Therapeutic Class Overview
Inhaled Antibiotics (Cystic Fibrosis)

Overview/Summary:
This review will focus on the use of inhaled antibiotics used in the management of cystic fibrosis. Inhaled aztreonam (Cayston®) is indicated to improve respiratory symptoms in cystic fibrosis patients infected with *Pseudomonas aeruginosa*, while inhaled tobramycin (TOBI®, TOBI® Podhaler, KITABIS PAK®, BETHKIS®) is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.[1-5] Cystic fibrosis is an autosomal recessive disease caused by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This leads to a change in ion transport (chloride and/or other ions), resulting in thick, viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract along with increased salt content in sweat gland secretions.[6] Patients with cystic fibrosis usually present with signs and symptoms including persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels.[6] The most common infection results from *Pseudomonas aeruginosa*, with over 70% of adults chronically infected.[7] Antibiotic selection, including how many are used, is generally based on in vitro susceptibility testing. The use of inhaled antibiotics in combination with oral and/or intravenous (IV) is insufficient, and thus use of inhaled antibiotics when systemic antibiotics are indicated is not recommended.[7] The majority of data involving the inhaled antibiotics involves chronic pulmonary infections.

Aztreonam is a monobactam antibiotic that binds to penicillin-binding proteins of susceptible bacteria leading to inhibition of bacterial cell wall synthesis and death of the cell.[2] Tobramycin is an aminoglycoside antibiotic that disrupts protein synthesis leading to a change in cell membrane permeability, progressive disruption of the cell envelope, and eventual death.[2-5] Tobramycin has been approved for use in children and adults aged six and older while aztreonam has only been approved for use in children and adults aged seven or older. Aztreonam can be used in pregnancy (category B), while tobramycin should be avoided due to fetal harm (category D). Caution and monitoring is advised when using aztreonam in patients with a history of a beta-lactam allergy as some should cross-reactivity may occur. On the other hand, tobramycin is contraindicated in patients with a history of aminoglycoside allergy. Generally, both aztreonam and tobramycin have minimal drug interactions, but it is recommended to avoid certain diuretics or drugs that have neurotoxic, nephrotoxic or ototoxic potential when using tobramycin as there is an increased risk for adverse effects. Administration times vary by drug and formulation and are done via either a nebulizer or Podhaler device. Administration times for Cayston® (aztreonam) is over two to three minutes; TOBI Podhaler® (tobramycin powder) over two to seven minutes; and BETHKIS, KITABIS PAK and TOBI (tobramycin solution) over approximately 15 minutes. Only tobramycin powder for inhalation (TOBI Podhaler®) can be stored outside of the refrigerator for an extended period of time. Aztreonam inhalation and tobramycin solution for inhalation may only be stored outside of the refrigerator for 28 days. Only inhaled tobramycin solution is currently available generically.[1-5]

Table 1. Current Medications Available in Therapeutic Class[1-5]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aztreonam (Cayston®)	Improve respiratory symptoms in cystic fibrosis patients infected with Pseudomonas aeruginosa*	Inhalation solution: 75 mg	-
Tobramycin (BETHKIS®, KITABIS PAK®, TOBI®*, TOBI Podhaler®)	Management of cystic fibrosis patients with Pseudomonas aeruginosa†	Inhalation powder, capsule: 28 mg (TOBI Podhaler®) Inhalation solution: 300 mg/5 mL (TOBI®) 303 mg/5 mL (KITABIS PAK®)	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		300 mg/4 mL (BETHKIS®)	

* Safety and effectiveness have not been established in pediatric patients below the age of seven years, patients with FEV_1 <25% or >75% predicted, or patients colonized with Burkholderia cepacia.
† Safety and effectiveness have not been established in pediatric patients below the age of six years, patients colonized with Burkholderia cepacia or patients with FEV_1 <25% or >75% predicted (TOBI® solution and KITABIS®), FEV_1 <25% or >80% predicted (TOBI® inhalation powder) or FEV_1 <40% or >80% predicted (BETHKIS®).

Evidence-based Medicine

- The safety and effectiveness of the inhaled antibiotics tobramycin and aztreonam in the management of chronic infections related to cystic fibrosis have been evaluated in several clinical trials.[12-31] There have been no studies that directly compare aztreonam to tobramycin at this time.
- Approval of inhaled tobramycin, including TOBI® and KITABIS PAK®, was based on a 24-week trial of 520 patients with stable cystic fibrosis. Tobramycin 300 mg was inhaled twice daily via jet nebulizer in 28-day cycles (on 28 days, off 28 days). When compared to a control group, FEV_1 was 10% higher at 20 weeks, there was a decreased density of *Pseudomonas aeruginosa* in the sputum and there was a 26% decrease in the likelihood of hospitalization.[12]
    - A two-year follow up of the patients involved in the pivotal study above showed that continued use of inhaled tobramycin both improved FEV_1 and led to an increase in body mass index. In addition, patients who had received placebo during the randomization portion of the study had their FEV_1 increased only when they started tobramycin in the open label phase.
- The two different concentrations of tobramycin solution were compared in an open label study over 56 weeks. The different concentrations were shown to provide similar clinical benefit in the short term, that was maintained over a long-term period.[22]
- A powdered form of tobramycin (for inhalation) was compared to the traditional inhalation solution in a 24-week study. The results of the study showed that the new formulation, which greatly reduced administration time, did not have an effect on the safety or efficacy of the treatment.[24]
- The use of inhaled aztreonam was shown to be effective and safe in open label and randomized-controlled clinical trials. In one such randomized trial, 211 subjects were randomized to receive inhaled aztreonam or placebo. The aztreonam group had a longer time before needing additional antipseudomonal antibiotics (92 days) when compared to the placebo group. Also, FEV_1 scores, pseudomonas density in sputum, and patient-reported respiratory scores were all significantly improved in the aztreonam group as compared to placebo.254 A second randomized trial with a similar protocol to the previous trial, involving 164 patients, showed a significant difference in favor of inhaled aztreonam when compared to placebo for improving respiratory symptom scores, FEV_1 predicted, and pseudomonas density in the sputum.
- Use of inhaled tobramycin was compared to use of inhaled colistin in several clinical trials. A short, one-cycle trial showed that both drugs reduced bacterial load, but only inhaled tobramycin was associated with an improvement in lung function (P=0.006).[29]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The Cystic Fibrosis Foundation recommends that patients who are six years of age and older and diagnosed with cystic fibrosis who have mild, moderate or severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways should be treated with chronic inhaled antibiotics tobramycin or aztreonam.[8,9]
    - Guidelines for the management hemoptysis and pneumothorax as a complication of cystic fibrosis recommend patients with at least mild (≥5 mL) hemoptysis should be treated with antibiotics. However, no consensus could be reached regarding the use of antibiotics in patients with a pneumothorax.[10]
    - Routine use of palivizumab prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present.[11]

- Other Key Facts:
  - Tobramycin has been approved for use in children and adults aged six and older while aztreonam has only been approved for use in children and adults aged seven or older.[1-5]
  - Aztreonam can be used in pregnancy (category B), while tobramycin should be avoided due to fetal harm (category D).[1-5]
  - Caution and monitoring is advised when using aztreonam in patients with a history of a beta-lactam allergy as some should cross-reactivity may occur. On the other hand, tobramycin is contraindicated in patients with a history of aminoglycoside allergy.[1-5]
  - Inhaled tobramycin solution is currently available generically.

References

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Overview/Summary

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Aztreonam is a monobactam antibiotic that binds to penicillin-binding proteins of susceptible bacteria leading to inhibition of bacterial cell wall synthesis and death of the cell.[2] Tobramycin is an aminoglycoside antibiotic that disrupts protein synthesis leading to a change in cell membrane permeability, progressive disruption of the cell envelope, and eventual death.[2-5] Tobramycin has been approved for use in children and adults aged six and older while aztreonam has only been approved for use in children and adults aged seven or older. Aztreonam can be used in pregnancy (category B), while tobramycin should be avoided due to fetal harm (category D). Caution and monitoring is advised when using aztreonam in patients with a history of a beta-lactam allergy as some should cross-reactivity may occur. On the other hand, tobramycin is contraindicated in patients with a history of aminoglycoside allergy. Generally, both aztreonam and tobramycin have minimal drug interactions, but it is recommended to avoid certain diuretics or drugs that have neurotoxic, nephrotoxic or ototoxic potential when using tobramycin as there is an increased risk for adverse effects. Administration times vary by drug and formulation and are done via either a nebulizer or Podhaler device. Administration times for Cayston® (aztreonam) is over two to three minutes; TOBI Podhaler® (tobramycin powder) over two to seven minutes; and BETHKIS, KITABIS PAK and TOBI (tobramycin solution) over approximately 15 minutes. Only tobramycin powder for inhalation (TOBI Podhaler®) can be stored outside of the refrigerator for an extended period of time. Aztreonam inhalation and tobramycin solution for inhalation may only be stored outside of the refrigerator for 28 days. Only inhaled tobramycin solution is currently available generically.[1-5]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Aztreonam (Cayston®)	Monobactam Antibiotic (inhaled)	-
Tobramycin (BETHKIS®, KITABIS PAK®, TOBI®*, TOBI Podhaler®)	Aminoglycoside Antibiotic (inhaled)	a

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-5]

Generic name	Improve respiratory symptoms in cystic fibrosis patients infected with *Pseudomonas aeruginosa*	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*
Aztreonam	a *	
Tobramycin		a †

*Safety and effectiveness have not been established in pediatric patients below the age of seven years, patients with FEV_1 <25% or >75% predicted, or patients colonized with Burkholderia cepacia.
† Safety and effectiveness have not been established in pediatric patients below the age of six years, patients colonized with *Burkholderia cepacia* or patients with FEV_1 <25% or >75% predicted (TOBI® solution and KITABIS®), FEV_1 <25% or >80% predicted (TOBI® inhalation powder) or FEV_1 <40% or >80% predicted (BETHKIS®).

Pharmacokinetics

Table 3. Pharmacokinetics[1-5]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aztreonam	Low	56	Liver (7)	Renal (10)	2.1
Tobramycin	Low	0 to 30	Not reported	Renal (60 to 85)	1.6 to 3.0

Clinical Trials

The safety and effectiveness of the inhaled antibiotics tobramycin and aztreonam in the management of chronic infections related to cystic fibrosis are outlined in table 4.[12-31] There have been no studies that directly compare aztreonam to tobramycin at this time.

Approval of inhaled tobramycin, including TOBI® and KITABIS PAK®, was based on a 24-week trial of 520 patients with stable cystic fibrosis. 300 mg to tobramycin was inhaled twice daily via jet nebulizer in 28-day cycles (on 28 days, off 28 days). When compared to a control group, FEV1 was 10% higher at 20 weeks, there was a decreased density of P. aeruginosa in the sputum and there was a 26% decrease in the likelihood of hospitalization.[12] A two-year follow up of the patients involved in the pivotal study above showed that continued use of inhaled tobramycin both improved FEV1 and led to an increase in body mass index. In addition, patients who had received placebo during the randomization portion of the study had their FEV1 increased only when they started tobramycin in the open label phase. Of note, those patients who started the tobramycin during the open label phase were not able to catch up to the improved FEV1 values attained by the patients that started the tobramycin earlier.[13] Additional studies involving the use of different concentrations of inhaled tobramycin solution have shown similar results.[14-21] The two different concentrations of tobramycin solution were compared in an open label study over 56 weeks. The two different concentrations were shown to provide similar clinical benefit in the short term, that was maintained over a long-term period.[22] A powdered form of tobramycin (for inhalation) was compared to the traditional inhalation solution in a 24-week study. The results of the study showed that the new formulation, which greatly reduced administration time, did not have an effect on the safety or efficacy of the treatment.[24]

The use of inhaled aztreonam was shown to be effective and safe in open label and randomized-controlled clinical trials. In one such randomized trial, 211 subjects were randomized to receive inhaled aztreonam or placebo. The aztreonam group had a longer time before needing additional antipseudomonal antibiotics (92 days) when compared to the placebo group. Also, FEV1 scores, pseudomonas density in sputum, and patient-reported respiratory scores were all significantly improved in the aztreonam group as compared to placebo.[25] A second randomized trial with a similar protocol to the previous trial, involving 164 patients, showed a significant difference in favor of inhaled aztreonam when compared to placebo for improving respiratory symptom scores, FEV1 predicted, and pseudomonas density in the sputum.[26] One open label study was conducted involving 271 patients from the two trials above. Each subject received aztreonam twice or three times daily for one month, every other

month, for up to nine cycles. Both treatment regimens were well tolerated with similar adverse effects. Although a statically significant difference could not be shown, the three times daily dose led to a numerically improved FEV1 compared to the twice daily group.

Use of inhaled tobramycin was compared to use of inhaled colistin in several clinical trials. A short, one-cycle trial showed that both drugs reduced bacterial load, but only inhaled tobramycin was associated with an improvement in lung function (P=0.006).[29] An open label, cross-over, extension study of the previous trial confirmed the results that inhaled tobramycin provided a statically significant improvement in lung function compared to inhaled colistin.[30]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ramsey et al[12] Tobramycin inhalation solution 300 mg BID for three cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	DB, MC, PC Patients at least six years of age with cystic fibrosis, a respiratory tract culture positive for *Pseudomonas aeruginosa,* ability to perform pulmonary function tests, and FEV_1 25 to 75% of predicted value	N=520 24 weeks	Primary: FEV_1 and the density of *Pseudomonas aeruginosa* in sputum at 20 weeks Secondary: Hospitalization and treatment with IV antipseudomonal antibiotics	Primary: At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average 10% increase in FEV_1, as compared to 2% decline for the patients receiving placebo (P<0.001). At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average reduction of 0.8 $\log_{10}$ colony forming unit per gram of sputum, as compared to the value at 0 weeks, whereas the density in the placebo group had increased by 0.3 $\log_{10}$ colony forming unit per gram (P<0.001). Secondary: Patients receiving tobramycin were 26% less likely to be hospitalized and 36% less likely to require IV antipseudomonal antibiotics.
Bowman et al[13] Tobramycin inhalation solution 300 mg BID for nine cycles (each cycle consisting of 28 days during which the study drug was administered and 28 days during which it was not administered)	OL Patients at least six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=396 48 weeks	Primary: Pulmonary function and antibiotic use Secondary: Not reported	Primary: At the start of the OL study period, the patients who had been receiving tobramycin inhalation solution continued to show mean FEV_1 values that remained above their baseline values. The patients who were crossed over from placebo to OL tobramycin inhalation solution had a marked improvement in their pulmonary function. However, mean FEV_1 in the placebo group did not reach the levels seen in patients who had received with tobramycin inhalation solution in the initial, DB phase. By the end of the 12th treatment cycle, the mean FEV_1 in the tobramycin inhalation solution-only group was 4.7% above the baseline value at the start of the study. Mean FEV_1 at endpoint in patients in the placebo- tobramycin inhalation solution XO group was slightly less than the baseline level, but was still greater than it had been at the end of the placebo phase (week 24). In addition to improvement in the FEV_1, patients who were treated with tobramycin inhalation solution had a significant reduction in the number of courses of IV anti-pseudomonal antibiotic use per year. The patients receiving placebo required 1.9 courses of anti-pseudomonal antibiotics per patient per year, while the patients receiving tobramycin inhalation solution (both the randomized and the OL portions of the trial, regardless of initial study group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				assignment) required approximately 1.25 courses per patient per year. A subgroup analysis was performed evaluating the change in FEV_1 for patients aged 13 to 17 years. The adolescent patients treated with tobramycin inhalation solution from the beginning had a marked improvement of approximately 15% in their FEV_1 over the first three cycles of treatment. This contrasts with an approximately 8% decline in FEV_1 for the adolescent patients treated with placebo. The patients who continued tobramycin inhalation solution maintained their level of improvement over the next nine cycles, ending with an FEV_1 that was still an average of 14.3% above their week 0 baseline after 12 cycles of tobramycin inhalation solution. The group of adolescent patients who crossed over from the conventional therapy with placebo aerosol to receive tobramycin inhalation solution in the OL phase showed a marked improvement during subsequent cycles. This degree of improvement was similar to that seen in the group who started on tobramycin inhalation solution in the DB study. The mean FEV_1 values of this XO group after nine cycles (72 weeks) of tobramycin inhalation solution were maintained at levels above those at the start of the OL part of the study. Secondary: Not reported
Murphy et al[14] Tobramycin inhalation solution 300 mg BID for seven cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	MC, OL, PG, RCT Patients six to 10 years of age with cystic fibrosis and chronic *Pseudomonas aeruginosa,* FEV_1 ≥70% and ≤110% of predicted value; patients 11 to 15 years of age with cystic fibrosis and FEV_1 >70% and <90% of predicted	N=184 56 weeks	Primary: Rate of lung function decline, FEV_1, rates of hospitalization, and concomitant antibiotic use Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution trended toward improvement in percent predicted FEV_1 over control group at weeks 20 and 32, but the improvement was not statistically significant. Significantly fewer tobramycin inhalation solution patients were hospitalized for worsening of respiratory symptoms (11.0 vs 25.6%; P<0.011), and fewer tobramycin inhalation solution patients were hospitalized overall (16.5 vs 27.8%; P<0.065). Fewer tobramycin inhalation solution patients received antibiotics other than the study drug (78.0 vs 95.6%), and significantly fewer patients received oral antibiotics (76.9 vs 91.1%; P<0.009). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	value			Not reported
Quittner et al[15] Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	RETRO Patients greater than six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 25 to 75% of predicted values	N=520 24 weeks	Primary: Improvement in quality of life Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution were more likely to report improvement in quality of life than those receiving placebo (P<0.005). Secondary: Not reported
Moss et al[16] Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	OL Patients 13 to 17 years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=128 2 years	Primary: Pulmonary function, *Pseudomonas aeruginosa* colony-forming unit density, incidence of hospitalization and IV antibiotic use, weight gain Secondary: Not reported	Primary: Patients originally randomized to tobramycin inhalation solution and placebo treatments exhibited improvements in FEV_1 percent predicted of 13.5 and 9.4%, respectively. Improvement in pulmonary function was significantly correlated with reduction in *Pseudomonas aeruginosa* colony forming unit density (P=0.0001). The average number of hospitalizations and IV antibiotic courses did not increase over time. Secondary: Not reported
Briesacher et al[17] Tobramycin inhalation solution	RETRO Patients with cystic fibrosis with at least one claim for tobramycin inhalation solution	N=804 Variable duration	Primary: Adherence and hospitalization Secondary: Not reported	Primary: Chronic use of tobramycin inhalation solution was low in patients with *Pseudomonas aeruginosa* as only 6% were dispensed four or more cycles per year. Tobramycin inhalation solution usage was similar for patients with and without the diagnosis of *Pseudomonas aeruginosa*. In comparison to patients with high utilization of tobramycin inhalation solution, those using less than four cycles a year were more likely to be hospitalized.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				High use of tobramycin inhalation solution was associated with a decreased risk of hospitalization relative to low use (AOR, 0.40; 95% CI, 0.19 to 0.84). A higher than average comorbidity risk (AOR, 7.53; 95% CI, 5.20 to 10.90), a coded diagnosis of *Pseudomonas aeruginosa* (AOR, 3.0; 95% CI, 2.13 to 4.32), and a coded diagnosis of failure to thrive/growth failure (AOR, 2.8; 95% CI, 1.09 to 7.14) were all independently associated with an increased risk of hospitalization. Secondary: Not reported
O'Sullivan et al[18] Tobramycin inhalation solution	RETRO Patients at least six years of age with cystic fibrosis and pulmonary infections	N=1,064 1 year	Primary: Health care utilization Secondary: Not reported	Primary: A higher percentage of children had at least one cystic fibrosis-related office visit (P=0.0046), cystic fibrosis-related outpatient hospital visit (P<0.0001), outpatient hospital visit for any reason (P=0.0016), and cystic fibrosis-related emergency room visit (P=0.0159) compared to adults. Adults with cystic fibrosis averaged about 12 office visits per year for any diagnosis, compared to about 10 visits per year among children (P=0.0067). Children had more cystic fibrosis-related outpatient hospital visits (P=0.004) as well as prescriptions for than tobramycin inhalation solution (P=0.0007) and dornase alfa (P<0.0001) compared to adult patients. Adults had more frequent inpatient stays for any diagnosis (P=0.0021) and numbers of prescriptions for antibiotics other than tobramycin inhalation solution and azithromycin compared to children (P=0.0009). Adults had an average of 43 prescriptions per year compared to 39 prescriptions per year for children (P=0.03). Secondary: Not reported
Ratjen et al[19] Tobramycin inhalation solution for an additional	MC, OL, RCT Patients at least six months with	N=123 56 days	Primary: Median time to recurrence of any strain of	Primary: The median time to recurrence of *Pseudomonas aeruginosa* was 26.12 and 25.82 months following than tobramycin inhalation solution for 28 and 56 days, respectively (P=0.593).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
28 days vs discontinuation of tobramycin	cystic fibrosis and early *Pseudomonas aeruginosa* infection who had already received 28 days of treatment with tobramycin inhalation solution		*Pseudomonas aeruginosa* Secondary: Proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment; time to recurrence of any strain of *Pseudomonas aeruginosa*; number of patients with the same genotype of *Pseudomonas aeruginosa* at baseline and recurrence or a new genotype at recurrence; proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment for sputum and non-sputum producers and by baseline characteristics, lung function and infection status;	At the time of each patient's final study visit, 66% of patients remained free of *Pseudomonas aeruginosa* in the 28-day than tobramycin inhalation solution group and 69% remained free of *Pseudomonas aeruginosa* in the 56-day than tobramycin inhalation solution group. Secondary: The proportion of patients free of *Pseudomonas aeruginosa* at day 28 and one month after the end of treatment was comparable in both groups. The proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment was similar in sputum producers and non-sputum producers. Paired samples (baseline and recurrence) were available in 21 patients, of which 12 had the same genotype at baseline and at recurrence. For the remaining patients (n=9), paired samples were of a different genotype. Two patients (5.3%) in the 56-day than tobramycin inhalation solution group were hospitalized on one occasion, each for a pulmonary exacerbation during the study. No major short- or long-term changes in spirometric parameters were observed during the study period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			number and length of hospital admissions for respiratory indications	
Chuchalin et al[20] [abstract] Tobramycin inhalation solution 300 mg/4 mL vs placebo Four-week treatment periods ('on' cycles) were followed by four-week periods without treatment ('off' cycles)	DB, MC, PC Patients with cystic fibrosis with chronic *Pseudomonas aeruginosa* infection	N=247 24 weeks Endpoint time assessment was at week 20	Primary: FEV_1 percent predicted normal Secondary: Forced vital capacity, forced expiratory flow at 25 to 75% of forced vital capacity, *Pseudomonas aeruginosa* susceptibility, MIC required to inhibit 90% of strains, rates of *Pseudomonas aeruginosa* - negative culture, *P. aeruginosa* persistence and superinfection, need for hospitalization and parenteral antipseudomonal antibiotics, loss of school/working days due to the disease, and nutritional status	Primary: FEV_1 was significantly increased in the tobramycin group and the adjusted mean difference between groups in the intention-to-treat population was statistically significant (P<0.001). Secondary: Tobramycin group had clinically relevant improvements in forced vital capacity (P=0.022) and forced expiratory flow at 25 to 75% of forced vital capacity (P=0.001). The microbiologic outcomes at the end of the last 'on' cycle period were better in the tobramycin group than the placebo group (P=0.024). There was a concomitant trend toward an increase in the minimum concentration required to inhibit 90% of strains of isolated *Pseudomonas aeruginosa* strains. Tobramycin group had a lower percentage of patients hospitalized (P=0.002) and had a lower need for parenteral antipseudomonal antibiotics (P=0.009) compared to the placebo group. Tobramycin group patients had fewer lost school/working days due to the disease (P<0.001). Compared to placebo, there was a favorable effect of tobramycin in terms of an increase in bodyweight and body mass index at all time points (P<0.01 and P<0.001, respectively). There were no significant changes in serum creatinine and auditory function. The proportion of patients with drug-related adverse events was 15% in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			(bodyweight and body mass index); safety parameters including adverse events, audiometry, and renal function	
Lenoir et al[21] Tobramycin inhalation solution 300 mg/4 mL BID for four weeks vs placebo	DB, MC, PC, PG, PRO, RCT Patients six years of age and older with cystic fibrosis with a FEV_1 ≥40 and ≤80% of predicted normal with *Pseudomonas aeruginosa* infection	N=59 8 weeks	Primary: Pulmonary function as measured by FEV_1, forced vital capacity, and forced expiratory flow at the midportion of vital capacity, *Pseudomonas aeruginosa* susceptibility, microbiologic results, and in vitro MIC for 90% of strains; safety as monitored by the recording of adverse events, audiometry (bone conduction at 250 to 8,000 Hz frequency), laboratory tests, physical examination, and general health condition	Primary: The tobramycin group had a significant increase in FEV_1 from baseline compared to the placebo group: the absolute difference between groups (intent-to-treat population) of predicted normal was 13.2% at week two (95% CI, 4.88 to 21.54; P=0.002) and 13.3% at week four (95% CI, 4.74 to 21.81; P=0.003). The forced vital capacity and forced expiratory flow at the midportion of vital capacity also increased in the tobramycin group compared to the placebo group: the estimated differences at week four visit were 10.65% (95% CI, 1.94 to 19.37; P=0.017) and 15.78% (95% CI, 5.24 to 26.32; P=0.004) for the two variables, respectively. There was no significant effects in terms of maintenance of *Pseudomonas aeruginosa* negative cultures at the end of the run-out phase in the tobramycin group (P=0.202 between-group comparison). There was no differences between treatments in the mean changes from baseline of MIC for 90% at the end of week four in patients with persistent *Pseudomonas aeruginosa* (P=0.780). There was no difference between the treatment groups in terms of drug-related adverse events (P=0.184). Results of audiometric tests did not show statistically significant differences between groups. There were no differences between treatment groups in increase in serum creatinine levels (P=0.850). There were no clinically significant changes in heart rate and blood pressure in either group at any time. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	
Mazurek et al[22] Tobramycin nebulization solution 300 mg/4 mL (28 days on-drug, 28 days off-drug) vs tobramycin nebulization solution 300 mg/5 mL (28 days on-drug, 28 days off-drug) Subset of patients continued receiving tobramycin nebulization solution 300 mg/4 mL only.	MC, OL, RCT (core phase) SA (extension phase) Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥40 and ≤80% predicted	N=321 (N=321: core phase; N=209: extension phase) 56 weeks (8 weeks: core phase; 48 weeks: extension phase)	Primary: Core phase: absolute change in FEV_1 percent predicted from baseline to week four; extension phase: long term safety of tobramycin nebulization solution 300 mg/4 mL; both phases: microbiological assessments, adverse events, and audiometry findings Secondary: Not reported	Primary: In the core phase, FEV_1 percent predicted increased similarly from baseline (absolute change) following a single on-treatment cycle for both groups: tobramycin nebulization solution 300 mg/4 mL, 7.0% vs tobramycin nebulization solution 300 mg/5 mL, 7.5% (difference between treatments, -0.5; 95% CI, -2.6 to 1.6). The baseline- and country-adjusted mean of absolute change from baseline to week four in FEV_1 percent predicted was 4.7 and 5.2% for 4 and 5 mL solution, respectively, with a significant (P<0.001) improvement vs baseline for both groups. These improvements were maintained throughout the extension phase. *Pseudomonas aeruginosa* sputum count reductions ranged between 0.6 (95% CI, 0.2 to 0.9) to 2.3 (95% CI, 2.0 to 2.6) log_{10} colony forming unit/g throughout the 56 weeks. No remarkable safety issues were identified throughout both study phases, with similar percentages of patients reporting adverse events in the two treatment groups during the core phase (4 mL, 31.4%; 5 mL, 28.0%; P=0.579). The adverse events that were judged to be related to the drug were also similar between the two groups (4 mL, 6.4%; 5 mL, 6.0%; P=1.000). Cough, rhinitis, pharyngitis, and pulmonary exacerbations were the most commonly reported adverse events, proportionally similar between the two groups. Serious adverse events occurred in six (3.8%) and two (1.2%) of patients treated with 4 and 5 mL solution, respectively (Fisher's test, P=0.161). During the extension phase, adverse events were reported by 148 patients (70.8%). Similar to the core phase, the most commonly reported adverse events included pulmonary exacerbation (24.9%), rhinitis (12.4%), cough (11%), pyrexia (7.7%), and bronchitis (7.2%). Bronchospasm and death was not reported in either core or extension phase. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Galeva et al[23] Tobramycin inhalation powder 112 µg, as capsules administered via dry powder inhaler, BID vs placebo	DB, MC, PC, RCT Patients six to 21 years of age with cystic fibrosis with FEV_1 ≥25 and ≤80% and a positive sputum or throat culture for *Pseudomonas aeruginosa* within six months of screening and a positive sputum culture for *Pseudomonas aeruginosa* at the screening visit	N=62 Duration not specified	Primary: Relative change in FEV_1 percent predicted from baseline to day 29 Secondary: Relative change in forced vital capacity percent predicted and forced expiratory flow 25 to 75% predicted from baseline to day 29; change from baseline in sputum density of *Pseudomonas aeruginosa*; rates of antipseudomonal antibiotic use and hospitalizations due to respiratory events; safety assessments: the incidence and severity of all adverse events and serious adverse events and regular monitoring of hematology, blood chemistry	Primary: Mean treatment difference was 5.9% (95% CI, -2.2 to 14.0; P=0.148) for relative change in FEV_1 percent predicted. Secondary: Mean treatment difference was 4.4% (95% CI, 0.0 to 8.8; P<0.05) for absolute change in FEV_1 percent predicted. Tobramycin inhalation powder significantly reduced sputum *Pseudomonas aeruginosa* density by -1.2 $\log_{10}$ colony forming unit (P=0.002). The tobramycin group had higher clearance rate for *Pseudomonas aeruginosa* compared to placebo (41.4 vs 0% at day 29). Antipseudomonal antibiotic use was reported to be used in three patients in each of the treatment groups. Hospitalization due to respiratory events occurred in one patient in the placebo group. Adverse events were mild to moderate in severity and they occurred in 26.7% patients in the tobramycin group compared to 34.4% patients in the placebo group. Drug-related adverse events occurred in five (16.7%) tobramycin-treated patients compared to two (6.3%) patients in the placebo group; the difference was due to adverse event of cough that was reported in three patients in the tobramycin group to be drug-related. There was no difference between the groups in serious adverse events. There were no major differences that were observed between the groups in any hematology, renal or biochemistry variables, or acuity.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and urine protein, vital signs, physical condition, and bodyweight	
Konstan et al[24] Tobramycin inhalation powder 112 µg via T-326 inhaler BID for three treatment cycles (28 days on-drug, 28 days off-drug) vs tobramycin inhalation solution 300 mg/5 mL via PARI LC PLUS nebulizer BID for three treatment cycles (28 days on-drug, 28 days off-drug)	OL, RCT Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥25 to ≤75% predicted	N=553 24 weeks	Primary: Safety assessments; relative chance in FEV_1 percent predicted from baseline, change in sputum *Pseudomonas aeruginosa* density, tobramycin susceptibility to *Pseudomonas aeruginosa* using MIC, antipseudomonal antibiotic use, respiratory-related hospitalizations Secondary: Not reported	Primary: More patients in the tobramycin inhalation powder group reported adverse events compared to tobramycin inhalation solution group (90.3 vs 84.2%; P<0.05). The percentage of adverse events was highest in cycle 1, 77.9% with tobramycin inhalation powder group and 66.5% with tobramycin inhalation solution group and decreased with cycles 2 and 3 (cycle 2: 67.0 vs 66.3%; cycle 3: 65.8 vs 58.5%, respectively). The most frequently reported adverse event was cough during the study period (tobramycin inhalation powder: 48.4% vs tobramycin inhalation solution: 31.1%). The rate of cough suspected to be study drug related was higher in tobramycin inhalation powder group (25.3 vs 4.3%). Twelve out of 308 (4%) tobramycin inhalation powder-treated patients discontinued due to cough vs 1% (2/209) of tobramycin inhalation solution-treated patients. Dysphonia (13.6 vs 3.8%) and dysgeusia (3.9 vs 0.5%) were also more commonly reported in the tobramycin inhalation powder group. The incidence of serious adverse events was similar in both groups. Both treatment groups had similar increases in FEV_1 percent predicted from baseline to day 28 of cycle 3 (least squares mean difference, 1.1% relative change [standard error, 1.75]). On day 28 of cycle 3, 11.6% tobramycin inhalation powder-treated patients and 9.9% tobramycin inhalation solution-treated patients had negative *Pseudomonas aeruginosa* cultures. The proportion of patients requiring any new antipseudomonal antibiotic was significantly higher with tobramycin inhalation powder group (64.9 vs 54.5%; P=0.0148). The number of patients hospitalized for respiratory-related events was similar in the tobramycin inhalation powder group vs tobramycin inhalation solution group (24.4 vs 22.0%). Administration time was significantly less for tobramycin inhalation powder compared to the solution formulation (mean, 5.6

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vs 19.7 minutes; P<0.0001). Secondary: Not reported
McCoy et al[25] AIR-CF2 Aztreonam inhalation solution 75 mg BID or TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with FEV_1 >25 and <75% who were on maintenance therapy for *Pseudomonas aeruginosa* and who had completed a 28-day course of tobramycin inhalation solution	N=211 84 days	Primary: Time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation Secondary: Changes in clinical symptoms, pulmonary function, *Pseudomonas aeruginosa* density, time to hospitalization, hospitalizations, and weight	Primary: The median time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation was 21 days longer for the aztreonam inhalation solution-pooled group than for the placebo group (92 vs 71 days; P=0.007). The median time to antibiotic need was also longer in the aztreonam inhalation solution-BID (>92 days; P=0.002) and aztreonam inhalation solution-TID (87 days; P=0.182) groups, compared to placebo (71 days). Secondary: Adjusted mean CFQ-R respiratory scores increased 5.01 points in the aztreonam inhalation solution-pooled group compared to placebo (day 28; 95% CI, 0.81 to 9.21; P=0.020). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo and the responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. Adjusted mean FEV_1 improved 6.3% in the aztreonam inhalation solution-pooled group compared to placebo (day 28; 95% CI, 2.5 to 10.1; P=0.001). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo. Responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. FEV_1 decreased during the follow-up period for all groups. Adjusted mean relative FEV_1 percent predicted improved in the aztreonam inhalation solution-pooled group compared to placebo (day 28; adjusted means; aztreonam inhalation solution-pooled, 4.1%; placebo, 22.5%; 95% CI, 2.8 to 10.4; P<0.001). Adjusted mean *Pseudomonas aeruginosa* sputum density decreased 0.66 $\log_{10}$ *Pseudomonas aeruginosa* cfu/g sputum in the aztreonam inhalation

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				solution-pooled group compared to the placebo group (day 28: 95% CI, 21.13 to 20.19; P=0.006). Significant decreases were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID compared to placebo groups. Time to first hospitalization and median days per number of patients hospitalized did not differ significantly between the treatment groups (days 0 to 84). Weight increased 0.77% for the aztreonam inhalation solution-pooled group compared to placebo (day 28: 95% CI, 0.00 to 1.55; P=0.051).
Retsch-Bogart et al[26] AIR-CF1 Aztreonam inhalation solution 75 mg TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis, FEV_1 >25 and <75%, *Pseudomonas aeruginosa* airway infection, and no recent use of antipseudomonal antibiotics or azithromycin	N=164 42 days	Primary: Change in symptoms Secondary: Changes in pulmonary function, hospitalizations, nonrespiratory CFQ-R scales, sputum *Pseudomonas aeruginosa* density	Primary: The adjusted mean CFQ-R-Respiratory scores increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 9.7 points; 95% CI, 4.3 to 15.1; P<0.001). Two weeks after treatment, CFQ-R-Respiratory scores had declined but remained above baseline values for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 6.3 points; 95% CI, 1.2 to 11.4; P<0.015). Secondary: The adjusted mean FEV_1 increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.3%; 95% CI, 6.3 to 14.3; P<0.001). Two weeks after treatment, the mean FEV_1 had declined but remained above baseline for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 5.7%; 95% CI, 2.1 to 9.4; P<0.002). The adjusted mean relative change in FEV% predicted values also increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.2%; 95% CI, 6.2 to 14.2; P<0.001) and declined for both groups after treatment (day 42 treatment difference, 5.7%; 95% CI, 2.0 to 9.4; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The adjusted mean sputum *Pseudomonas aeruginosa* density decreased for aztreonam inhalation solution-treated patients and remained near baseline for placebo-treated patients (day 28 treatment difference, -1.453 $\log_{10}$ cfu/g; 95% CI, -2.1 to -0.8; P<0.001). Two weeks after treatment (day 42), values were near baseline values for both treatment groups (P=0.822). There was a trend toward fewer hospitalized patients in the aztreonam inhalation solution group (5%) than in the placebo group (14%; days 0 to 42; P=0.064) and toward fewer mean hospitalization days (aztreonam inhalation solution group, 0.5 days; placebo group, 1.5 days; P=0.049). Weight increased 1.1% for the aztreonam inhalation solution-treated group and 0.1% for the placebo-treated group (day 28: 95% CI, 0.33 to 1.69; P=0.004). The responses of aztreonam inhalation solution-treated patients were significantly larger than those of placebo-treated patients for 6 of the 11 nonrespiratory CFQ-R scales; these scales included Eating, Emotional Functioning, Health Perceptions, Physical Functioning, Role Limitation/School Performance, and Vitality.
Oermann et al[27] AIR-CF3 Aztreonam inhalation solution 75 mg BID to TID for 28 days Patients received up to nine courses (28 days on/28 days off) of 75mg aztreonam inhalation solution BID or TID based on randomization in the previous trials.	OL Patients ≥6 years of age with cystic fibrosis and *Pseudomonas aeruginosa* airway infection, who previously participated in one of two Phase III studies (AIR-CF1 or AIR-CF2)	N=274 18 months	Primary: Disease-related endpoints (change from baseline FEV_1 percent predicted, FEV_1 absolute volume, CFQ-R-Respiratory scores, and density of *Pseudomonas aeruginosa* in sputum Secondary: Not reported	Primary: For treatment courses one through nine, percent change in FEV_1 (L) was positive at the end of each on-drug course. A greater response was observed for the TID regimen in general. The mean change in FVC from baseline ranged from -1.40 to 5.39% (BID) and from 0.97 to 6.18% (TID). The mean change in FEF_{25-75} from baseline ranged from -4.20 to 16.05% (BID) and from -5.02 to 14.14% (TID). For the on-treatment months, the mean increase in CFQ-R-Respiratory score was >4. Changes on other symptom scales of the CFQ-R were consistent with treatment benefit. There was a greater improvement in the TID group than in the BID group. In the TID group, mean improvements from baseline for the Physical Functioning, Vitality and Health Perceptions domains tended to be greater during each of the intervals when the patient was on treatment and less during each of the intervals when the patient was off treatment. For the TID group,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mean scores for the Weight domain tended to be above baseline throughout the nine treatment courses. Absolute changes from baseline for the remaining domains (emotional functioning, social functioning, body image, eating disturbances, role limitations/school performance and digestion) were variable and showed no apparent dose response. A total of 47.8% of patients were hospitalized at least once during the study. The median time to the first hospitalization for a respiratory event was 449 days, with median times of 431 and 449 days for the BID- and TID-treated groups, respectively. Median time to IV antipseudomonal antibiotics was 247 days (95% CI, 210 to 287), with similar times between the two regimen groups: 276 days for the BID-treated group (95% CI, 217 to 316) and 232 days for the TID group (95% CI, 179 to 288). Repeated courses of aztreonam inhalation solution resulted in consistent weight gain, which were sustained over the 18-month period. Improvement was greater among patients receiving TID compared to BID treatment. Mean adherence was 92.0% in the BID group and 88.0% in the TID group. Secondary: Not reported
Wainwright et al[28] Aztreonam inhalation solution 75 mg TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with an FEV_1 >75%, *Pseudomonas aeruginosa* airway infection, and who did not require immediate	N=157 42 days	Primary: Change from baseline at Day 28 on the CFQ-R RSS Secondary: Change from baseline at Days 14 and 42 on the CFQ-R RSS,	Primary: Adjusted mean change at Day 28 from baseline CFQ-R RSS scores was 3.22 for aztreonam inhalation solution-treated and 1.41 for placebo-treated patients (treatment effect 1.80; 95% CI, −2.83to 6.44; P=0.443). Secondary: Significant treatment effects favoring aztreonam inhalation solution were observed for several secondary efficacy endpoints: change from baseline at day 28 for adjusted mean $\log_{10}$ *Pseudomonas aeruginosa* CFUs in sputum (aztreonam inhalation solution, −1.4; placebo, −0.14; P=0.016) and adjusted mean relative change in FEV_1 percent predicted (aztreonam inhalation

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	antipseudomonal antibiotic treatment of an impending exacerbation		change from baseline at Day 28 on the CFQ-R Physical Functioning Scale, use of additional antipseudomonal antibiotics, proportion of patients hospitalized, and change from baseline at Day 28 for log_{10} *Pseudomonas aeruginosa* CFUs in sputum and FEV_1 percent predicted	solution, 0.29%; placebo, −2.5%; P=0.021). Amongst other efficacy endpoints, significant treatment effects favoring aztreonam inhalation solution were observed for relative mean change from baseline FEV_1 (L) at day 28 and CFQ-R Social Functioning scores. Use of PO, IV, or additional inhaled antibiotics was similar for the aztreonam inhalation solution and placebo groups during the entire study, with most use occurring during the follow-up period for both treatment groups.
Hodson et al[29] Tobramycin inhalation solution 300 mg BID vs colistin nebulized solution 80 mg inhaled BID	RCT Patients older than six years of age with cystic fibrosis, FEV_1>25%; *Pseudomonas aeruginosa* positive sputum culture	N=115 4 weeks	Primary: Mean change from baseline to week four in FEV_1 percent predicted Secondary: Change in sputum *Pseudomonas aeruginosa* density, tobramycin/colistin MICs, and safety assessment	Primary: Tobramycin inhalation solution produced a mean 6.7% improvement in lung function (P=0.006), while there was no significant improvement in the colistin-treated patients (mean change 0.37%). Secondary: Both nebulized antibiotic regimens produced a significant decrease in the sputum *Pseudomonas aeruginosa* density, and there was no development of highly resistant strains over the course of the study. No significant difference was detected between groups with respect to incidence of adverse events.
Adeboyeku et al[30]	ES, OL, RCT, XO	N=21	Primary: Mean change in	Primary: FEV_1 during colistin treatment had a slope of −0.88% per month, and during

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tobramycin inhalation solution 300 mg BID vs Colistin nebulized solution 80 mg inhaled BID Patients continued their original drug for five months then crossed over to the other treatment for five months (after a two-week wash out period).	Patients who completed one cycle (four weeks) of therapy during the previous study	10 months	FEV_1 percent predicted Secondary: Not reported	tobramycin treatment had a slope of 0.35% per month. This difference in the month by month treatment effects of the two antibiotics is statistically significant (P=0.0002). Secondary: Not reported There were no statistically significant differences in the number of days on intravenous or oral antibiotics, or quality of life. Two patients developed tobramycin resistant *Pseudomonas aeruginosa* which was treated with intravenous and inhaled colistin.
Berlana et al[31] Tobramycin inhalation solution vs colistin inhalation solution vs tobramycin inhalation solution plus colistin inhalation solution	OBS, PRO Adult patients with cystic fibrosis who received inhaled colistin, inhaled tobramycin or both to treat *Pseudomonas aeruginosa* bronchial colonization, a history of chronic *Pseudomonas aeruginosa* bronchial colonization, a diagnosis of bronchiectasis or chronic obstructive	N=81 4 years	Primary: Frequency and duration of hospitalizations for respiratory exacerbations Secondary: Emergence of bacterial resistance, antibiotic use during admission, emergence of other opportunistic microorganisms, achievement of sustained *Pseudomonas aeruginosa*	Primary: Significant differences were observed in the mean yearly rates for hospitalizations, duration of hospitalization, and duration of antibiotic use between the tobramycin and colistin plus tobramycin groups. No significant differences were found in hospitalizations, hospitalization days, or days of antibiotic use between tobramycin and colistin treatment. Secondary: Of the 93 microbiologically assessable antibiotic courses, 10 episodes of *Pseudomonas aeruginosa* were classified as eradicated, 20 reduced, 17 maintained negative, and 46 no response. Antimicrobial resistance was assessable in 72 episodes. The frequency of emergence of resistant strains differed significantly according to the antibiotic received (48% for tobramycin and 8% for colistin). The highest rate of emergence of other microorganisms was seen in the colistin plus tobramycin group. Only one patient was treated to control persistent isolation of *Aspergillus* species. Neither *Pseudomonas aeruginosa* eradication nor emergence of other microorganisms was linked to the inhaled antibiotic treatment received.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pulmonary disease, and who were receiving long-term treatment (≥12 weeks) of outpatient inhaled antibiotic therapy		eradication in the airways, mortality, safety, and changes in respiratory function	No significant differences were found in the mean change/year in pulmonary function tests between the treatment groups. The overall frequency of patients experiencing an adverse event was 40%. A total of 12 patients (14.8%) died during the study, all for respiratory causes. There were no significant differences in mortality between the study groups, and FEV_1 percent was linked to mortality (HR, 0.93; 95% CI, 0.86 to 0.98).

BID=twice a day, TID=three times a day
Study abbreviations: AC=active control, AOR=adjusted odds ratio, CI=confidence interval, DB=double blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SA=single arm, SC=single center, XO=cross over
Other abbreviations: CFQ-R=cystic fibrosis questionnaire-revised, CFU=colony formulating unit, FEF25-75=forced expiratory flow at 25 to 75%, FEV1=forced expiratory volume in one second, FVC=forced vital capacity, RSS=respiratory symptom scale

Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Aztreonam	Use has not been studied in the elderly. Indicated for use in patient ≥7 years of age; safety and effectiveness has not been established for patients <7 years of age.	No dosage adjustment required.	No dosage adjustment required.	B	Yes; unlikely to pose a risk to infants due to low systemic absorption.
Tobramycin	Use has not been studied in the elderly. Indicated for use in patient ≥6 years of age; safety and effectiveness has not been established for patients <6 years of age.	Use has not been studied in patients with renal impairment; changes in renal function are expected to affect the exposure of tobramycin, including risks of increased or greater adverse reactions; there is not enough evidence to make a recommendation for or against renal dose adjustment.	Use has not been studied in patients with hepatic impairment; as tobramycin is not metabolized, an increased exposure to tobramycin is not expected.	D	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events[1-5]

Adverse Event (%)	Aztreonam	Tobramycin			
		TOBI®	TOBI Podhaler®	BETHKIS®	KITABIS PAK®
Abdominal pain	7	12.8	-	-	-
Anorexia	-	18.6	-	-	-
Asthenia	-	35.7	-	-	-
Asthma	-	15.9	-	-	-
Back pain	-	7.0	-	-	-
Bronchitis	-	-	-	3	-
Bronchospasm	5	-	<2	-	-
Chest discomfort	8	-	6.5	-	-
Chest pain	-	26.0	-	-	-
Cough	54	-	48.4	-	-
Cough, productive	-	-	18.2	-	-
Cough increased	-	46.1	-	-	46.1

Diarrhea	-	6.2	4.2	2	-
Dizziness	-	5.8	-	-	-
Dysgeusia	-	-	3.9	-	-
Dysphonia	-	-	13.6	6	-
Dyspnea	-	33.7	15.6	-	33.7
Ear pain	-	7.4	-	-	-
Eosinophilia	-	-	-	2	-
Epistaxis	-	7.0	2.6	3	-
Fever	-	32.9	-	-	-
Headache	-	26.7	11.4	-	-
Hemoptysis	-	19.4	13.0	-	19.4
Hyperventilation	-	5.4	-	-	-
Immunoglobulins increased	-	-	-	2	-
Laryngitis	-	-	-	-	≤5
Lower respiratory tract infection	-	5.8	-	-	-
Lung disorder	-	31.4	33.8	-	-
Lung function decreased	-	16.3	-	-	16.3
Malaise	-	6.2	-	-	-
Musculoskeletal chest pain	-	-	4.5	-	-
Myalgia	-	-	-	-	≤5
Nasal congestion	16	-	8.1	-	-
Nausea	-	11.2	7.5	-	-
Oropharyngeal pain	-	-	14.0	-	-
Pain	-	12.6	-	-	-
Pharyngitis	-	38.0	-	-	38.8
Pharyngolaryngeal pain	12	-	-	3	-
Pyrexia	13	-	15.6	-	-
Rash	2	5.4	2.3	-	5.4
Rales	-	-	7.1	19	-
Red blood cell sedimentation rate increased	-	-	-	8	-
Rhinitis	-	34.5	-	-	-
Sinusitis	-	9.2	-	-	-
Sputum discoloration	-	21.3	-	-	-
Sputum increased		37.6	-	-	37.6
Taste Perversion	-	6.6	-	-	6.6
Throat irritation	-	-	4.5	-	-
Tinnitus	-	3	-	-	≤5
Tonsillitis	-	-	-	2	-
Upper respiratory tract infection	-	-	6.8	-	-
Voice alterations	-	12.8	-	-	12.8
Vomiting	9	14.0	6.2	-	-
Weight loss	-	10.1	-	-	-
Wheezing	16	-	6.8	5	-

-Not reported

Contraindications

Table 7. Contraindications[1-5]

Contraindication	Aztreonam	Tobramycin
Allergy to aminoglycosides		a
Allergy to the medication or to any of its components	a	a

Warnings/Precautions

Table 8. Warnings and Precuations[1-5]

Warnings/Precautions	Aztreonam	Tobramycin
Allergic reactions, us caution in patients allergic to beta-lactam antibiotics	a	
Bronchospasm	a	a
Drug resistant bacteria may develop if used in the absence of *Pseudomonas aeruginosa*	a	
Fetal harm can result if used during pregnancy		a
FEV1 decreased after 28-day treatment cycle	a	
Muscular (neuromuscular) disorders		a
Nephrotoxicity		a
Ototoxicity		a

Drug Interactions

There are no documented, clinically significant drug interactions associated inhaled aztreonam (Cayston®); however, it has not been formally evaluated for drug-drug interactions.[1]

When using inhaled tobramycin it is recommended that concurrent and/or sequential use of other drugs that have neurotoxic, nephrotoxic or ototoxic potential be avoided due to increased risk for adverse effects. In addition, certain diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Therefore, use inhaled tobramycin should not be used concomitantly with ethacrynic acid, furosemide, urea or mannitol.[2-5]

Dosage and Administration

Dosing guidelines can be found in table 9 below.

Cayston® (aztreonam) inhalation solution should only be administered via an Altera® Nebulizer System while TOBI®, BETHKIS® and KITABIS PAK® (tobramycin) inhalation solution should only be administered via a PARI LC PLUS™ reusable nebulizer with a DeVilbiss Pulmo-Aid® compressor. Neither should be administered subcutaneously, intramuscularly, intravenously or intrathecally. TOBI Podhaler® (tobramycin) capsule for inhalation is for use with the Podhaler device. These capsules are not intended to be swallowed and should be used for inhalation use only. Administration via the Podhaler device is generally administered in two to seven minutes, while administrations via the nebulizer devices are two to three minutes for aztreonam or 15 minutes for tobramycin. If multiple inhaled therapies are being used, it is recommended that aztreonam or tobramycin is administered last (regardless of dosage form). For Cayston® (aztreonam), it is recommended that a bronchodilator be used between 15 minutes and 4 hours prior to each dose (or 30 minutes to 12 hours prior for long-acting bronchodilators). For TOBI Podhaler® (tobramycin), a new Podhaler should be used every seven days.[1-5]

Table 9. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Aztreonam	Management of cystic fibrosis patients with Pseudomonas aeruginosa: Inhalation solution: 75 mg (one single use vial) inhaled via nebulizer three times a day (taken at least four hours apart) for 28 days (followed by 28 days off therapy)	Management of cystic fibrosis patients with Pseudomonas aeruginosa (patients ≥7 years of age): See adult dosing	Inhalation solution: 75 mg
Tobramycin	Improve respiratory symptoms in cystic fibrosis patients infected with Pseudomonas aeruginosa: Inhalation solution: 300 mg inhaled twice daily via nebulizer for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Inhalation powder: Four 28 mg capsules (112 mg) inhaled twice daily via Podhaler device for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle	Improve respiratory symptoms in cystic fibrosis patients infected with Pseudomonas aeruginosa (patients ≥6 years of age): See adult dosing	Inhalation powder, capsule: 28 mg (TOBI Podhaler®) Inhalation solution: 300 mg/5 mL (TOBI®) 303 mg/5 mL (KITABIS PAK®) 300 mg/4 mL (BETHKIS®)

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013)**[8]	Aerosolized antibiotics · For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. · For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. · For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. · For patients with cystic fibrosis, six years of age or older, who have mild

Clinical Guideline	Recommendations
	lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. · For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. <u>Anti-inflammatory agents</u> · For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. · For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations is not recommended. · For patients with cystic fibrosis, between six and 17 years of age, with an forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended. · For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. <u>Antipseudomonal antibiotics</u> · For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations. <u>Antistaphylococcal antibiotics</u> · For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. · For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended. <u>Bronchodilators</u> · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life

Clinical Guideline	Recommendations
	or reduce exacerbations. · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. Hypertonic saline · For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. Ivacaftor · For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. Macrolide antibiotics · For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. · For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. Recombinant human DNase · For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.
Cystic Fibrosis Foundation: **Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009)**[9]	Initial Diagnosis · Treatment for infants diagnosed with cystic fibrosis should be done at an accredited cystic fibrosis care center, with the goal of an initial visit within 24 to 72 hours of diagnosis (one to three working days in absence of overt symptoms). · These recommendations are for children less than two years of age unless otherwise mentioned. Nutritional Recommendations *Pancreatic Function and Pancreatic Enzymes:* · Pancreatic functional status should be measured by fecal elastase or coefficient of fat absorption in all individuals. · Pancreatic enzyme replacement therapy should be started in: o All infants with two CFTR mutations

Clinical Guideline	Recommendations
	o All infants with fecal elastase < 200 µg/g or CFA <85% (in infants < 6 months of age), or other objective evidence o All infants with unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. · Pancreatic enzyme therapy should not be started in infants with one or two CFTR mutations associated with pancreatic sufficiency unless: o An objective test of pancreatic function indicates fat malabsorption; or o The infant has unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. · Pancreatic enzyme replacement therapy should be initiated at a dose of 2,000 to 5,000 lipase units at each feeding, adjusted up to a dose of no greater than 2,500 lipase units per kg per feeding with a maximum daily dose of 10,000 lipase units per kg. · Generic, non-proprietary pancreatic enzyme therapy should not be used. Nutritional Recommendations *Feedings, Vitamins and Micronutrients*: · Use human milk as the initial type of feeding. · If infants are fed formula, standard infant formulas (as opposed to hydrolyzed protein formulas) should be used. · Calorie-dense feedings should be used if weight loss or inadequate weight gain is identified. · Positive feedings behaviors should be encouraged, such as by the provision of educational resources. · For children aged 1 to 12 years with growth deficits, intensive treatment with behavioral intervention in conjunction with nutritional counseling be used to promote weight gain. · Multivitamins designed to provide at least the recommended levels of vitamins A, D, E and K for patients with cystic fibrosis should be prescribed, beginning shortly after diagnosis. · Blood levels of fat-soluble vitamins should be measured approximately two months after starting vitamin supplementation and annually thereafter; measure more frequently if values are abnormal. · A trial of zinc supplementation (1 mg elemental zinc/kg/day in divided doses for six months) may be given to some infants who are not adequately growing despite adequate caloric intake and pancreatic enzyme replacement therapy. · Supplementation with 1/8 teaspoon table salt per day starting at diagnosis, increasing to 1/4 teaspoon of table salt per day at six months of age. · Patients aged six months to two years whose community water supply contains less than 0.3 ppm fluoride should be supplemented with 0.25 mg/dl of fluoride. · There is insufficient evidence to recommend supplementation with linoleic acid or docosahexaenoic acid or to not recommend supplementation. Pulmonary Recommendations · A smoke-free environment should be provided and that all caregivers are informed that cigarette smoke exposure harms children with cystic fibrosis.

Clinical Guideline	Recommendations
	Pulmonary Recommendations *Airway Clearance*: · Airway clearance therapy should be initiated in the first few months of life. · Albuterol should be used before percussion and postural drainage. · Do not use the head-down position for percussion and postural drainage. Pulmonary Recommendations *Infection Control, Surveillance and Treatment*: · Newly diagnosed patients should be separated from other patients cared for in cystic fibrosis clinics until adequate infection control education has been provided to and is understood by the caregivers. · Infection control measures should be implemented in compliance with cystic fibrosis Foundation recommendations to minimize transmission of bacterial infections to infants. · Annual influenza vaccination is recommended for infants with cystic fibrosis >6 months of age, all household members, and all healthcare providers caring for these infants. o Household contacts and out-of-home caregivers of children with cystic fibrosis <6 months of age also should receive annual influenza vaccine. · Use of palivizumab should be considered for prophylaxis of respiratory syncytial virus. · Oropharyngeal cultures should be performed at least quarterly. · Bronchoscopy and bronchoalveolar lavage should be considered in infants with symptoms or signs of lung disease, particularly those who fail to respond to appropriate intervention. · It is not recommended to use prophylactic oral antistaphylococcal antibiotics in asymptomatic infants. · There is insufficient evidence to recommend for or against active attempts to eradicate *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* (MRSA) in asymptomatic infants in asymptomatic infants. · It is not recommended to use chronic antibiotics for prophylaxis to prevent *Pseudomonas aeruginosa*. · New acquisition of *Pseudomonas aeruginosa*, defined as initial acquisition or new acquisition after 'successful' eradication therapy, should be treated with anti-pseudomonal antibiotics and increased airway clearance, regardless of the presence or absence of symptoms. · Infants who remain persistently colonized with *Pseudomonas aeruginosa* after two attempts at eradication be treated chronically with alternate month tobramycin solution for inhalation. Pulmonary Recommendations *Diagnostic Testing*: · There is insufficient evidence to recommend for or against use of pulse oximetry routinely as an adjunctive tool to detect lung disease. · Pulse oximetry measurements be obtained in the infant with cystic fibrosis with acute respiratory symptoms. · A baseline chest x-ray should be obtained within the first three to six months and once again within the first two years of life.

Clinical Guideline	Recommendations
	· It is not recommended to use chest computed tomography CT scans for routine surveillance. · Chest CT scans be considered in infants with symptoms or signs of lung disease who fail to respond to appropriate interventions. · Infant pulmonary function tests should be considered as an adjunctive tool to monitor respiratory status. Pulmonary Recommendations *Chronic Pulmonary Therapies*: · Dornase alfa (recombinant human DNase) may be used in symptomatic infants. · In symptomatic infants, 7% hypertonic saline may be used. · There is insufficient evidence to recommend for or against the routine use of chronic azithromycin in patients colonized with Pseudomonas. · For infants with cystic fibrosis under the age of two years without airway reactivity or asthma, use of inhaled corticosteroids to improve lung function or reduce exacerbations is not recommended.
Clinical Practice Guidelines for Pulmonary Therapies Committee: **Cystic Fibrosis Pulmonary Guidelines: Pulmonary Complications: Hemoptysis and Pneumothorax (2010)**[10]	· This summary will focus on the treatment of respiratory complications of cystic fibrosis with antibiotic management only. Treatment of Hemoptysis with antibiotics · Patients with at least mild (≥5 mL) hemoptysis should be treated with antibiotics. · Antibiotics may not be needed in patients with scant hemoptysis but without other features of a pulmonary exacerbation. · For scant or mild-to-moderate hemoptysis, no aerosol therapies should be stopped; for massive hemoptysis, patients should stop aerosolized hypertonic saline. o No other specific recommendations can be made Treatment of pneumothorax with antibiotics · No consensus could be reached regarding the use of antibiotics in patients with a pneumothorax. o No recommendation could be made. o Antibiotics are needed in patients with a pneumothorax who are having a pulmonary exacerbation, but additional information may be needed to confirm the pneumothorax was caused by a pulmonary exacerbation before prescribing antibiotics.
American Academy of Pediatrics: **Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection (2014)**[11]	· This summary will focus on only the use of Palivizumab in patients diagnosed with cystic fibrosis Children with Cystic Fibrosis · Routine use of palivizumab prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present. · An infant with cystic fibrosis with clinical evidence of chronic lung disease and/or nutritional compromise in the first year of life may be considered for prophylaxis. · Continued use of palivizumab prophylaxis in the second year may be considered for: o infants with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life

Clinical Guideline	Recommendations
	or abnormalities on chest radiography or chest computed tomography that persist when stable), or o weight for length less than the 10th percentile.

Conclusions

The inhaled antibiotics used for patients with cystic fibrosis are aztreonam (Cayston®) and tobramycin (TOBI®; TOBI Podhaler®, KITABIS PAK®, BETHKIS®). Each medication is given for 28-day cycles (28 days on, 28 days off).[1-5] The Cystic Fibrosis Foundation recommends these inhaled antibiotics when chronic *P. aeruginosa* infection is present.[7] More evidence exists for tobramycin, and it is typically recommended first, depending on susceptibility testing. Even when the infecting bacteria are susceptible to both medications there are several reasons why aztreonam may be selected over tobramycin. These reasons including adherence issues (several minutes to administer aztreonam compared to 15 minutes for tobramycin) or pregnancy. Use of other neurotoxic, nephrotoxic, ototoxic drugs, certain diuretics and renal status should also be considered before starting tobramycin therapy.[7] There are no head-to-head trials comparing the different active ingredients, so superiority of one agent over the other cannot be determined. However, tobramycin capsules for inhalation were compared to tobramycin solution. There was no difference between the two in terms of safety and efficacy.[24] The Podhaler device allows for much faster administration (instantaneously) of the medication.[3] Currently, only tobramycin solution is available generically.

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