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RESISTANCE MECHANISMS OF *Mycobacterium tuberculosis* IN THE TUBERCULOSIS PATHOGENICITY IN HUMANS: AN OVERVIEW

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ABSTRACT

Tuberculosis (TB) is a chronic and serious infectious disease caused by *Mycobacterium tuberculosis* that mainly affects the lungs, but it is also capable of infecting other organs/tissues in the body, which triggers extra-pulmonary TB. In recent years, there has been an increase in the number of re-emerging TB cases due to resistance of *M. tuberculosis* to the antibiotics used to treat this disease. On top of that, there is the emergence of multidrug-resistant *M. tuberculosis* for which many of the antibiotics previously used have no effect. For these reasons, it was aimed to investigate the resistance mechanisms of *M. tuberculosis* in the TB pathogenicity in humans, considering this as a factor associated with re-emergence cases of this disease. Thus, it was carried out an integrative literature review based on articles selected in the SciElo, PubMed and Science Direct databases by using terminology in Portuguese and in English. Studies highlighted that the resistance mechanisms of *M. tuberculosis* consist of the emergence of mutations in target-genes naturally selected over time, the presence of efflux pumps and some lipid substances in the bacterial cell wall that provide impermeability to the antibiotics with cytoplasmic activity. Furthermore, the inappropriate use of antibiotics during the antibiotic-therapy period causes the emergence of other types of resistance. Therefore, special attention must be given to the correct use of antibiotics during the TB treatment, as well as the development of new effective drugs against multidrug-resistant bacteria strains.

Keyword: Antibiotic-Therapy; Resistant Bacteria; Infectious Disease.

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INTRODUCTION

Tuberculosis (TB) is characterized as a chronic and serious infectious disease that has afflicted humanity for a long time (KHAWBUNG; NATH; CHAKRABORTY, 2021). The etiological agents of TB are bacteria gathered in a complex called *Mycobacterium*, in which there are two main species that occur in Brazil: *Mycobacterium bovis*, which is common in cattle, and *Mycobacterium tuberculosis*, which is related to human infections. *M. tuberculosis* is popularly known as Koch's Bacillus (KB) in honor of its discoverer, Robert Koch, one of the founders of modern microbiology along with some important studies related to the epidemiology of transmissible diseases (FERRI *et al*., 2014; RABAHI *et al*., 2017).

M. tuberculosis principally affects the lungs, in which the granulomatous response associated with intense inflammation and tissue damage is a clinically important finding to take into account (CAMPOS, 2006; MOUTINHO, 2011). As the bacteria spread through the bloodstream, they can strike different organs and tissues (extra-pulmonary TB), which results in moderate to severe injuries with a high mortality rate. The clinical forms of extra-pulmonary TB are differentiated based on the infection degree and on the tissues and/or organs in which the bacilli are installed (NOGUEIRA *et al*., 2012). Their presence in the body produces an infectious process that leads to the main symptoms of this disease: fatigue, weakness, fever, weight loss and night sweats (FERRI *et al*., 2014).

However, it should be noted the symptomatic period variation from person to person, since it depends on the immune system mingled to risk factors, such as, the use of certain medications, alcoholism, smoking, malnutrition, and HIV infection (DE LOUREIRO MAIOR *et al*., 2012; PADRAZZOLI *et al*., 2019). Although these factors may contribute to the emergence of TB cases, studies report that it has been occurring especially due to the *M. tuberculosis* resistance to the antibiotics used in the treatment of this disease (CAMPOS, 2009; ALÓS, 2015; Da COSTA; JÚNIOR, 2017; GÓMEZ-TANGARIFE *et al*., 2018; KHAWBUNG; NATH; CHAKRABORTY, 2021).

In fact, the appearance of resistant bacterial strains leads to an increase in the number of deaths, especially in immune-compromised patients. In addition, there is the emergence of multidrug-resistant *M. tuberculosis*, for which many of the antibiotics previously used do not grant any significant effects (DA SILVA, 2020). According to Rossetti *et al*., (2012), this fact causes great concern for patients affected by this disease, as it contributes to the increase in the number of deaths. Therefore, the possible solutions that emerge in order to mitigate such problems focus on the diligent use of antibiotics in the TB treatment, both by the health professional and by the patient during the antibiotic-therapy period, as well as in the development of new effective antibiotics against multidrug-resistant bacteria (MOTA *et al*., 2010; NAHID *et al*., 2016; SCHÖN *et al*., 2017; DA SILVA; LYRA; CHAVES, 2021).

Given the above, this work aims to investigate the resistance mechanisms of *M. tuberculosis* in the TB pathogenicity in human beings in overall, considering it as a factor associated with re-emergence cases of this disease.

METHODOLOGY

This study is characterized as an integrative literature review of an exploratory and investigative field, which allows the gathering of different information in order to formulate general conclusions about a given area of knowledge, through a synthesis of studies published in different databases (NETO *et al*., 2021). For that, the following steps were conducted:

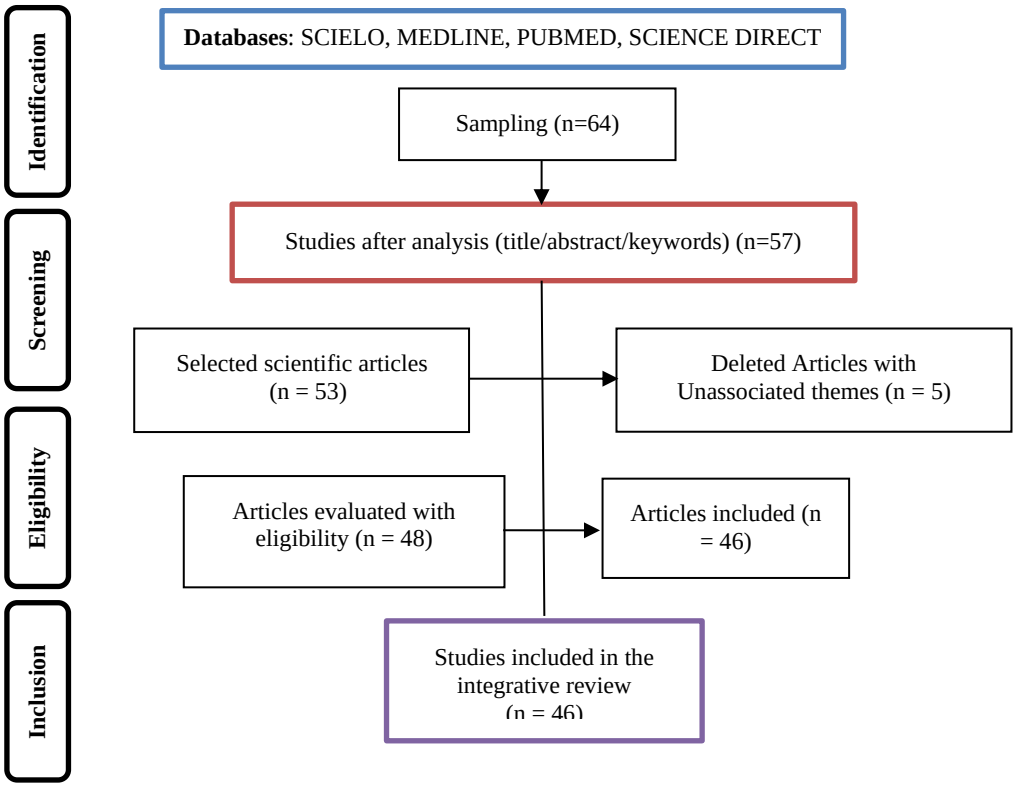
I. Identifying the theme for the elaboration of the integrative review;
II. Establishing the inclusion and exclusion criteria for studies or literature search;
III. Defining the information to be extracted from the selected studies;
IV. Evaluating the studies included in the integrative review and presentation of them.

The sources used in this research were: *Medical Literature Analysis and Retrieval System Online* (MEDLINE), *National Library of Medicine National Institutes of Health* (PUBMED), in addition to *Scientific Electronic Library Online* (SCIELO) and *Science Direct*. It was used the advanced method search based on the following categories: title, abstract and keywords. In each database, the subject descriptors were delimited and crossed by using the terms "AND"/"OR": "Resistance mechanisms of *Mycobacterium tuberculosis*", OR "multidrug-resistant *Mycobacterium tuberculosis*", AND "Tuberculosis re-emergence cases in sensitive patients" OR "Tuberculosis re-emergence cases in human beings".

Then, the articles were submitted to a filtering process consisting of the inclusion criteria: articles available electronically with full text online; in time horizon, classified as review articles, published in

Portuguese and in English. It followed the methodology previously described in the study carried out by Neto *et al*., (2021). The temporal scope of publication included works published in the last decade (Figure 1).

Figure 1. Flowchart of the article search and selection process.



Source: Developed by the Authors (2021) based on the methodology proposed by Neto *et al*., (2021).

RESULTS AND DISCUSSION

As previously pointed out, it has been observed in recent years an increase in *M. tuberculosis* resistance to antibiotics used in the TB treatment. Several studies have suggested that this resistance is due to the natural selection of bacterial strains capable of overcoming the effects of antibiotics on them, which results, consequently, in the proliferation of potentially pathogenic *M. tuberculosis* (SIQUEIRA, 2016; SCHÖN *et al*., 2017; FURTADO *et al*., 2019; GOOSSENS; SAMPSON; VAN RIE, 2020). From these resistant strains, multidrug-resistant bacterial strains are derived as one of the main reasons for TB re-emerging cases. As a matter, the emergence of multidrug-resistant *M. tuberculosis* strains is a phenomenon intensified by human carelessness mostly because of the erratic supply of antibiotics for the TB treatment, as well as the inadequate prior prescription and the poor adherence that many patients present to the antibiotic-therapy period (MOUTINHO, 2011; KHAWBUNG; NATH; CHAKRABORTY, 2021; DA SILVA; LYRA; CHAVES, 2021).

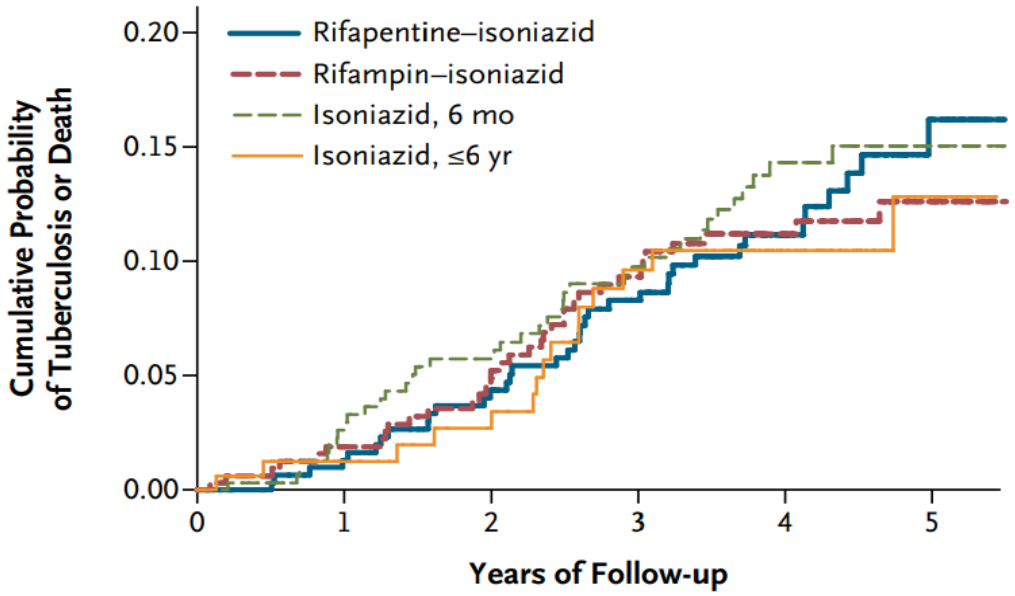
Moreover, the effects of antibiotics on bacteria consist of inhibiting targets for metabolic pathways essential to pathogen survival, including cell wall synthesis, protein transcription, translation, and DNA replication, which causes microorganism growth depletion or cell death without any adverse effects on human health (MOTA *et al*., 2010). In view of this, the main bacilli resistance mechanism is linked to their ability to survive in the medium containing antimicrobials owning to the appearance of new mutations in target-genes that are naturally selected over time (GURGEL; CARVALHO, 2018; GÓMEZ-TANGARIFE *et al*., 2018). According to Gygli *et al*., (2017), these mutations can grant antibiotic resistance through modification or overexpression/prevention of drug activation. Essentially, bacteria that become resistant to antibiotics can

exaggeratedly proliferate in the host organism, which hence results in generalized infections and, ultimately, it leads to the death of the individual (ALÓS, 2015; GOOSSENS; SAMPSON; VAN RIE, 2020).

Based on the existence of prior treatments, resistant bacteria that cause resistant TB in susceptible patients are classified as having acquired or primary resistance. The World Health Organization (WHO) defines acquired resistance when resistant *M. tuberculosis* is isolated in patients treated for TB for one month or more and primary resistance when resistant bacilli are isolated in patients without a previous treatment history, generally those who are immune-compromised. In addition to acquired and primary resistance, many authors consider the existence of intrinsic resistance of *M. tuberculosis* to the majority of antibiotics available for the TB treatment (ALMEIDA; PALOMINO, 2011; Da COSTA; JÚNIOR, 2017; GÓMEZ-TANGARIFE *et al*., 2018).

According to studies, the intrinsic resistance of the *M. tuberculosis* results from the evolutionary history complex itself which comprises some antibiotic-producing species that developed some mechanisms to protect themselves from the action of some antibiotics, such as: Isoniazid, Rifampicin, and Ethionamide (MORRIS *et al*., 2015; GYGLI *et al*., 2017). Because of this, several antibiotics currently used to treat TB are not effective, and it is also necessary to treat the patient with specific antibiotic combinations in an attempt to eliminate resistant strains (Da COSTA; JÚNIOR, 2017) (Figure 2). Nevertheless, the drug itself acts as a selective medium by eliminating bacteria that bear sensitive genotypes and, at the same time, by promoting the proliferation of bacteria with resistant genotypes (gradual acquisition of antibiotic resistance over the years of follow-up). This becomes even more difficult to deal with in patients who are in the risk group, for instance, patients with HIV (MARTINSON *et al*., 2011; SAMANDARI *et al*., 2011).

Figure 2. Cumulative probability of TB or death over the years of follow-up in patients treated with Rifapentine/isoniazid weekly for 12 weeks, Rifampin/isoniazid twice a week for 12 weeks, Isoniazid daily for 6 months, and Isoniazid daily for up to 6 years.



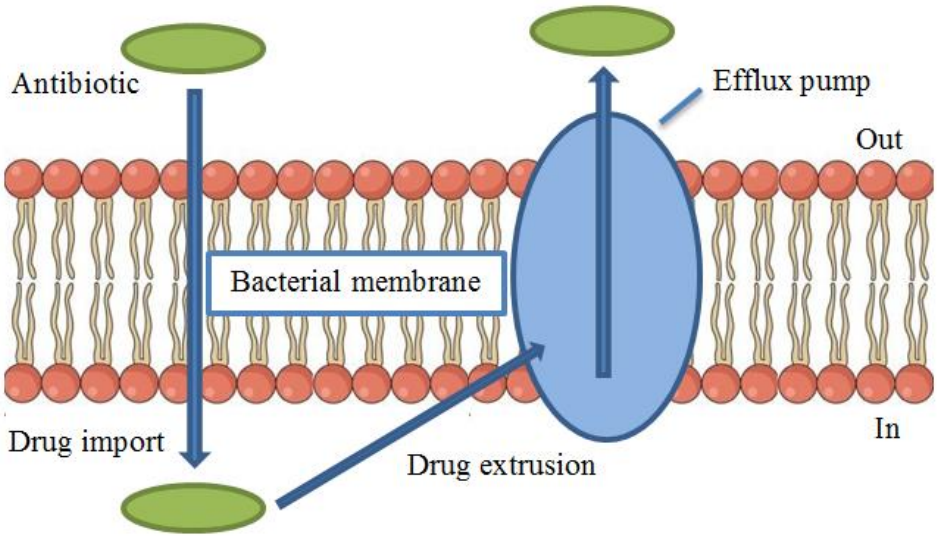
Source: Martinson *et al*., (2011).

As pointed out in clinical and laboratory studies, the mechanism of intrinsic resistance resides specially in the presence of complex lipids associated with mycolic acid and other substances present in the cell wall of the microorganism and it provides impermeability to the entry of antibiotics with cytoplasmic activity, which contributes to the M. tuberculosis pathogenicity and virulence (BAILO; BHATT; AÍNSA, 2015). Thus, the cell wall acts as a natural barrier and the thickening of its structure in response to antibiotic stress was proposed to be resulted in

a drug-tolerant state (NGUYEN, 2016). Similarly, manifold adaptations in *M. tuberculosis*'s altered redox homeostasis under drug pressure can influence cell wall permeability and it may contribute to a drug tolerant state as well (SINGH et al., 2019; GOOSSENS; SAMPSON; VAN RIE, 2020).

Moreover, this bacterium has several efflux pumps (i.e., transmembrane protein transporters) that pump various compounds, including antibiotics out of the cell, thus preventing their action on the microorganism (GÓMEZ-TANGARIFE et al., 2018) (Figure 3). The efflux pump promptly excretes the imported drug into the bacteria through a cascade of biochemical processes that involve the activation of transmembrane receptors and specific phosphorylated molecules in order to activate other molecules in an intrinsic biochemical reaction that is genetically up-regulated (GYGLI et al., 2017).

Figure 3. Schematic diagram showing the basic drug efflux mechanism in *M. tuberculosis.*



Source: Developed by the Viana (2021) based on Singh *et al*., (2019).

It is beyond the scope presented in this review to explain these mechanisms. Notwithstanding, it ought to be noted that the up regulation of the efflux pump expression works as an adaptive mechanism that can be activated upon drug pressure in genetically susceptible *M. tuberculosis* strains (GOOSSENS; SAMPSON; VAN RIE, 2020). According to these authors, efflux pumps have been found to be up regulated under antibiotic stress, either a specific drug or multiple structurally unrelated drugs. For example, the up regulation of the efflux pump activity and the metabolic shifting induced by the exposure to Rifampicin may result in cross-tolerance to ofloxacin, another antibiotic commonly used to treat patients with TB (LOUW *et al*., 2011). Other similar cases were observed in other studies (Table 1).

Table 1. Efflux pumps up-regulated under antibiotic stress.

Efflux pump	Induced under exposure to	Reduces susceptibility to	References
Rv1258c	Rifampicin Capreomycin	Rifampicin	Burian *et al*., (2010) Szumowski *et al*., (2013) Walter *et al*., (2015) Morris *et al*., (2015)
Rv3065	Isoniazid Levofloxacin	Multiple drugs	Balganesh *et al*., (2012) Walter *et al*., (2015) Singh *et al*., (2019)
Rv0849	Isoniazid Rifampicin	Rifampicin Amikacin	Balganesh *et al*., (2012) Li *et al*., (2015) Khawbung; Nath; Chakraborty (2021)
Multiple efflux pumps and transporter genes	Rifampicin	Rifampicin Ofloxacin Streptomycin	Louw *et al*., (2011) Walter *et al*., (2015) Khawbung; Nath; Chakraborty (2021)

Source: Developed by Viana (2021).

A pertinent factor associated with this intrinsic resistance, which can contribute to the TB re-emergence cases even in patients who have already had this disease, is that bacteria may become less susceptible to the attack proportionated by the body's defense cells (SIMONS *et al*., 2018). When *M. tuberculosis* invades the organism, it becomes a "foreign body" that is rapidly phagocytosed by macrophages. Some of the bacilli manage to escape this phagocytosis process due to a viscous substance produced and secreted by the bacteria's cell wall. On the other hand, bacteria exempt of this substance are easily phagocytosed and they are transformed into phagosomes, right after being destroyed inside the macrophage (WEISS; SCHAIBLE, 2015). Then, this type of cell exhibits pro-inflammatory and anti-inflammatory responses that have a key role in mediating early clearance of *M. tuberculosis* (HUSSELL; BELL, 2014; TORRELLES; SCHLESINGER, 2017).

Namely, this bacterium is recognized by multiple pattern recognition receptors at the cell surface or within the phagosome or even by the cytosolic recognition receptors after phagosomal rupture (MORTAZ *et al*., 2015). Subsequently, the outcome of infection depends on a variety of molecular mechanisms, for instance: phagosome–lysosome fusion, activation of the inflammasome cascade, activation of neutrophils, B and T lymphocytes, production of interferon gamma, antibodies and interleukias (MORTAZ *et al*., 2015; SIMONS *et al*., 2018). The mechanisms involved in this process are complex and it is beyond the scope of this review to explain them. Nonetheless, it is interesting to know that resistant bacteria use elaborate strategies, such as the inactivation of lysosomal enzymes and modifications in the phagosome, which facilitate the bacillus survival and replication, as well as its escape from the macrophage cytoplasm (MOUTINHO, 2011).

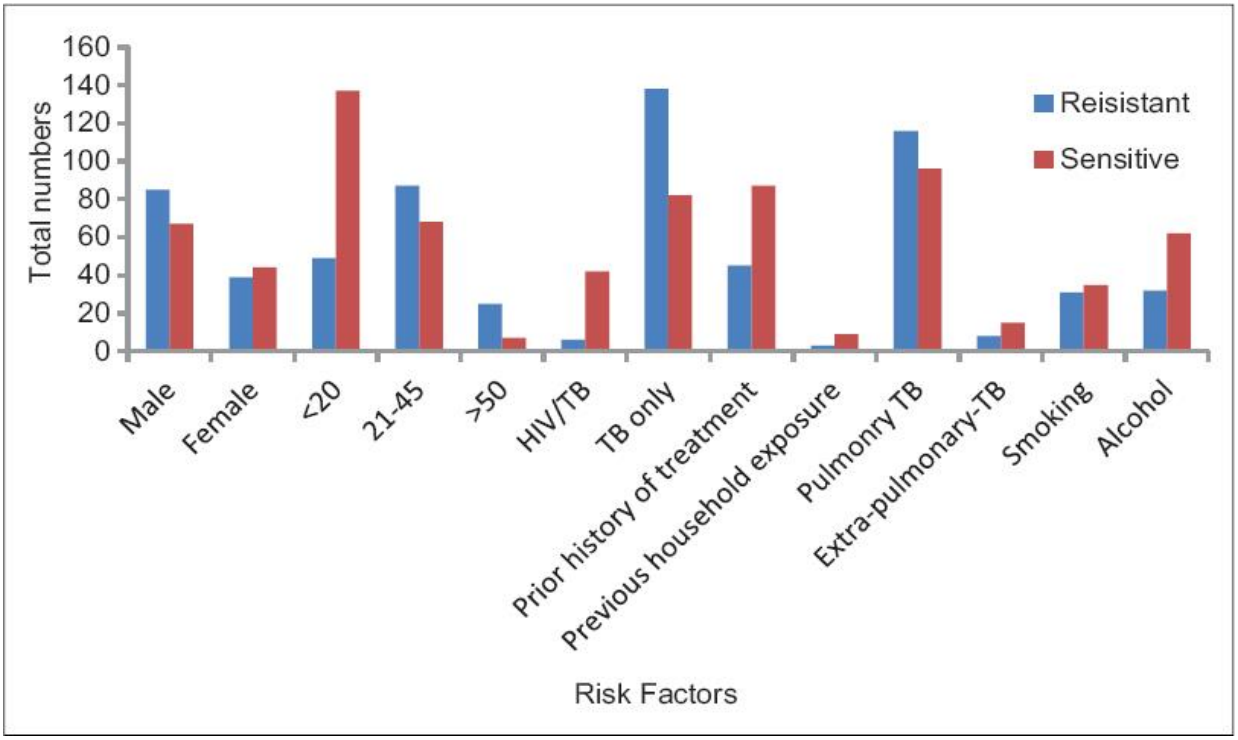
Associated with these resistance mechanisms, especially with intrinsic drug resistance mechanisms, specific genes have already been identified for conferring an increase in the *M. tuberculosis* pathogenicity. Some of these genes are responsible for the metabolism of the Koch's Bacillus and for encoding the proteins, lipids and carbohydrates in its cell wall, thus modulating its virulence (CAMPOS, 2006; GÓMEZ-TANGARIFE *et al*., 2018). For example, *whiB* genes encode transcriptional regulators involved in multiple cellular processes, including cell division, pathogenesis and the response to diverse stresses, including the exposure to antibiotics (ZHENG; LONG; XIE, 2012). In *M. tuberculosis*, *whiB3* and *whiB7* have been associated with intrinsic drug resistance (GEIMAN *et al*., 2016).

Gomez and McKinney (2014) point out that, during infection, *M. tuberculosis* may find itself confined in some compartments where the access to oxygen and nutrients is reduced. In order to survive, the bacillus enters in a dormant state, so its division ceases and its metabolism is minimized, which gives it a temporary resistance to certain antibiotics. Following this point of view, it is possible to characterize the phenotypic resistance, which is, the ability of some bacteria to survive from the action of some antibiotics without suffering any mutation that gives them acquired resistance (ALMEIDA; PALOMINO, 2011). This phenomenon is distinct from intrinsic resistance because it is not associated with

genetic alterations and the microorganism can become susceptible to the antibiotic when the stressful conditions are removed and it divides again by splitting (KARAKOUSIS; WILLIAMS; BISHAI, 2008). Together, these resistance mechanisms culminate in the emergence of multidrug-resistant *M. tuberculosis* strains, for which many of the antibiotics previously used have no effectiveness (GOOSSENS; SAMPSON; VAN RIE, 2020; KHAWBUNG; NATH; CHAKRABORTY, 2021).

In general, multidrug-resistant bacteria are defined as those ones not susceptible to at least one agent in three or more categories of antimicrobials (FURTADO *et al*., 2019). As claimed by Gurgel and Carvalho (2018), this multidrug resistance is due to the indiscriminate use of antibiotics by patients who do not have prior knowledge and decide to self-medicate, as well as the incipient training of professionals involved in the selection of antimicrobials, combined with the scarcity of specific treatment protocols. Siqueira (2016) emphasizes that economic, political and cultural factors have contributed to the growth of self-medication in the world, making it a public health problem, especially because the greater availability of drugs on the market generates greater familiarity of the lay users with the drugs (DA SILVA, 2020). Besides, multidrug-resistant tuberculosis may become prevalent because it includes some risk factors, namely age, gender, TB treatment, co-infection status (HIV, for example), pulmonary or extra-pulmonary TB, smoking history, and alcohol consumption (Figure 4).

Figure 4. Prevalence of multidrug-resistant tuberculosis according to risk factors.



Source: Journal of Global Infectious Disease (2020).

The specific mechanisms why men are more affected than women remain unknown. Nonetheless, it is necessary to consider the possibility that certain genetic influences contribute to a greater or lesser progression of this disease according to gender. Intriguingly, the young population (<20 years) is more susceptible to TB than the older population with regard to sensitivity. Patients with a prior history of treatment may become sensitive because of the constant exposure to the drugs, whilst bacteria strains become more resistant. Similarly, patients with HIV are more sensitive since CD4+ lymphocytes are negatively affected by this co-infection (MARTINSON *et al*., 2011). Therefore, the treatment of TB-resistant forms requires the use of drugs from the class of second-line antimicrobials, which implies in higher costs, greater toxicity for the patient and longer duration of the antibiotic-therapy period (LAPAUSA; PAREJA; ASENSIO, 2013; Da COSTA; JÚNIOR, 2017; SINGH *et*

al., 2019).

FINAL CONSIDERATIONS

To sum up, the main resistance mechanisms of *M. tuberculosis* to antibiotics used in the TB treatment in humans involve: the emergence of new mutations in target-genes naturally selected over time (natural resistance); the presence of certain lipid substances in the bacterial cell wall, as well as the existence of efflux pumps that take away/remove the antibiotic from inside the bacteria (intrinsic resistance). As pointed out in this review, other resistance forms may arise due to the inappropriate use of antibiotics during the TB treatment period (acquired resistance), or when the immune system is weakened because of other diseases, nonetheless without having prior treatments for TB (primary resistance).

Of importance, we have to consider the appearance of multidrug-resistant *M. tuberculosis* to several antibiotics previously used in the antibiotic-therapy history of this disease. Since resistance and multidrug resistance are the most relevant factors responsible for TB re-emergence cases in human beings, it is indispensable to adopt more effective treatment strategies in order to minimize the *M. tuberculosis* resistance and multi-resistance. As a matter of principle, this fact is based not only on the development of new compounds with better efficacy and safety profiles than those currently available to treat TB, but also on their proper use by patients along with the correct recommendations given by the health professional who must reliably prescribe the antibiotics and the respective length of treatment, conditions that vary from patient to patient.

Likewise, better knowledge of *M. tuberculosis* resistance mechanisms to antibiotics will contribute to the identification of therapeutic targets in the sense of designing new diagnostic tests and/or improving the methods currently available for detecting bacteria that cause resistant TB. Finally, future clinical and laboratory studies must be carried out in order to produce reliable antibiotics, which is an essential factor to delay the development of bacterial resistance and, thus, to avoid the appearance of multidrug-resistant bacteria strains.

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