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Review

Mycobacterium avium complex infection in pigs: A review

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ABSTRACT

Mycobacterial infections in pigs are caused particularly by the *Mycobacterium avium* complex (MAC) and these infections lead to great economic losses mainly within the countries with high pork meat production. The importance of the MAC infections in humans is rising because of its higher prevalence and also higher mortality rates particularly in advanced countries. In addition, treatment of the MAC infections in humans tends to be complicated because of its increasing resistance to antimicrobial agents. Several studies across Europe have documented the MAC occurrence in the slaughtered pigs - not only in their lymph nodes and tonsils, which are the most frequent, but also in the diaphragmas, other organs and not least in meat. This is why we need both more specific and more sensitive methods for the MAC infection detection. Different PCR assays were established as well as advanced intravital testing by the gamma interferon release test. On the other hand, tuberculin skin test is still one of the cheapest methods of mycobacterial infections detection.

1. Introduction

Nontuberculous mycobacteria (NTM) are a wide group of mycobacteria with the exception of *Mycobacterium tuberculosis* complex and *Mycobacterium leprae* [1]. This heterogeneous section mainly consists of ubiquitous environmental mycobacteria but some of them, above all *Mycobacterium avium* complex (MAC), are ranked among the opportunistic pathogens that can cause a wide range of infections – from localized lymphadenitis, most commonly, to disseminated infections in many kinds of animals and also humans.

Although many countries have been confirmed to be free of bovine tuberculosis, tuberculous lesions could still be found in lymph nodes and rarely in other organs of farm animals – both cattle and pigs [2,3]. Most of these mycobacteria were determined as members of *Mycobacterium avium* complex [4]. Nowadays, mycobacterial infections in pigs are not only believed to be related to the organic pig production [5] but also, based on several recent studies, play an increasing role even in modern pig farms, matched with strong economic impact [6].

Generally, mycobacteria are variously long (1–10 μm), thin, rod-shaped, immovable and non-sporulating bacteria. Except for higher CO₂ tension, they prefer to utilize nutrients with a high content of lipids and this is why culture media enriched by egg yolks and glycerol are used for cultivation in the laboratory [7].

Although mycobacteria are ranked among the Gram-positive bacteria, a radical differential staining technique, called Ziehl-Neelsen, has to be used for microscopic detection of mycobacteria, which are

capable of retaining the primary stain when treated by acid [8]. Mycobacteria included in the MAC could be described as slowly growing bacteria that might produce a yellow pigment in the absence of light. In addition, exposure to light could intensify this pigment production [9].

2. Taxonomy

Taxonomy of mycobacteria was quite difficult and has undergone a revolution with the boom of molecular-biological methods. Previously, the taxonomy of mycobacteria was based on the differentiation according to their morphological and phenotypical characteristics (e.g.: colony growth rate, pigments formation, etc). Mycobacteria were divided into several groups of significance: *Mycobacterium tuberculosis* complex (most pathogenic for humans), *Mycobacterium avium* complex (opportunistic human infections) and a group of other nontuberculous mycobacteria. Species belonging to the MAC group were determined mainly by serotyping in the past and a total of 28 serotypes had been identified [10].

MAC is composed of several members. The basic ones include *M. intracellulare* and *M. avium*, occurrence of other species belonging to this complex is quite rare. The *M. avium* species is further divided into four subspecies: *M. avium* subsp. *avium* (MAA), *M. avium* subsp. *hominissuis* (MAH), *M. avium* subsp. *silvaticum* (MAS) and lastly *M. avium* subsp. *paratuberculosis* (MAP) [11,12]. Turenne et al. (2008) performed a phylogenetic study, which had showed MAH subspecies as a diverse group of microorganisms, whereas MAA/MAS and MAP form

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independent groups [13]. MAP causes the Johne's disease in ruminants [14]. MAA/MAS primarily infect birds, while the primary hosts for MAH are pigs. Nevertheless, members of MAC can cause infections in a wide range of hosts, including humans [15].

3. The importance of the MAC infections in humans

The importance of the MAC infections in humans is constantly increasing due to its growing prevalence and associated mortality, mainly in advanced countries. For example, in Japan the MAC accounts for 80–85% of pulmonary non-tuberculous mycobacterial infections. This infection presents itself as a mixture of two basic radiological patterns: fibrocavitary and bronchectatic; while lobar consolidation and caseous pneumonia are quite rare in immunocompetent patients [16]. Similar findings are documented throughout Europe, for example, in Slovakia *Mycobacterium avium* is also among the most common nontuberculous mycobacteria causing lung disease in humans [1].

The main routes of infection in humans are breathing contaminated aerosol or skin erosion contact with the infectious agent [17]. Treatment of the MAC infections in humans can be difficult and has to integrate both medical and surgical approaches. Moreover, resistance to antimicrobial agents in these mycobacteria has increased nowadays [18].

The management of these non-tuberculous mycobacterial infections in humans is complicated. It tends to be very difficult in case of isolates resistant to antimicrobial agents, for example, *Mycobacterium avium* resistant to macrolides. A very alarming fact is that the survival rates for the macrolide-resistant *Mycobacterium avium* complex infection in lungs and the multidrug-resistant *Mycobacterium tuberculosis* infection are not significantly different [19].

There are many well-known risk factors identified for the MAC infection in humans leading to some level of immunodeficiency: HIV infection, cancer associated reduced immune competence, ongoing transplantation, primary lung disease, e.g. cystic fibrosis [20]. In case of the MAC, immunocompetent patients most frequently suffer from localized mycobacterial infections, such as cervical lymphadenitis [21,22]. On the other hand, MAC is the main cause of disseminated pulmonary infections in immunodeficient patients [23].

4. Sources of MAC

Ground water was proven to play the main role in the environment cycle of NTM. Mycobacteria were isolated from almost all types of water sources (wells, rivers, ponds, lakes etc.). Artesian wells were the only exception [24].

Potentially pathogenic mycobacteria are able to produce biofilms and supposedly due to this fact they could survive for a long time in the environment - both aquatic and terrestrial [25–27]. In addition, members of the MAC were confirmed to be resistant to several disinfectants [28].

Also plants, such as fresh or frozen fruits and vegetables, could be a source of NTM. Dziejzinska and coworkers [29] have proven that almost all of the 178 samples purchased from the market network were contaminated by more than twenty species of mycobacteria, yet, MAC was found only rarely.

Other materials, such as contaminated feedstuffs, bedding materials, kaolin, soil, sawdust, peat and possibly other materials, were identified as natural reservoirs of the MAC, predominantly MAH. Peat-bog is the environment, where mycobacteria proliferate quite easily [26,30–35]. The main sources of MAA are animals, especially wild birds [36]. Also small terrestrial mammals and invertebrates were proven to be vectors of the MAC [37–40].

All these facts are strong evidence that animals and humans are constantly surrounded by mycobacterial opportunists.

5. The MAC occurrence and transmission routes in pigs

Shitaye et al. [41] had been analyzing tissue samples from 3630 slaughtered pigs, which were positive for intradermal test to avian tuberculin throughout 1996–2004 in the Czech Republic. Mycobacteria were isolated not only from 73% (1290 from 1778) pigs with the proof of acid-fast bacteria (AFB) in Ziehl-Neelsen stained tissues but also from 16% (289 from 1852) pigs without the proof of AFB in Ziehl-Neelsen stained tissues. Almost all (95%) of the 1579 mycobacterial isolates belonged to the MAC.

There are quite similar findings across Europe. For example, in Croatia, up to 96% of mycobacterial isolates from the lymph nodes of slaughtered pigs belong to the MAC, as well as in Switzerland, the MAC dominates (91%) above all other kinds of mycobacteria isolated from the altered lymph nodes of slaughtered pigs [42,43]. The MAC infection in pigs could also be the reason for the quarantine of imported pigs [44,45].

Both the MAA and the MAH are proved to cause the infection of the swine gastrointestinal tract with the concentration in the lymph nodes. The main route of infection is the oral route [26,46]. The tonsils are thought to be a reservoir for the oral-faecal route of infection transmission [47]. Since it has been proven that MAH is present in pig tonsils in higher amounts than MAA, the hypothesis that MAH is more likely to spread by pig-to-pig contact than MAA was stronger. Despite this hypothesis, the direct transmission from pig-to-pig has not been clearly proven yet by molecular studies. A high level of genetic diversity of MAH strains has been observed in several epidemiological studies using genotyping tools to assess the origin of these strains, pointing at the environmental source of these infections rather than direct transmission between hosts [48–50]. The main route of infection of MAA in pigs is most likely after ingestion of contaminated materials, for example, bird shedding [36] or other contaminated natural materials [54].

One of the main differences between MAA and MAH is the level of bacteria excretion through faeces in experimentally infected pigs. Although MAA is detected in faeces only sporadically, MAH is excreted alive after six weeks from the infection. This fact supports the hypothesis that MAH creates higher infectious pressure in the pig herds [51].

Lower incidence of the MAA infections than the MAH infections in some countries could obviously be caused by the higher quality biosecurity system at the pig farms, which does not allow the entrance to wild birds, rather than a lower virulence of MAA [51,52]. Detection of MAA in different tissues of pigs, both lymph nodes and meat, points at the higher virulence potential of this subspecies [41,53–55].

Both subspecies of *Mycobacterium avium* – *avium* and *hominissuis* possess the ability to infect and also replicate within macrophages. Nevertheless, MAA was proven to perform higher rates of invasion and replication within porcine macrophages measured by the Macrophage infection assay [56]. Moreover, it has been described that the pro-inflammatory immune response of pigs to the MAA infection is stronger than in the case of MAH [52].

6. Course of the MAC infection in pigs

Experimentally infected animals show a short-term diarrhea very occasionally. There are mainly no clinical signs of infection [51,52]. The first sign that could point to an undergoing mycobacterial infection in the herd is an increasing number of condemned carcasses due to the typical findings in the lymph nodes (or together with the pathological findings in other specific organs) at the slaughterhouses [57].

First line investigation at the slaughterhouses represents the morphological inspection of the carcasses. Gross tuberculosis-like lesions in pigs are primarily situated in the various kinds of lymphatic organs (mainly the mesenteric lymph nodes, less *lymphonodi mandibulares* and Peyer's patches or tonsils), further in diaphragmas and other organs [51,58]. Generally, macroscopic lesions are not very frequently

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