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EDITORIAL I

What should we be doing about fungal infections in intensive care?

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The Surviving Sepsis Campaign guidelines recommend that empiric antifungal therapy is given to intensive care unit (ICU) patients when deemed warranted; it should be tailored to the local pattern of the most prevalent *Candida* species (*Candida* spp.), and account for any prior administration of azoles drugs.[1] In a recent issue of the *British Journal of Anaesthesia*, Chalmers and Bal[2] reported the results of a survey of UK practice, concluding that there is a need for greater awareness among UK intensivists of the current standards and guidelines relating to the management of fungal infections.

Questionnaires enquiring about normal practice and local guidelines were sent to all UK ICUs within either the Scottish Intensive Care Society Audit Group (SICSAG) or the Intensive Care National Audit and Research Centre (ICNARC) register. Only 30% of units responded, a rate which is disappointing although not out of keeping with other surveys.[3] Low response rates do, however, pose problems for the interpretation of such studies. Bias is naturally introduced and although it may be tempting to conclude that the non-responding units are less interested and therefore less likely to have protocols in place, this cannot be assumed for many reasons. For example, the failure to respond may have been simply because the questionnaires did not reach the right person or perhaps potential participants simply forgot. There are measures which have been shown to improve response rates,[4] such as stamped return envelopes, keeping the questionnaire short (although this can risk validity), and monetary incentives all improve initial response rates. Electronic formats do not necessarily improve performance. Second and third mailings can improve on the initial response by 30% since some responders will simply have forgotten and in this day of e-mail traffic, spam filters, and an overwhelming inbox, unsolicited contacts are easy to miss. Unfortunately, reminders were not sent out for this questionnaire.

Nevertheless, the results do suggest limited awareness of recommended standards of care for the management of fungal infection. Standards of care do exist, although not directly in the critical care literature, which may be why they are overlooked. They are published both in the UK[5] and the USA.[6] Proposed UK standards were published by the British Society of Medical Mycology in 2003 and were designed to provide standards for local audit, with recommendations for departments of microbiology, histopathology, radiology, and clinical specialities. Many are relevant to intensivists and the following is a summary of the main points for clinicians.[5]

(i) All request cards for microbiology, histology, and radiology from immunocompromised patients should be clearly identified as such in terms of patient information.
(ii) All patients with candidaemia should have central venous catheters removed or replaced within 48 h of candidaemia being documented, and preferably earlier, with the sole exception being long-term lines that need a careful individual assessment.
(iii) All patients with candidaemia should be treated with a systemic antifungal agent at an appropriate dose, and breakthrough fungaemia treated with an alternative agent.

(iv) All transplant recipients or profoundly neutropaenic patients with: a new positive culture of aspergillus or other mould, new pulmonary or cerebral abnormalities consistent with a fungal infection should be treated with a systemic antifungal agent at an appropriate dose active against moulds within 6 h of the positive culture or documentation of the pulmonary or cerebral abnormalities.

(v) All patients with cryptococcal meningitis should be treated initially with amphotericin B deoxycholate >0.7 or >4 mg kg^{-1} day^{-1} lipid-based amphotericin B with flucytosine 75–100 mg kg^{-1} day^{-1} (adjusted for renal function).[5]

With the exception of the last recommendation, the standards fall short of recommending specific antifungal agents, nor do they comment on the use of prophylactic antifungals. The American guidelines were issued by the Infectious Diseases Society of America (IDSA) with much more specific antifungal advice.[6] For non-neutropaenic immune-competent adults, the suggested first-line therapy is fluconazole with a loading dose of 12 mg kg^{-1}, followed by 6 mg kg^{-1} daily or one of the newer echinocandins. The echinocandins were also recommended for moderately severe to severe invasive infections and for patients with recent azole exposure, although transition to fluconazole after initial echinocandin therapy was suggested as appropriate if *Candida albicans* is confirmed. Treatment for proven candidaemia should be continued for 14 days after the first negative blood culture result, particularly in patients with solid organ tumours. Ophthalmological examination was recommended for all patients.[6] Fungal lesions in the eye as a consequence of candidaemia in critically ill patients have been reported as high as 13%. Ophthalmology review was identified in the survey as a significant omission in current UK practice.[2]

A retrospective analysis of the EPIC II study[7] has recently described for the first time the world-wide scale of the problems caused by serious fungal infection in ICU patients. Data from 14 414 patients were analysed and blood stream infection (BSI) by *Candida* spp. was found to affect 6.9 per 1000 patients. Associated mortality was high at 42.1%, even when compared with mortalities of 25.3% and 29.1% for Gram-positive and Gram-negative BSI, respectively. The study also illustrated well the geographic and regional basis of marked variations in the epidemiology of *Candida* spp. Overall, *C. albicans* accounts for 70% of all BSI caused by *Candida* spp., non-albican *Candida* spp. accounting for the rest. The epidemiology in Western Europe was very similar with 30% Candida non-albicans, but in Eastern Europe and Pacific, the incidence was 0% (although based on small numbers) and in Latin America, the rate was 43%.[7] There are more than 200 different species of *Candida*, not all of which are human pathogens. However, a significant number are and it is probable that not all have yet been identified. Of those which are recognized, the predominant type varies by region and even perhaps by institution. In North America, *Candida glabrata* is the most common non-albicans isolate (26%) followed by *Candida parapsilosis* (15.7%) and *Candida tropicalis* (8.1%),[8] whereas in Spain, *C. parapsilosis* (33%) predominates and *C. glabrata* is only the fourth most common (4.7%).[9] In Australia, *C. albicans* accounts for 62% of BSI followed by *C. glabrata* (18%) and *Candida krusei* (4%).[10]

A number of issues need to be considered when developing local protocols. Close negotiation with local microbiologists is mandatory for informed interventions and it is encouraging from the survey that this is considered routine for most intensive care departments, at least on an individual patient basis.[2] Understanding the local flora is essential for the development of good local protocols. Unfortunately, little is available in the literature about regional differences in *Candida* spp. within the UK, but anecdotally, there may be quite wide variations between, for example, London and Edinburgh. Different areas may warrant different first-line antifungal options and a local audit may go some way to understanding a particular region or hospitals requirements.

Early diagnosis remains difficult[11] and patients are frequently treated on the basis of risk and suspicion. Particular risk factors for invasive *Candida* spp. include colonization of skin and mucous membranes with alteration to natural barriers[12] including surgery (particularly abdominal or urogenital surgery), central venous access catheters, and urinary catheters. Immuno-compromised patients are most vulnerable but this is in its broadest sense and includes critically ill patients with prolonged admissions and altered natural flora due to the use of broad-spectrum antibiotics.[11] Chronic pulmonary disease and prolonged ventilation are risk factors for respiratory candidiasis and for invasive *Aspergillosis* spp.[13] Other risk factors include total parenteral nutrition, acute kidney injury, long-term corticosteroid use, severe underlying co-morbidities, upper gastrointestinal surgery, antacids, and prolonged length of stay.[14]

As with other forms of sepsis and infection, delays in treatment worsen outcome.[15 16] Newer methods of diagnosis are being developed and currently the most promising is amplification of fungal nucleic acids (PCR) with the advantage of early species identification.[17] Unfortunately, such methods are unlikely to be widely available for sometime.

Prophylactic antifungals have been suggested for high-risk patients, that is, patients with a $>10\%$ risk of invasive candidiasis in whom prophylactic fluconazole has been shown on meta-analysis to confer a 50% reduction in invasive infection rates.[18 19] Overall benefit to lower risk patients is less certain and indeed concern has been raised that overuse of fluconazole has already selected out more resistant *Candida* spp. Evidence for this, however, is conflicting[20 21] with recent reports on ICU patients concluding both no change in rates of *C. glabrata* with prophylactic fluconazole[20] and reduction in non-albican *Candida* spp. with control of fluconazole use.[21] Nevertheless, the consensus probably is that overuse of fluconazole does increase risk of emergence of certain *Candida* spp. (e.g. *C. krusei*).[11]

In the UK, fluconazole still remains the mainstay of empiric treatment for fungal infection.[2] There are some good reasons for this: fluconazole is well tolerated, readily absorbed with an

oral bioavailability of >90%, and remarkably unaffected by ingested food altered gastric pH, or disease state. Whether administered orally or parenterally, it has excellent tissue penetration, reaching therapeutic concentrations in cerebral spinal fluid (CSF), ocular fluids, and urine.[6] The risk with using fluconazole for empiric treatment is, of course, that the *Candida* spp. being treated is not *C. albicans*. Sensitivity to fluconazole varies among the non-albican *Candida* spp. *Candida krusei* and some strains of *C. glabrata* can be considered fully resistant and others (e.g. *C. tropicalis* and *C. parapsilosis*) have much higher minimum inhibitory concentrations than *C. albicans* and thus require significantly higher doses.[22] Fluconazole also profoundly inhibits cytochrome P450 3A enzymes. These enzymes account for the metabolism of >50% of all hepatic eliminated drugs and fluconazole is associated with drug interactions. In severe renal impairment, the dose of fluconazole should be adjusted.[23]

Of the alternative azoles, voriconazole may be useful for the treatment of invasive candidiasis and it is licensed for treatment of invasive aspergillus.[5] *Candida krusei* and *C. glabrata* are sensitive and penetration of tissues such as CSF is good. Voriconazole may be administered orally or parenterally but is not recommended at all in patients with moderate to severe renal dysfunction because of a molecule to which it is complexed in the i.v. formulation. Cyclodextrin will accumulate in patients with severe acute or chronic renal failure.[6] Drug interactions are common with voriconazole and may limit its use. Itraconazole has similar activity to voriconazole but is not available for parenteral administration, limiting its use in intensive care patients.

Amphotericin B is still used empirically if sensitivity to fluconazole is uncertain. Certainly, most forms of *Candida* spp. will be susceptible, and also *Aspergillus* spp. The use is limited by its toxicity, in particular nephrotoxicity, and although this may be partly mitigated by lipid soluble preparations, amphotericin B remains difficult to use.[6] Of course, one sensible strategy is to start amphotericin B as the empiric treatment to be modified to fluconazole, if *C. albicans* or other sensitive organism is confirmed.

The echinocandins are a new class of antifungal agents currently represented by caspofungin, anidulafungin, and micafungin and all have been shown to be effective for treatment of invasive candidiasis caused by the majority of recognized *Candida* spp. The minimum inhibitory concentrations for most are low and importantly this includes *C. krusei*. However, *C. parapsilosis* may be partially resistant and this may be very important in some regions where it can be the second most common *Candida* spp. encountered.[9] The echinocandins are fungicidal against the *Candida* spp. but may only be fungistatic against *Aspergillus* spp.[24] In terms of clinical use, they can only be administered parenterally but so far have been associated with few adverse effects.[6 24] All only need once daily dosing and do not require dose adjustment for renal impairment as the major route of elimination is non-enzymatic degradation. Dosage reduction with caspofungin is recommended for patients with severe hepatic dysfunction.[6] The i.v. dosing regimens recommended by IDSA for invasive candidiasis for the three compounds are: caspofungin, loading dose of 70 and 50 mg daily thereafter; anidulafungin, loading dose of 200 and 100 mg daily thereafter; and micafungin, 100 mg daily.[6]

So where does this leave us in the management of serious fungal infections? BSI with *Candida* spp. is an independent risk factor for death,[25] but the widespread use of prophylactic antifungals cannot be balanced with the increased risk of selecting out resistant species. There are more than 200 species of *Candida* and although the echinocandins appear to be active against the main species currently recognized as pathogenic in humans, injudicious use of any antimicrobial agent will select out resistant organisms given time. High-risk patients, however, may benefit from early empiric use of antifungals. Waiting for microbiological diagnosis in these patients, because of the lack of sensitivity of current diagnostic methods, will inevitably miss serious invasive infections. A recently developed candida score[26] is gaining some favour as a simple scoring system designed to identify the patient who may benefit from prophylactic or early empiric treatment.[11] The candida score components are: total parenteral nutrition, 1; surgery, 1; multifocal *Candida* species colonization, 1; and severe sepsis, 2.[26] Patients with a score of >2.5 were found to be 7.75 times more likely to have proven infection (risk ratio 7.75; 95% confidence interval, 4.74–12.66) than patients with a Candida score of <2.5. The benefits of this score remain to be tested, but it may provide a means of practically identifying the correct patients for empiric therapy. As to which agent to use, the current recommendations by the IDSA would seem to be a reasonable compromise with current understanding. A full-scale survey of UK *Candida* spp. epidemiology and UK practice would provide useful information and is something that should be considered by national bodies in ICU.

Conflict of interest

B.J.P. attended a conference in Brussels in March 2011 as a delegate courtesy of Astellas Pharma. She has no further conflicts of interest to declare.

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EDITORIAL II

Controversy of non-steroidal anti-inflammatory drugs and intracranial surgery: *et ne nos inducas in tentationem?*

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The paper by Williams and colleagues[1] in this issue of the *British Journal of Anaesthesia* touches on the contentious issue of the use of non-steroidal anti-inflammatory drugs (NSAIDs) and intracranial surgery. They found that 40 mg of i.v. parecoxib administered at dural closure in patients undergoing supratentorial neurosurgical procedures had no effect on morphine consumption or pain intensity compared with placebo. There were also no differences in side-effects such as postoperative nausea and vomiting (PONV) and sedation scores. While recording no major morbidity, one