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# ALIS (Amikacin Liposome Inhalation Suspension): The Beginning of a Wonderland?

*When I used to read fairy tales, I fancied that kind of thing never happened, and now here I am in the middle of one!*
*—Alice in Wonderland*

Fairy tales do come true. Once upon a time, 1868 to be exact, someone noticed that chickens developed "tuberculosis" (1). The cause of this disease was an "avian" mycobacteria. Probable human cases of "avian tuberculosis" were reported as early as the late 1880s. However, it was not until the 1930s that the causative strains were identified as human pathogens (1–3), and by 1942, only 25 cases of human avian tuberculosis had been reported (4, 5). Eventually, these causative organisms were identified as *Mycobacterium avium* (6), followed by identification of *Mycobacterium intracellulare* in 1949 (7). Today, these organisms, as well as at least 10 other species (8), are collectively referred to as *Mycobacterium avium* complex or MAC.

Early experience with treating MAC pulmonary disease was fraught with failure (9). It was not until the availability of macrolides that we began to see improvement in treatment outcomes (10). However, even today, treatment success rates average only 66% among patients with macrolide-susceptible disease who take the American Thoracic Society recommended regimen (9) for at least a year (10). When patients fail therapy, we have few options for treatment. We can continue the current treatment regimen in hopes of slowing progression, try to "strengthen" the regimen by adding additional antibiotics (none of which are approved for treatment of MAC), offer surgical resection, or simply stop treatment and hope for the best.

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Enter the Mad Hatter to the rescue. The study (CONVERT) by Griffith and colleagues (pp. 1559–1569) in this issue of the *Journal* reports the results of a phase III randomized, controlled, open-label trial of a novel formulation of inhaled amikacin referred to as amikacin liposome inhalation suspension (ALIS) (11). Adults with amikacin-susceptible MAC pulmonary disease who had sputum cultures positive for MAC despite at least 6 months of stable guidelines-based therapy (GBT) were randomly assigned to receive once-daily ALIS plus GBT versus GBT alone. The primary endpoint of the trial was culture conversion, defined as three consecutive monthly MAC-negative cultures by Month 6.

This multicenter study enrolled 336 patients (11). Culture conversion was achieved by 65 of 224 patients (29.0%) with ALIS plus GBT compared with 10 of 112 (8.9%) with GBT alone (odds ratio, 4.22; 95% confidence interval, 2.08–8.57; $P < 0.001$). These results are remarkably similar to the phase II trial that reported culture conversion status at Day 84 of treatment (12). Although culture conversion is a laudable goal for treatment of any infectious disease, there were no significant differences between arms in terms of patient-reported outcomes on the St. George's Respiratory Questionnaire and no difference between treatment arms in change in 6-minute-walk distance (unlike in the phase II trial) (12).

The bacteriologic success of ALIS plus GBT is all the more notable when you consider who was enrolled into the study. Although inclusion criteria required at least 6 months of prior therapy, patients had been on treatment for much longer, averaging more than 3 years. Moreover, the primary endpoint required that subjects who converted cultures by 6 months had to have done so by Month 4 and then have at least nine negative cultures before they could be considered to have reached the primary endpoint. Both trials demonstrated something that had not been heretofore quantified: if you continue treating with the

same initial regimen, culture conversion occurs in only 9% of patients. If nothing else, these studies should drive us to find better ways to treat out patients.

Not all is wonderful in Wonderland, however. Adverse reactions were very common and occurred in more than 90% of subjects in each arm. In the ALIS plus GBT arm, 82.5% of treatment-emergent adverse events (TEAEs) were considered ALIS related by the investigator, and 17.4% of patients had TEAEs leading to discontinuation of ALIS. TEAEs reported in 10% or more of patients in the ALIS plus GBT arm included dysphonia, cough, hemoptysis, dyspnea, fatigue, diarrhea, nausea, and oropharyngeal pain. All were more frequent with ALIS plus GBT than with GBT alone excluding hemoptysis, which occurred at similar rates in both arms. However, these events infrequently led to early discontinuation of ALIS (dyspnea, 3.1%; dysphonia, 2.2%; all others, <1%) or withdrawal from the study. Audiological TEAEs were generally similar in both arms although tinnitus was reported in 17 patients (7.6%) in the ALIS plus GBT arm compared with one event (0.9%) in the GBT arm. Serious TEAEs were reported in 45 patients (20.2%) and 20 patients (17.9%) in the ALIS plus GBT and GBT-alone arms, respectively.

On the basis of the results of this study and those from the previous trials, the U.S. Food and Drug Administration approved ALIS for treatment-refractory MAC pulmonary disease on Friday, September 18, 2018 under a novel mechanism, Limited Population Pathway for Antibacterial and Antifungal Drugs. This is more than a century after the chickens developed tuberculosis and humans were reported with avian tuberculosis. Why has it taken so long to get an approved drug for treatment of MAC pulmonary disease? There are many reasons for this delay, including the lack of recognition that MAC was a significant pulmonary pathogen in humans, the poor understanding of the epidemiology of disease, and a general lack of funding for research. Things are changing. In North America, the prevalence of nontuberculous mycobacterial pulmonary disease is increasing at extraordinary rates, while the number of tuberculosis cases has reached an all-time low and continues to decrease (13, 14).

*Would you tell me, please, which way I ought to go from here?*
*—Alice in Wonderland*

Although we are not yet in a Wonderland of new drugs for MAC, a small pipeline is developing that includes novel antimicrobials as well as host-directed therapies (15). The novel approval pathway for ALIS marks a milestone for spurring drug development targeting infections that lack effective therapies. However, the challenge for ALIS, as well as for subsequent drugs entering this space, will be to identify clinical correlates to microbiologic outcomes that demonstrate improvement in quality or quantity of life. As new agents move into clinical stages of development, there is likely to be a bottleneck, given the limited number of patients eligible for clinical trials. Stakeholders will need to work together in a coordinated fashion using novel trial designs to overcome the impending bottleneck. We hope this is just the beginning or our tale, and we will follow the advice of the Mad Hatter when he told Alice that something is impossible "only if you believe it is." ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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# Amyloidosis by Bacterial Infection in Critically Ill Patients?

Amyloid disorders comprise various diseases that are characterized by the formation and deposition of amyloid fibrils in affected tissues (1). Amyloid fibrils in a given disease and subcellular localization consist of a particular protein that misfolds into β-sheet–rich structures and thereby assembles by the thousands into elongated fibrils. Using electron microscopy, amyloid fibrils are readily visible and appear as unbranched filaments of several micrometers in length, with diameters of approximately 10 to 12 nm. The most common amyloid disease is Alzheimer's disease, a progressive neurodegenerative disorder that affects certain regions of the brain in which Aβ peptides deposit as amyloid fibrils in the extracellular space (β-amyloid plaques) and tau proteins aggregate into so-called "neurofibrillary tangles" in the cytoplasm of neurons (2). Smaller assemblies of Aβ and tau proteins, so-called oligomers, are also believed to contribute to the disease, although these species remain ill defined (3). Alzheimer's disease typically occurs at an older age and has a presymptomatic phase of more than 15 years, during which Aβ and tau deposits form and accumulate in significant amounts. This phase is followed by progressive neurodegeneration and cognitive decline over many years (2).

Neurological dysfunction and cognitive impairment are also frequently observed in survivors of critical illnesses that require treatment in the ICU and are now recognized as part of the post–intensive care syndrome (4).

In this issue of the *Journal*, Lin and colleagues (pp. 1575–1578) raise the hypothesis that cognitive impairment in post–intensive care syndrome might be related to Aβ and tau oligomer formation they attribute to nosocomial pneumonia in these patients (5). This hypothesis is derived from isolated observations in a small pilot study ($n = 4$ patients with nosocomial pneumonia, $n = 3$ uninfected patients) but could have far-reaching implications if verified independently in a larger cohort.

The authors report that supernatant prepared from lung endothelial cells infected *in vitro* with bacteria (*Klebsiella pneumoniae* or *Staphylococcus aureus*) isolated from BAL fluid of intubated patients with nosocomial pneumonia exhibits toxicity, as shown by the induction of gap formation in cultured brain endothelial cells (5). This effect was neutralized by preincubation with antibody A11 (a polyclonal antibody that is believed to recognize a generic epitope common to prefibrillar oligomers made of Aβ and other amyloidogenic proteins [6]) and polyclonal anti–tau oligomer antibody T22 (7), suggesting the presence of such oligomers in this preparation. In a separate experiment, similarly prepared supernatant from lung endothelial cells infected with laboratory strains of *Pseudomonas aeruginosa* impaired long-term potentiation in *ex vivo* electrophysiology assays and was dependent on the bacteria possessing an intact type 3 secretion system. A11 antibody was again able to neutralize this effect, whereas impairment of long-term potentiation was retained in the A11 eluate. Lin and colleagues also report that cerebrospinal fluid of patients with nosocomial pneumonia impairs long-term potentiation in rodent hippocampal slices and appears to contain Aβ and tau species that can be immuno-isolated and whose toxicity can be neutralized with the A11 antibody (5). These Aβ and tau species were absent or less prominent in cerebrospinal fluid samples obtained from uninfected intensive care patients.

These findings led the authors to propose a model in which bacterial pneumonia in critically ill patients induces the formation and release of A11- and T22-positive oligomers (presumably Aβ and tau oligomers, although more detailed assessment is needed) from lung endothelial cells that could presumably travel in the blood to the brain, where these oligomers could disrupt the brain endothelial barrier and may ultimately lead to neuronal dysfunction and cognitive impairment. In this scenario, it is conceivable that the cytotoxic oligomers persist and spread in the brain even after the initial pneumonia was overcome and continue to elicit a progressive proteinopathy and cognitive impairment.

In this regard, it is intriguing that Aβ has recently been reported to exhibit antimicrobial activity, although this remains controversial (8–10). Oligomerization of Aβ peptides seemed critical for this effect and appeared to protect against various fungal and bacterial infections in mouse, nematode, and cell culture models of Alzheimer's disease. Similarly, Alzheimer's disease brain homogenates inhibited growth of *Candida albicans* more than control brain homogenates. Binding of soluble Aβ oligomers to microbial cell wall carbohydrates via a heparin-binding domain was proposed as a model that would inhibit or diminish pathogen adhesion to host cells. Aβ oligomer and protofibril formation was suggested to also mediate agglutination and eventually entrapment of unattached microbes. However, this could be a two-edged sword, because accelerated Aβ plaque deposition and associated pathology was also observed in a mouse model of Alzheimer's disease infected with *Salmonella typhimurium* (8). This is an intriguing scenario, although it is currently unclear how this aligns with the complex proteolytic processing of the amyloid precursor protein (APP) that normally occurs in neurons and generates relatively small amounts of Aβ peptides relative to other APP fragments and how it relates to APP/Aβ's likely involvement in synaptic function (11). No direct antimicrobial activity has been reported for tau aggregates.

It should not go unnoticed though that all four of the pneumonia-affected patients and two of the noninfected patients had vascular or traumatic brain injury and required an external ventricular drain. The third noninfected patient had ventriculoperitoneal shunt failure. Traumatic brain injury can elevate Aβ and tau levels in the cerebrospinal fluid including oligomeric forms and is likely related to the underlying axonal

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