Author's response to reviews

Title: Ambulatory consolidation chemotherapy for acute myeloid leukemia with antibacterial prophylaxis is associated with frequent bacteremia and the emergence of fluoroquinolone resistant E. coli

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Author's response to reviews: see over
Re: “Ambulatory consolidation chemotherapy for acute myeloid leukemia with antibacterial prophylaxis is associated with frequent bacteremia and the emergence of fluoroquinolone resistant E. coli”

Dear Dr. Harris,

We thank you and the reviewers for their comments regarding our manuscript. We have made several modifications to address the issues that were raised and these are detailed below with reference being made to the revised manuscript for specific page and paragraphs where modifications were made.

The following editorial points were suggested and have been addressed:

1) Please clarify within your manuscript whether informed consent was required or if the ethics committee waived the need for this:

   Informed consent was not required from individual patients. Consent for the study was obtained from the Cancer Registry Data Access Committee and Research Ethics Board of the University Health Network, Toronto, Ontario and is highlighted within the text (Page 4, paragraph 1).

2) Please include a competing interest section:

   The authors have no competing interests. A competing interest section is presented within the text (Page 16, paragraph 3).

3) You may wish to include an acknowledgements section:
An acknowledgements section has now been included (Page 16, paragraph 4).

As per the suggestions of the two reviewers we have made a number of modifications. Reviewer 1 had suggested a number of major and minor revisions which are delineated below:

1) In the method section, Authors do not specify if patients received antibiotic prophylaxis during induction therapy. Data concerning this issue would contribute to clarify epidemiological findings in C1 and C2 and, therefore, should be provided.

   We have now indicated that patients routinely received only anti-fungal prophylaxis during induction chemotherapy (Page 5, paragraph 1).

2) Why did the Authors choose combination empiric antibiotic therapy and why tobramycin instead of amikacin? This is a quite unusual antibiotic schedule.

   As our patient cohort consisted of patients treated between 2002 -2008 we had utilised the 2002 IDSA guidelines for the management of febrile neutropenic patients which recommend the use of either monotherapy or a dual regimen consisting of an aminoglycoside and broad-spectrum penicillin. Based upon the local susceptibility patterns of the bacterial isolates within the hospital it was determined that virtually all isolates were sensitive to either tobramycin or pipricillin/tazocin therefore, in this high-risk population of AML patients, the combination was utilised. This has been highlighted on Page 5, paragraph 2.

   Tobramycin rather than amikacin was utilized as a matter of institutional policy.

3) Coagulase-negative staphylococci bloodstream infections are a relevant part of Gram-positive infections, but Authors do not define “CVC-related bloodstream infection”. Moreover, they consider that their results may be affected by an overestimation of gram-positive infections. In my opinion, this problem must be solved by Authors, as they speculate on the possible epidemiological impact of fluoroquinolones prophylaxis, which may be reconsidered after revision of the data.

   Approximately 30% of our cohort was followed in local community hospitals/clinics where the initial evaluation of febrile episodes occurred (Page 4 paragraph 2, Page 7 paragraph 1 and Page 13 paragraph 2).
Several of these institutions did not differentiate between CVC and peripheral blood cultures. As such, unfortunately, our data precluded any conclusions regarding the incidence of “CVC related bacteremia” (Page 8 paragraph 1, Page 13 paragraph 2).

All febrile neutropenic patients within our institution received broad-spectrum empiric antibiotics. In addition, regardless of whether common contaminants were isolated from 1, 2 or more culture bottles, those with bacteremia related to these organisms received a full course of antibiotic treatment. Thus, regardless of whether the bacteremia was clinically felt to be a contaminant (isolated from 1 culture bottle) or a true bacteremia (isolated from 2 or more culture bottles) patients received identical treatment (Page 6 paragraph 3). As this approach is utilized by a number of institutions in the setting of high-risk AML patients, we did not differentiate between possible contaminants and true bacteremias which likely contributed to our over-estimation of gram-positive bacteremias.

4) The Author should specify genera of streptococci and relative outcome (all viridians)

As per this suggestion, Table 1 now highlights the species of all Streptococci isolates. One patient had two isolates which are also highlighted.

5) Is there any difference in the incidence of E. coli bloodstream infections in the two age groups, as observed for streptococci?

This data was not included initially due to the small number of isolates in both the younger (0 in C1 and 4 in C2) and older (1 in C1 and 6 in C2) cohorts. Although limited, this data suggests that in contrast to the older cohort, younger patients had a statistically significantly higher incidence of E. coli bacteremia following C2 relative to C1 however the small numbers preclude any firm conclusions. We have highlighted this within the text (page 8 paragraph 2).

6) “How do the Authors explain that only E. coli seem to acquire fluoroquinolone resistance unlike other Enterobacteriaceae?

Given the increased incidence of fluoroquinolone resistance amongst E. coli that was observed within our cohort this is a particularly important question. However, the data are limited and no clear-cut answer is available.

Studies evaluating fluoroquinolone resistance have consistently demonstrated the increased incidence of fluoroquinolone resistant
amongst *E. coli*. This effect has been observed both in patients receiving fluoroquinolones for treatment and for prophylaxis. Although, several of these studies have reported on the occurrence of fluoroquinolone resistance in other *Enterobacteriaceae* and *Pseudomonas aeruginosa* the frequencies were significantly lower relative to *E. coli*. In our cohort ciprofloxacin resistant was observed in only 1 *Pseudomonas* isolate in C1 and none of the other *Enterobacteriaceae* in either C1 or C2. We have summarized these findings further within the results section (Page 9 paragraph 1) and provide a potential explanation within the discussion (Page 12 paragraph 2).

7) Definitions of C1 and C2 should be reported also in the text as well as in the abstract.

*Definitions of C1 and C2 have now been incorporated within the Methods section (page 4, paragraph 2) as well as the abstract.*

8) Table 1 should report also sex among patient’s characteristics.

*The male to female ratio is now incorporated into the text of Table 1 as the percentage of patients that were male within each cohort.*

As per the suggestions of Reviewer 2 the following point were addressed:

1) Data are quite old since recorded until 2008, and now we are in end 2012: 4 years is a very long period for selecting resistant pathogens!

*Our cohort consists of patients who were treated at the PMH between 2002 and 2008. After having obtained ethics approval the study was initiated in 2010. Data collection, statistical analyses, manuscript preparation and revision followed subsequently over the remaining time period.*

*During our initial analyses we considered the possibility of a temporal relationship to antibiotic resistance. To evaluate this relationship patients were divided into those that received treatment from 2002-2005 and those that were seen from 2005-2008. As we observed no significant differences in the bacterial isolates or the antibiotic resistance patterns over these two time periods the data was combined and subsequent analyses focused on the overall cohort.*

*Although we have not formally assessed the development of resistance subsequent to 2008 as a part of the current study, ongoing monitoring*
continues through the Departments of Infectious Diseases and Medical Microbiology.

2) I have major concerns about the definition of bacteremias due to Coagulase negative staphylococci: 2 blood cultures within 72 hours. This is not an acceptable definition, with the exception of very low birth weight neonates. But this is not the case. This very wide definition probably explain the very high frequency of this diagnosis.

Following presentation for febrile neutropenia and the initiation of broad-spectrum antibiotics most patients became readily afebrile and in these patients blood cultures became negative within 72 hours of initiating treatment. However, during this initial 72 hour period, a minority of patients continued to have recurring fevers. Occasionally, in these persistently febrile patients, repeated blood cultures yielded the same organism as identified in the initial blood cultures taken upon presentation. Under these circumstances, we did not consider the two bacterial isolates to be different if they had the same antibiotic susceptibility profile. This applied to all organisms including, but not limited to, coagulase negative staphylococci, Streptococci spp., and other gram-positive and gram-negative isolates.

We have clarified this point by removing reference to ‘72 hours’ and have stressed that repeat cultures in persistently febrile patients yielding the same organism with the same antibiotic susceptibility profile were considered as one isolate (Page 6, paragraph 2). If the positive blood cultures were separated by one or more negative blood cultures patients were considered to have two separate bacteremic episodes with two separate isolates (Page 6, paragraph 2).

3) As regards the use of ciprofloxacin in prophylaxis (as intended by the authors), the high proportion of resistant strains should discourage to continue its use (see IDSA Guidelines 2011).

The continued use of fluoroquinolone prophylaxis despite data suggesting the emergence of fluoroquinolone resistance has been contentious. The 2002 guidelines proposed by the IDSA did not recommend the routine use of prophylactic antibiotics due to concerns of antibiotic resistance. However, additional studies including those of Bucaneve et al. as well as the meta-analysis of Gafter-Gvili et al. and Leibovici et al. showing a survival benefit in high-risk patients have led the IDSA in the revised 2011 guidelines to suggest that chemoprophylaxis be considered for high-risk-
patients (expected durations of prolonged and profound neutropenia i.e. ANC<100 cells/mm$^3$ for >7 days).

The effect of discontinuing prophylactic antibiotics has been investigated in several studies with variable effects on mortality although virtually all have suggested an increase in gram-negative bacteremias. We have now presented several of these studies within the discussion (Page 12 paragraph 3 and Page 13 paragraph 1).

Despite these observations and recommendations the Princess Margaret Hospital and the affiliated hospitals have instituted several mechanisms to monitor the development of antibiotic resistance and adjust prophylactic antibiotic regimens and empiric treatments accordingly. At the current time, we are continuing the use of prophylactic antibiotics in this high-risk patient population, however based upon the results of our antibiotic resistance monitoring programs this may need to be further evaluated.

We feel that comments by the reviewers have helped improve the manuscript and we hope that we have been able to address their concerns. We look forward to hearing from you.

Sincerely,

Joseph Brandwein, MD