03/26/14

Roger Citron
Pharmacy DMAP Program Manger
Drug Use Research and Management

Dear Mr. Citron,

I was just recently alerted to the Oregon Medicaid hearing that will be held on the afternoon of March 27th, concerning the use of inhaled antibiotics. Unfortunately, I will be seeing patients in my clinic that afternoon and will not be available to testify at the hearing. However, I have significant concerns about the analysis of the use of inhaled antibiotics for children and adults with Cystic Fibrosis (CF). A detailed analysis of our use of these medications in our practice has been outlined in a separate letter by Dr. MacDonald and Cori Muirhead, PhramD from the OHSU CF Center. My letter is to voice additional concerns and give context to this issue.

We are the only CF Center in the State of Oregon and have expertise in treating this life threatening disease. We currently follow 240 children with CF and 115 adults with CF at OHSU. Approximately 50% of patients grow pseudomonas's and other gram negative bacteria and are candidates to be treated with Tobramycin inhalation solution (TIS) as well as Tobramycin Inhalation Powder. In addition inhaled Aztreonam is used in our center as well. The efficacy for all three of these medications is well established in clinical trials. The major outcome and the reason we use these medications is to improve lung function and reduce the frequency of pulmonary exacerbations and hospitalization. If we prevent one admission per year, that equals the cost of the inhaled medication, while promoting better clinical outcomes in our patients.

A major breakthrough for our patients has been the introduction of TIP and inhaled Aztreonam in order to reduce the time required to inhale the medication. The treatment burden is large for CF patients and improving adherence through more streamlined treatments is critical. These medications are approved at OHSU because they are cost neutral to the TIS. The use of inhaled antibiotics in CF patients has been associated with a much longer life expectancy over the past 15 years.

I urge you to consider TIS, TIP, and Aztreonam as equally effective and the use in an individual patient be determined by the clinical circumstances of each patient.

Sincerely,

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Wednesday, March 26, 2014

Dear Roger Citron,
Pharmacy DMAP Program Manager
Drug Use Research & Management

RE: Oregon Drug Use Review / Pharmacy & Therapeutics Committee – Inhaled Antibiotics for Cystic Fibrosis

We read with great interest the proposed recommendations for use of inhaled antibiotics in persons with Cystic Fibrosis (CF) covered by Oregon Health Authority plans. We would like to offer the following testimony based on our expertise as CF specialty care providers in the state of Oregon.

CF is a lifelong disease that is inherited genetically and results in altered salt and water movement that affect hollow organs including the pancreas, lung, and the gut. The impaired salt and water movement results in pancreatic insufficiency, retained pulmonary secretions, and bowel obstruction. However, 90% of all CF patients ultimately succumb to pulmonary disease and necessitates the importance of inhaled antibiotics for these patients. Pulmonary disease in CF is thought to occur because of chronic inflammation and destruction of the lung due to chronic bacterial colonization of the airways due to retained secretions. Thus, we agree as stated in the document CLASS UPDATE: INHALED ANTIBIOTICS FOR CYSTIC FIBROSIS "therapies that may decrease or eliminate colonization in addition to treating exacerbations are essential to improving outcomes."Agents that are typically employed are usually specialized formulations for inhalation and include tobramycin and aztreonam. Less utilized agents include colistimethate and vancomycin. Clinical trials of fluoroquinolones, dry powder vancomycin, and inhaled liposomal antifungal agents are also underway suggesting this category of agents will only get larger and will grow in use as CF patients continue to transition to adult CF centers and live longer than ever before.

We were puzzled at some statements in the document CLASS UPDATE: INHALED ANTIBIOTICS FOR CYSTIC FIBROSIS. We humbly point out that dornase alpha and hypertonic saline are used as inhaled mucolytic agents for essential daily airway clearance therapy. They are not considered antimicrobial and therefore should be excluded from this review. As the document points out, the CF Foundation expert panel has given inhaled antibiotic agents tobramycin *and* aztreonam a grade A or B recommendation dependent on severity of lung disease. As the only CF Foundation accredited center in Oregon, we adhere to these guidelines in our patients. Current thinking in field suggests these agents be used as chronic maintenance therapy to suppress growth of colonized Pseudomonas aeruginosa.

We were therefore confused when the review included discussion on the role of inhaled antibiotics combined with oral anti-pseudomonal agents as a treatment for CF pulmonary exacerbations. To our knowledge, there have been no expert opinions or guidelines supporting this treatment approach. In fact, the CF Foundation guidelines for exacerbation treatment clearly state the preferred approach is IV antimicrobial therapy in the hospital. This proposed role for inhaled antibiotics should not be considered in the Oregon Health Authority deliberation on the formulation of inhaled antibiotics in CF maintenance therapy. Additionally, CF pulmonary exacerbations are not consistent with a diagnosis of *pneumonia* and this term should be excluded from search strings to investigate inhaled antibiotics in CF. Current thought is that a CF pulmonary exacerbation represents a clonal expansion of the patient's colonized pathogens. This leads to increase airway mucus production throughout the lung, increased white blood cell infiltration to the airways, increased cytokines and inflammatory mediators which in a vicious cycle then leads to increased airway mucus, chest congestion, and dyspnea. Therapy is aimed at reducing bacterial colony counts by *systemic* antimicrobial therapy, expelling excess mucus, and nutritional support thru the illness. Incorporating chronic suppressive therapies such as inhaled antibiotics are then used to increase the interval between exacerbations which average 2.2 per year per patient in Oregon. In fact, current trials are examining the role inhaled antibiotics given every month rather than in 28 day cycles or alternating inhaled agents each month to enhance the bacterial suppression.

In our experience, adherence to twice daily dosing of inhaled antibiotics (any agent) is difficult for CF patients. Adherence to daily therapy has been estimated at 50% in the CF population. When we teach new CF families about care and treatment burden, we often advise that between 2 and 4 hours per day are needed for respiratory treatments, specialized meal preparation, pancreatic enzyme therapy, vitamins, and nutritional supplementation. Thus, *any* therapy that reduces the time burden associated with CF is greatly welcomed by CF patients and their families. Decreased therapeutic burden is postulated to be associated with improved adherence. We were surprised at the recommendation that tobramycin inhalation solution (TIS) be preferred over tobramycin dry powder for inhalation (TIP). In our experience, this represents two daily 20 minute nebulizer sessions versus a 2-5 minute, twice daily treatment burden. In addition, TIS has additional cleaning procedures and equipment requirements whereas the TIP preparation is entirely disposable, removing burden of nebulizer cleaning and risk of contamination. We would suggest an easier to use preparation will ultimately increase therapy adherence.

In our practice, we have been actively converting patients to TIP. This has been met with great excitement by patients and their families. Patient reports converting to TIP have been encouraging leading us to believe improvement in adherence will be realized. We suggest that any patient eligible for TIS should be allowed TIP and that TIP be the preferred tobramycin inhalation formulation for Oregon Health Authority. We are happy to provide any additional information or documentation needed by the committee.

Sincerely,

Kelvin D. MacDonald, MD RRT
Associate CF Center Director

Corinne Muirhead, PharmD
CF Center Pharmacist