Is Cystic Fibrosis Contributing Significantly to Infant Mortality Rate in India?

Cystic fibrosis is a life-limiting, genetic disease. Over the last 80 years, predicted life expectancy of affected individuals has improved from less than one year to the fifth decade of life, largely due to early initiation of aggressive supportive treatment [1]. In India, diagnosis of cystic fibrosis is made at an average age of 4.5 to 6.5 years and is associated with high mortality in childhood [2-4].

Over the last decade, at a tertiary care center in southern India, blood samples for *CFTR* mutation analysis were stored, with the permission of the parents after genetic counseling, for all critically ill young infant in the PICU with a presumptive diagnosis.

In this retrospective study, we reviewed the mortality data of young infants between 1 and 6 months of age during 3.5 years period from July, 2018. Institutional review board approval was obtained. There were total 81 young infant deaths. The diagnosis of cystic fibrosis was confirmed posthumously in six infants (mean age 3.7 month) by *CFTR* mutation analysis on stored blood. The clinical diagnosis at the time of death were severe community-acquired pneumonia in five and intracranial bleed in the sixth baby. Notably, all had failure to thrive, anemia (mean hemoglobin 6.9 g/dL, range 4.7-10.6g/dL) and hypo-albuminemia (mean serum albumin 1.9 g/dL, range 1.5 - 2.9g/dL). During the study period, cystic fibrosis was found to be the fourth most common cause of death in this age group, after cardiac disease (48%), pneumonia/sepsis (25%) and other congenital conditions (19%).

We believe, that these undiagnosed cystic fibrosis cases may be contributing to the infant mortality, especially in tertiary care centers located in geographic areas where *CFTR* mutation carrier frequency is high and endogamous marriages are practiced. Infant deaths due to cystic fibrosis can be prevented with timely genetic counseling, early diagnosis and initiation of supportive treatment. Accurate data on incidence and genetic profile of cystic fibrosis in India need to be generated to understand the true burden of this disease and the related infant mortality.

Pediatricians in India should have high index of suspicion for cystic fibrosis clinically. It should be suspected if there are two or more features of recurrent pneumonia, oily stools, history of consanguinity, history of sibling death, hypochloremic hypo-kalemic metabolic alkalosis and isolation of pseudomonas from respiratory specimens. With a presumptive diagnosis of cystic fibrosis, treatment can be started even without sweat chloride or genetic tests and confirmation may be done when feasible.

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Referencing Made Easy: Handling Reference Management Softwares

As a long-time user of the Zotero reference management system, I read with interest the recent article on reference management softwares [1]. I consider reference management systems (RMS) to be one of the most useful tools that have been brought for writers in the last two decades. Developments in the RMS field have been quite dynamic in recent years and therefore, I would like to underscore additional points regarding them.

The authors stated in Table I that Zotero does not allow reference sharing. I have been using groups in Zotero (*https://www.zotero.org/groups/)* for reference sharing for many years. Second, the authors stated that users of other RMS than Endnote, Mendeley and Citavi cannot use annotations as sticky notes and highlight texts in PDFs directly in RMS. This feature has been added to Zotero since version 6 was released in 2021 (*https://www.zotero.org/blog/zotero-6/*).

The authors have also stated that each author needs to meet the specific citation requirements of the journal. It is worth noting that many journals and international publishers do not

require strict formatting manuscripts and references by authors in the spirit of "Your Paper, Your Way" [2]. It may be mentioned that RMS can be used by editorial office to format references in manuscripts according to journal's requirements and authors do not need to meet journal's requirements when submitting a manuscript [3].

I would also like to comment on the CSL language mentioned in the paper. The CSL is a universal language and several dozen RMS use it for formatting citations and bibliography (*https://citationstyles.org/*). In contrast, other RMS use other (custom) style editors to format citations and bibliography. I consider the main advantage of RMS that use CSL is the support from the community, which has been able to add missing citation styles to the style repository in a short time since request by researchers (*https://github.com/citation-style-language/styles/blob/master/REQUESTING.md*). Thus, researchers do not have to learn to use the style editor function of the RMS to create bibliography in the missing format.

In the end, RMS is a powerful tool. However, there is no "the best" RMS because every RMS has its own strengths and weaknesses. Just like each of us has different working habits and everyone has different needs. Articles comparing different RMS, which can be found in the literature, are great for pre-selecting suitable RMS, but they are no substitute for personal experience. Therefore, I encourage everyone to try several RMS and after that he/she chooses the best one that suits them personally or the work team they work with.

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AUTHOR'S REPLY

We thank the reader for interest in our article and thank them for pointing out the updates in the reference management softwares (RMS). We also agree with the statement that since every single RMS has unique advantages and disadvantages, each user must find the RMS that best suits their needs [1].

We acknowledge their point regarding Table I. Zotero does allow for creation of groups (private; public, closed and public, open). Once a group is created and members invited, the Group folder appears in each member's Zotero (the software on their computer). Each member may add content to the shared folder, then sync. However it is important to note that group libraries are wholly separate from 'My Library' section on Zotero, and items may need to be dragged and dropped in the appropriate sections, if the permissions of the groups allow it [2,3].

It was interesting to know that Zotero 6, in its latest update has added many new tools which allow the user to open PDFs in a new built-in reader within the main Zotero window (in a new tabbed interface), allow them to mark up PDFs with highlights, notes, and image annotations, and allow addition of annotations to Zotero notes with automatic citations. It also allows for non-English spell checking [4[.

We agree some international/Indian journals do allow authors to submit their articles without meeting stringent formatting norms, atleast for the first draft, enabling them to primarily focus on the content and also increasing submission rates to journals. This was adopted primarily under the 'your paper, your way initiative' and currently many journals (mostly Elsevier) allow format free submissions [5,6]. But still, many Indian and international journals are very particular about submission being in a particular style and format, with articles being sent back at the initial stage.

We agree that most well established RMS have a huge support community, which keep on adding missing reference styles. But in some cases, the authors may not find the style that matches specific journal requirements (where they intend to submit). In such cases, knowing the style editor function may help bridge the gap.

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