Primary fungal pathogens

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Dissertation Introduction

Fungal pathogens can be separated into two distinct groups; true or primary fungal pathogens, and opportunistic pathogens. True or primary pathogens can cause disease in any individual, regardless of their health status. Examples of these include Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis and Paracoccidioides brasiliensis, which cause disease in areas of endemicity. Opportunistic fungal pathogens are not sufficiently pathogenic to cause infection in healthy individuals, but are known to cause disease in individuals with a weak or depleted immune system. Examples of these opportunists include Candida albicans, Aspergillus fumigatus and Cryptococcus neoformans, although in rare cases, Cryptococcus neoformans can cause infection in healthy individuals if a sufficient quantity is inhaled (Stein & Sugar 1989). True and opportunistic fungal pathogens can also be categorised as host acquired pathogenic fungi and environmental fungi, for example Candida albicans and Histoplasma capsulatum respectively (Casedevall and Pirofski 2006). Over 1. 5 million fungal species are known to exist and of these only around 150 have been identified as causing disease in humans. Even so, only a handful of these are frequently encountered in a clinical setting, most of these being opportunistic infections (Casadevall & Pirofski 2006, D'Enfert 2009). These can infect humans superficially, sub-cutaneousmly or systemically, the latter becoming the most significant over the last couple of decades.

These observations are due, at least in part, to factors such as the emergence and increase in incidence of other diseases and advances in medicine over the past couple of decades. The emergence of HIV/AIDS has

increased the immunocompromised population dramatically, this is supported by the statistics from the World Health Organisation (WHO) that shows there are now 33 million people living with the disease and in 2007 it was estimated that approximately 2. 7 million people were newly infected (www. who. int). The ability to perform solid organ transplants has given rise to an increase in immunosuppression due to the immunosuppressive drugs administered to the patient to prevent rejection of the transplanted organ by the patient's immune system. Age now has an impact on the immune system, as due to medical advances the elderly are living longer and there is increasing survival of premature neonates (Pfaller & Diekema 2004). These and a variety of other factors have lead to an increase in the number of people who have become immunocompromised.

An important issue surrounding the opportunistic fungal pathogens is the emergence of opportunistic pathogenic fungi which have either never before been recognised or were thought to be non-pathogenic, for example Candida dubliniensis. These pathogenic fungi are becoming increasingly important due to the fact that individuals are becoming more and more immunosuppressed due to disease and medical advances discussed previously. This gives fungi, otherwise thought as being non-pathogenic; the opportunity to invade the host and cause disease that would not be possible in immunocompetant individuals. It is also seen that the more immunosuppressed the host, then the more susceptible they are to infection from more obscure fungi (Sanchez & Noskin 1998).

The ability of the fungal pathogen to cause disease in the human host depends on a range of factors including the state of the host immune system

and any virulence factors that the micro-organism may possess. The state of the immune system is a particularly important factor for the opportunistic fungal pathogens to establish disease. Other risk factors that may be associated with an increased risk of infection may differ depending on the organism, for example, airborne dust has been recognized as a risk factor in the development of Coccidiodomycosis (Warnock 2006). Virulence factors associated with all of the pathogenic fungi are, in most cases, not sufficient enough to cause a symptomatic disease, but in immunocompromised individuals dissemination can occur, which carry high mortality rates as they are difficult to treat effectively (Casadevall and Pirofski 2006).

Nosocomial infections are an area of interest as many emerging opportunistic fungal pathogens are presented in these environments along with the more common opportunists. This has become more significant due to the rise of immunocompromised patients in the hospital setting, and the use of artificial surfaces, for example, plastic intravenous lines, which breach the skin barrier. This is especially true for patients suffering from candidemia, where an intravenous line is the most frequent gateway into the host (Verduyn et al 1999).

It is now recognised Candida species are the third most frequent nosocomial bloodstream isolates' (Perlroth et al 2007, Yoo et al 2009).

Due to the increasing immunocompromised population many of the emerging opportunistic fungal pathogens are seen to be resistant to certain antifungal therapies, for example azole resistance has been observed in Candida species (Yoo et al 2009). This problem is due to the fact that there is

a limited spectrum of antifungal drugs available to treat these diseases. Also treatment is usually prolonged to fully eradicate the fungus and prevent relapse which along with a limited availability of antifungals can result in increased possibility of resistance. To prevent this other procedures such as surgery and reversal of immunosuppression are used in addition to the use of antifungals. There are also currently no available vaccines against any human fungal infection and therefore immunity to these diseases cannot be achieved via this route (Casadevall & Priofski 2006, Pfaller & Diekema 2004).

Within this paper I aim to realize if the increase of immunodeficient individuals has been the main contribution to the increase in incidence of opportunistic infection and the emergence of new fungal pathogens or if other factors such as virulence factors and antifungal resistance play a more dominant part in the increase.

Histoplasma capsulatum is a dimorphic fungus that causes histoplasmosis in both immunocompetant and immunocompromised individuals (Kauffman 2007). H. capsulatum var. capsulatum is endemic in the USA, particularly in the Mississippi and Ohio River valleys, and Latin America (Wheat 2006). Soil rich in nitrogen is the natural habitat of the mould form of Histoplasma capsulatum, the source of nitrogen being the vast amounts of bird or bat guano which tend to be associated with the endemic areas (Kauffman 2007, Wheat 2006, CDC 2008, Anaissie et al 2009, Maresca et al 1994). Most cases of histoplasmosis are symptomless with the individual being unaware of the infection or mild cases which may be misdiagnosed. Only a small proportion of the patients with symptoms will go on to develop more serious conditions.

These include chronic pulmonary histoplasmosis and disseminated histoplasmosis in immunocompromised individuals.

Of the many species of Candida, Candida albicansis the most common fungal pathogen of humans and is the most common cause of fungal infection in a hospital setting in the USA (Lunel et al 1999). C. albicans is a dimorphic fungus that is found, in its yeast form, as part of the normal flora of humans on mucosal surfaces in the genitourinary and gastrointestinal tract. This commensalism does not have an adverse effect on the host unless the host immune system is depressed or the normal flora is altered, for example, in the immunocompromised and individuals treated with antibiotics (D'Enfert 2009).

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