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Literature Scan: Inhaled medications for Cystic Fibrosis

Month/Year of Review: May 2015 **Date of Last Review:** May 2014

Current PDL Class:
See **Appendix 1**.

Conclusions:

- There is limited new evidence on the efficacy or safety of inhaled agents for the treatment of Cystic Fibrosis (CF) that would change current PDL class management.
- There remains insufficient comparative evidence to directly compare inhaled tobramycin (TIS) to inhaled aztreonam (AZLI) for the treatment of *P. aerugonisa* in patients with CF and there is no evidence that continuous use is superior to the recommended 28-day cycle (on 28 days, off 28 days).
- There remains insufficient evidence to recommend for or against the chronic use of other inhaled antibiotics (ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations in patients with CF.
- For the early eradication of *P. aeruginosa,* there is evidence that treatment with inhaled antibiotics is better than no treatment in eradication; but there is no strong evidence of a superior regimen over another. There is also moderate quality evidence that there is no significant difference between 28 days of TIS and 56 days of therapy.
- There is low quality evidence that TIS administered by the PARI LC PLUS Nebulizer is effective in improving lung function in patients with CF.

Recommendations:

- Evaluate comparative costs in executive session; maintain at least one formulation of either inhaled tobramycin or aztreonam as preferred on the PDL for the treatment of chronic infection with *P. aerugonisa.*

Current Quantity Limit:

- A quantity limit of 56 vials/56 days and 84 vials/56 days (for cycles of 28 days on followed by 28 days off therapy) is in place for inhaled tobramycin solution (TIS) and aztreonam lysine for inhalation (AZLI), respectively.

Previous Recommendations:

- There is moderate quality evidence that both inhaled tobramycin and inhaled aztreonam improve lung function and quality of life in moderate to severe disease for individuals with CF and *Pseudomonas (P.) aeruginosa* persistently present in cultures of the airways. However, there is evidence that inhaled tobramycin reduces exacerbations in patients with CF, while the trials of inhaled aztreonam are short term with limited follow up.
- There is insufficient comparative evidence for the efficacy and safety of TIS and AZLI.
- There remains insufficient evidence to recommend for or against the chronic use of other inhaled antibiotics (ceftazidime, colistin, gentamicin) to improve lung function and quality of life or reduce exacerbations in patients with CF.
- There is insufficient evidence to recommend oral anti-psuedomonal antibiotics for pulmonary exacerbations or long-term treatment of chronic infection.
- There is low quality evidence that Tobi Podhaler is noninferior to tobramycin inhalation nebulizer solution in improving lung function.
- There is low quality evidence that Tobi Podhaler results in a higher incidence of discontinuations due to adverse events (14% vs. 8%) and total discontinuations (26.9% vs. 18.2%) than tobramycin nebulizer, respectively.
- There is moderate quality evidence that treatment with hypertonic saline for patients six years of age and older improves short term lung function, decreased pulmonary exacerbations, and has a small effect on improvement in quality of life. There is insufficient evidence to determine the long term effects of hypertonic saline on mortality in patients with CF.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

After limiting the Medline search to RCTs and systematic reviews, a total of 7 studies resulted, including 3 systematic reviews.[11,12,1] The remaining 4 trials were excluded due to irrelevant intervention, incorrect population, and no outcome of interest. One of the systematic reviews evaluated ivacaftor for the treatment of patients with the G551D mutation[1]; however, this was previously reviewed as part of the May 2014 P&T CF Class Update.

New Systematic Reviews:

1. An updated Cochrane Collaboration review was completed to evaluate which antibiotic treatment eradicates *P. aeruginosa,* delays the onset of chronic infection, and results in clinical improvement from the treatment of early infection (at the time of first isolation).[11] It is well known that once chronic infection occurs, it is very difficult to eradicate it and it is associated with negative outcomes. Therefore, research has been done to determine if early infection might be easier to eradiate. Only RCTs were included in the comparisons. A total of seven RCTs were selected for inclusion, with a duration of 28 days to 27 months. Most of these were small trials with a short follow-up period. The most common primary outcome measure was eradication of *P. aeruginosa* from respiratory secretions, though definitions of eradication varied considerably between trials. The trials could not be combined for the purpose of a meta-analysis due to the different interventions and outcomes evaluated in the trials.

   Two small trials showed that TIS was better than no treatment in eliminating early infection from *P. aeruginosa (*OR 0.15; 95% CI 0.03-0.65) and that this effect may last for up to 12 months. Another trial (n=88) showed no difference between 28 days and 56 days of nebulized tobramycin, as measured by time to next isolation of *P. aeruginosa* (26.12 months vs. 25.82 months). Four direct comparisons were identified and found no difference between any antibiotic combinations (oral or inhaled).

   One of the RCTs compared culture-based inhaled tobramycin therapy to cycled-based therapy, as well as oral ciprofloxacin versus placebo for two weeks with each 28 day course of TIS. There was a non statistically significant difference in the number of children having one ore more isolates on oral ciprofloxacin compared to placebo (34% vs. 37%, respectively). There was also no significant difference in time to severe exacerbation between those on oral ciprofloxacin and placebo.

   The authors of this review concluded that the data did not establish significant improvements in clinical outcomes following the early treatment of *P. aeruginosa* but nebulized antibiotics were better than no treatment for eradication of early infection. However, due to the small numbers and short durations, there may be insufficient power to detect differences in long-term clinical outcomes. While there is evidence that treatment to eradicate infection is better than no treatment, there is not strong evidence to support using one regimen over another.

2. Another Cochrane Systematic review assessed prophylactic oral antibiotic therapy for infections caused by *S. aureus* in young children with CF.[12] Overall, continuous oral anti-staphylococcal antibiotic prophylaxis may not be more effective than on-demand ("as needed") treatment for improving lung function, reducing hospital admissions, or other outcomes in infants and children with CF. Only four trials were included in the systematic review, which included 402 infants and children aged 0 to 7 years with CF. The studies had some methodological flaws, particularly two older studies which were not blinded. Continuous prophylaxis was associated with a reduced isolation of *S. aureus* from sputum at 1 year in an analysis of 2 trials (OR 0.27; 95% CI 0.15 to 0.48) with no significant difference in lung function (FEV1), bacterial growth, hospital admission or need for additional antibiotics. The authors concluded that although prophylaxis led to fewer children with *S. aureus* isolates, the clinical significance of this is unknown and further research is warranted.

New Guidelines:

1. **European Cystic Fibrosis Society:**
   A best practice statement was released in 2014 for the treatment of CF. [13] The following best practice recommendations were provided regarding the treatment of CF:
   - Treatment for the eradication of *P. aeruginosa* should be started promptly after a positive culture result. Options include 28 days of TIS and up to 3 months of a combination of nebulized colistin and oral ciprofloxacin.
   - If eradication fails, long term inhaled antibiotic therapy should be started with TIS on alternate months, with AZLI as an alternative option.
   - There is insufficient evidence to support prophylactic antibiotic therapy for other bacteria.

   These recommendations are clearly best practice statements and are not systematically developed from a thorough evidence review and evaluation.

New FDA Approved Indications:
None identified (ivacaftor reviewed separately).

Randomized Controlled Trials:
No relevant comparative RCTs identified.

New Formulations/Delivery Device:
In December 2014, the FDA approved a new formulation of generic TIS with a PARI LC PLUS Nebulizer (Kitabis pak®).[13] This is the first nebulized drug and device combination to be approved for patients with CF and is dosed as one single-use ampule (300 mg) administered via nebulizer twice daily (28 day on/off cycle). The product is co-packaged with tobramycin and the PARI LC PLUS nebulizer device. This is the only nebulizer studied for the delivery of TIS. It is indicated for the management of CF in adults and children 6 years of age and older with *P. aeruginosa.*

Two unpublished, identically designed, double-blind, randomized, placebo-controlled 24-week studies compared 28 days of TIS using the PARI Nebulizer (n=258) as an outpatient treatment to placebo (n=262), followed by 28 days off of therapy for 3 cycles. Lung function was significantly improved in the TIS group compared to those on placebo as measured by change in FEV1% predicted from baseline (11% vs. 0%).[13] There was a decrease in the number of days hospitalized for those on tobramycin; however the data and statistics were not available for full analysis. These studies are not published and there was not enough available information to adequately assess for the risk of bias and quality appraisal.

The most common adverse effects in the TIS group were cough, pharyngitis, and increased sputum. More patients treated with TIS experienced voice alteration compared to placebo patients (13% vs. 7%).[13]

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Appendix 1: Current Status on Preferred Drug List

- Preferred: SODIUM CHLORIDE FOR INHALATION, TOBRAMYCIN 300 MG/5 ML (TOBI®), TOBRAMYCIN 300 MG/4 ML (BETHKIS®), DORNASE ALFA (PULMOZYME®)
- Non-Preferred: TOBRAMYCIN CAP (TOBI PODHALER®), AZTREONAM (CAYSTON®)