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Managing invasive fungal infections: relying on clinical instincts or on a rational navigation system?

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The management of invasive fungal disease in the immunocompromised host is complex and requires the specialized knowledge of physicians whose primary interest is actually the underlying disease rather than infectious complications. This Supplement aims to provide these physicians with some tools that may help to guide them through the maze of suspicion that an invasive fungal disease is present by offering an integrated care pathway of rational patient management. Such pathways will inevitably vary in detail in different centres and depend for their success on the presence of multidisciplinary teams and an explicit agreement on at least the minimum requirements for effective management. The integrated care pathways presented constitute an objective instrument to allow regular audits for recognizing opportunities to change practice if and when weaknesses are identified.

Keywords: invasive fungus, guidelines, antifungal therapy, immunodeficiency

Introduction

The management of invasive fungal disease in the immunocompromised host remains, for various reasons, a very complex issue. Indeed, invasive fungal infections never occur spontaneously, but emerge surreptitiously in patients who suffer from aggressive diseases, such as haematological malignancies. These diseases are usually accompanied by an immunodeficiency that inevitably will be enhanced by modern, aggressive treatment modalities. As a result, life-threatening infections, including invasive mycosis, will emerge during treatment, and these infections need to be identified in a timely manner by physicians whose primary interest concerns the underlying disease and not the infectious complication. Moreover, adequate management is made difficult by the subtlety of the signs and symptoms of the infection as a result of the muted immune response that is typical for patients with a chemotherapy-induced granulocytopenia. This Supplement aims to provide the physicians who offer such patients care with some tools that may help to guide them out of the maze that is created by suspicion of the presence of an invasive fungal infection, to an integrated care pathway of rational patient management. All relevant questions, i.e. why, when and how to treat, as well as what to treat with, are addressed in five articles that were written on the basis of thorough discussions between all authors during specially arranged working party meetings. These meetings consisted of both plenary sessions attended by all participants in the project and workshops of the five different study groups, one each for risk assessment, detection and diagnosis, comparison of antifungals, treatment and timing, and, finally, optimizing management.

Main conclusions of the working parties

Risk factors

Pagano and his group described the factors that appeared to play a role in the aetiology of invasive fungal infections.[1] Although some individuals have a predisposition due to genetically impaired interleukin-10 production, mannose-binding lectin deficiency and Toll-like receptor polymorphisms, exposure to a high concentration of fungal spores remains a major risk factor.[2,3] When the patient has mucosal damage in combination with a low granulocyte count, the spores gain easy access to the airways and, subsequently, to other organs. In seriously ill non-neutropenic patients in intensive care units and in organ transplant recipients, the use of drugs that interfere with cellular immunity (such as corticosteroids, purine analogues and monoclonal antibodies) pose the most important risk. In addition, the longer and the more profound the impairment of the immune system, the higher the incidence of fungal infections will be. It is frustrating that most factors that facilitate the occurrence of an invasive fungal disease are unavoidable because they are directly connected to the underlying diseases as well as to their treatment, though increased awareness may help in developing a better surveillance strategy.

Detection

The high mortality rate of invasive mould disease is, to a large extent, related to the limited ability to diagnose these infections at an early, curable stage. It is often impossible to obtain the samples from deep tissues needed for classical microbiological investigations. In exceptional cases when clinical isolates from deep tissue sites are available, characterization to species level is mandatory, because the identity of the mould may have more important therapeutic consequences in the clinical setting than performing susceptibility testing. Microscopic examination is not very effective in diagnosing systemic fungal infections, but in many cases it is the only practical technique available. Measurement of antibodies is not an option during active infection, since the impaired immune system is obviously unable to mount a response to fungal antigens. Conversely, high-resolution CT and magnetic resonance imaging (MRI) scans have become accepted standard procedures, as they make it possible to detect both pulmonary and extrapulmonary invasive aspergillosis and other invasive fungal disease processes with a reasonable degree of certainty. Most patients with an invasive pulmonary mould disease show macronodules, many of which are surrounded by halo signs, particularly in combination with neutropenia. Other imaging findings are less common. Cuenca-Estrella and his colleagues[4] reviewed much of the literature on the laboratory investigation of immunocompromised patients suspected of having an invasive mould disease, and they proposed a set of minimal requirements. They emphasized the importance of alternative methods, such as the detection of specific antigens and certain components of the fungal cell or DNA. The serial quantification of galactomannan in serum or plasma, particularly in association with a high-resolution CT scan for the early detection of invasive aspergillosis, has proved valuable for patients with haematological malignancies. Moreover, there are indications that detection of galactomannan in other clinical samples may also be useful for neutropenic and non-neutropenic patients. However, blind navigation by galactomannan monitoring should be avoided since the reliability of the test is insufficient because of false-negative and false-positive results. There is substantially less evidence for recommending the β-D-glucan test for routine monitoring. Although included in the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) diagnostic criteria for invasive fungal disease[5] and considered to be a panfungal diagnostic test, it has to be kept in mind that β-D-glucan testing has not yet been validated extensively. Due to the limitations of conventional techniques, attempts to spot fungal nucleic acid sequences in clinical samples became fashionable. The results were promising but, so far, the theoretically high sensitivity of these PCR-based techniques has not been corroborated in clinical practice. Indeed, most studies published on this issue have employed different methodologies for nucleic acid extraction, different primers and probes, and different overall conditions. The multicentre trial to standardize *Aspergillus* DNA detection of *Aspergillus* species, as planned by the European *Aspergillus* PCR Initiative of the International Society of Human and Animal Mycology and the Infectious Disease Group of the EORTC, is urgently needed.

Comparison of antifungal drugs

In the vast sea of publications on the treatment of invasive mould disease, formal comparisons of the efficacy and safety of antifungal drugs in the first-line treatment of proven or probable aspergillosis are very rare fishes indeed. A mixed treatment comparison was undertaken in an attempt to glean strategic studies for information that may help to substantiate the recommendations for treatment of established disease.[6] Although 12 studies met the inclusion criteria for the three aims of the mixed treatment comparison, only six trials investigated first-line antifungal therapy for aspergillosis, and only the trial of voriconazole versus amphotericin B deoxycholate recruited a sufficiently large number of patients to allow a realistic comparison of two different drugs.[7] The strategy of starting with voriconazole was superior, and set a new standard of treatment. Liposomal amphotericin B produced similar results in a large study that compared two different dose regimens of the drug.[8] The four remaining studies were underpowered, which renders a conclusion on the potential efficacy of other drugs or combinations of drugs rather speculative.

Treatment and timing

The uncertainty about the possible presence of an invasive mould disease, together with the poor prognosis when the disease has become fully established, has motivated many investigators to explore a variety of antifungal strategies. After his trend-setting paper on a tailored approach to persisting fever in neutropenic patients, Maertens was the logical choice to chair the study group that addressed the timing of therapeutic interventions in patients suspected of having invasive mould disease.[9,10] The group concluded that the candidates for mould-active prophylaxis should be selected on the basis of the perceived risk, taking into consideration the recent improvements in the diagnosis of and new therapeutic options for invasive mould infections. In high-risk populations, most practitioners rely on antifungal prophylaxis. Empirical administration of antifungals in neutropenic patients with persisting fever gained great popularity during the 1980s and 1990s. It was believed that an early intervention would prevent a fatal flare-up of an already present though still undetectable infection. In fact, empirical antifungal therapy is usually instigated because the existence of an occult infection cannot be excluded. If all patients with persistent fever after 72 or 96 h of broad-spectrum antibiotic therapy were to receive empirical antifungals, as many as 90% would be exposed unnecessarily to potentially toxic and expensive drugs. Therefore, with the availability of much improved diagnostic tools there has been a shift from routine prophylaxis and empirical antifungal therapy to screening high-risk patients, so that appropriate antifungal therapy can be either started before infection evolves to a stage beyond which cure becomes untenable or, if already started empirically, stopped when the diagnostic work-up yields negative results. Meticulous assessment of clinical signs, in conjunction with CT scanning and panfungal and species-specific assays, appears to offer the opportunity of starting antifungal therapy pre-emptively, i.e. at the initial stage of the infection. The debate on the most appropriate strategy lingers on, albeit that the

diagnostic-driven approach is gaining ground in centres where the necessary diagnostic facilities are available.

Optimizing management

Optimal management of invasive mould diseases requires a multidisciplinary enterprise that involves many different healthcare professionals. Agrawal and colleagues[11] describe the various elements that are required to build an integrated care pathway for adequate management of invasive mould disease, and for implementing it in practice. Of course, such pathways will be inevitably varied in detail in different centres. Their success also depends upon the presence of multidisciplinary teams, and an explicit agreement on at least the minimum requirements for the effective management of these complex patients. An integrated care pathway constitutes an objective instrument that permits regular audits with the opportunity to change practice if weaknesses are identified.

Options in daily clinical practice

The jury is still out on whether empirical or pre-emptive antifungal therapy is the preferred option for the treatment of persistently febrile immunosuppressed patients.[12] The excellent negative predictive value of the antigen-based assays in combination with modern imaging as screening tools may persuade clinicians to withhold antifungal therapy in febrile patients who have no other clinical, radiological or microbiological evidence of fungal infection. However, not all centres have these diagnostic tools at their disposal and inevitably have to rely on a more conservative approach. As a consequence, there are two main therapeutic strategies, as discussed in the previous article by Agrawal *et al*.[11] The scheme for empirical therapy is the simplest, and therefore easy to read and understand. In centres lacking appropriate diagnostic facilities, treatment is started when fever does not respond to a 3–7 day course of adequate antibacterial therapy or, less frequently, when clinical signs and symptoms indicate a possible invasive fungal infection. Nevertheless, a few questions arise if the algorithm is followed through. While it cannot be overemphasized that even after antifungal therapy has been commenced, the search for a more definite diagnosis should be continued, it is difficult to understand how this will be done if there are no diagnostic facilities to hand. Might this not simply reflect the reluctance of clinicians to obtain the specimens necessary to attempt a diagnosis, since this usually requires an invasive procedure, and the results invariably arrive too late to make a real difference to the management? Even if the new diagnostic tools such as PCR, β-D-glucan and galactomannan have been fully validated, doctors at the bedside will need time to get accustomed to their use. Starting or changing therapy on the basis of a purely clinical assessment is a deeply rooted habit. However, laboratory tests and imaging can be immediately of value to confirm the accuracy of the decision that was made on clinical grounds. Parameters to evaluate the effect of empirically given antifungals are also rather limited, and consist of the course of fever together with the evolution of the clinical condition of the patient. In a clinically stable patient, if persisting unexplained fever was the reason for starting therapy, empirical treatment can be stopped when defervescence occurs. Reducing doses of antifungals does not appear to be a good idea, but a switch to an oral compound should be considered as soon as clinical circumstances allow this.

In the diagnostic-driven approach, persisting fever does not serve as a trigger to start antifungal therapy but may provide an impetus to use all diagnostic tools available. Alternatively, screening for galactomannan and perhaps other markers on a regular basis might also provide a trigger. The resulting algorithm is more complicated. Further diagnostic tests should be ordered in the case of a discrepancy between CT findings and standard screening tests. In the algorithm, therapy should be started when further diagnosis confirms invasive mould disease. However, therapy should at least be considered, even when invasive mould disease is not confirmed, as there will always be doubtful cases that deserve antifungal therapy until the uncertainty is resolved. Repeating the investigations without too long an interval when the findings are negative is a crucial part of a pre-emptive strategy. With regard to 'step-down' therapy the same considerations apply. Finally, in patients with proven or probable invasive mould disease, appropriate antifungal therapy should be continued as long as the patient remains seriously immunosuppressed. Indeed, the first step in the management of an established invasive fungal disease is a careful consideration of the clinical situation, and assessment of the risk factors that might have contributed to its emergence. Where possible, any drugs used that help sustain the compromised immunity should be avoided, as persistence of any immune defect is irreconcilable with complete resolution of an invasive mould disease.

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