Milano, Wednesday June 21, 2023

Unimib

Corso laurea magistrale

Malattia Genetiche: dalla diagnosi alla malattia

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OSPEDALE
SAN RAFFAELE

Introduction

NTM-host interaction, DITID-San Raffaele Scientific Institute, Milan.

Emerging Bacterial Pathogens Unit
Head by Daniela Cirillo

Research associate Nicola Lorè

NTM-host interaction:

- *Host Biomarkers in NTM-PD*
- *NTM-Host modellling infection (M. abscessus)*
- *Sequencing of M. abscessus clinical strains in CF*
- *New antimicrobials or therapeutics against Mabs*

Background

Genetic disease – Cystic Fibrosis CF

- Recessively inherited disorder caused by the presence of one mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (~ more than 1,500 possible mutations)
- incidence of clinical disease of 1 in 2,500 live births
- The mutations lead to the malfunction or loss-of-function of CFTR, a cyclic AMP-regulated chloride ion channel, resulting in defective chloride ion transport across epithelial cell surfaces.
- This decreases the volume of the periciliary fluid in the lower respiratory tract, which in turn interferes with the mucociliary clearance of inhaled microorganisms

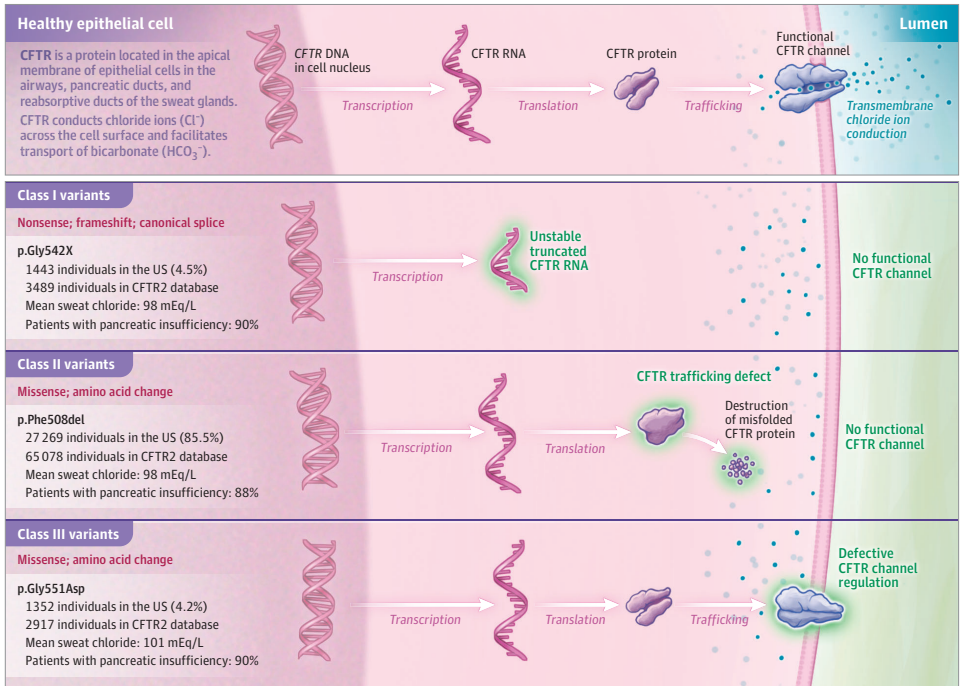
https://www.youtube.com/watch?v=YzjnxegMWfk&t=38s

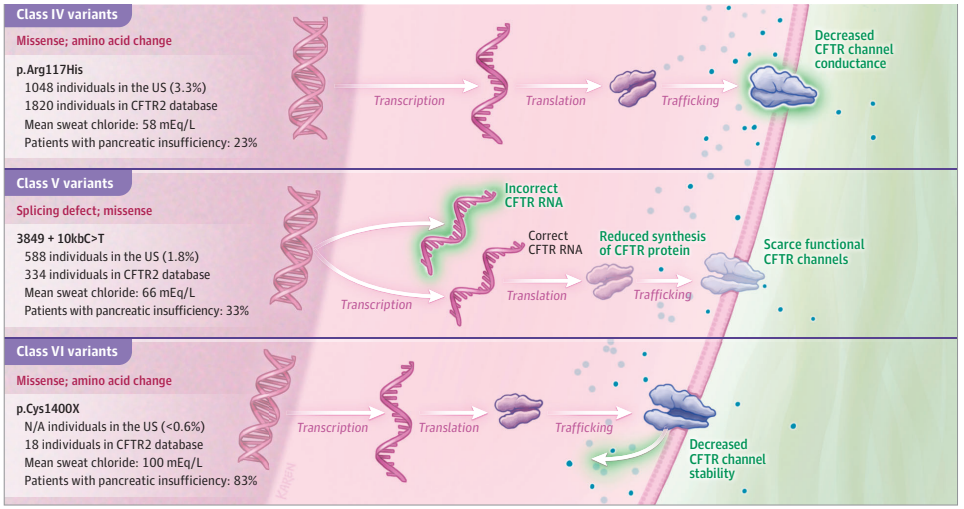
Folkesson A. et al Nat rev 2012
Rowe M.S. et al N engl j med 2005

Background

Genetic disease – Cystic Fibrosis CF

Figure 1. Cystic Fibrosis Transmembrane Conductance Regulator Variant Classes[1,5,6,19]



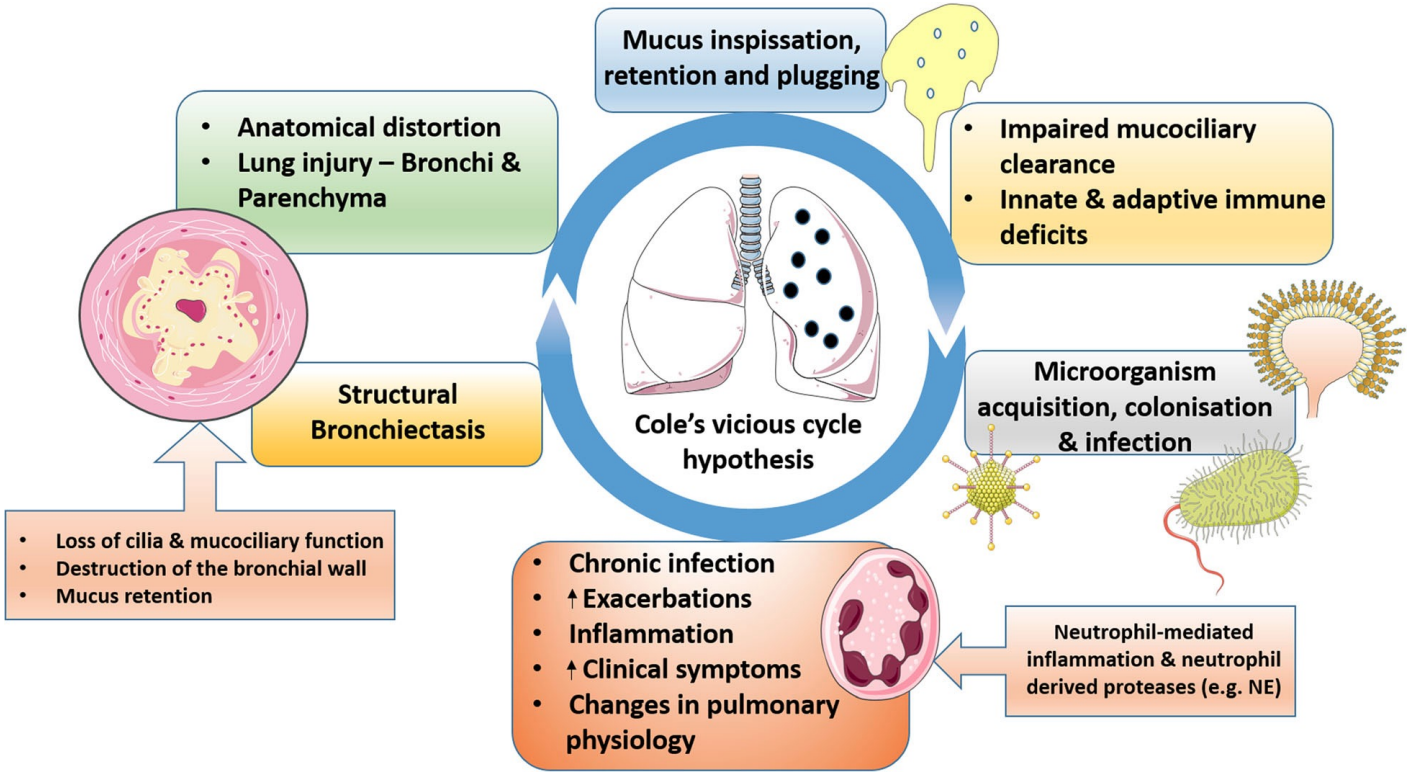


Cystic fibrosis transmembrane conductance regulator (*CFTR*) variants can be generally classified in 6 mechanistic classes based on how they alter CFTR RNA transcription, protein trafficking, channel function, and stability.[5,19] Reported prevalence, and clinical features (sweat chloride, pancreatic insufficiency) are summarized for exemplar variants per class.[1,6] The CFTR2 database provides information on all the *CFTR* variants and updates it as information becomes available.[6] The figure is adapted from Boyle and De Boeck.[5] N/A indicates number not available.

Rowe M.S. et al N engl j med 2005
Thida Ong, MD; Bonnie W. Ramsey, MD JAMA 2023

Background

Cycles of infection/inflammation



Adapted from Chandrasekaran et al. BMC Pulmonary Medicine 2018

Background

Cystic Fibrosis CF potentiator and Correctors

Thida Ong, MD; Bonnie W. Ramsey, MD JAMA 2023

Background

Cystic Fibrosis CF potentiator and Correctors

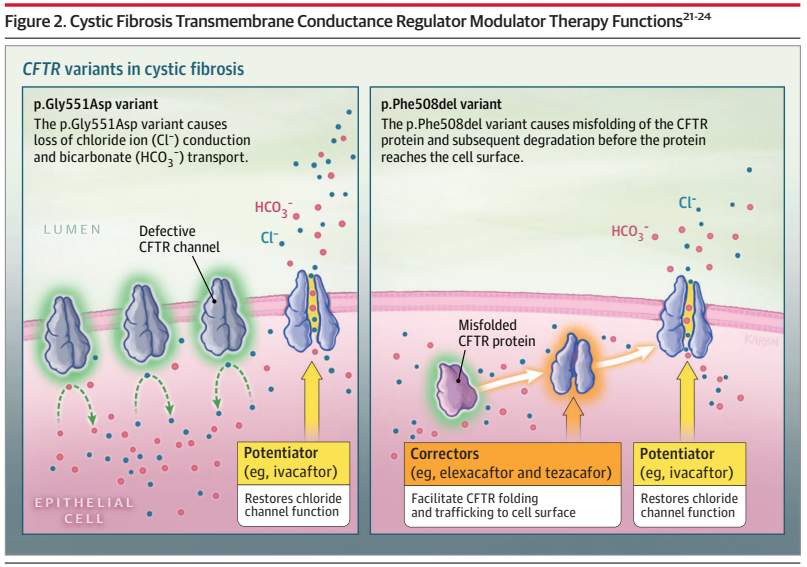


Figure 2. Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy Functions[21-24]

Actions of cystic fibrosis transmembrane conductance regulator (*CFTR*) modulators as *correctors* and *potentiators*.[21,24] People with at least 1 copy of the F508del variant or 177 other variants are responsive to elexacaftor-tezacaftor-ivacaftor combination therapy.[23,78] Adapted from Cutting.[24]

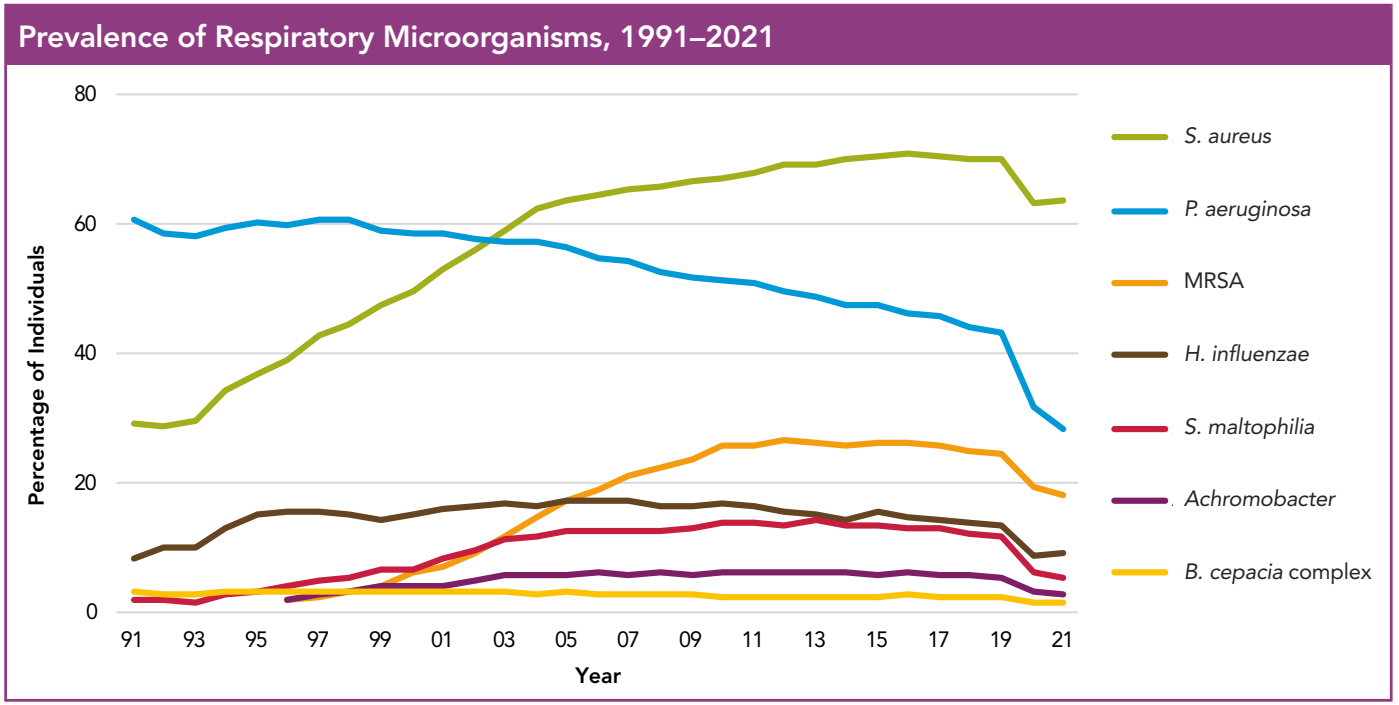
p.Gly551Asp indicates glycine at residue 551 replaced by aspartic acid; and p.Phe508del, phenylalanine deleted at position 508.

https://www.youtube.com/watch?v=7WTjQY0V4qI

Thida Ong, MD; Bonnie W. Ramsey, MD JAMA 2023

Background

Microbiology of CF lung disease

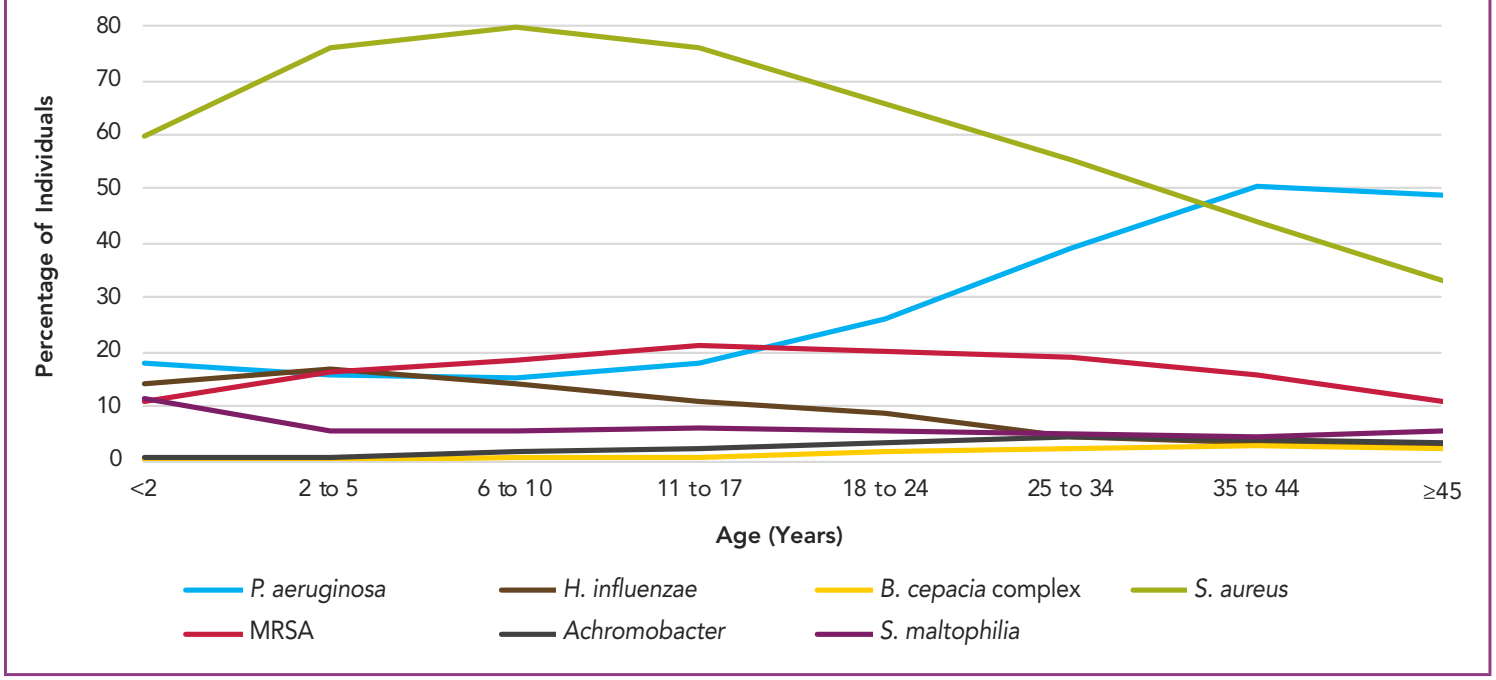


US CFF Registry 2021

Background

Microbiology of CF lung disease

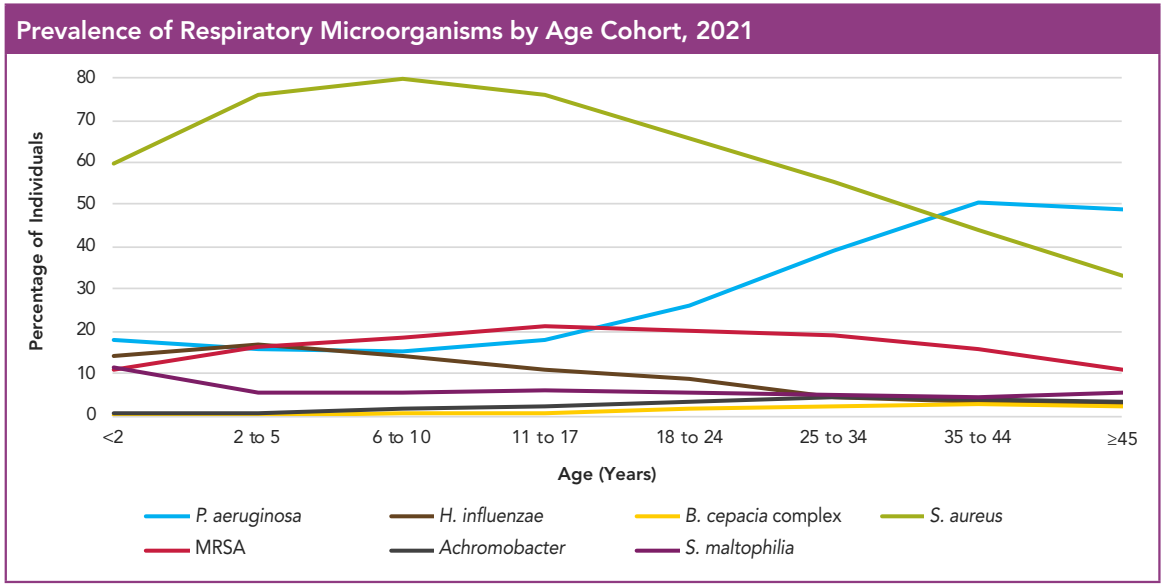
Prevalence of Respiratory Microorganisms by Age Cohort, 2021



US CFF Registry 2021

Background

Microbiology of CF lung disease

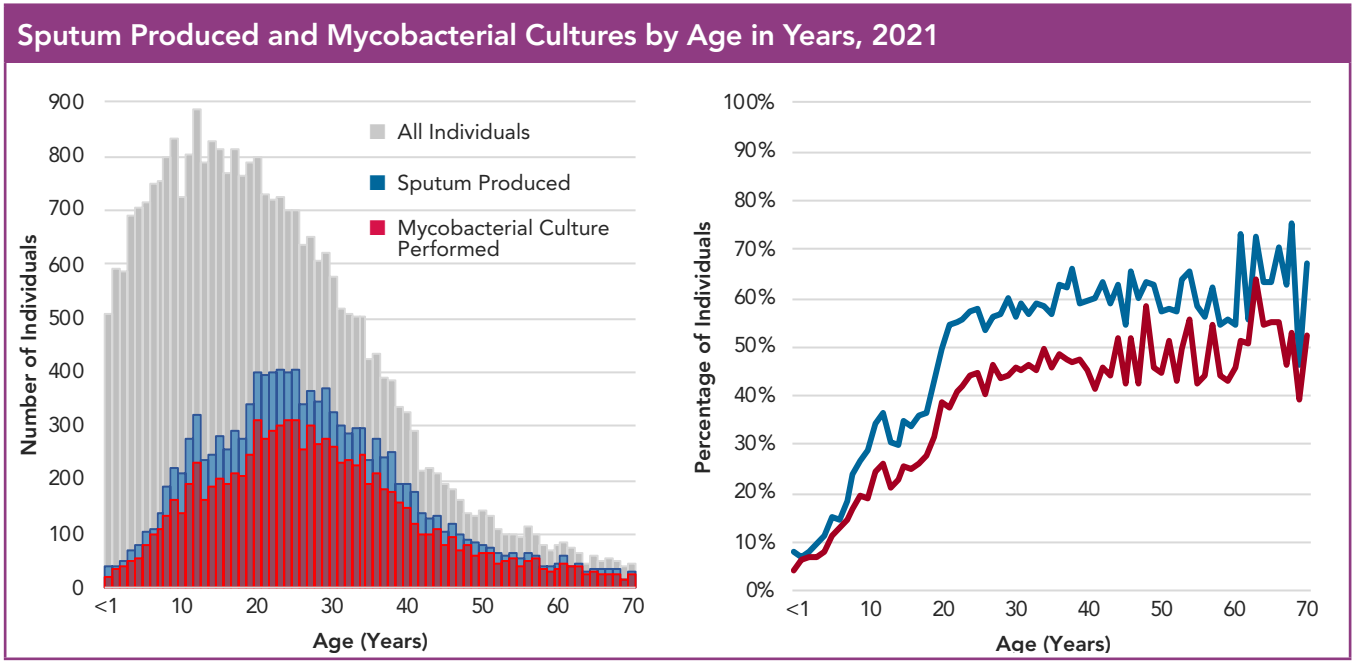


Bacteria	2018 Percent With Infection	2022 Percent With Infection
Pseudomonas aeruginosa	44%	26%
Stenotrophomonas maltophilia	12%	5%
Methicilin-resistant Staphylococcus aureus	25%	16%
Achromobacter xylosoxidans	6%	2%
Burkholderia cepacia complex	3%	1%
Nontuberculous mycobacteria	14%	10%

US CFF Registry 2021
US CFF Registry high 2022

Background

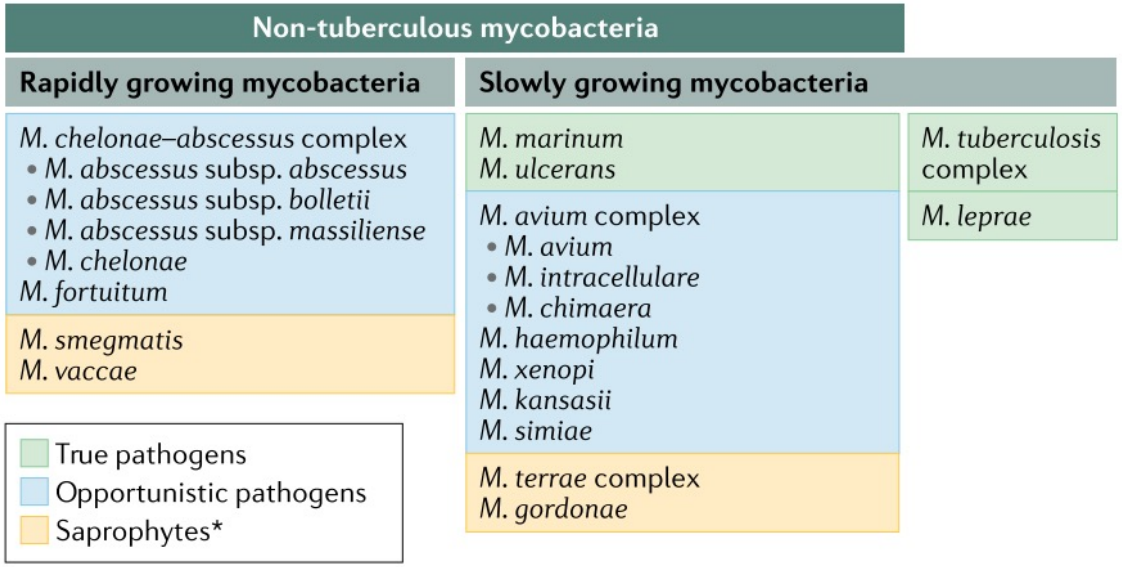
Nontuberculous mycobacteria (NTM) in cystic fibrosis



US CFF Registry 2021

Background

Nontuberculous mycobacteria (NTM)



Johansen MD et al, Nat Rev 2020
Tortoli et al., Infect Genet Evol. 2017
Ripoll et al., Plos one, 2009
Bernut et al., Cell Reports, 2019
Whang et al., Nature, 2017
Rhoades et al., J Immunol, 2009

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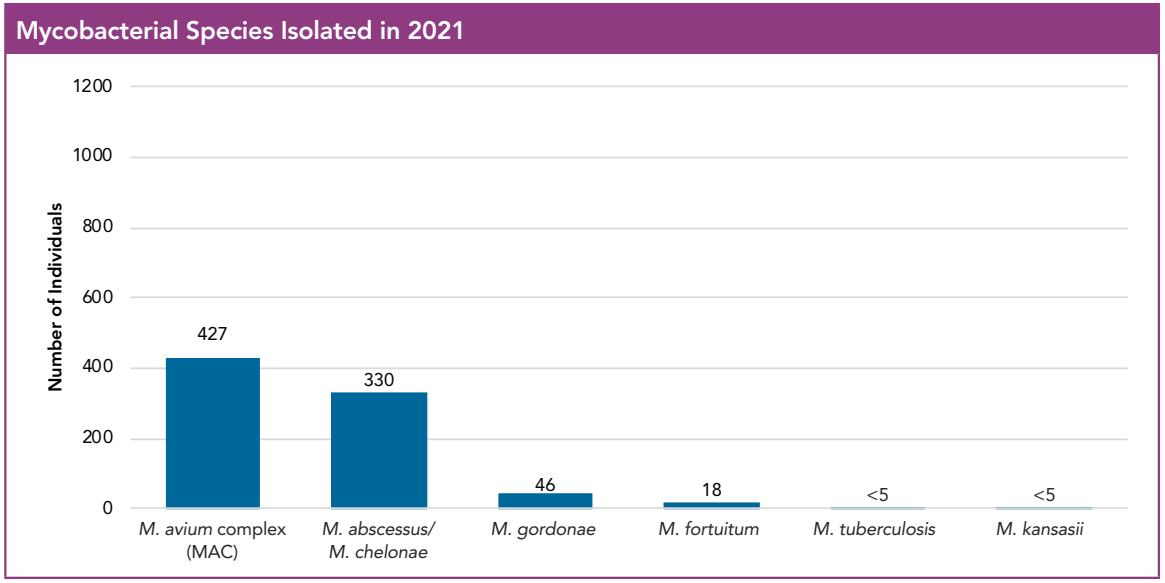
Nontuberculous mycobacteria (NTM) in cystic fibrosis

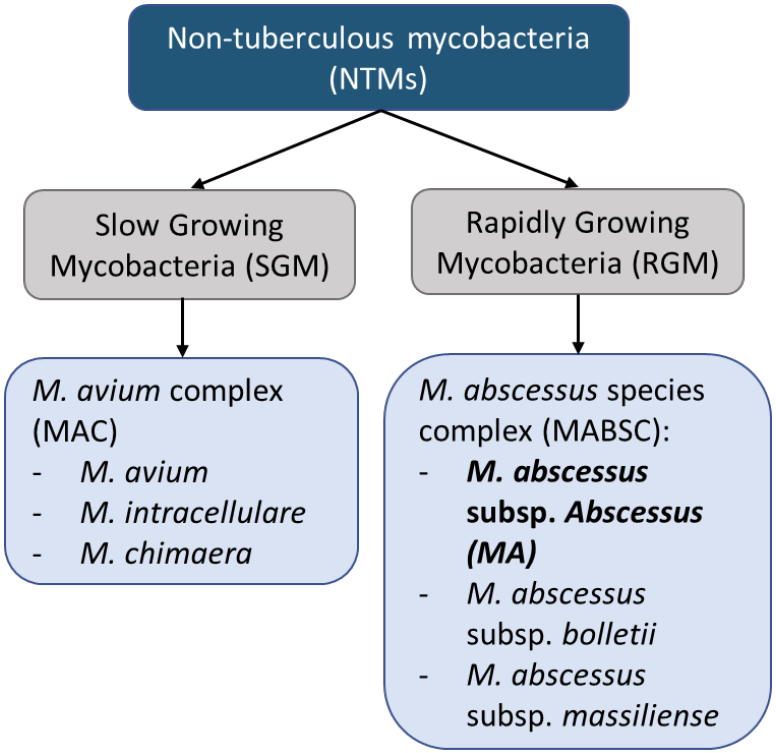


Data are not mutually exclusive. Some individuals had more than one species isolated in 2021.

US CFF Registry 2021

Background

Nontuberculous mycobacteria (NTM)



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Ripoll et al., Plos one, 2009
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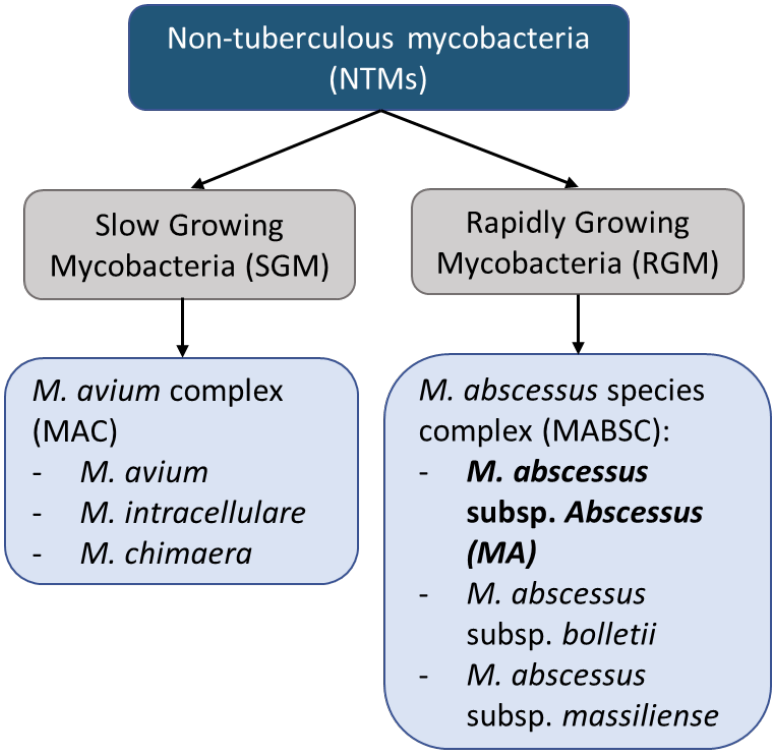
Background

Nontuberculous mycobacteria (NTM) lung disease in cystic fibrosis



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Ripoll et al., Plos one, 2009
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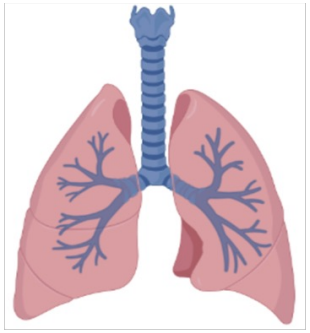
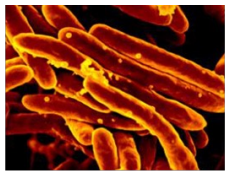
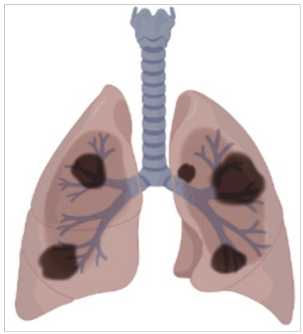


NTM^{+}-**PD^{-}**

Asymptomatic colonization



Several years of bacterial persistance



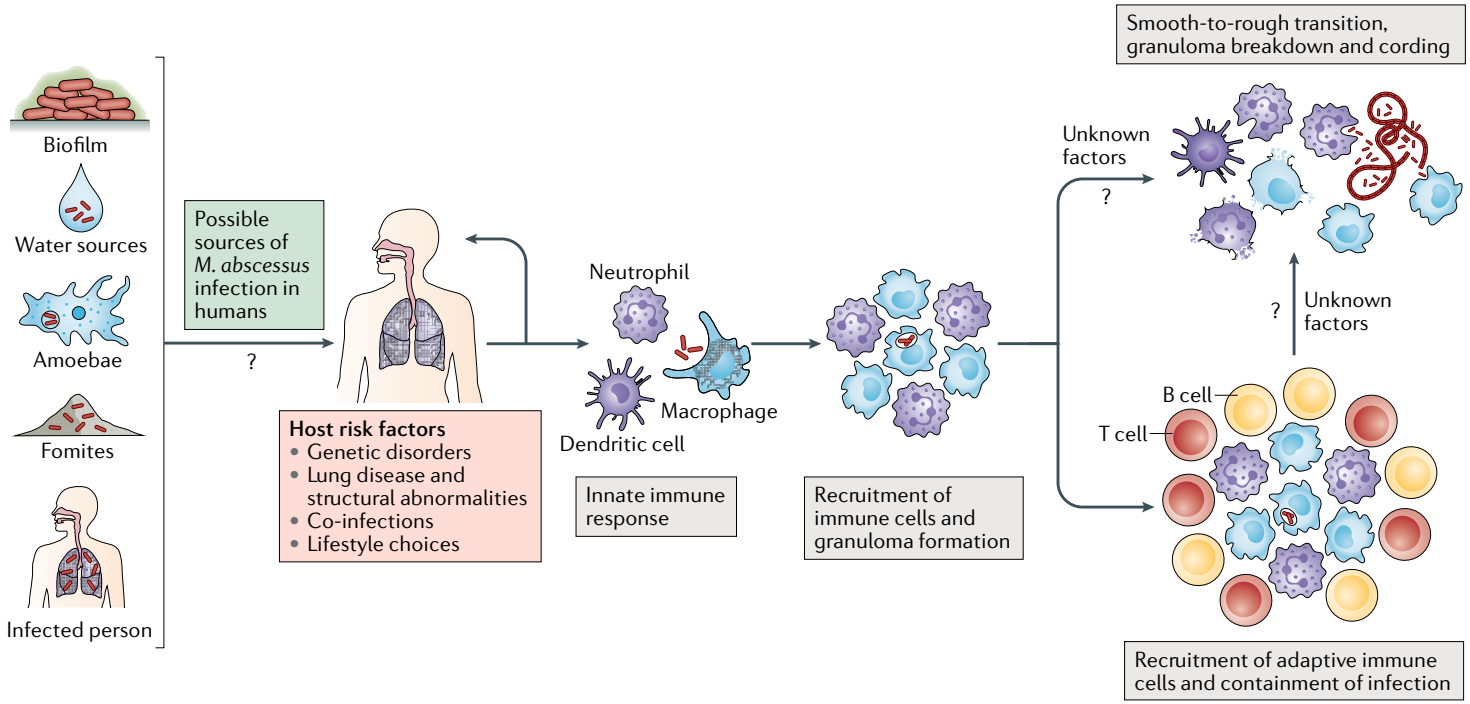
NTM^{+}-**PD^{+}**

NTM-pulmonary disease

Rowe M.S. et al., N Engl J Med, 2005
Johansen MD et al, Nat. Rev., 2020
Daley C. et al ERJ 2020

Background

Nontuberculous mycobacteria (NTM) pulmonary disease (NTM-PD)



Johansen MD et al, Nat. Rev., 2020
Daley C. et al ERJ 2020

Background

NTM-PD treatment

Review > Chest. 2022 Jan;161(1):64-75. doi: 10.1016/j.chest.2021.07.035. Epub 2021 Jul 24.

Treatment of Mycobacterium abscessus Pulmonary Disease

David E Griffith [1], Charles L Daley [2]

Affiliations + expand

PMID: 34314673 DOI: 10.1016/j.chest.2021.07.035

TABLE 5] Recommended Treatment Regimens for *Mycobacterium abscessus*

Mutational	Inducible	No. of Drugs	Preferred Drugs		Frequency of Dosing
Susceptible	Susceptible	Initial Phase ≥ 3	Parenteral (choose 1-2)[a] Amikacin[b] Imipenem (or cefoxitin) Tigecycline	Oral (choose 2)[c] Azithromycin[d] Clofazimine Omadacycline Linezolid or tedizolid Bedaquiline	Daily (3 times weekly may be used for parenteral aminoglycosides)
		Continuation phase ≥ 2	Oral/inhaled (choose 2-3)[a] Azithromycin[d] Clofazimine Omadacycline Linezolid or tedizolid Inhaled amikacin Bedaquiline		
Susceptible	Resistant	Initial phase ≥ 4	Parenteral (choose 1-2)[a] Amikacin Imipenem (or cefoxitin) Tigecycline	Oral (choose 2)[c] Azithromycin[e] Clofazimine Omadacycline Linezolid or tedizolid Bedaquiline	Daily (3 times weekly may be used for parenteral aminoglycosides)
		Continuation phase ≥ 2	Oral/inhaled (choose 2-3)[a] Azithromycin Clofazimine Omadacycline Linezolid or tedizolid Inhaled amikacin Bedaquiline		
Resistant	Susceptible or resistant		As above: treatment recommendations for macrolide-resistant *M abscesses* are the same regardless of the mechanism of macrolide resistance		
Resistant	Susceptible or resistant	Salvage therapy	Parenteral imipenem with ceftaroline or ceftaroline or ceftazidime; combine with best available oral/inhaled agents		Daily

Recommended antibiotic doses are consistent with the 2020 nontuberculous mycobacteria guidelines[22] unless specifically noted.
[a]Preferred order of choice for parenteral drugs for amikacin-susceptible *M abscessus*: amikacin, imipenem, cefoxitin, and tigecycline.
[b]Optimal amikacin dosing has not been established. Details are provided in the 2020 Guidelines.[22] We recommend expert consultation for amikacin dosing guidance.
[c]Preferred order of choice for oral medications for macrolide-susceptible *M abscessus*: clofazimine, omadacycline, tedizolid, linezolid, and bedaquiline.
[d]Azithromycin is active and can be counted as one of the active drugs in the treatment regimen.
[e]Azithromycin is unlikely to be active and cannot be counted as one of the active drugs in the treatment regimen but can be given as an immune modulator.

Acknowledge

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THANK YOU!

FFC #7/2022
FFC #23/2020

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Corso laurea magistrale

Malattia Genetiche: dalla diagnosi alla malattia

Fondazione Ricerca Fibrosi Cistica - Onlus

italian cystic fibrosis research foundation

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OSPEDALE SAN RAFFAELE