Human Fungal Infections: Need to Improve Diagnosis with New Biomarkers Developed by Translational Research

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The burden of invasive fungal disease (IFD) continues to increase as a result of improved medical intervention and supportive care [1]. The growing number of patients with a variety of risk factors (e.g. transplantation, chemotherapy, HIV infection, use of corticosteroids or new immunosuppressive agents) have caused an increase in incidence of invasive infections in recent years [2]. Millions of individuals worldwide are affected or at risk and mortality is high [3]. Despite these facts, IFD remains understudied and underdiagnosed as compared with other infectious diseases. Therefore, it is important to raise the general awareness of this problem. Over 600 different fungi have been reported to infect humans, ranging from common to fatal infections. This issue requires immediate attention. Moreover, there has been an increase in rare fungal infections [4]. This epidemiological shift indicates the need for fast and precise identification of the pathogen, as most of these fungi are either completely or at least partially resistant to available antifungals. Among these rare fungal infections, the Zygomycetes are the most commonly encountered, and in some institutions the increase in infection by these organisms appears to be associated with the use of newer antifungal drugs [5].

Robust, rapid, simple, and cheap diagnostics are needed to allow the best practice in patient management. Most diagnostics still suffer from long assay times and poor specificity and/or sensitivity [6]. These problems, combined with subtle clinical presentations, often result in missed or delayed diagnosis and compromised clinical care. Appropriate diagnostics would immediately affect mortality and reduce morbidity.

Historically, the diagnosis of infection has been limited to the correlation of clinical signs and symptoms of disease with recovery of the organism from, or histopathologic detection of the organism in, clinical specimens [7]. Nowadays, non-invasive diagnostic assays such as tests for detection of antibodies, cell wall components, and fungus-specific nucleic acids have great appeal. Fungal antigen testing is included in the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus definitions for diagnosing fungal infection [8] and is the standard of care for patients at risk of IFD [6]. Commercially available enzyme immunoassays (EIAs) to detect mannan (M-EIA) and galactomannan (GM-EIA) are available and show reasonable specificity but variable sensitivity [9]. Fewer data are available for the utility of b-D-glucan antigen testing. DNA-based tests for the diagnosis of IFD [10] have been hampered by lack of standardization. Semi-automated, standardized real-time PCR methodologies have been developed for Aspergillus and Candida [11] and preliminary evaluation has confirmed clinical usefulness.

Clinical specimens include serum or whole blood, for Candida and Aspergillus species, and respiratory samples (e.g., sputum or BAL fluid), for aspergillosis) [12]. Target sequences vary widely but most often include ribosomal genes (18S rRNA) or internal transcribed spacer regions [13]. Sensitivity ranges from 78% to 100% for candidiasis and from 33% to 100% in patients with proven invasive aspergillosis [13]. Specificity varies, especially with PCR for aspergillosis, where false-positive results may be seen when BAL fluid is tested.

The accurate diagnosis of fungal infections by use of conventional mycologic and histopathologic techniques is time consuming and arduous because of the suboptimal sensitivity of these methods. PCR for the diagnosis of IFD has not been widely used in clinical settings. It has not been shown convincingly that PCR can compensate for the limitations of culture in the rapid diagnosis. Real-time PCR and microarray platforms, coupled with fungal antigen detection, will likely be required to significantly ameliorate this difficult diagnostic problem. Facilitating an earlier and non-invasive means of diagnosing fungal disease continues to be a major focus for medical microbiologists and clinicians, particularly those who provide care to immunosuppressed patients. Although progress has been made during the past 2 decades much work is left to be done. Future efforts must be directed toward expanding the availability of new biomarkers for the diagnosis of IFD.

Translational Medicine bridges the gap between the laboratory and clinic by providing tools and approaches which promise to accelerate the development of effective therapeutic and diagnostic techniques. Translational medicine mainly utilizes omics sciences and bioinformatics tools for identification of novel biomarkers. Translational medicine provides the platform to explore novel biomarkers for IFD. There are enormous needs for translational microbiologists who can identify diagnostic and prognostic biomarkers. In addition, genetics based methodologies must be modified to increase sensitivity and specificity. Finally application of newly developing techniques such as Fluorescence Correlation Spectroscopy [14] to microbiology will permit diagnostic applications for IFD at an unprecedented level.

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References


