# Diagnosis, Definitions, Drugs and Dilemma's

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Diagnosing invasive fungal disease (IFD) has always presented a challenge. However with respect to invasive aspergillosis there have been some major advances. First and foremost it is now generally accepted that when faced with a patient at high risk typically, the allogeneic haematopoietic stem cell transplant recipient and those undergoing treatment for AML, the sooner the infection is detected the better will be the outcome. To help us many are now able to do a high resolution CT scan of the lungs, the foremost site of infection, to help determine whether there is a disease process consistent with invasive pulmonary aspergillosis. There is also clearer guidance on what to look for. In addition many centres have accepted the principle of screening for the presence of *Aspergillus* antigen using the validated and standardised EIA test while the patient is at risk and in hospital usually until he or she is no longer neutropenic. This approach not only provides a useful trigger for ordering an HR-CT scan but also permits monitoring of the response to therapy since persistently high levels of antigen portend a poor outcome. Many are also exploring PCR to detect DNA though, as yet, there is no standard for these tests. However a European initiative has been established to define a standard by which each centre can assess the validity of its own PCR technique. Hence, at least for aspergillosis, progress has been made. The same cannot be said for diseases caused by other moulds since, apart from obtaining a proper specimen for culture and microscopy, there are no specific indirect tests available. Obtaining an appropriate specimen also remains a problem as this invariably requires an invasive procedure which is seldom feasible. This remains an unmet need.

Defining IFD has been helped considerably by the development of the EORTC/MSG definitions in 2002 as these require a set of criteria to be met before assigning a level of certainty to the diagnosis. Importantly, defining proven IFD remained unchanged still requiring demonstration of fungal elements in tissue obtained from the diseased site. However few such infections are ever proven in life. To address this, the EORTC/MSG proposed that three elements, host factors, clinical features and mycological evidence be used to differentiate between probable and possible on the one hand and unlikely IFD the other hand. These definitions proved their worth in terms

of validating laboratory tests, epidemiology and in clinical trials. However there were obvious deficiencies so a second consensus group was formed to revised the IFD definitions to allow a wider net to be cast while retaining genuine cases of IFD. Hence the difference between probable and possible IFD is now clearer and is simply this -evidence of an infectious disease process most like due to fungal infection will be only considered **probable** when there is supporting mycological evidence and **possible** when there is not.

Clearly there are more drugs available now for managing IFD. Amphotericin B (AMB) desoxycholate has more or less left the scene but its two relatives lipid-complex AMB and liposomal AMB have taken its place. The azole drugs have a bigger team and now include fluconazole, itraconazole, voriconazole and posaconazole. Candins from the third class and include caspofungin, micafungin and anidulafungin. Choices enough one might think. However appearances can be deceptive. Voriconazole is the drug of choice for treating IFD due to *Aspergillus fumigatus* but liposomal AMB may do just as well all things being equal. This is often the case but voriconazole can prove difficult as its use can me limited by toxicity and interactions with other drugs. Conversely caspofungin results in very limited toxicity but its efficacy is likely to be lower than that of voriconazole. Undoubtedly liposomal AMB and lipid-complex allow amphotericin B to be delivered in effective doses in a safer way than is true of the desoxycholate formulation but they are both costly and the necessary comparative data are lacking. To add further confusion posaconazole has proven effective as prophylaxis but can only be given orally and has yet to been shown effective as first-line therapy. Clearly there is much work needed to help us identify the place of these drugs in managing IFD guided by the insights that have now been gained.