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Review on Pseudomoniasis in Laboratory Animals like Mice

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Summary: Pseudomonas aeruginosa is a dangerous, devastating disease which is difficult to treat by antibiotics easily. As the World Health Organization considers infections caused by Multiple Drug Resistant bacteria is a major public health problem. One of the organisms contributing to this problem is Pseudomonas aeruginosa which is an opportunistic gram-negative pathogen. It is a non-fermentative, aerobic, Gram-negative rod, motile with single terminal flagellum that normally lives in moist environments and it is the most common pathogen responsible for **nosocomical** and community-acquired infections at various body sites including the lower respiratory tract, urinary tract, cornea, and surgical or burn wounds. It results in hematogenous spread of the bacteria to multiple organs. Entry into the vascular system may be facilitated by pseudomonal proteases and bradykinin generated in infectious foci. *P. aeruginosa* grows well in most culture media and colonies are often a distinctive **blue green**.
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1. INTRODUCTION

The World Health Organization (WHO) considers infections caused by Multiple Drug Resistant bacteria (MDR) a major public health problem (Taylor, 2003). One of the organisms contributing to this problem is Pseudomonas aeruginosa MDR, which is an opportunistic gram-negative pathogen. P. aeruginosa has the ability to colonize catheters, breathing tubes, and (infrequently) surgical tools; as a result, it can cause among others things, burn infections, bacteremia, septicemia, respiratory infections and rarely, recurrent endocarditis, mainly in immunosuppressed patients (Welte and Pletz, 2010). Furthermore, P. aeruginosa has a high prevalence in Intensive Care Units (ICUs) because of the ability to form biofilms on catheters, heart valves and breathing tubes (Kerr and Senelling, 2009).

In recent years, both the frequency of MDR microorganisms, as well as the number of antibiotics to which bacteria are resistant, has increased rapidly. A number of ICUs have reported incidents of P. aeruginosa infections resistant to every available antibiotic, leaving a patient with no viable treatments. The problem is compounded when the search for new antibiotics is expensive, arduous and not incentivized. It is often not profitable for pharmaceutical companies to develop new antimicrobials, especially when resistant strains are found within less than two years after their introduction (Kutateladze and Adamia, 2010).

Pseudomonas aeruginosa is the most common pathogen responsible for nosocomical and community-acquired infections at various body sites including the lower respiratory tract, urinary tract, cornea, and surgical or burn wounds (Driscoll *et al*., 2010). P. aeruginosa has some advantages that help to establish acute or chronic infections under various host conditions (Doring and Pier, 2008). One of these advantages is its flagella. Polar flagella provide mobility and chemotaxis, and they also facilitate the adherence to cells and non-living surfaces, which confer the ability to colonize and invade throughout the early phases of infection (Spangenberg *et al*., 1996).

2. PSEUDOMONIASIS IN MICE

2.1. Definition

Pseudomonas aeruginosa is a non-fermentative, aerobic, Gram-negative rod, motile with single terminal flagellum that normally lives in moist environments (Angela *et al*., 2015).

2.2. Etiology

Mostly the Pseudomonas aeruginosa is the cause for Pseudomoniasis.

2.3. Epidemiology

Generally *Pseudomonas spp* are free living in the environment. Free living bacteria, including *P. aeruginosa* are ubiquitous in the environment (water and soil) and may even play a role in a nucleation of rain. They are commonly found in watering system for animals and humans. Unless specifically monitored for and excluded, many animals are likely to transiently harbor this organisms. Animals on long term antibiotics treatment with attendant disruption of gut flora may have longer term colonizations (McNairy *et al*., 2012).

2.4. Pathogens

Occasionally, *P. aeruginosa* can colonise mice body sites, with a preference for moist areas, such as the perineum, axilla, ear, nasal mucosa and throat; as well as stools. The prevalence of colonization by P. aeruginosa in healthy subjects is usually low, but higher colonization rates can be encountered following hospitalization, especially amongst subjects treated with broad-spectrum antimicrobial agents. Colonization is common in the respiratory tract of mechanically ventilated patients, in the gastrointestinal tract of patients receiving anticancer chemotherapy, and on the skin of burn patients. Also, sinks, mops, disinfectant solutions, respiratory equipment, food mixers and other moist environments can act as reservoirs of P. aeruginosa in the hospital setting (Pollack, 2000).

P. aeruginosa is typically an opportunistic pathogen that seldom causes disease in healthy subjects. Normally, for an infection to occur, some disruption of the physical barriers (skin or mucous membranes), or by-passing of them (e.g., by urinary catheters, endotracheal tubes or other invasive devices), and / or an underlying dysfunction of the immune defense mechanisms, such as neutropenia, is necessary. As a consequence, P. aeruginosa is mostly a nosocomial pathogen. According to data from the Centers for Disease Control and Prevention National Nosocomial Infection Surveillance System, in the USA, P. aeruginosa was the second most common cause of nosocomial pneumonia, the third most common cause of nosocomial urinary tract infections, and the seventh most common cause of nosocomial bacteremia. In Europe, P. aeruginosa was found to be the third most common isolate from nosocomial infections in intensive care units (ICUs) (Manfredi *et al*., 2000).

2.5. Pathogenesis

Clinical disease is due to invasion of deep tissues, resulting in hematogenous spread of the bacteria to multiple organs. Entry into the vascular system may be facilitated by pseudomonal proteases and bradykinin generated in infectious foci.

Flagella play a critical role in the initial stages of respiratory tract infection, as shown by comparing the virulence of flic mutants in a neonatal mouse model of pneumonia. There was no mortality in the flic mutants (Feldman, 1998). *P. aeruginosa* flagella are suggested to act in pathogenesis by tethering and adhering to epithelial cells through binding and interaction with epithelial membrane components. However, flagella are also very immunogenic, which renders them susceptible to the host clearance mechanisms and facilitating phagocytic clearance (Doring and Pier, 2008).

Consequently, it is not surprising that flagella have been considered as smart drugtargets for immunotherapy. On the other hand, efforts are underway to develop antimicrobials from classes of compounds for which specific resistance traits do not exist in nature. Therefore, new therapeutic options for *P. aeruginosa* infections can be explored (Krylov *et al*., 2013).

2.6. Interference with research

In mice and rat there is no known interference with research associate with carrier state. But immune deficient animals that will be rendered immune deficient for research purpose or animals intended for cystic fibrosis research should be free from *P. aeruginosa*.

Numerous publications have reported on the effects of *P. aeruginosa* on research involving immune compromised mice and rats. Most reports are from experimental infections. Effects include early death following exposure to radiation, cyclophosphamide treatment, cold stress; increased severity of infection following airway trauma; depressed contact sensitivity to oxazolone; stimulation of T-cell proliferation within splenocytes of nude mice; induction of thymic atrophy via apoptosis; inhibition of wound healing; inactivation of cytokines by bacterial proteases; possible T-cell-dependent immune system suppression mediated by the polysaccharide fraction of LPS; altered fluid transport across the lung epithelium; suppression of delayed hypersensitivity responsiveness; increase in

cardiac excitability and enhanced vulnerability to hypoxic insults; inhibition of macrophage function by bacterial rhamnolipids; and altered behavioral and clinical pathologic parameters following experimental infection of surgical wounds.

In addition, rodents with streptozotocin-induced diabetes mellitus are more susceptible to *P. aeruginosa* infection. Rodent *P. aeruginosa* systems have been developed as models for numerous human diseases and conditions, including indwelling-catheter infections, pyelonephritis, burn trauma, chronic mucosal colonization, immunization strategies, and infection accompanying cystic fibrosis. From these reports, it is apparent that natural infection of immune compromised mice and rats could affect a variety of research projects, depending upon the organ systems affected.

2.7. Clinical sign

In immunocompetent animals and many immunodeficient animals there is no clinical sign associated with P. *aeruginosa* colonization. *P. aeruginosa* becomes a significant clinical problem in neutropenic animals. However, such mice that is iiradiated or treated with anti-mitotic agents (such as many therapeutic compounds) in this severely immune deficient animals, *P. aeruginosa* transits nasopharyngeal or gut mucosal barrier and causes a systemic bacteremia and sepsis. Clinical sign may include death with no premonitory signs, conjunctivitis, nasal discharge or general sign of rodent's illness, include anorexia and refuel fur and hunched posture (Chung *et al.*, 2012).

Clinical signs are generally not observed in immune competent hosts, although the host response to *P. aeruginosa* infection varies among inbred mouse strains. For example, mice of the BALB/c strain are resistant to *P. aeruginosa* lung infection whereas mice of the DBA/2 strain are susceptible. Some immune compromised mice and rats may develop hunched posture, apathy, dullness, shortness of breath, ruffled coat, emaciation, circling movements around their longitudinal axis, and oblique head posture, and some of them will die.

2.8. Pathological lesions

Pathologic lesions are found in affected tissues and consist of multifocal necrosis, abscess formation, and suppuration. Lesions are often most severe in the lungs. Vegetative lesions may be found on heart valves of animals with infected indwelling vascular catheters.

2.9. Transmission

Overall, community-acquired infections by P. aeruginosa are uncommon. The most frequent are: (i) folliculitis and infections of the ear canal, mostly acquired after bathing in contaminated waters; (ii) cheratitis, usually associated with the use of a contact lens contaminated during lens care; (iii) malignant otitis externa with involvement of the underlying tissues and possibly of the temporal bone and basilar skull, primarily seen in diabetics and the elderly; (iv) osteomyelitis of the calcaneus in children, e.g., following puncture wounds through sneakers whose inner pad is contaminated by P. aeruginosa; and (v) endocarditis in intravenous drug users, resulting from the injection of contaminated drug solutions (Feldman *et al.*, 1998).

The latter is the most severe community-acquired P. aeruginosa infection, often requiring valve replacement, and is associated with high mortality rates. *P. aeruginosa* is also an uncommon cause of community-acquired pneumonia, which may occur in subjects (usually middle-aged and with a history of smoking) exposed to contaminated aerosolised water. In these cases, patients rarely receive appropriate empirical chemotherapy and mortality can be high (Prada, 2007).

2.10. Diagnosis

In diagnosis of *P. aeruginosa* infection is by culture and biochemical test identification in animals exhibiting clinical sign, those known to be leukopenic *P. aeruginosa* grows well in most culture media and colonies are often a distinctive **blue green**. *P. aeruginosa* is also fluorescence under ultra violet light.

2.11. Treatment of severe infections caused by multiple drug resistance *P. Aeruginosa*:

In-vitro susceptibility data are essential support for the selection of antimicrobial chemotherapy for P. aeruginosa infections, because of the frequency and variability of acquired resistance shown by clinical isolates. Susceptibility testing is well standardized for most anti-pseudomonal agents, but there are no recommended breakpoints for susceptibility testing of polymyxin B or colistin (Masuda *et al.*, 2000). Minimum inhibitory concentrations (MIC) determination is preferable in the case of these drugs as P. aeruginosa can be a lethal pathogen and the precocity of chemotherapy is critical to the outcome of the infection, empirical regimens adequate for *P. aeruginosa* coverage should always be initiated prior to receipt of the results of cultures and susceptibility testing when infection by this species is suspected.

2.12. The anti-pseudomonal drugs and acquired antimicrobial resistance in *P. Aeruginosa*

P. aeruginosa is intrinsically resistant to many antimicrobial agents, including most b-lactams, the older quinolones, chloramphenicol, tetracycline, macrolides, trimethoprim–sulfamethoxazole and rifampin. The chromosomal b-lactamase, the production of which is inducible, contributes to the intrinsic resistance of this species to ampicillin and to most cephems, which act as inducers and are degraded by this enzyme (Li *et al*., 2000). An overall low permeability of the outer membrane and the presence of a number of active multidrug efflux systems also contribute to the intrinsic resistance or reduced susceptibility of this species to several antimicrobial agents (Poole, 2001).

3. PREVENTION AND CONTROL

To prevent colonization of animals from *P. aeruginosa* the animal must be raised in strict bio exclusion housing as would be necessary for immune deficient mice. Water quality is of considerable importance and ideally should be sterilized before use with immune deficient animals, especially those that are neutropenic.

P. aeruginosa is susceptible to most common disinfectants used in animals' facilities. Theoretically, any chemical and mechanical sterilant will be effective against *P. aeruginosa* in the environment. However, *P. aeruginosa* are commonly found in growing biofilms which may shield it from disinfections sterilization agents unless the biofilm is first mechanically disrupted. To obtain animals without *P. aeruginosa* animals should be rederived through embryo transfer hysterectomy into/onto *P. aeruginosa* free dams (Feldman *et al*., 1998).

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