Author's response to reviews

Title: An etiological reappraisal of pancytopenia - largest series reported till date from a single tertiary care teaching hospital

Authors:

Arvind Jain (drarvind.jain@yahoo.com)
Manjiri Naniwadekar (drarvindj@rediffmail.com)

Version: 2 Date: 23 July 2013

Author's response to reviews: see over
Author's response to reviews

Title: An etiological reappraisal of pancytopenia - largest series reported till date from a single tertiary care teaching hospital

MS: 1554966599948522

Authors:
Arvind Jain (drarvind.jain@yahoo.com)
Majiri Naniwadekar (drarvindj@rediffmail.com)

Version: 2 Date: 23 July 2013

Author's response to reviews: see over

Dear Dr. Diana Marshall,

We refer to your e-mail dated 11th June 2013 and thank you and the two external reviewers for all your efforts with our manuscript. Thanks for your kind suggestion to revise and resubmit our piece of work to BMC Hematology.

The comments of the reviewers were highly insightful and enabled us to improve the quality of our manuscript. In the following pages are our point-by-point responses to each of the questions and comments of the reviewers, clearly indicating how and where in the manuscript (page numbers) changes have been made.

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in BMC Hematology. Thus herewith we would like to resubmit the revised version of our manuscript “An etiological reappraisal of pancytopenia - largest series reported till date from a single tertiary care teaching hospital” for publication as an original article in BMC Hematology.

We shall look forward to hearing from you at your earliest convenience.

Best wishes and Regards.

Yours sincerely,
Arvind Jain
Director / HOD – Laboratory Medicine Department,
Imperial College London Diabetes Centre (ICLDC),
P.O. Box no. – 222464,
Al Ain, U.A.E.
Response To Reviewer’s Comments

Reviewer: Zonghong Shao

Version: 1

Date: 30 April 2013

Reviewer's report:

Minor Essential Revisions

The authors in this study investigated the incidence of pancytopenia caused by various causes through a two years' study on 250 cases of pancytopenia. An etiological classification of pancytopenia was put forward, showing that hypersplenism, infections, myelosuppressants and megaloblastosis were the most common causes of pancytopenia in this centre of India. The authors also compared their findings with those of other similar studies in the world, and provided probable explanations for the differences and similarities. This is a significant work providing useful information for clinicians in differentiating and managing pancytopenia.

Response: Thank you

There are a few questions:

1. In Table 1, in the subtypes of "Infections", was there any crossing between "Septicemia" and "Enteric fever" or "Tuberculosis"? It would be better to describe the pathogens causing septicemia in detail.

We thank the reviewer for this important remark. No, there was no any crossing between ‘Septicemia’ and ‘Enteric Fever’ or ‘Tuberculosis’.

Overwhelming bacterial infections and fulminating septicemia are known to cause various hematological manifestations including pancytopenia. Both gram positive (Staphylococci, Streptococci, Pneumococci and Hemophilus influenzae) and gram negative (Meningococcus, Escherichia Coli, Pseudomonas and Kleibsiella) organisms have been found to be the common causative organisms.

In agreement with Reviewer #1’s suggestion, we have now added two small paragraphs on septicemia causing pancytopenia, one each in results (Page no. 6) and discussion (Page no. 11) sections of the manuscript.

2. Since pancytopenia caused by "Leukemia", "Lymphoma" and "Plasma cell dyscrasia" shared the same mechanisms of infiltration by malignant cells, they could be integrated into one group.
We totally agree with reviewer’s comment that ‘Leukemia’, Lymphoma’, Plasma cell Dyscrasia’ are commonly subclassified together under disorders replacing / infiltrating the bone marrow for the causes of pancytopenia. However, each of these disorders has different clinical presentation and different hematological findings at the time of presenting as pancytopenia. Also, there may be additional unique mechanisms playing their role in development of pancytopenia at different stages of the disease in addition to bone marrow infiltration.

For e.g. anemia and thrombocytopenia are common in majority of leukemia patients, the white cell count being more variable ranging between subnormal to markedly elevated values. Whereas in Plasma cell disorders, erythropoiesis is repressed the earliest and most frequently while granulopoiesis and thrombopoiesis are affected as the disease progresses. Also, it is much common to see leukemia patients present with pancytopenia than it is for the lymphoma or plasma cell dyscrasias.

All the studies conducted on this topic till date and as referred by us at the time of preparation of this manuscript have classified each of these causes separately instead of integrating them into one single group and so have we. We hope that Reviewer #1 will agree with this point of view and would allow us to keep our etiological breakup of 250 cases of pancytopenia unaltered for better comparability with other similar studies.

3. **Written English needs to be improved before publication.**

We thank Reviewer #1 for the constructive comments and suggestion. The entire piece has been carefully revised, placing particular emphasis on English grammar, careful language editing etc. and reads better now.

**Reviewer:** Vineeta Gupta

**Version:** 1

**Date:** 11 May 2013

**Reviewer's report:**

Authors have reported the possible etiological factors for pancytopenia from a single center in India. Specific comments are as follows:

**Title: It is too long and inappropriate.**

We believe that title should provide important information regarding the manuscripts content. It should be specific to the study, informative, descriptive and yet concise. It should be comprehensible to readers both within and outside our field and should allow sensitive and specific electronic retrieval of the article helping in indexing and searching of the article by researchers, a role it shares with keywords.
Many comparable standard journals allow over 150 characters and spaces for the title and 40 – 50 characters for the running title. Ours is well within these limits. This particular title was chosen after a lot of deliberation as we felt that this is what represents our article the best.

*Introduction*: The statement that "there aren't many comprehensive studies on this topic from developed world...." is incorrect. Do authors mean "developing countries"? There are many studies available on the topic is evident from the fact that the authors themselves have quoted 16 studies on the topic from developing countries. There are other studies also which have not been quoted. So the topic is well researched!

The statement that “there aren't many comprehensive studies on this topic from developed world....” is absolutely correct and is not any typing mistake in place of “developing countries”. Although, extensive studies have been done for individual etiological factors of pancytopenia like aplastic anemia, megaloblastic anemia, leukemia, myelodysplastic syndrome, etc. in developed part of the world.

Pancytopenia has been a relatively untouched topic by all prominent indigenous textbooks of Internal Medicine and Haematology. For years pancytopenia has been equated with aplastic anemia, resulting in unnecessary referral to a hemato-oncologist, resulting in unnecessary financial and emotional burden for the patient and his family. Etiological causes of pancytopenia as reported in literature from developed countries are completely different as compared to the patient profile we see in developing countries like India. Hence there was an imminent need for studies to determine etiology and generate a plan for evaluation and treatment of pancytopenia based on local factors.

Yes, we have quoted about 16 studies for comparison and to highlight the variety of different causes found by each study. The variation in the frequency of various diagnostic entities causing pancytopenia in different population groups has been repeatedly attributed to differences in methodology and stringency of diagnostic criteria, inclusion / exclusion criteria, referral population, period of observation, geographic area, age pattern, nutritional status, prevalence of infective disorders, genetic differences, population risk factors (varying exposure to myelotoxic agents viz. chemicals, drugs, agricultural pesticides, radiation etc.), availability of advanced laboratory workup facility, healthcare delivery system amongst other factors. The comparison table (Table no. 2) highlights this point very well.

Majority of literature on pancytopenia has been published in the last decade, more so from 2008 onwards. Considering the number of developing countries and the vastness of a country like India, we believe that there is still a lot of scope for more studies to be conducted and published on this topic. This will not only help in increasing awareness of treating physicians towards pancytopenia but will also prevent wrong diagnosis or misdiagnosis, at the same time avoiding unnecessary tests which not only add to the expense of treatment but sometimes also may result in delayed diagnoses and treatment.
We resonate with the findings of reviewer #1 that “this is a significant piece of work providing useful information for clinicians in differentiating and managing pancytopenia”.

**Material & methods: Inclusion criteria are not clear. Did all patients undergo a bone marrow examination?**

All the patients referred to the central clinical laboratory for routine complete blood count (CBC) and peripheral smear (PS) examination, from outpatient and inpatient departments were screened for pancytopenia and a total number of 250 cases were selected, based on the criteria’s defined by deGruchy [1] as follows –

1) Hemoglobin (Hb.) level – below 13.5 g/L for males and below 11.5 g/L for females
2) Total Leucocyte Count (TLC) - below $4 \times 10^9$/L
3) Platelet (Plt.) count – below $150 \times 10^9$/L

No, all patients did not undergo bone marrow examination. It was done wherever indicated and possible, avoiding the cases where the cause for pancytopenia was obvious like congestive splenomegaly, malaria, enteric fever, known case of AIDS and patients on myelosuppressants.

**What was the cellularity in cases of aplastic anemia?**

Bone marrow aspiration was done in all the 12 cases of hypoplastic / aplastic anaemia, which showed hypocellular fragments with moderate to severe hypocellularity and increased fat spaces. Marrow aspirate was found to be inadequate to give definite diagnosis in all the four cases of aplastic anaemia and hence a biopsy was recommended, which confirmed the diagnosis.

**Why were patients from 2 months to 95 years grouped together? Etiology of pancytopenia is very different in pediatric age group as compared to adults. Causes like alcoholic cirrhosis do not feature in pediatric population. The data would have been more informative if authors had divided patients according to age groups.**

As has been highlighted above and in the paper, variation in the frequency of various diagnostic entities causing pancytopenia in different population groups has been repeatedly attributed to differences in methodology and stringency of diagnostic criteria, inclusion / exclusion criteria, referral population, age pattern, etc. amongst other factors.

We did not want these factors to create a selection bias in our study and hence included all patients referred to the central clinical laboratory for routine complete blood count (CBC) and peripheral smear (PS) examination, from outpatient and inpatient departments and found to be pancytopenic, keeping our inclusion / exclusion criteria’s to the bare minimum which allowed us to minimize potential selection bias.
In agreement with Reviewer #2’s suggestion, a table (Table no. 3) indicating age distribution of various causes of pancytopenia has now been added in the manuscript.

**Results:** Patients on chemotherapy and radiotherapy should not be included in analysis as these are known causes of myelosuppression

We understand that many of the causes of pancytopenia other than chemotherapy and radiotherapy like aplastic anemia, acute leukemia, myelophthisis etc. are known causes of myelosuppression at some stage or the other of the disease and their clinical presentation and so being a myelosuppressant should not be the sole criteria to exclude them from the study or its analysis.

In spite of our institute being considered a regional referral centre for the treatment of cancer and despite of us having separate oncosurgery and radiotherapy units; myelosuppressants in the form of drugs, chemotherapy and radiotherapy came only as the third most common cause of pancytopenia highlighting the fact that there are still many other varied and important causes of pancytopenia.

We would have surely considered excluding myelosuppressants (chemo and radiotherapy) from our study group if it had turned out to be the commonest cause of pancytopenia or if we felt that it was unnecessarily creating a bias, but that was not the case.

We strongly feel that exclusion of patients developing pancytopenia secondary to myelotoxic chemotherapy for hematologic or other malignancies in few of the studies has caused a selection bias in these studies and has reduced the comparability of these studies with that of ours. However, there are few studies like ours who have included cases of pancytopenia secondary to chronic use of drugs including chemotherapy in their study of pancytopenia and have been found to have comparable results.

**Discussion:** Needs modification as per comments given above.

This study was the first study to be conducted in our institute on pancytopenia and based on the findings of this study; more study groups and pancytopenia task forces have been formed to study further the topic separately in pediatric and adult patient groups with different permutation and combination of various inclusion and exclusion criteria’s.

We reiterate that to avoid selection bias from creeping into our study we have kept our inclusion / exclusion criteria’s to the basic and have treated this study as a starting point for many more studies to come on this topic from our institute.

We thank Reviewer #2 for the interest in our work and for highlighting these important issues. We have now carefully revised our manuscript keeping the suggestions in mind.

**Quality of written English:** Acceptable