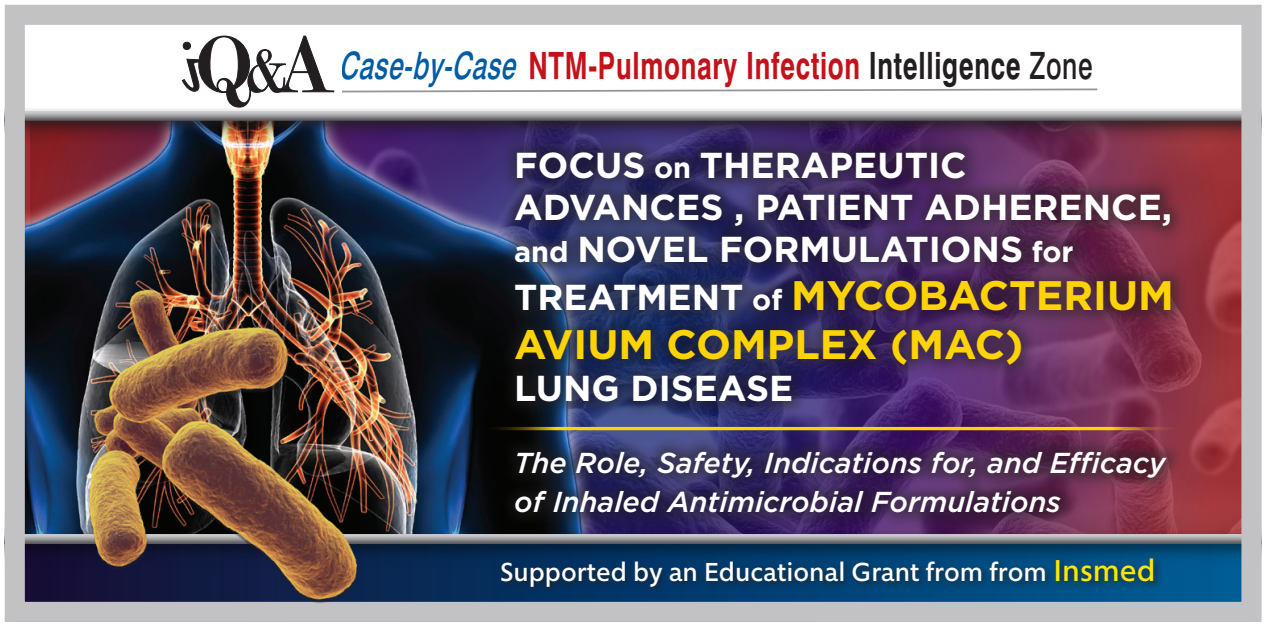
FOCUS on the THERAPEUTIC ADVANCES, PATIENT ADHERENCE, and NOVEL FORMULATIONS for TREATMENT of MYCOBACTERIUM AVIUM COMPLEX (MAC) LUNG DISEASE

The Role, Safety, Monitoring, Regimen Adherence Dimensions, and Trial-Based Evidence Supporting the Efficacy of Inhaled Antimicrobial Formulations—A Science-to-Best Practice Update for the Front Lines of **Pulmonary and Infectious Disease Management of MAC Lung Disease**



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QUESTION #1: What are the diagnostic challenges associated with MAC lung disease, what is the latency period between symptom onset and diagnosis, what is the disease burden as we understand it; and finally, what is the geographical distribution of this infection in the United States?

QUESTION # 2: What are the clinical phenotypes and variable presentations of MAC lung disease that practitioners should be aware of to ensure that patients who have NTM pulmonary disease are diagnosed in timely fashion? And how should such patients be evaluated when this infection is suspected?

QUESTION # 3: With respect to the patient who has bronchiectasis as a risk factor for MAC lung infection, how are these patients evaluated? In particular,what radiographic findings suggest the presence of MAC, and how do you risk stratify these individuals for alignment with specific therapeutic/antimicrobial interventions and dosing schedules?

QUESTION # 4: What novel dosing schedules and combination regimens are being investigated for oral agents commonly deployed and guideline-endorsed to treat MAC lung disease?

QUESTION # 5: Given the heterogeneous clinical profiles and presentations for NTM pulmonary disease what radiographic or other symptomatic criteria do you use to determine which individuals with culture positivity for MAC lung disease should be treated and which patients are suitable for a "watch, wait, and monitor" strategy? What is your current algorithm for making this determination?

QUESTION # 6: Which subgroup of patients with MAC lung disease, based on their radiographic findings and symptoms, are likely to manifest clinical improvement with oral antimicrobial therapy? And what role does their underlying co-morbid condition play in predicting response to therapy?

QUESTION # 7: How frequently should microbiological sampling—whether by sputum or bronchoscopy—be performed in patients with MAC culture positivity who are being treated with antimicrobial therapy? What is your treatment algorithm as it relates to sputum sample culturing at the front lines of treating MAC lung disease?

QUESTION # 8: What are the clinical triggers and/or ATS/IDSA guidelines that would prompt you to reach into your anti-infective toolkit and use amikacin for MAC lung disease, in either an IV or liposome aerosol suspension formulation? When do you deploy this agent from the outset, how do you monitor its side effects, and how do you dose this medication? And what is the role, evidence and rationale, based on the CONVERT trial for the amikacin liposome inhalation suspension?

QUESTION # 9: Once the decision is made to deploy amikacin in a patient with refractory MAC lung disease, what do we know about the problematic/toxicity/adherence and side effect pitfalls of IV amikacin? How problematic are these and how has the availability of the amikacin liposome inhalation suspension helped to potentially mitigate these barriers to optimizing use of this antimicrobial, based on results of the CONVERT trial?

QUESTION # 10: How have the results of the CONVERT trial and other studies, which have examined the safety and efficacy of amikacin liposome inhalation suspension, and other mechanistic/penetration features of this formulation, influenced your decision-making as it regards selecting an amikacin-based formulation at the front lines of treating MAC lung disease?

QUESTION # 11: When should the clinician suspect antimicrobial resistance in the setting of MAC lung disease? How is this confirmed?

QUESTION # 12: Are there any postulated strategies for preventing NTM pulmonary disease?

QUESTION # 13: What is your approach to MAC lung disease patients who fail to microbially convert despite intensive oral anti-infective therapy?

QUESTION # 14: Based on the current IDSA/ATS guidelines and recent clinical trials, including CONVERT that have investigated a new inhaled formulation of amikacin, what do you see as the most important advances in our understanding of NTM pulmonary disease, in particular, with respect to refractory MAC lung disease?

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QUESTION #15: Given the complexity, increasing recognition/prevalence and suboptimal understanding of MAC lung disease, can you summarize for us the disease burden, epidemiology, risk factors, and unmet needs for this infectious condition?

QUESTION #16: Which geographical regions of the U.S. is MAC lung disease particularly prevalent and what are the recognized risk factors? And why do some people acquire the infection while others do not?

QUESTION #17: Why is MAC lung disease, as a general rule, under-diagnosed and how can clinicians improve recognition of NTM pulmonary infection?

QUESTION #18: Based on the ATS and IDSA guidelines for ATM lung disease, what clinical symptomatology, microbiologic evidence, and/or radiographic findings should alert the clinician that the diagnosis of MAC lung disease should be considered and that the patient should be evaluated for this infection?

QUESTION #19: In a patient encounter in whom you suspect MAC lung infection, what is the preponderance of evidence and symptomatology you require to initiate antimicrobial therapy for NTM lung disease? Do all patients with MAC lung disease require treatment? Who does and who doesn't? Why or why not?

QUESTION #20: What is your protocol for establishing microbiological confirmation of MAC lung disease? How do you obtain samples and evaluate their quality? And what kind of samples do you obtain? How do you interpret the culture results?

QUESTION #21: What other conditions do you need to consider in patients referred to you for evaluation of NTM pulmonary disease? And what is the indication for bronchoscopy?

QUESTION #22: Do all patients with radiographic and microbiological confirmation of MAC lung infection receive and/or require antimicrobial therapy? Based on what clinical and/or radiographic and/or microbiological criteria should treatment be initiated? And what are the consequences of delaying treatment?

QUESTION #23: What percentage of your patients with culture-proven MAC lung disease are treated? And why do you withhold treatment in some cases?

QUESTION #24: Are there specific radiographic findings—cavities, diffuse nodules, or expansion of pulmonary nodules—or other triggers in patients with culture-positive MAC lung disease that rise to the level of actionability with respect to initiation of antimicrobial therapy?

QUESTION #25: What are the current expert- and consensus-based guidelines for initial anti-infective treatment of MAC lung infection? Are they current and are their variations that accepted by pulmonary or infectious disease experts?

QUESTION #26: How do you intensify therapy in patients with MAC lung disease who have more advanced disease or disease that is demonstrated to be refractory to the initial three-drug regimen? What is the role of amikacin and for how long should amikacin therapy be administered if indicated?

QUESTION #27: What strategies do you use to optimize tolerability of anti-MAC regimens? Do you ever deploy agents sequentially, or at lower doses, or reduced frequency, and if so, why? And for how long? How successful is this approach? Do you check drug levels?

QUESTION #28: How do you monitor patients with MAC lung disease over the long term, and how do you make modifications to address poor drug tolerability? And how do you monitor the success, or lack thereof, of the antimicrobial treatment regimen? And what is the role of repeat cultures as a guide to therapy?

QUESTION #29: How do you approach patients with MAC lung disease who are "treatment refractory" to their initial drug regimen?

QUESTION #30: When the patient shows progressive, symptomatic or radiographic disease, or the lack of antimicrobial conversion confirms treatment refractoriness with oral therapy, and amikacin is being considered for intensifying treatment for MAC lung disease, how do you decide between deployment of systemic IV amikacin and the liposome inhaled suspension of amikacin? What are the potential mechanistic or side effect-related advantages of the inhaled amikacin formulation?

QUESTION #31: What is the role of "adjunctive therapy"—that is, methods that should be used in addition to antibiotic-based treatment for MAC lung disease?

QUESTION #32: Once you have determined—based on the need to: (a) treat MAC-induced cavitary lung disease aggressively as an initial approach, or (b) address standard treatment-refractory disease—that amikacin is the appropriate intervention, what FDA-approved formulation of this antimicrobial do you consider? And how do the MOA and side effects differ between these options and does the MOA of the liposome inhaled suspension confer potential advantages? Which route do you prefer and when?

QUESTION #33: What is the evidence that the MOA—tissue penetration, intracellular tropism of the antibiotic, concentration in macrophages—of amikacin liposome inhalation suspension that you discussed previously translates into improved clinical outcomes in patients with MAC lung disease? Does this formulation address an important unmet need?

QUESTION #34: If we know that MAC-associated cavitary lung disease is a marker of poor outcomes and/or refractory disease at the time of initial presentation, what is the rationale for waiting before deploying the amikacin liposome inhalation suspension, even though this formulation is currently FDA-approved specifically for treatment refractory disease?

QUESTION #35: Given your experience with and positioning of amikacin liposome inhalation suspension in the setting of early severe and/or treatment refractory MAC lung disease, can you discuss the trial design, evidence, efficacy, rigor, safety, results, and clinical applications of the CONVERT trial?

QUESTION #36: What new advances in treatment—including the availability of amikacin liposome inhalation suspension—and other best practice innovations are positively reshaping our approach to managing MAC lung disease and helping reduce its considerable burden?

QUESTION #37: How do we optimize the clinical benefit of our current treatment regimens and what strategies do you recommend for making patients more adherent and improving tolerability of medications used for MAC lung disease?

QUESTION #38: As you've discussed, given the proven efficacy and need for effective and safe therapies such as amikacin liposome inhalation suspension for MAC lung disease, what clinical strategies do you recommend for optimizing regimen adherence, patient satisfaction, and tolerability for this formulation and route of administration?

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QUESTION #39: What data and experience have been accumulated over time that explain why NTM pulmonary infection has now become recognized as a significant disease problem with a formidable disease burden and unmet therapeutic needs?

QUESTION #40: What is the epidemiology of MAC lung disease and why is it important that clinicians are aware of the specific geographic and prevalence patterns that characterize and account for our increased recognition of NTM disease?

QUESTION #41: What do MAC lung patients look like? How do they present and what are both the typical and unusual clinical signatures that suggest need for further evaluation, including microbial confirmation?

QUESTION #42: What are the sequential steps—radiographic assessment, bronchoscopy, and microbial sampling, in particular—that constitute the workup of individuals suspected of NTM pulmonary infection? What are the pitfalls of sputum sampling and how do we overcome them?

QUESTION #43: Can you take us through the full spectrum of microbiological testing for NTM and MAC lung disease, emphasizing the specific tests required to confirm the diagnosis and the specific causative pathogens; and how and when such microbiological testing should be continued throughout the treatment course until cure or treatment refractoriness is established?

QUESTION #44: What clinical, microbiological, and radiographic triggers do you need in an individual with MAC lung infection to embark on anti-infective treatment? How often do you see patients with NTM disease and how do you make the decision to treat or monitor a patient, especially one with worsening of symptoms?

QUESTION #45: Given the tolerability issues associated with the currently applicable—although last issued in 2007—treatment guidelines for NTM lung disease, how do you sequence and titrate therapy in patients you commit to anti-infective treatment?

QUESTION #46: How long should treatment be continued with three-drug oral therapy before the regimen is considered to be successful or whether lack of culture conversion suggests intensification with amikacin is indicated?

QUESTION #47: How do you navigate the multiple branch points of guideline-endorsed therapy for MAC lung function? And how do you make modifications in dosing frequency, and in what patients do you consider such changes?

QUESTION #48: When does the accumulated clinical data—i.e. cavitation, symptom severity, etc.—support the use for amikacin, either systemically or with the inhaled liposome suspension, for MAC lung disease? And when do the mechanistic, drug delivery, convenience, and toxicity advantages of the liposome-based formulation of amikacin—as well as the evidence from clinical trials—support its preferential use in selected subgroups of patients with MAC lung disease?

QUESTION #49: Can you summarize your current perspective on advances in the treatment of MAC lung disease and what your position is on amikacin liposome inhalation suspension in patients who require intensification beyond three-drug oral treatment?

QUESTION #50: Given the complex clinical decision tree for NTM lung disease, what is your best counsel for how to optimize clinical outcomes across the severity range for this increasingly recognized pulmonary infection?

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QUESTION #51: Why we do need to have a heightened index of suspicion for recognizing patients who may have NTM lung disease? And what have we learned, specifically, about epidemiology, transmission, environmental sources, biofilm formation, exposure patterns, and clinical signatures for MAC, that help us identify patients with NTM infection and implement anti-infective therapy?

QUESTION #52: What are the specific regional and environmental differences in incidence and prevalence in the U.S. for NTM pulmonary infection; and for MAC lung disease, in particular?

QUESTION #53: What are the risk factors—i.e., gender, comorbid conditions, COPD, bronchiectasis, inhaled corticosteroid use—for MAC lung disease; and what populations of patients, in particular, appear to be more likely to acquire this infection? And how does this information help us risk stratify and confirm this diagnosis in patients with bronchocentric infections such as MAC?

QUESTION #54: What are the clinical patterns and presentations that characterize MAC lung disease? And how does the variability of NTM disease presentations make the diagnosis more challenging? Can you provide us with a MAC lung disease "recognition-and-risk decision tree?"

QUESTION #55: Once the presentation in an individual patient is suggestive of MAC lung disease, what canonical sequence of radiographic and microbiological confirmatory tests should follow prior to making an initial treatment decision?

QUESTION #56: What is the optimal way to obtain sputum samples for culture to confirm the diagnosis of MAC lung disease? What are the barriers—including impaired secretion clearance— to ideal sputum harvesting and what strategies in collaboration with the patient can we deploy to overcome these impairments to diagnostic assessment?

QUESTION #57: How do you analyze the complex clinical, radiographic, and microbiologic data to determine whether the patient should be started on antibiotic treatment?

QUESTION #58: What specific findings should, in your view, mandate treatment and encourage the patient to embark on a course of antimicrobial therapy? How should this multi-factorial analysis evolve and how should the patient be engaged in the decision-making process?

QUESTION #59: How do you put together the triad of critical data sets—stability or progression of disease by spirometry, radiographic findings and symptoms/clinical fragility—to make a final determination to expose the patient to the "burden of treatment," which is formidable in MAC lung disease?

QUESTION #60: What are the specific recommendations and concrete guidelines—albeit 12 years old—for treatment for MAC lung disease? Is there flexibility as far as dosing frequency? And are there recommendations based on antibiotic resistance susceptibility and/or risk severity, in particular, for the use of amikacin in cavitary or more severe refractory disease?

QUESTION #61: Based on mechanistic differences and clinical trial results—as well as issues related to reduced systemic toxicity, drug penetration, ease of administration, and antimicrobial conversion rates—what is the evidence-based rationale for deploying amikacin liposome inhalation suspension as the dominant route in refractory MAC lung disease patients who require intensification of their antimicrobial regimen?

QUESTION #62: Given the FDA approval for the amikacin liposome inhalation suspension, how do you, in the real world, position this formulation in the overall sequencing of anti-infective therapy for MAC lung disease? And what specific biologic features and pharmacokinetics of amikacin in the liposomal construct confer special potential advantages that might enhance microbial conversion and eradication?

QUESTION #63: Given the FDA approval for the amikacin liposome inhalation suspension in NTM infection, how do you, in the real world, utilize this formulation in the overall sequencing of anti-infective therapy for MAC lung disease? And what specific biologic features, drug penetration characteristics, and pharmacokinetic features of amikacin in the liposomal construct do you feel may confer special potential advantages that might enhance microbial conversion and eradication?

QUESTION #64: Based on the results of two recent papers, including the CONVERT trial, which evaluated the efficacy and safety of amikacin liposome inhalation suspension, what have we learned about when, in whom, and for how long this antimicrobial formulation should be continued in patients with MAC lung disease?

QUESTION #65: Although we don't have head-to-head trial comparison data for amikacin liposome inhalation suspension vs. IV amikacin, what do the mechanisms and data reported in the CONVERT trial in refractory, hard-to-treat patients teach us about whether the liposomal construct represents, potentially, a preferred strategy when amikacin-based treatment is warranted?

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QUESTION #66: What are the characteristics and/or risk factors that predispose patients to MAC lung infection? And what species are particularly relevant and widespread causative pathogens n NTM lung disease?

QUESTION #67: What is it about the non-specific symptomatology that characterizes the broad clinical spectrum of MAC lung disease that creates diagnostic challenges for the clinician? And what triad of findings is essential to confirm the diagnosis and appropriately risk stratify patients with NTM lung disease?

QUESTION #68: What are the most effective methods for sputum induction and microbiologic sampling? And, in your experience, in what percentage of cases is a bronchoscopy or lung biopsy necessary to achieve microbiologic confirmation of MAC lung disease? And how frequent should culture sampling be performed during the treatment phase?

QUESTION #69: What are the relevance, role, and clinical importance of obtaining and documenting in vitro culture drug sensitivity testing to antibiotics considered for treatment of MAC lung disease? Which antibiotics, in particular, should be tested and what are the patient-based risk factors for drug resistance?

QUESTION #70: What clinical findings absolutely mandate antibiotic treatment for individuals with culture-positive MAC lung disease? What is the gray area? What features of the initial clinical presentation are so ominous as to suggest the need for four-drug therapy—three-drug oral therapy plus amikacin—at the time of diagnosis?

QUESTION #71: What are the predictors of progressive MAC lung disease and what are the guideline-based (ATS/IDSA/BTS) recommendations for antibiotic treatment in these high-risk patients?

QUESTION #72: Why is continuous airway clearance an important pillar of therapy for patients with MAC lung disease?

QUESTION #73: What is the role of molecular diagnostics and speciating NTM organisms as part of the microbiological characterization for MAC lung infection?

QUESTION #74: When intensification of therapy with amikacin is being considered, or has been implemented in patients with moderate-to-severe MAC lung disease and/or in treatment refractory patients, how do you differentiate between and/or decide to initiate therapy with the IV vs. amikacin liposome inhalation suspension formulation? And how do the results of the CONVERT trial support your clinical approach? And what specific criteria must be met to qualify as "treatment refractory

QUESTION #75 What were the conclusions of the NTM-NET Consensus Guidelines as far as the definition of treatment refractoriness in MAC lung disease, and what's your assessment of these recommendations?

QUESTION #76: Once you've made the decision to deploy the FDA-approved amikacin liposome inhaled aerosol suspension in patients with refractory MAC lung disease, what strategies do you use to optimize patient adherence, tolerability and compliance with this treatment; and how do you mitigate any potential side effects, especially in patients with underlying disease, of inhaled liposomal amikacin therapy?

QUESTION #77: Can you share a specific, real world case study that exemplifies at least one clinical phenotype with MAC lung disease that is appropriately managed with amikacin liposome inhaled suspension? And can you discuss any measures that might have been taken to improve tolerability and adherence with the regimen?

QUESTION #78: What have you learned about the role of and approach to using amikacin liposome aerosol suspension from the previous—and similar other—cases of MAC lung disease that you have managed? And how are these airway-irritating side effects best addressed in collaboration with the patient? And how often is drug discontinuation observed?

QUESTION #79: Can you summarize the current evidence for amikacin liposome inhaled suspension, the patients in which it is appropriately and optimally deployed, and what supportive and educational measures improve toleration, patient adherence and durability of long-term treatment with this antibiotic formulation?

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QUESTION #80: What is the spectrum of NTM disease in the U.S., especially in patients with underlying lung disease?

QUESTION #81: What have you learned about the relationship between e-cigarettes/vaping and NTM lung disease?

QUESTION #82: In your VA Hospital setting, where there is a high incidence of background COPD and symptomatology emblematic of NTM lung disease, how do you maintain a high index of suspicion for this infection and what systemic approaches to diagnostic confirmation do you employ in this high-risk population? And what are the triggers for treatment?

QUESTION #83: Once you decide to initiate oral treatment, what regimen, in what sequence and frequency of dosing are currently recommended? And what are the expected microbial conversion rates based on the patient's underlying disease and other risk factors?

QUESTION #84: Considering your high risk NTM population, what are the indications for systemic (IV) amikacin therapy, what are the limiting and concerning side effects of systemic amikacin, and what are the potential side effect-mitigating properties—as well as penetration and other biological properties—of the FDA-approved amikacin liposome inhalation suspension in patients with MAC lung disease?

QUESTION #85: What, in your view, are the precise indications and clinical phenotypes with MAC lung disease in which the FDA-approved amikacin liposome inhalation suspension is most like to achieve microbial conversion and improve clinical outcomes?

QUESTION #86: What are the key results and translational implications of the CONVERT trial that supported the FDA approval of amikacin liposome inhalation suspension; and what percentage of treatment refractory patients achieved microbial conversion?

QUESTION #87: What strategies—communication with patient about treatment expectations, managing side effects, use of bronchodilators, and others—do you employ at the front lines of patient management to improve toleration, patient adherence, and compliance with treatment when using amikacin liposome inhalation suspension in patients with MAC lung disease? Can you take us through your protocol?

QUESTION #88: When starting amikacin liposome inhalation suspension, how and for what duration do you monitor the patient for microbial conversion and response to therapy?

QUESTION #89: Are there proven strategies for preventing NTM lung disease? If so, what are your recommendations?

QUESTION #90: What is likely to be the future burden of MAC and NTM lung disease as our populations ages?