Antibiotics, Inhaled
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
amikacin liposome (Arikayce®)[1]	Insmed	For the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy *Limited Population:* only indicated in adults who have limited or no alternative treatment options *Limitation of Use*: has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy; use is not recommended for patients with non-refractory MAC lung disease
aztreonam (Cayston®)[2]	Gilead	For the improvement of respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa* and a forced expiratory volume in 1 second (FEV_1) between 25% and 75% predicted Safety and effectiveness have not been established in pediatric patients < 7 years of age, patients with FEV_1 <25% or >75% predicted, or patients colonized with *Burkholderia cepacia*
tobramycin (Bethkis®)[3]	Chiesi USA, generic	For the management of cystic fibrosis in adults and pediatric patients ≥ 6 years of age with *P. aeruginosa* and a FEV_1 between 40% and 80% predicted, and patients with *B. cepacia*
tobramycin (Kitabis™ Pak)[4]	Pari Respiratory, generic*	For the management of cystic fibrosis in adults and pediatric patients ≥ 6 years of age with *P. aeruginosa* Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with FEV_1 < 25% or > 80% predicted, or patients colonized with *B. cepacia*
tobramycin (TOBI®)[5]	Novartis/Mylan, generic	For the management of cystic fibrosis patients with *P. aeruginosa* and a FEV_1 between 25% and 75% predicted Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with FEV_1 < 25% or > 75% predicted, or patients colonized with *B. cepacia*
tobramycin (TOBI Podhaler®)[6]	Novartis/Mylan, Mylan Specialty	For the management of cystic fibrosis patients with *P. aeruginosa* and a FEV_1 between 25% and 80% predicted Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with FEV_1 < 25% or > 80% predicted, or patients colonized with *B. cepacia*

* Authorized generic

OVERVIEW

Cystic Fibrosis

Cystic Fibrosis (CF) is the most common lethal genetic disease among Caucasians, affecting over 30,000 individuals residing in the United States (US).[7,8] It has been estimated that 4% to 5% of all Caucasians in North America are carriers of the CF gene. The incidence of CF by ethnic groups has also been reported as follows: Caucasians 1 in 2,500 to 3,500; Hispanic 1 in 9,200; Native American 1 in 10,900; African Americans 1 in 17,000; and Asian Americans 1 in 31,000.[9,10] Approximately 1,000 individuals are diagnosed with CF annually, with more than 75% diagnosed by 2 years of age.[11,12]

CF is an autosomal recessive disorder caused by mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene located on chromosome number 7.[13] Loss of functionality of the CFTR protein causes impairment of chloride transport in epithelial cells, which results in different physiologic consequences in different organs.[14] The typical manifestation of CF involves progressive obstructive lung disease that has been associated with impaired mucous clearance, difficulty clearing pathogens, and risk of chronic pulmonary infection and inflammation.[15] As a result, respiratory failure is the common cause of death in patients with CF. Due to advances in medication therapy, notably the availability of agents that target the CFTR protein, the median survival of patients with CF has increased dramatically in the past decade. The median expected survival age of patients born between 2015 and 2019 is 46.2 years. For patients born during 2019, the median expected survival age is 48.4 years.[16] CF also manifests as pancreatic insufficiency that has been associated with fat and protein malabsorption and, consequently, malnutrition.[17]

Universal newborn screening (NBS) for CF was implemented in the US in 2010.[18] The majority of patients with a positive NBS have a diagnosis of CF confirmed positive sweat chloride test (≥ 60 mmol/L). However, diagnosis of CF is not always clear, particularly in those born before 2010, since the age of onset and symptom severity can vary based on the level of CFTR dysfunction. In 2017, to address these challenges, the Cystic Fibrosis Foundation (CFF) published international consensus guidelines regarding the diagnosis of CF and other conditions associated with mutations in the CFTR gene (e.g., CFTR-related metabolic syndrome [CRMS] or CF screen positive, inconclusive diagnosis [CFSPID], and CFTR-related disorders). A diagnosis of CF is made when both a clinical presentation of the disease and evidence of CFTR dysfunction are present. In their algorithm outlining the hierarchy of diagnostic testing, CFF recommend testing in those with clinical presentation of CF (NSB+, signs/symptoms of CF, or family history) in the following order: sweat chloride test, *CFTR* genetic analysis (for sweat chloride 30 to 59 mmol/L), then CFTR physiologic testing (if *CFTR* genotype is undefined). If a CF diagnosis is still inconclusive, then CRMS/CFSPID or CFTR-related disorder should be considered.

The main objectives of CF treatment are to treat and prevent infection, promote mucus clearance, and improve nutrition.[19] Airway clearance can be achieved through different airway clearance techniques (e.g., manually assisted cough, chest physiotherapy), antibiotics, ibuprofen, inhaled hypertonic saline, inhaled beta$_2$ adrenergic receptor agonists, and mucolytic enzymes.[20,21,22] Since pulmonary infection is the main source of morbidity and mortality, antibiotics play an important role in CF therapy to control the progression of the disease. In their 2014 guideline for the prevention and eradication of *P. aeruginosa* infection, CFF recommends inhaled antibiotic therapy for the treatment of initial or new

growth of *P. aeruginosa*, with preference for tobramycin for 28 days.[23] They recommend against prophylactic antipseudomonal antibiotics to prevent infection.

Chronic use of inhaled tobramycin and inhaled aztreonam are recommended in the 2013 CF Pulmonary Guidelines to reduce exacerbation for patients who are ≥ 6 years of age with persistent *P. aeruginosa* cultures in the airways (strength of recommendation A for moderate to severe disease; strength of recommendation B for mild disease).[24] However, chronic use of oral azithromycin for patients ≥ 6 years of age with persistent *P. aeruginosa* culture is also recommended, though the strength of recommendation is not as strong. Additionally, in patients with pulmonary exacerbations marked by chronic infection of *P. aeruginosa*, treatment with the combination of an aminoglycoside and beta-lactam antibiotic is recommended.[25] Typical duration of treatment is 2 to 3 weeks of intravenous (IV) antibiotics, with clinical improvement usually seen after the first week of treatment.

In 2016, a clinical guideline for CF in preschool-aged children (ages 2 to 5 years) was developed by the CFF.[26] For this patient population, CFF recommends oral, inhaled, and/or IV antibiotics for treatment of pulmonary exacerbations and every other month administration of inhaled antibiotics in patients with persistent *P. aeruginosa* infection.

It has been shown that an intermittent regimen of inhaled antibiotic therapy (28 days on drug, followed by 28 days off drug) provides sustained clinical efficacy during the off drug period and may reduce the potential for antimicrobial resistance caused by continuous exposure to drug.[27]

Concomitant use of inhaled and IV antibiotics is frequently employed in the treatment of an exacerbation.[28] Although use of 2 delivery routes could enhance antibacterial effect due to improved drug exposure, increased risk of toxicity is possible. Few published data examine the safety or efficacy of this dual therapy. Furthermore, serum aminoglycoside levels to guide IV dosing, could be difficult to interpret when inhaled and IV aminoglycoside treatments are both used. The decision to continue an inhaled antibiotic in conjunction with the same IV antibiotic should be determined on a case-by-case basis.

Mycobacterium avium complex (MAC) lung disease

Mycobacterium avium complex (MAC) is the most common nontuberculous mycobacterial (NTM) lung infection. Treatment is continued until sputum cultures are consecutively negative for at least 12 months; typical duration exceeds 18 months. Eradication is difficult, and recurrence and relapse are common.[29]

The timing of treatment depends on the type of disease and the risk of progression. While fibrocavitary disease has a rapid progression and warrants prompt treatment, a course of observation may be reasonable for patients with nodular bronchiectasis disease, if the patient has minimal symptoms or radiographic findings or the patient has comorbid conditions that are considered to be more serious than the MAC lung infection. During observation, sputum cultures are generally monitored every 2 to 3 months, and repeat imaging occurs after approximately 6 months. Signs of disease progression (e.g., increased bacterial load, development of cavitation or worsening nodularity) indicate the need for antibiotic therapy.[30]

In 2020 the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) published an official clinical practice guideline on the treatment of nontuberculous mycobacterial (NTM) pulmonary disease.[31] Diagnosis of NTM lung disease aligns with the previous

2007 ATS/IDSA statement[32] and should be based on a minimum of chest radiography or chest high-resolution computed tomography (HRCT) scan, ≥ 3 sputum specimens for acid-fast bacilli (AFB) analysis, and exclusion of other conditions (e.g., tuberculosis, lung malignancy). Bronchoscopy or lung biopsy is not usually required. Due to the long therapy duration and potential for intolerance, treatment should only be considered in patients who meet the clinical, radiographic, and microbiologic criteria for the diagnosis of NTM. In patients who meet the diagnostic criteria for NTM pulmonary disease, initiation of treatment is suggested over watchful waiting, especially in the context of positive acid-fast bacilli sputum smears and/or cavitary lung disease (conditional recommendation, very low certainty in estimates of effect), and in patients with MAC pulmonary disease, susceptibility-based treatment is suggested for macrolides and amikacin over empiric therapy (conditional recommendation, very low certainty in estimates of effect). In patients with macrolide-susceptible MAC pulmonary disease, a 3-drug regimen that includes a macrolide is recommended over a 3-drug regimen without a macrolide (strong recommendation, very low certainty in estimates of effect), and azithromycin-based treatment regimens are suggested over clarithromycin-based regimens (conditional recommendation, very low certainty in estimates of effect). Furthermore, in these patients a treatment regimen with at least 3 drugs (including a macrolide and ethambutol) is suggested over a regimen with 2 drugs (a macrolide and ethambutol alone) (conditional recommendation, very low certainty in estimates of effect). If patients with MAC pulmonary disease have failed ≥ 6 months of therapy, the addition of amikacin liposome inhalation suspension (ALIS) to the current treatment regimen is recommended over a standard oral regimen only (strong recommendation, moderate certainty in estimates of effect). However, in those with newly diagnosed MAC pulmonary disease, inhaled amikacin (parenteral formulation) and ALIS are both suggested against as part of the initial treatment regimen (conditional recommendation, very low certainty in estimates of effect). An intravenous (IV) aminoglycoside (amikacin, streptomycin) should only be included in the initial treatment regimen if the patient has cavitary MAC, advanced/severe bronchiectatic, or macrolide-resistant MAC pulmonary disease (conditional recommendation, moderate certainty in estimates of effect). For patients with noncavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease, a 3-times per week macrolide-based regimen is suggested rather than a daily macrolide-based regimen (conditional recommendation, very low certainty in estimates of effect), but in those with cavitary or severe/advanced nondular bronchiectatic macrolide-susceptible MAC pulmonary disease, a daily macrolide-based regimen is suggested over a 3-times per week macrolide-based regimen (conditional recommendation, very low certainty in estimates of effect). Lastly, patients with macrolide-susceptible MAC pulmonary disease are suggested to receive therapy for ≥ 12 months after culture conversion (conditional recommendation, very low certainty in estimates of effect). Additional treatment recommendations are provided for *Mycobacterium kansasii*, *Mycobacterium xenopi*, *Mycobacterium abscessus*, and surgical resection.

The 2016 CFF and European Cystic Fibrosis Society's nontuberculous mycobacteria clinical care guidelines recommend susceptibility testing for MAC infections on isolates recovered prior to initiation of treatment, and sputum samples are recommended for culture every 4 to 8 weeks for the duration of treatment.[33] Intravenous amikacin is recommended in select patients. A daily oral antibiotic regimen containing a macrolide (preferably azithromycin), rifampin, and ethambutol is recommended for clarithromycin-sensitive *M. avium* complex pulmonary disease. Monotherapy with a macrolide or other antimicrobial should never be used for MAC pulmonary disease. Treatment is recommended for 12 months beyond culture conversion (e.g., 3 consecutive negative cultures following the date of the first of the 3 cultures) if no positive cultures are obtained during these 12 months. The group provides

additional recommendations for the treatment of *M. abscessus* complex; however, no agent in this therapeutic class is approved currently for this use.

Other FDA-approved inhaled antibiotics (e.g., aztreonam, tobramycin) are indicated for the treatment of patients with cystic fibrosis (CF) with *Pseudomonas aeruginosa*, an indication not held by Arikayce. Aerosolized injectable formulations of amikacin have been used off-label for NTM and *P. aeruginosa* in CF patients.[34] Amikacin liposome (Arikayce) inhalation represents the first FDA-approved inhaled antibiotic to treat MAC lung infection. Studies have not been performed comparing it to aerosolized parenteral amikacin formulations.

PHARMACOLOGY[35,36,37,38,39,40]

Inhaled aztreonam (Cayston) is a beta-lactamase-resistant monobactam antibiotic that only has activity against aerobic gram-negative bacteria, including *P. aeruginosa*.[41] Aztreonam exerts its effect by binding penicillin-binding protein of susceptible bacteria, forming elongated filamentous cells that eventually lyse and die.[42] Aztreonam is formulated for administration by inhalation through a nebulizer so that the drug is concentrated in the airway.

Inhaled tobramycin (generic, Bethkis, Kitabis Pak, TOBI, TOBI Podhaler) and inhaled amikacin (Arikayce) are aminoglycoside antibiotics that binds to a protein of the 30S subunit of the microbial ribosome, interfering with the function of messenger RNA.[43,44] As a result, abnormal, nonfunctional proteins are produced, causing a compromise of cell membrane permeability that eventually leads to cell death. Tobramycin has a bactericidal effect with activity against a wide range of gram-negative bacteria including *P. aeruginosa*. Tobramycin for inhalation is formulated for administration by inhalation through a nebulizer or a dry-powder inhaler so the drug is concentrated in the airway. Amikacin also exhibits bactericidal effects with activity against *P. aeruginosa*, as well as most gram-negative bacilli from the Enterobacteriaceae family, including Mycobacterium (e.g., *M. avium-intracellulare* [MAC]). Arikayce is an amikacin formulation enclosed in nanocapsules of lipids that allow for once-daily dosing.

PHARMACOKINETICS[45,46,47,48,49,50]

Drug	Sputum Concentration After Inhalation	Sputum Concentration During Chronic Use, After 10 Minutes of Inhalation	Serum Concentration After 1 Hour	Elimination Half-life (hour)
amikacin liposome (Arikayce)	nr	nr	nr	5.9 – 19.5
aztreonam (Cayston)	726 mcg/g	715 mcg/g	0.59 mcg/mL	2.1
tobramycin (Bethkis)	814 mcg/g	717 mcg/g	0.06 – 1.89 mcg/mL	4.4
tobramycin (Kitabis Pak)	1,237 mcg/g	1,154 mcg/g	0.95 mcg/mL	2
tobramycin (TOBI)	1,237 mcg/g	1,154 mcg/g	0.95 mcg/mL	2
tobramycin (TOBI Podhaler)	1,048 mcg/g	nr	1.02 mcg/mL	3

nr = not reported

Inhalation therapy with either tobramycin or aztreonam does not lead to drug accumulation after chronic use; therefore, no adjustment is necessary for patients requiring long-term use of these antibiotics. Both tobramycin and aztreonam are renally eliminated; however, dose adjustment of aztreonam for patients with renal impairment is not required because the drug has low systemic absorption. While tobramycin also has low systemic exposure, no specific guideline for dose adjustment is available for patients with renal impairment. Monitoring serum concentration for tobramycin in patients with normal renal function is not required; however, it is at the discretion of the treating physician to monitor serum level in patients with renal dysfunction. Neither of these inhaled antibiotics requires dose adjustment based on weight and age of the patient. TOBI Podhaler pharmacokinetic values appear generally equivalent to those for TOBI.

Following once daily inhalation of amikacin liposome (590 mg) in patients with MAC, sputum concentrations at 1 to 4 hours post-inhalation were 1,720, 884, and 1,300 mcg/g at 1, 3, and 6 months, respectively. After 3 months of once daily inhalation of amikacin liposome (590 mg) in MAC patients, the mean serum concentration was 23.5 mcg/-hr/mL with a mean serum C_{max} of 2.8 mcg/mL.

CONTRAINDICATIONS/WARNINGS[51,52,53,54,55,56]

Aztreonam (Cayston) is contraindicated in patients with a known allergy to aztreonam. Cross-reactivity may occur; therefore, physicians must use caution when prescribing aztreonam in patients with a known history of beta-lactam allergy. Bronchospasm with a reduction of ≥ 15% in FEV_1 may occur; therefore, healthcare providers should consider measuring a patient's baseline FEV_1 prior to initiating aztreonam for inhalation therapy.

Tobramycin (generic, Bethkis, Kitabis Pak, TOBI, TOBI Podhaler) is contraindicated in patients with a known hypersensitivity to any aminoglycoside. In patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction, physicians must exercise caution when prescribing tobramycin for inhalation. Physicians should also consider performing baseline auditory and renal function screening to determine if a patient is at an increased susceptibility for the adverse effects. Patients who are pregnant or plan to become pregnant should be aware and informed of the possible harm to the fetus. Patients concurrently receiving tobramycin inhaled and a parenteral aminoglycoside should be monitored as appropriate for toxicities associated with aminoglycosides, and serum tobramycin levels should be monitored.

Amikacin liposome (Arikayce) is contraindicated in patients with a known aminoglycoside hypersensitivity. Hypersensitivity pneumonitis has occurred with use of amikacin liposome as has serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis. Signs and symptoms include acute onset of skin and mucosal tissue hypersensitivity reactions, respiratory difficulty, gastrointestinal symptoms, as well as tachycardia, low blood pressure, syncope, incontinence, and dizziness. Additional warnings include hemoptysis, bronchospasm, and exacerbations of underlying pulmonary disease. Aminoglycoside use, including amikacin liposome, can result in ototoxicity, nephrotoxicity, neuromuscular blockade, and bilateral congenital deafness in pediatric patients exposed *in utero*.

DRUG INTERACTIONS[57,58,59,60,61,62]

No formal drug interactions have been noted with aztreonam for inhalation (Cayston). Concurrent use of inhaled tobramycin (generic, Bethkis, Kitabis Pak, TOBI, TOBI Podhaler) with other neurotoxic or

ototoxic drugs should be avoided. Diuretics, such as furosemide, ethacrynic acid, mannitol, and urea, can alter tobramycin serum and tissue concentrations; therefore, concurrent use with tobramycin should also be avoided to reduce aminoglycoside toxicity. Patients receiving concurrent inhaled tobramycin and parenteral aminoglycoside therapy should have serum tobramycin levels closely monitored due to the potential for toxicity.

ADVERSE EFFECTS[63,64,65,66,67,68]

Drug	Bronchospasm	Nasal Congestion	Tinnitus	Voice Alteration	Cough
amikacin liposome* (Arikayce)	29 (11)	nr	17** (10)	nr	40 (17)
aztreonam (Cayston)	3 (nr)	16 (12)	nr	nr	54 (51)
tobramycin (Bethkis)	0.5 (0)	nr	0 (0)	6 (2)	nr
tobramycin (Kitabis Pak)	reported	nr	3 (0)	12.8 (6.5)	46.1 (47.3)
tobramycin (TOBI)	reported	nr	3.1 (0)	12.8 (6.5)	46.1 (47.3)
tobramycin (TOBI Podhaler)	1.6 (0.5)	8.1 (7.2)	1.9 (2.4)	13.6 (3.8)	48.4 (31.1)

Adverse effects are reported as a percentage. Adverse effects data are reported from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group (for tobramycin inhalation in Podhaler data; open-label comparison) are indicated in parentheses. nr = not reported.

*The incidence of adverse effects for amikacin liposome are reported as a percentage and represent amikacin liposome plus background regimen for MAC. The incidences indicated in parentheses represent the background regimen alone.

**Includes all manifestations of ototoxicity, including dearness, deafness neurosensory, deafness unilateral, dizziness, hyperacusis, presyncope, tinnitus, and vertigo

Cough was reported at a lower rate in the inhaled aztreonam group compared to the placebo group (p=0.047). Three percent of patients using inhaled aztreonam experienced bronchospasm, which can be prevented by the use of a bronchodilator before the administration of aztreonam in at-risk patients. A safety study comparing TOBI Podhaler with TOBI inhalation solution reported bronchospasms in 1.6% of patients who used TOBI Podhaler and 0.5% in those who used the solution; TOBI Podhaler and TOBI labeling advise that bronchospasm should be treated as medically appropriate.

TOBI Podhaler has displayed more throat irritation than Bethkis and TOBI (4.5% for TOBI Podhaler versus 3% for Bethkis and 1.9% for TOBI/Kitabis Pak). TOBI Podhaler and Bethkis have displayed similar auditory adverse effects (e.g., hearing loss) but more than with TOBI (1% for TOBI Podhaler and 1.1% for Bethkis versus 0.5% for TOBI/Kitabis Pak).[69]

Tinnitus and voice alteration were reported in patients using inhaled tobramycin. Tinnitus was transient and resolved without discontinuation of the drug. Voice alteration was mild in severity and did not cause patient withdrawal from the study. Although tinnitus has not been reported during clinical studies with Bethkis, caution is warranted because it has been observed with other inhaled tobramycin solutions including Kitabis Pak, TOBI, and TOBI Podhaler.

Arthralgia and joint swelling have also been reported with inhaled aztreonam.

A single-arm, open-label, phase 4 study evaluating the safety of tobramycin inhalation powder (TOBI Podhaler) in adult and pediatric (≥ 6 years) patients (n=157) with CF and *P. aeruginosa* infection over 6 treatment cycles reported no meaningful changes in airway reactivity or FEV_1 percent predicted.[70] The most frequently reported adverse effect was cough, which was of short duration (< 4 minutes) and incidence reduced over time. In another study over a period of at least 1 year (up to 7 treatment cycles), incidence of adverse events associated with tobramycin inhalation powder was low and remained stable.[71] Improvement in lung function and decrease in density of *P. aeruginosa* were maintained over the study period.

In an open label, randomized, phase 3 trial in patients with refractory MAC lung disease where patients were randomized to either amikacin liposome plus a background regimen (e.g., macrolide, rifamycin, ethambutol) or background regimen alone for 8 months, the most common adverse events respectively were dysphonia (48% compared to 2%, respectively), cough (40% compared to 17%, respectively), bronchospasm (29% compared to 11%, respectively), hemoptysis (18% compared to 13%, respectively), musculoskeletal pain (18% compared to 9%), upper airway irritation (18% compared to 2%, respectively), and ototoxicity (17% compared to 10%, respectively).

SPECIAL POPULATIONS[72,73,74,75,76,77]

Pediatrics

Safety and efficacy of inhaled aztreonam (Cayston) have not been established in pediatric patients < 7 years of age. Safety and efficacy of inhaled tobramycin (generic, Bethkis, Kitabis Pak, TOBI, TOBI Podhaler) have not been established in pediatric patients < 6 years of age. No dose adjustment is required in pediatric patients for these drugs. Pyrexia is more commonly reported in pediatric patients than in adult patients during aztreonam treatment. The safety and effectiveness of inhaled amikacin liposome (Arikayce) have not been established in patients < 18 years of age.

Pregnancy

Previously Pregnancy Category B, labeling for aztreonam was updated to comply with the Pregnancy and Lactation Labeling Rule [PLLR] requirements. Available data on the use of aztreonam during pregnancy is inadequate to determine any drug-associated risks; however, systemic levels from inhaled aztreonam are likely minimal. The product labels for tobramycin (Bethkis, Kitabis Pak, TOBI, TOBI Podhaler) have been updated to comply with the PLLR; published data has shown use of another aminoglycoside during pregnancy has resulted in congenital deafness. Although inhaled tobramycin has not been studied in pregnant women and the drug-associated risks cannot be determined, inhaled administration results in minimal systemic levels. There are no data on the use of amikacin liposome in pregnant women to evaluate for any drug-associated risks. However, aminoglycosides can cause fetal harm (e.g., irreversible congenital deafness) when administered to pregnant women; therefore, patients who are pregnant or plan to become pregnant should be aware of the potential hazard to the fetus.

Renal Impairment

Inhaled aztreonam requires no dose adjustment in patients with renal impairment. Tobramycin inhalation should be prescribed with caution in patients with renal impairment; if a patient experiences

nephrotoxicity while on inhaled tobramycin therapy, it should be discontinued until tobramycin serum levels fall below 2 µg/mL. Amikacin liposome has not been studied in patients with renal impairment.

DOSAGES[78,79,80,81,82,83]

Drug	Dose	Administration	Duration	Average Length of Treatment (minutes)	Availability
amikacin liposome (Arikayce)	Adults: 590 mg once daily	Administer 1 vial using the Lamira™ Nebulizer System	Variable; recommended for 12 months following negative sputum (generally 12 to 18 months)	≈14	590 mg/8.4 mL (1 vial) inhalation suspension
aztreonam (Cayston)*	For adults and pediatric patients > 7 years old: 75 mg 3 times a day	Reconstitute 1 vial of powder with 1 ampule of saline immediately before use and administer dose only with Altera® Nebulizer System	28 days on treatment, followed by 28 days off	≈2 to 3	75 mg powder for inhalation solution (1 vial)
tobramycin (Bethkis)†	For adults and pediatric patients > 6 years old: 300 mg twice a day	Administer 1 ampule by using a hand-held PARI LC® PLUS Reusable Nebulizer with a PARI Vios® Air compressor	28 days on treatment, followed by 28 days off	≈15	300 mg/4 mL (1 ampule) for nebulization
tobramycin (Kitabis Pak)†	For adults and pediatric patients > 6 years old: 300 mg twice a day	Administer drug using PARI LC PLUS™ Reusable Nebulizer with a DeVilbiss® Pulmo-Aid® compressor as close to 12 hours apart as possible (not < 6 hours between doses)	28 days on treatment, followed by 28 days off	≈15	300 mg/5 mL (1 ampule) for nebulization
tobramycin (TOBI)†	For adults and pediatric patients > 6 years old: 300 mg twice a day	Administer drug using PARI LC PLUS Reusable Nebulizer with a DeVilbiss Pulmo-Aid compressor and as close to 12 hours apart as possible (not < 6 hours between doses)	28 days on treatment, followed by 28 days off	≈15	300 mg/5 mL (1 ampule) for nebulization
tobramycin (TOBI Podhaler)†	For adults and pediatric patients > 6 years old: 112 mg twice daily	Administered only with Podhaler device; capsules are inserted 1 at a time in the device and inhaled sequentially	28 days on treatment, followed by 28 days off	≈15	28 mg dry powder capsules for inhalation

* Aztreonam: No safety and efficacy information for patients < 7 years of age, patients with FEV_1 < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia*.

† Tobramycin: No safety and efficacy data for patients < 6 years of age, patients with FEV_1 < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia*.

Aztreonam and tobramycin should not be mixed with other medications in the nebulizer cup. Patients prescribed inhaled aztreonam (Cayston) who are taking several inhaled medications should be advised to use the medications in the following order of administration: bronchodilator, mucolytics, and, lastly, aztreonam.

Altera is a lightweight nebulizer system that operates on batteries or an alternating current (AC) power supply. Four new standard "AA" batteries provide about 2 hours of treatment. The PARI Vios and DeVilbiss Pulmo-Aid compressors are operated using an AC power supply.

The Podhaler is a plastic handheld inhaler device that pierces the tobramycin capsules to allow inhalation of the tobramycin powder. It does not require batteries or electricity. TOBI Podhaler is packaged as 4 weekly packs, each containing 56 capsules (7 blister cards of 8 capsules), 1 Podhaler device, and 1 reserve Podhaler device.

Aztreonam powder for reconstitution and tobramycin solutions (generic, Bethkis, Kitabis Pack, and TOBI) should be refrigerated, but may be stored at room temperature for up to 28 days. TOBI Podhaler blister cards should be kept at room temperature.

Pre-treatment with short-acting selective beta-2 agonists should be considered for patients taking amikacin liposome (Arikayce) if they have a history of hyperreactive airway disease, chronic obstructive pulmonary disease, asthma, or bronchospasm. Amikacin liposome is only to be administered with the Lamira Nebulizer System. Before being added to the nebulizer, amikacin liposome vials should be at room temperature and shaken for 10 to 15 seconds until the contents are well mixed. Patients prescribed amikacin liposome will initially receive 2 packages; a 1-time Lamira Nebulizer System, which contains the controller, connection cord, batteries, spare handset, and carrying case, and a 28-day drug kit, which contains 28 vials of amikacin liposome, 4 Lamira aerosol heads and 1 Lamira handset. Four new, standard "AA" batteries provide about 2 hours of treatment.

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

amikacin liposome (Arikayce) versus placebo

An open-label, multi-center trial evaluated the safety and efficacy of amikacin liposomal inhalation in patients with refractory MAC lung disease, confirmed by ≥ 2 positive cultures.[84] Refractory disease was defined as failure to achieve negative sputum cultures after ≥ 6 consecutive months of a background regimen that was either ongoing or stopped ≤ 12 months before the screening visit. Patients had nodular bronchiectasis and/or fibrocavitary disease confirmed by computed tomography (CT) scan and were willing to adhere to a multi-drug treatment regimen for the duration of the study. Patients were randomized to either amikacin plus a background regimen (n=224) or background regimen alone (n=112). Background regimens, based on the medical guidelines, included a macrolide, a rifamycin, and

ethambutol, and, at baseline, 55.6% of patients were on a triple regimen with all 3 medications. The primary endpoint was the proportion patients achieving cultural conversion, defined as 3 consecutive monthly negative sputum cultures by month 6. Patients who achieved culture conversion by month 6 were continued on study drug for a total of 12 months after the first negative sputum culture. The date of conversion was defined as the date of the first of the 3 negative monthly cultures, which needed to occur by month 4. At month 6, 29% of amikacin-treated patients achieved culture conversion compared to 8.9% on background therapy alone (p<0.0001). Sustained sputum culture conversion for up to 12 months of treatment after the first culture that defined culture conversion was reported in 18.3% of patients in the amikacin group and 2.7% in the background only group (p<0.0001). Furthermore, at 3 months after the completion of treatment, 16.1% of amikacin patients continued to have a durable culture conversion, compared to 0% of patients in the background only group (p<0.0001). In contrast, clinical benefit was not demonstrated in change from baseline to month 6 in 6-minute walk test distance and the Saint George's Respiratory Questionnaire.

aztreonam (Cayston) versus placebo

A randomized, double-blind, placebo-controlled international trial was conducted to evaluate the safety and efficacy of inhaled aztreonam 75 mg 3 times daily for 28 days.[85] A total of 164 CF patients with *P. aeruginosa* were enrolled. Exclusion criteria included recent (within the previous 28 days) administration of antipseudomonal antibiotics, azithromycin, or aerosolized hypertonic saline solution; current oral corticosteroid; positive culture of *Burkholderia cepacia* within the previous 2 years; daily oxygen supplementation; monobactam antibiotic hypersensitivity; intolerance to short-acting beta$_2$-agonists; lung transplantation; alanine transaminase (ALT) and aspartate aminotransferase (AST) levels > 5 times the normal values; serum creatinine > 2 times the normal value; pregnancy; lactation; recent change of antimicrobial, bronchodilator, anti-inflammatory, or corticosteroid medication; or new findings in the chest radiograph within the previous 90 days. The endpoints of the study were respiratory symptoms (determined by CF-Questionnaire-Revised Scale [CFQ-R]), pulmonary function, *P. aeruginosa* density in sputum, and non-respiratory CFQ-R scales. At the end of the 28-day treatment, patients in the treatment arm had a higher mean CFQ-R respiratory score (9.7 points difference; p<0.001), improved pulmonary function (10.3% difference in FEV_1 predicted, p<0.001), and less sputum *P. aeruginosa* density (28-day difference, -1.453 $\log_{10}$ colony forming units (CFU)/g; p<0.001). Inhaled aztreonam was well tolerated with similar adverse effects as the placebo group.

tobramycin (Bethkis) versus placebo

Two randomized, double-blind, placebo-controlled, parallel group studies (Study 1 and Study 2) were performed in 306 patients with CF infected with *P. aeruginosa*.[86] The osmolality of the to-be-marketed drug differed from the drug used in these studies. To rely on the efficacy and safety established in these studies, an additional study was performed as a bridge to the to-be-marketed drug. The bridging study examined 324 patients with CF and the efficacy and tolerability of aerosolized tobramycin inhaled solution with osmolality comparable to Bethkis over 4 weeks. The compressors used in the placebo-controlled and bridge studies differed from the PARI Vios used with Bethkis; however, *in vitro* cascade impaction studies indicated that the various compressors used in the studies delivered equivalent doses and respirable fractions compared to the PARI Vios used with the PARI LC Plus Reusable nebulizer. The study concluded that the tobramycin inhalation solution used in the bridge study had similar efficacy as seen in the placebo-controlled studies.

All patients in both studies had a baseline FEV_1 percent predicted ≥ 40% and ≤ 80% and infected with *P. aeruginosa*. Study 1 enrolled 59 patients, ≤ 30 years old, into a double-blind, single cycle (28 days on treatment followed by 28 days off treatment) study where they were randomized to receive Bethkis (n=29) or placebo (n=30).[87] The study found that Bethkis significantly improved lung function compared to placebo which was indicated by the change in FEV_1 percent predicted from baseline to the end of Cycle 1. The study resulted in absolute increases in FEV_1 percent predicted of 16% and 5% with Bethkis and placebo, respectively (p=0.003).

Study 2 randomized (2:1) 247 patients, who were ≤ 46 years old, into a double-blind, 3-cycle, placebo controlled trial of Bethkis (n=161) or placebo (n=86).[88] Each cycle consisted of 28 on treatment and 28 days off treatment. The study found that Bethkis significantly improved lung function compared to placebo indicated by the absolute change in FEV_1 percent predicted from baseline to the end of Cycle 3 "on" phase. The study resulted in absolute increases in FEV_1 percent predicted of 7% and 1% for Bethkis and placebo, respectively (p<0.001). Study 2 also observed 9.9% of patients treated with Bethkis and 24.7% of patients treated with placebo having an unplanned hospitalization due to the disease. Additionally, the study observed 6.2% and 16.5% of patients treated with Bethkis and placebo, respectively, received parenteral tobramycin.

Studies are lacking for the use tobramycin (Bethkis) in patients with CF who are colonized with *Burkholderia cepacia.*

tobramycin (TOBI) versus placebo

Two identical multicenter, double-blind, randomized, placebo-controlled trials were conducted to evaluate the safety and efficacy of inhaled tobramycin 300 mg twice daily for a total of 24 weeks in 3 on-off cycles.[89] A total of 520 patients with CF and *P. aeruginosa* infection were recruited from 69 CF centers in the United States. Exclusion criteria included receipt of antibiotics within the previous 2 weeks, hypersensitivity to aminoglycosides, impaired renal function (serum creatinine > 2 mg/dL), or recovery of *Burkholderia cepacia* infection within the previous 2 years. The endpoints of the study were pulmonary function, density of *P. aeruginosa* in sputum, and hospitalization. At the end of the study, patients in the treatment groups had an average increase in FEV_1 of 10%, while patients receiving placebo had a 2% decline in FEV_1 (p<0.001). Density of *P. aeruginosa* was decreased by an average of 0.8 $\log_{10}$ CFU/g of sputum in the active treatment groups compared to 0.3 $\log_{10}$ CFU/g in the placebo groups (p<0.001). Patients in active treatment groups were 26% (95% confidence interval [CI], 2 to 43) less likely to be hospitalized. Inhaled tobramycin was well tolerated with similar adverse effect rates between treatment and placebo groups. However, there were 2 side effects (tinnitus and voice alteration) that only occurred in the active treatment groups. These adverse effects were of mild to moderate severity and did not cause withdrawals from the study.

tobramycin inhalation powder (TOBI Podhaler) versus placebo

Two randomized, double-blind, placebo-controlled trials were conducted to evaluate the efficacy of TOBI Podhaler 4, 28 mg inhalation capsules twice daily versus placebo.[90] Participants in these studies had a confirmed diagnosis of CF and ranged in ages from 6 to 21 years of age and had not received inhaled antibiotic therapy for at least 4 months directly prior to the trial. In the first study, a total of 95 patients were randomized to TOBI Podhaler or placebo for a 28 day on treatment and 28 day off treatment cycle for a total of 24 weeks. The trial was stopped early due to demonstrated benefit in the interim analysis. In the study (n=61), TOBI Podhaler significantly improved lung function in comparison

to placebo as measured by the relative change in FEV_1 percent predicted from baseline to the end of cycle 1 dosing. After 28 days, treatment with TOBI Podhaler resulted in relative increase of FEV_1 of 12.54% compared to placebo FEV_1 increase of 0.09% (LS mean difference, 12.44%; 95% CI, 4.89 to 20; p=0.002).[91] However, a second randomized, double-blind, placebo-controlled trial of similar design which evaluated the efficacy of TOBI Podhaler versus placebo (n=62), failed to show statistically significant improvement in relative lung function FEV_1 for TOBI Podhaler. Treatment in this trial with TOBI Podhaler displayed a relative increase in lung function FEV_1 by 8.19% versus placebo of 2.27% which failed to achieve statistical significance in relative change in FEV_1 predicted (LS mean difference, 5.91%; 95% CI, -2.54 to 14.37; p=0.167).

tobramycin inhalation powder (TOBI Podhaler) versus tobramycin inhalation solution (TOBI)

A randomized, open-label, active-controlled, parallel-arm trial randomized 517 patients (3:2) to tobramycin inhalation powder (4, 28 mg capsules twice daily) or TOBI (300 mg/5 mL twice daily).[92] Three cycles, each cycle consisting of 28 days on therapy, followed by 28 days off therapy; the total treatment period was 24 weeks. Mean patient age 25.6 years. Patients had no inhaled antipseudomonal antibiotic use within 28 days prior to study drug administration. The open-label design of the study and missing values for the outcome of FEV_1 percent predicted posed limitations in interpreting the efficacy results. The proportion of patients with missing values for FEV_1 percent predicted at Weeks 5 and 25 in the TOBI Podhaler treated group were 13% and 27.9%, respectively, compared to 7.2% and 19.1%, respectively, in the TOBI treated group. Using imputation of the missing data, the mean differences (TOBI Podhaler minus TOBI) in the percent relative change from baseline in FEV_1 percent predicted at Weeks 5 and 25 were -0.87% (95% CI, -3.8 to 2.07) and 1.62% (95% CI, -0.9 to 4.14), respectively.

SUMMARY

Despite approval of newer oral treatment options for cystic fibrosis (CF), in general, pharmacologic treatments are few; thus, the role of antibiotics remains crucial in treatment of this disease. Currently, there are 2 molecular entities FDA-approved as inhaled antibiotics in the market for the management of CF in patients with *Pseudomonas aeruginosa*. These medications are taken chronically to suppress the growth of *P. aeruginosa* and reduce the risk of CF exacerbation. Inhaled aztreonam (Cayston) and inhaled tobramycin (generic, Bethkis, Kitabis Pak, TOBI, TOBI Podhaler) require no dose adjustment based on weight and age and are well tolerated. TOBI Podhaler may provide patients with an additional device option for self-administration of inhaled tobramycin; however, it may also increase risk of cough and throat irritation. Nephrotoxicity has been associated with aminoglycosides as a class; however, it has not been observed in clinical studies with inhaled tobramycin. Inhaled aztreonam does not require dose adjustment in patients with renal impairment.

The 2013 Cystic Fibrosis Foundation (CFF) Pulmonary Guidelines for CF, recommend inhaled tobramycin and inhaled aztreonam at the same rating to reduce exacerbation for patients who are ≥ 6 years of age with persistent *P. aeruginosa* culture in the airways. In their 2014 guideline for the prevention and eradication of *P. aeruginosa* infection, the CFF recommends inhaled antibiotic therapy for the treatment of initial or new growth of *P. aeruginosa*, with preference for tobramycin for 28 days. They recommend against prophylactic antipseudomonal antibiotics to prevent infection. In patients under the age of 6, they recommend oral, inhaled, and/or intravenous antibiotics for treatment of

pulmonary exacerbations and every other month administration of inhaled antibiotics in those with persistent *P. aeruginosa* infection.

Amikacin liposome (Arikayce) is the first FDA-approved inhaled antibiotic to be used in the treatment of refractory *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen. MAC is the most common nontuberculous mycobacterial (NTM) lung infection Treatment is continued until sputum cultures are consecutively negative for at least 12 months, and a typical duration exceeds 18 months. Eradication is difficult, and recurrence and relapse are common. Unlike all other treatments in this class, amikacin liposome does not carry an FDA-approved indication for the treatment of patients with CF with *P. aeruginosa*.

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