramphenicol:** • The use of oral chloramphenicol in patients chronically infected with P.aeruginosa, with a mild to moderate exacerbation of respiratory symptoms, has been anecdotally associated with improvement in small numbers of patients. Where there are few alternative antibiotics, due to the resistance pattern of the organism, a trial of chloramphenicol may be justified. The patient should be fully informed of the risks of chloramphenicol [D]. • • **Recommendations for use of oral macrolides:** • Macrolides are definitely beneficial in some patients with CF [A]. • A six month trial of oral azithromycin should be considered in patients who are deteriorating on conventional therapy, irrespective of their infection status. Not all patients will benefit from this therapy. The dose should be: 10 mg/kg/dose if body weight <15 kg; 250 mg if < 40 kg; 500 mg if > 40 kg, dose frequency three times per week [A]. Azithromycin is not licensed in children under 6 months of age. • Although there is anecdotal evidence that adding azithromycin to the regimen of all those chronically infected with P. aeruginosa is beneficial, there is insufficient evidence to recommend this [D]. • • **<u>NEBULISED ANTIBIOTICS</u>** • **Recommendations for eradication of P. aeruginosa when detected in respiratory secretions:** • First line therapy should be based on a regimen of nebulised colistin and oral ciprofloxacin. Many centres will use 3 months of treatment from the outset. An alternative is to use a 3 step

	regimen [A]. • Patients presenting with a new growth of P. aeruginosa and a respiratory exacerbation may receive two weeks of intravenous anti-pseudomonal antibiotics before commencing nebulised colistin and oral ciprofloxacin [D]. • TSI should be considered for patients showing early regrowth of P. aeruginosa and for those intolerant of colistin or ciprofloxacin [D]. • If in extenuating circumstances the physician wishes to administer a more prolonged course of inhaled antibiotic, it is recommended that nebulised antibiotic treatment is withdrawn after a year of negative P. aeruginosa cultures [D]. • • **Recommendations for patients chronically infected with P. aeruginosa:** • Patients with chronic P. aeruginosa infection should be considered for regular nebulised antipseudomonal antibiotic treatment [A]. • Initial treatment should be with nebulised colistin [D]. • If colistin is not tolerated or if clinical progress is unsatisfactory, TSI should be used at a dose of 300 mg twice daily for 28 days followed by 28 days off treatment and then repeat. (TSI should be administered 12 hourly. If a shorter interval between morning and evening doses is needed for practical reasons, then the interval should not be less than 6 hours) [C]. • • **Recommendations for nebulised anti-fungals in patients with ABPA (allergic bronchopulmonary aspergillosis):** • Amphotericin or liposomal Amphotericin (Ambisome®, Gilead, Cambridge UK) should be prescribed at a dose of 25 mg bd. Reconstitution and administration is as follows [D]: o Conventional amphotericin: 50 mg dissolved in 8 ml of water for injection and 4 ml (25 mg) used. o Liposomal amphotericin: A 50 mg vial dissolved in 12 ml of sterile water and 6 ml (25 mg) used. • • **Recommendations for nebulised vancomycin for the treatment of MRSA (Meticillin-resistant Staphylococcus aureus):** • Nebulised vancomycin has been used as part of treatment protocols for the eradication of MRSA in patients with CF but there are no trials comparing one regimen with another. Five days treatment with nebulised vancomycin may be used as part of an eradication protocol [D]. Dosage: o Adults: 250 mg bd or qds (200 mg/4 ml sterile water or 0.9% sodium chloride can be used for acceptable nebulisation time – for standard nebuliser/compressor systems). o Children: 4 mg/kg (max 250 mg) in 4 ml sterile water or 0.9% sodium chloride bd or qds –for standard nebuliser/compressor systems. • • In adults and children nebulised vancomycin should be preceded by an inhaled bronchodilator. • • **Recommendations for administration of nebulised antimicrobials:** • The first dose should be administered in hospital and

	bronchoconstriction excluded by pre and post inhalation spirometry where possible and by chest auscultation for all patients. Follow up should exclude cumulative tightness [C]. • Bronchoconstriction usually occurs immediately after nebulised antibiotic administration and may be prevented by pre dose bronchodilator inhalation [C]. • Nebulised antibiotics should be taken after airway clearance to ensure maximum deposition [C]. • A mouthpiece is preferable to a facemask to maximise pulmonary deposition [C]. • Children below 3 years of age will usually require a mask held firmly on the face but inhalation will be ineffective if the child is crying [C]. • The new generation nebuliser systems e.g. eFlow® rapid (Pari Medical, West Byfleet, UK) and I-neb® (Respironics, Chichester, UK) are preferred by many patients [D]. • • Breathing patterns should be observed and corrected if inhaling from a device delivering continuous nebulisation. Computer software e.g. I-neb® Insight AAD® System, (Respironics, Chichester UK) gives visual feed back and aids training for the I-neb® [D]. • Adherence to treatment should be checked subjectively after a period of home use. Irregular usage is not recommended and is a reason for stopping treatment. The I-neb® Insight AAD® System objectively monitors the delivered dose to allow clinicians to work with patients to improve adherence [D]. • • **Recommendations to minimise systemic adverse effects:** • Clinicians should be aware of the potential for systemic absorption and toxic antibiotic effects [D]. • Nebulised antibiotic administration should usually be suspended during intravenous antibiotic treatment. For patients with renal impairment TSI may be preferred to the parenteral route for acute exacerbations but there is little direct evidence of efficacy. Nebulised colistin may be continued for the treatment of multiresistant infection [D]. • If a facemask is used the face should be washed after nebulisation [D]. • The pros and cons of continuing nebulised antibiotic treatment during pregnancy should be individually assessed [D]. • • **Recommendations on nebuliser maintenance:** • Patients should be instructed to carefully follow manufacturer's instructions for cleaning nebulisers [D]. • An electrical compressor should have an inlet filter, which should be changed according to manufacturer's instructions [D]. • Hospitals issuing nebuliser/compressor systems should arrange for their regular servicing. Patients who have purchased their own nebuliser/compressor systems should have their equipment serviced by the hospital where they attend for their CF care. The I-neb® is the property of the manufacturer. Repairs and replacement consumables are dealt with directly between the patient and company [D]. • • **<u>Intravenous Antibiotics:</u>** • CF patients suffering from a pulmonary exacerbation or from persisting low grade symptoms, unresponsive to oral

	antibiotics should receive intravenous antibiotics. Intravenous treatment should accommodate (where possible) the commitments of the patients and family such as work, exams and holidays [D]. • Patients who experience frequent exacerbations may benefit from regular rather than as required intravenous antibiotics but regular treatment is not indicated for most patients [D]. • For organisms other than P.aeruginosa a single agent may be appropriate. For P.aeruginosa, a combination of 2 antibiotics with a different mechanism of action should be used for intravenous treatment in CF patients. Ceftazidime and tobramycin are commonly used but meropenem and colistin is a suitable alternative combination [A]. • Home treatment is an acceptable (and cheaper) option for selected patients. First doses of repeated antibiotic courses do not need to be given in hospital [D]. • A once daily aminoglycoside regimen may be more convenient for most patients, though some find the use of a 30 minute infusion difficult. Once daily tobramycin is associated with less acute nephrotoxicity in children. Tobramycin is the aminoglycoside of choice and gentamicin should be avoided. Co-administration of other nephrotoxic drugs should be avoided [A]. • Plasma creatinine should be measured before the 1st dose of tobramycin and again before the 8th dose. Trough and peak serum aminoglycoside levels should be measured depending upon the dosing regimen used [B]. • In patients receiving repeated courses of nephrotoxic antibiotics, glomerular filtration rate should be measured or estimated annually, along with plasma magnesium as a measure of renal tubular function [B]. • Consideration should be given to an annual pure tone audiogram in patients receiving frequent courses of an aminoglycoside [B]. • In order to reduce cochlear and vestibular toxicity the use of an aminoglycoside should be restricted to alternate courses of intravenous antibiotics, where the patient's clinical condition permits [D]. • Drug allergy should be managed with an appropriate desensitisation regimen [D]. •

UK 2011: STANDARDS OF CARE AND GOOD CLINICAL PRACTICE FOR THE PHYSIOTHERAPY MANAGEMENT OF CYSTIC FIBROSIS. Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF).	• **<u>AIRWAY CLEARANCE:</u>** • **Active cycle of breathing techniques (ACBT):** *Strong* • The ACBT should be considered when recommending an airway clearance technique for all patients with cystic fibrosis (as long as they are able to follow instruction) *(QoE – low).* **Autogenic drainage (AD):** *Strong* • Consider autogenic drainage when choosing an airway clearance technique. There is some evidence to suggest that autogenic drainage is as effective as other airway clearance techniques *(QoE – low).* *Weak* • Consider autogenic drainage particularly in those with airway hyper-reactivity *(QoE – very low).* • Consider autogenic drainage when choosing an airway clearance technique for a patient with cystic fibrosis who has shown decreases in oxygen saturations with other airway clearance techniques *(QoE –very low).* **Positive expiratory pressure (PEP):** *Strong* • PEP should be considered when recommending an airway clearance technique for all patients with cystic fibrosis *(QoE – low).* **Oscillatory devices in cystic fibrosis:** *Strong* • Consider oscillatory devices when recommending an appropriate ACT for a patient with CF *(QoE – low).* **Intrapulmonary percussive ventilation (IPV):** *Weak* • Consider intrapulmonary percussive ventilation when recommending an airway clearance technique for adults with mild to moderate cystic fibrosis *(QoE – very low).* **<u>EXERCISE:</u>** *Strong* • Exercise (and assessment of adherence) should be an integral part of the management of patients with CF *(QoE – moderate).* • Physical training programs should incorporate a range of types of exercise (e.g. aerobic and anaerobic exercise) *(QoE – moderate).* *Weak* • Physical training should aim to reach the minimum level of activity as per Physical Activity guidelines (QoE – low). • Patients should be familiarized regarding the use of subjective measures of perceived exertion or breathlessness in order to gauge levels of physical exercise (i.e. moderate versus vigorous) *(QoE – low).* • Formalized physical training programs should be introduced to supplement unstructured activities to ensure patients achieve the recommended levels of exercise *(QoE – low).* • Patients with CF who do not meet the current guidelines should be encouraged to increase their exercise levels incrementally and in ways that they enjoy *(QoE – very low).* • Patients with CF who meet/exceed the current guidelines should be encouraged to maintain their current levels of exercise and vary the types of exercise *(QoE – very low).* • Flexibility and posture exercises should be incorporated into

	physical training programs in CF *(QoE – very low).* **Risks associated with specific exercise:** **Weak** • Patients should be made aware of any increased medical risks associated with specific exercise or sporting activities *(QoE – low).* • Specific types of strength training (e.g. power lifting, body building and maximal lifts) should be avoided until physical and skeletal maturity *(QoE – low).* • Specific guidance should be given on fluid replacement and dietary/insulin requirements when appropriate (QoE – low). • Patients who exhibit desaturation should be assessed for supplementary oxygen during exercise *(QoE – low).* **MUSCULOSKELETAL ISSUES AND POSTURAL MANAGEMENT:** *Weak* • Musculoskeletal intervention and postural advice should be considered in all patients *(QoE – very low).* **INHALATION THERAPY:** *Strong* • A test dose should be performed in order to assess suitability and/or effectiveness of the medication for the individual *(QoE – moderate).* • Consideration should be given to intelligent nebuliser technologies such as AAD and VMT *(QoE –low).* *Weak* • Relaxed tidal volume breathing through the mouth and not the nose is recommended for patients using nebulised antibiotics *(QoE – very low).* • Expiratory filters should be used to avoid environmental contamination with exposure of others to the medication and also to avoid damage to property *(QoE – very low).* **NON-INVASIVE VENTILATION:** *Strong* • NIV should be considered for all people with CF demonstrating nocturnal hypoventilation with a rise in pCO2 (*QoE – moderate).* *Weak* • NIV should be considered if fatigue is limiting airway clearance *(QoE – low).* • NIV should be considered as an adjunct where desaturation is present during airway clearance *(QoE – very low).* • NIV should be considered where there is difficulty clearing secretions with other techniques *(QoE – very low).* • NIV should be considered for those in ventilatory failure in terms of improved oxygenation *(QoE – low).*

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Strength of Overall Evidence of Effectiveness	Estimate of Net Benefit (*benefit minus harms*)			
	Substantial	Moderate	Small	Zero/Negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Definition of abbreviation: I = insufficient evidence.

* Strength of overall evidence and estimate of net benefit determine the grade.

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Strength of recommendations (4): *Recommendation level A*—the committee strongly recommends that clinicians routinely provide [the service] to eligible patients. (The committee found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.) *Recommendation level B*—the committee recommends that clinicians routinely provide [the service] to eligible patients. (The committee found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.) *Recommendation level C*—the committee makes no recommendation for or against routine provision of [the service]. (The committee found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of the benefits and harms is too close to justify a general recommendation.) *Recommendation level D*—the committee recommends against routinely providing [the service] to patients. (The committee found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.) *Recommendation level I*—the committee concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.)

Quality of evidence: *Good*—Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes. *Fair*—Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes. *Poor*—Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidenced, or lack of information on important health outcomes.

▲

Grade	Definition	Suggestions for Practice
A	The committee recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The committee 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/provide this service.
C	The committee recommends against routinely providing the service. There may be considerations that support providing the service to an individual patient. There is moderate or high certainty that the net benefit is small.	Offer/provide this service only if other considerations support offering or providing the service to an individual patient.
D	The committee 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	The committee 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 clinical considerations section of the recommendations. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

(Adapted from Reference 92.)

Detaillierte Darstellung der Recherchestrategie:

MEDLINE (PubMed) nach Leitlinien am 29.10.2012

Suchschritt	Suchfrage	Treffer
#4	Search "Cystic Fibrosis"[Mesh]	26409
#5	Search cystic fibrosis[Title/Abstract]	30022
#6	Search mucoviscidosis[Title/Abstract]	1387
#7	Search ((#4) OR #5) OR #6	35110
#8	Search guideline*[Title]	43785
#9	Search (#7) AND #8	81
#11	Search ((#4) OR #5) OR #6 Filters: Practice Guideline; Guideline	62
#12	Search (#9) OR #11	110
#13	Search (#9) OR #11 Filters: Publication date from 2007/01/01 to 2012/12/31	53

#13 16 Treffer in Datenbank aufgenommen

Darüber hinaus wurde in den HTA- und Leitliniendatenbanken AWMF, GIN, NGC und Trip nach aktuellen Publikationen mit den Suchbegriffen „cystic fibrosis“, „mucoviscidosis“ in verschiedenen Variationen gesucht.
Nach Dublettenkontrolle ergab die Recherche insgesamt **36** Quellen.

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