The manuscript entitled ‘Contemporary Strategies in Stem Cell Transplantation for Chronic Granulomatous Disease’ reviewed approaches for hematopoietic stem cell transplant in patients with chronic granulomatous disease, including impact of patient and donor characteristics on outcomes, conditioning regimens, and continued challenges of transplant-related morbidity and post-transplant autoimmunity. This research has certain clinical value. However, there are still some minor issues that need to be addressed before the paper is accepted for publication.

Comment 1: Due to risks, HSCT was initially reserved for individuals with severe disease. What are the main risks of HSCT? What are the new developments in response to these risks?
Reply 1: We thank the reviewer for these comments and have added additional information to address both of these questions to the manuscript (lines 70-72 and 75-78). Inclusion of these details helps to better frame the primary thesis of the manuscript with more detailed discussion of these topics in the subsequent sections of the manuscript.

Comment 2: While HSCT is increasingly utilized for patients with CGD, existing comorbidities can adversely impact outcomes and toxicities. What co-morbidities will affect outcomes and toxicities?
Reply 2: We have edited the text to further clarify this question (line 83). The details are further discussed in the “Patient characteristics” subsection.

Comment 3: Post-transplant complications, though, were significant, including severe graft-versus-host disease (GVHD), viral reactivation, progression of ongoing fungal infection, and new infection with Pneumocystis jiroveci pneumonia. Are there any early prediction and prevention measures for these complications?
Reply 3: We thank the reviewer for raising this question. Unfortunately, there are no tools available for early prediction of which patients will develop these complications. This is applicable to transplants in general, in addition to its importance for CGD patients undergoing transplant. There are several preventative measures that are implemented in the post-transplant period to try to prevent occurrence of these complications. Current practice relies primarily on prophylaxis with antibacterial, antifungal and antiviral medications in combination with immune suppression to prevent GVHD. We have added a statement to the text to highlight the lack of predictive tools and the importance of supportive care post-HSCT to prevent complications (lines 106-108).

Comment 4: In addition to age, active infection and chronic inflammatory bowel
disease were associated with decreased survival after HSCT. Can preoperative control of active infection and IBD increase the survival rate after HSCT?

Reply 4: We thank the reviewer for this question. Several published studies have highlighted that patients with CGD who had active infection or active inflammation, including IBD, have higher risk of complications post-transplant. Indeed, in some reports (Soncini et al 2009) these were the only patients who had mortality or severe GVHD post-transplant. Pre-transplant control of active infection does reduce risk of progression of infection post-transplant and risk of associated post-transplant mortality. Data from studies also suggests that reduction in pre-transplant inflammation, i.e. control of IBD, reduces risk of GVHD post-transplant. However, the quantitative benefits of this are not entirely clear and delaying transplant for resolution of infection/inflammation is not always best nor always translate to better outcomes. There are not studies specifically whether perioperative control (i.e., ileostomy, colectomy) of IBD impact survival post-HSCT. Further studies are needed to better address these specific questions. We have included additional details in the text to clarify these points (lines 118-126).

Comment 5: Patients with CGD may be at increased risk for the development of autoimmune disease post-transplant due to higher immune dysregulation and inflammation prior to transplant. Further research is necessary to quantify the incidence of autoimmune disease with newer transplant regimens, to delineate specific risk factors, and to develop strategies to mitigate this complication. Can immune regulation and inflammation be reduced before transplantation to reduce complications?

Reply 5: Thank you for this thoughtful comment. The increased incidence of posttransplant autoimmune disease in CGD patients has been postulated to be related to the underlying immune dysregulation and inflammation in CGD patients. It's not evident from the available literature, though, if the increased incidence is due to active immune dysregulation/inflammation at the time of transplant or if there’s a predisposition that is inherit to generally to CGD, regardless of whether there is active immune dysregulation/inflammation. We clarified this in the revised manuscript (lines 276-279).

Comment 6: While new approaches to transplant and GVHD prophylaxis have reduced its incidence and severity, GVHD continues to be a serious complication with potential for a deleterious impact on survival and quality of life, particularly with the use of alternative and mismatched donors. What are the potential causes of GVHD? What treatments are available to prevent GVHD?

Reply 6: Following HSCT, GVHD is triggered by the combination of alloreactive T cells and tissue injury. In CGD patients, this tissue injury can be induced by transplant specific factors (i.e., conditioning therapy, medications) or by CGD-specific factors, such as pre-existing infections, inflammation or organ injury. How much transplantversus CGD-specific factors independently contribute to GVHD incidence is not known. It is evident from available publications that CGD patients with pre-existing infections and inflammation have higher rate of post-HSCT complications, including GVHD. This is discussed in the “Patient characteristics” section and in the revised text.
in response to Comments 3 and 4. Regarding prevention of GVHD, novel approaches to immune suppression and graft manipulation have been successful in reducing incidence and severity of GVHD post-transplant in CGD patients. We edited the text in the revised manuscript to address both of these questions (lines 303-307).