

cutoff optical index to 1.0 may result in reduced test sensitivity, which is highly undesirable. If the authors aimed for the nonneutropenic population, they should have clearly stated that bronchoalveolar lavage (BAL) samples are much rather preferred—and in these cases the discussion on optimal GM cutoff would go beyond the purpose of this letter.

We would be happy to hear from authors regarding the change on cutoff optical index values for GM, because no clear data are presented in this revised version of the MSG/EORTC criteria.

## Note

**Potential conflicts of interest.** In the past 5 years, Dr Pasqualotto has received research grants from Gilead, Pfizer, and MSD, which are drug companies that make antifungal drugs. R. M. has no conflict of interest to declare. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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## Reply to Mafacioli and Pasqualotto

TO THE EDITOR—Mafacioli and Pasqualotto [1] question the proposal in the recently published update of the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) definitions of invasive fungal diseases to adopt a cutoff of 1.0 for the galactomannan index (GMI) for both serum and bronchoalveolar lavage (BAL) fluid specimens [2]. They are particularly concerned that this threshold differs from the 0.5 recommended by the manufacturer. In fact, the group involved in the 2008 revision actually failed to reach a consensus on the cutoff for GM and so decided to place the onus on the manufacturer and to adopt whatever threshold values they recommended [3]. Originally, the Platelia *Aspergillus* assay was released with a cutoff index of 1.5, but after review, it was decided to lower this to 0.5 to maximize sensitivity [4]. This increased the utility of galactomannan in clinical practice by allowing cases of invasive aspergillosis to be identified earlier. However, the consensus definitions of the EORTC/MSGERC are actually intended to facilitate clinical research in invasive fungal disease and to enable comparisons between studies. They are not, and never were, intended to direct or guide patient care [2].

By way of illustration, since the publication of the 2008 EORTC/MSG definitions update, two major clinical trials of antifungal agents have actually used other cutoff GMIs to enroll patients with invasive aspergillosis. In the study of Marr *et al*, mycologic criteria for a diagnosis of probable invasive aspergillosis were satisfied when a GMI of at least 0.5 was determined in 2 serum samples or in a single BAL fluid [5]. By contrast, in the study of Maertens *et al* the mycological criteria of probable invasive aspergillosis were met after serum GM test yielded a GMI  $\geq 0.7$  in a single sample or a GMI  $\geq 0.5$  in two consecutive sera. Detecting GM in BAL fluid was not accepted as a mycologic criterion because the assay had not yet been approved by the US FDA for this specimen [6].

The decision to adopt a GMI of  $\geq 1.0$  was not taken lightly but was chosen to help ensure enrollment in clinical trials of patients with a high-likelihood of having invasive aspergillosis. The higher GMI will increase the specificity of the test by lowering the rate of false-positivity although this will inevitably result in a lower sensitivity as was pointed out by Leeflang *et al* [7]. There are even sound arguments for returning the threshold to its original level of 1.5 or even higher to increase the positive predictive value further still. However, as clinical trials on invasive aspergillosis are difficult enough to conduct a very high cutoff could severely limit the number of patients that would be eligible for enrollment. Therefore a cutoff of 1.0 was chosen as the best compromise, both for serum and for BAL-fluid. We hope that the current recommended GMI cutoff will help to further standardize clinical studies in patients with invasive aspergillosis and allow greater inter-study consistency.

## Notes

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## Factors Affecting Inappropriate Antibiotic Prescribing: Illness Severity, Early Nonresponse, and Clinician Seniority

TO THE EDITOR—We read with interest the recent article by Cressman et al exploring physician-acceptable thresholds for organism coverage in empiric antibiotic therapy for sepsis [1]. Their results support the hypothesis that prescribers respond to undifferentiated, unwell patients by selecting broader-spectrum antimicrobial therapy. They postulate that this approach is underpinned by a lower tolerance for inadequate therapy in patients with high acuity or concern that resistant organisms may be associated with a higher acuity presentation. This has led us to reflect on the results of our own recent study, which examined whether clinicians selected broader antimicrobials when presented with scenarios describing severely ill patients, even when the causative pathogen(s) was known.

An anonymous scenario-based survey was sent to doctors of all seniorities (junior medical officer, specialty trainee, and specialist) in internal medicine, surgery, and intensive care at 2 tertiary referral hospitals in Sydney, Australia. This survey consisted of 6 scenarios describing patients with sepsis. In each case the causative organism(s) and their antibiotic susceptibilities had been identified and the patient had received appropriate directed therapy for 48 hours. Half of the scenarios described patients who were either stable or improving while the other half remained severely unwell or were

clinically deteriorating. Respondents were asked to nominate how likely they would be to broaden the current antibiotic regimen using a 9-point Likert scale. To ensure accessibility and prevent information overload, we limited the use of investigations and observations, instead using key phrases such as “stable,” “worsening sepsis,” and “deteriorating.”

The results of our study are summarized in the table. The survey was sent to 1001 clinicians and 171 responded (response rate, 17.1%). Overall, doctors of all seniorities reported that they were more likely to broaden the spectrum of therapy in the “severe” scenarios compared with the “less severe” ( $P < .001$ ). Junior doctors were more likely to broaden therapy than doctors undergoing specialty training or specialists in a number of scenarios (Table 1). There were no significant differences between the responses of specialist trainees and specialists ( $P = .18$ ). The response rate from surgical or intensive care specialties was too low to compare these groups with internal medicine clinicians.

In summary, clinicians of all seniorities and specialties favored broadening antibiotic therapy in patients with more severe infection, mirroring the findings of Cressman et al. However, this behavior persisted despite an established microbiological diagnosis and across a variety of infection sites and pathogens. These results support the idea that clinicians understand antimicrobial therapy using a hierarchical framework in which broader-spectrum agents are perceived to be “stronger” or more effective. This concept, as well as the influence of socio-cultural beliefs on antibiotic prescribing more broadly, has been identified in qualitative interviews with prescribers [2–5]. Clinicians respond to risk and may inadvertently change therapy despite clear clinical data of therapeutic adequacy. We feel that understanding this belief is key to driving effective antimicrobial stewardship interventions and recognizing that prescribing guidelines alone may be insufficient to change clinical practice.