Reply to Crépy and Getsios

To the Editor—We are very pleased that our analysis published in Clinical Infectious Diseases [1] received a close examination by Crépy and Getsios [2]. However, in their letter, Crépy and Getsios stated that they found a discrepancy between the case fatality rates (CFRs) used in our study and their own computations. Specifically, they believe that in our study there exists a significant underestimation of invasive meningococcal disease CFRs attributable to—in their argument—an incorrect calculation.

We disagree with their argument. As we stated in our study [1], we did use meningococcal serogroup-specific CFRs that are concurrent with surveillance data. Figure 1 presents case fatality data from the Active Bacterial Core surveillance system for serogroups C, Y, and W135 by age group averaged over the period 1993–2002 (dark gray bars). These CFRs were estimated using precisely the method represented by the first equation in the letter from Crépy and Getsios [2].

To consider year-to-year variations, these CFRs were imputed into our simulation model. Specifically, with use of standard risk analysis techniques, we fitted probability distributions to the CFR of each age group with feasible and evidence-supported upper and lower values. Figure 1 presents the probability values of the CFRs from each age group (light gray bars) as well as the ranges over which fitted probability functions were distributed. As usually observed when fitting probability distributions and performing simulations, minor differences (mean difference, 5%) were observed between some modeled values reported in our study [1] and the actual data. However, in all cases, the range of probability functions includes the surveillance rate value.

To facilitate comparison, Figure 1 (triangles) also presents the “recalculated” estimates as reported in table 1 of the letter from Crépy and Getsios [2]. It is unclear what source of data they used in their attempt to recalculate the CFRs but, taken at face value, it can be seen that, with the exception of 3 age groups whose rates values are relatively close to the higher end of the intervals used in our model, most of the values presented by Crépy and Getsios show a marked inflation. Even with year-to-year variations, the rates presented by Crépy and Getsios are beyond that which has been observed and reported by the Active Bacterial Core surveillance system for the period 1993–2002 (Figure 1) or other periods (data not shown).

The upward bias of the rates presented by Crépy and Getsios, which are on average 75% higher than the Active Bacterial Core surveillance system rates, will overestimate the number of deaths attributable to the C, Y, and W135 serogroups and would have substantial and questionable consequences for any cost-effective analysis. On further evaluation, we still support our modeling approach, data, and results.

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References

Empirical versus Preemptive Antifungal Therapy for Fever during Neutropenia

To the Editor—We congratulate Coridonier et al [1] on successful completion of a trial that addresses a very complicated issue: the relative utility of antifungal therapy administered “empirically” for fever during neutropenia, compared with a “preemptive” approach that relies on diagnostonic monitoring. As mentioned in the accompanying editorial by de Pauw and Donnelly [2], a challenge to the paradigm of treating fever with antifungals is long overdue, with little supporting evidence generated in the most contemporaneous cohorts of patients. However, there are issues with the design and interpretation of the study that we think deserve further attention.

First, we are concerned that the results of the trial, which measured overall survival as a primary end point and invasive fungal infection (IFI) as a secondary end point, were biased by the institutionally driven rather than protocol-driven administration of effective anti-Candida prophylaxis. Antifungal prophylaxis was particularly uncommon in the group of patients undergoing induction therapy, which is the group in which most of the IFIs occurred. Thus, absence of prophylaxis could have resulted in more breakthrough infection due to Candida species in the preemptive treatment arm, because the preemptive “comprehensive” diagnostic approach relied largely on radiographic abnormalities and use of galactomannan antigen screening, which are more suitable for detection of aspergillosis. Although the monitoring also incorporated sepsis and mucositis as indicators for preemptive therapy, these would occur relatively late or would be poor predictors for driving preemptive therapy. Indeed, the 5 cases of candidemia that occurred in the preemptive treatment arm developed in patients who were not receiving antifungal prophylaxis, supporting the thesis that the secondary end point of IFI may have been driven by lack of effective prophylaxis, not the intervention. If candidiasis was excluded to account for lack of standardization in azole prophylaxis, it appears that IFI in the preemptive therapy arm would be no different than that in the empirical therapy arm, with 7 versus 3 cases of aspergillosis (or 5 vs 3 cases of aspergillosis that would be potentially detected using the lower galactomannan cutoff value of 0.5). Have the investigators analyzed the results on the basis of receipt of antifungal prophylaxis? Also, considering that the definition of “breakthrough infection” only required administration of the study drug for 24 h, the timing of infection onset relative to the start of drug treatment would provide more indication of the impact of prior antifungal therapies. What was the timing of IFI relative to start of amphotericin-based therapy?

Also, the strategy of preemptive therapy is considered to be a tailored strategy of “early” intervention. Ironically, in this study, preemptive therapy driven largely by clinical criteria was “late,” compared to empirical antifungal therapy driven by fever. Thus, the differences in IFI and death that were observed are, to some extent, simply a function of late therapy. With this in mind, the study design did not address preemptive therapy as a form of early intervention that might be expected to impact overall survival.

Finally, perhaps the most important consideration was touched upon by the authors already, but it might not have been fully considered. This strategy is designed to prevent a complication (IFI) that has a relatively low prevalence in the setting of febrile neutropenia. As clinicians, we consider a 10% prevalence to be high—especially for a potentially fatal disease. However, the positive predictive value of the monitoring strategy remained low and was largely capped by a prevalence <25% (Figure 1) [3]. For instance, if the prevalence is 10%, a diagnostic test that is 80% sensitive and 80% specific will generate a positive predictive value of only 31% and a negative predictive value of 97%. In this scenario, using the test to drive treatment implies that 20 of 1000 patients will need therapy but will not receive it, and 180 of 1000 patients will receive therapy but will not need it. One needs to view this in context of the resulting risks that occur in the setting of the mistake—is it worse to not treat someone with disease or to treat someone who doesn’t need it? With these considerations in mind, perhaps we are asking the wrong question when applying frequent monitoring to “predict” and “preempt” development of IFI. In this setting, the negative predictive value remains high—and we are more able to estimate when patients do not need antifungal therapy, compared to when they need it. Because the prevalence of IFIs remains relatively low, essentially capping the positive predictive value of using a test preemptively, and because fever remains a poor predictor of IFI, limiting the utility of empirical therapy, perhaps we should instead be embracing the use of diagnostic monitoring to drive more of a de-escalation strategy. In this setting, we would allow the test result to tell us when therapy is not needed. With this approach, we would be attempting to capture the 20 patients who needed therapy but were missed by the assay. Admittedly, this is a small number to pick up in a large group of negatives. The other approach towards optimization would be to determine how to identify the subgroup that has a high enough pretest probability to support preempt.