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REVIEW

The Use of Amikacin Liposome Inhalation Suspension (Arikayce) in the Treatment of Refractory Nontuberculous Mycobacterial Lung Disease in Adults

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Abstract: Nontuberculous mycobacteria (NTM) can cause and perpetuate chronic inflammation and lung infection. Despite having the diagnostic criteria, as defined by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA), clinicians find it challenging to diagnose and treat NTM-induced lung disease. Inhaled antibiotics are suitable for patients with lung infection caused by *Pseudomonas aeruginosa* and other organisms, but until recently, their utility in NTM-induced infection was not established. The most common NTM pathogens identified are the slow-growing *Mycobacterium avium* complex (MAC) and the rapid-growing *M. abscessus* complex (MABSC), both of which include several subspecies. Other less commonly isolated species include *M. kansasii, M. simiae*, and *M. fortuitum*. NTM strains are frequently more resistant than what is found in bacterial sputum cultures. Until recently, there was no approved inhaled antibiotic therapy for patients who were culture positive for pulmonary NTM infection. Of late, inhaled amikacin has been under investigation for the treatment of NTM-induced pulmonary infection. The FDA approved Arikayce (amikacin liposome inhalation suspension or ALIS) based on results from the ongoing Phase 3 CONVERT trial. In this study, the use of Arikayce met its primary endpoint of sputum culture conversion by the sixth month of treatment. The addition of Arikayce to guideline-based therapy led to negative sputum cultures for NTM by month 6 in 29% of patients compared to 8.9% of patients treated with guideline-based therapy alone. The effectiveness of Arikayce holds promise. However, due to limited data on Arikayce's safety, it is currently useful only for a specific population, particularly patients with refractory NTM-induced lung disease. Future trials must verify the target group and endorse the clinical benefits of Arikayce.

Keywords: Arikayce, amikacin liposome inhalation suspension, nontuberculous mycobacterium, *Mycobacterium avium* complex, *Mycobacterium abscessus* complex, aminoglycosides

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Introduction

Mycobacteria are aerobic, nonmotile, rod-shaped bacteria that are difficult to identify with Gram staining. Instead, the Ziehl-Neelsen stain is typically used to identify acid-fast organisms of the genus *Mycobacterium*. Due to their unique, impermeable cell walls, mycobacterial infections are difficult to treat. The ability of mycobacteria to form biofilms augments antibiotic resistance. Nontuberculous

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mycobacteria strains are found in water sources, soil, certain aerosols, animals, and food products.[1] These findings are due to the ability of these species to survive in high temperatures and environments with a relatively low pH.[1] Although growth rates within the Mycobacterium genus are generally slow, the variation in growth rates serves as the basis of their subdivision between fast-growing and slow-growing species.[3]

Mycobacteria are largely divided into three categories: *Mycobacterium leprae*, the bacterium that causes Hansen's Disease (ie, leprosy), *Mycobacterium tuberculosis* complex (MTC or MTBC), which includes species that cause tuberculosis, and NTM, which includes species that can cause pulmonary diseases that may clinically resemble tuberculosis. Unlike tuberculosis, NTM infections are not required to be reported. This further hinders exploration of the limited knowledge on NTM-induced lung disease. NTM infections can be opportunistic in nature, making it potentially dangerous for patients with a history of bronchiectasis, chronic obstructive pulmonary disease (COPD), and cystic fibrosis, and particularly lethal for immunocompromised patients such as transplant patients or patients with human immunodeficiency virus.[2,4]

Mechanism of Infection and Epidemiology

Currently, there are over 160 species of mycobacteria identified and the number continues to grow as new organisms are identified.[6] This is largely due to new molecular research techniques, particularly the ability to detect small changes in the highly conserved 16S rRNA gene among different species of mycobacteria.[7] The most common species associated with NTM-induced lung infections are the *Mycobacterium avium* complex (MAC), followed by *M. abscessus* complex (MABSC), and *M. kansasii*.[2,7] MAC and MABSC include several subspecies that are grouped together (ie complex) as they are difficult to differentiate. The most common species identified in human infections caused by MAC include *M. avium* and *M. intracellulare*.[8] In MABSC-induced infections in humans, the most common species identified are *M. abscessus* subsp. *abscessus, M. abscessus* subsp. *bolletti*, and *M. abscessus* subsp. *massiliense*.[9] This does not preclude other NTM species such as *M. gordonae* or *M. chelonae* from leading to lung infections.[2]

Unlike tuberculosis, NTM-induced infections are not considered to be contagious. However, recent evidence suggests person-to-person transfer among patients with cystic fibrosis.[11,12] Historically, NTM strains are isolated from natural sources such as water supplies and soil.[2,10] NTM strains are found in constructed sources such as bathroom showers and household water heaters where temperature settings are insufficient to kill the organism, thus leading to aerosolization of the organism that makes it capable of infiltrating alveoli.[2] Other sources of NTM contamination include hospital equipment such as bronchoscopes, endoscopes, and dialysis solutions, posing a significant risk for hospital-acquired infections.[2] A feature of NTM species that make them abundant in different environments is its hydrophobicity. A lipid-rich, hydrophobic outer membrane allows NTM species to prevail at water surfaces due to the air-water interfaces.[10] This hydrophobicity enables NTM species to become aerosolized and also aids in formation of biofilms.[10] In pulmonary infections, inhalation of aerosolized droplets contaminated with NTM is the likely mode of transmission.[2,12] The mechanisms of NTM-induced infection are similar to that of tuberculosis. Alveolar macrophages recognize and phagocytose the pathogens. Organisms then thrive intracellularly.[5] This process leads to an immune response that results in granuloma formation, a phenomenon that allows NTM strains to survive.[5,13] The consequences of tuberculosis infections (*M. tuberculosis*) are typically more severe and are characterized by cavitary lung disease that leads to increased mortality. It is important to note, however, that lung cavity formation is present in some rare cases of NTM infection.[5] The symptoms of NTM-induced pulmonary disease are variable, but nearly all patients present with a chronic or recurring cough.[29] Variable symptoms include fever, fatigue, increased sputum production, hemoptysis, dyspnea, chest pain, and weight loss.[29] Preexisting pulmonary diseases such as bronchiectasis, COPD, cystic fibrosis, and pneumoconiosis may impede patient evaluations for NTM-induced lung infection given that physical exam findings (eg, chest auscultation) are imprecise and variable due to the extent of a patient's underlying lung disease.[29]

The frequency of NTM-induced lung disease is increasing worldwide. Increases in incidence rates of NTM infection have occurred in North America,[14,15] South America,[16] Europe,[17–19] Asia,[20–23] Africa,[24–26] and Australia.[27] From a global perspective, more population-based data must be collected from differing geographic regions that connect clinical presentation to specific species of NTM. These studies will lead to a more thorough understanding of NTM infections. The most common species group associated with NTM-induced disease in North America and

East Asia is MAC.[28] Other species such as *M. kansasii, M. xenopi*, and *M.malmoense* are more common in Europe.[28] The current diagnostic criteria for NTM-induced lung disease by the ATS and IDSA involves chest radiographs or high-resolution computed chest tomography (HRCT). If no cavitation exists on chest imaging, three or more sputum analyses for acid-fast, bacilli bacteria should be sent while ensuring other conditions, such as tuberculosis, are excluded.[29] Unfortunately, due to limited data on other NTM species, these diagnostic criteria are only reliable for MAC, MABSC, and *M. kansasii*.[29] The ATS/IDSA guidelines for treatment of NTM-induced lung disease were released in 2007. Although the ATS/IDSA guidelines have been reaffirmed in recent years, new guidelines may be needed as new species of NTM are continually identified.

Treatment for NTM-Induced Lung Disease

Current treatments for NTM-induced lung disease involve a multidrug treatment regimen of antibiotics with possible surgical lung resection in very rare cases of cavitary disease.[30–32] The treatment goal is to maintain therapy until negative cultures are obtained for at least twelve months. Selection of antibiotics is dependent on many factors such as the species of NTM causing disease, severity of disease (cavitary vs nodular form or disseminated vs localized), patient age, immune status, and comorbidities.[42] Nonetheless, throughout the treatment regimen, assessments of the treatment's clinical benefit and financial burden on patients under treatment requires continual assessment. Additionally, treatment plans are not exact. Much of the currently published treatment plans are based on limited clinical trials and clinical judgement. Some of the current treatment strategies on the most common NTM species that cause pulmonary infections are summarized in Tables 1-3 below.

When using amikacin to treat NTM-induced lung disease, systemic toxicities and efficacy remain a concern. In recent years, aerosolized amikacin has been used in clinical settings to reduce systemic toxicities and to increase drug concentrations in endobronchial tissue. In a study conducted by Olivier et al (2014), patients treated with aerosolized amikacin showed microbiological and

Table 1 Treatment of *Mycobacterium avium* Complex (MAC) in the Lungs

Clinical Indication	Treatment Regimen	Duration of Therapy	Adverse Effects
Fibrocavitary form	Azithromycin 250–500 mg daily[29,31,40,43] *or* clarithromycin 1000 mg daily[29,31,40,43] and rifampin 450–600 mg daily[29,31,40,43] or rifabutin 150–300 mg daily[29,31] (or clofazimine 100–300 mg daily if intolerant to rifamycins[31]) and ethambutol 15 mg/kg daily*[29,31,40,43] Also, consider intravenous amikacin or streptomycin for up to 3 months[31] or inhaled amikacin for a minimum of 12 months after culture conversion.[29,31,43]	12 months post-culture conversion	Amikacin (inhaled): dysphonia and respiratory symptoms such as dyspnea and bronchiectasis exacerbation[42] Amikacin (intravenous): nephrotoxicity and ototoxicity[31,42] Azithromycin and clarithromycin: gastrointestinal irritation, ototoxicity, and QTc prolongation[31,42] Clofazimine: gastrointestinal irritation, skin discoloration with possible discoloration of secretions, and QTc prolongation[31,42] Ethambutol: optic neuritis and hyperuricemia[31,42] Isoniazid: hypersensitivity, hepatitis, and peripheral neuropathy[42] Moxifloxacin: tendinitis, tendon rupture, peripheral neuropathy, CNS effects, and QTc prolongation[42] Rifabutin: red/orange discoloration of secretions, gastrointestinal irritation, loss of taste, hypersensitivity, and uveitis[31,42] Rifampin: red/orange discoloration of secretions, gastrointestinal irritation, and hepatitis[31,42] Streptomycin: gastrointestinal irritation, ototoxicity[31]
Nodular bronchiectatic form	Azithromycin 500 mg TIW[29,31,40,43] or clarithromycin 1,000 mg TIW[29,31,40,43] and rifampin 600 mg TIW[29,31,40,43] or rifabutin 150–300 mg TIW[31] and ethambutol 25 mg/kg TIW*[29,31,40,43]	12 months post-culture conversion	
Macrolide-resistant form	Rifampin 450–600 mg daily[40,43] and ethambutol 15 mg/kg daily[40,43] and isoniazid 300 mg daily[40,43] or moxifloxacin 400 mg daily[40,43] Also, consider intravenous amikacin for up to 3 months[43] or inhaled amikacin for a minimum of 12 months after culture conversion.[40,43]	12 months post-culture conversion	

Notes: *Maximum dose of ethambutol per day: 2.4 g. Oral administration of drugs unless indicated.
Abbreviation: TIW, three times per week.

Table 2 Treatment of *Mycobacterium kansasii* in the Lungs

Treatment Regimen	Duration of Therapy	Adverse Effects
Isoniazid 300 mg daily[29,31,41,43] and rifampin 600 mg daily[29,31,41,43] and ethambutol 15 mg/kg daily*[29,31,41,43]	12 months of negative cultures post-culture conversion	Ethambutol: optic neuritis and hyperuricemia[31,42] Isoniazid: hypersensitivity, hepatitis, and peripheral neuropathy[31,42] Rifampin: red/orange discoloration of secretions, gastrointestinal irritation, and hepatitis[31,42]

Note: *Maximum dose of ethambutol per day: 2.4 g; Oral administration of drugs unless indicated.

symptomatic improvement. Patients were given amikacin sulfate 250 mg/mL which was diluted with 3 mL of saline and inhaled through a jet nebulizer. Patients were initially started at 250 mg daily and were instructed to titrate to twice daily if no dysphonia occurred after two weeks. If the patients were able to successfully increase dosing without dysphonia, they were instructed to maintain a dose of 500 mg twice a day.[36] Of the 20 patients who met entry criteria, 8 patients (40%) had at least one negative culture and 5 patients (25%) had persistently negative cultures during the study.[36] Furthermore, 9 patients (45%) showed a decrease in smear quantity and symptom scores improved in 9 patients (45%) during the study.[36] The study determined that aerosolized amikacin was associated with fewer toxicities when compared to systemic amikacin.

In another study conducted by Yagi et al (2017), 26 patients who were culture-positive for NTM-induced lung disease were recruited. Of the 26 patients, 23 patients were treated with aerosolized amikacin for at least 3 months.[44] Of the 23 patients, 21 out of 23 patients (91.3%) who were culture-positive for MAC were treated with aerosolized amikacin for at least 3 months and 2 out of 3 patients (66.7%) who were culture-positive for MABSC were treated with aerosolized amikacin for at least 3 months.[44] Ten of the 23 patients (43.5%) who received treatment for at least 3 months showed sputum conversion, which was defined as 3 consecutive months of negative cultures in this study.[44] Seven of the 23 patients (30.4%) showed improvement in HRCT imaging.[44] Severe adverse effects, such as renal toxicity, were not reported. One of the 26 patients (3.8%) reported tinnitus, but the symptoms were reversible after a brief

Table 3 Treatment of *Mycobacterium abscessus* Complex (MABSC) in the Lungs

MABSC Species	Treatment Regimen	Duration of Therapy	Adverse Effects
M. abscessus subsp. *massiliense*	Azithromycin 250 mg daily[29,31,43] or clarithromycin 1000 mg[29,31,43] and cefoxitin 2 g BID or TID IV for at least 2 months[31] or imipenem 500–1000 mg BID or QID IV[31] and amikacin 15–25 mg/kg IV TIW[31,43] Also, consider moxifloxacin 400 mg daily.[31]	12 months of negative cultures post-culture conversion	Amikacin (intravenous): nephrotoxicity and ototoxicity[31,42] Azithromycin and clarithromycin: gastrointestinal irritation, QTc prolongation, and ototoxicity[31,42] Cefoxitin: rash, neutropenia, and thrombocytopenia[31,42] Clofazimine: gastrointestinal irritation, skin discoloration with possible discoloration of secretions, and QTc prolongation[31,42] Imipenem: gastrointestinal irritation, seizures, rash, and cytopenia[31,42] Linezolid: myelosuppression, metabolic acidosis, peripheral neuropathy, and serotonin syndrome[31,42] Moxifloxacin: tendinitis, tendon rupture, peripheral neuropathy, CNS effects, and QTc prolongation[31,42]
M. abscessus subsp. *abscessus* or *M. abscessus* subsp. *bolletii*	Initially: clofazimine 100–300 mg daily[31] and cefoxitin 2 g BID or TID IV[31] and amikacin 15–25 mg/kg IV TIW[31] Then: clofazimine 100–300 mg daily[31] and amikacin 15–25 mg/kg IV TIW[31] and linezolid 600 mg BID[31]	12 months of negative cultures post-culture conversion	

Note: Oral administration of drugs unless indicated.
Abbreviations: BID, two times per day; TID, three times per day; QID, four times per day; TIW, three times per week; IV, intravenous administration.

halt in treatment, and the patient was able to successfully continue treatment.[44]

Nevertheless, due to limited data, aerosolized amikacin is used as salvage therapy among physicians. A big challenge in treating NTM-induced lung disease is refractory NTM-induced lung disease, defined as a failure to achieve negative sputum cultures after six or more months of a multidrug regimen. Recently, the FDA has approved Arikayce for the treatment of refractory NTM-induced lung disease.

Arikayce

Arikayce, also known as amikacin liposome inhalation suspension (ALIS), is a concentrated form of amikacin that is packaged into liposomes and delivered into the lung via aerosol nebulization.[33] The aminoglycoside amikacin is used to treat bacterial infections. Some of the more common aminoglycosides used in the United States include amikacin, streptomycin, gentamicin, tobramycin, and neomycin. Aminoglycosides are cationic in nature and bind to the anionic surfaces of bacterial cell walls.[33,34] Ionic interactions result in uptake of aminoglycoside molecules intracellularly where they act in bacterial cell cytoplasm.[33,34] Specifically, amikacin molecules bind to the 30S bacterial ribosome where it disrupts polypeptide chain elongation resulting in polypeptide mistranslation.[33,34] Out of all the aminoglycosides currently FDA-approved for human use, amikacin is considered to be the most resistant to aminoglycoside modifying enzymes that trigger antibiotic resistance.[34] However, beyond this molecular action, various mechanisms exist that confer antibiotic resistance to amikacin.[34]

Current Data on Arikayce

Although intravenous liposome-encapsulated amikacin is effective in treating NTM species such as *M. avium*, treatment of pulmonary *M. avium* infections by intravenous liposome-encapsulated amikacin provides only brief inhibition of bacterial proliferation before increases in bacterial growth occurs following completion of therapy.[35] Fewer toxic side effects of inhaled amikacin occur than during drug delivery through enteral or parenteral routes.[36] In NTM-induced pulmonary infections, inhalation of aerosol amikacin is a promising method of drug delivery. Zhang et al (2018) showed that aerosolization of liposome-encapsulated amikacin produces up to 274-fold higher amikacin levels in lung tissues, airways, and pulmonary macrophages when compared to intravenous amikacin in rat models.[45] Confocal microscopy has revealed that liposomal amikacin penetrates and kills MAC biofilms.[45] Inhalation of unencapsulated amikacin alone is less effective compared to liposome-encapsulated amikacin, indicating liposomal delivery to be therapeutically superior.[45]

In the Phase 3 CONVERT clinical study conducted by Griffith et al (2018), treatment of refractory MAC-induced lung disease with aerosol liposome-encapsulated amikacin showed promise. In this study, 336 patients with refractory MAC-induced lung disease (as defined by ATS/IDSA guidelines) from North America, East Asia, and Europe were enrolled.[37] Of the 336 patients, 112 were assigned to guideline-based therapy (GBT) that included a three-drug regimen consisting of a macrolide, ethambutol, and rifamycin. The remaining 224 patients were assigned to aerosol liposome-encapsulated amikacin and GBT (ALIS + GBT). The mean age of patients enrolled was approximately 64.7 years. Female patients were predominant in this study at 69.3% of patients. Many of the enrolled patients had underlying lung disease such as bronchiectasis (62.5%), COPD (14.3%), or both (11.9%). The primary endpoint of this study was to achieve culture conversion by month 6 of treatment. To meet the primary endpoint, culture conversion, defined as three consecutive months of negative cultures, was required by month four of treatment. Those who remained culture-negative by month 6 were allowed to continue treatment for an additional twelve months from the month that first culture conversion was achieved. Patients were kept under observation for twelve months following completion of treatment regimens. Failure to achieve culture conversion by month 6 resulted in conclusion of study for patients at month eight. Some patients were eligible for an open-label extension study. Secondary endpoints at sixth months of treatment included: 1) 6-minute walk distance compared to baseline 6-minute walk distance, 2) time to culture conversion, and 3) changes from baseline of St. George's Respiratory Questionnaire scores. A nebulizer was used to administer approximately 70% liposome-encapsulated amikacin and 30% free amikacin in the ALIS + GBT group. This was due to the fact that upon nebulization, ALIS liposomes released some free amikacin while delivering liposome-encapsulated amikacin. Parenteral administration of amikacin or streptomycin resulted in disqualification from the study. Patients with bronchospasm were allowed to receive a bronchodilator prior to administration of ALIS. Emergent events were monitored by the investigators.

In this investigation, the primary endpoint of culture conversion by month 6 was achieved in 65 of 224 patients (29%) treated with ALIS + GBT. Only 10 of 112 patients (8.9%) in the GBT group achieved the primary endpoint (odds ratio: 4.22; 95% confidence interval: 2.08–8.57; $P < 0.001$). Patients in the ALIS + GBT group exhibited higher sputum culture conversion rates than the GBT group (hazard ratio: 3.90; 95% confidence interval: 2.00–7.60). The difference between baseline 6-minute walk distance and the sixth month 6-minute walk distance was insignificant in both groups. Patients with culture conversion showed improved in 6-minute walk distance when compared to patients without culture conversion (16.8 meters vs −7.9 meters; $P = 0.011$), indicating improved physical health. The St. George's Respiratory Questionnaire scores trivial differences favored the GBT group, but due to confounding variables and a lack of validity of use of this questionnaire in NTM-induced lung disease, questionnaire scores were not considered reliable. Follow-up studies by Griffith et al (2019) revealed that of the 65 patients in the ALIS + GBT group who achieved the primary endpoint of culture conversion, 52 of those patients (80%) maintained culture conversion at the end of their treatment regimen and 41 of those patients (63%) maintained culture conversion three months after completing their treatment regimen.[38] Importantly, in comparison to the 10 patients who successfully achieved culture conversion in the GBT group alone, only 3 patients (30%) maintained culture conversion at the end of their treatment regimen. None of these patients maintained culture conversion three months after completing treatment.[38]

The outcomes from the trials discussed previously are encouraging. However, the trials mentioned earlier focus only on *M. avium* complex infections. Recently, Siegel et al (2019) studied the efficacy of ALIS in treating MABSC-induced lung infections. In this study, 32 patients with MABSC-induced lung infection were recruited of which 30 patients received ALIS + GBT for 4 months or greater. Two patients withdrew 3 months into the study as they could not tolerate the drug. The average age of patients enrolled was approximately 53 years (range: 14, 81 years).[39] The primary endpoint of this study was to achieve culture conversion, defined as 3 consecutive months of culture conversion by month 12 without reversion. Among the 8 cystic fibrosis patients enrolled, 2 patients (25%) converted without culture reversion while 1 patient (12.5%) converted but reverted in later cultures. Among the 24 non-cystic fibrosis patients enrolled, 1 patient (4.2%) converted without reversion and 3 patients (12.5%) converted but reverted in later cultures. Overall, 6 out of 32 patients (18.75%) who received aerosol liposome-encapsulated amikacin for 6 months met sputum conversion criteria. However, half of these patients reverted during the treatment regimen. Although the sample size in Siegel's trial was small, the results indicate that treatment of MABSC-induced lung disease is historically difficult. Another limitation of this study was the lack of distinction between refractory and newly diagnosed patients with MABSC-induced lung disease.

Adverse Effects

In the CONVERT trial by Griffith et al (2018), *treatment-emergent adverse effects* (TEAEs) were documented. Of the 224 patients in the ALIS + GBT group, 219 patients (98.2%) experienced TEAEs.[37] In the GBT alone group, 102 of the 112 patients (91.1%) had frequent TEAEs. The most common TEAEs reported in both groups were respiratory events (87.4% in the ALIS + GBT group and 50% in the GBT group). TEAEs leading to death occurred in 6 of the 224 patients in the ALIS + GBT group (2.7%), and 5 of the 112 patients (4.5%) sustained fatalities in the GBT alone group. TEAEs such as dysphonia, cough, hemoptysis, dyspnea, fatigue, diarrhea, nausea, and oropharyngeal pain were more common in the ALIS + GBT group than the GBT alone group. The frequency of such symptoms declined significantly in both groups following the first month of treatment. Nephrotoxicity was deemed infrequent in both groups and adverse effects to systemic exposure of amikacin were also uncommon. Audiologic TEAEs, such as tinnitus, were reported to be similar in both groups. Although adverse effects due to treatment were also recorded in the study conducted by Siegel et al (2019), comparisons to the CONVERT trial are difficult given the small sample size in Siegel's study.

Conclusion

ALIS is a novel but promising treatment option for patients with refractory NTM-induced lung disease. Inhalation of liposomal-encapsulated amikacin indicates improved drug delivery while reducing systemic toxicities. However, currently available data for treatment of refractory NTM lung infections worldwide remains scarce. Multicenter trials must be conducted in countries where refractory NTM lung infections are common in order to understand the treatment efficacy of liposome-encapsulated amikacin administered by aerosol. Due to the limited amount of data, future trials must attempt to verify results of prior studies such as the CONVERT trial. As with any antibiotic, resistance remains a particular concern. New trials and upcoming research must evaluate the risk of antibiotic resistance which may occur with liposome-encapsulated amikacin administered by aerosol. Nonetheless, as the frequency of NTM-induced lung infections increases globally, aerosol administration of liposome-encapsulated amikacin is a refreshing newcomer and is one that may improve the lives of patients suffering from NTM-induced lung disease.

Disclosure

Omer Khan works as a research volunteer with Dr. Chaudary. Dr. Chaudary is an Associate Professor of Medicine and Director of the Adult Cystic Fibrosis Center at Virginia Commonwealth University Medical Center. Dr. Chaudary reports grants from CF Foundation, advisor for PARI Advisory Board, peer connect PV consultant for PARI PV Briefing, and provided CME talk for Abcomm. The authors report no other conflicts of interest in this work.

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