

1 **Cystic Fibrosis Foundation and European Cystic Fibrosis Society Guidelines for**
2 **the Management of Nontuberculous Mycobacteria in Individuals with Cystic**
3 **Fibrosis**

4
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60 **ABSTRACT**

61

62 **Background:** Nontuberculous mycobacteria (NTM) are ubiquitous environmental
63 organisms that can cause chronic pulmonary infection, particularly in individuals with
64 pre-existing inflammatory lung disease such as cystic fibrosis (CF). Pulmonary disease
65 caused by NTM has emerged as a major threat to the health of individuals with CF but
66 remains difficult to diagnose and problematic to treat. In response to this challenge, the
67 U.S. Cystic Fibrosis Foundation and the European Cystic Fibrosis Society convened an
68 expert panel of specialists to develop consensus guidelines for the screening,
69 investigation, diagnosis and management of NTM pulmonary disease in individuals with
70 CF.

71

72 **Methods:** Nineteen experts were invited to participate in the guidelines development
73 process. The committee consisted of adult and pediatric CF physicians, transplant
74 surgeons, microbiologists, infectious disease specialists, and a parent of an individual
75 with CF. An anonymous voting process was used by the committee to reach consensus.
76 Committee members were asked to rate each statement on a scale of 0, completely
77 disagree, to 9, completely agree, with 80% or between 7 and 9 being considered 'good'
78 agreement. All committee members were required to vote on each recommendation
79 statement regardless of their role or expertise. Additionally the committee solicited
80 feedback from the CF communities in the U.S. and Europe and considered the
81 feedback in the development of the final recommendation statements.

82

83 **Results:** Three rounds of voting were conducted to achieve 80% consensus for each
84 recommendation statement. Fifty-three (53) statements were included in the first round
85 of voting and 50 statements in the second and third rounds. Final recommendation
86 statements and the consensus are reported.

87

88 **Conclusion:** We have generated a series of pragmatic, evidence-based
89 recommendations for the screening, investigation, diagnosis, and treatment of NTM
90 infection in individuals with CF as an initial step in optimising management for this
91 challenging condition.

92

93 **BACKGROUND:**

94
95 **Epidemiology of Nontuberculous mycobacteria in individuals with cystic fibrosis**

96
97 Nontuberculous mycobacteria (NTM) are increasingly being isolated from sputum of
98 adults and children with cystic fibrosis (CF) both in North America and Europe¹⁻¹⁷.
99 Estimates of the prevalence of NTM in the CF population have ranged from 1.3% in the
100 earliest study reported in 1984¹ to 32.7% in a review of CF patients over age 40 in
101 Colorado⁹. The largest studies published to date examined 986⁶, 1,216¹⁶, and 1,582¹³
102 CF patients and reported rates of NTM-positive cultures of 13.0%, 13.7%, and 6.6%,
103 respectively.

104
105 The NTM species most commonly identified in individuals with CF from North America
106 and Europe are the slow growing *Mycobacterium avium* complex (MAC) (including *M.*
107 *avium*, *M. intracellulare* and *M. chimaera*) which can be found in up to 72% of NTM
108 positive sputum cultures⁶ and the rapid growing *M. abscessus* complex (MABSC)
109 (comprising the subspecies *M. abscessus subsp. abscessus* (*M. a. abscessus*), *M. a.*
110 *bolletii*¹⁸ and *M. a. massiliense*^{19,20} which in many centres has now become the most
111 common NTM isolated from individuals with CF^{7,13,16,19,21}. Other less commonly isolated
112 species include *M. simiae*¹¹, *M. kansasii* and *M. fortuitum*²². There are geographical
113 differences in both the prevalence of NTM-positive cultures and also the relative
114 frequency of different species^{6,13,23}.

115
116 NTM acquisition is strongly associated with age of individuals with CF with prevalence
117 increasing from 10% in children aged 10, to over 30% in adults over the age of 40⁹. In
118 individuals with an adult diagnosis of CF, over 50% (mostly females) have NTM positive
119 airway cultures⁹. There appears to be species-specific differences in age-related
120 prevalence within CF cohorts, with MAC more commonly isolated from adults over 25
121 years of age^{6,7,13,15,23} while MABSC is isolated from all age groups, but peaks between
122 age 11 and 15 years in some studies^{13,24}. There may also be species-specific
123 differences in virulence: individuals with MABSC positive cultures are more likely to
124 meet ATS/IDSA criteria for diagnosing NTM pulmonary disease (See Section D) and
125 have worse morbidity and mortality associated with a more rapid decline in lung
126 function^{16,23,25,26}.

127
128 There has been a rise in the reported prevalence of NTM positive cultures in respiratory
129 samples from individuals with CF over the last three decades^{1,6,13,16,21} an increase in
130 part mirroring temporal changes seen in the non-CF cohort²⁷⁻³⁴. While increasing
131 detection rates may reflect enhanced surveillance and/or improved microbiological
132 detection^{6,23,35-38} there are a number of lines of evidence suggesting a true rise in the
133 frequency of NTM infection. A number of CF studies (for example Renna et al³⁹) show
134 year on year increases in NTM positive cultures with no change in surveillance intensity
135 or culture methodology. There has been an increase over time in rates of skin test
136 reactivity to NTM antigens in US population-based testing studies⁴⁰, potentially
137 indicating increasing exposure to NTM (see below). Furthermore, the relative frequency
138 of *M. abscessus* detection in NTM positive samples from individuals with CF has

139 increased remarkably over time in both the US and Europe^{2,6,13,16,21,23}, suggesting real
140 changes in NTM acquisition rates (rather than increased sampling).
141 Possible reasons for the potential increased frequency of NTM positive cultures in
142 individuals with CF include: increases in environmental exposure to NTM (through more
143 permissive temperature settings of home water heaters⁴¹ and more contact with shower
144 aerosols^{42,43}, increased antibiotic usage creating more NTM permissive lung niches²³,
145 greater chronic use of medications which might impair host immunity to NTM³⁹ and/or
146 spread of NTM through person-to-person transmission^{44,45}.

147

148 ***NTM Pulmonary Disease in individuals with CF***

149

150 NTM can cause progressive inflammatory lung damage, a condition termed 'NTM
151 pulmonary disease' (NTM-PD)^{46,47}, which is defined by the presence of specific
152 microbiological, clinical and radiological features described in Section D. However, it
153 has become clear that NTM can also transiently, intermittently, or permanently reside
154 within the lungs of CF individuals without causing NTM-PD, thus representing
155 asymptomatic infection and creating considerable difficulties in deciding how best to
156 screen for and diagnose NTM²⁶. Further challenges exist in knowing how best to identify
157 NTM in respiratory samples, when and how to initiate treatment for NTM-PD (as
158 highlighted by a recent Cochrane review⁴⁸) and how NTM may impact in individuals
159 under consideration for lung transplantation. As a consequence, the CFF and ECFS
160 sought to generate a consensus guidelines document to support and standardize the
161 management of NTM infection in individuals with CF, permitting prospective evaluation
162 of current best practice and forming a foundation for future research programs.

163

164

165 **METHODS**

166

167 **Expert committee structure**

168

169 The Cystic Fibrosis Foundation and the European Cystic Fibrosis Society (ECFS)
170 invited experts to participate in the guidelines development process. The 19 member
171 committee consisted of professionals with expertise in CF and NTM and included adult
172 and pediatric CF physicians, transplant surgeons, microbiologists, infectious disease
173 specialists, and a parent of an individual with CF. The committee convened in May 2012
174 and divided into 5 sub-groups, each responsible for a specific topic: Epidemiology and
175 Risk Factors, Screening, Microbiology, Treatment, and Transplantation. Each sub-group
176 developed topic specific questions using the PICO format (Population, Intervention,
177 Comparison, Outcome).⁴⁹ Questions were reviewed and approved by the entire
178 committee before literature searches were conducted.

179

180 **Review process and consensus vote**

181

182 The members of each sub-group used the PICO questions to guide literature searches
183 in PubMed. Searches were limited to English language and the period 1984 to 2013.
184 Sub-group members also searched for topic relevant guidelines through searches of the

185 ATS website, the IDSA website, the Clinical Laboratory Standards Institute website, and
186 the United Kingdom (UK) CF Trust website.

187
188 After reviewing relevant literature and existing guidelines, sub-group members drafted
189 recommendation statements. In October 2012, a second meeting was convened and
190 sub-groups finalized draft recommendation statements. The committee also voted to
191 set 80% agreement of all 19 members as the threshold for acceptance of a
192 recommendation statement.

193
194 Each sub-group submitted final draft questions for entry into an electronic survey tool
195 (Survey Monkey) for the purposes of anonymous voting and comment by all members.
196 A project coordinator administered the survey and committee members were asked to
197 rate each statement on a scale of 0, completely disagree, to 9, completely agree, with
198 80% or between 7 and 9 being considered 'good' agreement. Space for entering free
199 text was also provided after each statement to allow members to cite literature in
200 support of their opinions or suggested revisions. All committee members were required
201 to vote on each statement regardless of their role or expertise. Multiple rounds of voting
202 and revisions to the statements were conducted and for each round committee
203 members were requested to complete their voting within 3 weeks time. The committee
204 chairs reviewed the results from each round and updated the statements based on
205 comments entered by respondents for subsequent rounds.

206 207 **External review**

208
209 A draft of the recommendations was presented at the 2013 North American Cystic
210 Fibrosis Conference and the European Cystic Fibrosis Society Meeting. Additionally the
211 committee solicited feedback from the CF communities in the U.S. and Europe, which
212 included physicians, nurses, physical and respiratory therapists, parents and individuals
213 with CF. Comments collected from this process were considered by the committee in
214 the development of the final recommendation statements.

215 216 **RESULTS**

217 218 **Final Recommendations and results of the consensus vote**

219
220 Three rounds of voting were conducted to achieve 80% consensus for each statement.
221 Fifty-three (53) statements were included in the first round of voting and 50 statements
222 in the second and third rounds. Final statements and the consensus are reported in
223 Table 1.

224 225 **A. RISK FACTORS**

226
227 **Are there modifiable risk factors for the development of NTM pulmonary disease**
228 **in individuals with CF?**

229

230 **Recommendation 1: The CF Foundation and the ECFS recommend that the**
231 **potential for cross-infection of NTM (particularly *M. abscessus* complex) between**
232 **individuals with CF should be minimised by following national infection control**
233 **guidelines.**

234
235 CF-related lung disease is a clear risk factor for the development of NTM pulmonary
236 disease and is presumed to relate to the presence of structural lung damage, impaired
237 mucociliary clearance and inflamed airways; all of which are thought to favour the
238 development of chronic NTM infection⁵⁰. Cystic Fibrosis Transmembrane Conductance
239 Regulator (CFTR) dysfunction may, of itself, predispose to NTM infection (although the
240 pathophysiology is unknown), since rates of heterozygosity for CFTR mutations within
241 the non-CF population with pulmonary NTM disease are high (30-50%)^{51,52}.

242
243 However, other risk factors that predispose specific individuals with CF to acquire NTM
244 or develop NTM pulmonary disease are, for the most part, poorly understood with many
245 studies presenting conflicting results. Potential risk factors for NTM acquisition are listed
246 below.

247 248 ***Lung function***

249
250 There have been conflicting reports on whether an individual's spirometry results are
251 related to the likelihood of finding NTM positive samples with some studies suggesting
252 no association with lung function¹⁴, a positive association of NTM acquisition with higher
253 FEV₁ % predicted⁶ or conversely, with worse lung function^{11,16,26}. Support for the
254 possibility that NTM acquisition is more likely in CF individuals with severe lung disease
255 comes from observations that the prevalence of NTM-positive sputum samples in
256 patients referred for lung transplantation has been reported to be as high as 19.7%²⁵.

257 258 ***Lung infection with specific pathogens***

259
260 In some studies, CF individuals with NTM positive samples are more likely to have
261 *Staphylococcus aureus* infection and less likely to have *Pseudomonas aeruginosa*
262 chronic pulmonary infection^{6,7,53}. Other studies, however, have reported NTM positivity
263 associated with higher rates of *P. aeruginosa* infection¹¹, no difference or higher
264 rates^{6,53} of *S. maltophilia* infection, and also showed higher prevalence of *S. maltophilia*
265 infection with *M. abscessus* in CF patients⁵⁴. In contrast, *Aspergillus fumigatus* has
266 consistently been associated with the presence of NTM positive cultures^{11,16,54}, with
267 some reports indicating an association with allergic bronchopulmonary aspergillosis
268 ^{7,23,55}.

269 270 ***Medications***

271
272 ***Corticosteroids:*** The impact of systemic steroids on NTM acquisition is controversial.
273 There have been suggestions that steroids may protect against⁵³ or predispose towards
274 NTM infection⁵⁵ or may not influence the risk of NTM acquisition^{4,11,12}.

275

276 *Proton pump inhibitors (PPI)*: The impact of PPI is unclear. PPI use has been reported
277 to be associated with the development of MAC pulmonary disease in non-CF cohorts⁵⁶
278 and may promote gastro-intestinal survival of NTM and subsequent lung infection
279 through gastric aspiration.

280
281 *Azithromycin*: Particular attention has recently been paid to the role of long-term
282 azithromycin use as a risk factor for the acquisition of NTM. In a single centre study of
283 CF adults, Renna et al reported increases in annual rates of NTM infection associated
284 with chronic azithromycin use³⁹, postulating, through *in vitro* studies and mouse
285 infection models that azithromycin blocked autophagic killing of NTM within
286 macrophages. While supporting findings from a previous case-control study reporting
287 increased azithromycin use in NTM patients¹¹, other large retrospective studies have
288 shown no such association^{12,14,54,57-59}. This includes a recent nested case-control
289 analysis within the CF registry that suggested suppressive Azithromycin use protected
290 against incident NTM infection⁵⁹.

291 292 ***Acquisition of NTM through cross-infection***

293 Person-to-person transmission of NTM has traditionally been considered unlikely. Two
294 separate studies have shown that patients, even siblings living in the same household
295 for more than 10 years, have unique strains^{7,60} suggesting a lack of person-person-
296 transmission. However, a case report from the University of Washington described a
297 possible outbreak of *M. a. massiliense* in five patients⁴⁴ with potential transmission
298 occurring during synchronous clinic visits. More recently, whole genome sequencing
299 and antimicrobial susceptibility testing performed on 168 consecutive isolates of *M.*
300 *abscessus* from 31 patients attending an adult CF centre in the UK revealed frequent,
301 probably indirect, transmission of *M. a. massiliense* between individuals with CF despite
302 conventional cross-infection measures⁶¹. The results of these studies indicates that
303 cross-infection may be an important mechanism for the acquisition of *M. abscessus* (at
304 least within the CF population). To date there is no published evidence suggesting
305 person-to-person transmission of other NTM species.

306
307 Other factors extrapolated from data in non-CF populations or studies on *M.*
308 *tuberculosis* which might contribute to NTM acquisition in individuals with CF include:
309 low vitamin D^{62,63}, the presence of gastro-esophageal reflux disease^{56,64}, low body mass
310 index^{51,65} or malnutrition⁶⁶.

311 312 **B. SCREENING**

313
314 **How often should individuals with CF be screened for NTM?**

315
316 ***Recommendation 2:*** The CF Foundation and the ECFS recommend that cultures
317 for NTM be performed annually in spontaneously expectorating individuals with a
318 stable clinical course.

319
320 ***Recommendation 3:*** The CF Foundation and the ECFS recommend that in the
321 absence of clinical features suggestive of NTM pulmonary disease, individuals

322 **who are not capable of spontaneously producing sputum do not require**
323 **screening cultures for NTM.**

324
325 Over the past two decades, a number of expert opinions and reviews have urged
326 routine screening for NTM in the general CF population. However, the optimal frequency
327 and methodology for NTM surveillance in individuals with CF are not known. NTM are
328 common in the environment, and are likely to be transiently introduced into the airways
329 of individuals with CF on a regular basis. More frequent screening will therefore result in
330 detection of more positive cultures⁶⁷, many of which will not be associated with the
331 presence of NTM pulmonary disease^{6,26,68}, generating anxiety in patients and caregivers
332 and initiating further (potentially invasive) investigations. However, signs and symptoms
333 of NTM disease are often subtle and nonspecific, and the diagnosis can be delayed for
334 years or missed altogether in the absence of effective surveillance⁴. Furthermore
335 systematic screening may help researchers more accurately identify factors influencing
336 poorly understood host susceptibility, acquisition, transmission and virulence of NTM. It
337 is important to emphasise that screening refers to obtaining samples from individuals
338 with no clinical, microbiological or radiological suspicion of NTM infection and should be
339 distinguished from strategies to investigate and diagnose NTM disease (covered in
340 Section D).

341
342 While our understanding of which factors predispose individuals with CF to NTM
343 infection is incomplete, there is nevertheless agreement that certain patient populations
344 are at greater risk and therefore probably require more frequent surveillance. These
345 populations include: those with advanced lung disease, previous NTM positive cultures,
346 and those living in areas with high NTM prevalence. Conversely, in individuals with no
347 recognised risk factors, the prevalence of NTM infection is likely to be low, and thus less
348 frequent, perhaps annual, surveillance is warranted. In addition, NTM screening is
349 important before starting long-term azithromycin treatment to avoid inadvertent
350 macrolide monotherapy in individuals with undiagnosed NTM infection (in keeping with
351 published guidelines⁶⁹)

352
353 **How should screening for NTM be performed?**

354
355 ***Recommendation 4:* The CF Foundation and the ECFS recommend that culture**
356 **and smears for acid fast bacilli from sputum should be used for NTM screening.**

357
358 ***Recommendation 5:* The CF Foundation and the ECFS recommend against the**
359 **use of oro-pharyngeal swabs for NTM screening.**

360
361 The majority of published reports describing the prevalence of NTM in the CF
362 population utilized AFB smear and culture from sputum as the standard screening
363 method^{4,70-74}. To date, there has been no direct comparison between the sensitivity of
364 samples from spontaneously expectorated sputum samples and sputum induced with
365 hypertonic saline. Analysis of induced sputum provides equal or better detection of
366 “standard” CF pathogens⁷⁵ and the procedure is in widespread use to collect samples
367 for mycobacterial culture among CF Centers worldwide. However the Consensus

368 Committee felt that, due to its inconvenience, induced sputum collection should not be
369 used as a screening tool in individuals with no features suggestive of NTM pulmonary
370 disease who are incapable of spontaneously producing sputum. As discussed in
371 Section C below, there are currently no other validated screening methods to detect
372 NTM in individuals with CF. Although positive cultures have been detected through
373 laryngeal suction, oropharyngeal swabs, or gastric aspirate there are insufficient data to
374 support their use. Skin testing for delayed-type hypersensitivity against NTM antigens
375 does not appear sufficiently sensitive or specific to use for surveillance in the CF
376 population. Serologic assays, such as IgG against mycobacterium antigen A60 for NTM
377 surveillance appear promising^{45,38} but have not been validated in the CF population.
378

379 **C. MICROBIOLOGY**

380
381 **What respiratory tract samples should be used to evaluate individuals with CF for**
382 **suspected NTM pulmonary disease?**
383

384 ***Recommendation 6:*** The CF Foundation and the ECFS recommend that culture
385 and smears for acid fast bacilli (AFB) from sputum, induced sputum, bronchial
386 washings or broncho-alveolar lavage samples can be used to evaluate individuals
387 with CF suspected to have NTM pulmonary disease.
388

389 ***Recommendation 7:*** The CF Foundation and the ECFS recommend against the
390 routine use of transbronchial biopsies to detect NTM in individuals with CF
391 suspected to have NTM pulmonary disease.
392

393 ***Recommendation 8:*** The CF Foundation and the ECFS recommend against the
394 use of oro-pharyngeal swabs to perform diagnostic smears and cultures in
395 individuals with CF suspected to have NTM pulmonary disease.
396

397 Currently sputum, induced sputum, bronchial washings and bronchoalveolar lavage
398 samples are routinely used to evaluate individuals for suspected NTM pulmonary
399 disease⁷⁶. Samples for NTM should be processed for smear microscopy, preferably by
400 immunofluorescence, and culture (see below). Microscopy allows for direct evaluation of
401 the bacterial burden, and may indicate false negative culture results through excessive
402 sample decontamination or overgrowth of conventional bacteria (see below). Oro-
403 pharyngeal swabs should not be used for the detection of NTM, since they do not
404 consistently provide sufficient material for culture⁷⁶.
405

406 A staged approach should be adopted for obtaining diagnostic samples; testing
407 spontaneously expectorated or induced sputum (if available) before resorting to
408 bronchoscopy. Although there are no published studies comparing the relative
409 performance of these different methods for detection of NTM, the presence of negative
410 sputum samples in individuals with radiologic and clinical suspicion of NTM disease
411 should prompt CT-guided bronchoscopic sampling, as for example in nodular
412 bronchiectatic disease⁷⁷⁻⁷⁹. While trans-bronchial biopsies can reveal NTM (on
413 microscopy or culture) and may demonstrate granulomatous inflammation (supporting

414 NTM disease rather than transient colonization), they should not be obtained routinely in
415 individuals with CF given the significant risks of bleeding and pneumothorax⁸⁰.

416

417 **How should respiratory tract samples from individuals with CF be cultured for**
418 **NTM?**

419

420 ***Recommendation 9:*** The CF Foundation and the ECFS recommend that
421 **respiratory tract samples should be cultured using both solid and liquid media.**

422

423 ***Recommendation 10:*** The CF Foundation and the ECFS recommend that the
424 **incubation duration for NTM cultures should be for a minimum of 6 weeks.**

425

426 ***Recommendation 11:*** The CF Foundation and the ECFS recommend that an NTM
427 **culture should be processed within 24 hours of collection to optimize the**
428 **detection of NTM in respiratory samples. If a delay in processing is anticipated,**
429 **refrigeration of samples is advised.**

430

431 The most sensitive and rapid way to detect viable mycobacteria is to culture samples
432 (following decontamination to remove conventional bacteria and fungi) in liquid media
433 using an automated growth detection system (such as MGIT^{76,81,82}); a process widely
434 used around the world. However, concomitant culture on solid media may increase the
435 diagnostic yield since^{46,47} NTM can be detected despite incomplete sample
436 decontamination⁸³. Since decontamination procedures substantially reduce the viability
437 of mycobacteria in samples, attempts have been made to use highly selective agar for
438 solid culture of unprocessed sputum. A recent study, using agar designed for
439 *Burkholderia cepacia* complex culture⁸³, demonstrated an improvement in detection of
440 rapidly growing mycobacteria from 0.7% with conventional liquid culture to 2.8%. The
441 duration of both liquid and solid culture methods has not been rigorously tested but the
442 vast majority of pathogenic NTM will grow by 6 weeks; the current recommended
443 duration in US and European laboratories⁷⁶.

444

445 Laboratory processing of samples should ideally be performed within 24 hours of
446 collection to avoid overgrowth by conventional bacteria, which can reduce NTM
447 viability⁸⁴ and prevent successful decontamination⁸⁴. Studies have shown that
448 refrigeration of samples may improve NTM detection from sputum samples⁸⁵ and should
449 be considered if delays longer than 24 hours in processing are anticipated.

450

451 **How should respiratory tract samples from individuals with CF be**
452 **decontaminated to optimize the detection of NTM?**

453

454 ***Recommendation 12:*** The CF Foundation and the ECFS recommend that
455 **respiratory tract samples should be decontaminated using the standard N-Acetyl**
456 **L-cysteine NALC (0.5%) – NaOH (2%) method.**

457

458 ***Recommendation 13:*** The CF Foundation and the ECFS recommend that if a
459 **sample remains contaminated with gram-negative bacteria after standard NALC-**

460 **NaOH decontamination, it should be further treated with either 5% oxalic acid or**
461 **1% chlorhexidine.**

462
463 Adequate sample decontamination to remove conventional bacteria and fungi is
464 essential to permit culture-based detection of mycobacteria^{76,86,87}, but often fails in CF
465 samples given high densities of *P. aeruginosa* and other microbes^{35-37,88,89}. Since
466 enhanced decontamination protocols adversely impact on NTM viability in samples⁸⁹ a
467 two-step approach to sample processing should be adopted³⁷. Virtually all U.S. and
468 European clinical microbiology laboratories currently use an N-Acetyl L-cysteine-NaOH
469 decontamination step prior to mycobacterial culture^{37,86,87}.

470
471 The addition of a second decontamination step using oxalic acid has been shown to
472 permit the recovery of NTM from persistently contaminated samples albeit with reduced
473 sensitivity³⁶. Alternatively, use of 1% chlorhexidine as a first step may improve the
474 recovery of mycobacteria, but at the expense of higher rates of residual sample
475 contamination⁸⁸. Chlorhexidine negatively affects the performance of the MGIT
476 automated liquid culture system, because it needs to be neutralized with lecithin; lecithin
477 generates random fluorescence reactions from the MGIT system sensor, limiting its
478 use⁸⁸.

479
480 **Should non-culture based methods be used for to detect NTM in respiratory tract**
481 **samples from individuals with CF?**

482
483 ***Recommendation 14:* The CF Foundation and the ECFS recommend against the**
484 **use of non-culture based methods for detecting NTM in respiratory tract samples.**

485
486 A number of studies have been published on the use of polymerase chain reaction
487 (PCR)-based detection methods for NTM from respiratory samples⁹⁰⁻⁹⁶. To date
488 however, none have been robustly evaluated for CF sputum samples nor demonstrate
489 sufficiently high sensitivity and specificity on smear-negative samples⁹⁰ to recommend
490 their routine diagnostic use. Furthermore, the clinical significance of PCR positive
491 respiratory samples is currently unknown.

492
493 **How should NTM isolates from individuals with CF be identified?**

494
495 ***Recommendation 15:* The CF Foundation and the ECFS recommend that all NTM**
496 **isolates from individuals with CF should undergo molecular identification.**

497
498 ***Recommendation 16:* The CF Foundation and the ECFS recommend that all NTM**
499 **isolates from individuals with CF should be identified to the species level, except**
500 **for *M. intracellulare*, *M. avium* and *M. chimaera*, where identification can be**
501 **limited to *M. avium* complex (MAC), and *M. abscessus* complex, which should be**
502 **sub-specified.**

503
504 As individual NTM species differ in their potential to cause clinical disease in humans⁹⁷.

505 and their response to specific antibiotics, correct species identification of NTM isolates
506 is clinically important. Moreover, in the case of *M. abscessus*, the ability to identify
507 isolates to the subspecies level (*M. a. abscessus*, *M. a. bolletii*, *M. a. massiliense*) may
508 predict treatment response⁹⁸ and potentially permit targeted therapy⁹⁹. *M. a.*
509 *massiliense* harbors a partial *erm41* gene deletion preventing inducible macrolide
510 resistance^{98,100} and leads to more successful outcomes with macrolide-based antibiotic
511 regimens than in *M. a. abscessus* (which has a full length, functional *erm41* gene)
512 disease⁹⁸.

513
514 There is no gold standard for NTM species identification. Molecular methods have now
515 surpassed biochemical tests for NTM identification in many laboratories^{95,101-107}.
516 Although matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass
517 spectrometry has shown promise in providing rapid speciation of NTM¹⁰⁸⁻¹¹², the optimal
518 method for protein extraction from mycobacteria and the exact discriminatory power of
519 this method have yet to be established.

520
521 Among molecular methods, three techniques are in current clinical use. The first are line
522 probe assays¹⁰⁶, which are easy to perform but costly, and permit accurate identification
523 of the most frequently encountered NTM species but not sub-speciation of *M.*
524 *abscessus*. Second is PCR product restriction analysis (PRA) in which amplified gene
525 fragments are restriction digested to yield different sized fragments which are then
526 resolved by gel electrophoresis and correlate with specific species¹¹³. This technique is
527 mostly used in low-resource settings and is at least comparable to the line probe
528 assays¹⁰⁶. The third technique is (partial) gene sequencing which permits a higher level
529 of discrimination, often to subspecies level, but is only available in laboratories with
530 access to sequencing facilities. The choice of the optimal sequencing strategy is not
531 straightforward. Although 16S rRNA gene sequencing provides insufficient
532 discrimination, particularly between *M. abscessus* and *M. chelonae*¹¹⁴, a number of
533 other gene sequences (such as partial *hsp65* and *rpoB* gene sequences) have been
534 successfully used^{107,115}. For subspeciation of *M. abscessus*, a multi locus sequence
535 typing (MLST) approach has recently been validated¹¹⁵⁻¹¹⁷. An alternative strategy close
536 to subspeciation is to measure *erm* gene associated inducible macrolide resistance by
537 phenotypic drug susceptibility testing. This does not distinguish accurately between *M.*
538 *abscessus* subspecies but does offer the data for which the subspeciation is generally
539 done: whether or not there is inducible macrolide resistance.

540
541 **Should drug susceptibility testing be performed on NTM isolates from individuals**
542 **with CF?**

543
544 **Recommendation 17:** The CF Foundation and the ECFS recommend that for *M.*
545 **avium complex, clarithromycin susceptibility testing should be performed on an**
546 **isolate recovered prior to initiation of treatment. Clarithromycin susceptibility**
547 **testing should also be performed on subsequent isolates if the patient a) fails to**
548 **culture convert after six months of NTM treatment; b) recultures *M. avium***
549 **complex after initial culture conversion while on NTM treatment; or c) recultures**
550 ***M. avium* complex after completion of NTM treatment.**

551
552 **Recommendation 18:** The CF Foundation and the ECFS recommend that for *M.*
553 **abscessus complex, susceptibility testing should include at least clarithromycin,**
554 **cefoxitin and amikacin (and preferably also tigecycline, imipenem, minocycline,**
555 **moxifloxacin and linezolid).**

556
557 **Recommendation 19:** The CF Foundation and the ECFS recommend that drug
558 **susceptibility testing should be performed in accordance with CLSI guidelines.**

559
560 Based on current published data, the exact role of drug susceptibility testing and its
561 potential to guide regimen selection and predict outcomes in NTM lung disease in CF
562 patients remain unknown¹¹⁸. The Clinical Laboratory Standards Institute (CLSI) has
563 published guidelines on drug susceptibility testing (DST) of NTM^{13,119}. Its European
564 counterpart, the European Committee on Antimicrobial Susceptibility Testing
565 (EUCAST), has presently no guidelines for DST of NTM⁷⁶.

566
567 It is important to appreciate that, although CLSI guidelines provide breakpoint
568 concentrations to interpret minimum inhibitory concentrations (MICs) as ‘susceptible’ or
569 ‘resistant’, these cut-offs have had very limited clinical validation, and no clinical
570 validation has been performed in CF patients. Moreover, whereas limited
571 pharmacokinetic data are now available for MAC lung disease to support breakpoint
572 concentrations¹²⁰, there are no representative pharmacokinetic or pharmacodynamic
573 data to guide treatment of CF patients.

574
575 Breakpoints for clarithromycin susceptibility of MAC have been validated in HIV-related
576 disseminated MAC disease and in retrospective series of MAC lung disease^{118,121,122}.
577 Since the presence of macrolide resistance predicts worse clinical outcomes^{123,124} and
578 requires augmented treatment¹²⁴, susceptibility to macrolides should be tested on
579 isolates prior to treatment initiation and during treatment in refractory cases (defined as
580 those individuals who a) fail to culture convert after six months of NTM treatment; b)
581 reculture *M. avium* complex after initial culture conversion while on NTM treatment, or c)
582 reculture *M. avium* complex after completion of NTM treatment.

583 A very recent study has shown that amikacin MICs ≥ 64 mg/L are measured only in *M.*
584 *avium* complex isolates that have mutations associated with amikacin resistance, i.e. in
585 the 16S rDNA gene. These strains are cultured from patients with significant
586 aminoglycoside exposure, such as CF patients, and for disease caused by these
587 strains, amikacin is unlikely to have any beneficial effect¹²⁵.

588 For rapidly growing mycobacteria including *M. abscessus*, clinical validation has only
589 been performed in series of extra-pulmonary disease¹²⁶ and only for cefoxitin,
590 aminoglycosides and co-trimoxazole. In series of *M. abscessus* lung disease, the
591 outcomes of macrolide-based treatment are generally poor and do not correlate well
592 with *in vitro* susceptibilities^{118,127} potentially due to erm (41)-dependent inducible
593 macrolide resistance and relative short duration of adequate regimens, which were
594 often interrupted because of toxicity. The CLSI has recommended routine testing for
595 inducible macrolide resistance by performing extended incubation of isolates in the
596 presence of clarithromycin as inducible resistance may predict treatment failure¹¹⁹ For

597 *M. simiae*, the role of DST is unknown, although the generally poor outcomes of
598 treatment have been correlated with a lack of synergistic activity between rifampicin and
599 ethambutol, an *in vitro* observation that still awaits clinical validation¹²⁸. Some molecular
600 methods to assess drug susceptibility exist, but are not yet routinely available. For
601 example, sequencing of the 16S rRNA and 23S rRNA genes can reveal mutations
602 associated with high-level resistance to aminoglycosides and macrolides
603 respectively^{118,125} ..

604

605 **D. DIAGNOSIS OF NTM PULMONARY DISEASE IN CF**

606

607 **Should the ATS/IDSA criteria for the diagnosis of NTM pulmonary disease be**
608 **used in individuals with CF?**

609

610 ***Recommendation 20:* The CF Foundation and the ECFS recommend that**
611 **ATS/IDSA criteria for the diagnosis of NTM pulmonary disease should be used in**
612 **individuals with CF (ATS / IDSA 2007 Statement).**

613

614 ***Recommendation 21:* The CF Foundation and the ECFS recommend that other**
615 **CF pathogens and co-morbidities should be considered as potential contributors**
616 **to a patient's symptoms and radiological features when determining the clinical**
617 **significance of NTM positive cultures.**

618

619 ***Recommendation 22:* The CF Foundation and the ECFS recommend that NTM**
620 **treatment should be considered for individuals with CF who have ATS/IDSA**
621 **defined NTM pulmonary disease.**

622

623 ***Recommendation 23:* The CF Foundation and the ECFS recommend that**
624 **individuals receiving azithromycin as part of their CF medical regimen who have**
625 **a positive NTM culture should not continue azithromycin treatment while**
626 **evaluation for NTM disease is underway as azithromycin monotherapy may lead**
627 **to resistance. A macrolide agent may be included in a multi-drug treatment**
628 **regimen if criteria are met for NTM disease.**

629

630

631

632

633 In contrast to *M. tuberculosis*, a single positive culture of NTM does not necessarily
634 indicate that an individual has inflammatory lung damage caused by NTM infection, a
635 condition termed 'NTM pulmonary disease' (NTM-PD).

636

637 To address the difficulty of making a diagnosis of NTM-PD, the ATS/IDSA proposed a
638 set of clinical, radiological and microbiological criteria required to define an individual as
639 having NTM-PD²² (Table 3). Although these criteria have not been validated for
640 individuals with CF, they have been widely adopted by NTM specialists around the
641 world and provide a operational definition for NTM-PD, which supports clinical decision-
642 making and facilitates research. The Consensus Committee therefore concluded that, in

643 the absence of an alternate, CF-validated definition, the ATS/IDSA criteria should be
644 used for the definition of NTM-PD in individuals with CF.

645

646 ***Microbiological criteria for NTM-PD***

647 Individuals should have two or more positive sputum cultures of the same NTM species
648 or one positive culture from bronchoscopic lavage or wash. The threshold for the
649 number of positive sputum samples is derived from an observational study of non-CF
650 patients with MAC in which 98% individuals with at least two positive sputum cultures
651 developed progressive radiographic change compared to only 2% with one positive
652 culture¹²⁹. The type of NTM species isolated is also important. Thus, isolation of *M.*
653 *abscessus* is more likely to reflect NTM-PD than culturing usually non-pathogenic
654 species such as *M. goodnae* and *M. terrae*.

655

656 ***Radiological criteria for NTM-PD***

657

658 In the context of CF-related lung disease, a chest radiograph is unlikely to be of use for
659 the investigation of NTM-PD. High resolution CT (HRCT) scan changes supporting a
660 diagnosis of NTM-PD would include: inflammatory nodules, new tree-in-bud opacities
661 (particularly in areas of mild underlying bronchiectasis) and cavitation¹³⁰. However,
662 these changes are non-specific particularly in individuals with severe CF-related lung
663 disease and may reflect infection with more common CF pathogens, inadequate airway
664 clearance or the development of allergic bronchopulmonary aspergillosis (ABPA).

665

666 ***Clinical criteria for NTM-PD***

667

668 NTM-PD should be suspected in individuals with worsening respiratory symptoms
669 (breathlessness, increased cough and sputum production) and/or declining pulmonary
670 function tests which do not respond to antibiotic therapy targeting conventional CF-
671 associated bacteria and optimised airway clearance. Night sweats, fevers, chest pains,
672 and weight loss (although uncommon) may also suggest possible NTM-PD.

673 NTM treatment should be considered in individuals with CF who fulfil ATS/IDSA criteria
674 for NTM-PD. However, the decision to start treatment is a clinical one based upon an
675 amalgamation of patient factors, the NTM species involved, the risks of treatment side
676 effects, adherence concerns, and the expected outcomes of treatment.

677

678 ***Recommended Clinical Practice for Diagnosis***

679

680 When being investigated for potential NTM-PD, individuals should discontinue drugs
681 liable to compromise NTM culture (such as macrolides, fluoroquinolones,
682 aminoglycosides, co-trimoxazole, linezolid and doxycycline) prior to sputum sample
683 collection. In the case of azithromycin, intracellular accumulation within phagocytes may
684 require a washout period of two weeks or more to allow for drug clearance^{131,132}. If
685 sputum samples are persistently culture negative, but clinical or radiological suspicion of
686 NTM-PD remains, bronchoscopy with targeted sampling of areas with suggestive HRCT
687 changes may be indicated. Individuals receiving azithromycin as part of their CF
688 medical regimen who have a positive surveillance NTM culture should not continue

689 azithromycin treatment while evaluation for NTM disease is underway as azithromycin
690 monotherapy may lead to the development of macrolide resistance.

691
692 Other CF pathogens and co-morbidities should be considered as potential contributors
693 to a patient's symptoms and radiological features when determining the clinical
694 significance of NTM positive cultures. All aspects of CF care should be reviewed and
695 optimized in order to determine the clinical significance of NTM in the sputum.
696 Specifically, consider a trial of NTM sparing intravenous antibiotics (*i.e.* avoid
697 carbapenems, ceftazidime, tigecycline, and amikacin) targeting conventional bacteria,
698 assess for CF-related diabetes, uncontrolled gastrointestinal reflux disease, and clinical
699 and immunological features of ABPA. Likewise, adequate treatment of sinus disease,
700 nutritional support and effective airway clearance strategies should be implemented.
701 Before starting NTM treatment, side-effects, the importance of adherence to therapy
702 and complications of treatment should be discussed with patients and those discussions
703 summarised in the medical notes. Discussion of the risk of treatment failure should be
704 clearly documented.

705 706 **E. TREATMENT**

707
708 **What antibiotic regimen should be used in individuals with CF who have**
709 **ATS/IDSA defined Mycobacterium abscessus complex pulmonary disease?**

710
711 ***Recommendation 24:*** The CF Foundation and the ECFS recommend that
712 **treatment of *M. abscessus* complex pulmonary disease should involve an**
713 **intensive phase followed by a continuation phase.**

714
715 ***Recommendation 25:*** The CF Foundation and the ECFS recommend that the
716 **intensive phase should include a daily oral macrolide (preferably azithromycin) in**
717 **conjunction with 3-12 weeks of intravenous amikacin and one or more of the**
718 **following: intravenous tigecycline, imipenem or ceftazidime, guided but not dictated**
719 **by drug susceptibility testing. The duration of intensive phase therapy should be**
720 **determined by the severity of infection, the response to treatment and the**
721 **tolerability of the regimen.**

722
723 ***Recommendation 26:*** The CF Foundation and the ECFS recommend that the
724 **continuation phase should include a daily oral macrolide (preferably**
725 **azithromycin) and inhaled amikacin, in conjunction with 2-3 of the following**
726 **additional oral antibiotics: minocycline, clofazimine, moxifloxacin and linezolid,**
727 **guided but not dictated by drug susceptibility testing.**

728
729 ***Recommendation 27:*** The CF Foundation and the ECFS recommend that
730 **individuals with *M. abscessus* complex pulmonary disease should be managed in**
731 **collaboration with experts in the treatment of NTM and CF as drug intolerance**
732 **and drug-related toxicity occur frequently and changes in antibiotic therapy are**
733 **often required.**

734

735 **Recommendation 28: The CF Foundation and the ECFS recommend that**
736 **monotherapy with a macrolide or other antimicrobial should never be used in the**
737 **treatment of *M. abscessus* complex pulmonary disease.**
738

739 There are no published randomized controlled trials evaluating treatment outcomes in
740 individuals with *M. abscessus* pulmonary infections. Current treatment
741 recommendations from the ATS and IDSA recommend consideration of a multidrug
742 treatment regimen but note that long-term sputum conversion is difficult to achieve and
743 thus, alternative goals such as: symptomatic improvement, radiographic regression of
744 opacities or microbiologic improvement, may be more realistic²². The ATS/IDSA
745 recommendations were based primarily on a single large study of 154 patients with lung
746 disease caused by rapidly growing mycobacteria, in which more than 80% of patients
747 were infected by *M. abscessus*¹³³. Treatment outcomes were extremely poor; however
748 the patients did not receive the currently recommended combination of antibiotics.
749

750 Since the publication of the last ATS/IDSA guidelines²², there have been several studies
751 that reported treatment outcomes in non-CF patients with pulmonary disease due to *M.*
752 *abscessus*. Jeon and colleagues¹³⁴ described treatment outcomes in 65 non-CF adults
753 in the Republic of Korea with *M. abscessus* lung disease who received a standardized
754 treatment regimen. The regimen included 4 weeks of amikacin (15 mg/kg/day in two
755 divided doses) and cefoxitin (200 mg/kg/day in three divided doses) along with
756 clarithromycin (1000 mg/day in two divided doses), ciprofloxacin (1000 mg/day in two
757 divided doses) and doxycycline (200 mg/day in two divided doses). The total duration of
758 therapy was 24 months and at least 12 months after sputum culture conversion. Fifty-
759 four (83%) patients responded with improved symptoms and 48 (74%%) with improved
760 HRCT findings. Sputum conversion and maintenance of negative sputum cultures for
761 more than 12 months was achieved in 38 (58%) patients. This rate was significantly
762 lower (17%) in patients whose isolates were resistant to clarithromycin. In contrast, in
763 the 14 (22%) patients who underwent resectional surgery, negative sputum cultures
764 were achieved and maintained in 7 (88%) of 8 with preoperatively positive cultures. The
765 authors concluded that a standardized regimen was moderately effective, but adverse
766 reactions were frequent.
767

768 Among 107 patients with *M. abscessus* pulmonary infection at National Jewish Health in
769 Denver, CO, 69 non-CF individuals were treated and followed for a mean duration of 34
770 months¹²⁷. Patients were treated with individualized treatment regimens following
771 ATS/IDSA recommendations. Twenty (29%) patients remained culture positive, 16
772 (23%) converted but experienced relapse, 33 (48%) converted to negative and did not
773 relapse, and 17 (16%) died during the study period. There were significantly more
774 surgical patients than medical patients whose culture converted and remained negative
775 for at least 1 year (57% vs 28%, p=0.022). As in the previous study from South Korea,
776 surgery may have been beneficial. However, surgical management is less likely to be
777 applicable in CF patients in whom focal pulmonary disease is uncommon.
778

779 In a follow-up study, Koh and colleagues⁹⁸. reported significant differences in outcomes
780 based on which subspecies of *M. abscessus* was causing the infection. Treatment

781 response rates to a standardized multidrug regimen were much higher in patients with
782 '*M. massiliense*' (now part of *M. abscessus* subsp. *bolletii*) than with *M. a. abscessus*:
783 sputum culture conversion occurred in 88% of patients with '*M. massiliense*' (now part
784 of *M. abscessus* subsp. *bolletii*) compared with 25% with *M.a. abscessus* (p <0.001). All
785 of the *M. a. abscessus* isolates contained a full length, functional *erm*(41) which, was
786 shown to result in inducible macrolide resistance when the isolates were incubated with
787 clarithromycin. In contrast, the MIC of '*M. massiliense*' (now part of *M. abscessus*
788 subsp. *bolletii*) strains did not increase after incubation with the macrolide agent
789 because the *erm*(41) gene contained a deletion making it nonfunctional. Recent data
790 from this same group of investigators have indicated that clarithromycin is a much
791 stronger inducer of *erm*(41) than azithromycin suggesting that the latter macrolide may
792 be a better choice when treating *M. abscessus* ssp *abscessus* infections⁹⁹.

793
794 Despite the clinical significance of *M. abscessus* lung infection in patients with CF, data
795 on treatment outcomes are extremely limited. There is one anecdotal report that
796 describes eradication of *M. abscessus* in a CF patient who received a prolonged course
797 of therapy with alternating month inhaled amikacin plus oral clarithromycin¹³⁵. However,
798 this appears to be an uncommon outcome in practice. A recent case series of 52
799 individuals, including 15 with CF, with *M. abscessus* and or *M. chelonae* infection
800 suggests that tigecycline-based regimens may be of benefit with 10/15 individuals
801 showing some improvement¹³⁶.

802

803 **Recommended Clinical Practice for antibiotic treatment for *M. abscessus*** 804 **pulmonary disease in CF**

805

806 Given the lack of clinical trial data to inform treatment decisions there is a lot of variation
807 in how patients are treated. An initial intensive phase is typically used to rapidly
808 decrease the bacterial load. A combination of two intravenous drugs with demonstrated
809 *in vitro* activity is administered for several weeks to months in combination with one or
810 more oral drugs. Intravenous drugs such as amikacin, cefoxitin, imipenem (or
811 tigecycline are the most commonly used drugs. Oral drugs with demonstrated *in vitro*
812 activity include the macrolides (clarithromycin and azithromycin), linezolid, clofazimine,
813 and occasionally ciprofloxacin and/or moxifloxacin. After the intensive phase of therapy,
814 patients are usually treated with at least two oral drugs or oral and inhaled antibiotics.

815

816 However there is growing concern that treatment of *M. abscessus* isolates which has
817 either a functional *erm*(41) gene (resulting phenotypically in inducible macrolide
818 resistance) or a 23S ribosomal RNA mutation (leading to high level constitutive
819 macrolide resistance) may be compromised by switching from iv to oral therapy (given
820 the relatively poor efficacy of oral antibiotics) and therefore continuous/very extended
821 intravenous therapy with two or more effective antibiotics may be indicated in these
822 cases.

823 The choice of intravenous agents is based on *in vitro* activity and the toxicity profile of
824 the drug. In addition to amikacin, imipenem is perhaps the best choice as companion iv
825 therapy; the drug shows *in vitro* activity and the side-effect profile is better than that of

826 cefoxitin and tigecycline. In the study reported by Jeon and colleagues¹³⁴, 60% of the
827 patients that were started on cefoxitin had to have the drug discontinued due to drug-
828 related toxicity after a median of 22 days of treatment. Neutropenia occurred in 51%
829 and thrombocytopenia in 6% of patients on cefoxitin. Tigecycline has a low MIC against
830 *M. abscessus* and showed efficiency against *M. abscessus* in combination¹³⁶. However,
831 it is associated with significant nausea and vomiting that has made it difficult to
832 administer for a prolonged period¹³⁶.

833
834 There are few oral drugs with significant *in vitro* activity against *M. abscessus*; the
835 macrolides are the only oral drugs with consistent activity although their use may be
836 potentially limited by inducible resistance (as described above) or acquired point
837 mutations in the 23S ribosomal RNA. There are no clinical trials comparing azithromycin
838 to clarithromycin in *M. abscessus* infection so the choice of which macrolide to use is
839 typically based on the *in vitro* activity, side-effect profile and consideration of drug
840 interactions. Clarithromycin has slightly better *in vitro* activity than azithromycin but
841 there are conflicting reports regarding the impact of *erm*(41) gene expression with each
842 of these drugs^{99,137,138}. Clarithromycin is a stronger inhibitor of the P450 enzyme system
843 than azithromycin so drug interactions are more common.

844
845 Linezolid shows *in vitro* activity in approximately 50% of *M. abscessus* isolates
846 (although there is considerable geographical variation); however, hematological
847 (anemia, thrombocytopenia) and neurological (peripheral neuropathy, optic neuritis)
848 toxicities are common, particularly when linezolid is dosed 600 mg twice daily for
849 prolonged courses. For this reason, many practitioners give 600 mg once daily to
850 reduce the risk of adverse effects. The fluoroquinolones and minocycline/doxycycline
851 rarely show *in vitro* activity although they were included in the standardized treatment
852 regimen used in the report by Jeon and colleagues⁹⁹. Finally, clofazimine has significant
853 *in vitro* activity against *M. abscessus*¹³⁹. However, this drug, used to treat leprosy, is not
854 readily available in the US at this time, although it can be obtained with an IRB-
855 approved protocol through submission of an individual patient use IND to the FDA.
856 Instructions for this process can be found on the NTM Info and Research, Inc. website
857 (<http://www.ntminfo.org/clofazimine>).

858
859 The lack of oral antibiotics with activity against *M. abscessus* has led clinicians to use
860 inhaled amikacin usually during the continuation phase of therapy. There are no studies
861 that have correlated treatment outcomes in patients with *M. abscessus* infection with the
862 dose of inhaled amikacin and, therefore, there is a great deal of variation in the dose
863 used (250 to 500 mg) and frequency of administration (daily to twice daily). A recent
864 study targeting treatment refractory NTM patients, most of whom were non-CF patients
865 with *M. abscessus*, evaluated the effect of adding inhaled amikacin to their oral and/or
866 intravenous drug regimens¹⁴⁰. Among the 20 patients with persistently positive cultures,
867 8 (40%) had at least one negative culture and 5 (25%) had persistently negative
868 cultures after addition of inhaled amikacin. Inhaled amikacin was stopped in 7 (35%)
869 due to toxicity. There is currently significant interest in the potential use of a liposomal
870 formulation of amikacin (which may improve drug delivery within the lung and into

871 infected macrophages) as part of a multidrug regimen for both *M. abscessus* and MAC.
872 Large multi-centre studies are planned.

873
874 The optimum duration of therapy is not known. Based on studies in non-CF patients
875 even prolonged treatment regimens were associated with high rates of failure and
876 recurrence. In many patients who do not convert their cultures to negative on therapy or
877 who suffer recurrent disease, repeated courses of therapy may be necessary

878 879 **Treatment for MAC**

880
881 **What antibiotic regimen should be used in individuals with CF who have**
882 **ATS/IDSA defined Mycobacterium avium complex pulmonary disease?**

883
884 ***Recommendation 29:*** The CF Foundation and the ECFS recommend the same
885 antibiotic regimen for treatment of all species within the *M. avium* complex.

886
887 ***Recommendation 30:*** The CF Foundation and the ECFS recommend that
888 clarithromycin-sensitive *M. avium* complex pulmonary disease should be treated
889 with a daily oral antibiotic regimen containing a macrolide (preferably
890 azithromycin), rifampin and ethambutol.

891
892 ***Recommendation 31:*** The CF Foundation and the ECFS recommend against the
893 use of intermittent (three-times-per week) oral antibiotic therapy to treat *M. avium*
894 complex pulmonary disease.

895
896 ***Recommendation 32:*** The CF Foundation and the ECFS recommend that
897 monotherapy with a macrolide or other antimicrobial agent should never be used
898 in the treatment of *M. avium* complex pulmonary disease.

899
900 ***Recommendation 33:*** The CF Foundation and the ECFS recommend that an initial
901 course of intravenous amikacin should be considered for the treatment of *M.*
902 *avium* complex pulmonary disease in the presence of one or more of the
903 following: i) AFB smear positive respiratory tract samples ii) radiological
904 evidence of lung cavitation or severe infection iii) systemic signs of illness

905
906 ***Recommendation 34:*** The CF Foundation and the ECFS recommend that
907 clarithromycin-resistant *M. avium* complex pulmonary disease should be
908 managed in collaboration with experts in the treatment of NTM and CF.

909
910 There are very few published randomised controlled trials evaluating treatment for MAC
911 pulmonary disease (MAC-PD) in non-HIV positive patients and none in individuals with
912 CF. In the pre macrolide era, a UK trial of individuals without CF and with largely
913 cavitary disease reported that those randomised to receive rifampicin and ethambutol
914 had a combined failure / relapse rate of 41% compared to 16% of patients randomised
915 to receive rifampicin, ethambutol and isoniazid ($p=0.033$)¹⁴¹. In a subsequent study, on
916 a similar cohort, patients randomised to receive rifampicin, ethambutol and

917 clarithromycin had an all-cause mortality of 48% compared to 30% of patients
918 randomised to receive rifampicin, ethambutol and ciprofloxacin¹⁴². However, only 13%
919 of patients in the clarithromycin group failed treatment or relapsed compared to 23% in
920 the ciprofloxacin group.

921
922 In addition, there have been several non-comparator studies evaluating outcomes in
923 HIV negative patients with MAC-PD. The majority utilised a three oral drug regimen
924 including a macrolide (clarithromycin or azithromycin), a rifamycin (rifampin or rifabutin)
925 and ethambutol, in combination with an initial course of an aminoglycoside
926 (streptomycin, amikacin or kanamycin)^{122,123,143-146}. The culture conversion rate varied
927 considerably between studies (13-82%), but on the whole 55-65% of patients culture
928 converted after 6-12 months treatment and when reported, the mean time from starting
929 treatment to culture conversion was 3- 5 months^{122,123}. Treatment failure was associated
930 with previous MAC-PD treatment, cavitary disease, smear positivity, clarithromycin
931 resistance at initiation of treatment, intolerance of NTM therapy, and acquired
932 clarithromycin resistance^{122,123,143,145-147}.

933
934 An alternative regimen using clofazimine with a macrolide and ethambutol resulted in a
935 culture conversion rate of 87%¹⁴⁸. Although five (19%) subjects relapsed an average of
936 17 months after completing treatment, all MAC isolates remained clarithromycin
937 sensitive, raising the possibility of reinfection rather than treatment failure¹⁴⁹. In another
938 case series utilising clofazimine in combination with clarithromycin and minocycline, the
939 culture conversion rate was 64% in patients completing the study (47% overall), which
940 may indicate the importance of ethambutol as part of the multidrug regimen in the
941 treatment of MAC-PD¹⁵⁰.

942
943 Clarithromycin resistance developed in up to 15% of patients receiving treatment for
944 MAC-PD and this was generally associated with clarithromycin monotherapy or the
945 prescription of inadequate companion medications^{122-124,144-147}. When taken in
946 combination with ethambutol and a rifamycin, acquired clarithromycin resistance
947 developed in only 12/303 (4%) of patients. In the context of clarithromycin resistance,
948 the best treatment responses were seen in patients who underwent surgical resection
949 and received greater than six months of an injectable aminoglycoside¹²⁴ where 11/14
950 (79%) achieved culture conversion compared to 1/27 (4%) of those not surgically
951 resected and not receiving injectables.

952
953 While intermittent and daily dosing regimens appear equally effective in many case
954 series, intermittent regimens may be associated with less toxicity, better tolerability and
955 adherence and less cost^{145,146}. However, a large multicentre study utilising an
956 intermittent dosing regimen in individuals with moderate or severe MAC-PD (including
957 many with cavitary disease and with prior treatment failure) reported a culture
958 conversion rate of only 13% after 12 months treatment^{144,149}. There have to date been
959 no studies in individuals with CF to determine an optimal dosing regimen for MAC
960 therapy but concerns about drug absorption and lung penetration in CF have meant that
961 many centres have adopted daily dosing protocols.

962

963 It is unclear if use of an aminoglycoside during the initial phase of MAC antibiotic
964 therapy is beneficial. In a multicentre study involving 146 HIV-negative patients with
965 MAC-PD, participants were randomised to receive intramuscular streptomycin
966 (15mg/kg) or placebo thrice weekly for the first three months of therapy, in addition to
967 clarithromycin, rifampin and ethambutol. Streptomycin treated patients had a
968 significantly higher culture conversion rate after approximately two years of treatment
969 than placebo patients (71% vs 51%, $p < 0.05$), but a third of patients in each group
970 experienced sputum relapse and there were no significant differences in symptoms or
971 radiological response between groups¹⁵¹.

972
973 Furthermore, there was no statistically significant difference in culture conversion rates
974 between individuals that received an initial course of intramuscular kanamycin (78%)
975 compared to those that did not (58%) in a non-randomised study involving patients with
976 MAC-PD¹²³. More recently, the use of aerosolised amikacin in addition to standard
977 multidrug macrolide-based regimens was reported in six HIV-negative individuals with
978 MAC-PD who had failed standard therapy¹⁵². While four patients were culture negative
979 after six months of therapy, one later cultured *M. chelonae* (resistant to amikacin), two
980 re-cultured MAC and one patient was unable to tolerate prolonged therapy with
981 aerosolised amikacin. A more recent case series of the impact of nebulised amikacin¹⁴⁰
982 in 20 non-CF individuals with treatment refractory NTM-PD (of which 5 had MAC)
983 reported high rates of drug toxicity. As mentioned above, studies examining the use of
984 liposomal amikacin (which may have a better side-effect profile) for the treatment of
985 NTM in individuals with CF are planned.

986 987 **Recommended Clinical Practice antibiotic treatment for MAC pulmonary disease** 988 **in CF**

989
990 Individuals with clarithromycin sensitive MAC-PD should be treated with a daily oral
991 antibiotic regimen that includes a macrolide, rifampin and ethambutol (15mg/kg),
992 *consistent with the ATS/ IDSA recommendations for individuals with severe nodular*
993 *bronchiectatic disease*²². Intermittent oral antibiotic therapy is not recommended due to
994 the nature of the underlying lung disease and concerns regarding antibiotic absorption
995 in CF. Whilst there are no head to head trials showing a difference in outcome between
996 individuals with MAC-PD treated with clarithromycin or azithromycin, the latter may be
997 the macrolide of choice in CF as it can be taken once daily, its serum levels may be less
998 affected by rifamycins¹²⁰ and it has well established benefits in individuals with CF in
999 addition to its effects on NTM.

1000
1001 Individuals with a high bacterial load (suggested by smear positivity, radiological
1002 evidence of lung cavitation and/or significant inflammatory change or the presence of
1003 systemic symptoms) may benefit from an initial (1 – 3 month) course of intravenous
1004 amikacin or streptomycin, in addition to the standard three-drug regimen for MAC-PD.
1005 While the available data do not show a difference in toxicity between amikacin regimens
1006 dosed at 15mg/kg once daily or 25mg/kg thrice weekly, ototoxicity was found in 37% of all
1007 participants (associated with older age and larger cumulative dose), vestibular toxicity in
1008 8% (usually reversible) and nephrotoxicity in 15% (usually mild and reversible)¹⁵³.

1009 Streptomycin, although less widely used than amikacin for MAC-PD, may have less
1010 ototoxicity than amikacin¹⁵³. The use of aerosolised amikacin in place of an intravenous
1011 aminoglycoside may be preferable in terms of reduced burden of care and toxicity, but
1012 outcome data are limited and it is unlikely to be helpful for patients with cavitory disease
1013 in whom drug levels at the site of infection may be sub-therapeutic. As mentioned
1014 above, liposomal formulations of amikacin, currently under evaluation, may potentially
1015 prove more effective.

1016
1017 The major risk factors for the development of clarithromycin resistant MAC-PD are
1018 macrolide monotherapy and prior macrolide treatment with inadequate companion
1019 medications. Thus, macrolides (often prescribed for their anti-inflammatory effects in
1020 CF) should be discontinued immediately following isolation of a mycobacterial species
1021 and macrolides should never be prescribed in the treatment of MAC-PD without two
1022 appropriate companion antibiotics.

1023
1024 Macrolide therapy is not generally recommended in the context of clarithromycin
1025 resistant MAC-PD²², but macrolides may still be beneficial in this context in CF due to
1026 their non-antibiotic properties. Individuals with clarithromycin resistant MAC-PD may
1027 respond to a regimen including an intravenous aminoglycoside, a rifamycin and
1028 ethambutol, in addition to one or more companion medications (accepting that there are
1029 limited data to guide practice^{22,124,142}.) such as a quinolone or clofazimine, Rifabutin may
1030 be useful in the treatment of clarithromycin resistant MAC-PD, but adverse events
1031 (particularly blood dyscrasias, gastrointestinal upset and polyarthralgia) are more
1032 common and often necessitate dose reduction or complete cessation of treatment¹⁵⁴⁻¹⁵⁶.
1033 Surgical resection might also be helpful in selected individuals with localised severe
1034 bronchiectatic disease, but this management is less likely to be useful in CF as MAC-
1035 PD is more likely to be diffuse.

1036
1037 Ethambutol ocular toxicity (optic or retrobulbar neuritis) may present with blurred vision,
1038 decreased acuity, central scotomas, impaired red-green colour discrimination and
1039 peripheral visual field defects. Ocular toxicity was identified in 6% of patients with MAC-
1040 PD receiving ethambutol at a dose of 25mg/kg/day for the first two months followed by
1041 15mg/kg/day for the remainder of treatment¹⁵⁷. Ocular toxicity is more likely to occur in
1042 the context of MAC-PD than in patients receiving TB treatment due to the longer
1043 duration of therapy. While individuals prescribed ethambutol should have regular visual
1044 acuity and colour vision testing, visual symptoms often occur before measurable
1045 changes can be identified. Thus, patients should be educated about the potential side
1046 effects of ethambutol and encouraged to self-report changes in vision, following which
1047 ethambutol therapy should be discontinued until an ophthalmological assessment has
1048 taken place.

1049
1050 It is not uncommon for more than one NTM species to be isolated from an individual
1051 with CF^{26,140}. In these circumstances, continued microbiological surveillance is
1052 advisable to determine the predominant organism. NTM pulmonary disease is also
1053 commonly associated with ABPA and / or the identification of *Aspergillus* species in
1054 sputum or lavage specimens. As rifamycins increase the hepatic metabolism of azole

1055 antifungal agents, the treatment of *Aspergillus* in the context of MAC-PD is more
1056 difficult. One approach is to use rifabutin in place of rifampin (as it is the rifamycin with
1057 the least cytochrome P450 enzyme induction) in conjunction with the usual companion
1058 medications for MAC and voriconazole, with adjustment of drug doses according to
1059 levels¹⁵⁸. If therapeutic drug monitoring is not available, an alternative approach is to
1060 use clofazimine in place of rifampin¹⁴⁸.

1061

1062 **Treatment: Generic recommendations**

1063

1064 **What outcome monitoring should be performed in individuals with CF receiving**
1065 **treatment for NTM pulmonary disease?**

1066

1067 ***Recommendation 35:*** The CF Foundation and the ECFS recommend that
1068 individuals with CF receiving NTM treatment should have expectorated or
1069 induced sputum samples sent for NTM culture every 4-8 weeks throughout the
1070 entire course of treatment to assess the microbiological response.

1071

1072 ***Recommendation 36:*** The CF Foundation and the ECFS recommend that a
1073 schedule for detecting drug toxicity (including hearing loss, visual loss, renal
1074 impairment and liver function test abnormalities) should be set in place at the
1075 time of NTM treatment initiation and implemented throughout treatment based on
1076 the specific drugs prescribed.

1077

1078 ***Recommendation 37:*** The CF Foundation and the ECFS recommend that a HRCT
1079 scan of the lungs should be performed shortly before starting NTM treatment and
1080 at the end of NTM treatment to assess the radiological response.

1081

1082 **What duration of antibiotic therapy is recommended for individuals with CF**
1083 **receiving treatment for NTM pulmonary disease?**

1084

1085 ***Recommendation 38:*** The CF Foundation and the ECFS recommend that NTM
1086 antibiotic therapy should be prescribed for 12 months beyond culture conversion
1087 (defined as three consecutive negative cultures, with the time of conversion
1088 being the date of the first of the three negative cultures) as long as no positive
1089 cultures are obtained during this 12 months.

1090

1091 ***Recommendation 39:*** The CF Foundation and the ECFS recommend that
1092 individuals who fail to culture convert despite optimal NTM therapy may benefit
1093 from long term suppressive antibiotic treatment.

1094

1095 **Treatment: Therapeutic Drug monitoring**

1096

1097 **Should therapeutic drug monitoring be performed in individuals with CF receiving**
1098 **treatment for NTM pulmonary disease?**

1099

1100 ***Recommendation 40:*** The CF Foundation and the ECFS recommend that when

1101 amikacin is given intravenously or when streptomycin is given intravenously or
1102 intramuscularly, serum levels should be monitored and dosing adjusted to
1103 minimize ototoxicity and nephrotoxicity.

1104
1105 **Recommendation 41:** The CF Foundation and the ECFS recommend against
1106 routinely obtaining serum levels of other anti-mycobacterial drugs. However,
1107 absorption of oral medications is often reduced in CF. Therefore use of
1108 therapeutic drug monitoring should be considered for individuals failing to
1109 improve despite taking recommended drug regimens or for those on concomitant
1110 medications with significant interactions with NTM drugs.

1111
1112 Therapeutic drug monitoring (TDM) seeks to quantify the relationship between drug
1113 dose, serum (plasma) concentration, and clinical response¹⁵⁹ and thereby maximise
1114 therapeutic response while avoiding toxicity. The potential benefits of TDM during NTM
1115 treatment in individuals with CF include adjusting drug dosing to:

- 1116
- 1117 a) *Correct for drug-drug interactions that could adversely affect serum antibiotic levels.*
1118 Drug-drug interactions frequently occur among agents used to treat NTM. Rifampin
1119 (more than rifabutin) may increase the metabolism of several drugs including
1120 clarithromycin, azithromycin, and moxifloxacin, while rifabutin increases
1121 azithromycin levels and decreases moxifloxacin levels^{120,160}.
 - 1122
 - 1123 b) *Maximise the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of*
1124 *antibiotics to optimise efficacy.* The PK/PD indices that correlate with clinical
1125 efficacy vary by antimicrobial agent^{120,161,162}. To exert maximal activity, drugs such
1126 as aminoglycosides and ethambutol require high peak concentrations relative to the
1127 pathogen's minimal inhibitory concentration (C_{max}/MIC). Ciprofloxacin and rifampin
1128 require a high concentration-time or area under the plasma concentration curve
1129 measured over 24 hours to MIC ratio (AUC_{0-24}/MIC) and β -lactam agents require as
1130 much time as possible whereby the concentration persists above the infecting
1131 organism's MIC (%T > MIC). Macrolide agents such as azithromycin have weak
1132 concentration-dependent effects and time effects, but these agents exert their
1133 activity through intracellular activity, tissue penetration, and prolonged, persistent
1134 effects due to their long half-life¹⁶³.
 - 1135
 - 1136 c) *Overcome CF related differences in absorption, distribution and clearance of drugs.*
1137 CF patients have different renal and non-renal clearance of several drugs when
1138 compared with non-CF patients due to reduced bioavailability, increased volume of
1139 distribution, and more rapid clearance. In addition, hepatic disease and diabetes
1140 may further influence drug metabolism and absorption. Several recent reviews have
1141 addressed evidence-based dosing for various agents used for treatment of
1142 pulmonary exacerbations in CF¹⁶⁴⁻¹⁶⁷. While the relevance of the recommended
1143 dosing schedules is unknown for treatment of NTM, it is feasible that CF patients
1144 would need higher dosages of mycobacterial drugs.
- 1145

1146 With the exception of aminoglycosides, the clinical utility of TDM during treatment for
1147 NTM is unknown for both CF and non-CF patients due to a lack of rigorous studies
1148 although some experts have recommended TDM for mycobacterial agents on a case-
1149 by-case basis¹⁶². A recent retrospective study assessed the pharmacokinetic and
1150 pharmacodynamic parameters for 481 patients with disease caused by *M. avium*
1151 complex¹²⁰. Peak serum concentrations within reference/normal ranges were only
1152 achieved for ethambutol, clarithromycin, and azithromycin in 52%, 44% and 65% of
1153 patients, respectively. In addition, pharmacodynamic targets for C_{max}/MIC or AUC_{0-}
1154 $_{24}/MIC$ were rarely achieved. However, these observations were not linked with clinical
1155 outcomes.

1156
1157 Another recent evaluation of the potential utility for TDM in 130 non-CF patients treated
1158 for MAC found no association between peak plasma/ MIC ratios for clarithromycin,
1159 rifampin, or ethambutol and clinical outcomes¹⁶⁸. As previously observed, rifampin had a
1160 substantial impact on clarithromycin levels; those treated with both drugs had a median
1161 peak plasma clarithromycin concentration of 0.3 µg/ml, while those treated with rifabutin
1162 had a median peak plasma concentration of 1.8 µg/ml, and those with *M. abscessus*
1163 (n=60) treated without rifampin had a median peak plasma concentration of 3.8 µg/ml.
1164 In all, 97% of patients with MAC treated with daily therapy and 100% of patients on
1165 intermittent therapy reached the target for clarithromycin of 2 µg/ml. These experts
1166 concluded that TDM for treatment of MAC lung disease may not be beneficial (although
1167 the effects of dose optimisation on clinical outcomes were not evaluated).

1168
1169 To our knowledge, there is only one case series, published over a decade ago, that
1170 examined the potential role of TDM in CF. Ten CF patients with mycobacterial disease
1171 (6 with MAC, 3 with *M. abscessus* and 1 with *M. tuberculosis*) had serum drug
1172 concentration measurements performed 2 and 4 hours after ingestion¹⁶¹. Monitoring
1173 serum levels at two time points helped distinguish between poor absorption and delayed
1174 absorption. Half of the subjects had inadequate serum levels for one or more drugs and
1175 one patient clinically improved following dose adjustments that achieved target serum
1176 levels. However, target concentrations were not achieved for several patients. Notably,
1177 this study did not compare outcomes in patients with and without TDM.

1178

1179

1180 **Treatment: Adjuvant therapy & Surgery**

1181

1182 In the context of infectious disease, adjuvants have been defined as “therapies that act
1183 by rendering the organism more susceptible to attack by antibiotics or the host immune
1184 system, by rendering it less virulent or killing it by other means”¹⁶⁹. A number of
1185 approaches have been proposed as candidates for adjuvant therapy in NTM infection in
1186 CF, including interferon gamma (or agents which promote interferon gamma release)
1187 and vitamin D. Drug delivery vehicles, such as liposomes, may be considered
1188 adjuvants. Liposomes have been studied as a mode of delivering amikacin for infection
1189 with *Pseudomonas aeruginosa* in CF¹⁷⁰, and this approach is also being evaluated
1190 (clinicaltrials.gov/show/NCT01315236) for NTM.

1191

1192 **Does interferon gamma (IFN γ) therapy improve treatment outcomes in individuals**
1193 **with CF who have NTM pulmonary disease?**

1194
1195 **Recommendation 42: The CF Foundation and the ECFS recommend against the**
1196 **use of Interferon gamma as adjuvant therapy for NTM pulmonary disease in**
1197 **individuals with CF.**

1198
1199 IFN γ plays a critical in the host defense against NTM infection: a) Deficiencies in IFN γ
1200 signaling (caused by deleterious mutations¹⁷¹ or neutralizing autoantibodies¹⁷²) lead to
1201 (usually disseminated) NTM infection in non-CF individuals. b) Inoculation of mice
1202 deficient in IFN γ or IFN γ receptor results in disseminated NTM infection¹⁷³. c) Addition
1203 of IFN γ to NTM-infected human macrophages *in vitro* enhances intracellular killing
1204 probably through autophagy stimulation³⁹.

1205
1206 In non-CF individuals, adjuvant IFN γ therapy in NTM infection has been examined in
1207 several studies^{174,175}. An uncontrolled trial of IFN γ was conducted in seven patients with
1208 presumed primary immunodeficiency (three with familial susceptibility to MAC and four
1209 with idiopathic CD4 lymphopaenia) who had disseminated NTM disease refractory to
1210 conventional antibiotic therapy¹⁷⁴. All patients improved with the introduction of
1211 subcutaneous IFN γ two or three times per week.

1212
1213 In a randomised, placebo controlled trial, 32 patients with pulmonary NTM disease (30
1214 with MAC) were randomised to receive either intramuscular IFN γ (1 x 10⁶ IU) or placebo
1215 once daily for four weeks and then three times weekly for 20 weeks^{2,175} in addition to
1216 daily oral azithromycin, ciprofloxacin, ethambutol and rifampin. The primary outcome (a
1217 composite endpoint of improvements in symptoms, radiology and microbiology) was
1218 achieved at six months by 72% (13/18) of patients in the IFN γ arm compared to 36%
1219 (5/14) receiving placebo (p = 0.037). The greater response rate with IFN γ was sustained
1220 at 12 months after completion of treatment. However, the small study size, the use of
1221 composite end points and the lack of microbiological response after six months
1222 treatment mean that these data need to be interpreted with caution

1223
1224 Furthermore three large trials (ClinicalTrials.gov Identifiers NCT00001318,
1225 NCT00111397 and NCT00043355) examining IFN γ therapy for pulmonary NTM
1226 disease remain unpublished or have been terminated (potentially due to lack of
1227 efficacy), again questioning the role of IFN γ adjuvant therapy.

1228
1229 **Does vitamin D supplementation improve treatment outcomes in individuals with**
1230 **CF who have NTM pulmonary disease?**

1231
1232 **Recommendation 43: The CF Foundation and the ECFS recommend that vitamin**
1233 **D should be supplemented according to national CF care guidelines.**

1234
1235 Vitamin D is thought to play a critical role in host defence against mycobacteria. *In vitro*
1236 and *ex vivo* treatment with vitamin D of human macrophages infected with *M.*
1237 *tuberculosis* enhances intracellular killing (through stimulating antimicrobial peptide

1238 production¹⁷⁶ and autophagy¹⁷⁷). Furthermore, several epidemiological studies have
1239 shown an association of vitamin D deficiency with reactivation of tuberculosis [reviewed
1240 in^{178,179} and, more recently, the presence of NTM-PD⁶³. However interventional trials of
1241 Vitamin D supplementation in patients with active pulmonary TB have had mixed
1242 results¹⁸⁰ and there are no trials of vitamin D as an adjuvant treatment for NTM disease.
1243

1244 **Should surgery be considered in individuals with CF who have NTM pulmonary**
1245 **disease?**
1246

1247 ***Recommendation 44:* The CF Foundation and the ECFS recommend that lung**
1248 **resection should only be considered in extraordinary circumstances and in**
1249 **consultation with experts in the treatment of NTM and CF.**
1250

1251 Surgical resection has been used extensively in the management of pulmonary
1252 mycobacterial infection in order to excise localised infection, debulk severe disease or
1253 excise cavities or damaged lung into which antibiotic penetration may be impaired. In
1254 no cases, however has surgery been used as a substitute for antibiotic therapy. There
1255 are, however, no randomised trials of surgery for the treatment of pulmonary NTM
1256 disease in any patient group. While many publications report the use of lung resection
1257 (pneumonectomy, lobectomy or segmentectomy) with combination antibiotic therapy in
1258 NTM infection, most are case reports with no comparator group receiving only medical
1259 therapy thereby preventing objective assessment of the efficacy of surgery.
1260 Nonetheless, three series of non-CF patients do contain some comparison data
1261 although the potential for selection bias of patients considered suitable for surgery
1262 makes interpretation difficult. The first¹³⁴ comprised 65 patients from South Korea, with
1263 pulmonary *M. abscessus* infection. Surgery was performed in 14 patients who: failed to
1264 achieve sputum culture conversion, became culture positive again after a period of
1265 culture positivity or experienced disease-related complications such as haemoptysis. Of
1266 the eight patients who were sputum culture positive before surgery, seven became
1267 culture negative post-operatively (compared to culture conversion rates of 38/65 for the
1268 group as a whole). A second study, from the US¹²⁷, reported outcomes for 69 patients
1269 with pulmonary *M. abscessus* infection all treated with combination antibiotics, 23 of
1270 whom underwent additional surgical resection. Indications for surgery included the
1271 presence of localised bronchiectasis, cavitary disease and haemoptysis. In the
1272 surgical group significantly more patients (13 / 23) became persistently sputum culture-
1273 negative compared to the medical treatment only group (13 / 46). A third study, also
1274 from the US, described outcomes in 51 patients with macrolide-resistant MAC-PD [ref
1275 Griffith et al AJRCCM 2006 174; 928]. Individuals receiving both surgical resection and
1276 injectable aminoglycoside therapy had greater sputum conversion rates (11/14 patients)
1277 than those receiving neither treatment modality (2/37 patients).
1278

1279 A recent review of case series published over the last 40 years¹⁸¹ suggests that
1280 localised resection (lobectomy or segmentectomy) should be considered for severe,
1281 localised, unilateral NTM disease which has failed to respond to conventional antibiotic
1282 therapy. In the context of CF however, localised NTM disease is extremely rare (or at

1283 least very difficult to identify) and the risks of thoracic surgery are high and therefore the
1284 potential benefits of surgical resection are limited.

1285
1286 **F. TRANSPLANTATION:**

1287
1288 **Should individuals with CF with current or previous NTM positive cultures be**
1289 **referred for lung transplantation?**

1290
1291 **Recommendation 45:** The CF Foundation and the ECFS recommend that all
1292 individuals with CF being considered for lung transplantation should be
1293 evaluated for NTM pulmonary disease.

1294
1295 **Recommendation 46:** The CF Foundation and the ECFS recommend that the
1296 presence of current or previous respiratory tract samples positive for NTM should
1297 not preclude individuals being considered for lung transplantation.

1298
1299 **Recommendation 47:** The CF Foundation and the ECFS recommend that
1300 individuals with CF who have NTM pulmonary disease and are being evaluated
1301 for transplantation should commence treatment prior to transplant listing.

1302
1303 **Recommendation 48:** The CF Foundation and the ECFS recommend that
1304 individuals with CF receiving NTM treatment with sequential negative cultures
1305 may be eligible for transplant listing.

1306
1307 **Recommendation 49:** The CF Foundation and the ECFS recommend that
1308 individuals with CF who have completed treatment for NTM pulmonary disease
1309 with apparent eradication of the organism may be eligible for transplant listing.

1310
1311 **Recommendation 50:** The CF Foundation and the ECFS recommend that the
1312 presence of persistent *M. abscessus* complex or *M. avium* complex infection
1313 despite optimal therapy is not an absolute contraindication to lung transplant
1314 referral.

1315
1316 The International Society for Heart and Lung Transplantation (ISHLT) International
1317 Guidelines lists 'colonisation with highly resistant or virulent mycobacteria' as a relative
1318 contra-indication for selection as a lung transplant candidate¹⁸². There is, however,
1319 limited published information on transplant outcomes for individuals with previous or
1320 concurrent NTM infection with very few reports (usually from single centres) specifically
1321 examining CF cohorts^{183,184}.

1322
1323 The risk of NTM infection post-transplantation is not well defined. A study of 201 CF and
1324 non-CF transplant recipients¹⁸⁵ suggested that post-operative NTM acquisition was
1325 associated with increased mortality (HR 2.61), independent of bronchiolitis obliterans
1326 syndrome. However these data should be interpreted with the following in mind: very
1327 little data was available on the presence of pulmonary NTM pre-transplant; the vast
1328 majority of patients did not have CF or even bronchiectasis; and that non-NTM related

1329 causes were major contributors to death in fatal cases. In contrast, a more recent study
1330 of CF and non-CF transplant recipients¹⁸⁶ reported that 53 of 237 individuals (22.4%)
1331 acquired NTM positive cultures post-operatively (70% MAC, 10% MABSC) of which 2
1332 fulfilled ATS/IDSA criteria for NTM-PD. Although overall mortality was not affected by
1333 NTM acquisition, four patients developed persistent surgical site infection (three with *M.*
1334 *abscessus*) of whom one died of disseminated NTM infection. The potential for *M.*
1335 *abscessus* to cause significant post-operative complications is supported by a review of
1336 outcomes from 31 transplant centres¹⁸⁷ indicating frequent soft tissue and surgical site
1337 infections and two deaths attributable to *M. abscessus* infection.
1338

1339 The largest CF-specific case series comes from the University of North Carolina Chapel
1340 Hill experience between 1990-2003²⁵. 146 patients with CF underwent lung
1341 transplantation and 31 listed for transplantation. Of those individuals referred, 19.7%
1342 were NTM culture positive pre-transplant. Rates of NTM following lung transplantation
1343 were 3.4%. Pre-transplant infection with *M. abscessus* was recognized as a significant
1344 risk factor for recurrence of NTM post-transplantation. Although there was no effect on
1345 mortality, post-transplant NTM infection caused significant morbidity as patients
1346 developed *M. abscessus* associated skin and soft tissue infection or pulmonary disease
1347 caused by MAC and other NTM species. There are several published case series of
1348 successful outcomes for individuals with CF who have culture positive *M. abscessus*
1349 infection at the time of transplantation¹⁸³. However, NTM-related complications in this
1350 group may be more frequent, and include persistent soft tissue or wound infections¹⁸³,
1351 empyema and disseminated NTM infection^{161,188}. Although a small series, the UNC
1352 report suggests no affect of the presence of pre-transplant *M. abscessus* positive
1353 cultures on post transplant mortality¹⁸⁴.
1354

1355 The Consensus Committee concluded that all individuals with CF should be evaluated
1356 for NTM disease prior to referral for lung transplantation, given the very high reported
1357 rates of NTM culture positivity for this group, and that untreated NTM infection may
1358 represent an increased (and potentially modifiable) post-operative risk. Consequently, if
1359 NTM-PD is diagnosed, treatment should be commenced prior to transplant listing.
1360

1361 **CONCLUSION**

1362

1363 The management of individuals with CF infected with NTM is extremely challenging.
1364 The limited amounts of published research and clinical trial data provide inadequate
1365 evidence to base management decisions on how best to screen, diagnose, detect and
1366 treat NTM pulmonary disease. As a response to this urgent clinical need, the CF
1367 Foundation and ECFS formed a committee of clinicians, scientists and infectious
1368 disease experts to develop recommendations to guide and assist clinicians in the
1369 management of NTM-PD in individuals with CF. The Guidelines committee believe
1370 these guidelines should serve as a benchmark for current medical care while providing
1371 a framework to inform the development of clinical, translation and basic research
1372 studies to generate robust evidence to base future iterations of these management
1373 guidelines leading to better outcomes for individuals with CF infected with NTM.
1374

1375 **Table 1: NTM Recommendation Statements**

Recommendation	Consensus
<i>Recommendation 1:</i> The CF Foundation and the ECFS recommend that the potential for cross-infection of NTM (particularly <i>M. abscessus</i> complex) between individuals with CF should be minimised by following national infection control guidelines.	94%
<i>Recommendation 2:</i> The CF Foundation and the ECFS recommend that cultures for NTM be performed annually in spontaneously expectorating individuals with a stable clinical course.	94%
<i>Recommendation 3:</i> The CF Foundation and the ECFS recommend that in the absence of clinical features suggestive of NTM pulmonary disease, individuals who are not capable of spontaneously producing sputum do not require screening cultures for NTM.	100%
<i>Recommendation 4:</i> The CF Foundation and the ECFS recommend that culture and smears for acid fast bacilli from sputum should be used for NTM screening.	100%
<i>Recommendation 5:</i> The CF Foundation and the ECFS recommend against the use of oro-pharyngeal swabs for NTM screening.	100%
<i>Recommendation 6:</i> The CF Foundation and the ECFS recommend that culture and smears for acid fast bacilli (AFB) from sputum, induced sputum, bronchial washings or broncho-alveolar lavage samples can be used to evaluate individuals with CF suspected to have NTM pulmonary disease.	100%
<i>Recommendation 7:</i> The CF Foundation and the ECFS recommend against the routine use of transbronchial biopsies to detect NTM in individuals with CF suspected to have NTM pulmonary disease.	100%
<i>Recommendation 8:</i> The CF Foundation and the ECFS recommend against the use of oro-pharyngeal swabs to perform diagnostic smears and cultures in individuals with CF suspected to have NTM pulmonary disease.	100%
<i>Recommendation 9:</i> The CF Foundation and the ECFS recommend that respiratory tract samples should be cultured using both solid and liquid media.	100%
<i>Recommendation 10:</i> The CF Foundation and the ECFS recommend that the incubation duration for NTM cultures should be for a minimum of 6 weeks.	100%
<i>Recommendation 11:</i> The CF Foundation and the ECFS recommend that an NTM culture should be processed within 24 hours of collection to optimize the detection of NTM in respiratory samples. If a delay in processing is anticipated, refrigeration of samples is advised.	100%
<i>Recommendation 12:</i> The CF Foundation and the ECFS recommend that respiratory tract samples should be decontaminated using the standard N-Acetyl L-cysteine NALC (0.5%) – NaOH (2%) method.	100%
<i>Recommendation 13:</i> The CF Foundation and the ECFS recommend that if a sample remains contaminated with gram-negative bacteria after standard NALC-NaOH decontamination, it should be further treated with either 5% oxalic acid or 1% chlorhexidine.	100%
<i>Recommendation 14:</i> The CF Foundation and the ECFS recommend against the use of non-culture based methods for detecting NTM in respiratory tract samples.	100%
<i>Recommendation 15:</i> The CF Foundation and the ECFS recommend that all NTM isolates from individuals with CF should undergo molecular identification.	100%
<i>Recommendation 16:</i> The CF Foundation and the ECFS recommend that all NTM isolates from individuals with CF should be identified to the species level, except for <i>M.</i>	83%

<i>intracellulare</i> , <i>M. avium</i> and <i>M. chimaera</i> , where identification can be limited to <i>M. avium</i> complex (MAC), and <i>M. abscessus</i> complex, which should be sub-speciated.	
Recommendation 17: The CF Foundation and the ECFS recommend that for <i>M. avium</i> complex, clarithromycin susceptibility testing should be performed on an isolate recovered prior to initiation of treatment. Clarithromycin susceptibility testing should also be performed on subsequent isolates if the patient a) fails to culture convert after six months of NTM treatment; b) recultures <i>M. avium</i> complex after initial culture conversion while on NTM treatment; or c) recultures <i>M. avium</i> complex after completion of NTM treatment.	94%
Recommendation 18: The CF Foundation and the ECFS recommend that for <i>M. abscessus</i> complex, susceptibility testing should include at least clarithromycin, cefoxitin and amikacin (and preferably also tigecycline, imipenem, minocycline, moxifloxacin and linezolid).	89%
Recommendation 19: The CF Foundation and the ECFS recommend that drug susceptibility testing should be performed in accordance with CLSI guidelines.	100%
Recommendation 20: The CF Foundation and the ECFS recommend that ATS/IDSA criteria for the diagnosis of NTM pulmonary disease should be used in individuals with CF (ATS / IDSA 2007 Statement).	100%
Recommendation 21: The CF Foundation and the ECFS recommend that other CF pathogens and co-morbidities should be considered as potential contributors to a patient's symptoms and radiological features when determining the clinical significance of NTM positive cultures.	100%
Recommendation 22: The CF Foundation and the ECFS recommend that NTM treatment should be considered for individuals with CF who have ATS/IDSA defined NTM pulmonary disease.	100%
Recommendation 23: The CF Foundation and the ECFS recommend that individuals receiving azithromycin as part of their CF medical regimen who have a positive NTM culture should not continue azithromycin treatment while evaluation for NTM disease is underway as azithromycin monotherapy may lead to resistance. A macrolide agent may be included in a multi-drug treatment regimen if criteria are met for NTM disease.	89%
Recommendation 24: The CF Foundation and the ECFS recommend that treatment of <i>M. abscessus</i> complex pulmonary disease should involve an intensive phase followed by a continuation phase.	100%
Recommendation 25: The CF Foundation and the ECFS recommend that the intensive phase should include a daily oral macrolide (preferably azithromycin) in conjunction with 3-12 weeks of intravenous amikacin and one or more of the following: intravenous tigecycline, imipenem or cefoxitin, guided but not dictated by drug susceptibility testing. The duration of intensive phase therapy should be determined by the severity of infection, the response to treatment and the tolerability of the regimen.	83%
Recommendation 26: The CF Foundation and the ECFS recommend that the continuation phase should include a daily oral macrolide (preferably azithromycin) and inhaled amikacin, in conjunction with 2-3 of the following additional oral antibiotics: minocycline, clofazimine, moxifloxacin and linezolid, guided but not dictated by drug susceptibility testing.	89%
Recommendation 27: The CF Foundation and the ECFS recommend that individuals with <i>M. abscessus</i> complex pulmonary disease should be managed in collaboration with	89%

experts in the treatment of NTM and CF as drug intolerance and drug-related toxicity occur frequently and changes in antibiotic therapy are often required.	
<i>Recommendation 28:</i> The CF Foundation and the ECFS recommend that monotherapy with a macrolide or other antimicrobial should never be used in the treatment of <i>M. abscessus</i> complex pulmonary disease.	100%
<i>Recommendation 29:</i> The CF Foundation and the ECFS recommend the same antibiotic regimen for treatment of all species within the <i>M. avium</i> complex.	94%
<i>Recommendation 30:</i> The CF Foundation and the ECFS recommend that clarithromycin-sensitive <i>M. avium</i> complex pulmonary disease should be treated with a daily oral antibiotic regimen containing a macrolide (preferably azithromycin), rifampin and ethambutol.	89%
<i>Recommendation 31:</i> The CF Foundation and the ECFS recommend against the use of intermittent (three-times-per week) oral antibiotic therapy to treat <i>M. avium</i> complex pulmonary disease.	89%
<i>Recommendation 32:</i> The CF Foundation and the ECFS recommend that monotherapy with a macrolide or other antimicrobial agent should never be used in the treatment of <i>M. avium</i> complex pulmonary disease.	100%
<i>Recommendation 33:</i> The CF Foundation and the ECFS recommend that an initial course of intravenous amikacin should be considered for the treatment of <i>M. avium</i> complex pulmonary disease in the presence of one or more of the following: i) AFB smear positive respiratory tract samples ii) Radiological evidence of lung cavitation or severe infection iii) Systemic signs of illness.	94%
<i>Recommendation 34:</i> The CF Foundation and the ECFS recommend that clarithromycin-resistant <i>M. avium</i> complex pulmonary disease should be managed in collaboration with experts in the treatment of NTM and CF.	89%
<i>Recommendation 35:</i> The CF Foundation and the ECFS recommend that individuals with CF receiving NTM treatment should have expectorated or induced sputum samples sent for NTM culture every 4-8 weeks throughout the entire course of treatment to assess the microbiological response.	94%
<i>Recommendation 36:</i> The CF Foundation and the ECFS recommend that a schedule for detecting drug toxicity (including hearing loss, visual loss, renal impairment and liver function test abnormalities) should be set in place at the time of NTM treatment initiation and implemented throughout treatment based on the specific drugs prescribed.	100%
<i>Recommendation 37:</i> The CF Foundation and the ECFS recommend that a HRCT scan of the lungs should be performed shortly before starting NTM treatment and at the end of NTM treatment to assess the radiological response.	94%
<i>Recommendation 38:</i> The CF Foundation and the ECFS recommend that NTM antibiotic therapy should be prescribed for 12 months beyond culture conversion (defined as three consecutive negative cultures, with the time of conversion being the date of the first of the three negative cultures) as long as no positive cultures are obtained during this 12 months.	94%
<i>Recommendation 39:</i> The CF Foundation and the ECFS recommend that individuals who fail to culture convert despite optimal NTM therapy may benefit from long term suppressive antibiotic treatment.	94%
<i>Recommendation 40:</i> The CF Foundation and the ECFS recommend that when amikacin	100%

is given intravenously or when streptomycin is given intravenously or intramuscularly, serum levels should be monitored and dosing adjusted to minimize ototoxicity and nephrotoxicity.	
<i>Recommendation 41:</i> The CF Foundation and the ECFS recommend against routinely obtaining serum levels of other anti-mycobacterial drugs. However, absorption of oral medications is often reduced in CF. Therefore use of therapeutic drug monitoring should be considered for individuals failing to improve despite taking recommended drug regimens or for those on concomitant medications with significant interactions with NTM drugs.	100%
<i>Recommendation 42:</i> The CF Foundation and the ECFS recommend against the use of Interferon gamma as adjuvant therapy for NTM pulmonary disease in individuals with CF.	89%
<i>Recommendation 43:</i> The CF Foundation and the ECFS recommend that vitamin D should be supplemented according to national CF care guidelines.	94%
<i>Recommendation 44:</i> The CF Foundation and the ECFS recommend that lung resection should only be considered in extraordinary circumstances and in consultation with experts in the treatment of NTM and CF.	83%
<i>Recommendation 45:</i> The CF Foundation and the ECFS recommend that all individuals with CF being considered for lung transplantation should be evaluated for NTM pulmonary disease.	100%
<i>Recommendation 46:</i> The CF Foundation and the ECFS recommend that the presence of current or previous respiratory tract samples positive for NTM should not preclude individuals being considered for lung transplantation.	94%
<i>Recommendation 47:</i> The CF Foundation and the ECFS recommend that individuals with CF who have NTM pulmonary disease and are being evaluated for transplantation should commence treatment prior to transplant listing.	100%
<i>Recommendation 48:</i> The CF Foundation and the ECFS recommend that individuals with CF receiving NTM treatment with sequential negative cultures may be eligible for transplant listing.	100%
<i>Recommendation 49:</i> The CF Foundation and the ECFS recommend that individuals with CF who have completed treatment for NTM pulmonary disease with apparent eradication of the organism may be eligible for transplant listing.	100%
<i>Recommendation 50:</i> The CF Foundation and the ECFS recommend that the presence of persistent M. abscessus complex or M. avium complex infection despite optimal therapy is not an absolute contraindication to lung transplant referral.	94%

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1378 **Table 2: Antibiotic dosing regimens used to treat Mycobacterium avium complex**

1379 **and Mycobacterium abscessus complex pulmonary disease in Cystic Fibrosis**

Antibiotic	Route	Dose suitable for children / adolescents	Dose suitable for adults
Amikacin*	Intravenous	Children: 15-30mg/kg/dose once daily Adolescents: 10-15mg/kg/dose once	10-30mg/kg once daily or 15mg/kg/day in two divided doses

		daily Maximum dose 1500mg daily	Daily to 3x weekly dosing
Amikacin**	Nebulized	250-500mg/dose once or twice daily	250-500mg once or twice daily
Azithromycin	PO	Children: 10- 12mg/kg/dose once daily Adolescents: adult dosing regimen Maximum dose 500 mg	250-500mg once daily
Cefoxitin	Intravenous	50mg/kg/dose thrice daily (maximum dose 12g per day)	200mg/kg/day in three divided doses (maximum dose 12g per day)
Clarithromycin	PO	7.5mg/kg/dose twice daily (maximum dose 500mg)	500mg twice daily
Clarithromycin	Intravenous	Not recommended	500mg twice daily
Clofazimine**	PO	1-2mg/kg/dose once daily (maximum dose 100mg)	50-100mg once a day
Cotrimoxazole (Sulfamethoxazole and Trimethoprim)	PO	10-20mg TMP/kg/dose twice daily	960mg twice daily
Cotrimoxazole (Sulfamethoxazole and Trimethoprim)	Intravenous	10-20mg TMP/kg/dose twice daily	1.44g twice daily
Ethambutol	PO	Infants and children: 15mg/kg/dose once daily Adolescents: 15mg/kg/dose once daily	15mg/kg once daily
Imipenem	Intravenous	15-20mg/kg/dose twice daily (maximum dose 1000mg)	1g twice daily

Linezolid**	PO	<12 years old: 10mg/kg/dose thrice daily 12 years and older: 10mg/kg/dose once or twice daily (maximum dose 600mg)	600mg once or twice daily
Linezolid**	Intravenous	<12 years old: 10mg/kg/dose thrice daily 12 years and older: 10mg/kg/dose once or twice daily (maximum dose 600mg)	600mg once or twice daily
Moxifloxacin	PO	7.5-10mg/kg/dose once daily (maximum dose 400mg daily)	400mg once daily
Minocycline	PO	2mg/kg/dose once daily (maximum dose 200mg)	100mg twice daily
Rifampin (Rifampicin)	PO	10-20mg/kg/dose once daily (maximum dose 600mg)	<50kg 450mg once daily >50kg 600mg once daily
Rifabutin	PO	5-10mg/kg/dose once daily (maximum dose 300mg)	<50kg 450mg once daily >50kg 600mg once daily
Streptomycin*	Intramuscular / Intravenous	20-40mg/kg/dose once daily (maximum dose 1000mg)	15mg/kg once daily (maximum dose 1000mg)
Tigecycline**	Intravenous	8-11 years: 1.2mg/kg/dose twice daily (maximum dose 50mg) 12 years and older: 100mg loading dose and then 50mg once	100mg loading dose and then 50mg once or twice daily

	or twice daily	
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*Adjust dose according to levels

**As tolerated

Table 3²²

TABLE 3. CLINICAL AND MICROBIOLOGIC CRITERIA FOR DIAGNOSING NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE*

Clinical (both required)

1. Pulmonary symptoms, nodular or cavitory opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, I)*

and

2. Appropriate exclusion of other diagnoses (A, I)

Microbiologic

1. Positive culture results from at least two separate expectorated sputum samples (A, II). If the results from (1) are nondiagnostic, consider repeat sputum AFB smears and cultures (C, III).

or

2. Positive culture result from at least one bronchial wash or lavage (C, III)

or

3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM (A, II)

4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination (C, III)

5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded (C, III)

6. Making the diagnosis of NTM lung disease does not, *per se*, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients (C, III)

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Table 4. Important Side Effects/ Toxicities of Antibiotics and Advisable Monitoring Procedures for MAC and MABSC in CF

Drug	Common Side Effects / Toxicity	Monitoring procedures
Amikacin	Nephrotoxicity	Regular serum amikacin levels Regular serum creatinine levels
	Auditory-vestibular toxicity (specifically high frequency hearing loss)	Symptoms, baseline and interval audiograms
Azithromycin	Nausea, vomiting, diarrhoea	Symptoms
	Auditory-vestibular toxicity	Symptoms, audiogram
	Prolonged QT	ECG
Clarithromycin	Auditory-vestibular toxicity	Symptoms, audiogram
	Hepatitis	Liver function tests
	Taste disturbance	Symptoms
	Inhibited hepatic metabolism of rifabutin	Serum rifabutin levels
Cefoxitin	Fever, rash	Symptoms
	Eosinophilia, anaemia, leucopenia, thrombocytopenia	Full blood count
	Interference with common assays to measure serum creatinine	Use alternative assay
Clofazimine	Discoloration of skin*	Symptoms
	Enteropathy (sometimes mimicking pancreatic insufficiency)*	Symptoms
Co-trimoxazole	Nausea, vomiting, diarrhoea	Symptoms
	Anaemia, leucopenia, thrombocytopenia	Full blood count
	Fever, rash, Stevens-Johnson Syndrome	Symptoms
Ethambutol	Optic neuritis	Symptoms (loss of colour vision/acuity) Baseline and interval testing for colour vision and acuity** Ophthalmology opinion if symptoms occur
Imipenem	Hepatitis	Liver function tests
	Anaemia, leucopenia, thrombocytopenia	Full blood count
	Nausea, vomiting, diarrhoea	Symptoms

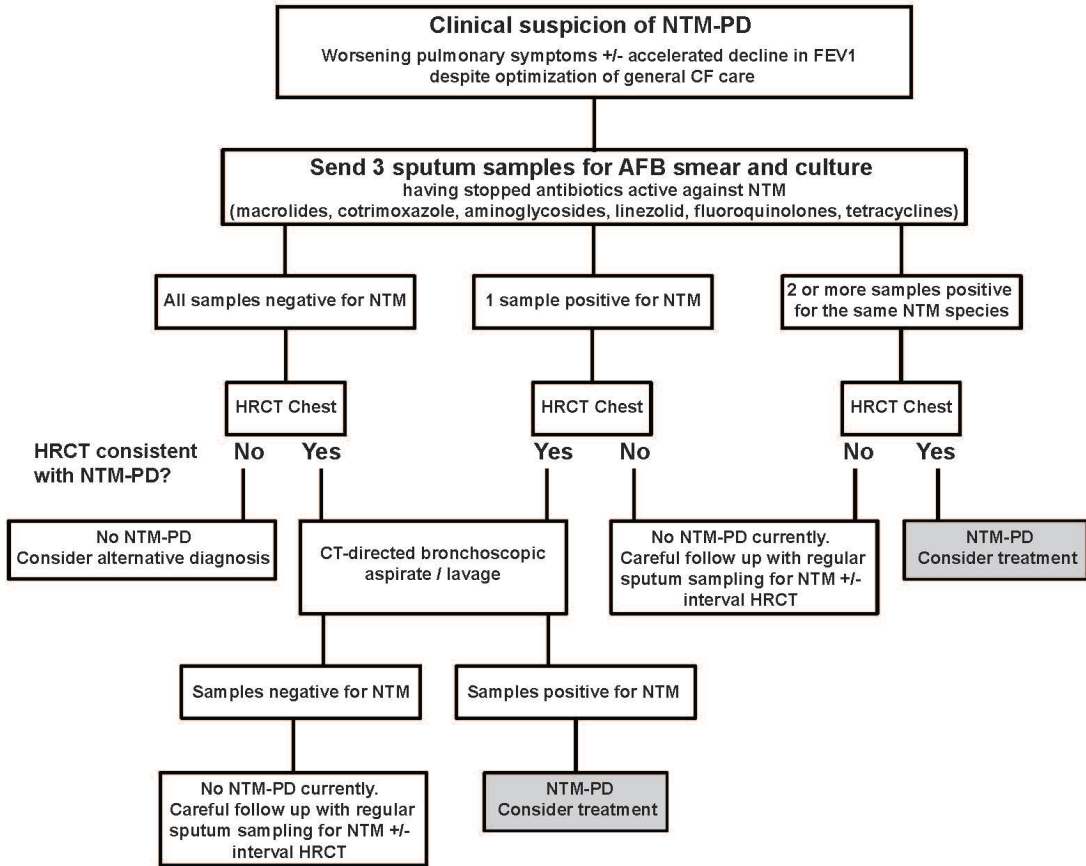
Linezolid	Anaemia, leucopenia, thrombocytopenia	Full blood count
	Peripheral neuropathy	Symptoms/clinical evaluation/electrophysiology
	Optic neuritis	Symptoms (loss of colour vision/acuity) Baseline and interval testing for colour vision and acuity** Ophthalmology opinion if symptoms occur
Moxifloxacin	Nausea, vomiting, diarrhoea	Symptoms
	Insomnia, agitation, anxiety	Symptoms
	Tendonitis	Symptoms
	Photosensitivity	Symptoms
	Prolonged QT	ECG
Minocycline	Photosensitivity	Symptoms
	Nausea, vomiting, diarrhoea	Symptoms
	Vertigo	Symptoms
Rifampin & Rifabutin	Orange discoloration of bodily fluids (can stain contact lens)	Symptoms
	Hepatitis	Liver function tests
	Nausea, vomiting, diarrhoea	Symptoms
	Thrombocytopenia	Full blood count
	Renal Failure (Rifampin)	Blood tests
	Increased hepatic metabolism of numerous drugs	Dose adjustment of other medications/serum levels where available
Rifabutin	Leucopenia,	Full blood count
	Anterior Uveitis (when combined with clarithromycin)	Symptoms
	Polyarthralgia, polymyalgia	Symptoms
Streptomycin	Nephrotoxicity	Regular serum amikacin levels Regular serum creatinine levels
	Auditory-vestibular toxicity (specifically high frequency hearing loss)	Symptoms, baseline and interval audiograms
Tigecycline	Nausea, vomiting, diarrhoea	Symptoms
	Hypoproteinemia	Serum albumin
	Bilirubinemia	Serum bilirubin

1390 * It may take up to 3 months for toxicity to resolve following cessation of clofazimine
1391 due to its long half life

1392 ** Monthly checks if receiving 25 mg/kg/d

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Figure: 2 Diagnostic Algorithm for NTM



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