MYCOBACTERIUM ABSCESSUS – DIAGNOSTIC AND THERAPEUTIC FRONTIERS IN INFECTION MANAGEMENT

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Abstract

Mycobacterium (M.) abscessus, a highly pathogenic non-tuberculous mycobacterium, is responsible for several clinical manifestations. A very frequent occurrence is proven in patient with various lung diseases. Furthermore, it can result in complications such as skin and soft tissue diseases, central nervous system infections, bacteremia, eye infections, and others. *M. abscessus* is a clinical contraindication in cystic fibrosis patients awaiting a lung transplant, as it can exacerbate disease progression. Its pathogenicity and the emergence of resistance are influenced by factors including the composition of the cell envelope, rough and smooth *M. abscessus* morphotypes, efflux pumps, antibiotic-modifying/inactivating enzymes, and genetic polymorphisms in target genes. Management of the infection requires multicomponent therapy due to the high level of resistance. The following antibiotics are recommended according to the guidelines from the year 2017: amikacin, tigecycline, and imipenem with a macrolide. In order to properly manage patients with *M. abscessus* infection, correct identification of the subspecies as well as determination of resistance is essential. To achieve this goal, molecular-genetic techniques, such as whole-genome sequencing, are becoming increasingly favored in modern clinical practice. In this review, we provide up-to-date information on the issue of infections caused by non-tuberculous *M. abscessus*. We focus on its characteristics, possible infectious diseases, cystic fibrosis, and resistance, as well as the benefits of whole-genome sequencing.

Keywords: Mycobacterium abscessus, resistance, whole-genome sequencing

INTRODUCTION

While non-tuberculous mycobacteria (NTM), enviromental opportunistic pathogenic bacteria, are not responsible for causing tuberculosis, they present a distinct set of challenges in clinical practice. Therefore, an accurate identification is critically important in setting the correct treatment regimen (1).

Mycobacterium (M.) tuberculosis (MTB) is characterised by inhalation way of transmission by patients with a symptomatic disease, while NTM spread from the environment to the patient. After the inhalation, both are stored in the form of persisters, which are antibiotic-resistant bacteria cells found inside macrophages (2).

NTM are bacterial species stained acid-fast (3) and are generally less virulent compared to MTB. They consist of more than 190 species and subspecies (4), including rapidly-growing species like *M. abscessus* (5). NTM can cause diseases in both immunocompromised and immunocompetent hosts. The most common NTM clinical manifestation is lung disease and it mainly occurs in patients with pre-existing lung conditions (6). Importantly, many of the

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patients do not have obvious risk factors. The treatment of NTM lung disease is challenging, prolonged, and costly (3).

The incidence of NTM infectious diseases and related deaths is steadily on the rise. Studies from North America, Europe, and Asia have shown a rising incidence of NTM disease over the past two decades. For clarification, the estimated prevalence of NTM disease in the United States increased from 2.4 cases per 100,000 in the early 1980s to 15.2 cases per 100,000 by 2013. Between 1997 and 2007, there was a more than twofold increase in prevalence among the elderly population (>65 years), rising from 20 cases per 100,000 to 47 cases per 100,000. A study conducted in the UK revealed similar trends, as NTM infection rates more than tripled, increasing from 0.9 cases per 100,000 in 1995 to 2.9 cases per 100,000 in 2006 (7). A summary of this information is provided in the table (Tab. 1). Similar trends were observed in Germany and Denmark (7–9).

Table 1 An overview of the increase in NTM cases in United States (7)

Year duration	Increase in cases per 100 people
from the early 1980s to 2013	from 2.4 to 15.2
1997-2007 among the elderly population (>65 years)	from 20 to 47
1995-2006	from 0.9 to 2.9

These findings also confirmed that the prevalence of infections increases with the age as a result of age-related immune system changes. The number of NTM pulmonary infections rises globally primarily due to the availability of molecular-based detection. On the other side, not all of these detected isolates indicate actual lung disease. Despite its importance, long-term data are not available for many countries (e.g., there is only a limited number of studies from Eastern Europe and South America). The identification and interpretation of results has become more difficult because of Covid-19 pandemic, lower reporting, and the war in Ukraine (10) .

In addition to lung diseases, NTM are also responsible for infections in other sites of the body, e.g skin and soft tissue, central nervous system, bacteremia, and eyes (11).

MYCOBACTERIUM ABSCESSUS

M. abscessus was first isolated in 1953 by Moore and Frerichs from a knee infection (12). Several studies indicate that *M. abscessus* belongs to the most pathogenic bacteria among NTM (13). It is characterized as a rod-shaped acid-fast bacillus (14) and is considered as one of the most antibiotic-resistant organisms within the NTM group (15).

Mycobacterium abscessus complex (MABC) belongs to the phylum *Actinobacteria* and is a part of the *M. chelonae-abscessus* group which consists of three species: *M. chelonae, M. abscessus*, and *M. immunogenum* (11,12). These microorganisms are characterized by a high content of guanine and cytosine in their DNA. Their distinct outer membrane possesses various characteristics enhancing their resistance to antibiotics. Outer membrane consists of mycolic acid and an arabinogalactan layer (Fig. 1). Other components, such as glycopeptidolipids (GPLs), trehalose-6,6-dimycolate (TDM), trehalose monomycolate (TMM), trehalose polyphleates (TPPs), and phosphatidyl-myo-inositol dimannoside (PIM) are involved in their pathogenity (16).

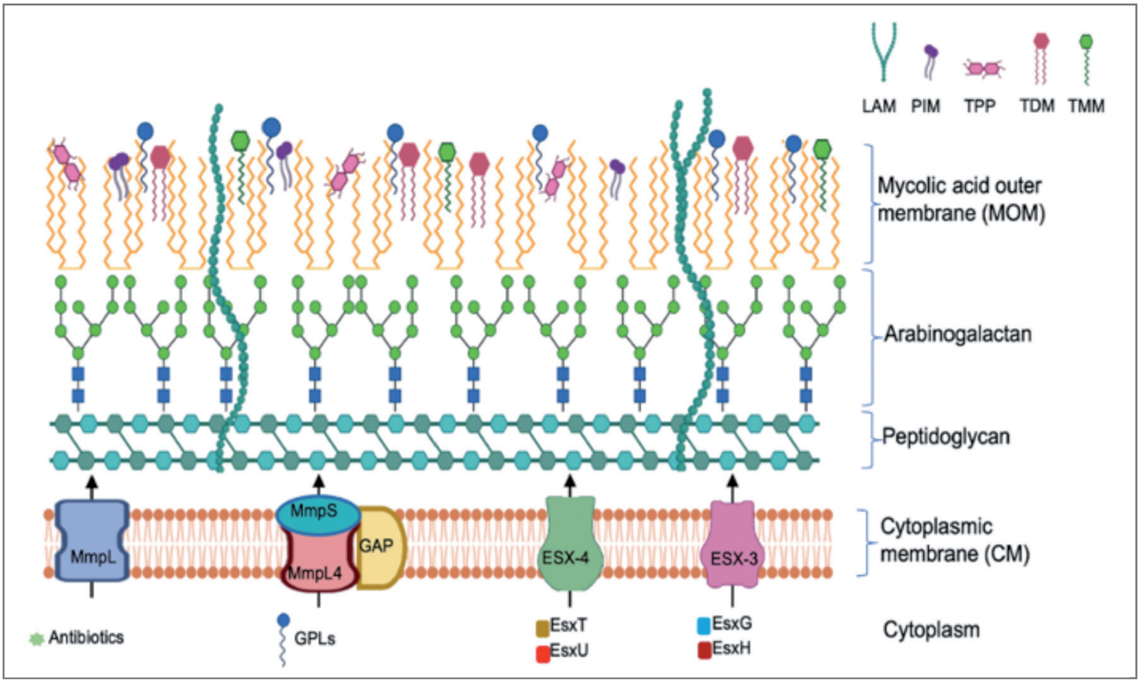

Fig. 1 Modification of components in the cell envelope of *M. abscessus* (16)

The composition of the cell wall plays a crucial role in the antibiotic resistance. Drug efflux through membrane pumps, biofilm formation, and glycopeptidolipids (GPLs) in mycobacterial outer membrane (MOM) are other factors contributing to the resistance. A reduced amount of GLPs leads to an increased hydrophobicity of the MOM. Several antibiotic substances are hydrophilic; therefore, a low sensitivity to these therapeutic agents was documented (16).

ROUGH AND SMOOTH COLONY VARIANTS OF MYCOBACTERIUM ABSCESSUS

M. abscessus is present in two unique morphological types (*M. avium* or *M. smegmatis*), and these types impact their characteristics. The first one is the smooth type, non-cording, but motile and can form biofilms. The second one is the rough type, immobile, and not able to form biofilms (Fig. 2) (17). Smooth colonies represent a wild-type due to their conversion to the rough type. This transformation is mediated by a reduction of surface glycopeptidolipids in the cell envelope of rough form. As mentioned above, a decrease in GLPs leads to an increase in hydrophobicity of the membrane. MABC strains involved in chronic infectious respiratory diseases were shown to be predominantly rough type. In contrast, the smooth morphotype is typically associated with skin abscesses and transient airway colonization (18).

In summary, the morphological variations of *M. abscessus* are important to be characterized especially in cystic fibrosis (CF) patients. In the early stages of this dissease, the MABC smooth forms of the bacterium are prevalent in lung infections, producing GLPs, and forming biofilms. In a more advanced stage, rough types become dominant in more invasive infection, and associated production of trehalose dimycolate leads to the cord formation (20).

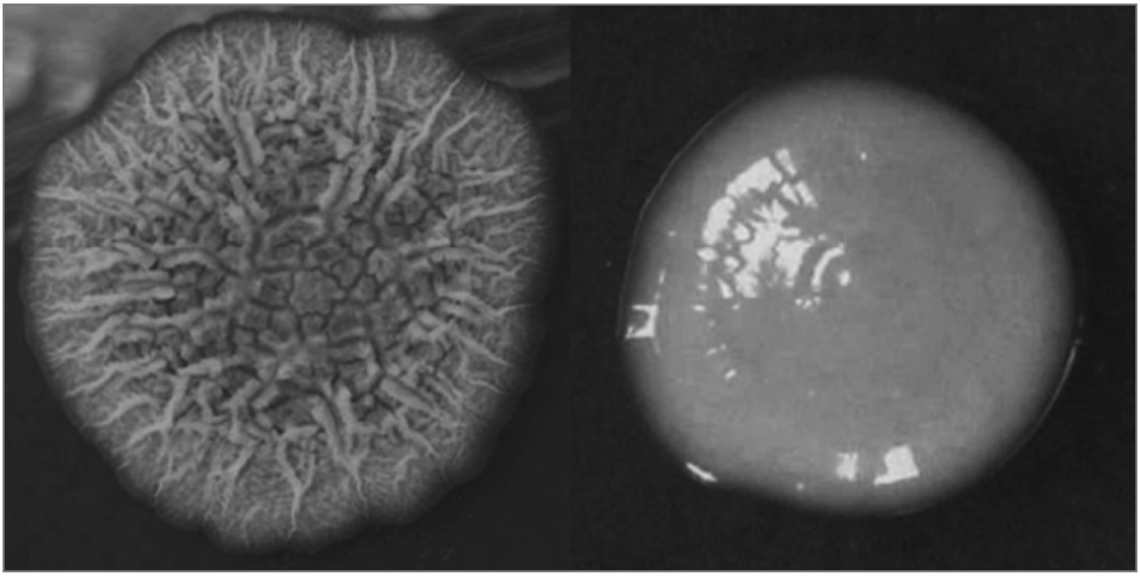

Fig. 2 Rough (left) and smooth (right) colonies of *M. abscessus* on solid agar media (19)

CYSTIC FIBROSIS

NTM, such as *M. abscessus*, commonly affect patients with ongoing lung disease. In patients with CF, infection by *M. abscessus* can exacerbate the underlying disease and lead to the prolongation of its treatment (21).

CF is a multisystemic, chronic, and genetic disease. It is inherited in an autosomal recessive manner (Fig. 3), primarily caused by genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, located on the long arm of chromosome 7 (22,23).

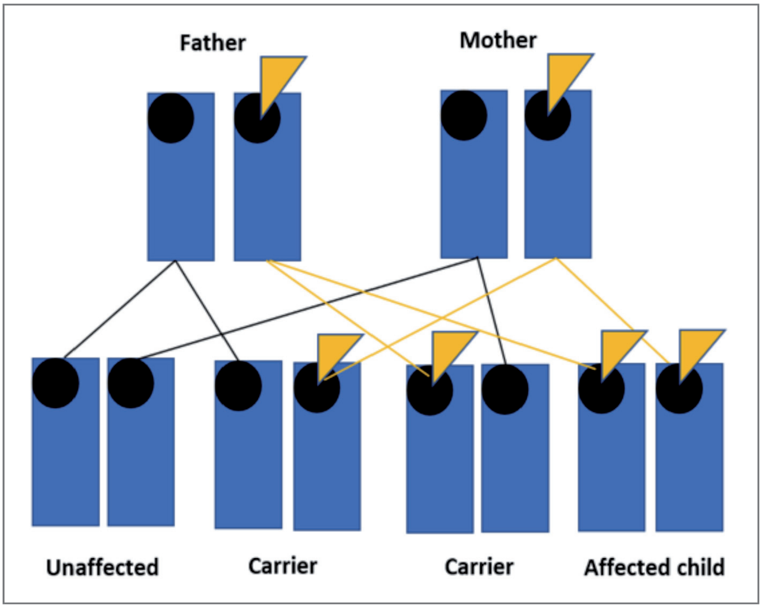

Fig. 3 Recessive inheritance in CF (adjusted based on the work of Gulani a Weiler [25])

This leads to an abnormal CFTR (chloride) channel function, unregulated chloride (Cl^-) excretion, and concomitant sodium (Na^+) release. It is associated with increased concentrations of salt (NaCl) in the sweat of patients, which characterizes the abnormal transport of electrolytes from the sweat gland (22).

Malfunction of CFTR proteins leads to a decrease in chloride secretion into the cellular spaces and, concurrently, an increase in sodium reabsorption. This increased sodium absorption causes the retention of water. As a result of these processes, there is a certain pathological organ manifestation, related to a specific gene mutation of the CFTR channel. It leads to thicker mucus, and to clogging of organ systems. Furthermore, loosing the hypotonicity of periciliar fluid leads to a higher risk of bacterial colonisation. CF primarily affects the lungs, pancreas, liver, biliary system, intestines, and sweat glands (25).

Over the past few decades, there have been improvements in the treatment of people with CF. Previously, this disease was often fatal in infants and young children (26). Nowadays, the majority of individuals are diagnosed for CF either through newborn screening at birth or before the age of two years (27). The progression of the disease in young children was primarily observed in the period of 6 months. A difference in treatment outcomes was noted at initiation of treatment at 4 to 13 months. Improvement in both the respiratory and digestive systems in children under six years of age were observed, if the treatment is initiated within two months from birth (28).

The lung environment with thick mucus creates suitable conditions for the survival of *M. abscessus* (29). Factors such as reduced immunity, reinfection, and repeated lung damage further support the growth of these bacteria in such environment (30).

NTM infections in patients with CF can contribute to many complications and worsen already existing progression of the disease. This also includes an increased number of hospitalizations, severe and progressive decline in lung function, and a risk of reinfections, which may require more aggressive and complicated treatment regimens, and leads to a reduced quality of life (31). Consequently, contamination by *M. abscessus* is considered as a contraindication for CF patients awaiting a lung transplant.

Management of infection is difficult and requires a correct choice of the antibiotic regimen with limited undesirable side effects. These can include e.g. severe nausea, deafness, impaired liver function, etc. (30,32).

CF is disease occured worldwide, related to region and population. It occurs mostly in developed countries, e.g. United States, Canada, the United Kingdom, Ireland, and Australia. Reduced prevalence is documented in Asia, Africa, and certain parts of Southern Europe, most probably as a result of different genetic backgrounds of the disease (33).

TREATMENT AND RESISTANCE

The management of *M. abscessus* infections requires a tailored and personalized strategy due to the frequent and significant resistance. This strategy comprises a prolonged course of therapy and a combination of multiple antibiotics.

Bacteria commonly responsible for lung diseases are primarily associated with the Mycobacterium avium complex (34). Additionally, M. abscessus is the second most common NTM associated in lung diseases and is further classified into three subspecies, i.e. abscessus, massiliense, and bolletii. Bacteria that cause lung disease are most often members of Mycobacterium avium complex. M. abscessus subsp. abscessus is characterized as the most resistant mycobacterial species due to acquired and innate drug resistance (32). These subspecies are associated with different clinical outcomes and antibiotic susceptibility. Subspecies abscessus and bolletii are characterized by an inducible gene (erm(41)) responsible for intrinsic resistance to macrolides. In contrast, subspecies massiliense does not contain the active erm(41), which means that it is naturally sensitive to this group of antibiotics. In comparison to azithromycin (AZM), clarithromycin (CLR) has been shown to induce the erm(41) gene more effectively, with higher mRNA expression, and MIC decreases during a longer incubation time. Therefore, AZM is more preferred for the therapy of M. abscessus infections. In addition, this species is susceptible to acquired resistance to mutational macrolides, which occurs at low rates due to point mutations at 2058 or 2059 of the 23S rRNA rrl gene positions. It is worth to mention that M. abscessus is naturally resistant to antituberculotics such as rifampicin and ethambutol (15).

In summary, among the most important treatment priorities is the preservation of susceptibility of M. abscessus strains to macrolides, because these antibiotics represent a crucial part of the multidrug therapy. This can be ensured by combining macrolides with other antibiotics (5,23,32). The British Thoracic Society guidelines from the year 2017 recommended a revision of the drug combination as follows: intravenous amikacin, tigecycline, and imipenem with a peroral macrolide, e.g., clarithromycin, for the initial treatment phase (35,36). Based on previous information, in the treatment of MABC lung disease (MABC-LD), a combination of intravenous drugs together with effective oral antibiotics, especially new-generation macrolides, is recommended. However, patient compliance can be reduced and potentially influenced by adverse effects and insufficient evidence of their effectiveness (24).

For amikacin, successful treatment outcomes have been demonstrated. In the case of MABC-LD caused by drug-resistant strains, the use of amikacin and tobramycin in the form of aerosols can be also considered. This helps to get the drug directly to the lungs where the infection is most problematic (36–38). However, a resistance to aminoglycosides has also been demonstrated in *M. abscessus*. This is primarily mediated by mutation in rrs gene with an increased resistance to amikacin and kanamycin. Furthermore, it is also charateristic by a distinct resistance determinants, AAC(2 '), Eis2 and Eis1 through gene deletion (39), shown in the table (Tab. 2).

Table 2 Enhanced susceptibility of NTM to aminoglycosides through gene deletion (39)

Deletion of gene	Increased susceptibility to antibiotic
AAC(2 ')	kanamycin B, tobramycin, dibekacin, and gentamicin C
Eis2	capreomycin, hygromycin B, amikacin, and kanamycin
Eis1	no affect on drug susceptibility

On the other side, low MICs of apramycin, arbekacin, isepamicin, and kanamycin A is not associated with an inactivation by either AAC(2 ') or Eis enzymes (39).

However, in the case of intravenous tigecycline, the efficacy for MABC-LD needs to be further investigated and confirmated (24).

Fluoroquinolones, such as moxifloxacin, and to a lesser extent levofloxacin and ciprofloxacin, have shown potential for the treatment of infections caused by *M. abscessus in- vivo* (40). In general, these antibiotics are not recommended in pediatric population and information on their use is limited due to concerns about the development of arthropathy (41). On the other hand, the use of these drugs in pediatric patients with CF represents a potential exception in their indication. Therefore, fluoroquinolones can be also considered to use in the treatment, therefore, it is important to update treatment guidelines based on targeted clinical trials in children (42).

WHOLE-GENOME SEQUENCING

Understanding the connection between pathological phenomena and DNA variations is one of the fundamental goals of human genetics. One approach involves the cataloging of genetic variations, known as single nucleotide polymorphisms (SNPs), throughout the genome, aiming to identify distinct variants associated with specific phenotypes (43). In recent decades, there have been significant advancements in methods based on functional genome analysis. They have changed from traditional real-time polymerase chain reaction to more complex methods, e.g. next-generation sequencing, whole-genome sequencing (WGS), or mass spectrometry. They are designed to analyze various aspects, including genomics, epigenomics, proteomics, and interactomics (44).

WGS is one of preferred technologies that provides a detailed inshights into various aspects related to bacterial genome (45). The method helps to analyze the entire genome of bacteria and helps to determine genetic variation and diversity within this species. Thanks to WGS it is possible to identify single nucleotide polymorphisms (SNPs), deletions, insertions, copy number variations, or structural variants in the genome (46–48). Technological advancements in recent years have significantly simplified the process, lowered the costs, and reduced the time required for sequencing (48).

WGS offers various other valuable applications. One of these is phylogenetic analysis, which offers insight into the evolutionary relationships between genes and species through phylogenetic trees. This analytical tool aids in the identification of unknown species or strains by comparing their genetic data with reference sequences (49). Additionally, WGS has been utilized in several studies to characterize transmission patterns using sets and combinations of SNPs. They represent a measure of epidemiological data and/or phylogeny or genetic distance and this information serves to confirm the transmission of bacterial strains between patients. Furthermore, WGS brings the possibility to distinguish variation between isolates due to its higher resolving power. Another option is a statistical framework that helps determine the direction of transmission. This framework integrates data with additional information and facilitates the estimation of probabilities associated with hypothetical transmission chains, rather than exclusively pinpointing specific transmission events (50).

This technology also enables the identification of antibiotic resistance, playing a vital role in effective patient care (21), as we can rapidly identify resistance mechanisms based on genetic mutations. Early detection of these processes also has implications for clinical trial design and also becomes essential in ongoing clinical trials. In general it helps to distinguish an exogenous reinfection from a relapse of primary infection. This distinction plays a crucial role in evaluating the effectiveness of investigational drugs or treatment regimens (51).

WGS can be used in specific cases, such as tracking and identifying outbreaks of infections in healthcare facilities and prevent them from further transmission (52). In relation with MABC diagnostics, it can be utilized in strain identification, antibiotic susceptibility testing, differentiation between other mycobacteria, or reccurence monitoring (53).

The choice of methods depends on the set objectives. Research often uses a combination of these methods to achieve comprehensive insights from whole-genome sequencing data.

CONCLUSION

M. abscessus represents a challenge in healthcare and microbiology. It is characterized by high pathogenicity, complex subspecies, and genetic variability. Its pathology is associated with many clinical manifestations. Consequently, tailored treatment regimens and a multidisciplinary approach are needed due to its natural antibiotic resistance and other factors. Here, WGS plays an important role in understanding genetics, identifying subspecies, and determining antibiotic resistance and thus offers new ways of understanding and more effective management of *M. abscessus* infections.

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REFERENCES

1. Brown-Elliott BA, Wallace RJ. Clinical and taxonomic status of pathogenic nonpigmented or late-pigmenting rapidly growing mycobacteria. Clin Microbiol Rev. 2002 Oct;15(4):716–46.
2. Gopalaswamy R, Shanmugam S, Mondal R, Subbian S. Of tuberculosis and non-tuberculous mycobacterial infections - a comparative analysis of epidemiology, diagnosis and treatment. J Biomed Sci. 2020 Jun 17;27(1):74.
3. Wassilew N, Hoffmann H, Andrejak C, Lange C. Pulmonary Disease Caused by Non-Tuberculous Mycobacteria. Respir Int Rev Thorac Dis. 2016;91(5):386–402.
4. Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ Jr, Andrejak C, et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. Clin Infect Dis. 2020 Aug 14;71(4):905–13.
5. Griffith DE, Daley CL. Treatment of Mycobacterium abscessus Pulmonary Disease. Chest. 2022 Jan;161(1):64–75.
6. Sharma SK, Upadhyay V. Epidemiology, diagnosis & treatment of non-tuberculous mycobacterial diseases. Indian J Med Res. 2020 Sep;152(3):185.
7. Ratnatunga CN, Lutzky VP, Kupz A, Doolan DL, Reid DW, Field M, et al. The Rise of Non-Tuberculosis Mycobacterial Lung Disease. Front Immunol [Internet]. 2020 [cited 2023 Oct 15];11. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2020.00303
8. Diel R, Jacob J, Lampenius N, Loebinger M, Nienhaus A, Rabe KF, et al. Burden of non-tuberculous mycobacterial pulmonary disease in Germany. Eur Respir J. 2017 Apr;49(4):1602109.
9. Andréjak C, Thomsen VØ, Johansen IS, Riis A, Benfield TL, Duhaut P, et al. Nontuberculous Pulmonary Mycobacteriosis in Denmark. Am J Respir Crit Care Med. 2010 Mar;181(5):514–21.
10. Przybylski G, Bukowski J, Kowalska W, Pilaczyńska-Cemel M, Krawiecka D. Trends from the Last Decade with Nontuberculous Mycobacteria Lung Disease (NTM-LD): Clinicians' Perspectives in Regional Center of Pulmonology in Bydgoszcz, Poland. Pathogens. 2023 Jul 28;12(8):988.
11. Lee MR, Sheng WH, Hung CC, Yu CJ, Lee LN, Hsueh PR. Mycobacterium abscessus Complex Infections in Humans. Emerg Infect Dis. 2015 Sep;21(9):1638–46.
12. Moore M, Frerichs JB. An unusual acid-fast infection of the knee with subcutaneous, abscess-like lesions of the gluteal region; report of a case with a study of the organism, Mycobacterium abscessus, n. sp. J Invest Dermatol. 1953 Feb;20(2):133–69.
13. Medjahed H, Gaillard JL, Reyrat JM. Mycobacterium abscessus: a new player in the mycobacterial field. Trends Microbiol. 2010 Mar 1;18(3):117–23.
14. Boudehen YM, Kremer L. Mycobacterium abscessus. Trends Microbiol. 2021 Oct 1;29(10):951–2.
15. Nessar R, Cambau E, Reyrat JM, Murray A, Gicquel B. Mycobacterium abscessus: a new antibiotic nightmare. J Antimicrob Chemother. 2012 Apr;67(4):810–8.
16. Parmar S, Tocheva EI. The cell envelope of Mycobacterium abscessus and its role in pathogenesis. PLOS Pathog. 2023 5;19(5):e1011318.
17. Roux AL, Viljoen A, Bah A, Simeone R, Bernut A, Laencina L, et al. The distinct fate of smooth and rough Mycobacterium abscessus variants inside macrophages. Open Biol. 2016 Nov;6(11): 160185.
18. Jönsson B, Ridell M, Wold AE. Phagocytosis and cytokine response to rough and smooth colony variants of Mycobacterium abscessus by human peripheral blood mononuclear cells. APMIS. 2013;121(1):45–55.
19. Rüger K, Hampel A, Billig S, Rücker N, Suerbaum S, Bange FC. Characterization of rough and smooth morphotypes of Mycobacterium abscessus isolates from clinical specimens. J Clin Microbiol. 2014 Jan;52(1):244–50.
20. Degiacomi G, Sammartino JC, Chiarelli LR, Riabova O, Makarov V, Pasca MR. Mycobacterium abscessus, an Emerging and Worrisome Pathogen among Cystic Fibrosis Patients. Int J Mol Sci. 2019 Nov 22;20(23):5868.
21. Harris KA, Kenna DTD. Mycobacterium abscessus infection in cystic fibrosis: molecular typing and clinical outcomes. J Med Microbiol. 2014;63(10):1241–6.

22. López-Valdez JA, Aguilar-Alonso LA, Gándara-Quezada V, Ruiz-Rico GE, Ávila-Soledad JM, Reyes AA, et al. Cystic fibrosis: current concepts. Bol Méd Hosp Infant México [Internet]. 2021 [cited 2023 Sep 27];78(6). Available from: https://www.bmhim.com/frame_esp.php?id=279
23. Recchia D, Stelitano G, Stamilla A, Gutierrez DL, Degiacomi G, Chiarelli LR, et al. Mycobacterium abscessus Infections in Cystic Fibrosis Individuals: A Review on Therapeutic Options. Int J Mol Sci. 2023 Feb 27;24(5):4635.
24. Gulani A, Weiler T. Genetics, Autosomal Recessive. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Nov 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK546620/
25. Yu E, Sharma S. Cystic Fibrosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Sep 29]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK493206/
26. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med. 2020 Jan;8(1):65–124.
27. Cystic Fibrosis in Children | Symptoms, Diagnosis & Treatment [Internet]. [cited 2023 Oct 16]. Available from: https://www.cincinnatichildrens.org/health/c/cystic-fibrosis
28. VanDevanter DR, Kahle JS, O'Sullivan AK, Sikirica S, Hodgkins PS. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. J Cyst Fibros. 2016 Mar 1;15(2):147–57.
29. Surette MG. The Cystic Fibrosis Lung Microbiome. Ann Am Thorac Soc. 2014 Jan;11(Supplement 1):S61–5.
30. Brugha R, Spencer H. Mycobacterium abscessus in cystic fibrosis. Science. 2021 Apr 30;372(6541): 465–6.
31. Olivier KN, Weber DJ, Wallace RJ, Faiz AR, Lee JH, Zhang Y, et al. Nontuberculous Mycobacteria. Am J Respir Crit Care Med. 2003 Mar 15;167(6):828–34.
32. Richard M, Gutiérrez AV, Kremer L. Dissecting erm(41)-Mediated Macrolide-Inducible Resistance in Mycobacterium abscessus. Antimicrob Agents Chemother. 2020 Jan 27;64(2):e01879-19.
33. Scotet V, L'Hostis C, Férec C. The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the CFTR Gene Discovery. Genes. 2020 May 26;11(6):589.
34. Daley CL, Winthrop KL. Mycobacterium avium Complex: Addressing Gaps in Diagnosis and Management. J Infect Dis. 2020 Sep 15;222(Suppl 4):S199–211.
35. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax. 2017 Nov;72(Suppl 2):ii1–64.
36. Haworth CS, Banks J, Capstick T, Fisher AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax. 2017 Nov 1;72(Suppl 2):ii1–64.
37. Rose SJ, Neville ME, Gupta R, Bermudez LE. Delivery of aerosolized liposomal amikacin as a novel approach for the treatment of nontuberculous mycobacteria in an experimental model of pulmonary infection. PloS One. 2014;9(9):e108703.
38. Kang N, Jeon K, Kim H, Kwon OJ, Huh HJ, Lee NY, et al. Outcomes of Inhaled Amikacin-Containing Multidrug Regimens for Mycobacterium abscessus Pulmonary Disease. Chest. 2021 Aug 1;160(2):436–45.
39. Rominski A, Selchow P, Becker K, Brülle JK, Dal Molin M, Sander P. Elucidation of Mycobacterium abscessus aminoglycoside and capreomycin resistance by targeted deletion of three putative resistance genes. J Antimicrob Chemother. 2017 Aug 1;72(8):2191–200.
40. Caballero AR, Marquart ME, O'Callaghan RJ, Thibodeaux BA, Johnston KH, Dajcs JJ. Effectiveness of fluoroquinolones against Mycobacterium abscessus in vivo. Curr Eye Res. 2006 Jan; 31(1):23–9.
41. Jafri HS, McCracken GH. Fluoroquinolones in Paediatrics. Drugs. 1999 Oct 1;58(2):43–8.
42. Sabin AP, Ferrieri P, Kline S. Mycobacterium abscessus Complex Infections in Children: A Review. Curr Infect Dis Rep. 2017 Nov;19:46.

43. Anderson MW, Schrijver I. Next Generation DNA Sequencing and the Future of Genomic Medicine. Genes. 2010 May 25;1(1):38–69.
44. Gasperskaja E, Kučinskas V. The most common technologies and tools for functional genome analysis. Acta Medica Litu. 2017;24(1):1–11.
45. Gautam SS, KC R, Leong KW, Mac Aogáin M, O'Toole RF. A step-by-step beginner's protocol for whole genome sequencing of human bacterial pathogens. J Biol Methods. 2019 Mar 15;6(1):e110.
46. Lewin A, Kamal E, Semmler T, Winter K, Kaiser S, Schäfer H, et al. Genetic diversification of persistent Mycobacterium abscessus within cystic fibrosis patients. Virulence. 2021 Dec 31;12(1):2415–29.
47. Austin-Tse CA, Jobanputra V, Perry DL, Bick D, Taft RJ, Venner E, et al. Best practices for the interpretation and reporting of clinical whole genome sequencing. Npj Genomic Med. 2022 Apr 8;7(1):1–13.
48. Dohal M, Porvaznik I, Kusnir P, Mokry J. Whole-Genome Sequencing in Relation to Resistance of. Acta Medica Martiniana. 2019 Apr 1;19(1):12–21.
49. Pinto ACSM, De Pierri CR, Evangelista AG, Gomes AS de LPB, Luciano FB. Deoxynivalenol: Toxicology, Degradation by Bacteria, and Phylogenetic Analysis. Toxins. 2022 Feb;14(2):90.
50. Hatherell HA, Colijn C, Stagg HR, Jackson C, Winter JR, Abubakar I. Interpreting whole genome sequencing for investigating tuberculosis transmission: a systematic review. BMC Med. 2016 Mar 23;14:21.
51. Köser CU, Ellington MJ, Peacock SJ. Whole-genome sequencing to control antimicrobial resistance. Trends Genet. 2014 Sep 1;30(9):401–7.
52. Parcell BJ, Gillespie SH, Pettigrew KA, Holden MTG. Clinical perspectives in integrating whole-genome sequencing into the investigation of healthcare and public health outbreaks – hype or help? J Hosp Infect. 2021 Mar;109:1–9.
53. Dohal M, Porvaznik I, Solovic I, Mokry J. Whole Genome Sequencing in the Management of Non-Tuberculous Mycobacterial Infections. Microorganisms. 2021 Oct 27;9(11):2237.

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