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FOCUS ON: CRITICAL CARE: ANTIBIOTICS AND ICU

Fungal infection

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Summary Fungal infection was rare, difficult to diagnose and with limited treatment options that were toxic. It is now more common, it is still difficult to diagnose but with a much enhanced range of treatments available that are less toxic.

Definitive diagnosis with blood cultures may be very late in the course. Instead the use of clinical features combined with colonization of sites allows much earlier diagnosis based on probability rather than certainty and, thereby, prompt intervention. The range of drugs available has proliferated over the last few years. New azoles have a better spectrum for the species of Candida now prevalent and also for Aspergillus. The echinocandins also offer a broader spectrum of activity with and toxicity. The potential roles of these agents and the existing drugs are discussed.

Introduction

Fungal infection in the critically ill is a significant problem, although its magnitude is difficult to determine. The EPIC study, looking at a snapshot of infection on a single day suggested a high rate of fungal infection in the intensive care unit (ICU) but for many units those figures did seem very high. The incidence almost certainly varies considerably between units determined in large part by the patient population. The incidence may be increasing due to the treatment of sicker patients, the widespread use of potent broad spectrum antibiotics and importantly, increased awareness and therefore a lower threshold for diagnosis amongst clinicians.

The traditional model for diagnosis and treatment of fungal infection is derived from the approach in the immuno-compromised patient. There are fundamental differences between these patients and the critically ill population and direct extrapolation from one population to the other may be problematic.

The immuno-compromised patient has an inherent vulnerability to fungal infection because of impaired immune function. This may be a relatively isolated problem in an otherwise fit patient, at least in terms of other organ dysfunction. The threat of fungal infection is real and the risk known and is potentially quantifiable. The risks from treatment in terms of aggravating organ system failure are relatively small.

This contrasts with the critically ill population with massive disease heterogeneity. There the immune dysfunction is hard to quantify and is

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Table 1 General differences between immuno-compromised and critically ill populations.

Mechanism	Immuno-compromised	Critically ill
Underlying problems	Single/simple	Multiple
Immune system problem	Defined	Non-specific
Relevance of underlying problem	Direct	Indirect
Risk assessment of likelihood of fungal infection	Easy	Difficult
Physiological derangement	Minimal	Extensive
Organ systems	Reasonable condition	Often damage, always vulnerable
Attributable mortality	Direct relationship	Indirect and difficult to assess
Treatment toxicity	Unlikely	Probable

usually secondary to their initial illness and general dysfunction of one or more organs. The morbidity and mortality of the initial illness is often hard to quantify and this is compounded by the addition of secondary morbidities. The vulnerability to fungal infection is ill defined but dependent on the severity of their illness and also secondary factors, such as damaged integument, indwelling catheters, broad-spectrum antibiotics and fungal overgrowth. Organ failure in particular renal or liver failure may be present and needs to be considered in terms of the potential risks associated with treatment. Fungal infection in these patients is a clinical sign of severe illness and the attributable mortality of that infection is difficult or impossible to quantify (see Table 1).

In the following section, Candida infection, which is common, will be discussed. Aspergillus's, while common in the immuno-compromised, is less common in ITU generally. Cryptococcus, Fusarium and other fungal problems are beyond the remit of this article.

Candida infection

Candida is an extremely common organism that colonizes many individuals without clinical sequelae. In susceptible individuals, it can cause symptomatic problems, such as 'thrush', which may be of minor significance. As an intracellular organism, it starts as a blastopore which divides by budding, a process that involves new material being derived at a site on the blastopore. When the blastopore matures nuclear division ensues and the two elements are separated by a cell wall. As this new cell divides it starts to form a hypha, which is a key feature of Candida. Candida invades by adhering to local tissue, especially to the subendothelial extracellular matrix. This may be fundamentally important because it may fit with the observation that Candida invasion seems more likely in the presence of a damaged integument, in particular endothelium. The ability of various Candida species to adhere to surfaces may be influential in their intrinsic pathogenicity. *Albicans* adheres better than either *tropicalis* or *parapsilosis*. The ability of the Candida to produce proteinases which may assist in breaking though the keratin surface of the integument may be important as is the individual fungal resistance to oxidative assault by neutrophils.

At macroscopic level other factors play a role. In the GI tract, Candida colonies are held in check by the ecology and integrity of the intestine. Anaerobes are said to help prevent adhesion to the mucosa, and the integrity of that mucosa is obviously important. Anything which disrupts that ecology may encourage overgrowth with Candida and coupled with mucosal damage the scene is set for invasion. It has always been suggested that the total Candida 'load' may have a bearing on likelihood of invasion, although such evidence as there is would be considered circumstantial. Broad spectrum antibiotics allow overgrowth and sometimes minor concomitant illness can encourage Candida growth. It is only in the immuno-compromised and those with a severely damage integument where there is real potential for this organism to cause major problems.

Diagnosis

Diagnosis is a problem. Positive blood cultures identify definite infection but are invariably found late if at all. Therefore, earlier means of diagnosis are essential. This in effect means looking at probability rather than certainty. (This will be addressed below and summarized in Table 4.)

Risk

To some extent the populations at risk can be identified (see Table 2). A group of particular