NHS England

Evidence Review:

Continuous aztreonam lysine for cystic fibrosis (all ages)

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First published:	November 2015
Updated:	Not applicable
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1. Introduction

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting over 10,000 people across the UK.

It is caused by a genetic mutation; specifically a mutation in a gene call CFTR. The CFTR gene normally creates a protein that regulates levels of sodium and chloride in cells. If the gene is defective, it results in a build up of thick, sticky mucus in the body which is particularly damaging to the lungs, the gut and the pancreas, blocking the airways and the flow of digestive juices in the gut. This can result in problems with the digestion and absorption of food resulting in poor growth, and long-term infection and inflammation in the lungs (which is the main cause of morbidity and mortality).

Current standard treatments for cystic fibrosis aim to minimise the symptoms and include: (i) frequent chest physiotherapy (ii) specialist dietary advice, supplements and enzyme replacement therapy, and (iii) medication to relieve bronchospasm and inflammation in the lungs, reduce the viscosity of mucus in the airways or treat serious infection in the lungs.

Pseudomonas aeruginosa is the most frequent and important pathogen responsible for chronic infection in people with cystic fibrosis. NHS England currently has a formal commissioning policy for the use of inhaled therapies for patients (over the age of 6 years) with cystic fibrosis and chronic pseudomonas aeruginosa infection (A01/P/b 2014). This policy confirms that three antibiotics are funded in sequence: tobramycin, colistimethate sodium and aztreonam lysine. Inhaled tobramycin and aztreonam lysine have been licensed for alternate month use due to theoretical concerns regarding bacterial resistance. As most people with cystic fibrosis will feel worse during the month with no antibiotic cover, alternating regimens are usually prescribed.

Aztreonam lysine is only considered if there is progressive loss of lung function (defined as greater than 2% per year decline in forced expiratory volume (FEV1) as % of predicted) or where there is continued need for intravenous therapy for exacerbations i.e. more than two per year despite therapy with an alternating regimen of tobramycin and colistimethate sodium.

For a small number of patients, alternating treatment with aztreonam and tobramycin or colistimethate sodium may not be suitable due to intolerance or contraindications to both tobramycin and colistimethate sodium. For this subgroup, continuous aztreonam lysine may be the only available therapy that achieves adequate symptom relief for sustained periods.

2. Summary of results

This evidence review was concerned with the cost and clinical effectiveness of continuous treatment with aztreonam lysine via a nebuliser, in adults and children with cystic fibrosis who have chronic infection with Pseudomonas aeruginosa.

In summary, no published evidence was found for the continuous use of inhaled aztreonam lysine (AZLI). Furthermore there is currently no published evidence comparing continuous aztreonam lysine and cyclical aztreonam lysine (28 days on AZLI followed by 28 days on a different antibiotic).

There is level 1 evidence for the clinical effectiveness of aztreonam lysine (AZLI) to treat infection by Pseudomonas aeruginosa (P. aeruginosa), compared to a placebo. There is also evidence from one randomised control trial (RCT) to support the superiority in clinical effectiveness of AZLI compared to tobramycin, coming from one RCT. A single study found that AZLI use was more cost effective than tobramycin.

All of the studies examined either a period of 28 days using AZLI or a cycle of using AZLI for 28 days, followed by 28 days with no antibiotics. There is evidence extrapolated from a single level 1 study that 28 days on tobramycin maintains the clinical benefits of 28 days on AZLI.

Clinical Evidence Review Questions

Research question 1: Is continuous treatment with aztreonam lysine via a nebuliser clinically effective in adults and children with cystic fibrosis who have chronic infection with Pseudomonas aeruginosa?

There is level 1 evidence for the efficacy of AZLI compared to a placebo. An often used measure of clinical effectiveness is to measure the percentage change, from the baseline value measured before the trial, in forced expiratory volume in 1 second (% change from baseline (%CFB) in FEV1). Three RCTs have all found, at the end of a 28 day trial, an improvement in the %CFB in FEV1 of between 0.3 to 8% in the AZLI arm and a deterioration in the placebo arm of between -2 to -2.5% (McCoy et al. 2008; Retsch-Bogart et al., 2009; Wainwright et al., 2011). Other metrics, such as the change in respiratory symptoms scale of the revised cystic fibrosis questionnaire (CFQ-R RSS) also demonstrate analogous improvements, compared with a placebo.

Likewise there is level 1 evidence that AZLI is superior to TOB, coming from the RCT (Assael et al., 2013), that compared the 75 mg AZLI, taken three times a days, in 28 days on / 28 days off cycles, with a similar TOB treatment. At the end of a 28 day cycle the mean %CFB in FEV1 was 8.4% for AZLI compared with 0.55% for TOB. During the off cycle there was an observed deterioration, but after three cycles there was still an overall improvement of 2.05%, compared with TOB at -0.66%. The study also found that, compared with TOB, patients treated with AZLI had:
- fewer hospitalisations (p=0.044)
- lower CFQ-R RSS scores (p=0.005)
- fewer respiratory events, needing additional antibiotics (p=0.004)

It also should be noted that the trial had an extension in which all patients received AZLI in a 28 days on / 28 days off cycle and there was no difference between the patients who had received TOB/AZLI and those receiving AZLI/AZLI. The deterioration in %CFB in FEV1 during the off periods was observed in all trials. There is also level 2 evidence that the improvement in FEV1 is greater when AZLI is being taken three times a day compared to when it is being taken twice a day (Oermann et al., 2010).

The only RCT identified that examined the continuous use of antibiotics for longer than 28 days was (Trapnell et al., 2012), which used 28 days of AZLI to establish a consistent baseline for a TOB trial. There is evidence extrapolated from a level 1 study that 28 days on TOB maintains the benefits of 28 days on AZLI, but no further improvement in FEV1 is made.

In terms of safety outcomes, patients with chronic pseudomonas aeruginosa infections display a wide range of adverse events. The most common of these is coughing (30-80%), but also pyrexia, oropharyngeal pain, dyspnea and many others. In the majority of trials, there was no statistically significant difference between the rates of adverse events in the trial and placebo arm. One exception to this was (Retsch-Bogart et al., 2009) found AZLI treated patients had a lower incidence of productive cough than placebo treated patients, but this was based on a small sample size (31 of 160 patients) and was not observed in other trials. Likewise there was no statistically significant difference in the numbers of adverse events in patients treated with AZLI, compared with those treated with TOB (Assael et al., 2013).

Research question 2: Is continuous treatment with aztreonam lysine via a nebuliser cost effective in adults and children with cystic fibrosis who have chronic infection with Pseudomonas aeruginosa?

One study was found that compared the cost of AZLI, taken three times a day on a 28 day on/28 day off cycle, with an analogous TOB treatment (Schechter et al., 2015). The study found that the total cost over 3 years of AZLI was 16% less than TOB (AZLI: £148,710 TOB: £176,268) [Original figures provided in US dollars and converted to the nearest full pound based on conversion rate on 17/11/2015 of £1 to $1.52 and is provided as a guideline for comparison only]. This saving was predominantly coming from the assumed reduction in number of hospitalisation, with a slight reduction in drug costs. It was also based on a US healthcare model. The study also found AZLI marginally increased the number of quality adjusted life years.

A final point which is noteworthy is that, with the exception of (Trapnell et al., 2012), all of the RCTs were funded by Gilead, sole manufacturer of Cayston (trademark name for AZLI). Also there was considerable overlap in the authors of the majority of the RCTs and that many of these authors had received grants from Gilead, notably Oermann, McCoy, Retsch-Bogart, Gibson and Wainwright.

3. Research questions

Is continuous treatment with aztreonam lysine via a nebuliser clinically effective in adults and children with cystic fibrosis who have chronic infection with Pseudomonas aeruginosa?

Is continuous treatment with aztreonam lysine via a nebuliser cost effective in adults and children with cystic fibrosis who have chronic infection with Pseudomonas aeruginosa?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the appendix.

Appendix One

Level	Study design and			Outcomes					Reference	Other		
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
1-	Systematic	Total 946 patients in 5 RCTs	5 RCTs with Aztreonam 75mg	Clinical effectiveness of the intervention compared to existing interventions	% Change in FEV1	Improved FEV1 (McCoy, Retsch - Bogart 2009, Wainwright, Oermann) No significant change in FEV1 (Retsch - Bogart 2008)	Time to need for additional antibiotics (McCoy et al. 2008) Change in resporatatory symptom score (Retsch - Bogart 2009, Wainwright 2009)	Increased time to need for additional antibiotics. (McCoy) No change in symptom score (Wainwright) Change in symptom score (Retsch-Bogart 2008)	Das, Rashmi Ranjan; Kabra, Sushil Kumar; Singh, Meenu. Treatment of pseudomonas and Staphylococcus bronchopulmonary infection in patients with cystic fibrosis. ScientificWorldJournal. 2013,	-	-	Population: >6 years. CF and chronically-infected with Psedomonas aeruginosa. Comments: This systematic review has made a useful literature review and found 5 RCT's of relevance to the research question. No meta-analysis or numerical results quoted.
1+	RCT	100	75mg of Aztreonam (AZLI) TID	Clinical effectiveness of the intervention	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	At week 24 with standard error in bracket: AZIL 0.16 (1.5) vs placebo -0.75 (1.43) p=0.663	Cystic Fibrosis Questionnair - revised (CFQ-R) score Safety	CFQ-R: AZIL 2.97 (1.7) vs placebo 2.79 (1.58) p=0.939 Wheezing (AZLI 20.8% vs placebo 5.8%), chils (AZIL 12.5% vs placebo 3.8%)	Tullis, D. Elizabeth; Burns, Jane L.; Retsch-Bogart, George Z.; Bresnik, Mark; Henig, Noreen R.; Lewis, Sandra A.; Lipuma, John J.. Inhaled aztreonam for chronic Burkholderia infection in cystic fibrosis: a placebo-controlled trial. J. Cyst. Fibros.. 2014	-	-	Population: >6 years, mean 26.3 years. CF and chronically-infected with Burholderia. Comments: This RCT has focused on patients with CF who have a chronic Burholderia infection. Hence it is not directly relevant to the research questions, although it is useful to note the side effects of AZIL (i.e. Wheezing and chils) and also to note that AZIL does not demonstrated a statisitically significance improvement in %CFB in FEV1 of patients with Burholderia.

1+	Systematic	(Retsch-Bogart 2008): 164 patients (McCoy 2008): 211 patients (Wainwright) 157 patients (Assael) 268 patients	4 RCTs with Aztreonam 75mg Assael 3 cycles of 28 days on TID, 28 days off.	Clinical effectiveness of the intervention compared to existing interventions	Change in CFQ-RSS Time to need for additional antibiotics (McCoy)	McCoy: 92 days AZLI vs 71 days Placebo (Retsch Bogart): at 28 days, 7.1 AZLI vs -2.6 placebo Wainwright: 3.22 AZLI vs 1.41 placebo Assael: AZLI 8.2 vs 2.6 TIS	% Change in FEV1	McCoy: 92 days increase with AZLI 6.3 % (Retsch Bogart): increase with AZLI 10.3% compared with placebo Wainwright: AZLI 0.29% vs Placebo -2.5% Assael: TIS 0.55% vs AZLI 8.35% after 3 cycles AZLI 2.05 % vs -0.66% TIS	Máiz, Luis; Girón, Rosa M.; Olveira, Casilda; Quintana, Esther; Lamas, Adelaida; Pastor, Dolores; Cantón, Rafael; Mensa, Josep. Inhaled antibiotics for the treatment of chronic bronchopulmonary Pseudomonas aeruginosa infection in cystic fibrosis: systematic review of randomised controlled trials. Expert Opin Pharmacother. 2013	-	Assael: extension period patients offered to switch to AZIL, patients who received TIS / AZIL had comparable results to AZIL / AZIL.	Population: >6 years. CF and chronically-infected with Psedomonas aeruginosa. Comments: This systematic review makes a reliable and useful comparisson of a number trials. Here we quote the results for three aztreonam lysine - placebo trials and one aztreonam lysine (AZLI) - tobramycin (TOB). But review also includes two colistin (COL) - placebo trial, eight TOB - placebo and three COL-TOB trial. AZIL was demonstrated to be superior to TOB. Thee trials comparing TOB with COL. Two found COL to be inferior to TIS in terms of change in FEV1, one found approximately the same change.

1+	RCT	268: 136 AZIL vs 132 TNS	75mg of Aztreonam (AZLI) TID in 28 days on / 28 days off treatments	Clinical effectiveness of the intervention compared to existing interventions	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	At day 28, AZIL 8.35% vs. 0.55% TNS p<0.001 After 24 weeks, (i.e. with 3 on/off cycles) AZIL 2.05% vs TNS -0.66% p=0.002	CFQ-R, Respiratory symptoms scale (RSS) Respiratory hospitalisations	Avearge CFQ-R score AZIL 6.3 vs TNS 2.2 p=0.019 No. of hospitalisations : AZIL 40 vs TNS 58 p=0.044 No. of resperatory events requiring anti-biotics: AZIL: 84 vs TNS 121 p=0.004 Large number of adverse side effects. Most common was a cough (AZIL 70.6% vs TNS 78.8%). Severe adverse events: AZIL 16.2% vs TNS 8.3% p=0.063. No statistically significant difference between number of adverse events in TNS and AZIL.	Assael, Baroukh M.; Pressler, Tacjana; Bilton, Diana; Fayon, Michael; Fischer, Rainald; Chiron, Raphael; LaRosa, Mario; Knoop, Christiane; McElvaney, Noel; Lewis, Sandra A.; Bresnik, Mark; Montgomery, A. Bruce; Oermann, Christopher M.; AZLI Active Comparator Study Group. Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial. J. Cyst. Fibros.. 2013	-	-	Population: >6 years. CF with P. aeruginosa positive sputum and FEV1 <75%. Comments: This RCT makes a comparision between inhaled Aztreonam (AZLI) and Tobramycin (TNS). AZLI is found to be superior to TNS in terms of efficacy and safety. In particular AZIL reduced numbers of pulmonary exacerbations, delayed time to need additional antibiotics and increased weight of patient. The study was based on three cycles of 28 days on and 28 days off intervention (not 28 days AZIL 28 days TNS). It found that such cycles were still partially effective with AZIL (%CFB in FEV1 = 2.05%) but not TNS (%CFB in FEV1 = -0.66%). Although continuous use of AZIL found to be superior (%CFB in FEV1 = 8.35% at 28 days) vs TNS (%CFB in FEV1 = 0.55% at 28 days). The sudy had an extension in which all patients received AZIL in 28 days on, 28 days off cycles. During this extension period there was no statistically significan difference between patients who had received AZIL/AZIL and TNS/AZIL.

1-	Systematic	Total 946 patients in 5 RCTs	75 mg BID TID 150 mg 225 mg	Clinical effectiveness of the intervention	Clinical efficacy: Change in CFQ-RSS Time to need for additional antibiotics (McCoy) Symptoms change from baseline in CFQ-R	Look at Retsch-Bogart(2008), McCoy(2008), Retsch-Bogart(2009), Oermann(2010) , Wainwright (2011), Results quoted elsewhere.	Pharmacokinetics and Phamacodynamics: Concentrations in Sputum with respect to time (Gibson 2006) Concentrations in plasma and sputum 10 mins after dose, (McCoy 2008, Retsch-Bogart 2008, 2009)	For adults, 10 mins after dose sputum concentration were 383 mu g/g (for 75 mg dose), 879 mu g/g (for 150 mg), 985 mg g/g (for 225 mg). See paper for other times.	Pesaturo, Kimberly A.; Horton, Evan R.; Belliveau, Paul. Inhaled aztreonam lysine for cystic fibrosis pulmonary disease-related outcomes. Ann Pharmacother. 2012	-	-	Population: >6 years. CF and chronically-infected with Psedomonas aeruginosa. Comments: This review summarises the 5 RCTs examining Aztreonam, Retsch-Bogart(2008), McCoy(2008), Retsch-Bogart(2009), Oermann(2010), Wainwright (2011), in addition to another study (case series) examining . The results on clinical efficacy have been quoted elsewhere, but it does also summarise differenr sputum and plasma concentrations and also adverse side effects. In particular, in all 5 trials, between 32-90% of patients developed a cough, 7-44% had Oropharyngewal or pharyngolaryngeal pain. See table 4 for full list.
1+	Systematic + Meta Analysis	In 3 studies on Aztreonam , total of 574 patients	Tobramycin inhalation powder (TIP) with 112mg and 122mg tobramycin twice daily (BID) Tobramycin inhalation solution (TIS-T) with 300mg/5ml tobramycin BID Tobramycin inhalation solution (TIS-B) with 300mg/4ml tobramycin BID colistimethate sodium (colistin) 80mg/3ml and 1MU/3ml tobramycin BID aztreonam lysine for inhalation (AZIL) 75mg three times a day (TID) or BID	Clinical effectiveness of the intervention	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	The three studies involving Aztreonam give the results: (McCoy, 2008) AZIL 4.5 vs placebo -2.0 based on 162 patients BID and TID (Retsch-Bogart, 2009) AZIL 8.03 vs placebo -2.44 based on 142 patients TID (Oermann, 2011) AZIL 8.35 TID vs TIS-T 0.55 BID based on 268 patients	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 20 weeks	Insufficient data for reliable meta-analysis. Too much variation in age and other factors.	Littlewood, Kavi J.; Higashi, Kyoko; Jansen, Jeroen P.; Capkun-Niggli, Gorana; Balp, Maria-Magdalena; Doering, Gerd; Tiddens, Harm A. W. M.; Angyalosi, Gerhild. A network meta-analysis of the efficacy of inhaled antibiotics for chronic Pseudomonas infections in cystic fibrosis. J. Cyst. Fibros.. 2012	(Oermann et al., 2011) excluded from meta-analysis because 'study arm populations differed regarding naieve/exposed status'.	-	Population: 5 studies < 18 years (mean baseline 11-16) 6 studies > 18 years (mean baseline 20-32) . CF and chronically-infected with Psedomonas aeruginosa Comments: This study attempts to combine 8 RCTs and 3 Cohort studies in a meta-analysis which compares the difference in %CFB in FEV, at 4 weeks, for patients treated with different antibodies. This meta-analysis is based on a Bayesian network meta analysis, 'with non-informative priors to synthesize the results of included studies'. The principle result of relevance to this review is that the difference in %CFB in FEV, between Aztreonam and other treatments are; 9.28 (placebo), -4.28 (TIS-T), -4.28 (TIS-B), -2.13 (Colistin) and 3.64 (TIP). The systematic review is useful and can't be faulted, although there are concerns about the results of the meta-analysis. Principally, it is not clear in the paper how they have accounted for differences in the respective trials, e.g. differences in the populations etc. This is demonstrated by the fact that the meta-analysis predicted a difference between AZLI and TIS-T at -4.19 (95 % CL -8.14 - 0.21), whereas (Oermann et al., 2011) measured the difference at 7.80, albeit with a mixture of exposures.

1+	RCT	119	Fosfomycin/tobramycin (FTI) 80/20 mg vs 160/40 mg.	Clinical effectiveness of the intervention compared to existing interventions	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	%CFB in FEV1 for placebo -6.5%, for FTI 80/20 mg 1.0 % and for FTI -0.3 %	CFQ-R,	change in CFQ-R Placebo: -7.88, 80/20 mg -1.1, 160/40 mg -0.3	Trapnell, Bruce C.; McColley, Susanna A.; Kissner, Dana G.; Rolfe, Mark W.; Rosen, Jonathan M.; McKevitt, Matthew; Moorehead, Lisa; Montgomery, A. Bruce; Geller, David E.; Phase 2 FTI Study Group. Fosfomycin/tobramycin for inhalation in patients with cystic fibrosis with pseudomonas airway infection. Am. J. Respir. Crit. Care Med.. 2012	-	-	Population: >18 years, mean 18 years. CF with P. aeruginosa positive sputum and 25% < FEV1 <75%. Comments: This RCT makes a comparisson between different doses of Tobramycin (FTI) with a placebo, however it uses a treatment of 75 mg aztreonam (AZIL), three times a day, for 28 days before the trial, in order to bring the patients to a consistant base level. Hence the study provides level 1 evidence for the extent to which 28 days of Tobramycin maintains the benefits of 28 days of AZIL, compared to a placebo. Hence the most relevant result of this paper is that FTI maintains the improvement of AZIL in FEV1 with an increase of 1% for 80/20 of FTI, -0.3% for 160/40 mg and -6.5% for placebo. However, there is a slight decrease in CFQ-R score, -1.1 for 80/20 mg of FTI, -4.1% for 160/40 mg and -7.8 for placebo.
1+	RCT	160	75 mg Aztreonam 52.5mg lysine monohydrate (AZLI) Three times a day (TID)	Clinical effectiveness of the intervention	Cystic Fibrosis Questionaire - Revised CFQ-R respiratory symptoms scale RSS, change in baseline score. Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	CFQ-R RSS: placebo 1.41 vs AZLI 3.22 Mean (%CFB in FEV1) placebo: -2.5 % vs AZLI: 0.29% p=0.021	Adverse events	One or more adverse event: Placebo 76.5% vs AZIL 77.6% Pulmonary function test decreased: Placebo 3.7% vs AZIL 0%	Wainwright, C. E.; Quittner, A. L.; Geller, D. E.; Nakamura, C.; Wooldridge, J. L.; Gibson, R. L.; Lewis, S.; Montgomery, A. B.. Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and P. aeruginosa. J. Cyst. Fibros.. 2011	-	-	Population: 6-17 years. CF with P. aeruginosa positive sputum and 25% < FEV1 <75%. Comments: This RCT did a straight comparison between a placebo and 75 mg of Aztreonam (AZLI) take three times a day. The study was based on continuous use of AZLI over a 28 day period with a 14 day follow up. The study found AZIL to be superior to the placebo in terms of clinical efficacy and had statistically similar levels of adverse events.

2+	Cohort	274	75 mg Aztreonam 52.5mg lysine monohydrate (AZLI) Three times a day (TID)	Clinical effectiveness of the intervention compared to existing interventions	Cystic Fibrosis Questionaire - Revised CFQ-R respiratory symptoms scale RSS, change in baseline score. Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	Both treatments found improvements from baseline in FEV1 during on period and approximate return to FEV1 during off period. Range of improvements was -4.2% to 16.05% for BID and -5.02 to 14.14% for TID. Analogous results for CFQ-R RSS.	Survival rates Changes in weight Hospitiliation rates Serious adverse events	Mean number of hospitalisation days: BID 8.32 vs TID 12.46 No statistically significant vchange in weight gain between BID and TID, both approx 1.5 Kg over 18 months. Serious adverse events: 44.7 % BID vs 52.4 % TID	Oermann, Christopher M.; Retsch-Bogart, George Z.; Quittner, Alexandra L.; Gibson, Ronald L.; McCoy, Karen S.; Montgomery, A. Bruce; Cooper, Peter J.. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr. Pulmonol.. 2010	-	-	Population: >6 years mean age: 28.5 years. CF with P. aeruginosa positive sputum. Comments: This study presents the results of a long term 18 months trial comparing patients taking 75 mg of Aztreonam three times a day (TID) vs two times a day (BID), using a 28 days on /28 days off. Both treatments display similar results in terms of clinical efficacy, in particular both treatments found improvements from baseline in FEV1 during on period and approximate return to FEV1 during off period. BID appears to display reduced hospitalisation rates, compared with TID, but it is suspected that this is not statistically significant, although this is not clear from the paper. There are a number of concerns of bias in the paper. Firstly the two arms were not even sizes, 89 (BID) vs 189 (TID). Secondly 51.5 % of patients continued to use >300 mg of Tobramycin throughout study, this does appear to have been treated in a systematic way or included in the analysis.
1+	RCT	164	75 mg Aztreonam 52.5mg lysine monohydrate (AZLI) Three times a day (TID)	Clinical effectiveness of the intervention	Cystic Fibrosis Questionaire - Revised CFQ-R respiratory symptoms scale RSS, change in baseline score. Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	CFQ-R RSS: placebo -2.66 vs AZLI 7.1 p<0.001 difference in Mean (%CFB in FEV1) between placebo and AZLI : 10.3% p<0.001	CFQ-R other scores adverse effects	Statistically significant improvements, for AZLI, in CFQ-R scores in Eating, Emotional functioning, Health perceptions, Physical functioning, Role/School, vitality. Fewer AZLI patients with productive cough, 12.5% vs 25% (placebo) p=0.047. Other adverse effects similar between two treatments.	Retsch-Bogart, George Z.; Quittner, Alexandra L.; Gibson, Ronald L.; Oermann, Christopher M.; McCoy, Karen S.; Montgomery, A. Bruce; Cooper, Peter J.. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest. 2009	-	-	Population: 7-74 years. CF with P. aeruginosa positive sputum and 25% < FEV1 <75%. Comments: This RCT compares the use of 75 mg aztreonam (AZLI) three times a day with a placebo, over a 28 day period. The trial found clear evidence for the clinical efficay of AZIL with a 10.3% difference in %CFB in FEV1, between AZLI and the placebo. Patients also displayed a lower incidence of productive cough, but other adverse effects were the same between placebo and AZLI. Many CFQ-R scores were statistically better in AZLI arm than placebo.

1+	RCT	246	75 mg Aztreonam 52.5mg lysine monohydrate (AZLI) Three times a day (TID) or twice day (BID).	Clinical effectiveness of the intervention compared to existing interventions	Cystic Fibrosis Questionaire - Revised CFQ-R respiratory symptoms scale RSS, change in baseline score. Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 4 weeks	Both TID and BID displayed the same level of improvement in FEV1, with a mean difference, with placebo, in %CFB in FEV1 of 6.3%. Likewise no difference between BID and TID in CFQ-R RSS, but improvement, when compared with placebo, of 5.01 point (p=0.002). CFQ-R RSS correlated with %CFB in FEV1 with correlation coef. 0.33	Adverse events	No significant difference in adverse events between placebo and AZIL except productive cough, placebo 17.1%, BID 13%, TID 13.6%.	McCoy, Karen S.; Quittner, Alexandra L.; Oermann, Christopher M.; Gibson, Ronald L.; Retsch-Bogart, George Z.; Montgomery, A. Bruce. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. Am. J. Respir. Crit. Care Med.. 2008	-	-	Population: 7-65 years. CF with P. aeruginosa positive sputum and 25% < FEV1 <75%. Comments: This RCT made a comparison between a placebo and 75 mg of Aztreonam (AZLI) take three times a day (TID) and twice a day (BID). The study was based on continuous use of AZLI over a 28 day period with a 56 day follow up. The study found AZLI to be superior to the placebo in terms of clinical efficacy and had statistically similar levels of adverse events. The study found no statistical difference between BID and TID.

1-	RCT	105	75 mg Aztreonam (AZLI) or 226 mg Aztreonam twice day (BID).	Clinical effectiveness of the intervention compared to existing interventions	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) measured at 7 days, 14 days and 28 days	%CFB in FEV1 at 7 days: 6.9% (75 mg) 6.8% (225 mg), approx 3% (placebo estimated from graph) %CFB in FEV1 at 14 days: 6.2% (75 mg) 2.1% (225 mg), approx 1.4% (placebo) %CFB in FEV1 at 28 days (estimated from graph, values not quoted): 1% (placebo), 1% (75 mg) 1.2% (225 mg) Upon spliting patients into FEV1 < 75% %CFB in FEV1 at 14 days (estimated from graph, values not quoted): 9.5% (75 mg) 6% (225 mg), approx 3% (placebo) and FEV1 > 75% %CFB in FEV1 at 14 days (estimated from graph, values not quoted): 1.5% (75 mg) -0.5% (225 mg), approx 1% (placebo).	Adverse events	adverse events 71% (placebo), 70% (75 mg), 73% (225 mg)	Retsch-Bogart, George Z.; Burns, Jane L.; Otto, Kelly L.; Liou, Theodore G.; McCoy, Karen; Oermann, Christopher; Gibson, Ronald L.; AZLI Phase II Study Group. A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. Pediatr. Pulmonol.. 2008	-	-	Population: Mean age 26 years. CF with P. aeruginosa positive sputum. Comments: This is one of the earlier RCTs, by the same authors, that compares 75mg and 225 mg of Aztreonam administered over 14 days with a 14 day follow up. The study found no difference in clinical efficacy, between 75 mg and 225 mg, at 7 days. However, at 14 days 75mg was found to be superior. It was also noted that the efficacy drops considerably when considering patients with FEV1 > 75%. There was no difference in reported rates of adverse events. Concerns with this RCT are primarily due to the sample size (approx 30 patients per arm) and length of time of study. There was also no attempt to standardise the baseline before the trial.

1-	RCT	35	All patients received 75mg on day 1, 150mg on day two and 225 mg on day three.	Safety of the intervention	Concentrations of Aztreonam in sputum and plasma.	Median sputum concentrations, 2 hours post dose (micro g /g): 38 (75 mg), 83 (150 mg) 78 (225 mg). Other primary outcome results of no relevance to research questions.	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1)	%CFB in FEV1 Adults (after 2 hours): Placebo: -7.4% day 1, -5.1% day 2, -5.9% day 3. -3.94% 75mg, -5.8% 150 mg, -5.33% 225mg.	Gibson, Ronald L.; Retsch-Bogart, George Z.; Oermann, Christopher; Milla, Carlos; Pilewski, Joseph; Daines, Cori; Ahrens, Richard; Leon, Kevin; Cohen, Morty; McNamara, Sharon; Callahan, Tracy L.; Markus, Richard; Burns, Jane L.. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. Pediatr. Pulmonol.. 2006	-	-	Population: Adults: 19-54 years, adolescents: 13-17 years. CF with P. aeruginosa positive sputum. Comments: Although technically a RCT, in practice this was closer to a cohort study due to the size of the sample and design of the study. It's primary objective was to determine the Pharmacokinetics and microbiology of Aztreonam. Although it is interesteing to note that 2 hours after dose there was no statistically significant difference between placebo and active arm. Other results of the paper are of little relevance to research questions.
3	Other	NA	75 mg Aztreonam 52.5mg lysine monohydrate (AZLI) Three times a day (TID) 28 days on / 28 days off	Cost effectiveness	Total cost	AZLI: $226,352 Tobramycin: $268,298	-	-	Schechter, Michael S.; Trueman, David; Farquharson, Rachel; Higuchi, Keiko; Daines, Cori L.. Inhaled aztreonam lysine versus inhaled tobramycin in cystic fibrosis. An economic evaluation. Ann Am Thorac Soc. 2015	-	-	Population: >6 years. CF with P. aeruginosa positive sputum and FEV1 <75%. Comments: This study looked at the cost effectiveness of using 75mg Aztreonam (AZLI), three time a day, on a 28 days on / 28 days off cycle for three years, compared with using Tobramycin (TOB) on the same 28 days on / 28 days off cycle. The review concluded that AZLI was 16% cheaper than TOB, (AZLI $226,352, TOB $268,298). This saving is largely coming from the reduction in the number of hopsitalisations in AZLI treatment. The drug costs are also assumed to be cheaper with AZLI (AZLI: $98,558 TOB $107,581). This is based on a US health care model. The quality adjusted life years also increase with AZLI 1.916 vs TOB 1.887.

2+	Cohort	105	75 mg of Aztreonam three times a day for 28 days.	Clinical effectiveness of the intervention	Proportions of patients with cultures negative for P. aeruginosa.	58.2% of patients remained culture negative through 24 week follow up.	Percentage change from baseline in forced expiratory volume in 1 second (%CFB in FEV1) Adverse events.	Patients >6 who reached primary endpoint (culture negative) remained near baseline until week 16 and then had a mean -2.5 % decrease by week 28. For patients not reaching primary endpoint, %CFB in FEV1 at weeks 8, 16 and 28 were -4.2%, -5.1% and -8.9%. at week 4, approximately at baseline. 16% hospitalised, most common adverse event was coughing (41%).	Tiddens, H. a. W. M.; De Boeck, K.; Clancy, J. P.; Fayon, M.; H G M, Arets; Bresnik, M.; Derchak, A.; Lewis, S. A.; Oermann, C. M.; ALPINE study investigators. Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: The ALPINE study. J. Cyst. Fibros.. 2015	-	-	Population: 3 months - 18 years. Mean 6.26 years. CF with P. aeruginosa positive sputum, FEV > 80% . Comments: This cohort study is primarily designed to ascertain the extent to which aztreonam (AZLI) can be used to eradicate P. aeruginosa in children with FEV1 > 80%. The primary result is that 89% were free at end of the treatment, 75% were free after 4 weeks and 58% were free after 24 weeks. The improvement in FEV1 was no observed, because it studied FEV1 > 80% patients.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
Updated search terms - Population	Cystic fibrosis AND Pseudomonas
Updated search terms - Intervention	Aztreonam Cayston
Updated search terms - Comparator	None
Updated search terms - Outcome	None
Inclusion criteria	General inclusion criteria
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Title/Abstract Publication date <5 yrs, <10 yrs RCTs, SRs, Mas English language
Exclusion criteria	General exclusion criteria
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	None