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Comment on: Nephrotoxicity of continuous amphotericin B in critically ill patients with abdominal sepsis: a retrospective analysis with propensity score matching

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We read with great interest the paper written by Geersing *et al.*,[1] in which continuous infusion of conventional amphotericin B (CCAB) combined with therapeutic drug monitoring (TDM) was discussed for the pre-emptive treatment of invasive fungal disease (IFD) in patients with abdominal sepsis in the ICU. The authors state that this treatment did not lead to renal dysfunction and can thus be safely applied in this patient group. We share the opinion that antifungals may be used pre-emptively in the surgical ICU but would like to point out several arguments and viewpoints with which we strongly disagree.

According to the European Society of Clinical Microbiology and Infectious Diseases, prophylactic usage of fluconazole is recommended in patients who have recently undergone abdominal surgery and have recurrent gastrointestinal perforations or anastomotic leakage.[2] The Infectious Diseases Society of America has likewise made a recommendation for prophylactic use of fluconazole in high-risk adult ICU patients with a high rate of invasive candidiasis. Empirical therapy should be considered for patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis, including recent abdominal surgery and anastomotic leaks.[3] IFD other than candidiasis remains negligible in the setting of non-neutropenic surgical patients.[4]

In light of these recommendations, we are surprised about the uncritical approach in this study.[1] CCAB was applied in both centres as a pre-emptive treatment in the case of abdominal sepsis with secondary peritonitis after intestinal perforation.[1] CCAB is neither approved by the European Medicines Agency nor the U.S. Food and Drug Administration and is not recommended in current guidance documents.[2,3] The benefit of prophylactic therapy with CCAB was not reviewed by an appropriate endpoint or questioned in any way. We consider this concept unsound, given that fluconazole is well tolerated and has been successfully implemented in the surgical ICU to reduce the incidence of IFD. To prevent one case of IFD, the number needed to treat with fluconazole prophylaxis is nine in a high-risk patient population.[4]

The main point of this study by Geersing *et al.*[1] was to scrutinize the nephrotoxicity of CCAB. As a matter of fact, previous studies have demonstrated comparable results with a trend towards a lower nephrotoxicity.[5] Nonetheless, there are several aspects that seem to have been ignored. The potential toxicodynamic advantage of a continuous-infusion dosing strategy may compromise the therapeutic efficacy. Pharmacodynamic data derived from murine disseminated candidiasis models have demonstrated that amphotericin B (AmB) peak serum levels correlate with outcome.[6] Continuous infusion of AmB therefore negatively impacts this concentration-dependent antifungal activity. Furthermore, in this study, TDM reference values were chosen to prevent nephrotoxicity, not to promote effective pre-emptive treatment. In fact, in one of the two centres, the TDM range was lower as suggested in another study by the authors, in which they deemed AmB serum levels >0.5 mg/L effective to obtain peritoneal levels above MIC values.[7]

Aside from that, conventional AmB has been also shown to cause a number of other untoward effects, including infusion-related adverse events, anaemia and electrolyte disorders such as hypokalaemia and hypomagnesaemia.[8] None of these well-known complications was examined in this publication.

The retrospective design of this study has, however, allowed for potential biases. Patients with a history of kidney disease or poor renal function could have been consistently excluded from CCAB by the attending physicians. Such selection bias is ultimately reinforced by the applied propensity matching, as patients with good pre-existing conditions are compared with patients with similar physical health. Another data distortion could have been caused by the exclusion of patients receiving conventional AmB for less than 72 h. Cases in which therapy was discontinued

because of a decreasing renal function or other side effects would consequently induce a bias towards better outcomes.

Last but not least, we want to address the issue of cost-effectiveness. We believe that the targeted use of antifungals is not only important for the avoidance of resistance development and prevention of adverse effects but also helps to save costs in the healthcare system through shorter treatment durations and earlier hospital discharge. A direct comparison of costs for the broadly available and inexpensive therapeutic-standard fluconazole with CCAB and TDM was not conducted by the authors. Aside from that, elaborate diagnostic methods, such as TDM using liquid chromatography–mass spectrometry, are neither practical nor inexpensive for hospitals with limited resources.

All things considered, there is no good reason to use CCAB as a pre-emptive treatment of IFD.

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Author contributions

J.G. and R.S. drafted the initial manuscript. O.A.C. conceived the idea, critically revised the initial manuscript and contributed to manuscript writing. All authors revised and approved the final manuscript.

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Nephrotoxicity of continuous amphotericin B in critically ill patients with abdominal sepsis: a retrospective analysis with propensity score matching—authors' response

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