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“One Health implementation will help protect and/or save untold millions of lives in our generation and for those to come.”

“Between animal and human medicine there are no dividing lines--nor should there be.”

Rudolf Virchow, MD (the father of cellular pathology)

Posted One Health Initiative website July 24, 2013

Submitted exclusively to One Health Initiative website June 28, 2013

***Aspergillus felis – One-health & Public Health Implications**

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Invasive aspergillosis is a global health concern because of high mortality rates and treatment costs. The aetiological agents of aspergillosis are ubiquitous in the environment and the likelihood that infection will occur following inhalation or implantation of spores largely depends on host factors. As the number of immunosuppressed patients worldwide rises, invasive aspergillosis has emerged as a major problem in several groups of these patients. Those at greatest risk include persons with hematological malignancies, hematopoietic stem cell transplant recipients, solid organ transplant recipients, individuals receiving high-dose corticosteroid treatment and persons with neutrophil deficiencies or dysfunction. Emerging at-risk populations include persons with acquired immunodeficiency syndrome, patients receiving intensive care and patients with chronic obstructive pulmonary disease.

Invasive aspergillosis primarily affects the respiratory tract. Although there are over 260 species of *Aspergillus*, fewer than 40 have been documented to cause disease in humans or animals, and some of these have been reported only once. *Aspergillus fumigatus* accounts for most human cases of aspergillosis. However in recent years, *A. fumigatus*-like or “cryptic” species such as *A. udagawae* and *A. viridinutans* have been identified to cause

disease. These infections are more refractory to treatment due to innate antifungal resistance and propensity to spread across adjacent anatomical planes. We describe an emerging agent of invasive aspergillosis, *Aspergillus felis*, in humans and companion animals, namely domestic cats and dogs. Further, we present evidence that triazole antifungal drug resistance is common amongst *A. felis* isolates.

A. felis is a novel *A. fumigatus*-like species in the *Aspergillus* section *Fumigati*. In characterizing *A. felis* we applied a polyphasic taxonomical approach incorporating a combination of multilocus sequence data, morphological, physiological characteristics and ecologic data. Our data satisfy biological, morphological and phylogenetic species concept definitions. Our discovery of a novel heterothallic fungus with a fully functional reproductive cycle in the *Aspergillus* section *Fumigati* is significant and will provide unique opportunities for future translational research.

A. felis was isolated from two individuals in our study that were both receiving immunosuppressive therapy – a male adult human and a dog. Infections in both cases were fatal. The human patient had type II diabetes mellitus and was being treated for rheumatoid arthritis with prednisolone, etanercept and methotrexate, while the dog received prednisolone and cyclosporine for immune-mediated haemolytic anemia. In the human patient, fungal infection was protracted over 18 months and extended from a solitary lung nodule across anatomic planes to involve cervical lymph nodes and pleural space. The dog had a more acute course of disease and developed disseminated invasive aspergillosis. More curiously, the pet cats in our study, from which *A. felis* was isolated in 17 cases, did not have evidence of systemic immunosuppression. Disease in these cats was typically confined to the upper respiratory tract, with involvement of the sinonasal cavity and orbit, as well as contiguous anatomic structures such as the oral cavity and paranasal subcutaneous tissues.

Feline upper respiratory aspergillosis (URTA), is a relatively new disease in cats and of the 55 or so cases now described, more than two-thirds were reported in the last five years. Interestingly, cats of brachycephalic conformation, especially Persian and Himalayan breeds, make up more than a third of all documented cases. To date no studies have been performed to investigate innate or immune-responses in cats with URTA. A number of single nucleotide polymorphisms (SNPs) in pattern recognition receptors expressed by phagocytic cells, that increase susceptibility to invasive aspergillosis have been described in humans including SNPs in toll-like receptors 1, 3, 4 and 6, and in the C-type lectin receptors Dectin-1 and DC-SIGN. Whether similar genetic mutations could be associated with increased susceptibility to URTA in Persian/Himalayan cats has not been investigated.

Alternatively, the increased risk of URTA observed in brachycephalic cats could reflect reduced mucociliary clearance from abnormal sino-nasal cavity conformation. A decrease in sinus aeration and drainage of respiratory secretions secondary to infection, polyps and allergic rhinosinusitis is a risk factor for invasive fungal rhinosinusitis in humans. Mucosal edema and impaired drainage of upper respiratory tract secretions due to turbulent airflow and abnormal facial conformation has been proposed as a risk factor for fungal colonization in brachycephalic cats. Additional risk factors such as previous viral upper respiratory infection or recurrent antimicrobial therapy may also be involved. In particular, chronic feline herpes virus-1 infection can severely alter sino-nasal cavity architecture because of turbinate lysis secondary to intense inflammation, resulting in altered local mucosal defence mechanisms.

Sino-orbital aspergillosis in cats due to *A. felis* is strikingly similar in presentation to another form of aspergillosis that occurs in immunocompetent humans, known as granulomatous fungal rhinosinusitis (FRS). This disease predominantly occurs in the Sudan, Middle-East

and Indian subcontinent. Risk factors for infection include hot, dry environmental conditions, poor hygiene and low socioeconomic status. In contrast to other forms of FRS in humans that are mostly caused by *A. fumigatus*, chronic granulomatous FRS is predominantly caused by *A. flavus*, which has a propensity to colonise the nasal and paranasal sinuses in hot, dry climates.

Importantly, companion animals with aspergillosis due to *A. felis* are unlikely to be a source of transmission of infection to humans. *Aspergillus* species are amongst the most common molds on earth encountered by humans and animals. Their environmental niche is decaying vegetation in soil, where they have an important role in recycling carbon and nitrogen. The abundant spores of *Aspergillus* species are aerosolised and disseminated widely in wind currents, as demonstrated by isolation of *A. felis* from an indoor air sample in Germany, in our study.

*** Note:** The original published scientific article "***Aspergillus felis* sp. nov., an Emerging Agent of Invasive Aspergillosis in Humans, Cats, and Dogs (Australia)**"

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0064871>, Barrs VR et al. 2013 - PLoS ONE 8(6): e64871; doi:10.1371/journal.pone.0064871 by this interdisciplinary team of co-authors was posted on the One Health Initiative website's Publications page <http://www.onehealthinitiative.com/publications.php> Friday, June 21, 2013.

**** Dr. Barrs** is a known One Health supporter <http://www.onehealthinitiative.com/supporters.php>.

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0064871>