4-2018

Implementation of a Guideline-based Non-tuberculous Mycobacteria Management Algorithm

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NTM in CF

- NTM are ubiquitous environmental organisms that can cause chronic pulmonary infection
- Prevalence among CF patients is increasing
  - 1.3% in the earliest study reported in 1984
  - CF Registry with average of 12% but significant range (0–28%)
  - 32.7% reported among patients ≥ 40 years in Colorado
- Generally categorized as “slow growers” and “rapid growers”

	Organism	Prevalence
Slow Growers		
Mycobacterium avium complex (MAC)	M. avium	2/3
	M. intracellulare	
	M. chimaera	
M. kansasii		Rare
M. simiae		Rare
Rapid Growers		
M. abscessus complex (MABSC)	M. a. abscessus	1/3
	M. a. bolletii	
	M. a. massiliense	
M. fortuitum		Rare

- Age-related prevalence
  - 10% in children aged 10 years
  - > 30% in adults ≥ 40 years
  - > 50% (mostly women) of patients diagnosed as adults
- Significant geographic variability in prevalence and species

CFF & ECFS Guidelines

- Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, Noone PG, Bilton D, Corris P, Gibson RL, Hempstead SE, Koetz K, Sabadosa KA, Sermet-Gaudelus I, Smyth AR, van Ingen J, Wallace RJ, Winthrop KL, Marshall BC, Haworth CS; US Cystic Fibrosis Foundation and European Cystic Fibrosis Society. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax. 2016 Jan;71 Suppl 1:i1-22. doi:10.1136/thoraxjnl-2015-207360
  - 19-member committee including professionals with expertise in CF and NTM and the parent of an individual with CF
  - Iterative Delphi methodology
  - 80% agreement on statements
  - 50 recommendations for diagnosis and management

- Risk Factors: NTM likely linked to poor lung function; ? association with pathogens (PA, ABPA); ? association with steroids, PPIs, azithromycin; cross infection well documented
- Screening: recommended annually for expectorating patients (induced sputum and BAL are acceptable); AFB smear and culture should done
- Microbiology: specific recommendations for obtaining, processing, and testing specimen; PCR and other non-culture based testing not recommended; molecular speciation recommended; specific drug susceptibility testing recommend based on species
- Diagnosis: ATS/IDSA criteria for diagnosis should be used; other pathogens and comorbidities should be considered; azithromycin should be stopped until evaluation completed

Clinical (both required)

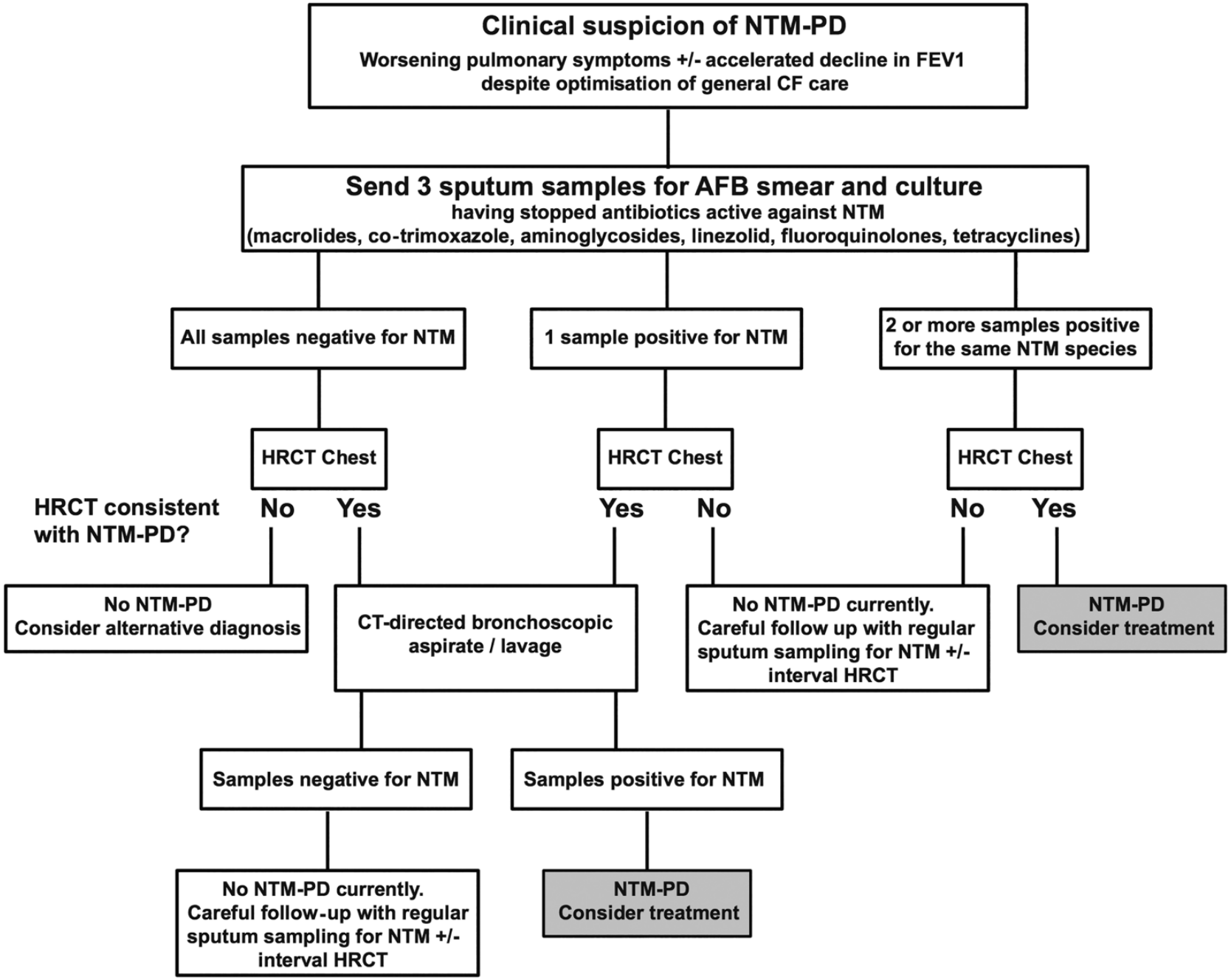
1. Pulmonary symptoms with nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows multifocal bronchiectasis with multiple small nodules.
2. Appropriate exclusion of other diagnoses.

Microbiologic (one of the following required)

1. Positive culture results from at least two expectorated sputum samples.
2. Positive culture results from at least one bronchial wash or lavage.
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathological features and one or more sputum or bronchial washings that are culture positive for NTM.

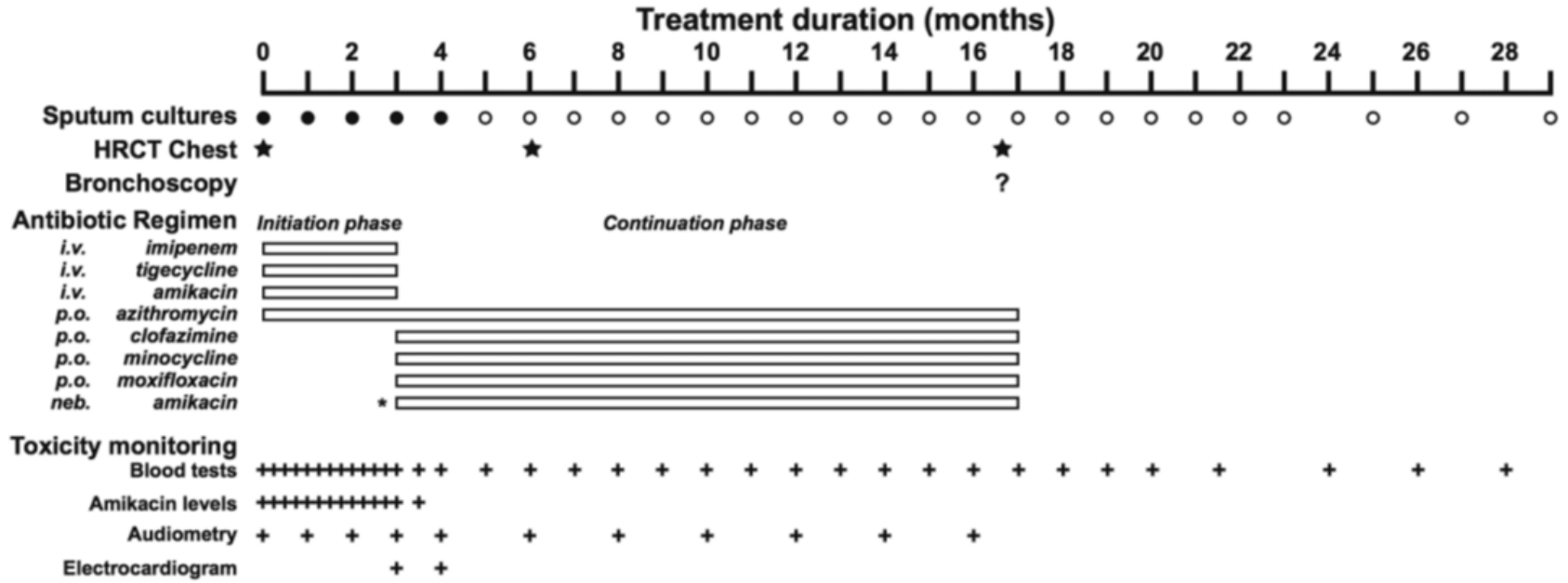
Other

1. Expert consultation should be obtained when either infrequently encountered NTM or those usually representing environmental contamination are recovered.
2. Patients who are suspected of having NTM-PD but who do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded.
3. Making the diagnosis of NTM-PD does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients.

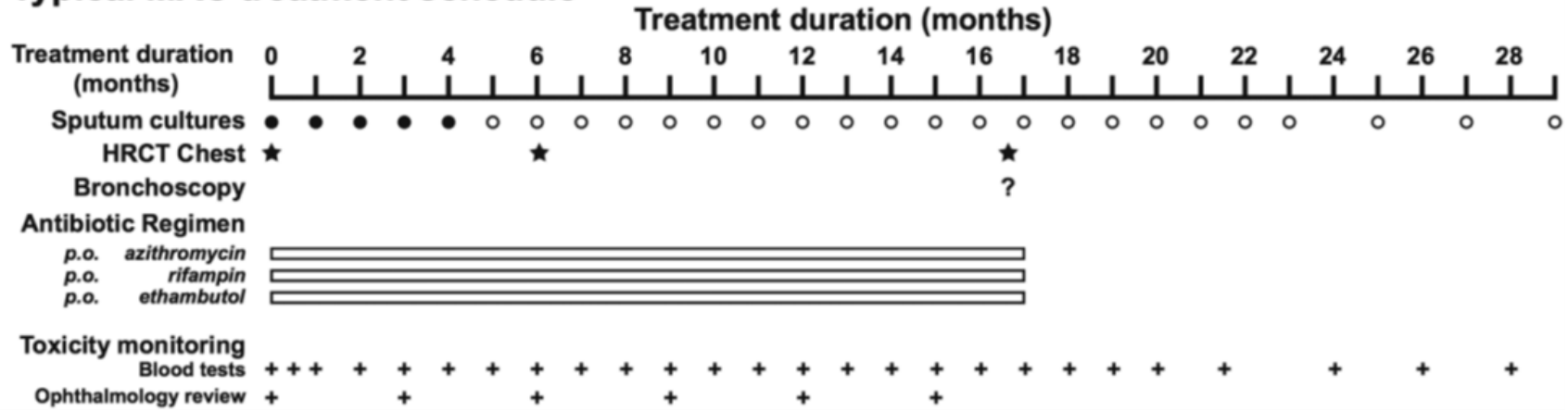


- Treatment:
  - **MABSC** pulmonary disease should involve an **intensive phase** (Daily oral macrolide [preferably azithromycin] in conjunction with 1 – 3 months of intravenous amikacin and one or more of the following: intravenous tigecycline, imipenem or cefoxitin, guided but not dictated by DST. The duration of intensive phase therapy should be determined by the severity of infection, the response to treatment and the tolerability of the regimen) followed by a **continuation phase** including (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 DST)
  - **MAC** should be treated with a macrolide (preferably azithromycin), rifampin and ethambutol; intravenous amikacin should be considered for 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 and (iii) systemic signs of illness
  - Complete list of antibiotic dosing regimens in Table II
  - Antibiotic adverse effects/toxicities in Table III
  - Specific outcome measures include: repeat sputum smear and culture (every 4-8 weeks); drug-specific monitoring; HRCT
  - Therapy should be continued for 12 months following culture conversion; continuous therapy for patients who do not have culture conversion

A Typical *M. abscessus* treatment schedule



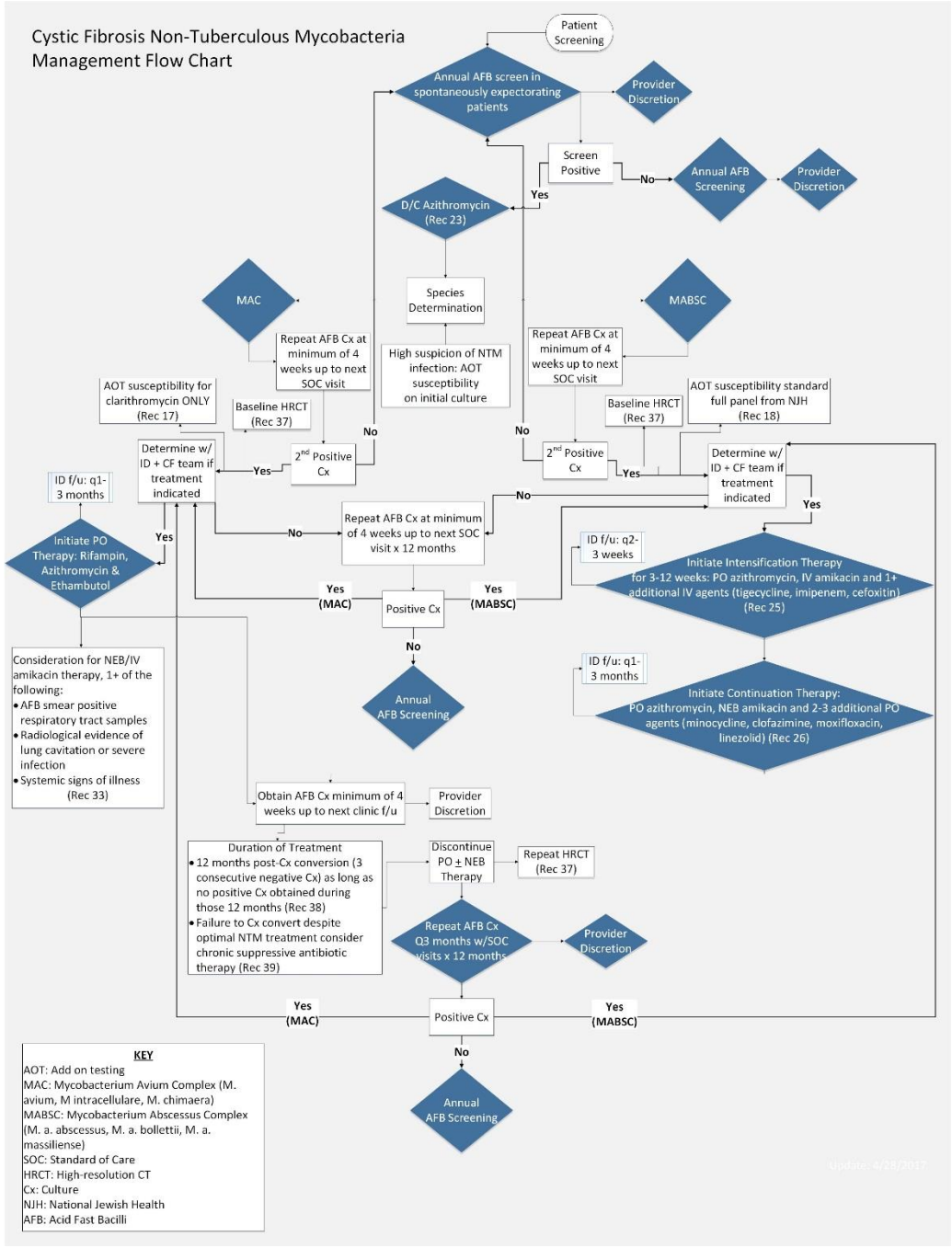
B Typical MAC treatment schedule



Children's Mercy Kansas City NTM Experience

- Increasing prevalence of NTM prompted closer attention to existing practice patterns and guidelines
- NTM Working Group
  - CF Center Director, CF Center Coordinator, PharmD, ID provider with NTM expertise, Director of Clinical Microbiology and Virology Laboratory
  - NTM Management Guide
    - Diagnosis and Management Algorithm
    - Medication Resource Guide and Patient Tracker

Cystic Fibrosis Non-Tuberculous Mycobacteria Management Flow Chart



BEST CHILDREN'S HOSPITALS U.S.News 2013-14

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

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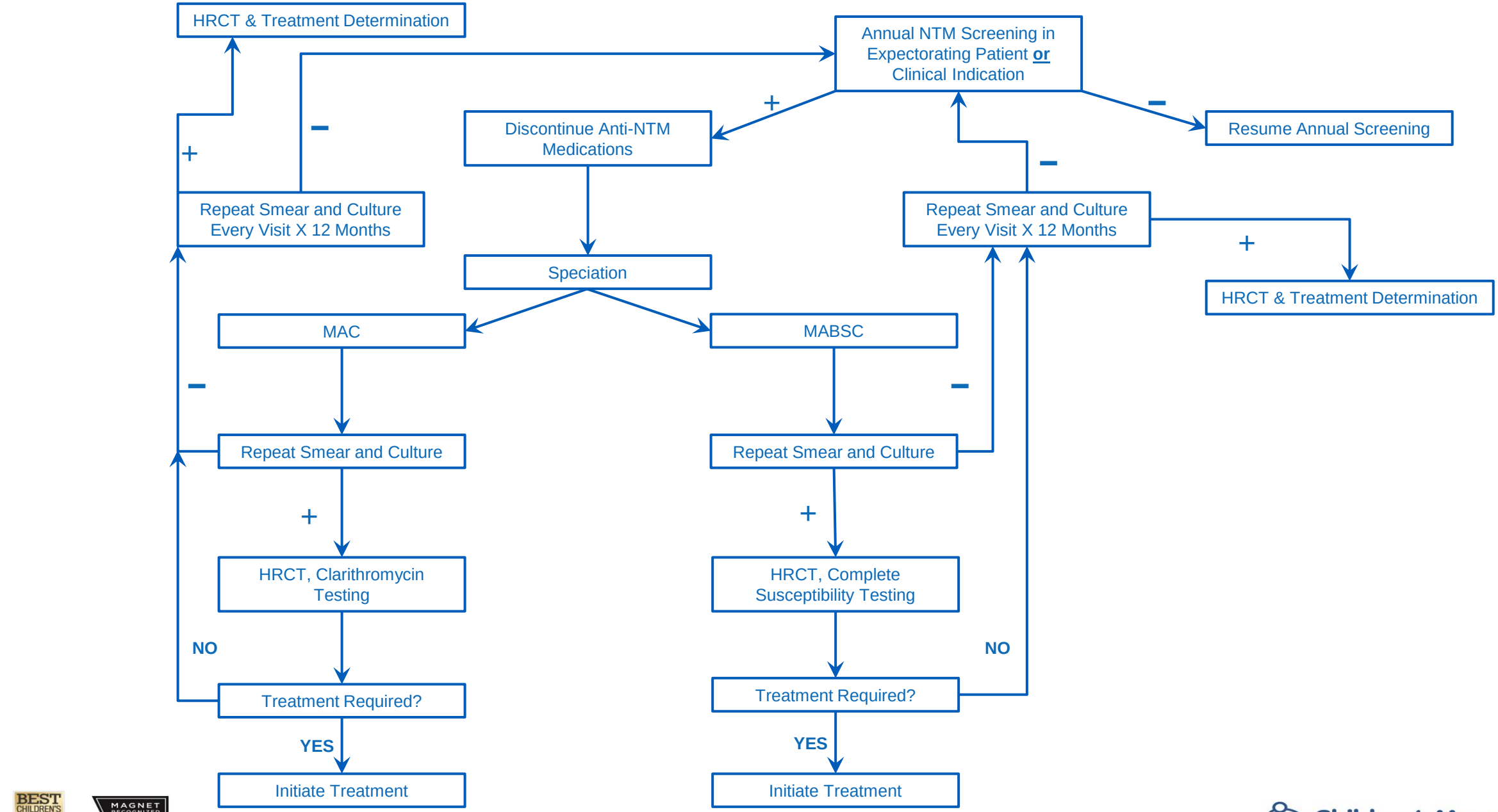
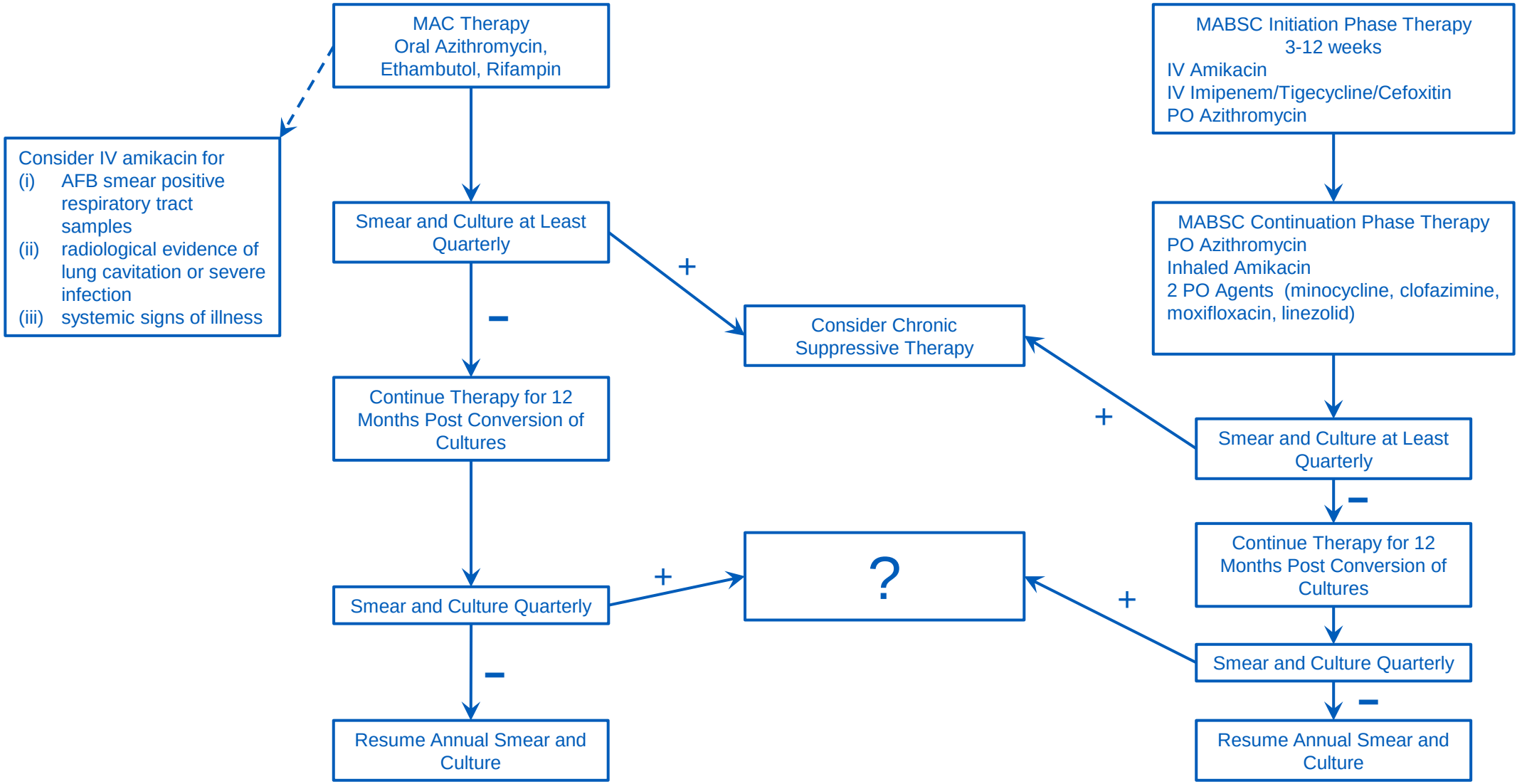
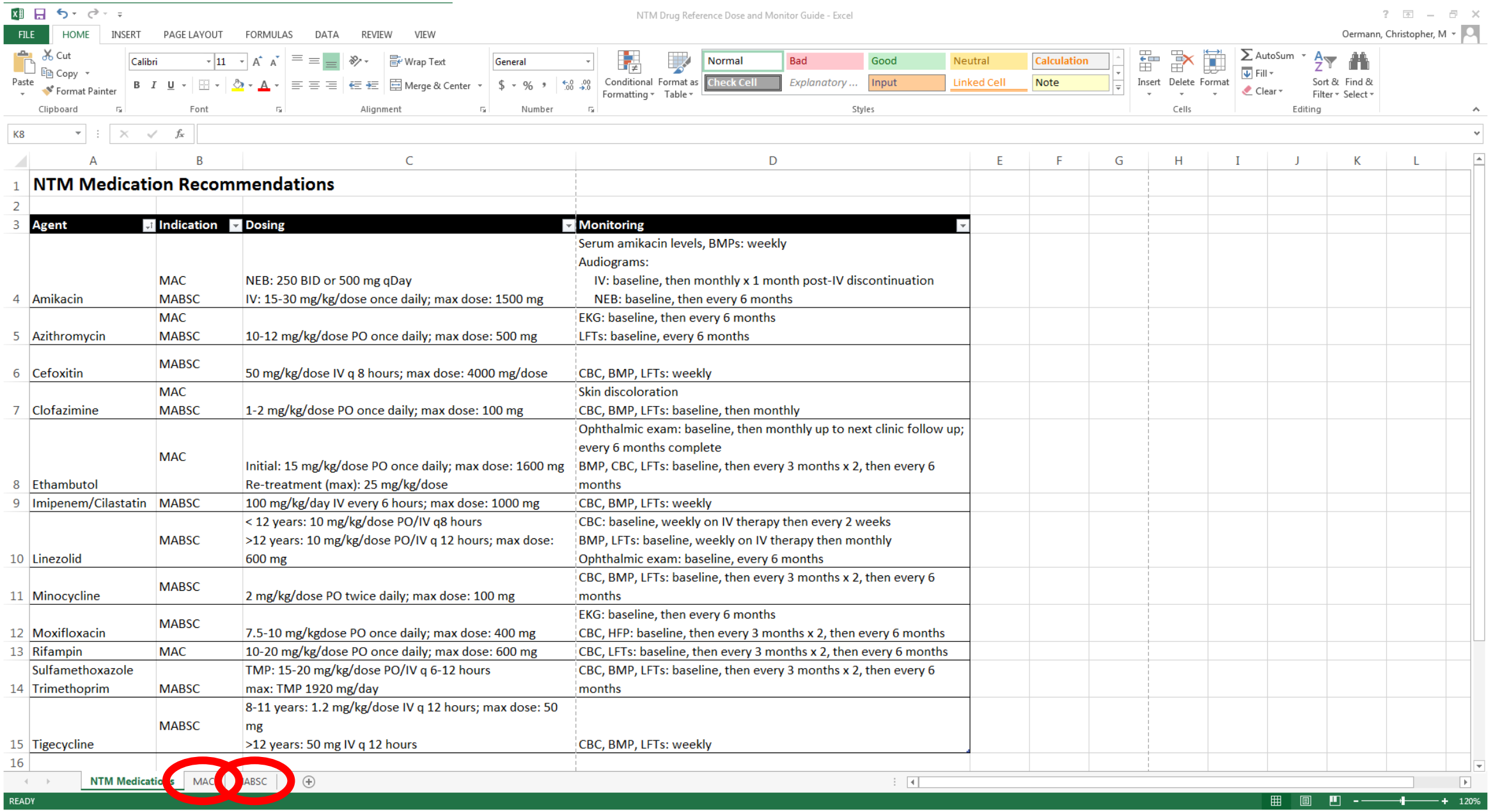

HRCT & Treatment Determination
Annual NTM Screening in Expectorating Patient or Clinical Indication
+
−
Discontinue Anti-NTM Medications
Resume Annual Screening
+
−
Repeat Smear and Culture Every Visit X 12 Months
Repeat Smear and Culture Every Visit X 12 Months
+
HRCT & Treatment Determination
Speciation
MAC
MABSC
−
−
Repeat Smear and Culture
Repeat Smear and Culture
+
+
HRCT, Clarithromycin Testing
HRCT, Complete Susceptibility Testing
NO
NO
Treatment Required?
Treatment Required?
YES
YES
Initiate Treatment
Initiate Treatment


MAC Therapy
Oral Azithromycin, Ethambutol, Rifampin
Consider IV amikacin for
(i) AFB smear positive respiratory tract samples
(ii) radiological evidence of lung cavitation or severe infection
(iii) systemic signs of illness
Smear and Culture at Least Quarterly
+
-
Consider Chronic Suppressive Therapy
Continue Therapy for 12 Months Post Conversion of Cultures
Smear and Culture Quarterly
+
?
-
Resume Annual Smear and Culture
MABSC Initiation Phase Therapy
3-12 weeks
IV Amikacin
IV Imipenem/Tigecycline/Cefoxitin
PO Azithromycin
MABSC Continuation Phase Therapy
PO Azithromycin
Inhaled Amikacin
2 PO Agents (minocycline, clofazimine, moxifloxacin, linezolid)
+
Smear and Culture at Least Quarterly
-
Continue Therapy for 12 Months Post Conversion of Cultures
+
Smear and Culture Quarterly
-
Resume Annual Smear and Culture



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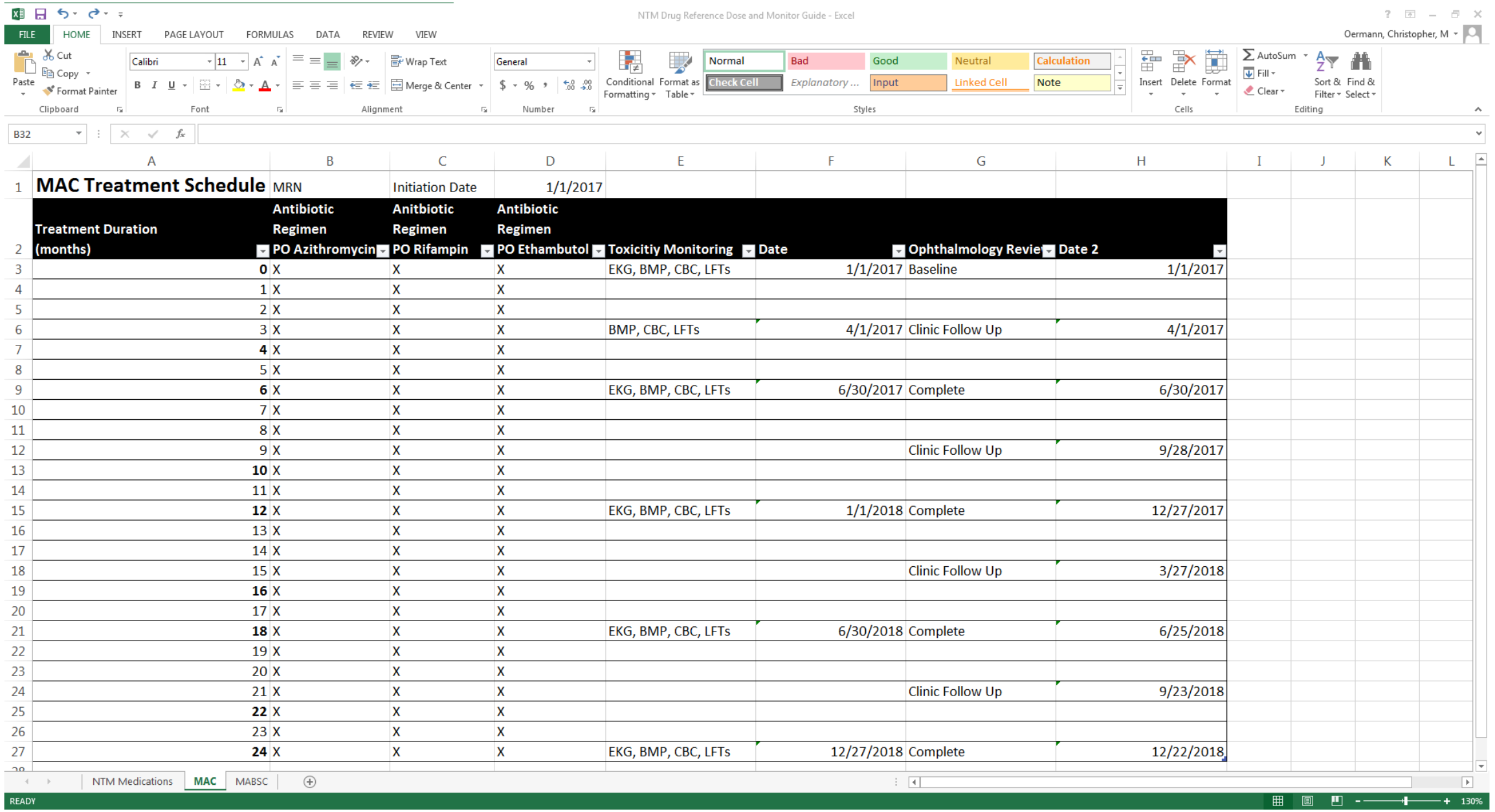

NTM Drug Reference Dose and Monitor Guide - Excel

FILE HOME INSERT PAGE LAYOUT FORMULAS DATA REVIEW VIEW

Oermann, Christopher, M

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General Number

Conditional Formatting Format as Table

Normal Bad Good Neutral Calculation Check Cell Explanatory ... Input Linked Cell Note Styles

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	A	B	C	D	E	F	G	H	I	J	K	L
1	**MAC Treatment Schedule**	MRN	Initiation Date	1/1/2017								
2	**Treatment Duration (months)**	**Antibiotic Regimen PO Azithromycin**	**Anitbiotic Regimen PO Rifampin**	**Antibiotic Regimen PO Ethambutol**	**Toxicitiy Monitoring**	**Date**	**Ophthalmology Revie**	**Date 2**				
3	**0**	X	X	X	EKG, BMP, CBC, LFTs	1/1/2017	Baseline	1/1/2017				
4	1	X	X	X								
5	2	X	X	X								
6	3	X	X	X	BMP, CBC, LFTs	4/1/2017	Clinic Follow Up	4/1/2017				
7	**4**	X	X	X								
8	5	X	X	X								
9	**6**	X	X	X	EKG, BMP, CBC, LFTs	6/30/2017	Complete	6/30/2017				
10	7	X	X	X								
11	8	X	X	X								
12	9	X	X	X			Clinic Follow Up	9/28/2017				
13	**10**	X	X	X								
14	11	X	X	X								
15	**12**	X	X	X	EKG, BMP, CBC, LFTs	1/1/2018	Complete	12/27/2017				
16	13	X	X	X								
17	14	X	X	X								
18	15	X	X	X			Clinic Follow Up	3/27/2018				
19	**16**	X	X	X								
20	17	X	X	X								
21	**18**	X	X	X	EKG, BMP, CBC, LFTs	6/30/2018	Complete	6/25/2018				
22	19	X	X	X								
23	20	X	X	X								
24	21	X	X	X			Clinic Follow Up	9/23/2018				
25	**22**	X	X	X								
26	23	X	X	X								
27	**24**	X	X	X	EKG, BMP, CBC, LFTs	12/27/2018	Complete	12/22/2018				

NTM Medications MAC MABSC

READY 130%

Results

- 11 patients treated for NTM pulmonary disease between 2011 and 2016
  - Treatment regimens non-standardized and included clarithromycin, amikacin, trimethoprim/sulfamethoxazole, levofloxacin, minocycline and clofazimine
  - Monitoring for treatment efficacy and potential adverse effects were inconsistent
    - Adverse effects included cytopenias, gastrointestinal intolerance, peripheral neuropathy, ototoxicity, and bronchospasm
- 3 patients started on therapy in 2017
  - Consistent treatment regimens
  - Consistent AE monitoring

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Thank You!

Questions?