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REVIEW ARTICLE

Pharmacologic Management of *Mycobacterium chimaera* Infections: A Primer for Clinicians

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Mycobacterium chimaera, a member of the *Mycobacterium avium* complex, can cause infections in individuals after open heart surgery due to contaminated heater-cooler units. The diagnosis can be challenging, as the incubation period can be quite variable, and symptoms are nonspecific. In addition to aggressive surgical management, combination pharmacologic therapy is the cornerstone of therapy, which should consist of a macrolide, a rifamycin, ethambutol, and amikacin. Multiple second-line agents may be utilized in the setting of intolerances or toxicities. *In vitro* susceptibility of these agents is similar to activity against other species in the *Mycobacterium avium* complex. Drug–drug interactions are frequently encountered, as many individuals have chronic medical comorbidities and are prescribed medications that interact with the first-line agents used to treat *M. chimaera*. Recognition of these drug–drug interactions and appropriate management are essential for optimizing treatment outcomes.

Keywords. amikacin; azithromycin; clarithromycin; clofazimine; drug–drug interactions; ethambutol; *Mycobacterium chimaera*; rifabutin; rifampin.

Background of Organism Identification and Infection

Mycobacterium chimaera is a slow-growing mycobacterium that belongs to the *Mycobacterium avium* complex (MAC). *M. chimaera* was initially misidentified as *Mycobacterium intracellulare*, a closely related species; however, in 2004, Tortoli et al. identified *M. chimaera* as a separate species within the MAC complex. The correct identification of *M. chimaera* requires sequencing of the 16-23S rRNA internal transcriber spacer (ITS) region. Identification based solely on sequencing of the 16S rRNA leads to misidentification as *M. intracellulare*, as they only have 1 nucleotide mismatch [1]. *M. chimaera* has since been implicated in pulmonary infections, soft tissue and bone infections, and disseminated infections. The first report of *M. chimaera* infection in patients who had undergone open heart surgery was published in 2013 by Achermann et al. [2], but a nosocomial link was not identified at the time. In July 2014, the Federal Office of Public Health in Switzerland reported *M. chimaera* infection in patients after exposure to contaminated heater-cooler units (HCUs) during open-chest cardiac surgery [3]. HCUs are used during cardiopulmonary bypass operations and extracorporeal membrane oxygenation (ECMO). Mycobacteria become aerosolized when the cooling fan blows the mist escaping the water tanks of the HCU into the operating room, allowing bacteria to contaminate the surgical field [4]. Since the initial publication in 2014, several reports from around the world have been published suggesting that HCUs produced by 1 manufacturer in Germany were contaminated at the production site, which served as the source of the outbreak. Investigations using molecular methods such as whole-genome sequencing of *M. chimaera* isolates from individuals and the HCUs demonstrated that most cases of these infections were related to cardiothoracic surgeries in Switzerland, Germany, United Kingdom, Netherlands, United States, Denmark, Italy, Canada, and Australia and were caused by a common source [5–7].

Clinical Manifestations

Before 2004, pulmonary infections—and possibly disseminated infections in immunocompromised patients—caused by *M. chimaera* were likely diagnosed and managed similarly to other MAC infections. Since the species was recognized, *M. chimaera* has been found to cause pulmonary infections in cystic fibrosis patients and immunocompetent patients [8–10]. Some reports have highlighted the low virulence of this species compared with *M. intracellulare* [11, 12]. Individuals typically present with signs and symptoms of infection over a year after the inoculation (ie, surgery). In some instances, the latency period can be as long as 6 years [7]. However, a prolonged latency period has been noted in other nosocomial infections caused by nontuberculous mycobacteria (NTM) as well [13, 14]. After

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the onset of symptoms, diagnosis of *M. chimaera* infection following cardiothoracic surgery is also delayed and could occur as much as 1 year later.

The most common clinical manifestations are fever (80%), malaise (80%), and weight loss (60%). Less frequent symptoms include cough, dyspnea, chest pain, arthralgia, abdominal pain, and back pain. Distinctive physical findings are new cardiac murmur, hepatomegaly, splenomegaly, sternal wound dehiscence, skin lesions, and choroiditis. Common laboratory findings are lymphopenia (63%), thrombocytopenia (47%), elevated liver enzymes with a cholestatic pattern (70%), and elevated inflammatory markers [2, 15, 16]. Histopathology shows granulomatous infection of various organs such as myositis, osteomyelitis, hepatitis, nephritis, myocarditis, pneumonitis, and involvement of the spleen and bone marrow [5, 16]. Individuals may present with intrathoracic infection, including sternal wound infection, retrosternal abscess, empyema, and extrathoracic infections such as vertebral osteomyelitis, granulomatous hepatitis, prosthetic valve endocarditis (PVE), aortic graft or other vascular hardware infection including left ventricular assist device (LVAD), ocular infections, and disseminated infections [2, 5, 16–20]. Choroiditis is commonly encountered with disseminated infections [19–23]. The mortality rate with *M. chimaera* infections following cardiothoracic surgery ranges from 20% to 67% [7].

Diagnosis

Establishing the diagnosis of *M. chimaera* infection following cardiothoracic surgery requires a high level of suspicion, especially if there are no prior reported cases at the institution. A number of factors specific to the pathogenesis of *M. chimaera* infections can lower suspicion for such an infection, increasing the likelihood for misdiagnosis. These include a long latency period, slowly progressive symptoms that are usually nonspecific, especially during the beginning of infection, and the absence of obvious physical signs and radiological findings. In scenarios where sternal wounds are debrided due to dehiscence and drainage, or when a mediastinal abscess is drained, fluid and tissue should be sent for mycobacterial cultures, especially if previous cultures do not identify an organism. If MAC is identified in mycobacterial cultures using a commercial probe, the isolate should be sent to a reference laboratory for species identification and susceptibility testing. Rapid quantitative polymerase chain reaction (PCR) assay to detect *M. chimaera* in the blood and fluid has been developed and has demonstrated high sensitivity and specificity [24]. There are a number of commercially available diagnostic molecular biology kits that can be utilized [24, 25]. In suspicious cases wherein tissue from the infection site was not submitted for mycobacterial culture and only formalin-fixed tissue is available, molecular analysis of the fixed tissue can be pursued to look for evidence of *M. chimaera* DNA in order to establish the diagnosis.

When a case is suspected or confirmed based on culture or histopathology results, a comprehensive workup should be performed to determine if the infection is localized or disseminated. All patients should have at least 3 sets of mycobacterial blood cultures collected. A total of 8–10 mL of whole blood should be collected in a green top tube (sodium or lithium heparin) or a yellow top tube (Sodium polyanethole sulfonate/isolator tube). The specimen should be processed by the lab within 72 hours. Data regarding the sensitivity of mycobacterial blood cultures for *M. chimaera* are not available. Mycobacterial cultures of sputum, urine, or fluid/tissue from any organ that might be involved should be considered. Bone marrow biopsy should be performed to investigate cytopenias, and the aspirate should be submitted for mycobacterial culture and *M. chimaera* molecular testing. Transesophageal echocardiogram should be performed to evaluate for the diagnosis of endocarditis or aortic graft infection, as transthoracic echocardiogram has been found to have low sensitivity (33%) in patients with *M. chimaera* infections [15]. Fundoscopic examination by an ophthalmologist should be performed to evaluate for evidence of chorioretinitis. Imaging studies such as a computed tomography (CT) scan of the chest, abdomen, and pelvis are needed to determine the extent of the infection. Furthermore, a positron emission tomography/CT scan can be very helpful in cases where hardware is present [7].

PHARMACOLOGIC MANAGEMENT

Combination therapy with multiple antimycobacterial classes of medications is essential for the treatment of *M. chimaera* infections. Macrolides are considered the backbone of therapy, similar to other NTM infections. Additional first-line agents include rifamycins (ie, rifampin or rifabutin), ethambutol, and amikacin [26]. There are multiple second-line agents, including clofazimine, bedaquiline, linezolid, and moxifloxacin, which can be considered in patients who are not candidates for first-line agents. This is generally due to toxicities or intolerances and is less commonly due to drug resistance. Consultation with an infectious disease expert is highly recommended for optimal pharmacologic management.

Unfortunately, clinical outcomes with *M. chimaera* infections remain poor, despite aggressive surgical and pharmacologic therapy. The optimal duration is not known; however, most individuals receive therapy for at least 12 months. Longer durations may be considered in patients with suboptimal source control, slow tissue or blood culture sterilization, or failure of clinical improvement. Retention of infected hardware, such as a left ventricular assist device, likely requires long-term therapy well beyond 12 months to prevent recurrent or relapsed infections, typically with a simplified drug regimen to help minimize toxicities. Below, each medication class will be discussed, with a focus on in vitro activity against *M. chimaera*

Table 1. Summary of *M. chimaera* Pharmacotherapy Recommendations

Drug	Dosing Strategy	Adverse Effects	Additional Comments
Azithromycin	250–500 mg PO daily	Nausea, vomiting, abdominal pain, hepatotoxicity, QTc prolongation, ototoxicity	Caution in individuals with myasthenia gravis Long-term use may be associated with hearing loss
Clarithromycin	500 mg PO twice daily	Nausea, vomiting, abdominal pain, hepatotoxicity, QTc prolongation, ototoxicity, eosinophilic pneumonia	Reduce dose by 50% if CrCl <30 mL/min Caution in myasthenia gravis
Rifampin	600 mg PO daily	Hepatotoxicity, bone marrow suppression, red-orange bodily fluid discoloration, nausea	Avoid in patients on calcineurin inhibitors and/or mycophenolate
Rifabutin	300 mg PO daily	Hepatotoxicity, bone marrow suppression, red-orange bodily fluid discoloration, nausea, uveitis	Reduce dose by 50% if CrCl <30 mL/min
Amikacin	10–15 mg/kg IV daily or 15–25 mg/kg IV thrice weekly	Nephrotoxicity, ototoxicity	Baseline and periodic audiograms are recommended while on therapy Recommended duration of 6–12 wk of therapy to increase likelihood of blood and/or tissue culture sterilization
Ethambutol	15 mg/kg PO daily or 15–25 mg/kg PO thrice weekly	Optic neuropathies, impairment of green-red color discrimination	Baseline and periodic ocular assessments are recommended while on therapy
Clofazimine	100–200 mg PO daily	GI toxicities, skin discoloration, QTc prolongation	Must obtain from pharmaceutical manufacturer and submit IND application with the FDA
Bedaquiline	400 mg PO daily for 2 wk; then 200 mg PO thrice weekly	QTc prolongation	Boxed warning for increased mortality observed in bedaquiline arm of clinical trial
Linezolid	600 mg PO/IV daily or twice daily or 300 mg PO/IV twice daily	Thrombocytopenia, neutropenia, anemia, peripheral and optic neuropathies, lactic acidosis	Lower daily doses associated with less toxicity Consider therapeutic drug monitoring in patients with renal dysfunction or hematologic toxicities
Moxifloxacin	400 mg PO/IV daily	Tendinitis and tendon rupture, QTc prolongation, neurotoxicities, dysglycemia	Avoid in individuals with myasthenia gravis Boxed warning for serious adverse reactions including tendinopathies, peripheral neuropathy, and CNS effects

Abbreviations: CNS, central nervous system; CrCl, creatinine clearance; FDA, Food and Drug Administration; GI, gastrointestinal; IV, intravenous; IND, Investigational New Drug; PO, per os (oral).

isolates, clinical utility in treatment of *M. chimaera* infections (if present), and common drug toxicities. Drug–drug interactions (DDIs) will be discussed in a separate section. A summary of pharmacologic therapy recommendations and dosing is provided in Table 1.

Macrolides

Inclusion of a macrolide, clarithromycin or azithromycin, for the treatment of NTM infections is considered the mainstay of therapy [26]. This drug class harbors activity against mycobacterial organisms by inhibiting natural messenger RNA-directed cell-free polypeptide synthesis, achieved by binding to the 23S rRNA of the 50S subunit within the 70S ribosomes [27, 28].

Clarithromycin has a 14-member ring that is adjusted for the acid instability of erythromycin by replacing the hydroxyl group at C-6 with a methoxy group [27–30]. Azithromycin has a 15-member ring structure, which places it within the azalide subclass and gives it an expanded spectrum of activity [27, 28, 31]. The structural alteration includes a methyl-substituted nitrogen instead of a carbonyl group within the aglycone ring. As a result, azithromycin does not undergo metabolism into a hemiketal, minimizing acid instability concerns [28, 31]. Additional pharmacokinetic (PK) benefits of azithromycin compared with erythromycin and clarithromycin include the lack of cytochrome (CYP) 3A4 inhibition and longer half-life [27, 28, 32].

It is also important to mention that the Clinical and Laboratory Standards Institute (CLSI) recommends that clinical isolates be tested against clarithromycin rather than azithromycin for MAC. This is due to increased clarithromycin solubility at higher concentrations. Azithromycin susceptibility can be inferred from clarithromycin susceptibility interpretation [33]. Clarithromycin has demonstrated potent in vitro activity against *M. chimaera* isolates. Using a CLSI minimum inhibitory concentration (MIC) breakpoint of ≤8 mcg/mL, a study of clinical isolates demonstrated that 100% of isolates were susceptible with clarithromycin, with an MIC_{90} of 4 mcg/mL [34]. In a 2021 study of clinical isolates, 47 of 48 isolates exhibited an MIC ≤4 mcg/mL. One isolate had an MIC of 32 mcg/mL; however, no mutations were observed [35].

There are multiple macrolide resistance mechanisms, but point mutations at the 23S rRNA gene are the most common. These are often associated with macrolide monotherapy or combination with a fluoroquinolone [36–38]. In a retrospective review of 34 patients with macrolide-resistant MAC pulmonary disease, 27 of the 28 isolates available for testing were found to have point mutations of the 23S rRNA gene. Most of the 34

patients had been given a standard 3-drug regimen, consisting of a macrolide, ethambutol, and a rifamycin, and all were receiving a macrolide-based regimen for a median duration of 30.4 months before the emergence of resistance. However, after identification of the resistant phenotype, unfavorable outcomes occurred in 85% of patients, with 5-year mortality of 47% [38]. In a recent retrospective analysis of patients with pulmonary *M. chimaera* infections, the authors noted significantly better radiographic responses in patients with a macrolide-based regimen compared with non-macrolide-based regimens. However, there was no difference in culture conversion or mortality rates between the 2 treatment groups [39]. Unfortunately, these findings are limited to pulmonary disease, as there are no data evaluating treatment outcomes between macrolide-based regimens and non-macrolide-based regimens in other infections, including endovascular and disseminated infections. Despite the limited evidence, every effort should be taken to avoid the development of macrolide resistance, as treatment outcomes are generally worse in most MAC infections with macrolide-resistant organisms. Outside of managing higher bioburdens, one of the most effective means to achieve this is to utilize antimycobacterial drug synergy with additional first-line agents. These agents will be addressed in the following sections.

Adverse Effects

Adverse effects of the macrolide drug class include nausea, vomiting, diarrhea, abdominal pain, QTc interval prolongation, and hepatotoxicity [40–43]. Clarithromycin and azithromycin are associated with a lower incidence of abdominal pain compared with erythromycin, which is thought to be secondary to metabolism changes and decreased motilin receptor activation [32, 42].

QTc interval prolongation has been noted as a class effect, but it is dependent on numerous other variables including genetics, sex, clinical status, and concomitant medications [44]. Azithromycin has been shown to cause the least amount of prolongation in studies [44, 45]. Macrolide-induced hepatotoxicity typically manifests in the form of cholestatic hepatitis after 1–4 weeks of exposure [43]. Similar to other class effects of the macrolides, azithromycin has the lowest association with hepatotoxicity. Sensorineural hearing loss caused by the macrolides has been reported, but data have not yet proven the association [46–48]. Additional adverse effects can include clarithromycin-induced eosinophilic pneumonia, myasthenia gravis exacerbation, and anaphylaxis [49–51].

Azithromycin

Azithromycin is considered first-line therapy by most clinicians over clarithromycin due to less concern about DDIs and adverse effects. Current clinical evidence is inconclusive regarding which agent is more effective [52–54]. While randomized controlled trials (RCTs) evaluating macrolides for the management of *M. chimaera* infections are lacking, extrapolations have been made from other MAC infections. Interestingly, just 2 RCTs comparing macrolide-containing regimens with macrolide-free regimens are available, and each study has limitations [55, 56]. Unlike most agents used for treatment of MAC infections, there is a correlation between in vitro susceptibility interpretation and clinical response with macrolides (perhaps the only additional exception is amikacin, which will be addressed in a separate section) [57–60]. Therefore, macrolide susceptibility is crucial, as treatment success, most commonly defined as culture conversion, has been shown to be significantly increased for macrolide-susceptible isolates compared with macrolide-resistant isolates. One systematic review found that up to 65.7% of patients with macrolide-susceptible MAC pulmonary disease could achieve treatment success if treated with a macrolide-based 3-drug regimen for at least 1 year [58]. In comparison, another systematic review and meta-analysis of macrolide-resistant MAC pulmonary infections identified a pooled culture conversion rate after combined multiple antibiotics or surgical resection of just 21% [59].

Rifamycins

Rifamycins such as rifampin and rifabutin are considered an essential component of combination therapy as they inhibit the DNA-dependent RNA-polymerase enzyme at the beta-subunit of bacteria and mycobacteria, preventing chain initiation [61]. Similar to macrolides, much of the in vitro susceptibility data for rifamycins has been extrapolated from MAC isolates; however, rifampin and rifabutin have demonstrated in vitro activity against *M. chimaera* in separate analyses [35].

In vitro synergy has been demonstrated with rifamycins and ethambutol, in which the combination MICs for both drugs are significantly lower than when evaluated separately. While the clinical relevance of this in vitro synergy has come into question [62], multiple studies have demonstrated more favorable clinical outcomes when the 2 drugs are combined for MAC infections [63]. As such, it is recommended to include ethambutol with rifampin or rifabutin for optimal management of *M. chimera* infections [26].

Adverse Effects

The most common adverse effects associated with rifamycins are hepatotoxicity, bone marrow suppression and cytopenias, hypersensitivity reactions, nausea, and orange-red bodily fluid discolorations. These are generally considered class effects. Hepatotoxicity is thought to be more common with rifampin than with rifabutin. Additionally, multiple studies have demonstrated favorable outcomes in patients treated for *M. tuberculosis* infections with rifampin-associated hepatotoxicity who were rechallenged with rifabutin [63]. Uveitis is a rare adverse effect that is thought to be more associated with rifabutin than with

other rifamycins [64]. However, most cases of uveitis have been described in patients on concurrent clarithromycin therapy, which is known to significantly increase rifabutin concentrations, while demonstrating minimal effect on rifampin concentrations [65, 66]. Although the mechanism for this adverse effect has not been completely elucidated, clinicians should be aware of this potential complication in patients with acute vision changes.

Rifampin

Rifampin is generally considered the rifamycin of choice for the treatment of both wild-type and drug-resistant infections, as it has the most evidence to support its clinical efficacy and safety in the management of *M. chimaera* and other MAC infections. Rifampin has a half-life of ∼2–4 hours, significantly shorter than rifabutin [67]. Perhaps the biggest drawback to rifampin is the considerable DDIs. As *M. chimaera* infections typically occur in patients with multiple medical comorbidities, significant DDIs are common. As previously mentioned, rifamycins demonstrate synergistic activity when combined with ethambutol, and combination MICs are often provided for ethambutol and rifampin when performing antimicrobial susceptibility testing [68]. While an isolate may be nonsusceptible to rifampin and/or ethambutol when tested individually, the combination of the 2 agents can produce a synergistic effect that yields a combination MIC that is susceptible [68, 69].

Rifabutin

Despite a similar magnitude of protein-binding, rifabutin has a much longer half-life than rifampin, with a terminal half-life of ∼45 hours. Unlike rifampin, rifabutin dose adjustments need to be considered in patients with renal dysfunction, as urinary excretion of rifabutin is ∼50%, compared with ∼30% with rifampin [70].

In vitro susceptibilities of clinical and environmental *M. chimaera* isolates have demonstrated more potent in vitro activity for rifabutin compared with rifampin. In 1 study, the MIC_{50}/MIC_{90} for rifabutin was ≤0.25/1 mcg/mL vs 4/8 mcg/mL for rifampin. Approximately 2% of isolates were categorized as resistant to rifabutin compared with 16% for rifampin. However, it is important to note that susceptibility to rifabutin was determined via tentative epidemiological cutoff values (ECOFFs) vs pharmacokinetic/pharmacodynamic breakpoints for rifampin, as no CLSI breakpoints exist for either drug or *M. chimaera* isolates [34]. Tentative ECOFF values for rifampin could not be determined, as previous data have shown MIC distributions for rifampin that were truncated toward the upper end of the concentrations that were tested (>8 mcg/mL). This study concluded that despite the more potent in vitro activity, additional clinical evidence is needed to determine optimal rifamycin selection, dosing strategy, and duration of therapy for treatment of NTM infections, and in particular *M. chimaera* infections [71].

Unfortunately, in vitro synergy testing for rifabutin and ethambutol is not currently performed by reference laboratories for *M. chimaera* susceptibility testing. In this scenario, the interpretation of rifampin-ethambutol synergy testing is sometimes used as a surrogate for rifabutin-ethambutol synergy; however, the true magnitude of synergy for this combination is not well established. Additional studies are warranted to determine the appropriateness of using rifampin and ethambutol in vitro synergy testing as a surrogate for rifabutin and ethambutol synergy.

Ethambutol

Ethambutol binds to the arabinosyltransferases EmbA, EmbB, and EmbC, which are membrane-embedded proteins in mycobacteria. Ethambutol appears to bind to active sites within these proteins and prevent transfer of arabinose, an essential process for the synthesis of the mycobacterial cell wall [72]. Ethambutol is a first-line agent in the treatment of slow-growing mycobacterial infections, particularly MAC infections. It is also a first-line agent for the treatment of *M. chimaera* infections [26, 53]. The activity of ethambutol against clinical *M. chimaera* isolates has been assessed in multiple studies. Using a PK/pharmacodynamic (PD) breakpoint of ≥8 mcg/mL, 89% of isolates were susceptible to ethambutol, with an MIC_{50}/MIC_{90} of 4 and 8 mcg/mL, respectively [34].

Ethambutol is primarily excreted in the urine and requires renal dose adjustment, with glomerular filtration and tubular secretion accounting for ∼80% of its elimination [53, 73]. Therapeutic drug monitoring of ethambutol may be considered in patients with renal dysfunction until the drug reaches steady state concentrations [26].

Adverse Effects

The most common adverse effects with ethambutol are optic neuropathies, which appear to be dose related [74]. These typically manifest as retinal changes, which can result in alterations in color vision, particularly red-green discrimination. Previously, these toxicities have been described as reversible, though case reports have described permanent changes in vision [75, 76]. Ophthalmologic examinations and visual acuity examinations should be conducted before initiation and periodically while on therapy [26, 53, 77].

Amikacin

Amikacin inhibits mycobacterial protein synthesis via binding to 30S ribosomal subunits. It exhibits concentration-dependent activity against mycobacterial organisms [78]. Amikacin is recommended for the first 6–12 weeks of treatment for *M. chimaera* infections to increase the rate of blood culture and tissue sterilization; however, this recommendation is based on expert

opinion. Currently, there are no studies that have evaluated the effect of amikacin on microbiologic outcomes. Some clinicians may continue amikacin in individuals past 12 weeks, especially in the scenario of drug resistance or infections refractory to therapy; however, toxicities may prevent extended durations [26].

Amikacin is typically dosed at 10–15 mg/kg daily or 15–25 mg/kg 3 times weekly in individuals with *M. chimaera* infections [26, 53, 79, 80]. Individuals may be initiated on a daily dosing regimen and then transitioned to a thrice-weekly regimen for convenience and/or to mitigate toxicities. In elderly individuals and individuals with significant baseline renal dysfunction, the typical amikacin starting dose is decreased to 8–10 mg/kg either twice or thrice weekly [80]. Alternatively, 15 mg/kg twice weekly has also been recommended [26, 53, 79]. A baseline and serial audiogram and monitoring of vestibular function are recommended for all individuals on amikacin [26, 53, 79].

With regards to in vitro susceptibility testing, the breakpoints are extrapolated from rapidly growing mycobacteria, particularly *M. abscessus* (susceptible: ≤16 mcg/mL; intermediate: 32 mcg/mL; resistant: ≥64 mcg/mL) [81]. Susceptibility testing is recommended to optimize dosing to target patient-specific PK/PD parameters [26, 53, 79, 80]. Additionally, susceptibility testing may be useful for determination of alternative drug therapy in the case of an amikacin-resistant isolate, especially in individuals at higher risk for amikacin-associated toxicities.

Therapeutic Drug Monitoring

Therapeutic drug monitoring should be routinely performed for all patients on amikacin. With daily dosing regimens, a peak of 25–40 mcg/mL is the typical initial drug target. Troughs should be <1 mcg/mL to minimize the likelihood of drug accumulation, which may progress to nephrotoxicity [26, 53, 79–83]. A drug-free interval, or a period in which the drug concentration is undetectable before the next dose is given, is strongly recommended to minimize the risk of adverse effects. In most scenarios, a drug-free interval of 4–6 hours is desirable. This is generally not achievable with daily dosing in individuals with renal dysfunction, but the likelihood is much higher in thrice-weekly dosing regimens.

Peak values with thrice-weekly dosing regimens are typically higher than with daily dosing regimens, as higher weight-based doses are often prescribed. In these dosing regimens, typical peak values range from 35 to 50 mcg/mL; however, it is not uncommon to see values of 60 to 70 mcg/mL [82]. The optimal peak value is not well known based on current evidence, but clinicians may target values 4–5-fold higher than the amikacin MIC. In vitro susceptibility of amikacin is similar to other mycobacteria, with 1 study demonstrating MIC_{50}/MIC_{90} values of 8/16 mcg/mL based on 87 isolates; isolates with MICs ≥32 mcg/mL may be encountered clinically [34]. The utility of amikacin in the latter scenario is uncertain, as achieving optimal PK/PD is highly unlikely using the standard doses of amikacin for mycobacterial infections. Additional studies are needed to evaluate the role of amikacin and clinical outcomes in isolates with elevated MICs (>16 mcg/mL).

Adverse Effects

The most common adverse events are nephrotoxicity and ototoxicity. Ototoxicity may manifest as either cochlear or vestibular toxicity. Some individuals may experience both toxicities simultaneously.

After initial pharmacokinetic calculations, it is recommended to repeat serum creatinine and amikacin troughs after the first 1–2 weeks of therapy to ensure appropriate drug clearance. In patients with stable renal function, it is recommended to repeat a serum creatinine and amikacin trough every month. Although not a component of therapeutic drug monitoring, it is important to note that vestibular function and baseline audiograms are recommended in all individuals at baseline and monthly thereafter. The benefit of therapeutic drug monitoring in reducing ototoxicity is more nebulous than nephrotoxicity. Some studies have demonstrated that cumulative AUC and dose appear to be better predictors of ototoxicity than peak and trough values [84]. These toxicities may be only partially reversible; therefore, clinicians may need to consider early discontinuation of amikacin in these scenarios.

Clofazimine

The exact mechanism of clofazimine has not been completely elucidated, as it appears to exert its antimicrobial activity via several different mechanisms [85]. It has been postulated that clofazimine is a prodrug and generation of multiple compounds via different enzymatic pathways may be responsible for the antimicrobial properties [86–88].

Clofazimine is primarily used in the treatment of *M. leprae* infections [85]; however, it has demonstrated potent in vitro activity against many mycobacterial species, including slow-growing mycobacteria. In 1 study evaluating clofazimine activity against clinical *M. chimaera* isolates, MIC_{50}/MIC_{90} values were 0.5 mcg/mL and 1 mcg/mL, respectively. The authors postulated an ECOFF value of 2 mcg/mL by visual inspection of clofazimine MIC distribution [35]. In vitro synergy has been demonstrated with clofazimine and multiple antimycobacterial agents, including azithromycin, amikacin, and bedaquiline, though the relevance of this synergy with regards to clinical outcomes is not well established [89, 90]. Currently, clofazimine is considered a second-line agent in the treatment of *M. chimaera* infections, but it should be considered in the presence of drug resistance or refractory infections [26].

While clofazimine resistance has not been demonstrated in *M. chimaera* clinical isolates, there have been case reports of resistance in *M. intracellulare* and *M. abscessus* isolates. Resistance is thought to be driven primarily by mutations in

efflux pumps, specifically in the TetR regulators of MmpS5-MmpL efflux pumps. Interestingly, these isolates were not associated with an MIC increase [91, 92].

Limited data exist regarding the clinical utility of clofazimine in the treatment of *M. chimaera* infections. Clofazimine has been used successfully in the treatment of NTM infections, particularly disseminated MAC and pulmonary *M. abscessus* infections. While clofazimine is a US Food and Drug Administration (FDA)–approved medication, it is no longer commercially available in the United States. For the treatment of other NTM infections, including *M. chimaera* infections, an investigational new drug application must be submitted to the US Food and Drug Administration, and the medication must be obtained from the pharmaceutical manufacturer (Novartis Pharmaceuticals Corporation).

Clofazimine is metabolized through multiple pathways [93]. The first pathway is hydrolytic dehalogenation, which is then excreted in the urine. In the second pathway, clofazimine undergoes hydrolytic deamination. In the third pathway, it is hydrated. Both metabolites from the second and third pathway are further conjugated with glucopyranosiduronic acid for urinary excretion [94]. Clofazimine does not undergo renal elimination or require renal dose adjustment.

Adverse Effects

The most common adverse effects associated with clofazimine are gastrointestinal toxicities, QTc prolongation, and skin discoloration. Gastrointestinal toxicities due to accumulation of drug crystals can deposit in multiple organ systems, including the gastrointestinal tract [85]. Individuals may first complain of nausea and vomiting, but more severe manifestations including splenic infarcts and severe gastrointestinal bleeding have also been reported [95]. In settings of significant gastrointestinal adverse effects, the dose of clofazimine can be decreased to help mitigate toxicity. Clofazimine has also been associated with QTc prolongation; however, more recent studies have suggested that the prolonging effect associated with clofazimine is relatively low [96, 97]. It is important to note that multiple agents utilized for the treatment of *M. chimaera* infections are also associated with QTc prolongation, including azithromycin and bedaquiline. Lastly, long-term clofazimine use has been associated with dermatologic toxicities, most notably skin discoloration. This toxicity is thought to be partially reversible; however, it may take months to years before improving [98].

Linezolid

Oxazolidinones, including linezolid and tedizolid, disrupt the bacterial translation process by binding to the 23S ribosomal RNA of the 50S subunit, which hinders the establishment of a functional 70S initiation complex [99, 100]. Although linezolid is primarily known for its gram-positive activity in bacterial infections, it has demonstrated mycobactericidal activity against MAC isolates in vitro [101]. However, its activity against *M. chimaera* isolates is quite variable. Using a CLSI breakpoint of 8 mcg/mL, only 22% of 87 clinical isolates were susceptible, with an MIC_{90} of 32 mcg/mL [70]. To achieve bactericidal activity against these elevated MICs, the required humanized doses would likely lead to toxicities. Therefore, the CLSI recommends reporting linezolid MIC and interpretation only in cases of macrolide-resistant MAC infections [33].

Linezolid is currently recommended as a second-line agent in the treatment of *M. chimaera* infections [26]. It may also be considered as add-on therapy in patients with refractory infections; however, it should be noted that clofazimine is considered the preferred fifth agent due to its more potent in vitro activity against *M. chimaera* as well as its in vitro synergy with other agents. If linezolid is used for treatment, a dosing strategy of 600 mg orally or intravenously twice daily is considered standard [26]; however, doses of 600 mg daily have been utilized in other NTM infections, which have been associated with lower rates of adverse effects.

Therapeutic Drug Monitoring

Studies evaluating therapeutic drug monitoring of linezolid have found an association between thrombocytopenia and C_{min} >2 mg/L [102, 103]. In a systematic review, meta-analysis, and Monte Carlo simulation (MCS) of linezolid pharmacokinetics in multidrug-resistant tuberculosis, a therapeutic efficacy target of $fAUC_{0-24}$:MIC >119 mg/L/h and safety target of fC_{min} <1.38 mg/L (equivalent to total drug C_{min} of 2 mg/L) were investigated. Linezolid doses of 300 mg every 24 hours, 300 mg every 12 hours, 600 mg every 24 hours, and 600 mg every 12 hours were included. The dosing regimens with the greatest likelihood of reaching the efficacy targets in the MCS were 300 mg every 12 hours and 600 mg every 12 hours. However, just 1.42% of simulated patients receiving the standard dose of 600 mg every 12 hours were found to attain the safety target, compared with 79.3% of patients receiving 300 mg every 12 hours [104]. As a result of PK/PD studies and clinical experience, linezolid doses may be decreased to 300 mg every 12 hours or 600 mg every 24 hours to minimize the toxicities seen with standard doses. Until further clinical trials are performed to validate these findings, therapeutic drug monitoring may be performed when toxicities manifest, particularly hematologic toxicities [105].

Adverse Effects

Linezolid use has been associated with bone marrow suppression, most notably thrombocytopenia. This typically manifests after 3–4 weeks of therapy. Long-term use has also been associated with neuropathies, including optic neuritis, which may be only partially reversible. Lactic acidosis is rare but has been associated with long-term use. Linezolid is also a weak monoamine oxidase inhibition. As such, there is a theoretical

risk of serotonin syndrome, particularly in patients on multiple serotonergic medications [106]. Multiple studies have suggested that this risk is lower than previously thought; however, some medications have been associated with higher risk than others, including specific selective serotonin reuptake inhibitors and methadone [107–109]. Given the theoretical risk, individuals should be counseled with regards to warning signs of serotonin syndrome, which include fevers, hyperreflexia, seizures, diarrhea, and diaphoresis.

Vitamin B6 administration has been evaluated to reduce the incidence of thrombocytopenia; however, its impact on reversing or mitigating hematologic toxicities is variable [110, 111]. Despite the inconclusive evidence, vitamin B6 is frequently coadministered with long-term linezolid use, particularly in patients with multidrug-resistant tuberculosis. Unfortunately, there have not been published studies evaluating the benefit of therapeutic drug monitoring and association of neuropathies, and there does not appear to be a clear benefit in coadministration of vitamin B6.

Moxifloxacin

Fluoroquinolones inhibit bacterial DNA topoisomerase IV and DNA gyrase necessary for bacterial replication [112]. Moxifloxacin is the preferred quinolone for treatment of mycobacterial infections given its superior in vitro activity [113]. However, many clinical *M. chimaera* isolates have demonstrated variable susceptibility to moxifloxacin. Using the same CLSI breakpoints as *M. abscessus* (susceptible: ≤1 mcg/mL; intermediate: 2 mcg/mL; resistant: ≥4 mcg/mL), the authors demonstrated that 63.1% (128 of 203) of *M. chimaera* isolates were resistant to moxifloxacin [35, 71]. Given variable in vitro activity, the paucity of clinical data specific to *M. chimaera*, and the better in vitro and clinical data to support other agents, moxifloxacin is considered a second-line agent for the treatment of *M. chimaera* infections [26].

Adverse Effects

Long-term use of fluoroquinolones has been associated with multiple adverse drug reactions, which often limits the use of this agent, more so than unpredictable in vitro activity. These adverse effects include gastrointestinal toxicities, central nervous system disturbances, hepatic enzyme elevation, musculoskeletal abnormalities including tendinopathies, and QT prolongation. Common moxifloxacin-related adverse effects are nausea, diarrhea, headache, and dizziness [114, 115]. Despite the effect that moxifloxacin can have on QTc prolongation, moxifloxacin-induced cardiac events, including *torsade de pointes*, are rare [116]. Regardless, caution should be taken with co-administration of moxifloxacin with other QTc-prolonging agents. This is of particular importance given that the other agents used in the treatment *M. chimaera* infections, such as macrolides, clofazimine, and bedaquiline, possess the same adverse effect. Caution should be taken among patients with other risk factors for a prolonged interval (eg, electrolyte disturbances, preexisting cardiac conditions, critical illness) [44]. Baseline and periodic electrocardiogram monitoring is advised while on therapy. Some clinicians have adopted a staggered approach to medication initiation to more closely monitor the individual effects that these agents can have on the QTc interval. Elevated QTc findings should prompt discussion on potential need for discontinuation, especially considering more robust in vitro and clinical data for previously mentioned antimycobacterial agents, including macrolides and clofazimine.

Bedaquiline

Bedaquiline is a first-in-class diarylquinolone that is FDA approved for the treatment of adults with multidrug-resistant pulmonary tuberculosis as part of a combination regimen [117, 118]. Bedaquiline acts via inhibition of adenosine triphosphate (ATP) synthase, as it binds to the membrane-bound c subunit of F1F0-ATP synthase, thereby preventing subunit rotation and proton transfer, halting energy production, and ultimately resulting in cellular death [119]. Bedaquiline has potent in vitro activity against slow-growing mycobacteria; however, it should be noted that MICs are generally higher for these mycobacteria than for *M. tuberculosis* [117–120]. Currently, bedaquiline is considered a second-line agent for the treatment of *M. chimaera* infection primarily given the lack of clinical data to support its use.

Bedaquiline demonstrates potent in vitro activity against *M. tuberculosis* with an MIC range of 0.002 to 0.13 μg/mL [117, 118, 121, 122]. However, activity against MAC and *M. chimaera* isolates is less potent, with MICs several-fold dilutions higher, at 0.007–0.25 μg/mL and 0.007–0.06 μg/mL, respectively [34, 35, 122, 123]. In addition, the corresponding MBC/MIC ratios are >4, resulting in a bacteriostatic rather than bactericidal effect when tested against these slow-growing NTMs [122, 123]. Interestingly, bedaquiline has also demonstrated in vitro synergy when combined with clofazimine [124]. Bedaquiline has been proven effective as a salvage regimen for patients with NTM infections [125, 126]. However, microbiological relapse has also been reported due to acquired mutations resulting in increased drug efflux [91]. Resistance may also occur as a result of mutations in the gene *atpE,* which encodes for the c subunit of ATP synthase [127].

Adverse Effects

Commonly reported adverse drug effects associated with bedaquiline use include nausea, arthralgia, headache, hemoptysis, and chest pain. There is a boxed warning for QTc prolongation and increased risk of mortality. Both bedaquiline and its metabolite, M2, are associated with QT prolongation [115, 128, 129]. However, published clinical data suggest only a modest impact on QTc, with most studies demonstrating an average change

from baseline of <20 milliseconds [91, 126]. Careful consideration should be made with co-administration of bedaquiline with other QTc-prolonging agents, including moxifloxacin, macrolides, and/or clofazimine, given the potential for an additive toxicity. Lastly, bedaquiline was associated with an increased risk of mortality in a phase 2b clinical trial, in which individuals with newly diagnosed, smear-positive, multidrug-resistant tuberculosis had numerically higher rates of mortality in the bedaquline arm (n = 10, 13%) than in the placebo arm (n = 2, 2%) [130]. It remains unclear as to the cause of the difference in mortality observed in this trial.

DRUG–DRUG INTERACTIONS

Multiple agents utilized in the treatment of *M. chimaera* infections are associated with significant DDIs. Virtually all patients with *M. chimaera* infections, especially those who develop infections following open heart procedures, have significant medical comorbidities and are prescribed multiple medications that have the potential for DDIs with first-line agents. Screening and management of DDIs play a pivotal role in achieving successful outcomes while limiting drug-related toxicities. Previous reviews have discussed drug-drug interactions with antimycobacterial agents and commonly prescribed medications, including antihypertensive, anticoagulant, and antiplatelet medications. This review will address drug-drug interactions with antimycobacterials and immunosuppressive agents commonly used in solid organ transplantation, as management is complex and requires aggressive monitoring to optimize therapy. The medications with the highest potential for DDIs and those medications that are used for treatment of *M. chimaera* infections will be discussed in the following sections, which are summarized in Table 2. These medications include rifamycins, macrolides, and clofazimine. While ethambutol can inhibit CYP450 enzymes, the potential for clinically relevant DDIs is low, as it only strongly inhibits CYP1A2 and CYP2E1, which have less proclivity for DDIs compared with other enzymes like CYP3A4 and P-glycoprotein [131]. Amikacin is almost completely eliminated through glomerular filtration; therefore, there is no potential for DDIs. While DDIs may be encountered with moxifloxacin, linezolid, and bedaquiline, these medications are not considered first-line therapy for *M. chimaera* infections. Therefore, they will not be specifically addressed in the following sections.

DDIs With Rifamycins

All rifamycins possess the potential to cause significant DDIs, primarily through induction of multiple enzymatic pathways, including CYP450 hepatic enzymes and P-glycoprotein. However, management of these DDIs is generally more favorable with rifabutin than with rifampin.

Rifampin potently induces multiple hepatic CYP substrates, including CYP3A4, 1A2, 2D6, 2C9, and 2C19 [132]. Additionally, rifampin strongly induces non-CYP enzymes involved in drug transport and metabolism including P-glycoprotein, organic anion transporters, and uridine glucuronosyltransferases (UGT) [133, 134]. The concentration of many drugs that are substrates of these enzymes may be significantly reduced, including narrow–therapeutic index agents, such as warfarin, direct oral anticoagulants (DOACs), tacrolimus, sirolimus, everolimus, and mycophenolate.

Unlike rifampin, rifabutin is only a moderate inducer of CYP3A4 and a weak inhibitor of CYP2C9 and UGT1A4 [133, 134]. Substrates of these enzymes are less affected by rifabutin than with rifampin, which may result in a lower likelihood of subtherapeutic concentrations. The exact mechanism for this is unknown, but one hypothesis is attributed to structural differences between rifabutin and rifampin. Unlike rifampin, rifabutin does not possess a piperazinyl iminomethyl group, which may contribute to structural differences that create steric hindrance, preventing the ability to bind to cellular receptors that would lead to cytochrome induction [135].

An additional consideration is the metabolism of rifamycins themselves, as they are substrates of various enzymes responsible for drug transport and metabolism. Inhibition or induction of these enzymatic pathways may affect the concentration of the rifamycins. As rifabutin is a major CYP3A4 substrate, potent CYP3A4 inhibitors, such as posaconazole and clarithromycin, have been noted to significantly increase rifabutin C_{max} and area under the curve (AUC) [66, 136]. This may result in increased risk of adverse effects including bone marrow suppression, hepatotoxicity, and uveitis due to supratherapeutic rifabutin exposure. Rifabutin dose adjustments may need to be considered empirically or in patients who experience toxicities. Rifampin, on the other hand, is not a CYP3A4 substrate. Rather, it is primarily transported and metabolized via non-CYP pathways, including anion transporter proteins. Therefore, rifampin concentration is less likely to be affected by clinically relevant DDIs compared with rifabutin, as fewer medications interfere with the rifampin metabolic pathway. Therapeutic drug monitoring may be considered in select circumstances; however, the therapeutic range of rifabutin has not been well established in *M. chimaera* or other NTM infections.

DDIs With Macrolides

Clarithromycin is a moderate CYP3A4 inhibitor, which can lead to supratherapeutic concentrations of CYP3A4 substrates. As rifabutin is a CYP3A4 substrate, clarithromycin can inhibit metabolism of rifabutin, which may lead to supratherapeutic exposure. This may expose individuals to a higher risk of uveitis [66]. Additionally, clarithromycin can increase the serum concentrations of multiple narrow–therapeutic index agents including warfarin, DOACs, and immunosuppressive agents, which may increase the risk for toxicities. Empiric dose

Table 2. Summary of DDIs With Immunosuppressive Medications and Primary Agents for the treatment of *M. chimaera* infections

Antimycobacterial	Immunosuppressive Medication	Interaction Mechanism	Extent of Interaction	Recommendation
Macrolides				
Clarithromycin	CSA, TAC, SRL, EVR	CPY3A4 inhibition	Strong	Avoid use if possible; utilize azithromycin as alternative If cannot utilize azithromycin, empirically reduce immunosuppression dose by 50% with frequent therapeutic drug monitoring
	Prednisone, methylprednisolone	CYP3A4 inhibition	Moderate	Utilize azithromycin as alternative
Rifamycins				
Rifampin	CSA, TAC, SRL, EVR	CYP3A4 induction	Strong	Avoid use if possible; utilize rifabutin as alternative If cannot utilize rifabutin, empirically increase immunosuppression dose by 100% with frequent therapeutic drug monitoring
	MMF, MPA	UGT induction OATP induction	Strong	Avoid use if possible; utilize rifabutin as alternative If cannot utilize rifabutin, consider therapeutic drug monitoring; however, therapeutic index not well established
	Prednisone, methylprednisolone	CYP3A4 induction	Strong	Consider dose increases
Rifabutin	CSA, TAC, SRL, EVR	CYP3A4 induction	Moderate	Consider empiric dose increases with frequent therapeutic drug monitoring
Miscellaneous Antimycobacterials				
Clofazimine	CSA, TAC, SRL, EVR	CPY3A4 inhibition*	Strong	No data to recommend empiric dose adjustments; consider frequent therapeutic drug monitoring
	Prednisone, methylprednisolone	CYP3A4 inhibition*	Moderate-Strong	No data to recommend empiric dose adjustments; adjust corticosteroid dose according to clinical response

*Clofazimine is predicted to be a strong CYP3A4/5 inhibitor from dynamic modeling studies; however, its effect on drug concentrations of CYP3A4 substrates is unknown. Abbreviations: CSA, cyclosporine; DDI, drug–drug interaction; EVR, everolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; OATP, organic anion transporting polypeptide; SRL, sirolimus; TAC, tacrolimus; UGT, uridine glucuronosyltransferase.

adjustments may be required for major CYP3A4 substrates. Unlike clarithromycin, azithromycin is not an inhibitor of CYP3A4. Therefore, it does not have the same potential for DDIs as clarithromycin.

DDIs With Clofazimine

Dynamic modeling has predicted that clofazimine could be a moderate to strong inhibitor of CYP3A4/5 and a weak inhibitor of CYP2C8 and CYP2D6. In the same analysis, the authors suggested that clofazimine co-administration with major CYP3A4/5 substrates could result in a significant increase in the AUCs of those substrates [94]. However, the effect of this potential on concentrations of CYP3A4 substrates has not been further evaluated in human pharmacokinetic studies. Further studies are necessary to evaluate the true extent of this DDI, primarily with regards to moderate and major CYP3A4 substrates.

PHARMACOLOGIC CONSIDERATIONS IN PATIENTS ON IMMUNOSUPPRESSIVE THERAPY

As previously mentioned, significant attention to concomitant medications is necessary in individuals with *M. chimaera* infections on maintenance immunosuppression, particularly heart transplant recipients. Interactions between antimycobacterial agents and immunosuppressants are significant, virtually always requiring pharmacotherapy modifications.

Calcineurin & mTOR Inhibitors

Tacrolimus binds to FK binding protein-12 to inhibit calcineurin phosphatase, ultimately preventing the activation of T cells [137]. Cyclosporine is another calcineurin inhibitor, but unlike tacrolimus, it binds directly to cyclophilin to inhibit calcineurin activity [138]. Both medications are associated with significant DDIs, as they are major substrates for CYP3A4 and P-glycoprotein/ABCB1 [137–139]. The most significant DDI encountered with calcineurin inhibitors is with rifamycins. As a potent inducer of both CYP3A4 and P-glycoprotein, rifampin can lead to significant reductions in both tacrolimus and cyclosporine concentrations, significantly increasing the risk for organ rejection. In healthy volunteers, co-administration of rifampin and tacrolimus resulted in a ~50% reduction in AUC [139]. In multiple case studies of solid organ transplant recipients, significant tacrolimus dose increases were required to maintain therapeutic concentrations, with some individuals requiring escalations >100% of the original dose [140–142]. One case report identified a patient requiring a dose increase of 10 times the original dose in order to yield a therapeutic trough concentration [141]. Cyclosporine concentrations appear to be affected in a similar manner as tacrolimus when co-administered with rifampin. Studies have suggested 2- to 3-fold increases in cyclosporine doses in order to maintain therapeutic drug concentrations [133]. In a case series of 3 heart transplant recipients on stable doses of cyclosporine who were co-administered rifampin, tacrolimus

concentrations decreased 39%–70% within 48 hours of rifampin administration [143].

Sirolimus and everolimus inhibit mammalian target of rapamycin (mTOR), suppressing T-lymphocyte proliferation. Like calcineurin inhibitors, mTOR inhibitors are also major CYP3A4 substrates, whose concentrations can be significantly decreased by rifamycins [144, 145]. The impact of rifampin on the metabolism of these agents is substantial, with studies demonstrating significant increases in drug clearance and subsequent decreases in AUC. In healthy volunteers, rifampin has been shown to decrease sirolimus and everolimus AUCs by up to 82% and 63%, respectively [146, 147]. Case reports describe significant increases in mTOR inhibitor doses needed to achieve therapeutic concentrations (sirolimus: 5–6-fold increase; everolimus: 24-fold increase) [148, 149].

Due to the significant DDIs between rifampin and both calcineurin inhibitors and mTOR inhibitors, many clinicians have preferentially used rifabutin in place of rifampin to mitigate the extent of these interactions [146–151]. While rifabutin can induce CYP3A4, the overall magnitude is significantly lower than that encountered with rifampin. Clinical experience with rifabutin in transplant patients is limited but promising. In a case report of a renal transplant recipient who required tacrolimus dose escalation while on rifampin, initiation of rifabutin allowed for therapeutic drug concentrations to be achieved using tacrolimus doses similar to the prerifampin dose [150]. In another report of a transplant recipient treated for latent tuberculosis, transition from rifampin to rifabutin necessitated a 2.5-fold tacrolimus dose increase from baseline, compared with a 3.8-fold increase observed with rifampin coadministration [151]. Similar experiences have been described with the mTOR inhibitors sirolimus and everolimus, with one author estimating that the induction potential of rifabutin was ∼4–5-fold lower than rifampin based on pharmacokinetic analysis [149].

Other notable drug interactions between *M. chimaera* treatment options and calcineurin or mTOR inhibitors include the interaction with macrolides [152]. As previously described, clarithromycin is a moderate CYP3A4 inhibitor, resulting in increased concentrations of both calcineurin and mTOR inhibitors. Pharmacokinetic studies have demonstrated up to 10-fold increases in tacrolimus AUC_{24} with clarithromycin [152, 153]. Azithromycin is not an inhibitor of CYP3A4; therefore, it does not affect the metabolism of either calcineurin or mTOR inhibitors. Given the effect that clarithromycin can have on drug metabolism and the lack of effect seen with azithromycin, it is recommended to utilize azithromycin when possible. In instances where azithromycin is not an option, it is recommended that doses of tacrolimus, cyclosporine, everolimus, or sirolimus be empirically reduced by 50% upon initiation [154, 155].

Mycophenolate

Mycophenolate concentrations can also be significantly affected by enzyme induction due to rifamycins. Mycophenolate is metabolized by UGTs to the inactive form, 4-hydroxyphenyl-B-glucorinde (MPAG). Mycophenolate undergoes enterohepatic recirculation, which accounts for 40% of the AUC. Biliary excretion and reabsorption of mycophenolate involve organic anion-transporting polypeptides, multidrug resistance-related proteins, and UGTs [156–158]. UGT induction due to rifampin plays a significant role in mycophenolate metabolism. This induction is thought to occur secondary to induced gene expression of nuclear pregnane X, which leads to increased glucuronidation of mycophenolate to its inactive form, which can ultimately result in subtherapeutic mycophenolate exposure [158].

Despite the concerns regarding co-administration of rifampin and mycophenolate, there are limited clinical data to support specific dosage recommendations. A 3-fold dose increase in mycophenolate mofetil was required to achieve therapeutic mycophenolate concentrations in a case report of a heart transplant recipient also receiving rifampin [157]. Additionally, rifampin co-administration resulted in a ∼20% decrease in mycophenolic acid (MPA) AUC when assessed in 8 renal transplant recipients. This effect was primarily driven by decreased enterohepatic recirculation, a result of increased induction of MPA glucuronidation [158].

Corticosteroids

Corticosteroids are one of the mainstays of immunosuppression in solid organ transplantation, as they are utilized for induction and maintenance regimens, as well as for both cellular- and antibody-mediated immunity. Multiple corticosteroids, including prednisone and (methyl)prednisolone, are CYP3A4 substrates. Rifampin has been shown to increase clearance of prednisolone and decrease AUC by up to 66% [159]. As prednisone is converted to prednisolone by 11-beta-hydroxy steroid dehydrogenase, the effect on prednisone is expected to be similar. One case study reports on 2 patients prescribed oral prednisone who were co-administered rifampin. Prednisolone clearance increased by ∼2-fold, with a corresponding decrease in half-life of 40%–60%. The authors proposed a dose increase of nearly 100% to achieve therapeutic concentrations of prednisolone when co-administered with rifampin [160]. Despite these findings, there are no specific dosing recommendations available in consensus guidelines; however, clinicians should be made aware of the significant effect that rifampin can have on prednisolone concentrations and increase doses according to clinical response.

Rifamycins in Solid Organ Transplantation

In summary, the use of rifampin should be avoided whenever possible in solid organ transplant recipients due to the

significant effect that rifampin can have on multiple maintenance immunosuppressive medications, a recommendation that is also supported by the American Society of Transplantation (AST) Infectious Diseases Community of Practice (IDCOP) guidelines on the management of DDIs [154, 155]. Rifabutin is considered the preferred rifamycin in these clinical scenarios. Rifabutin is still likely to induce CYP3A4; therefore, dose increases of immunosuppressive medications are still expected in order to achieve therapeutic concentrations; however, the doses required are likely to be considerably lower than those required with rifampin. In cases where rifabutin is unavailable and rifampin is subsequently initiated, it is recommended that doses of tacrolimus, cyclosporine, sirolimus, and everolimus be doubled empirically. Regardless of the rifamycin prescribed, the trough levels of these immunosuppressive medications should be monitored within 7 days of rifamycin initiation to assess the extent of the interaction and to provide appropriate dose adjustments. With regards to mycophenolate, the AST IDCOP provides the same recommendations for rifampin and rifabutin. Similar to calcineurin inhibitors, rifabutin should be used preferentially over rifampin in an attempt to mitigate the extent of DDIs encountered with co-administration of these immunosuppressive medications. There is no recommendation for dose adjustments of mycophenolate when co-administered with rifabutin [154, 155]. However, as rifabutin is a less potent inducer of UGT, it is not expected to have the same effect on mycophenolate metabolism as rifampin. The role of therapeutic drug monitoring of mycophenolate is unclear as the therapeutic index is not well established in solid organ transplant recipients.

Reducing Immunosuppression

An aspect of immunosuppression management that is not well elucidated is the role of reducing the degree of immunosuppression in patients with *M. chimaera* infections. Currently, it is recommended to reduce the degree of immunosuppression when feasible, but this a weak recommendation based on low quality of evidence [155]. It is a particularly difficult situation, as excessive immunosuppression can lead to clinical failure; however, inadequate immunosuppression increases the risk for allograft rejection. Further studies are needed to describe the impact of reduced immunosuppression on the resolution of infection while maintaining optimal allograft function in individuals with *M. chimaera* infections.

CONCLUSIONS

The clinical diagnosis of *M. chimaera* infections can be difficult. Infection should be suspected in patients with postoperative infections following open heart surgery in which HCUs were used for cardiopulmonary bypass. In addition to aggressive surgical intervention, combination antimycobacterials are the standard of care for all patients with *M. chimaera* infections. First-line therapy includes a 4-drug regimen, consisting of a macrolide, a rifamycin, ethambutol, and amikacin. Multiple second-line agents can be utilized in the setting of clinical failure, intolerances, or toxicities, but clinical data to support their use are limited. Clinical outcomes in individuals with *M. chimaera* infections are poor, with mortality rates as high as 50%–67% in infections post–cardiothoracic surgery; however, more long-term clinical outcomes data are needed in patients treated with combination first-line and second-line recommended agents [7, 161]. Additionally, there are no studies that have compared the effectiveness of different antimicrobial regimens on treatment outcomes. DDIs are a major component of optimal management of *M. chimaera* infections, as many patients are likely to be prescribed concomitant medications that can interact with at least 1 antimycobacterial agent. These interactions are particularly challenging in solid organ transplant recipients. Therapeutic drug monitoring is highly recommended and can help to ensure appropriate concentrations of immunosuppressive therapy, balancing the tradeoff between clinical failure due to overimmunosuppression vs allograft rejection due to inadequate immunosuppression. Consultation with an infectious disease expert is highly recommended for optimal management of antimycobacterials. With regards to DDIs, consultation with a transplant and/or infectious disease pharmacist is also highly recommended to maximize the likelihood of clinical success and avoidance of toxicity. More studies are needed to assess long-term treatment outcomes and to define optimal pharmacologic management, including preferred drug combinations and duration of therapy.

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