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Review scientific paper

TUBERCULOUS AND NONTUBERCULOUS MYCOBACTERIA IN HUMAN AND ANIMAL INFECTION[2*]

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Abstract: Within the genus Mycobacterium (M.) more than 170 different types of mycobacteria have been identified. In relation to humans, they are divided into three groups. M. tuberculosis complex, which includes ten species that cause tuberculosis in mammals. The type of M. tuberculosis within M. tuberculosis complex remains the major cause of tuberculosis in humans in the world. Except for a long time known species (M. bovis, M. africanum, M. microti, M. canetti, M. caprae), new members of the group have recently been discovered. M. pinnipedii in seals, M. munghi in mongoose, M. orygis in arabian oryx and M. suricattae in the meerkat. The same causes have been proven in people living nearby. M. leprae is the cause of the leprosy in humans. The disease has been proven in nine banded armadillos (Dasypus novemcinctus) and represents the natural reservoir of M. leprae. The largest number of mycobacteria (more than 160 species) belongs to nontuberculous mycobacteria. They are found in the environment, they are very resistant and adapted to growth and development, and to humans and animals are often exposed to them. Some are important potentially pathogenic species and they sometimes cause severe pathological processes in humans and animals.

Key words: mycobacteria, environment, humans, animals

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INTRODUCTION

Mycobacterium is the single genus within the family of Mycobacteriaceae. The number of species within the genus Mycobacterium has been changing over the last few years, and more than 170 different species have been identified. Each year, three to ten new types of mycobacterium are discovered (Tortoli, 2014). In the period from 2003 to 2012, more than 60 different types of mycobacteria were detected (Biet and Boschiroli, 2014; Žolnir-Dovč and Pate, 2015). In relation to humans, the genus Mycobacterium can be divided into three main groups: 1. Mycobacterium tuberculosis complex, this group includes species that cause tuberculosis in mammals (M. tuberculosis, M. africanum, M. canettii, M. bovis, M. caprae , M. microti, M. pinnipedii, M. mungi, M. orygis, and in 2013 the species M. suricattae was described); 2. Mycobacterium leprae - this group belongs to the M. leprae species that causes leprosy in humans; 3. Nontuberculous mycobacteria (NTM) - includes all other species (> of 160 species), which, unlike the previous groups, doesn't include obligate pathogens. Most of these mycobacteria are saprophytes, symbionts and commensals, and are found in our environment. Some of them may be potentially (opportunistic) pathogens in animals and humans, and man and animals may be infected by direct contact or aerosol (Van Ingen, 2013). It is known that pathogenic mycobacterium have their preferred hosts, but occasionally they can cause infection in other species. Diseases caused by mycobacterium in domestic animals are usually chronic and progressive. Members of the M. tuberculosis complex cause very different pathological changes in different types of mammals (Table 1). (Quinn et al., 2011).

Table 1. Review of mycobacterium pathogenic to animals and humans (Quinn et al., 2011).

Mycobacterium Species	Main host	Occasionally infected species	Disease
M. tuberculosis complex			
M. tuberculosis	Man, primates (captivated)	Dogs, cattle, psittacines, canaries	Tuberculosis (the whole world)

M. bovis	Cattle	deer, badgers, opossums,cats, man, other mammals	Tuberculosis
M. africanum	Man	Sometimes other types of mammals	Tuberculosis (mainly Western Africa)
M. canettii	Man		Tuberculosis (mainly Eastern Africa)
M. microti	Voles	Sometimes other types of mammals	Tuberculosis
M. caprae	Goat	Cattle	Tuberculosis
M. pinnipedii	Seal, sea lions	Sometimes other types of mammals including humans	Tuberculosis
M. avium kompleks	Many bird species except psittacines	Pigs, cattle	Tuberculosis
M. marinum	Fish	Humnas, aquatic mammals, amphibians	Tuberculosis
M. ulcerans	Man	Koala, opossum	Buruli ulcer
M. leprae	Man	Armadillos, chimpanzees	Leprosy
M. lepraemurium	Rats, mice	Cats	Rat leprosy, Feline leprosy
M. avium subsp. paratuberculosis	Cattle, sheep, goats, deer	Other ruminants	Paratuberculosis
Unspecified rapidly growing mycobacteria	Cattle		It is classified as skin tuberculosis (causes bovine sensitization during tuberculinization)
M. senegalense M. farcinogenes	Cattle		Chronic lymphadenitis

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MYCOBACTERIUM TUBERCULOSIS COMPLEX

Species from the M. tuberculosis complex remain the main causes of tuberculosis in the world, especially in developing countries, despite considerable progress in diagnosis and treatment (Sinha et al., 2016). M. tuberculosis is the cause of tuberculosis in humans, and occasionally it can cause tuberculosis in animals. It appears in the whole world. It can be divided into two major types: the classical type originally isolated by Koch and the South Indian or Asian type. The South Indian or Asian type is isolated in Madras in southern India, and it differs from a classical in regard to low virulence for guinea pigs, it is virulent for humans and causes similar illness as the classical type. About 60% of the tuberculosis isolated in Madras region was of this type, and it was discovered in Asian communities and in other parts of the world. The incidence of infection with M. tuberculosis in animals decreases in proportion to the rarer occurrence of tuberculosis in humans. The following animals are susceptible to M. Tuberculosis: donkeys, horses, cattle, carnivores, pigs, elephants, aquatic mammals, deer, antelopes and psittacines (Grange and Redmond, 1978; Smith, 2003) M. bovis is primarily pathogenic to cattle but goats, camels, horses, pigs, dogs and cats are also susceptible to this bacterium. M. bovis causes a small number of cases of tuberculosis in humans. The causative agent in many countries has economic significance in wild and domestic animals around the world, especially in underdeveloped countries where there is little data on the incidence of M. Bovis infection in humans (LoBue et al., 2010).

M. africanum, a common cause of tuberculosis in western Africa, was first recognized in Senegal in 1968 as a subspecies of the M. tuberculosis complex. It is divided into two variants: the African I variant , which is isolated from the man in East Africa and the African II variant isolated in West Africa and similar to M. bovis. It is similar to M. bovis because it's microaerophilic and susceptible to TCH, but it is also similar to M. tuberculosis due to its susceptibility to pyrazinamide. Isolates from Africa (Dakar, Mauritania) are more similar to M. bovis, while those from eastern Africa (Rwanda and Burudni) are similar to M. tuberculosis. Biochemical tests of M. africanum give very variable results, so molecular genotyping is used in the identification. A revised classification was proposed including West African 1 and West African 2 as distinct sub-species within the M. tuberculosis complex (De Jong et al., 2009).

M. microti was first isolated from tuberculous processes in voles. It is slightly different from M. tuberculosis and some researchers consider it to be a subspecies of M. tuberculosis. Tuberculosis in wild rodents was first discovered in 1927 as part of a study of cyclic density changes in vole populations. Common voles, wood mice and various

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other types of mice are particularly susceptible to infection with M. microti. However, other small mammals such as guinea pigs, rabbits, mice and rats are resistant to M. microti infection, even at high doses of infection. Sporadic cases are described in larger mammals (cattle, llama, cat) and in humans (Emmanuel et al., 2007). M. canetti was first described by the French microbiologist Georges Canetti in 1969. In 1997, it was described in more details on the basis of isolates isolated from a 2-year-old Somali child with lymphadenitis. Later, abdominal lymphatic TB was diagnosed in a 56-year-old Swiss man with HIV infection who lived in Kenya. Miltgen et al. (2002) identified an unusual type of mycobacteria in two patients with pulmonary tuberculosis. M. canettii species was identified from the samples. Tuberculosis caused by M. canetti appears as an important disease in southern Africa. As traveling to this area becomes more common, and techniques for identification of mycobacteria are improving, it is expected that the number of diagnosed cases caused by this species will be higher. Possible natural reservoirs and mode of transmission are still not fully known (Van Soolingen et al., 1997; Pfyffer et al., 1998).

M. caprae is a new member of the M. tuberculosis complex, isolated in 1999 from the lymph nodes and lungs of goats. By its phenotypic and genotypic traits it differs from other members of this complex. Several years later (2002 and 2003) it was confirmed that this was a new species called Mycobacterium caprae. M. Caprae is a common cause of bovine tuberculosis in many countries of Europe, identified in deer and wild boars. In 2006, it was proved in cattle, pigs and people in Croatia (Aranaz et al., 2003; Cvetni et al., 2007). In 2006, it was detected in cattle, pigs and people in Croatia (Aranaz et al., 2003; Cvetni et al., 2007).

M. pinnipedii is a species isolated from seals in Australia, Argentina, Uruguay, Great Britain and New Zealand. A comparison of isolates from seals in Australia, Argentina, Uruguay, Great Britain and New Zealand was undertaken to determine their relationships to each other and their taxonomic position within the complex. Isolates from six species of seals were compared to representative and standard strains of the M. tuberculosis complex. Based on host preference, phenotypic and genetic tests, isolates differed from other species within the M. tuberculosis complex. Seals appear to be the natural host for this organism causing granulomatous lesions in the peripheral lymph nodes, lungs, pleura, spleen and peritoneum. Cases of disseminated disease have been found. The causative agent is thought to be the most commonly transmitted by aerosol (Cousins et al., 2003).

Several epizootics of tuberculosis in banded mongoose (Mungos mungo) caused by M. mungi, have been described. in the Chobe District in Botswana. Banded mongooses are social animals living in close association with humans and they

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scavenge human waste. Tuberculosis disease in banded mongooses was initially identified in 2000 and infection spread through cities and the national park. The causative agent was identified by its characteristics similar to those of the M. tuberculosis complex (Alexander et al., 2002). From 2000 to 2010 there were seven epidemics with a higher number of banded mongooses, and the disease was identified in broad areas, including protected areas and urban centers. Tuberculosis was detected only in mongooses and humans. The estimation and distribution of tuberculosis in humans has not been performed. Isolation of the new agent presents a new threat to human health (Alexander et al., 2010).

M. orygis is a causative agent of tuberculosis in animals and humans from Africa and South Asia. It is first isolated from the Arabic oryx antelope (Oryx leucoryx). M. orygis was first characterized based on examination of 22 isolates ,eleven of these isolates were from animals (a and 11 were from humans from South Asia. It was proven to cause tuberculosis in animals and people from Africa and South Asia. Mycobacteria were isolated from samples originating from gazelles, deer, antelopes and water buffaloes. Bacterial isolates from antilopes are phylogenetically

different from other members of the M. tuberculosis complex, and it was proposed that M.orygis was attributed a subspecies status (Van Ingen et al., 2012).

M. suricattae is a microorganism that causes tuberculosis in meerkats (Suricata suricatta). Genetic analysis has shown that it is a new member of the Mycobacterium tuberculosis complex and is very similar to M. mungi. A study of meerkats in the Kalahari Desert shows that the disease is caused by a unique strain belonging to the M. tuberculosis complex. The new species is called M. suricattae (Parsons et al., 2013). Tuberculosis was first diagnosed in free-living meerkats in South Africa's Kalahari Desert with detailed description of epidemiology and pathology of the disease (Drewe et al., 2009; Drewe, 2010). Microbacteria previously isolated from meerkats were usually identified as M. tuberculosis (Alexander et al., 2002), M. bovis (Drewe et al., 2009) or as a member of the M. tuberculosis complex (Drewe, 2011). The authors express concern about the appearance of tuberculosis in meerkats, and they believe that this is the result of anthropogenic exposure of these animals. Such infected populations may pose a risk for infection of other wild and domestic animals and humans (Drewe et al., 2009).

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MYCOBACTERIUM LEPRAE

M. leprae takes a special place in the division of mycobacteria because in vitro cultivation is not generally possible in spite of many efforts (Pattyn, 1994). This does not mean that in certain environmental conditions it can not be reproduced. One of the properties is that M. leprae is pathogenic to humans. In the US, Louisiana and Texas, leprosy has been detected in naturally infected armadillos (Dasypus novemcinctus). The disease has also been identified in one species of monkey (Cercocebus atys) and in chimpanzees (Walker and Lochwood, 2007).

NONTUBERCULOUS MYCOBACTERIA

Nontuberculous mycobacteria (NTM) are opportunistic pathogens of humans and animals. They are found in a wide variety of habitats to which humans and animals are exposed, including drinking water distribution systems and household water and plumbing, soil and dust. Human activities have had direct impacts on their ecology and thereby their epidemiology. In the middle of the 20th century mycobacteria that do not cause tuberculosis, are divided in four groups according to the rate of growth, the morphology of colonies and the production of pigments in light: slow-growing mycobacterium (non-chromogens, photochromogens and scotochromogens) and rapid growing mycobacterium. Different terms such as "atypical mycobacteria", mycobacteria from the environment, opportunistic mycobacteria or "other mycobacteria except M. tuberculosis" were used for them. Buhler and Pollack (1953) discovered lung disease in humans caused by M. kansasii, which was incredibly similar to tuberculosis. Since then, the attention to the pathogenic potency of nontuberculous mycobacteria has been intensified. The occurrence of human immunodeficiency (HIV) and the finding of a large number of different types of NTM even more increases the interest in these microorganisms. The development of new laboratory techniques, particularly in molecular biology, significantly influenced the detection, identification and evidence of new NTM species, which culminated in the later years of the 20th century. According to clinical relevance, they were divided into conditional pathogens, opportunistic mycobacteria and pure saprophytes (Davidson, 1989; Jankovic-Makek, 2014). NTM are oligotrophic, able to grow at low organic matter concentrations and over a wide range of temperatures and even at low oxygen concentrations. They are resistant to disinfection, heavy metals and antibiotics, and compared to other types of mycobacteria they are highly resistant. NTM have been shown

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to be normal residents of drinking water distribution systems. They are resistant to various antimicrobial agents used for disinfection of drinking water and can spread to water distribution systems (Falkinham, 2010).

NONTUBERCULOUS MYCOBACTERIA AND THE ENVIRONMENT

For almost three decades, it is known that non-tuberculous mycobacteria do not spread person-to-person and it is widely accepted that their source is the environment. The largest number of mycobacteria belonging to the genus Mycobacterium are nontuberculous mycobacteria. These are important, indispensable opportunistic pathogenic microorganisms and sometimes cause severe pathological processes in humans, poultry, birds and fish. Nontuberculous mycobacteria are saprophytes, symbionts and commensals, and are isolated from the environment, most commonly from water and soil, domestic and wild animals, milk and dairy products, as well as from less well-known media such as biofilm, invertebrates and protozoa. Two of the most important factors are the cell wall of mycobacteria and their great adaptability (Biet et al., 2005; Falkinham, 2009; Faria et al., 2013). In Western countries it has been proven that as the number of infections with M. tuberculosis species decreases, the incidence of infections caused by nontuberculous mycobacteria is increasing (Hoefsloot et al., 2013). In the last few years, it has been proven that the amoeba is a large and important reservoir of nontuberculous mycobacteria. In the aquatic system of the hospital, the growth of Mycobacterium avium in Acanthamoeba lenticulata was proven. (Ovrutsky et al., 2013) An important feature of the mycobacterial cell is the presence of a hydrophobic, lipid-rich lipid membrane. Hydrophobicity is one of the most important features because it favors aerosolization, bacterial adhesion to surfaces, biofilm formation and resistance to disinfection and antibiotics. The NTM are oligotrophs, able to grow at low carbon levels , making them effective competitors in low nutrient, and disinfected environments such as water. Biofilm formation and oligotrophia led to survival and growth in drinking water systems and distributions (Falkinham, 2009). There are very interesting differences in the geographical distribution of certain types of nontuberculous mycobacteria, which for now can not be fully explained. The species from the M. avium complex prevail in most western countries and countries of the European Union, followed by M. gordonae and M. xenopi, the other members of M. avium complex (M. Avium-intracellulare) and M. fortuitum are the following most frequently isolated nontuberculous mycobacteria (Van der der Werf et al., 2014). The species of M. avium complex is often isolated in the United States, followed by M. kansasii and M. abscessus. The study carried out in the

Middle East is significantly different, where the main isolated species were M. abscessus, M. fortuitum and M. intracellulare, followed by M. kansasii, M. gordonae and M. avium (Faria et al., 2015). In India M. fortuitum was most commonly isolated. In other Asian countries between the west (Singapore) and the east (Japan), species from the M. avium complex cause most of the infections (Simons et al., 2011).

MYCOBACTERIOSIS IN HUMANS

Nontuberculous mycobacteria can cause mycobacteriosis in humans. The disease mostly affect people with impaired immune system, the elderly, people with already existing lung diseases and occasionally in people with normal immune function. So far about 25 types of NTM is often associated with mycobacteria in humans, other species (of which more than 160) are rarely associated with diseases, and most of them are microorganisms from the environment, so far not described as causing disease in humans (Van Ingen et al., 2013). Mycobacteriosis in humans can be roughly divided into four clinical forms (Griffith et al., 2007). Pulmonary mycobacteriosis is the most common clinical form of mycobacteriosis, and the symptoms are similar to pulmonary tuberculosis and can hardly be distinguished without laboratory diagnostics. They mainly occur in patients with pulmonary disease (eg cystic fibrosis, chronic bronchitis or chronic obstructive pulmonary disease - COPD). Pulmonary mycobacteriosis is usually manifested as slow progressive and very difficult to cure. The most common causes are M. avium and M. abscessus. Other forms of the disease are rare, and most commonly occur as lymphadenitis in children, especially those who are vaccinated with M. bovis BCG vaccine. The most common causitive agents are M. marinum, M. fortuitum, M. chelonae and M. abscessus. The disseminated form of mycobacteriosis is most common in people with a weakened immune system, such as patients with acquired immune deficiency syndrome (AIDS). This type of disease is most commonly caused by mycobacteria from the M. avium complex, M. simiae. There is also kin and soft tissue infection manifested by the formation of subcutaneous nodes, abscesses, ulcers, and are caused by M. abscessus, M. chelonae. Often granulomatous inflammation on the hands and feet can also be caused by the M. marinum species or rapidly growing mycobacteria such as M. fortuitum (Griffith et al., 2007; Van Ingen et al., 2011; Žmak et al., 2013).

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NONTUBERCULOUS MYCOBACTERIA -CAUSATIVE AGENTS OF ANIMAL INFECTIONS

Many nontuberculous mycobacteria are opportunistic pathogens in animals and can cause lymphadenitis, lung, skin, soft tissue, tendon, joint and bone infections (Falkinham, 1999). It is well known that mycobacteria cause fish morbidity and mortality. Mycobacteriosis can occur in saltwater and freshwater fish that live in nature or are grown for human consumption or as decorative aquarium fish. For certain species of fish are M. marinum, M. fortuitum and M. chelonae are among the most common microbacterial agents.These mycobacteria may cause long-lasting illness that is difficult to treat in humans, especially those with low immune system (Gauthier and Rhodes, 2009). M. marinum is a well-known and important mycobacteria that causes skin and soft tissue infections, and infected fish and contaminated water are the sources of infection. This type of mycobacteria is considered the most common nontuberculous mycobacterium that causes outbreaks of lung infections in humans (Aubry et al., 2017).

More mycobacterial species can cause tuberculosis in birds, which is important in poultry production and breeding birds as pets. The most common cause of bird tuberculosis is M. avium, followed by M. genavense, and other less common types of mycobacteria, e.g. M. intracellulare, M. scrofulaceum and M. fortuitum (Dhama et al., 2011). Sensitivity to mycobacteria that causes tuberculosis in bird varies from species to species. The most sensitive is domestic poultry, sparrows, pheasants and partridges, and the most resistant is the domestic pigeon. Infected birds and contaminated water and soil are the most important source of infection, and these types of mycobacteria can survive for months in the environment. The disease is more common in crowded areas with poor hygiene (Tell et al., 2001). Similar differences in sensitivity to NTM were also observed among other animal species. Thus, pigs are particularly sensitive to infection caused by M. avium which can cause much damage to the economy (Cvetnić et al., 2006). Wild birds, pigs and some mammals today are the main reservoir of avian tuberculosis in nature. In the past few years in the poultry industry in the developed world this disease is declining, as a result of many changes in production and positive measures in the past. Lesser-known species of NTM have so far been isolated in domestic and wild animals, but their role in these hosts, especially in the absence of clinical signs and pathomorphological changes, has not yet been clarified (Dhama et al., 2011).

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