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Review

Pulmonary nontuberculous mycobacterial infections among women with cystic fibrosis and non-cystic fibrosis bronchiectasis

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***Abstract*:** Nontuberculous mycobacteria (NTM) are ubiquitous, opportunistic pathogens that can cause lung disease in people with non-cystic fibrosis bronchiectasis (NCFB) and cystic fibrosis (CF). The incidence of NTM pulmonary infections and lung disease has continued to increase worldwide over the last decade among both groups. Notably, women with NCFB NTM pulmonary disease (NTM-PD) bear a disproportionate burden with NTM rates increasing in this population as well as having consistently higher incidence of NTM-PD compared to men. In contrast, among people with CF, an overall increased risk among women has not been observed. In the United States, the majority of people with CF are taking highly effective cystic fibrosis transmembrane conductance regulator (CFTR) modulators, and these numbers are increasing worldwide. The long-term impact of CFTR modulator medications on NTM infections is not entirely understood. Guidelines for the screening, diagnosis, and management of NTM-PD exist for people with NCFB and CF, but do not consider unique implications relevant to women. This review highlights aspects of NTM-PD among women with NCFB and CF, including the epidemiology of NTM infection, special considerations for treatment, and unmet research needs relevant to women with NTM-PD.

Plain language summary

Nontuberculous mycobacterial lung infections in women

Nontuberculous mycobacteria (NTM) are bacteria that can cause lung disease in people with non-cystic fibrosis bronchiectasis (NCFB) and cystic fibrosis (CF). The incidence of NTM pulmonary infections and lung disease has continued to increase worldwide over the last decade among both groups. Notably, women with NCFB NTM pulmonary disease (NTM-PD) are more likely than men to get infected with NTM and to get disease. In contrast, among people with CF, women and men are equally likely to get NTM infection and disease. More people with CF across the globe are getting highly effective treatment using CF transmembrane conductance regulator (CFTR) modulators. We don't understand how these medications will affect the chance of getting NTM infections if people take them for many years. Guidelines for the screening, diagnosis, and management of NTM-PD exist for people with NCFB and CF, but do not consider unique implications relevant to women. This review highlights aspects of NTM-PD among women with NCFB and CF, including the epidemiology of NTM infection, special considerations for treatment, and unmet research needs relevant to women with NTM-PD.

Keywords: breastfeeding, cystic fibrosis, epidemiology, *Mycobacterium abscessus*, *Mycobacterium avium* complex (MAC), non-cystic fibrosis bronchiectasis (NCFB), nontuberculous mycobacterial (NTM) pulmonary disease, pregnancy, women's health

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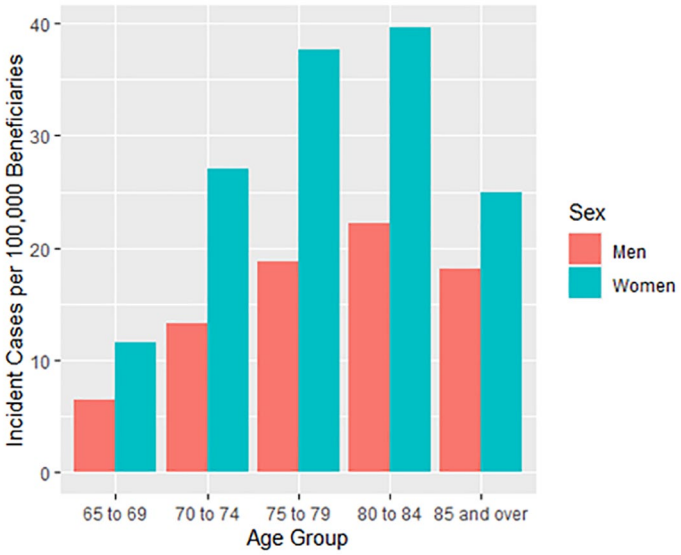

Figure 1. Average annual incidence of nontuberculous mycobacterial pulmonary disease by sex, Medicare beneficiaries aged >65 years, 2010–2019, United States.
Source: DRP who is a federal employee and the work is in public domain.

Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous, opportunistic pathogens that can cause lung disease in susceptible human populations.[1] People with bronchiectasis, including people with cystic fibrosis (CF)[2] and people with non-cystic fibrosis bronchiectasis (NCFB)[3] lung disease, are most at risk and have the highest rates of pulmonary NTM infections. *Mycobacterium avium* complex (MAC) and subspecies of *Mycobacterium abscessus* are the leading causes of NTM infections in both groups. Our understanding of the sources and modes of NTM infection acquisition and transmission are improving, and include acquisition from soil, water, and water biofilms from natural and built environments[4–7] including homes[8] and CF care centers[9–11] as well as person-to-person transmission.[9,10,12–15] Nonetheless, significant gaps to inform infection prevention remain.[16] NTM infections are challenging to treat and eradicate and are often associated with toxicity and intolerances.[2,3] Notably, postmenopausal women have the highest rates of infection among those with NCFB.[7] Among children and adults with CF, 20% will have an NTM-positive culture within a 5-year timeframe, but gender-based differences in infection rates are not apparent.[17] In this review, we discuss features of NTM infections relevant to women with CF and NCFB highlighting the epidemiology, special considerations for treatment, and address unmet research needs.

Epidemiology

United States

In the United States, NTM pulmonary infections and disease are an increasing concern in both the high-risk CF population as well as the general populations, with distinct patterns in each group. In the US non-CF population, particularly among older adults over age 50, the incidence of NTM pulmonary infections and disease has continued to increase. Additionally, the impact among women has been increasing, with a consistently higher incidence among women.[18] In a recent analysis among 30 million Medicare beneficiaries, a case of NTM pulmonary disease (NTM-PD) was defined as two claims for NTM-PD (ICD9 0310 or ICD10 A0310), with an incident case defined as having NTM-PD with no claims in the prior 24 months.[18] Throughout the study period 2010–2019, incidence was 1.4- to 2-fold higher among women than men across age groups (Figure 1); the average annual incidence increased by 6.4% among women and 4.0% among men (Figure 2). During this period, the overall average annual incidence was 20 per 100,000 persons.[18]

The disproportionate burden among women, as well as the increasing incidence, are patterns consistent with analyses over the past 20 years. In a separate national study of insurance claims data across all age groups, NTM-PD was defined as

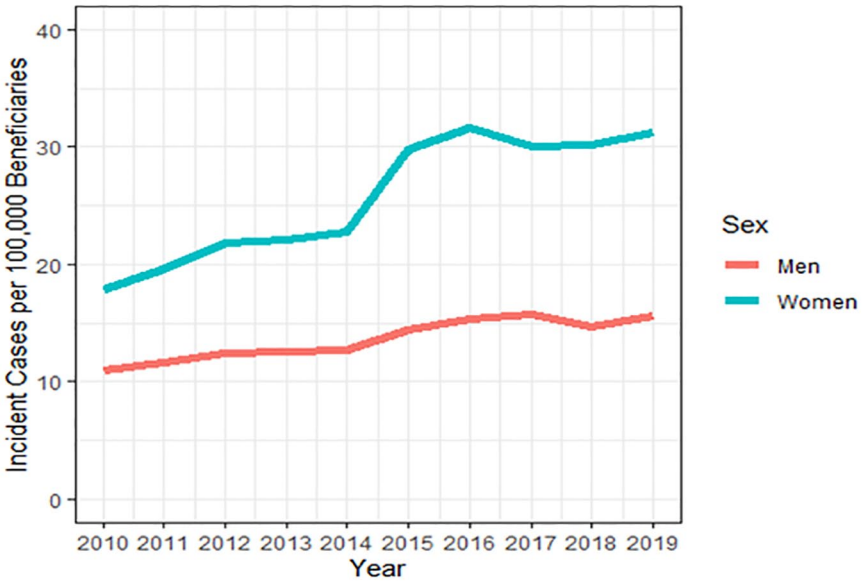

Figure 2. Annual incidence of nontuberculous mycobacterial pulmonary disease by sex, Medicare beneficiaries aged > 65 years, 2010–2019, United States.
Source: DRP who is a federal employee and the work is in public domain.

two claims with NTM-PD ICD codes separated by 30 days. From 2008 to 2015, incidence among women increased from 4.2 to 6.7 per 100,000 person-years, with an increase of 2.0 to 2.7 per 100,000 person-years among men during the same period.[19] In an earlier study across five integrated health care systems using American Thoracic Society (ATS) microbiologic criteria to define disease, incidence and prevalence were similarly higher among women compared with men. Among women over age 60, 1 of every 3370 women was affected, compared with 1 of 4347 men.[20]

People with CF

Among people with CF (pwCF), an overall increased risk of infection among women has not been observed. From 2010 to 2018, based on analyses of CF Foundation Patient Registry (CFFPR) data using microbiologic data to define cases of pulmonary infection (one positive culture), 52% of cases were among men and 48% among women.[17,21] In this population, older age[22] and age at initial CF diagnosis[17] are the most significant host-related predictors of NTM. However, among pwCF aged > 60 years, an interaction of body mass index (BMI) and sex was observed: women with BMI < 25 had the highest NTM prevalence, whereas men with BMI > 25 had the highest prevalence.[17] With respect to trends, from 2010 to 2019, the annual incidence of NTM pulmonary infections (NTM-PI) among pwCF increased significantly by 3.5% per year, with an average annual incidence of 58 per 100,000; the highest rates were observed for *M. abscessus* in the South and for MAC in the Northeast[21] (Figure 3). NTM-PI was defined as a single pulmonary isolate after two negative isolates.

Among CF NTM prevalence studies, North Americans have a higher prevalence of MAC over *M. abscessus*[21] when compared with Europeans, who generally demonstrate a predominance of *M. abscessus*.[23–26] A US population-based study among pwCF reported that NTM was more common in adults when compared to children with CF.[22] A study of French children and adults with CF found NTM-positive cultures were highest among adolescents aged 13–17, with more *M. abscessus* infections in children and MAC equally distributed among children and adults.[27] In contrast, another French study found NTM prevalence was low among children under 15 years with *M. abscessus* common among children and adults, and MAC was never recovered prior to age 15.[28] In a U.S. study, the prevalence of NTM-positive cultures and NTM infection were highest among women diagnosed with CF in adulthood

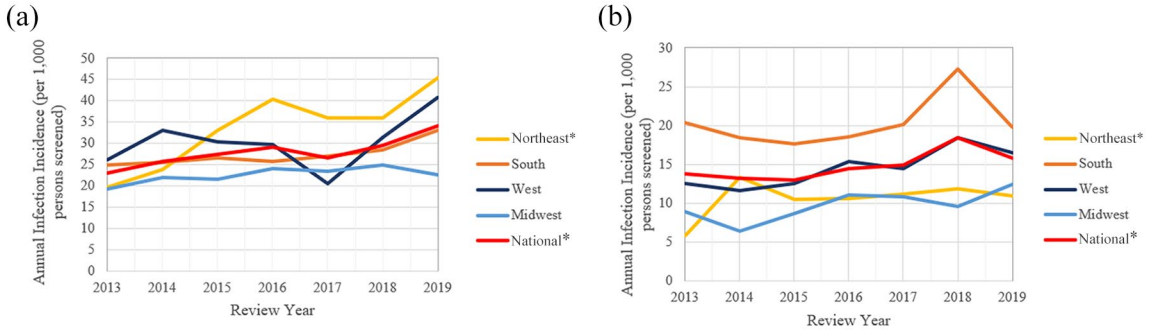

Figure 3. (a) Annual Incidence of *Mycobacterium avium* complex pulmonary infection by United States (U.S.) region (2010–2019). (b) Annual incidence of *Mycobacterium abscessus* pulmonary infection by U.S. region (2010–2019).
*Significant annual percent change ($p < 0.05$).
Source: DRP who is a federal employee and the work is in public domain.

(74% female) compared to those diagnosed in childhood.[29]

Species distribution in people with CF and NCFB

The geographic distribution of NTM clinical isolates across the United States is similar for persons with and without CF, reflecting environmental conditions and mycobacterial niches which predispose to increased NTM abundance with increased risk. However, the prevalence of *M. abscessus* infections is higher among pwCF compared with the NCFB. Overall, in an analysis of data from the CFFPR for 2010–2019, 48% of incident cases had MAC infection and 25% had *M. abscessus*. The species-specific incidence varied by region, with the highest incidence of MAC observed in Northeast, and the highest incidence of *M. abscessus* observed in the South.[21]

Among persons without CF who were tested through a commercial lab network (Labcorp), an analysis of respiratory cultures sent for acid-fast bacillus (AFB) culture from 2019 to 2022 found a similar geographic distribution of isolates, with a MAC predominance in the Northeast and an *M. abscessus* predominance in the South. Among positive isolates, the proportion of MAC varied from 61.8% to 88.9% and was highest in the Northeast, while the proportion of *M. abscessus* ranged from 3.8% to 19.7% and was highest in the Southeast.[30] A separate national study using microbiologic data from a large electronic health record system during 2009–2015 found an overall AFB testing rate of 45/10,000 with an increasing annual percent change (APC) of 3.2%. The isolation rate for pathogenic NTM also increased with an APC of 4.5% and was highest among pwCF and those with bronchiectasis.[31]

Europe, Asia, Australia

Although data are not available from all global regions, data from Europe, Asia, and Australia, where population-based data have been used to describe NTM epidemiology, indicate an overall 4% increase in both NTM pulmonary infection (defined as a single isolate) and pulmonary disease (defined as at least two isolates).[32] Age- and sex-specific patterns across countries and regions reflect to some degree the prevalence of underlying risk factors in the population, particularly chronic obstructive pulmonary disease (COPD) and lung neoplasms: COPD has tended to be predominantly male, which largely reflects smoking patterns in the population.

In Europe, species isolated from respiratory specimens or causing NTM-PD varies widely among, and even within, countries. Notably, differences include a high percentage of NTM-PD caused by *M. xenopi* in Croatia, Czech Republic, and Serbia, *M. kansasii* in Poland and some Spanish regions, and *M. malmoense* in Scotland and The Netherlands.[33] A recent systematic review found that MAC ($n = 505$, 36.4%) and *M. kansasii* ($n = 495$, 35.6%) were the most frequent disease-causing species followed by *M. xenopi* ($n = 126$, 9.1%) and *M. abscessus* complex ($n = 74$, 5.3%).[33]

In East Asia where data are available primarily from Japan, South Korea, and Taiwan, the species

distribution shows *M. intracellulare* predominance in China and Korea, but *M. avium* in Japan. Population-based epidemiological data have been reported from Taiwan, Korea, and Japan since 2014, using primarily insurance claims data. These reports show a consistent upward trend. Overall, *M. avium/intracellulare* predominated in Japan and S Korea, whereas *M. abscessus* predominated in multiple studies from China. Of interest is the finding that the proportions of cases with *M. abscessus* species are higher in the southern regions of China, Taiwan, and Japan.[7]

Nontuberculous mycobacterial lung disease in people with NCFB

The pathogenesis of NCFB is multifactorial and therefore the clinical presentation is quite variable. It is a disease that is associated with older age with a median age of 67 years in the United States[19] and Europe.[34] Gender differences exist related to the etiology of the disease. An evaluation of the European Bronchiectasis Registry (EMBARC) noted that COPD-related bronchiectasis was more common among men than women (18% vs 5%; *p*, 0.001), whereas asthma-related bronchiectasis (2% vs 4%; $p=0.036$) and idiopathic bronchiectasis (35% vs. 44%; $p=0.003$) were more common among women.[34] Underlying bronchiectasis is a significant risk factor for the development of NTM-PD. In a study from Korea, patients with bronchiectasis had a 19-fold greater risk of developing NTM-PD than those without bronchiectasis,[35] and in the United States, among Medicare beneficiaries aged >65 years, persons with NTM-PD were 75-fold more likely to have bronchiectasis than those without NTM.[36] The 2017 report of the US Bronchiectasis and NTM Registry (BRR) noted that 63% of patients had a history of NTM infection or NTM isolation at baseline. This rate is much higher than the observation from the EMBARC data noting an NTM prevalence of 18%.[37] Age was similar (67 year) between these two registries, but a higher proportion of female sex was noted in the BRR versus EMBARC (79% vs 61%) and lower BMI (22 vs 24.9 kg/m^2).[38] However, in a more generalizable nationally distributed sample of persons with bronchiectasis in the United States, among the 56% of persons with a sample taken for microbiologic analysis over an average observation time of 3.6 years, only 4% had MAC infection, of whom 70% met the definition for disease.[39] These data suggest that the US BRR overrepresents persons with NTM, due to the expertise of the tertiary care centers where patient recruitment occurs.

Two phenotypes of NTM-PD have been observed, coined the fibrocavitary type (FC) and nodular-bronchiectatic type (NB). Persons presenting with FC disease are more likely to be men with a history of COPD, whereas women without a history of smoking comprise the majority of patients with the NB type of infection. The FC type is associated with all-cause and MAC-specific mortality.[40,41] This NB type is an independent predictor for recurrence after successful treatment.[42] Most of these recurrences are related to a new infection versus a relapse of the prior infection, suggesting an innate host vulnerability to NTM infection.[43]

A large genome-wide association study in Japan attempted to define this mechanism of vulnerability. One thousand sixty-six individuals with pulmonary MAC were screened for genetic mutations. A significant single nucleotide polymorphism (SNP; rs109592) was identified in the intronic region of CHP_2 which regulates pH expressed in epithelial cells of the lungs. This SNP was found to be a risk factor among different populations (Japanese, Korean, and American) and was more common in the NB type of NTM lung disease.[44]

The distinct morphotype of women presenting with NTM-PD has been well described. The characteristics include age >50 years, tall stature, slender body habitus, right middle lobe, and lingular bronchiectasis with comorbidities of pectus excavatum, scoliosis, and mitral valve prolapse.[45–47] A systematic review and meta-analysis of MAC disease (in the absence of predisposing structural lung disease or immunocompromising conditions) found important differences between women and men ($n=65, 52$). Women had a lower BMI (21.42 vs 23.54 kg/m^2, $p<0.001$) and a greater degree of right middle lobe predominant disease (72% vs.48%, $p=0.01$). They were also found to have more severe disease as characterized by greater rates of cavitation (38% vs 19%, $p=0.03$), more extensive treatment history (75% vs 56%, $p=0.03$), and a trend toward higher rates of macrolide resistance (15% vs 3%, $p=0.07$).[48] A key factor related to disease susceptibility and progression is BMI. In a recent study in Hawai'i (HI) including nearly 300,000 Kaiser Permanente

HI beneficiaries, in which baseline BMI was measured prior to NTM infection, low BMI was a risk factor for NTM infection.[49] However, the effect of BMI varied by sex: decreasing BMI was associated with a higher NTM-PD risk for women than for men.[49] This observation deserves further investigation.

A large prospective study in South Korea over a 9-year period which was based on health insurance claims found that lower BMI at baseline as well as weight loss during the study period were associated with higher NTM-PD risk.[50] Proposed mechanisms for increased risk among persons with low BMI include fat loss with changes in adipokines (e.g., leptin, resistin, and adiponectin). Studies of mice have shown that experimental fat ablation can contribute to increased lung disease during mycobacterial infection.[51] Leptin levels decreased with lower BMI, and pulmonary bacterial loads after *Mycobacterium tuberculosis* infection in mice that were genetically deficient in leptin were higher.[52] The relationship between low body fat and sex hormones is well recognized. Females who are anorexic cease menstruating.[53] Lower adipokines lead to low follicle-stimulating hormone (FSH) and luteinizing (LH) hormone. This disruption of the FSH/LH-estrogen axis due to leptin deficiency may help explain why such thin individuals are predisposed to NTM infections.[54]

Gender differences are noted in several airway diseases including asthma, COPD, and bronchiectasis. A key hypothesis is related to sex hormones. The female sex hormones estrogen and progesterone affect ciliary beat frequency. An in vitro study of human lung epithelial cells from male and female transplant donors noted progesterone (P4) decreased cilia beat frequency (CBF) by 42.3%. Inhibition of CBF was prevented by coadministration of P4 with the active form of estrogen, 17b-estradiol.[55] In a murine model experiment of ovariectomized mice, investigators noted the number of bacilli in the lungs of infected mice who received ovariectomy was significantly larger than that in the lungs of sham-operated control mice. Treatment of ovariectomized mice with exogenous E2 restored the burden of bacilli to the same level as that in the sham-operated control mice. Additionally, they found estrogen enhanced the anti-MAC activity of murine macrophages by modifying reactive nitrogen intermediates production, which may partly explain the effects of estrogen in vivo.[56]

In a Korean nationwide population-based longitudinal study, reproductive factors were evaluated to determine associations with the development of bronchiectasis. A total of 959,523 pre-menopausal and 1,362,401 post-menopausal subjects were included. They were followed for a mean of 8.3 and 8.1 years, respectively. During the study, the incidence of bronchiectasis in the pre-menopausal cohort was 190.2 cases per 100,000 person/year, while the incidence in the post-menopausal cohort was 468.7 cases per 100,000 person/year. A shorter lifetime exposure to endogenous female sex hormones (a later menarche in premenopausal women as well as later menarche, earlier menopause, and shorter reproductive period in postmenopausal women) correlated with an increased incidence of bronchiectasis.[57]

In a cross-sectional study comparing patients with *Mycobacterium avium* pulmonary disease (MAC-PD) and healthy controls, low serum estradiol was independently associated with MAC-PD.[58] With registry data, we are beginning to unravel the natural history of bronchiectasis and NTM-PD. In a 5-year longitudinal analysis of patients with bronchiectasis in the US registry, the presence of NTM infection did not affect mortality or worsening of other clinical outcomes. Individuals with NTM infection at baseline were older, had a lower BMI, were more likely to be female, were more likely to have smoked, had a higher FEV1 percent predicted (75% vs 71%), and fewer had a positive test result for *P. aeruginosa* (15% vs 28%). All-cause mortality at 5 years was 12%. Risk factors associated with 5-year mortality included increased age, hospitalization in the 2 years before baseline, low BMI, low FEV1 percent predicted, increased modified medical research council (mMRC) dyspnea scale score, oral steroid use, antibiotic use, use of medications for GERD, male sex, and a diagnosis of COPD.[40,59] In a separate study of 300 patients with bronchiectasis followed for a median of 4 years, of whom 74% had any history of NTM infection, the 6 minute walk distance (6MWD) as well as Pulmonary Symptom Severity Score were independent predictors of mortality (after controlling for age, BMI, *M. abscessus* infection, and FC disease).[60]

Nontuberculous mycobacterial lung disease in people with CF

The significance of a first-time NTM-positive culture is difficult to ascertain as the progression of infection may be transient and self-resolving, intermittently positive without signs of disease, or chronically positive with declining lung function and meeting criteria for NTM-PD.[61] Guidelines for the screening, diagnosis, and management of NTM-PD initially did not include pwCF,[3] but internationally endorsed CF-specific guidelines have since been published.[2] The CFFPR tracks the annual occurrence of a positive NTM culture but does not assess if the patient meets the criteria for NTM disease or treatment status. As a result, knowing the rates of NTM pulmonary disease, treatment, and outcomes among the US CF population is difficult to estimate.

Studies of age and forced expiratory volume in 1 second (FEV1) as a risk factor have produced conflicting results. One prevalence study demonstrated NTM culture-positive subjects were adults with higher lung function than subjects without an NTM-positive culture.[22] In a study of people with end-stage CF, 19.7% of lung transplant candidates had an NTM-positive culture, but there was no difference in age, sex, forced vital capacity (FVC), FEV1, BMI, or colonization with typical CF pathogens (*Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Staphylococcus aureus*) compared to lung transplant candidates without NTM-positive cultures.[62] An NTM-positive culture has been associated with the colonization of multiple common CF pathogens including *Staphylococcus aureus*,[22,63] *Stenotrophomonas*,[61,64] and *Aspergillus* in the absence[24,61,64,65] or presence of allergic bronchopulmonary aspergillosis.[66] Other studies have concluded long-term azithromycin use decreases the incidence of NTM infection.[24,64] None of these studies concluded female sex was a risk factor. Two large clinical trials are ongoing, designed to standardize the diagnosis (PREDICT, NTC02073409)[67] and treatment (PATIENCE, NTC02419989) of NTM for pwCF. These studies will better inform our understanding of CF NTM infections among women.

CF transmembrane conductance regulator (CFTR) modulators are a class of small molecule drugs that bind the CFTR protein and are currently in one of two categories: corrector or potentiator. Corrector modulators increase the quantity of CFTR protein at the cell surface and potentiators improve the channel function of CFTR protein.[68] Two CFTR modulator medications are considered "highly effective," ivacaftor and the triple combination of elexacaftor/tezacaftor/ivacaftor.[69] The long-term impact of highly effective CFTR modulators on NTM infections is not entirely understood due to recent widespread availability in the US with much more limited availability worldwide. A large study of 25,987 pwCF represented in the CFFPR found a significantly reduced risk of NTM-positive cultures (hazard ratio, 0.88) among people taking CFTR modulators, either ivacaftor monotherapy, the first highly effective modulator approved for use in pwCF, or combination therapy.[70] The pharmacology of other highly effective modulators is expected to have a similar impact.[71] No studies to date have identified specific mechanisms by which CFTR modulators directly affect NTM susceptibility. With the advent of CFTR modulator therapies, the median age of survival has increased to 56 years and more adults are now living with CF than children.[72] Along with this trend, the number of pregnancies has steadily increased, with over 600 pregnancies annually from 2020 to 2022.[72] With the use of highly effective modulator therapies, more women with CF are healthier, living longer, and desiring pregnancy.[73] Data on the number of women with CF desiring pregnancy, pregnant, or breastfeeding in the setting of NTM infection are lacking. A large multicenter observational study, called Maternal and Fetal Outcomes in the Era of CFTR modulators (MAYFLOWERS, NCT04828382) will help address questions regarding pregnancy and infant outcomes for women with CF.[74]

Treatment considerations in nontuberculous mycobacterial pulmonary disease

Not all patients who meet the diagnostic criteria for NTM-PD require treatment. In a cohort of 488 patients from Korea, 62.5% progressed within 3 years of their diagnosis and were treated. Those individuals with smear-positive disease, cavitary lung disease, or more extensive involvement radiographically were more likely to progress requiring treatment.[75] Predictors for an increased risk of all-cause mortality included a low BMI, anemia, low albumin, and elevated inflammatory markers.[41] The recommendation for treatment of MAC pulmonary disease depends on the clinical phenotype. For those with NB

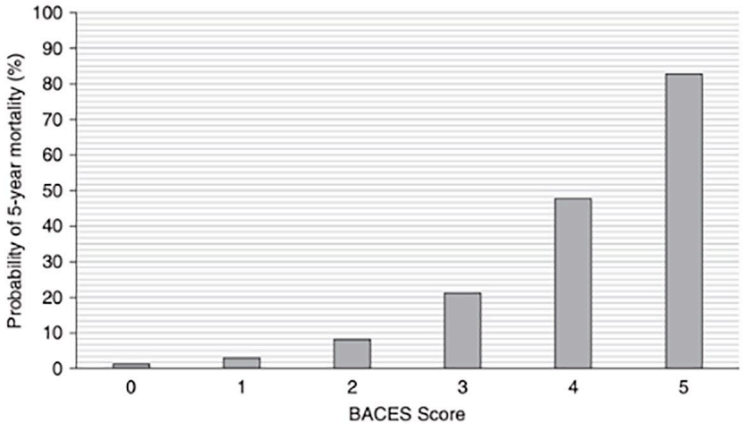

Figure 4. Estimated probability of 5-year mortality in patients with nontuberculous mycobacterial pulmonary disease, according to BACES (body mass index, age, cavity, erythrocyte sedimentation rate, and sex) score. Source: Kim et al.[78] Reprinted with permission of the American Thoracic Society. Copyright © 2024 American Thoracic Society. All rights reserved. DRP who is a federal employee and the work is in public domain.

disease, the regimen includes three antibiotics (macrolide, ethambutol, and a rifamycin) given thrice weekly. In those with severe disease or cavitary disease, the recommendation includes daily three drug oral therapy with the addition of intravenous amikacin for the first 8–12 weeks. Treatment should be administered for at least 12 months after culture conversion. In a meta-analysis of 16 studies, the rate of microbiologic treatment success (12 months of negative cultures while on therapy) was 60%. Default rates, principally due to drug side effects, were 16% overall and 12% among subjects given thrice-weekly therapy. When subjects who defaulted within 12 months were excluded, the treatment success rate was 74%.[76] In a retrospective study of 352 patients with cavitary MAC LD, the culture conversion rate was 69.8%. For the patients with and without culture conversion, all-cause mortality was significantly lower for the culture conversion group (5.3% vs 35.8% $p < 0.001$).[77] Importantly, this study found an increased mortality rate associated with a microbiologic outcome.

A severity scoring system, referred to as BACES (BMI, age, cavity, erythrocyte sedimentation rate (ESR), and sex), was developed based on a derivation and validation cohort to predict the prognosis of NTM-PD. Each variable equates to one point: BMI $< 18.5\,kg/m^2$, age > 65 years, presence of cavity on computed tomography, elevated ESR (15 mm/h in men and 20 mm/h in women), and male sex. A score of 0–1 is mild, 2–3 moderate, and 4–5 severe. The estimated 5-year probability of death based on the BACES score was as follows; 1.2% for a score of 0, 3.2% for a score of 1, 8.4% for a score of 2, 21.3% for a score of 3, 47.8% for a score of 4, and 82.9% for a score of 5 (Figure 4).[78] Using the validated BACES score, a study of 712 patients noted culture conversion rate was higher in those individuals in the mild group than in the moderate or severe group (conversion rate in the overall study period: 89% in the mild group vs 81% in the moderate group and 65% in the severe group; $p < 0.001$). Importantly, this study also noted that culture conversion was an independent predictor for survival. Culture conversion at 6-months demonstrated a significant negative correlation with death (crude hazard ratio (HR), 0.46, 95% CI, 0.33–0.65; adjusted HR, 0.51, 95% CI, 0.35–0.74) and 12-month culture conversion was also associated with reduced death (adjusted HR, 0.51; 95% CI, 0.33–0.78). In a large retrospective study of regimen tolerability in 4626 Medicare recipients, the azithromycin, ethambutol and rifampin combination was better tolerated than clarithromycin, ethambutol, and rifabutin. The adjusted hazard ratio comparing regimen change/discontinuation with clarithromycin-ethambutol-rifabutin and azithromycin-ethambutol-rifampin was 1.64 (95% CI, 1.43–1.64).[79] If sputum cultures have not converted to negative after 6 months of guideline-based treatment, the guidelines recommend the use of amikacin liposome inhalation suspension as part of the continuation treatment regimen. This intensification of treatment was associated with a significant fourfold

increased odds of culture conversion in a large randomized controlled trial; culture conversion by month 6 was achieved by 65/224 (29.0%) patients with ALIS+GBT vs 10/112 (8.9%) with GBT-alone (OR 4.22, 95% CI 2.08–8.57, *p*, 0.001).[80]

Mycobacterium abscessus has innate resistance to multiple antibiotics. Inducible resistance to macrolides is conferred through an erythromycin methylase gene (ERM41). If the isolate harbors a mutation in the ERM 41 gene, the macrolides are effective and should be used in the treatment regimen. A meta-analysis noted a significant difference in cure rates depending on this single characteristic of macrolide sensitivity (88% vs 23%).[81] Treatment typically includes 3–4 antimicrobial agents. The intensive phase of treatment includes 2–3 intravenous antibiotics such as amikacin, imipenem-cilastin and tigecycline, while the oral agents employed to treat this infection include a macrolide (if sensitive), clofazimine, oxazolidinones, omadacycline, and bedaquiline. The duration of therapy is unknown. Experts suggest that cultures are monitored monthly and treatment continue with an attempt to achieve 12 months of negative cultures.[82]

Special considerations for treatment of women with nontuberculous mycobacterial pulmonary disease

Guideline-based NTM treatment is recommended and is notable for the complexity and duration of the therapeutic regimen, requiring the concurrent use of multiple antibiotics for months to years.[2,3] These antibiotics come with their own unique set of side effects, some of which can be more frequently seen, or may be more impactful to women. In general, most antibiotics used to treat NTM cause gastrointestinal (GI) side effects such as nausea, diarrhea, vomiting, and abdominal pain.[83] No clear gender-based differences in GI symptoms have been observed. When antibiotics are combined, overlapping toxicities can make these regimens difficult to tolerate. Adding a probiotic, antiemetics, or administering with food, when appropriate, may help to minimize these symptoms.[84] A summary of drugs used in the treatment of NTM-PD is shown in Table 1.

QTc prolongation has been reported with the use of macrolides, fluoroquinolones, clofazimine and bedaquiline and caution should be used when combining multiple agents known to cause QTc prolongation. Female sex inherently increases the risk for altered cardiac conduction as does older age. EKG monitoring is recommended before initiation and periodically throughout treatment as well as with the addition of any QTc prolonging agent.

Aminoglycosides, as a class, are known to cause nephrotoxicity and ototoxicity. Older adults are at a higher risk of experiencing kidney damage particularly if they also receiving concomitant nephrotoxic medications. Nephrotoxicity is typically reversible, but ototoxicity, specifically sensorineural hearing loss, may often be permanent. Therefore, high-frequency audiometry is recommended at baseline and every 1–2 weeks during the use of parenteral aminoglycosides,[85] although monthly monitoring is often used in clinical practice. The differing guideline recommendations for audiometry are summarized.[86] Similarly, macrolides are also associated with ototoxicity, specifically hearing loss and tinnitus. However, unlike aminoglycosides, this effect is generally reversible. Evidence is conflicting as to whether or not ototoxicity is more prevalent in males[87] versus females[88] or not associated with sex.[89,90] Genetic testing is now available to screen for the genetic mutation m.1555A > G.[91] This mutation is associated with aminoglycoside-induced ototoxicity and some studies have begun implementing this testing in neonates, but routine testing is not currently recommended.

Antibiotics such as rifampin and rifabutin can frequently cause hepatotoxicity, while macrolides, omadacycline, and bedaquiline may also cause liver damage in rare instances. Liver function monitoring is warranted throughout the course of treatment and antibiotics should be discontinued if significant transaminitis occurs. Laboratory monitoring should also include a complete blood count (CBC) with differential as myelosuppression can occur with oxazolidinones, rifamycins, and trimethoprim-sulfamethoxazole. Gender-based disparities in hepatotoxicity and myelosuppression are not known.

Lastly, rifamycins and clofazimine may cause benign changes to skin and body fluids. Specifically, rifamycin may cause body fluids such as sweat, tears, and urine to develop a red-orange discoloration. Similarly, clofazimine can cause discoloration of body fluids but much more

Table 1. Guidance on key side effects, pregnancy, and lactation considerations, DDI, and monitoring.

Drug class	Adverse effects	Pregnancy considerations[104]	Breastfeeding considerations[104]	Notable drug-drug interactions	Monitoring parameters[82,83]
Macrolides	-Gastrointestinal -QTc prolongation -Tinnitus/hearing loss	Compatible	Compatible	*Clarithromycin*: major CYP3A4 substrate; strong CYP3A4 inhibitor	-CBC, CMP -ECG
Clofazimine	-Tanning of the skin/ dry skin -Gastrointestinal	Not FDA approved therefore not classified. Crosses placenta, see text for further information.	Not FDA approved, and therefore not classified. Present in breast milk and may appear tinted red. Skin discoloration of infants has been reported. See text for further information.	Potential CYP3A4/5 and CYP2D6 inhibitor	-Hepatic panel -ECG
Ethambutol	-Optic neuropathy -Peripheral neuropathy	Compatible. Crosses placenta.	Limited Human Data—Probably Compatible. Present in breastmilk. AAP was classified as compatible with breastfeeding in 2001.		-CBC, BMP -Vision Exam
Oxazolidinones *Linezolid* *Tedizolid*	-Peripheral neuropathy* -Myelosuppression* *Less for tedizolid compared to linezolid	Compatible—Maternal Benefit >> Embryo-Fetal Risk. Linezolid likely to cross the placenta based on MW. No Human Data—Maternal Benefit >> Embryo/Fetal Risk. Based on MW and long half-life likely to cross placenta.	Limited Human Data—Probably Compatible. Present in breastmilk, though estimated exposure is less than the recommended treatment dose of 30 mg/kg/day for children < 5 years old. No Human Data—Probably Compatible. Based on MW and long half-life likely to be present in breast milk, though high degree of plasma protein binding may limit excretion.	*Linezolid*: Monoamine Oxidase inhibitor	-CBC
Ciprofloxacin	-QTc prolongation -Tendon rupture -Hepatotoxicity	Contraindicated (Use only if no other alternatives). Linked with fetal cartilage damage and resulting arthropathies, though the relative risk may be low and in some reviews, there was a lack of pattern among defects, authors concluded there are generally safer alternatives depending on indication.	Limited Human Data—Potential Toxicity. Present in breast milk, concentrations tested showed the highest concentrations of ciprofloxacin at 2 h post-dose and the lowest 24 h post-dose. Based on unpublished data available to the manufacturer, ciprofloxacin was undetectable in breastmilk 36–48 h after a dose, so the manufacturer recommends resuming breastfeeding 48 h after the last dose. The AAP classified fluoroquinolones as compatible with breastfeeding in 2021, though at least one published case report of fetal harm was not cited in decision.	Moderate CYP1A2 inhibitor	-CBC, BMP -Hepatic panel -ECG
Levofloxacin	-QTc prolongation -Tendon rupture -Hepatotoxicity	Contraindicated (use only if no other alternatives). See ciprofloxacin above.	Limited Human Data—Probably Compatible. Present in breast milk. Concentrations tested in a single lactating woman resulted in peak levels 5 h post-dose. Minimal levels were detected 65 h post-dose. See AAP decision in ciprofloxacin.		-CBC, BMP -Hepatic panel -ECG

(Continued)

Table 1. (Continued)

Drug class	Adverse effects	Pregnancy considerations[104]	Breastfeeding considerations[104]	Notable drug-drug interactions	Monitoring parameters[82,83]
Rifamycins *Rifampin* *Rifabutin*	-Hepatotoxicity -Myelosuppression -Body fluids discoloration	Compatible Prophylactic vitamin K_1 recommended to prevent hemorrhagic disease of the newborn No Human Data—Animal Data Suggest Moderate Risk. Likely to cross placenta.	Compatible No Human Data—Potential Toxicity. Expected to be present in breast milk, may be brown-orange tinted. Potential effects of exposure include leukopenia, neutropenia, and rash.	Strong CYP3A4, 2C19 inducer; moderate CYP2C9 inducer Major CYP3A4 substrate; moderate CYP3A4 inducer	-CBC, BMP -Hepatic panel
Aminoglycosides *Amikacin* *Streptomycin*	-Ototoxicity -Nephrotoxicity	Human Data Suggest Low Risk. No reports of ototoxicity to fetus have been documented. Human Data Suggest Risk. May cause fetal ototoxicity, particularly with prolonged exposure which would be expected in intensive phase of treatment.	Compatible Excreted into breast milk in low concentrations, oral absorption minimal.		-BMP -Therapeutic drug concentrations -Audiogram
Cephalosporins	-Rash	See text for individual agents	See text for individual agents		
Carbapenems (*meropenem, imipenem/cilastatin*)	-CNS effects -Nausea	Limited Human Data—Animal Data Suggest Low Risk	Limited Human Data—Probably Compatible. Similar concentrations in milk to other beta-lactams. Monitor infant for most common side effects in adults: nausea, headache, constipation, diarrhea, anemia, vomiting, and rash.	Carbapenems decrease levels of valproic acid/divalproex, which could result in breakthrough seizures.	-CBC, CMP
Tetracyclines	-Phototoxicity -Hepatotoxicity	Omadacycline is not formally classified, however, tetracyclines generally avoided due to potential for permanent discoloration of teeth and reversible inhibition of bone growth. See text for more information.	Omadacycline is not formally classified, however, tetracyclines generally avoided similar rationale to pregnancy. The manufacturer does not recommend breastfeeding during therapy or for 4 days after the last omadacycline dose. See text for more information.		-CBC, BMP -Hepatic panel
Bedaquiline	-QTc prolongation -Nausea -Arthralgias -Headache	Limited Human Data—Animal Data Suggest Low Risk. Expected to cross placenta, though high plasma protein binding may limit exposure. See text for further information.	No Human Data—Potential Toxicity. See text for further information.	Major CYP3A4 substrate	-CMP -Mg -ECG

AAP, American Academy of Pediatrics; BMP, basic metabolic panel; CBC, complete blood count with differential; CMP, comprehensive metabolic panel; DDI, drug-drug interactions; ECG, electrocardiogram; Mg, magnesium; MW, molecular weight; QTc, corrected QT interval.
*Peripheral neruopathy and myleosuppression are lesswith tedizolid compared tolinezolid.

commonly causes an orange-brown discoloration of the skin. While these side effects are reversible and not harmful, patients should be counseled in advance that this may occur. Additionally, patients should take precautions to avoid sun exposure while taking clofazimine as it can be photosensitizing. There are no known gender-based differences with these side effects.

Physiological differences between men and women lead to pharmacokinetic and pharmacodynamic variations. Women tend to have higher fat stores meaning lipophilic medications such as benzodiazepines have a longer duration of action and greater effects. As a result, the FDA recommends starting benzodiazepines, such as zolpidem, at lower doses in females. Additionally, females tend to have more CYP3A4 and CYP2D6 activity compared to males. Despite this difference, most drugs do not result in significantly different concentrations between males and females. Medications that are renally eliminated are cleared more quickly in men due to larger renal blood flow, glomerular filtration, tubular secretion, and tubular reabsorption. As a result, women may require lower doses of renally cleared medications such as aminoglycosides, though initial dosing recommendations do not differ by sex.[92,93]

Pregnancy

CFTR modulator therapy has been associated with increased fertility among women with CF.[94] Though clinicians and patients may elect to delay treatment in the setting of pregnancy, select cases where pregnant patients have severe disease or have become pregnant during treatment may arise. There is insufficient data to endorse starting or stopping treatment in the setting of pregnancy and breastfeeding. Ultimately, treatment decisions should be discussed between the patient and the provider. Much of the pregnancy data for NTM pharmacotherapy comes from the treatment of tuberculosis (TB). The risks of untreated TB include high mortality that increases with pregnancy and transmission of TB to the infant, therefore treatment for TB may be more urgently indicated due to the risk of congenital transmission.[95] Clinicians should carefully consider the risk-benefit profile of NTM treatment during pregnancy. Additionally, pregnancy safety data for other antimicrobials utilized in NTM management may have been single dose or much shorter treatment periods for other infectious disease indications.

Historically, medication safety in pregnancy in the US was classified by a letter system (A, B, C, D, and X). However, effective June 30, 2015, this labeling was removed by the Food and Drug Administration to allow for more detailed discussion from registry data. This is intended for the clinician and patient to carefully weigh the risks and benefits of treatment.[96] Countries outside of the United States have unique pregnancy and lactation safety labeling and comparing international guidance for medication use is beyond the scope of this paper. Readers are encouraged to reference local regulatory guidance.

Importantly, physiologic changes due to pregnancy, such as an increase in weight, blood volume, renal blood flow, and hepatic blood flow as well as prolonged gastric emptying can impact pharmacokinetics (PK) and potentially antimicrobial efficacy. The volume of distribution of medications may be impacted due to changes in blood volume and body composition. Certain CYP enzymes responsible for drug metabolism may increase or decrease in activity. CYP3A4 and renal drug transporter p-glycoprotein (p-gp) typically increase in activity which could result in decreased concentrations of medications metabolized via these pathways. Renal clearance also increases beginning in the first trimester up to 37%–45% after 4–5 months gestation.[97]

Rifampin and ethambutol, antibiotics integral to the treatment of NTM PD, are commonly used in the treatment of TB. Drawing from the current CDC TB treatment guidelines, rifampin and ethambutol are part of the preferred initial regimen in pregnancy.[98] Rifampin has been associated with hemorrhagic disease of the newborn in at least three cases. Prophylactic phytonadione (vitamin K1) treatment is recommended.[99] Often considered the "backbone" of NTM treatment in susceptible strains, macrolides are considered compatible therapy during pregnancy.[99]

Bedaquiline use in pregnancy is limited. In a group of 58 pregnant women in South Africa there was no difference in pregnancy outcomes between fetuses exposed to bedaquiline in-utero as compared to those without this exposure. Babies born to women exposed to bedaquiline on average had lower birthweights than those not

exposed, though by 1 year of age more than 80% were developing as expected.[100] A recent longitudinal pharmacokinetics (PK) study investigated the effect of pregnancy on bedaquiline treatment in patients with HIV and rifampin-resistant TB. Because drug exposure is most impacted in the third trimester, samples were collected from thirteen women twice during that time frame and six returned for sampling after birth on average 7 weeks post-partum. Bedaquiline and its metabolite, M2, concentrations were 50% lower than those observed previously in nonpregnant women. The authors attributed this to bedaquiline's metabolism via CYP3A4, high protein binding, and to a lesser extent change in body size. Interestingly, bedaquiline levels were still lower than expected postpartum, though this may be related to the long terminal half-life of 5 months or more. Authors emphasized they only tested total drug concentrations, so the actual unbound, active drug available is unknown.[101]

Omadacycline use during the last half of pregnancy may result in permanent yellow/gray/brown discoloration of the infants' teeth and enamel hypoplasia. Furthermore, omadacycline may inhibit the rate of fibula growth, however, this has been shown to be reversible once exposure to the medication has ended.[102] As a class, tetracyclines are generally avoided in pregnancy due to these adverse effects; however, there may be situations where the clinician deems the benefits of treatment outweigh these potential risks.

Cephalosporins as a class are generally considered safe in pregnancy with low evidence of teratogenicity based on a large population-based study, with most patients taking cephalexin.[103] Human data for cefoxitin in pregnancy specifically is more limited. Cefoxitin is expected to cross the placenta and is a recommended treatment for prophylaxis prior to cesarean delivery.[104] The carbapenems meropenem and imipenem may also be potential options during pregnancy, though their PK may be altered considerably. This is important as they exhibit time above minimum inhibitory concentration (MIC) antimicrobial activity. Imipenem/cilastatin PK after a single 500 mg dose was studied in twenty pregnant women and showed decreased time above MIC for common pathogens and an increase in nonrenal clearance. This supports that a potential dosage adjustment is needed in pregnant women for comparable PK, though widely accepted dose adjustments are not available.[105]

Intravenous amikacin and fluoroquinolones are considered contraindicated by the CDC for use during pregnancy.[98] Fluoroquinolones have animal data supporting cartilage damage and arthropathies and human data does include birth defects, though lack consistency. Due to the potential for birth defects, particularly in the first trimester, fluoroquinolones are contraindicated unless there are no other acceptable alternatives.[104] Systemic aminoglycosides, particularly streptomycin, have been associated with eighth cranial nerve toxicity in the fetus and are considered a class effect. There is also concern for irreversible deafness via the aminoglycoside's known side effect of ototoxicity.

In contrast to intravenous amikacin, the expected systemic exposure of inhaled liposomal amikacin is low, with even less expected to reach the developing fetus. In a PK study consisting of 14 nonpregnant subjects, only 7.4% of the total inhaled amikacin dose was excreted in urine compared to the documented 94% when given intravenously. The average *C*max after 3 months of daily administration among 12 patients was 2.8 mcg/mL (range 1–4.4 mcg/mL).[106] There is no published data on inhaled amikacin use in pregnancy, though its counterpart inhaled tobramycin is rated as "compatible" with pregnancy and considered safe to continue if necessary for clinical stability in pwCF.[107]

Breastfeeding

Although there are no data on the rate of breastfeeding among women with CF, the use of highly effective CFTR modulators has significantly improved the fertility and overall health of women, resulting in increased interest in parenthood inclusive of breastfeeding.[94] Similar to pregnancy, treatment decisions during breastfeeding should consider both the risks and benefits to the mother and the infant. When determining the safety of agents in breastfeeding, the clinician should consider if the antibiotic is transferred into breast milk and at what fraction of the maternal serum dose, oral absorption, pediatric dosing for other indications if available, and recommended monitoring of the newborn if necessary. Azithromycin, rifampin, cefoxitin, and

ethambutol are all present in breastmilk, though considered compatible with breastfeeding.[104]

Linezolid has limited data in breastfeeding and tedizolid has no human data; they are classified as probably compatible and likely compatible, respectively. In single case studies, the amount of linezolid excreted into breastmilk was lower than the recommended dose in infants and peaked at 2 h and remained present in breast milk 24 h after administration.[108,109] It is recommended babies be monitored for the most common documented side effects in pediatric dosing including diarrhea, vomiting, anemia, nausea, and headache.

There is recent data of bedaquiline use in breastfeeding mothers. Bedaquiline does accumulate in breastmilk and a recent PK study demonstrated that newborn and maternal serum concentrations of bedaquiline and M2 are comparable. They also found much higher concentrations of bedaquiline in breast milk than maternal plasma concentrations. The authors concluded that the risks of such high concentrations are unknown, but more information is likely needed to determine the safety to the newborn.[101]

Clofazimine is present in breast milk and may cause red tinting based on findings from use in people with Hansen's disease. Similar to adults, babies exposed to clofazimine may exhibit skin discoloration that typically fades after breastfeeding cessation.[104] The manufacturer recommends the decision to breastfeed be an individualized risk-benefit discussion.

The manufacturer does not recommend breastfeeding while on omadacycline or until 4 days after the last dose of omadacycline.[102] Tetracyclines as a class have similar concerns in breastfeeding as they do in pregnancy as previously discussed. Similarly, fluoroquinolones have limited human data and are listed as potentially toxic to nursing babies.[104]

In contrast to pregnancy recommendations, administration of systemic amikacin is considered compatible in breastfeeding due to poor oral absorption and low amounts found in breastmilk. When given intramuscularly to four pregnant women, only two patients had detectable amikacin levels at 6 h after administration.[110]

Drug-drug interactions

An important consideration of NTM antibiotics is their propensity toward interacting with other medications. Drug interactions may dictate which antibiotics can or cannot be used on a case-by-case basis. Rifampin is a potent inducer of CYP3A4, which is the primary enzyme for metabolizing many other medications.[111] These can include anticoagulants, thyroid replacement medications, and CFTR modulators. Through its induction effects, rifampin decreases the serum concentrations of these aforementioned medications, thereby decreasing their therapeutic effects. Conversely, clarithromycin is a potent inhibitor of CYP3A4.[112] Although it will interfere with the same medications, the inhibition of the CYP3A4 enzyme would increase their therapeutic concentrations and lead to increased risk of drug toxicities. Dose adjustments may be necessary when interacting medications are taken with rifampin or clarithromycin. Due to the importance of CFTR modulators, rifampin is often avoided in CF patients and an alternative antibiotic class must be selected. If clarithromycin is used, CFTR modulator doses need to be adjusted.[113] Should a patient on thyroid medications need to start rifampin, thyroid stimulating hormone monitoring at baseline and 4–8 weeks after initiation is recommended due to rifampin's inducing properties.[114]

Regarding medications specific to females, rifampin and clarithromycin may interfere with birth control and hormone replacement therapy. Rifampin when taken with combined oral contraceptives has been shown to reduce progesterone area under the curve (AUC) by 30%–83% and ethinyl estrogen AUC by 42%–66%.[113] Back-up contraceptive methods are recommended; however, given the duration of NTM treatment, an alternative contraceptive method may be preferred. Rifabutin has shown fewer pharmacokinetic changes due to less CYP3A4 induction and may be a reasonable alternative. An important consideration for menopausal women on hormone replacement therapy is that rifampin will significantly reduce hormone concentrations resulting in a flare in hormonal symptoms such as hot flashes or changes in mood. Clarithromycin increases estrogen levels in combined oral contraceptives and hormonal replacement therapy. Females should monitor for side effects such as

hypertension, thrombosis, and depression. Azithromycin has far less CYP3A4 activity, which is one of the reasons it is often used as the preferred macrolide. Linezolid inhibits monoamine oxidase and should be used with caution with serotonergic medications such as sertraline or trazodone as this combination could result in serotonin syndrome.[113] Other antibiotics such as ethambutol, imipenem and amikacin are metabolized and/or eliminated via the kidneys and are generally not implicated in drug interactions.

If emergency contraception is indicated, patients should be counseled that levonorgestrel or the "morning after pill" may have decreased efficacy if taking rifampin or rifabutin as it is a major CYP3A4 metabolite. FDA labeling notes decreased effectiveness when combined with CYP3A4 inducers but does not provide any suggested dose adjustments. A PK study found that doubling the recommended dose of levonorgestrel to 3 mg resulted in a similar AUC to the control group of women receiving levonorgestrel 1.5 mg without a CYP3A4 inducer. Ulipristal acetate, available as prescription only in the United States, is not recommended as rifampin reduces exposure of ulipristal and its active metabolite by about 90%.[115] Placement of a copper or progestin intrauterine device (IUD) should be considered in these cases.

Osteoporosis

A single-center study from Japan showed a higher incidence of osteoporosis in women ages 50–79 years with NTM PD as compared to age-matched females in the Japanese general population.[116] They demonstrated female sex, low BMI, and older age as independent risk factors for osteoporosis. Further analysis indicated low serum estradiol levels and 25-hydroxyvitamin D (25OHD) were significantly associated with osteoporosis. Additional 25OHD screening and supplementation may be warranted in women; however, further studies are needed to assess the impact/outcome of this intervention. None of the above-mentioned antibiotics have pertinent drug-drug interactions with medications currently available for the treatment of osteoporosis.[87–91]

Future research needs

The rates of NTM-PD among people with NCFB and CF are increasing worldwide. Among people with NCFB and NTM-PD, postmenopausal women are disproportionately affected compared to men. In contrast, no sex predilection is observed among pwCF.

With improvements in CF therapeutics, more adults are living with CF than children. Additionally, with the use of highly effective CFTR modulator therapy, more women with CF are becoming pregnant. We are just beginning to uncover the impact of CFTR modulator therapy and its relationship to infection and disease mitigation. Rates of NTM among pregnant women with CF are not well defined. Questions remain regarding general CF management strategies for pregnant women with CF, including management of NTM. Improved collection of data is warranted in the CFFPR on the rate of pregnancy and breastfeeding among women with a positive NTM culture, including subspeciation as well as previous or active history of NTM infection, disease, and treatment. More research is needed to guide decision-making regarding the initiation or continuation of NTM treatment during pregnancy and breastfeeding, which may be a clinical conundrum presented to clinicians more regularly with the widespread use of CFTR modulators. Currently, the CFFPR does not capture NTM pharmacotherapy treatment details which, if added, could make analysis of this population easier. Additional data capture in the CFFPR could lead to an evidenced-based algorithm for screening, monitoring, and treating women with NTM infection during childbearing years as well as during pregnancy and lactation. Clinicians should also be encouraged to report any exposures to NTM pharmacotherapy during pregnancy or breastfeeding to the drug manufacturer.

In both CF and NCFB, drug toxicity and intolerance are significant challenges for patients with NTM-PD, especially related to rifamycins. Individuals who experience toxicity or intolerance are often placed on second-line agents. We lack prospective data on the long-term efficacy or safety of these second-line agents. Additionally, we lack sensitive biomarkers to determine who will progress requiring NTM treatment and whether there are characteristics within different NTM species or strains that portend a poor prognosis. Furthermore, more research is needed to better understand sex-specific treatment outcomes and response rates to different therapeutic regimens.

More research is needed to better understand the unique contribution female hormones play, both during reproductive and non-reproductive years, and how they impact NTM acquisition, infection, and disease. There is a need for an improved understanding of the interplay of estrogen, adipokines, and BMI in the host-pathogen interactions driving increased risk for NTM-PD, especially among postmenopausal women as they represent the majority of individuals suffering from NTM-PD. Importantly, women on hormone replacement therapy who require rifamycin will experience a decrease in estrogen effect. We do not know how this interaction may affect their treatment outcomes or quality of life. In summary, we have much to learn about the unique aspects of NTM-PD among women.

Conclusion

On a global scale, pulmonary NTM infections are an increasing concern among susceptible populations including people with CF and NCFB. The incidence of both NTM pulmonary infections and disease has continued to increase, with a disproportionate burden impacting among women in all groups except for people with CF. Our understanding of the significance of a first-time NTM-positive culture remains difficult to ascertain as the progression of infection may be transient and self-resolving, intermittently positive without signs of disease, or chronically positive and meeting criteria for NTM-PD. Additionally, not all patients meeting diagnostic criteria for NTM-PD require treatment. Internationally endorsed guidelines for screening, diagnosis, and management of NTM-PD are available and are notable for the complexity and duration of the antibiotic regimen. The multi-drug treatment approach is frequently associated with unique and significant side effects, some of which are more impactful to women. However, current guidelines do not address specific considerations for women with NTM-PD. The majority of NTM-PD occurs in older adults over 50 years with postmenopausal women being disproportionately affected compared to men. Low serum estradiol and other female sex hormonal changes may play a role in increasing the incidence of other complications associated with NTM-PD including, but not limited to, osteoporosis. In contrast, people with CF have NTM-PD across the age spectrum, including during the reproductive phase of life. CFTR modulators are improving the survival and quality of life among people with CF, and the number of pregnancies is increasing. Data on the number of women with CF desiring pregnancy, pregnant, or breastfeeding in the setting of NTM infection are lacking, but cases have been observed in clinical settings. Additional studies are needed to better understand the unique contribution female hormones play, both during reproductive and non-reproductive years, and their impact on NTM acquisition, infection, and disease.

Declarations

Ethics approval and consent to participate

IRB approval was not required for publication of this review of the literature.

Consent for publication

Patient consent was not required for publication of this review of the literature.

Author contributions

Jane E. Gross: Conceptualization; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests

S.K. declares the following conflicts of interest: Insmed (speaker, consultant, investigator), AN2 (consultant), Paratek (speaker, consultant), and Zambon (consultant). J.E.G., D.R.P., M.C.J., and A.B. have no conflicts of interest to report.

Availability of data and materials

All data was collected via an electronic PubMed search and is available on request.

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References

1. Cowman S, van Ingen J, Griffith DE, et al. Non-tuberculous mycobacterial pulmonary disease. *Eur Respir J* 2019; 54: 1900250.
2. Floto RA, Olivier KN, Saiman L, et al. US cystic fibrosis foundation and European cystic fibrosis society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax* 2016; 71(Suppl. 1): i1–22.
3. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; 175(4): 367–416.
4. Abbas M, Khan MT, Iqbal Z, et al. Sources, transmission and hospital-associated outbreaks of nontuberculous mycobacteria: a review. *Future Microbiol* 2024; 19(8): 715–740.
5. Falkinham JO, 3rd. Nontuberculous mycobacteria in the environment. *Tuberculosis (Edinb)* 2022; 137: 102267.
6. Honda JR. Environmental sources and transmission of nontuberculous mycobacteria. *Clin Chest Med* 2023; 44(4): 661–674.
7. Prevots DR, Marshall JE, Wagner D, et al. Global epidemiology of nontuberculous mycobacterial pulmonary disease: a review. *Clin Chest Med* 2023; 44(4): 675–721.
8. Thomson R, Tolson C, Carter R, et al. Isolation of nontuberculous mycobacteria (NTM) from household water and shower aerosols in patients with pulmonary disease caused by NTM. *J Clin Microbiol* 2013; 51(9): 3006–3011.
9. Gross JE, Caceres S, Poch K, et al. Investigating nontuberculous mycobacteria transmission at the colorado adult cystic fibrosis program. *Am J Respir Crit Care Med* 2022; 205(9): 1064–1074.
10. Gross JE, Finklea JD, Caceres SM, et al. Genomic epidemiology of Mycobacterium abscessus at an adult cystic fibrosis programme reveals low potential for healthcare-associated transmission. *ERJ Open Res* 2024; 10(4): 00165-2024.
11. Gross JE, Teneback CC, Sweet JG, et al. Molecular epidemiologic investigation of mycobacterium intracellulare subspecies chimaera lung infections at an adult cystic fibrosis program. *Ann Am Thorac Soc* 2023; 20(5): 677–686.
12. Aitken ML, Limaye A, Pottinger P, et al. Respiratory outbreak of Mycobacterium abscessus subspecies massiliense in a lung transplant and cystic fibrosis center. *Am J Respir Crit Care Med* 2012; 185(2): 231–232.
13. Bryant JM, Grogono DM, Rodriguez-Rincon D, et al. Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacterium. *Science* 2016; 354(6313): 751–757.
14. Johnston DI, Chisty Z, Gross JE, et al. Investigation of Mycobacterium abscessus outbreak among cystic fibrosis patients, Hawaii 2012. *J Hosp Infect* 2016; 94(2): 198–200.
15. Yan J, Kevat A, Martinez E, et al. Investigating transmission of Mycobacterium abscessus amongst children in an Australian cystic fibrosis centre. *J Cyst Fibros* 2020; 19(2): 219–224.
16. Gross JE, Martiniano SL and Nick JA. Prevention of transmission of Mycobacterium abscessus among patients with cystic fibrosis. *Curr Opin Pulm Med* 2019; 25(6): 646–653.
17. Adjemian J, Olivier KN and Prevots DR. Epidemiology of pulmonary nontuberculous mycobacterial sputum positivity in patients with cystic fibrosis in the United States, 2010-2014. *Ann Am Thorac Soc* 2018; 15(7): 817–826.
18. Bents SJ, Mercaldo RA, Powell C, et al. Nontuberculous mycobacterial pulmonary disease (NTM PD) incidence trends in the United

States, 2010–2019. *BMC Infect Dis* 2024; 24(1): 1094.

19. Winthrop KL, Marras TK, Adjemian J, et al. Incidence and prevalence of nontuberculous mycobacterial lung disease in a large U.S. Managed Care health plan, 2008-2015. *Ann Am Thorac Soc* 2020; 17(2): 178–185.

20. Prevots DR, Shaw PA, Strickland D, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. *Am J Respir Crit Care Med* 2010; 182(7): 970–976.

21. Marshall JE, Mercaldo RA, Lipner EM, et al. Incidence of nontuberculous mycobacteria infections among persons with cystic fibrosis in the United States (2010-2019). *BMC Infect Dis* 2023; 23(1): 489.

22. Olivier KN, Weber DJ, Wallace RJ, Jr., et al. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. *Am J Respir Crit Care Med* 2003; 167(6): 828–834.

23. Catherinot E, Roux AL, Vibet MA, et al. Mycobacterium avium and Mycobacterium abscessus complex target distinct cystic fibrosis patient subpopulations. *J Cyst Fibros* 2013; 12(1): 74–80.

24. Coolen N, Morand P, Martin C, et al. Reduced risk of nontuberculous mycobacteria in cystic fibrosis adults receiving long-term azithromycin. *J Cyst Fibros* 2015; 14(5): 594–599.

25. Qvist T, Gilljam M, Jonsson B, et al. Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia. *J Cyst Fibros* 2015; 14(1): 46–52.

26. Seddon P, Fidler K, Raman S, et al. Prevalence of nontuberculous mycobacteria in cystic fibrosis clinics, United Kingdom, 2009. *Emerg Infect Dis* 2013; 19(7): 1128–1130.

27. Cavalli Z, Reynaud Q, Bricca R, et al. High incidence of non-tuberculous mycobacteria-positive cultures among adolescent with cystic fibrosis. *J Cyst Fibros* 2017; 16(5): 579–584.

28. Pierre-Audigier C, Ferroni A, Sermet-Gaudelus I, et al. Age-related prevalence and distribution of nontuberculous mycobacterial species among patients with cystic fibrosis. *J Clin Microbiol* 2005; 43(7): 3467–3470.

29. Rodman DM, Polis JM, Heltshe SL, et al. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. *Am J Respir Crit Care Med* 2005; 171(6): 621–626.

30. Marshall JE, Mercaldo RA, Lipner EM, et al. Nontuberculous mycobacteria testing and culture positivity in the United States. *BMC Infect Dis* 2024; 24(1): 288.

31. Dean SG, Ricotta EE, Fintzi J, et al. Mycobacterial testing trends, United States, 2009-2015. *Emerg Infect Dis* 2020; 26(9): 2243–2246.

32. Dahl VN, Molhave M, Floe A, et al. Global trends of pulmonary infections with nontuberculous mycobacteria: a systematic review. *Int J Infect Dis* 2022; 125: 120–1231.

33. Dahl VN, Laursen LL, He Y, et al. Species distribution among patients with nontuberculous mycobacteria pulmonary disease in Europe. *J Infect* 2023; 87(5): 469–472.

34. Lonni S, Chalmers JD, Goeminne PC, et al. Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. *Ann Am Thorac Soc* 2015; 12(12): 1764–1770.

35. Yang B, Ryu J, Kim T, et al. Impact of bronchiectasis on incident nontuberculous mycobacterial pulmonary disease: a 10-Year national cohort study. *Chest* 2021; 159(5): 1807–1811.

36. Bents SJ, Mercaldo RA, Powell C, et al. Nontuberculous mycobacterial pulmonary disease (NTM PD) incidence trends in the United States, 2010-2019. *BMC Infect Dis* 2024; 24(1): 1094.

37. Wagner D, van Ingen J, van der Laan R, et al. Non-tuberculous mycobacterial lung disease in patients with bronchiectasis: perceived risk, severity and guideline adherence in a European physician survey. *BMJ Open Respir Res* 2020; 7(1): e000498.

38. Chalmers JD, Polverino E, Crichton ML, et al. Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). *Lancet Respir Med* 2023; 11(7): 637–649.

39. Dean SG, Blakney RA, Ricotta EE, et al. Bronchiectasis-associated infections and outcomes in a large, geographically diverse electronic health record cohort in the United States. *BMC Pulm Med* 2024; 24(1): 172.

40. Diel R, Lipman M and Hoefsloot W. High mortality in patients with Mycobacterium avium complex lung disease: a systematic review. *BMC Infect Dis* 2018; 18(1): 206.

41. Hayashi M, Takayanagi N, Kanauchi T, et al. Prognostic factors of 634 HIV-negative patients with Mycobacterium avium complex lung

disease. *Am J Respir Crit Care Med* 2012; 185(5): 575–583.

42. Koh WJ, Moon SM, Kim SY, et al. Outcomes of *Mycobacterium avium* complex lung disease based on clinical phenotype. *Eur Respir J* 2017; 50(3): 1602503.
43. Wallace RJ, Jr., Brown-Elliott BA, McNulty S, et al. Macrolide/Azalide therapy for nodular/bronchiectatic *Mycobacterium avium* complex lung disease. *Chest* 2014; 146(2): 276–282.
44. Namkoong H, Omae Y, Asakura T, et al. Genome-wide association study in patients with pulmonary *Mycobacterium avium* complex disease. *Eur Respir J* 2021; 58(2): 1902269.
45. Kartalija M, Ovrutsky AR, Bryan CL, et al. Patients with nontuberculous mycobacterial lung disease exhibit unique body and immune phenotypes. *Am J Respir Crit Care Med* 2013; 187(2): 197–205.
46. Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. *Am J Respir Crit Care Med* 2008; 178(10): 1066–1074.
47. Reich JM and Johnson RE. Mycobacterium avium complex pulmonary disease presenting as an isolated lingular or middle lobe pattern. The Lady Windermere syndrome. *Chest* 1992; 101(6): 1605–1609.
48. Holt MR, Kasperbauer SH, Koelsch TL, et al. Similar characteristics of nontuberculous mycobacterial pulmonary disease in men and women. *Eur Respir J* 2019; 54(1): 1900252.
49. Blakney RA, Ricotta EE, Frankland TB, et al. Incidence of nontuberculous mycobacterial pulmonary infection, by Ethnic Group, Hawaii, USA, 2005-2019. *Emerg Infect Dis* 2022; 28(8): 1543–1550.
50. Song JH, Kim BS, Kwak N, et al. Impact of body mass index on development of nontuberculous mycobacterial pulmonary disease. *Eur Respir J* 2021; 57(2): 2000454.
51. Ayyappan JP, Ganapathi U, Lizardo K, et al. Adipose tissue regulates pulmonary pathology during TB infection. *mBio* 2019; 10(2): e02771-18.
52. Wieland CW, Florquin S, Chan ED, et al. Pulmonary Mycobacterium tuberculosis infection in leptin-deficient ob/ob mice. *Int Immunol* 2005; 17(11): 1399–1408.
53. Hebebrand J, Muller TD, Holtkamp K, et al. The role of leptin in anorexia nervosa: clinical implications. *Mol Psychiatry* 2007; 12(1): 23–35.
54. Grayeb DE, Chan ED, Swanson LM, et al. Nontuberculous mycobacterial lung infections in patients with eating disorders: plausible mechanistic links in a case series. *AME Case Rep* 2021; 5: 9.
55. Jain R, Ray JM, Pan JH, et al. Sex hormone-dependent regulation of cilia beat frequency in airway epithelium. *Am J Respir Cell Mol Biol* 2012; 46(4): 446–453.
56. Tsuyuguchi K, Suzuki K, Matsumoto H, et al. Effect of oestrogen on Mycobacterium avium complex pulmonary infection in mice. *Clin Exp Immunol* 2001; 123(3): 428–434.
57. Yang B, Lee DH, Han K, et al. Female reproductive factors and the risk of bronchiectasis: a nationwide population-based longitudinal study. *Biomedicines* 2022; 10(2): 303.
58. Uwamino Y, Nishimura T, Sato Y, et al. Low serum estradiol levels are related to *Mycobacterium avium* complex lung disease: a cross-sectional study. *BMC Infect Dis* 2019; 19(1): 1055.
59. Aksamit TR, Locantore N, Addrizzo-Harris D, et al. Five-Year Outcomes among U.S. Bronchiectasis and NTM Research Registry Patients. *Am J Respir Crit Care Med* 2024; 210(1): 108–118.
60. Blakney RA, Ricotta EE, Follmann D, et al. The 6-minute walk test predicts mortality in a pulmonary nontuberculous mycobacteria-predominant bronchiectasis cohort. *BMC Infect Dis* 2022; 22(1): 75.
61. Martiniano SL, Sontag MK, Daley CL, et al. Clinical significance of a first positive nontuberculous mycobacteria culture in cystic fibrosis. *Ann Am Thorac Soc* 2014; 11(1): 36–44.
62. Chalermskulrat W, Sood N, Neuringer IP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. *Thorax* 2006; 61(6): 507–513.
63. Albrecht C, Ringshausen F, Ott S, et al. Should all adult cystic fibrosis patients with repeated nontuberculous mycobacteria cultures receive specific treatment? A 10-year case-control study. *Eur Respir J* 2016; 47(5): 1575–1577.
64. Binder AM, Adjemian J, Olivier KN, et al. Epidemiology of nontuberculous mycobacterial infections and associated chronic macrolide use among persons with cystic fibrosis. *Am J Respir Crit Care Med* 2013; 188(7): 807–812.
65. Levy I, Grisaru-Soen G, Lerner-Geva L, et al. Multicenter cross-sectional study of nontuberculous mycobacterial infections among

cystic fibrosis patients, Israel. *Emerg Infect Dis* 2008; 14(3): 378–384.

66. Bar-On O, Mussaffi H, Mei-Zahav M, et al. Increasing nontuberculous mycobacteria infection in cystic fibrosis. *J Cyst Fibros* 2015; 14(1): 53–62.

67. Martiniano SL, Caceres SM, Poch K, et al. Prospective evaluation of nontuberculous mycobacteria disease in cystic fibrosis: the design of the PREDICT study. *J Cyst Fibros* 2024; 23(1): 50–57.

68. Middleton PG and Taylor-Cousar JL. Development of elexacaftor – tezacaftor – ivacaftor: Highly effective CFTR modulation for the majority of people with Cystic Fibrosis. *Expert Rev Respir Med* 2021; 15(6): 723–735.

69. Jia S and Taylor-Cousar JL. Cystic fibrosis modulator therapies. *Annu Rev Med* 2023; 74: 413–426.

70. Ricotta EE, Prevots DR and Olivier KN. CFTR modulator use and risk of nontuberculous mycobacteria positivity in cystic fibrosis, 2011-2018. *ERJ Open Res* 2022; 8(2): 00724–2021.

71. Akkerman-Nijland AM, Akkerman OW, Grasmeijer F, et al. The pharmacokinetics of antibiotics in cystic fibrosis. *Expert Opin Drug Metab Toxicol* 2021; 17(1): 53–68.

72. 2022 Cystic Fibrosis Foundation Patient Registry Highlights Bethesda, MD, https://www.cff.org/sites/default/files/2023-05/2022-Cystic-Fibrosis-Foundation-Patient-Registry-Highlights-Handout.pdf (2023, accessed 12 July 2024).

73. Jain R, Kazmerski TM, Zuckerwise LC, et al. Pregnancy in cystic fibrosis: review of the literature and expert recommendations. *J Cyst Fibros* 2022; 21(3): 387–395.

74. Jain R, Magaret A, Vu PT, et al. Prospectively evaluating maternal and fetal outcomes in the era of CFTR modulators: the MAYFLOWERS observational clinical trial study design. *BMJ Open Respir Res* 2022; 9(1): e001289.

75. Hwang JA, Kim S, Jo KW, et al. Natural history of Mycobacterium avium complex lung disease in untreated patients with stable course. *Eur Respir J* 2017; 49(3): 1600537.

76. Kwak N, Park J, Kim E, et al. Treatment outcomes of mycobacterium avium complex lung disease: a systematic review and meta-analysis. *Clin Infect Dis* 2017; 65(7): 1077–1084.

77. Lee JK, Kim S, Chong YP, et al. The Association between sputum culture conversion and mortality in cavitary *Mycobacterium avium* complex pulmonary disease. *Chest* 2024; 166(3): 442–451.

78. Kim HJ, Kwak N, Hong H, et al. BACES score for predicting mortality in nontuberculous mycobacterial pulmonary disease. *Am J Respir Crit Care Med* 2021; 203(2): 230–236.

79. Ku JH, Henkle E, Carlson KF, et al. Tolerability outcomes of American Thoracic Society/Infectious Diseases Society of America guideline-recommended multidrug Antibiotic treatment for Mycobacterium avium complex pulmonary disease in US Medicare beneficiaries with bronchiectasis. *Chest* 2024; 165(5): 1058–1069.

80. Griffith DE, Eagle G, Thomson R, et al. Amikacin Liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium Complex (CONVERT). A prospective, open-label, randomized study. *Am J Respir Crit Care Med* 2018; 198(12): 1559–1569.

81. Pasipanodya JG, Ogbonna D, Deshpande D, et al. Meta-analyses and the evidence base for microbial outcomes in the treatment of pulmonary Mycobacterium avium-intracellulare complex disease. *J Antimicrob Chemother* 2017; 72(suppl_2): i3–i19.

82. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J* 2020; 56(1): 2000535.

83. Cimino C, Rivera CG, Pearson JC, et al. Pharmacotherapeutic considerations in the treatment of nontuberculous mycobacterial infections: a primer for clinicians. *Open Forum Infect Dis* 2024; 11(4): ofae128.

84. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA* 2012; 307(18): 1959–1969.

85. Durrant JD, Campbell K, Fausti S, et al. Position statement and clinical practice guidelines: ototoxicity monitoring, https://www.audiology.org/wp-content/uploads/2021/05/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf (2009, accessed 29 July 2024).

86. Sawka A and Burke A. Medications and monitoring in treatment of nontuberculous mycobacterial pulmonary disease. *Clin Chest Med* 2023; 44(4): 815–828.

87. Vasconcelos KA, Frota S, Ruffino-Netto A, et al. The importance of audiometric monitoring in patients with multidrug-resistant tuberculosis. *Rev Soc Bras Med Trop* 2017; 50(5): 646–651.

88. Aznar ML, Marras TK, Elshal AS, et al. Safety and effectiveness of low-dose amikacin in nontuberculous mycobacterial pulmonary disease treated in Toronto, Canada. *BMC Pharmacol Toxicol* 2019; 20(1): 37.

89. Peloquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clin Infect Dis* 2004; 38(11): 1538–1544.

90. Sogebi OA, Adefuye BO, Adebola SO, et al. Clinical predictors of aminoglycoside-induced ototoxicity in drug-resistant Tuberculosis patients on intensive therapy. *Auris Nasus Larynx* 2017; 44(4): 404–410.

91. McDermott JH. Genetic testing in the acute setting: a round table discussion. *J Med Ethics* 2020; 46(8): 531–532.

92. Soldin OP and Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2009; 48(3): 143–157.

93. Whitley H and Lindsey W. Sex-based differences in drug activity. *Am Fam Physician* 2009; 80(11): 1254–1258.

94. Jain R and Taylor-Cousar JL. Fertility, Pregnancy and lactation considerations for women with CF in the CFTR modulator era. *J Pers Med* 2021; 11(5).

95. Hughes J. Pharmacokinetics and safety of group A and B anti-tuberculosis drugs used in treatment of rifampicin-resistant tuberculosis during pregnancy and post-partum: a narrative review. *Pathogens* 2023; 12(12): 1385.

96. Pregnancy and Lactation Labeling (Drugs) Final Rule: U.S. Food and Drug Administration, https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule (2021, accessed 30 July 2024).

97. Tasnif Y, Morado J and Hebert MF. Pregnancy-related pharmacokinetic changes. *Clin Pharmacol Ther* 2016; 100(1): 53–62.

98. Elimination DoT. Treatment for TB during pregnancy: Centers for Disease Control and Prevention, https://www.cdc.gov/tb/topic/treatment/pregnancy.htm (2020, accessed 30 July 2024).

99. Eggermont E, Logghe N, Van De Casseye W, et al. Haemorrhagic disease of the newborn in the offspring of rifampicin and isoniazid treated mothers. *Acta Paediatr Belg* 1976; 29(2): 87–90.

100. Loveday M, Hughes J, Sunkari B, et al. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. *Clin Infect Dis* 2021; 72(7): 1158–1168.

101. Court R, Gausi K, Mkhize B, et al. Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis. *Br J Clin Pharmacol* 2022; 88(8): 3548–3558.

102. Highlights of Prescribing Information: Nuzyra Boston. MA: Paratek Pharmaceuticals, Inc., https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209816_209817lbl.pdf (2018, accessed 28 July 2024).

103. Czeizel AE, Rockenbauer M, Sorensen HT, et al. Use of cephalosporins during pregnancy and in the presence of congenital abnormalities: a population-based, case-control study. *Am J Obstet Gynecol* 2001; 184(6): 1289–1296.

104. Briggs GG, Freeman RK, Tower CV, et al. *Brigg's drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 12th ed. Lippincott Williams & Wilkins, 2021.

105. Heikkila A, Renkonen OV and Erkkola R. Pharmacokinetics and transplacental passage of imipenem during pregnancy. *Antimicrob Agents Chemother* 1992; 36(12): 2652–2655.

106. Highlights of Prescribing Information: Arikayce: Insmed Inc., https://www.arikayce.com/pdf/full_prescribing_information.pdf (2018, accessed 28 July 2024).

107. Middleton PG, Gade EJ, Aguilera C, et al. ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases. *Eur Respir J* 2020; 55(2): 1901208.

108. Rowe HE, Felkins K, Cooper SD, et al. Transfer of linezolid into breast milk. *J Hum Lact* 2014; 30(4): 410–412.

109. Sagirli O, Onal A, Toker S, et al. Determination of linezolid in human breast milk by high-performance liquid chromatography with ultraviolet detection. *J AOAC Int* 2009; 92(6): 1658–1662.

110. Matsuda S. Transfer of antibiotics into maternal milk. *Biol Res Pregnancy Perinatol* 1984; 5(2): 57–60.

111. Rifandin Prescribing Information: sanofi-aventis U.S. LLC, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050420s073,050627s012lbl.pdf (2010, accessed 28 July 2024).

112. Highlights of Prescribing information: Biaxin. North Chicago, IL: AbbVie Inc., https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/0

50662s044s050,50698s026s030,050775s015s019lbl.pdf (2018, accessed 28 July 2024).

113. Jordan CL, Noah TL and Henry MM. Therapeutic challenges posed by critical drug-drug interactions in cystic fibrosis. *Pediatr Pulmonol* 2016; 51(S44): S61–S70.

114. Kim HI, Kim TH, Kim H, et al. Effect of rifampin on thyroid function test in patients on levothyroxine medication. *PLoS One* 2017; 12(1): e0169775.

115. Highlights of Prescribing information: ella (ulipristal acetate). Afaxys Pharma LLC, https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf (2018, accessed 30 July 2024).

116. Tanaka H, Asakura T, Suzuki S, et al. Osteoporosis in nontuberculous mycobacterial pulmonary disease: a cross-sectional study. *BMC Pulm Med* 2022; 22(1): 202.