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Mycobacterium biofilms

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ABSTRACT

The genus *Mycobacterium* includes some of the deadliest pathogens of History (*Mycobacterium tuberculosis, Mycobacterium leprae*), but most of the species within the genus are environmental microorganisms. Because some of these nontuberculous mycobacteria (NTM) species can be human pathogens, the study of these mycobacterial biofilms has increased during the last decades, and the interest in this issue increased as well as the growing number of patients with diseases caused by NTM. Different molecular mechanisms have been described, being especially well known the importance of glycopeptidolipids. Moreover, the knowledge of the extracellular matrix has shown important differences with other microorganisms, especially because of the presence of lipidic molecules as a key component of this structure. The clinical importance of mycobacterial biofilms has been described for many chronic diseases, especially lung diseases and implant-related ones, both *in vitro* and *in vivo*, and even in patients. Moreover, the biofilm-producing capacity has been proven also in *M. tuberculosis*, while its importance is not well understood. Biofilm studies have also shown the increasing resistance of mycobacteria in sessile form, and the importance of this resistance in the management of the patients is beyond doubt, being surgery necessary in some cases to cure the patients. Diagnosis of mycobacterial diseases is still based on culture-based techniques designed for the detection of *M. tuberculosis*. Molecular biology-based methods are also broadly used but again designed for tuberculosis diagnosis. Antimicrobial susceptibility testing is also well developed for tuberculosis, but only some species of NTM have standardized techniques for this purpose. New tools or approaches are necessary to treat these patients, whose importance is increasing, as the number of potential hosts is also increasing throughout the world.

1. Introduction

Over 200 nontuberculous mycobacteria (NTM) species have been described, with only a few species causing serious and often opportunistic infections in humans (Table 1) [1]. Compared with *Mycobacterium tuberculosis*, NTM has lower virulence, but they can be the cause of infections in humans, especially those with some underlying factors [2–4]. NTM are considered environmental microorganisms that can be found in different environments, mostly water-related, but also in soil, dust particles, and aerosols. This is because they can grow in a wide range of temperatures, pH, salinity, and oxygen tension [2]. Water-related NTM isolates have been described in sources such as drinking water, dental aerosols, cooling water distribution systems, and even in hospital bronchoscopes, and the filters used to wash them [5,6]. However, the distribution of the different mycobacteria in these sources is not uniform, and they can be affected by many environmental circumstances, such as the presence of different disinfectants [7]. Several studies have noted temporal differences in the isolation of NTM in human samples [8] or between different countries [9]. Thus, it has been shown that these differences may partly determine the frequency and manifestations of NTM lung disease in each geographic location [9]. These differences probably originate from the presence of these mycobacteria in environmental samples, which have been described as the main source of the different infections.

In these natural environments, NTM are usually found in biofilms, especially polymicrobial ones [10], where mycobacteria develop different relationships with other microorganisms, including eukaryotic cells such as free-living amoebae. The ability to form biofilms is probably the most important pathogenic factor in many NTM infections, being the essential life form of most *Mycobacterium* species, and has important implications in all aspects of the NTM diseases [11] because these structures may protect pathogenic mycobacterial species from the host immune system and could help bacteria persist during treatment [12].

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Table 1
Mycobacterial species of importance in human pathology.

Rapidly Growing Mycobacteria		Slowly Growing Mycobacteria	
Not pigmented	Pigmented	*Mycobacterium tuberculosis* complex	Non-tuberculous *Mycobacterium*
Mycobacterium abscessus	*Mycobacterium bacteriemicum*	*Mycobacterium tuberculosis*	*Mycobacterium kansasii*
Mycobacterium chelonae	*Mycobacterium celeriflavum*	*Mycobacterium bovis* sp. *bovis*	*Mycobacterium avium*
Mycobacterium fortuitum	*Mycobacterium cosmeticum*	*Mycobacterium bovis BCG*	*Mycobacterium intracellulare*
Mycobacterium porcinum	*Mycobacterium neoaurum*	*Mycobacterium bovis* sp *caprae*	*Mycobacterium chimaera*
Mycobacterium fortuitum group		*Mycobacterium africanum*	*Mycobacterium lentiflavum*
Mycobacterium mucogenicum group		*Mycobacterium microti*	*Mycobacterium marinum*
Mycobacterium smegmatis group			*Mycobacterium xenopi*

2. Biofilm formation and composition

Both pathogenic and nonpathogenic species of mycobacteria can form biofilms because this ability is not essentially a virulence mechanism and has been considered the essential form of microbial life [13,14]. They have been described in the early years of bacteriology, although with a different name since the structures are quite similar to those described today as tuberculosis biofilms [15], and which can be found in the old descriptions of *Mycobacterium tuberculosis* cultures (Fig. 1) [16].

Biofilm development usually begins with bacterial adherence to a surface. Adherence of mycobacteria to inorganic surfaces could be not only a species characteristic but a strain-dependent one, according to the study by *Zamora* et al. [17]. In this study, performed with rapidly growing mycobacteria and suture filaments of polypropylene, many clinical and collection strains were tested, looking for differences in the number of CFUs adhering to the filaments. There are clear differences between species and even between strains, with important differences between the clinical and the collection ones. The study concludes that some species seem to adhere more effectively than others, especially the most pathogenic ones (with the notable exception of *M. abscessus*) [17].

Most of the pathogenic factors of the genus *Mycobacterium* are found in the cell wall. It is unique because it includes different lipid molecules such as trehalose dimycolate (cord factor). Different species of mycobacteria can develop cords, which are considered classically a pathogenic expression, and structures like cords have been described in some mycobacterial biofilms (Fig. 2) [18,19]. Other molecules involved in biofilm development have been described, such as glycopeptidolipids (GPLs) [20–24], type III polyketide synthases [25], ESX-1 secretion system [26], GroEL1 chaperone [27], FabG4 [28], Peptidyl-prolyl isomerase [29], FAS-II components [30], protein kinase PknF [31] and many others in different mycobacterial species, most of them rapidly growing [32–34]. Most of these molecules and systems are involved in the mycolic acid synthesis and the metabolism of different components of the mycobacterial cell wall. Some of these components, such as GPLs, short-chain mycolic acids, monomeromycolyl diacylglycerol, and others, play an important role in biofilm formation. Thus, for example, a mycobacterial mutant lacking GroEL1 failed to develop complex architecture and was also defective in mycolic acid production. This suggests that GroEL1 has a specific role in the synthesis of the C_{56}–C_{68} mycolic acids and that its absence has striking consequences for the development of mature biofilms [27]. These components confer a hydrophobic character to the mycobacterial cell surface that facilitates cell-cell interaction [12]. Nevertheless, the best-known molecules involved in the development of mycobacterial biofilms are the GPLs [35]. These molecules have been described in many different species, including pathogenic rapidly growing mycobacteria (like *M. abscessus*) [36] or slowly growing ones (like the *M. avium* complex) [23]. There are differences between the GPLs that have been described in the different species, all of them with a common lipopeptide core but with differences in glycosylation methylation or acetylation [35]. GPLs have been related not only to biofilm formation but also to sliding motility [22] or the smooth or rough colony phenotype [20], despite these relationships are not clear in all strains, at least among rapidly growing mycobacteria [37,38]. In fact, according to these studies, the colony phenotype should not be used to assess the clinical significance of a strain in human specimens

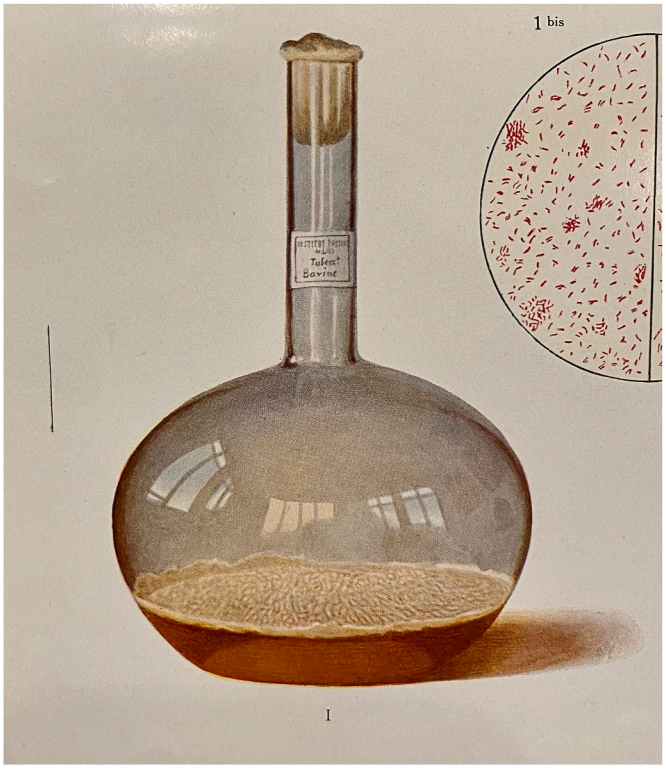

Fig. 1. Drawing of biofilm-like structures in liquid cultures [16].

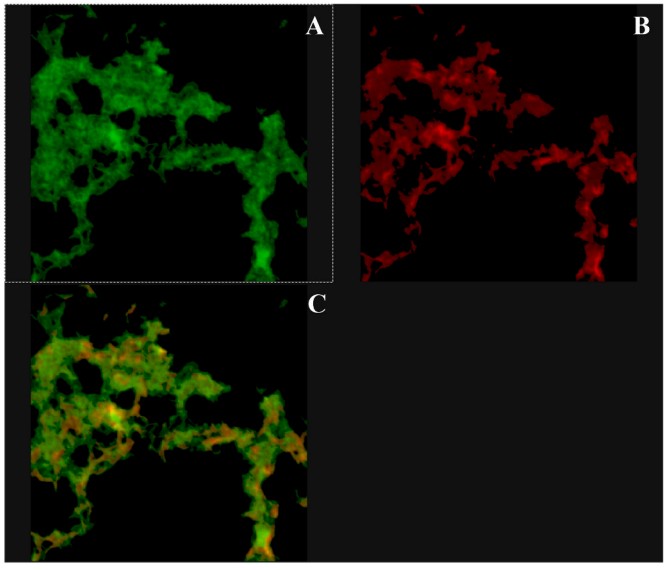

Fig. 2. Cording inside *M. abscessus* biofilm (CLSM, Backlight® Live/Dead Stain). A): Live bacteria; B) Dead bacteria; C) Combined image.

[38]. Moreover, the rough colony in *M. abscessus* is usually associated with high pathogenicity, but among the *M. avium* complex, it is the smooth phenotype that appears more pathogenic [39].

Biofilms are usually surrounded by an extracellular matrix (ECM) that contributes to their structural integrity and protection of the bacterial community. It is required for cell aggregation, adhesion to surfaces, retention of water, and nutrient provision. It also serves as a physical barrier, allowing bacteria a significant degree of resistance to water treatment, disinfectants, and antibiotics [40,41]. ECM can be as diverse as biofilms, containing polysaccharides, exopolysaccharides, lipids, proteins, and sometimes even nucleic acids [12,42–44]. Some bacteria, such as mycobacteria, do not fit this mold. They are capable of forming robust biofilms but do not produce exopolysaccharides as part of biofilm formation. Scrutiny of mycobacterial genomes suggests that they do not possess the capability for exopolysaccharide production [45]. Carbohydrates are the main components of the ECM of *M. tuberculosis* and *M. chelonae* biofilms [43,46]. Glucose was the predominant sugar present in the ECM of *M. chelonae*, and its relative abundance decreased in established biofilms [43]. In *M. tuberculosis* biofilms the ECM is primarily composed of polysaccharides, with cellulose being a key component [46]. eDNA has been identified in biofilms of *M. tuberculosis, M. avium, M. abscessus, M. fortuitum, and M. chelonae*, and plays an important structural role in promoting adhesion to surfaces and facilitating bacterial aggregation, as DNase-treated biofilms become less structurally strong and more vulnerable to antibiotics [43,47–50]. Different models of *M. tuberculosis* biofilm formation have been proposed to study the factors that regulate biofilm formation. It has been proven that the ECM of *M. tuberculosis* biofilms includes a large number of lipid molecules (mainly keto-mycolic acids), whereas leukocyte lysate-induced and thiol-reductive stress-induced biofilms possess polysaccharides as the main component of the ECM [12]. A better understanding of the ECM of biofilms will facilitate the development of a shorter treatment regimen.

In natural polymicrobial biofilms, mycobacteria establish different relationships with different microorganisms. Recently, several studies have demonstrated the ability of *M. abscessus* and *P. aeruginosa* to coexist in an *in vivo* model of polymicrobial biofilms, where they can establish a competitive relationship [51–53]. In these studies, *P. aeruginosa* limits the growth of *M. abscessus*, and this species can be found in the bottom of these biofilms [51], and the changes caused by antibiotics if *P. aeruginosa* can affect the growth of mycobacteria, with differences related to the presence of human cells [52,53]. This ability could have important implications in the development of infections caused by these organisms and in the selection of the best available treatment for these patients [53]. The interaction of *P. aeruginosa* and mycobacteria has also been studied with other species *in vivo* in cell cultures, like the *M. avium* complex. In this recent study, *P. aeruginosa* was seen to multiply more rapidly when cells were previously infected *in vitro* with *M. avium* complex or *M. tuberculosis* and induced IL-1β production. The stimulation of *P. aeruginosa* by mycobacteria provides evidence to explain their common clinical association [54]. In this sense, mycobacterial control strategies may be useful in reducing *P. aeruginosa* colonization in these types of patients [55].

3. Clinical relevance

NTM are usually considered opportunistic pathogens, as opposed to *M. tuberculosis* complex or *M. leprae*. They are capable of causing a wide variety of infections such as lymphadenitis and infections of the lungs, skin, soft tissues, bursae, joints, tendon sheaths, and bones [2], and many of these mycobacterial diseases (including tuberculosis) have been described as biofilm-related diseases [15,56]. Among immunocompetent patients, respiratory disease is the most frequent one. Most cases of lung infection in these cases are associated with some predisposing condition such as cystic fibrosis, the presence of bullae, past tuberculosis scars, bronchiectasis, and other chronic lung diseases [57,58]. In soft tissues, bursae, joints, tendon sheaths, and bones are often associated with trauma or surgical procedures [2]. Other syndromes are usually related to the presence of different types of implants, like catheter-related bacteremia [59], or are associated with different medical procedures, such as aesthetic surgery [60,61], in many cases appearing as outbreaks [62,63].

Chronic lung infections are probably the most common diseases that can be caused by NTM in humans. Some specific hosts, such as patients with cystic fibrosis, appear to be more susceptible to these infections. Among these patients, two different forms have been described: cavitary disease and fibronodular disease [64]. Cavitary disease (Fig. 3) usually appears in patients with previous underlying conditions such as bullae or other cavitary diseases. In these patients, the mycobacterial strain first colonizes the cavity and then develops a disease that is difficult to differentiate from tuberculosis. Fibronodular disease (Fig. 4) appears in patients with chronic bronchiectasis or cystic fibrosis. In these cases, the mycobacteria are probably able to colonize the bronchial tree with other pathogens, like *P. aeruginosa*, and to develop disease through an unknown process that involves the complex relationships that can exist between the different pathogens [65]. Since NTM can colonize the respiratory tract without causing infection, diagnostic protocols have been developed considering this fact, trying to avoid undesired side effects from treatments that are not necessary.

Classically, the acquisition of NTM from environmental sources has been considered the main route of contagion. Water systems have been considered the most probable source in these cases, and some outbreaks related to an identified environmental source have been described [62,63,66]. Different molecular biology techniques have been described as useful for the identification of these outbreaks [8,67,68]. However, the recent development of new molecular tools based on whole genome sequencing has suggested the possibility of interhuman transmission of some strains [69,70]. These reports open new possibilities for the knowledge of the actual epidemiology of these microorganisms, and to establish new control methods that allow us to avoid the contagion and development of these diseases among susceptible hosts.

Other types of infection that can be considered biofilm-related are some outbreaks related to environmental sources. This source is usually related to water, or the aqueous environment (colonized humidifiers, heater-cooler devices, imperfect disinfection, hospital water sources, etc.) [7]. The number of outbreaks related to NTM outbreaks is increasing because of heightened awareness and better diagnostic tests for species-level identification of mycobacteria [62,71]. Most of these outbreaks involve a limited number of patients with a common source, although there is increasing evidence that transmission in this patient population can occur through either direct or indirect patient-to-patient spread [62]. An outbreak of special interest because of the high number of patients (and countries) involved was the outbreak of *M. chimaera* [72,73]. This outbreak was due to the contamination of heat cooling systems used in cardiac surgery at the point where these devices are

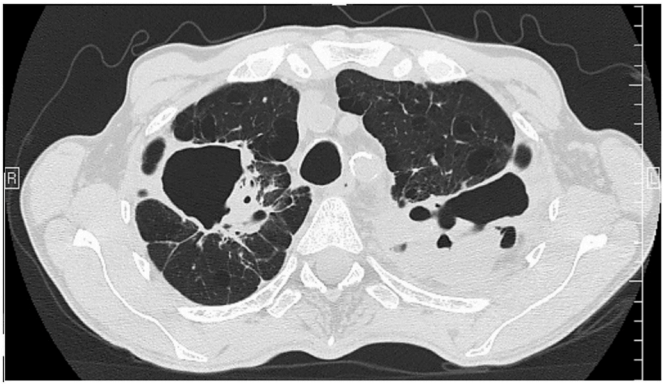

Fig. 3. Cavitary disease caused by *M. kansasii* (CT-Scan).

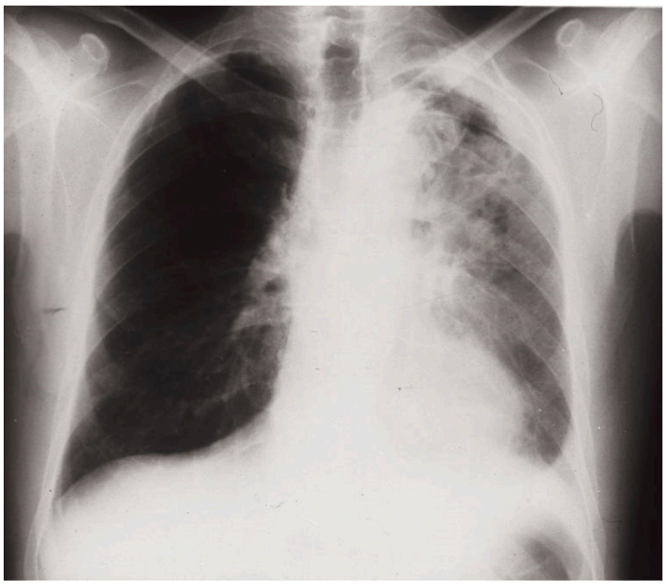

Fig. 4. Fibronodular disease caused by *M. abscessus* (Thoracic X-ray).

produced, and then all the contaminated machines were delivered to many different places [74]. *M. chimaera* spread through aerosols and infected many patients in different countries. Biofilms formed by this species present on the machines are considered to be the key pathogenic factor in this outbreak [72,73].

The presence of a foreign body or biomaterial is also a risk factor for some infections caused by NTM. Many different syndromes of biomaterial-related infections caused by NTM have been described, including catheter-related bacteremia and endocarditis [59], prosthetic joint infection [75,76], peritonitis associated with peritoneal dialysis [77], post-surgical infections [78], augmentation mammaplasty [79] and others. In all these cases, removal of the biomaterial is essential to cure the patients [80,81], because the antibiotic treatment alone is not able to eradicate the biofilm. In some cases, not only NTM, but *M. tuberculosis* complex may be the cause of these biomaterial-associated infections [75], probably because these species are also able to form a biofilm. However, the role of biofilm in pulmonary tuberculosis (or other infections without any relation to implants or biomaterials) is still less defined, and the importance of the clinical evolution of the disease and the management of the patients is not well established [56].

4. Diagnosis

The management of mycobacterial infections must necessarily take into account the isolated species and their *in vitro* sensitivity when appropriate, as well as the characteristics of the patient. Hence the importance of a good clinical and microbiological diagnosis [58]. The clinical diagnosis will depend on the signs and symptoms of the patient, which are influenced by the species of mycobacteria and location. Thus, for example, the clinical diagnosis of pulmonary tuberculosis is suspected in patients with relevant clinical manifestations, such as persistent and productive cough, hemoptysis, fever, weight loss, and an epidemiological link with tuberculosis. Clinical observations can also be confirmed by chest x-ray findings and other tests [82].

The microbiological diagnosis of tuberculosis and the rest of mycobacteriosis has traditionally been based, and probably will continue to be so in the future, on direct examination and culture. Microscopy, although relatively insensitive, remains the only diagnostic test capable of providing a rapid response (first 24 h) for many laboratories, regardless of their budget and sophistication, especially in many countries where tuberculosis is highly endemic. In addition, it gives us an assessment of the degree of infectivity of the patient with pulmonary tuberculosis because it can be quantified.

In the recent decades, an important set of new culture-based techniques have appeared that can generate a rapid and complete results. It has gone through the use of radiometric and non-radiometric liquid culture systems for isolation and antimicrobial susceptibility studies, the application of chromatographic techniques and the development of nucleic acid-based techniques for rapid identification of the isolated mycobacteria, and detection of *M. tuberculosis* complex directly in clinical samples. More recently molecular typing for monitoring strains of interest and, finally, DNA sequencing and MALDI-TOF MS for identification has been integrated in the mycobacteriology laboratory for their routine use [83]. It is important to emphasize that the use of the different techniques is not advisable for all the cases and patients, and the interpretation of their results must be prudent and the clinical and radiological data must be taken into account [84]. Most of these methods have been developed for the diagnosis of tuberculosis and the isolation of *M. tuberculosis* complex species. However, most NTM can also be isolated with these systems, and criteria for the interpretation of the microbiological results have been developed for a clear interpretation of the isolation of these environmental species [58]. In the present moment, some specific media for NTM have been developed and have been used, not only for clinical samples, but for environmental ones [85–87]. These later samples are of special interest, because NTM grow in them as part of polymicrobial biofilms, and because the slow growing of all species (compared with other bacteria) the isolation of them can be problematic. Of interest, sonication techniques (developed for implants with biofilm-related infections) have been able to isolate some NTM from implant-related infections if special culture media are used or if conventional bacteriology cultures prolong their incubation [88,89].

Each laboratory must define the techniques to be used according to its possibilities and epidemiological characteristics of its area. Moreover, microbiology laboratory excellence will not be effective if there is no close collaboration between the laboratory and clinicians. A sample received in good condition and with all the necessary information will allow the laboratory to select the best available techniques for mycobacterial diagnosis.

5. Susceptibility testing

A critical feature of tuberculosis diagnosis is identifying susceptibility to first- and second-line antibiotics quickly and accurately for efficient treatment. While MDR-TB cases are resistant at least to the first-line drugs isoniazid (INH) and rifampicin (RIF), XDR-TB cases are resistant to INH, RIF, any fluoroquinolone, and at least one of the second-line injectable drugs (amikacin, kanamycin, and capreomycin) [90,91]. Detection of drug-resistant MTB is often performed using the accurate but slow culture-based drug sensitivity testing (DST). Standardized antibiotic susceptibility testing procedures require eight to 12 weeks to determine resistance on solid culture media, and using automated liquid culture systems have been proved faster and with better sensitivity. However, even with liquid cultures, it takes two to four weeks to obtain antimicrobial susceptibility of a *M. tuberculosis* strain. In response to the relative time to generate a DST phenotypic result, faster nucleic acid amplification tests have been developed that are able to detect critical resistance mutations even inclinical samples. For example, the Cepheid GeneXpert MTB/RIF assay (Cepheid, USA) detects mutations associated with RIF resistance, while the Hain MTBDR Plus (Hain, Germany) and Abbott RealTime MTB RIF/INH (Abbott, USA) detects mutations associated with RIF and INH resistance, all of them in clinical samples [92,93].

On the other hand, NTM species show significant heterogeneity in their susceptibility to standard *anti*-TB drugs. Susceptibility studies in NTM are limited to a few species where these methods have been standardized, including the MAC, *Mycobacterium kansasii*, *Mycobacterium marinum,* and non-pigmented rapidly growing mycobacteria of clinical significance. There is a standardization of sensitivity studies for

these organisms, where microdilution is established as the reference technique for these studies [94].

6. Treatment

The treatment of these diseases must consider the presence of biofilm as a fact that needs specific approaches to cure patients. These infections are often recalcitrant to treatment and require long-term multidrug therapy [58,95], and in many cases, the rate of failures is high [96]. Some of these infections (endocarditis, meningitis, endovascular prosthesis-related bacteremia) have a high mortality rate, so adequate treatment is mandatory. Along with implant removal, long periods of treatment (usually with antibiotic combinations) are usually necessary.

One of the most important problems encountered in *Mycobacterium* biofilms is antibiotic and antimicrobial resistance. Sessile bacteria usually need higher antibiotic concentrations to be killed than planktonic forms, and this is also true for mycobacteria. *In vitro* biofilms of mycobacteria are more persistent against antibiotics than their single-cell planktonic counterparts in several *in vitro* studies [15,97]. Different mechanisms have been proposed to explain this resistance [98,99], but probably their relative importance of them is different. In the study of *Ortiz-Perez* et al., antibiotic penetration in the biofilm of rapidly growing mycobacteria seems to have a minor importance in the resistance of the biofilm [100], but in the study by *Greendyke and Byrd*, the alteration of the metabolic state seems to be the determinant mechanism for the antimicrobial resistance among sessile bacteria [99]. The relative importance of other mechanisms, such as activation of resistance mechanisms (efflux pups, inducible methylases) or any other, is still to be investigated.

New approaches are needed to cure patients with biofilm-related mycobacterial diseases. One approach is the use of molecules with an antibiofilm effect (usually with activity against the extracellular matrix), such as N-acetylcysteine (NAC) and Tween 80, which demonstrated a synergistic effect with antibiotics [101].

Another approach is the use of some microorganisms (e.g. *Methylobacterium* sp.) that have the property of inhibiting mycobacterial biofilms. This property can be demonstrated using not only live cells but also dead cells and even the crude extract of the bacteria in several *in vitro* studies with different NTM species [102,103]. *Methylobacterium* extract even can be used to pre-treat surfaces to prevent biofilm development by *M. chimaera* (and probably other NTM) [104]. Further research could lead to the study of proteins and other molecules that appear in the *Methylobacterium* sp. extract and that can be tested as antibiofilm agents [104].

Other approaches for the treatment of mycobacterial biofilms include nanoparticles, phototherapy, phage therapy, vaccines, antimicrobial peptides, and new antibiotics. All of these approaches (and those described above) must be tested not only *in vitro*, but in experimental *in vivo* studies and, recently, in clinical practice [105–111]. These possibilities, together with the development of new antibiotics active against mycobacterial biofilms, are necessary because of the high degrees of resistance of many of the NTM, and the problems that appear with the treatment of some species, like *M. abscessus*, that is considered nowadays an emerging species with many treatment problems [112].

7. Conclusions

A majority of the species of the genus *Mycobacterium* (probably almost all of them) can form biofilms, both *in vitro* and, probably, *in vivo*. These structures are probably the main form of life for all environmental NTM, and probably are important in the life cycle of *M. tuberculosis* and other members of its complex. The importance of mycobacterial biofilms in modern medicine is beyond doubt, is considered nowadays as the key pathogenic factor for most NTM diseases, and probably could have a role in the pathogenesis of tuberculosis, too. The presence of these structures is also of crucial importance in the management of patients because of the resistance of the sessile bacteria against most antibiotics. Trying to overcome this problem, some strategies have been developed and others are under research. The growing importance of these microorganisms in modern medicine made these efforts more important than before, because we need more tools to fight against these emerging pathogens.

CRediT authorship contribution statement

Maria-Carmen Muñoz-Egea: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Arij Akir:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Jaime Esteban:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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