Reviewer’s report

Title: Antifungal Prophylaxis in Chemotherapy-Associated Neutropenia: a Retrospective, Observational Study

Version: Date: 6 December 2006

Reviewer: Giorgio Bedogni

Reviewer’s report:

General

The authors performed a retrospective comparison of 2 cohorts of patients taking antifungal medications. I am not able to comment on the clinical relevance of the findings - something already done by the other 2 referees - but I find that in its present form the paper has several statistical problems, which may be partly due to the lack of clarity about how statistical analysis was performed.

---------------------------------------------Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

In ‘Statistical analysis’, the Authors wrote that continuous variables were ‘log-transformed and analyzed using mixed effects logistic regression’. The outcome of (binary) logistic regression is dichotomous, so I suppose that these ‘continuous’ variables were used as predictors. However, I found no reference to them either in the text or in the tables. The same is true for the ‘discrete variables that were analyzed random effects logistic regression’. The Authors must specify their mixed models because there is no reference to them in the text and many outcomes appear to have been analyzed as “simple” 2 x n Tables. Even more important, they should explain why they preferred mixed to fixed effects models. The reason that “the bias was statistically minimized” is not tenable because: 1) bias is never modeled adequately post-hoc and, 2) mixed models have problems on their own.

In Table 1, the Authors should give the standard deviation and the range (min-max) of all continuous variables. The standard deviation (SD) is a measure of the variability between individuals while 95%CI are obtained from the standard error, which is a measure of uncertainty at the population level. For variables that are not normally distributed, the Authors should use the median and interquartile range instead of mean and SD.

Which test was used to compare continuous variables between AMB and AZ patients?

Table 1 identifies potential confounders of the relations of interest (age, days from admission to start of antifungal therapy, duration of therapy). However, no multivariable analysis is reported in the text. It is vital that the potential confounding effect of these and other clinically relevant variables be taken into account in the evaluation of outcomes.

As pointed out by the other referees, another potential confounder is the dosage of antifungal agents, which is not reported. Also this should be taken into account by multivariable models.

The kinds of therapy sum to 181 for AMB patients and this equals the total of patients. However, they sum to 235 for AZ patients, which is greater than the total of 216 patients. Why this difference? Moreover, there are 0 AMB patients in the twin-transplant category, making the evaluation of this 2 x 6 table more complicated. Performing an exact Pearson’s chi-square test I obtained a p value of 0.01051, which is very different from that obtained by the Authors (p = 0.09). Why this difference?

In table 2, the outcome ‘probable infection’ (yes/no) is tested against the kind of therapy (AMB vs AZ). Using a Fisher’s exact test, the p-value is 0.06509, which is different from that obtained by the Authors (p = 0.23). Why this difference? Despite the lack of statistical significance, the trend of more infections in the AZ group may be clinically relevant. I also obtain different values of asymptotic and exact values of p for the probable/definite outcome infection (not shown). If the analysis was obtained by logistic regression, the results should be the same of the Fisher’s (exact) test. If other factors or covariates were included as predictors, this should be specified.

The authors should add confidence intervals to the estimates of outcomes.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Why not adding a Table for hepatic toxicity as done for renal toxicity?

Discretionary Revisions (which the author can choose to ignore)

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What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests