Author’s response to reviews

Title: Hospital days, hospitalization costs, and inpatient mortality among patients with mucormycosis: a retrospective analysis of U.S. hospital discharge data

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Author’s response to reviews:

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Ms. Philippa Harris
Executive Editor
BMC Infectious Diseases

Dear Ms. Harris,

On behalf of my co-authors, I am pleased to submit a revision of the manuscript, titled “Hospital days, hospitalization costs, and inpatient mortality among patients with mucormycosis: a retrospective analysis of U.S. hospital discharge data” to be considered for publication in BMC Infectious Diseases.

All reviewers provided valuable and insightful comments and suggestions. A common observation across reviewers was the lack of clinical detail provided in describing the cases of mucormycosis, such as the site of infection. We have acknowledged in our responses to comments that such granularity was not available in the database (the Healthcare Cost and Utilization Project’s [HCUP] Nationwide Inpatient Sample [NIS]). While we recognize this limitation of the selected data source, we believe that the generalizability of a nationally-representative and large database such as the NIS is a great strength of our study, especially given that mucormycosis is an extremely rare infection.

Please find below our responses to all reviewers’ comments. Within the responses, we have included a description of any changes made to the manuscript since the previous submission.

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Reviewer: Georgios Samonis
Mortality rates (22%) are substantially lower than those reported in the literature (50% to 90%). The authors need to comment on that by providing information on mortality related to the type of infection (e.g., skin and soft tissue infection, pneumonia, disseminated, rhinocerebral, GI etc).

Authors’ Response: While the reviewer raises a valid point, we cannot speculate on the above, as the data do not contain information relating to the site of infection. Furthermore, we focused exclusively on in-hospital mortality and could not follow patients post-discharge.

In addition, separate analysis should be performed on other epidemiological features related to the type of infection.

Authors’ Response: We agree that this would be a valuable supplement to the current analysis; however, clinical data were not available in the database to identify the site of the mucormycosis infection. Therefore we were unable to identify additional confounding clinical characteristics. We have noted this in the discussion section.

Another important feature should be the trends in epidemiology of mucormycosis over the years of the study. For example, did the prevalence, LOS etc remained stable during the study. This is important to note because new therapeutic interventions (e.g., posaconazole treatment) became available over the latter years of the study.

Authors’ Response: We agree that this is an important consideration and have added data on mortality changes over time to the Results section.

Is there any information on mortality and LOS etc related to type of therapy, surgery etc administered to the patients?

Authors’ Response: While such information would be interesting to assess, however, as the NIS data are essentially cross-sectional in nature, they do not allow for analysis of whether a given treatment/procedure preceded or followed the onset of mucormycosis.

Definition of diagnosis of mucormycosis is not provided by the authors. It is important that the authors clarify criteria (e.g., EORTC MSG) used for diagnosis. It is also important to clarify that many cases of probable or possible diagnosis may have been missed. This is particularly relevant in view of the absence of surrogate markers for diagnosis of mucormycosis as opposed to other IFIs.

Authors’ Response: Unfortunately, the data do not contain elements that would allow for further definition of mucormycosis beyond the ICD-9-CM diagnosis code. We have explained this in the text and also added this limitation to the discussion section.

It would have been much more informative to compare the prevalence, length of hospital stay and economic burden in comparison to invasive aspergillosis or other IFIs. The authors should try to analyze these parameters.

Authors’ Response: The reviewer raises a good point; an outcomes comparison
between mucormycosis and invasive aspergillosis would be valuable, however such a direct comparison was not an objective of our analysis. We believe our comparison to Menzin et al. (Ref 12) in the Discussion section to be adequate for our research purposes, as Menzin et al. assessed similar outcomes among a broad IFI population consisting of cases of both aspergillosis, as suggested, and mucormycosis.

Finally, it is important to state the limitations of this and other epidemiology studies in capturing true incidence of mucormycosis that are related to the challenges in achieving a timely diagnosis.

Authors’ Response: We agree and have added relevant limitations to the discussion section.

Reviewer: Maria Drogari-Apiranthitou

In more recent years, in the era of an expanding population of immunocompromised patients, especially those with hematological malignancies, trends regarding underlying diseases have resulted in substantially different proportions than those presented in the ‘classic’ study of Roden et al. cited in the introduction. As this infection constitutes a global threat, I would suggest the more recent data from Europe be also mentioned.


Authors’ Response: We agree that such recent data should be incorporated; the above two references and their associated conclusions have been added to the introduction.

Reviewer: Sebastian Heimann

Major Compulsory Revisions

Methods

1. The authors argue that identification of individuals was not (is not) possible. I have several concerns due to three main aspects: (i) mucormycosis is a very rare fungal infection, (ii) very detailed patient characteristics (e.g. age, sex, race, household income, payer type, underlying disease, comorbidities) were analyzed from the HCUP-NIS database and (iii) hospital characteristics (e.g. geographic region, urbanicity, teaching status, number of beds) could be analyzed, too. To my mind, the above mentioned aspects potentially allow an identification of
human subject data. This raises the question of whether an ethic vote would be needed or not? This and the above mentioned aspects of potential identification of human subject data should be clarified in the methods section.

Authors’ Response: The reviewer raises a good point. To address such concerns regarding identification, we have refrained from reporting cell sizes with N < 10, which is deemed by AHRQ to be an adequate protection against individual patient identification. We have added this explanation to the Methods section.

2. What was the reference time when group distribution of categories A-D was performed? At admission to hospital or during hospitalization? To my mind, in some circumstances, groups are not clear definable. For example, a patient who was severe immunocompromised due to neutropenia after chemo-therapy regimen or stem cell transplantation and an afterwards admission to intensive care unit (and the need of mechanical ventilation for >96h) could be categorized in group A or B. This should be clarified.

Authors’ Response: We have clarified in the text that the reference time was the entire hospitalization; codes by date and time were not available. We have also added this limitation to the discussion section.

3. Are the calculated costs specifically attributed to mucormycosis? More precisely, are e.g. chemotherapy regimens excluded from cost calculation?

Authors’ Response: This analysis assessed all-cause direct medical costs from a hospital perspective. The NIS data do not allow for assessment of specific cost components, attributable costs, nor non-medical costs. We have provided this clarification in the Methods section.

Results

1. A significantly longer LOS was analyzed when comparing the case vs. control group (mean= 16.5 days) resulting in mean excess costs of USD 64,526 for the case group. This means that additionally costs are approximately USD 4,000/day. My main feeling is that these additionally costs per day are higher than expected. Is it possible to make a more precisely cost analysis of the most important cost drivers when treating a patient with mucormycosis? This would be most informative for the reader.

Authors’ Response: While valuable, a micro-costing analysis was not possible with this database due to the lack of details such as hospital units (e.g., ICU) that contribute to these high costs. Such an analysis was also outside the scope of this study, however, we agree that it would be useful for future research.

2. Table 2 & 3 and cost calculation in general: Analysis and calculation of costs and charges is very limited with respect to the main cost drivers or items with the lowest relevance of contribution to the total costs. What was the amount for the treatment on general ward, treatment on ICU, antimycotic respectively antiinfective treatment, diagnostic measures? This information is deeply interesting and should be added if possible. Furthermore it is not clear what kind of costs were analyzed in the study. Were direct medical or non-medical costs
included in cost calculation? This should be also clarified in the manuscript, too.
Authors’ Response: Please refer to our response to Question 3 under “Methods” above.

Discussion

1. In the last sentence of the discussion is written that “…this study likely underestimated the true burden of mucormycosis”. This could be true because e.g. indirect costs were not included in the analysis but caution is warranted because calculation of direct costs for the treatment of mucormycosis was possibly overrated due to the reasons as written in discussion (costs before onset of mucormycosis were potentially included in cost calculation).
Authors’ Response: The reviewer raises a good point; we have modified the text to say, “may have underestimated” as opposed to “likely underestimated”, as we do not know the net effect of both potential over- and under-counting.

Minor Essential Revisions

Methods

1. The type of health economic evaluation should be clarified in the method section. Is it a cost-of-illness analysis without calculation of indirect costs?
Authors’ Response: We have specified in the text that the study was a cost-of-illness evaluation.

2. I have difficulties to understand the meaning of “number of discharge diagnoses” as written in the section of “study measures”. This should be clarified more precisely.
Authors’ Response: The NIS provides up to 25 diagnoses fields, including principal and additional discharge diagnoses. The measure in question refers to the number of such diagnoses on each discharge record. We now refer to this measure as “listed discharge diagnoses” in the manuscript text to provide further clarity.

3. In the last sentence of “study measures” is written that “all costs and charges were adjusted to 2011”. What kind of adjustment was performed? Potentially a discounting due to the analyzed timeframe of 8 years? If so, what discount rate was used?
Authors’ Response: Cost estimates were not discounted since costs for each patient did not span more than one year; this rationale has been added to the manuscript text.

Results

1. Please indicate the percentage of African American and Hispanic in the second paragraph of the results.
Authors’ Response: This has been added to the results section.
2. I have difficulties to understand the meaning of “number of discharge diagnoses” and “number of procedures” as written in table 1. This should be clarified.

Authors’ Response: Please refer to our response to Question 2 under “Methods” above.

Discussion

1. In the last sentence of the second paragraph is written that “data are highly generalizable as they represent the entire complement of the US acute care institutions.” What do the authors mean with “our data”? The clinical outcome, the calculated costs or both? This should be clarified. Furthermore, caution is warranted when comparing the results with other healthcare systems due to very different reimbursement or pricing systems.

Authors’ Response: “Our data” refers to both our clinical and economic results; we have clarified this in the Discussion section. We have also revised the text to avoid the implication that results may be generalizable to ex-US healthcare system, as the reviewer raises a good point that this may not be the case.

Conclusion

1. Most information in this section is redundant with respect to the results and discussion (e.g. increase of hospital resource of 16 days and excess costs of USD 65,000).

Authors’ Response: We agree with the reviewer’s point and have removed actual results from this section to avoid such redundancy.

Discretionary Revisions

Background

1. The following two references could be added in this section because they give a comprehensive overview of clinical data and treatment response of antimycotic therapy:


Authors’ Response: We agree that the suggested sources provide valuable background information and have added them and their associated conclusions to the Introduction section.

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We hope that you find this revised manuscript suitable for publication, and we look forward to your decision.
Sincerely,
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