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Mohakhali, Dhaka-1212, Tel : 8825005-6, 8856616, 9884189, 9884194, 9891865 Ext. 124, Fax : 880-2-8828928,
E-mail : <bcps@bcps-bd.org> Editor's e-mail: journal.bcps@gmail.com

Journal of Bangladesh College of Physicians and Surgeons (JBCPS)

INFORMATION FOR AUTHORS

MANUSCRIPT PREPARATION AND SUBMISSION

Guide to Authors

The Journal of Bangladesh College of Physician and Surgeons, provides rapid publication (quarterly publication) of articles in all areas of the subject. The Journal welcomes the submission of manuscripts that meet the general criteria of significance and scientific excellence.

Papers must be submitted with the understanding that they have not been published elsewhere (except in the form of an abstract or as part of a published lecture, review, or thesis) and are not currently under consideration by another journal published by **INTERNATIONAL RESEARCH JOURNALS** or any other publisher.

The submitting (Corresponding) author is responsible for ensuring that the article's publication has been signed approved by all the other coauthors. It is also the authors' responsibility to ensure that the articles emanating from a particular institution are submitted with the approval of the necessary institutional requirement. Only an acknowledgment from the editorial office officially establishes the date of receipt. Further correspondence and proofs will be sent to the corresponding author(s) before publication unless otherwise indicated. It is a condition for submission of a paper that the authors permit editing of the paper for readability. All enquiries concerning the publication of accepted papers should be addressed to -

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BCPS Bhaban
67 Shaheed Tajuddin Sarani
Mohakhali, Dhaka 1212,
BANGLADESH
Phone: +8802-8825005 +8802-8825005
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Submit manuscripts as e-mail attachment to the editorial office at: journal.bcps@gmail.com

A manuscript number will be mailed to the corresponding author within two working days.

The **cover letter** should include the corresponding author's full address and telephone/fax numbers and should be in an e-mail message sent to the editor, with the file, whose name should begin with the first author's surname, as an attachment.

The Journal of Bangladesh College of Physicians and Surgeons will only accept manuscripts submitted as e-mail attachments or triplicate Hard copy with a soft copy

Article Types

Five types of manuscripts may be submitted:

Editorials: It will be preferably written invited only and usually covers a single topic of contemporary interest.

Original Articles: These should describe new and carefully confirmed findings, and experimental procedures should be given in sufficient detail for others to verify the work. The length of a full paper should be the minimum required to describe and interpret the work clearly.

Short Communications: A Short Communication is suitable for recording the results of complete small investigations or giving details of new models or hypotheses, innovative methods, techniques, images in clinical practice, letter to editors, short reports or apparatus. The style of main sections need not conform to that of original article. Short communications are 2 to 4 printed pages (about 6 to 12 manuscript pages) in length.

Reviews: Submissions of reviews and perspectives covering topics of current interest are welcome and encouraged. Reviews should be concise and no longer than 4 to 6 printed pages (about 12 to 18 manuscript pages). It should be focused and must be up to date. Reviews are also peer-reviewed.

Case Reports: This should cover uncommon and/or interesting cases with appropriate confirmation process.

Review Process:

All manuscripts are initially screened by editor and sent to selective reviewer. Decisions will be made as

rapidly as possible, and the journal strives to return reviewers' comments to authors within 3 weeks. The editorial board will re-review manuscripts that are accepted pending revision. The JBCPS editorial board will try to publish the manuscript as early as possible fulfilling all the rigorous standard journal needs.

I. A. Preparing a Manuscript for Submission to JBCPS

Editors and reviewers spend many hours reading manuscripts, and therefore appreciate receiving manuscripts that are easy to read and edit. Much of the information in this journal's Instructions to Authors is designed to accomplish that goal in ways that meet each journal's particular editorial needs. The following information provides guidance in preparing manuscripts for this journal.

Conditions for submission of manuscript:

- All manuscripts are subject to peer-review.
- Manuscripts are received with the explicit understanding that they are not under simultaneous consideration by any other publication.
- Submission of a manuscript for publication implies the transfer of the copyright from the author to the publisher upon acceptance. Accepted manuscripts become the permanent property of the Journal of Bangladesh College of Physicians and Surgeons and may not be reproduced by any means in whole or in part without the written consent of the publisher.
- It is the author's responsibility to obtain permission to reproduce illustrations, tables etc. from other publications.

Ethical aspects:

- Ethical aspect of the study will be very carefully considered at the time of assessment of the manuscript.
- Any manuscript that includes table, illustration or photograph that have been published earlier should accompany a letter of permission for re-publication from the author(s) of the publication and editor/publisher of the Journal where it was published earlier.
- Permission of the patients and/or their families to reproduce photographs of the patients where identity is not disguised should be sent with the manuscript. Otherwise the identity will be blackened out.

Preparation of manuscript:

Criteria: Information provided in the manuscript are important and likely to be of interest to an international readership.

Preparation:

1. Manuscript should be written in English and typed on one side of A4 (290 x 210cm) size white paper.
2. Margin should be 5 cm for the header and 2.5 cm for the remainder.
3. Style should be that of modified Vancouver.
4. Each of the following section should begin on separate page :
 - o Title page
 - o Summary/abstract
 - o Text
 - o Acknowledgement
 - o References
 - o Tables and legends.

Pages should be numbered consecutively at the upper right hand corner of each page beginning with the title page

I. A. 1. a. General Principles

- The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is a direct reflection of the process of scientific discovery.
- Long articles may need subheadings within some sections (especially Results and Discussion) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, probably need to be formatted differently.
- Electronic formats have created opportunities for adding details or whole sections, layering information, crosslinking or extracting portions of articles, and the like only in the electronic version.
- Authors need to work closely with editors in developing or using such new publication formats and should submit supplementary electronic material for peer review.
- Double-spacing all portions of the manuscript—including the title page, abstract, text, acknowledgments, references, individual tables, and

legends—and generous margins make it possible for editors and reviewers to edit the text line by line and add comments and queries directly on the paper copy.

- If manuscripts are submitted electronically, the files should be double-spaced to facilitate printing for reviewing and editing.
- Authors should number on right upper all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.

I. A. 1. b. Reporting Guidelines for Specific Study

Designs

Research reports frequently omit important information. Reporting guidelines have been developed for a number of study designs that JBCPS journals ask authors to follow. Authors should consult the Information for Authors of this journal. The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged also to consult reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (<http://www.equator-network.org/home/>) or CONSORT network (<http://www.consort-statement.org>).

I. A .2. Title Page

The title page should have the following information:

1. Article title. Concise titles are easier to read than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying type of trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.
2. Authors' names and institutional affiliations.
3. The name of the department(s) and institution(s) to which the work should be attributed.
4. Disclaimers, if any.
5. Contact information for corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript .
6. The name and address of the author to whom requests for reprints should be addressed or a Statement that reprints are not available from the authors.

7. Source(s) of support in the form of grants, equipment, drugs, or all of these.
8. A short running head or footline, of no more than 40 characters(including letters and spaces). Running heads are published and also used within the editorial office for filing and locating manuscripts.
9. The number of figures and tables. It is difficult for editorial staff and reviewers to determine whether he figures and tables that should have accompanied a manuscript were actually included unless the numbers of figures and tables are noted on the title page.

I. A. 3. Conflict-of-Interest Notification Page

To prevent potential conflicts of interest from being overlooked or misplaced, this information needs to be part of the manuscript. The ICMJE has developed a uniform disclosure form for use by ICMJE member journals (http://www.icmje.org/coi_disclosure.pdf) and JBCPS has accepted that.

I. A. 4. Abstract

- Structured abstracts are essential for original research and systematic reviews. structured abstract means introduction, methods, results and conclusion in abstract
- Should be limited to 250 words
- The abstract should provide the introduction of the study and blinded state and should state the study's purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), principal conclusions. It should emphasize new and important aspects of the study or observations. Articles on clinical trials should contain abstracts that include the items that the CONSORT group has identified as essential (<http://www.consort-statement.org>).
- Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that they accurately reflect the content of the article

I. A. 5. Introduction

- Provide a context or background for the study (that is, the nature of the problem and its significance). It should be very specific, identify the specific knowledge in the aspect, reasoning and what the study aim to answer.
- State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question.
- Both the main and secondary objectives should be clear.
- Provide only directly pertinent primary references, and do not include data or conclusions from the work being reported.

I. A. 6. Methods

The Methods section should be written in such way that another researcher can replicate the study.

I. A. 6. a. Selection and Description of Participants

- Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report—for example, authors should explain why only participants of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way. When authors use such variables as race or ethnicity, they should define how they measured these variables and justify their relevance.

I. A. 6. b. Technical Information

- Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures insufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs

and chemicals used, including generic name(s), dose(s), and route(s) of administration.

- Authors submitting review article should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

I. A. 6. c. Statistics

- Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals).
- Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated).
- Define statistical terms, abbreviations, and most symbols.
- Specify the computer software used.

I. A. 7. Results

- Present results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Please keep the result the sequence of specific objective selected earlier.
- Do not repeat all the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.
- When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.
- Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables.

- Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Where scientifically appropriate, analyses of the data by such variables as age and sex should be included.

I. A. 8. Discussion

- Emphasize the new and important aspects of the study and the conclusions that follow from them in the context of the totality of the best available evidence.
- Do not repeat in detail data or other information given in the Introduction or the Results section.
- For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.
- Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly as such.

I. A. 9. References

I. A. 9. a. General Considerations Related to References

- Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible.
- On the other hand, extensive lists of references to original work of a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published

papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

- Avoid using abstracts as references. References to papers accepted but not yet published should be designated as “in press” or “forthcoming”; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication.
- Information from manuscripts submitted but not accepted should be cited in the text as “unpublished observations” with written permission from the source.
- Avoid citing a “personal communication” unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication. Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed or print copies from original sources.
- Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions.

I. A. 9. b. Reference Style and Format

- References should be numbered consecutively in the order in which they are first mentioned in the text.
- Identify references in text, tables, and legends by Arabic numerals in superscript.
- References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

I. A. 10. Tables

- Tables capture information concisely and display it efficiently.

- Use tables /fig that are relevant to study
- Try to limit the number of tables/figure
- Type or print each table with double-spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each.
- Do not use internal horizontal or vertical lines. Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use the following symbols, in sequence:
*, †, ‡, §, —, ¶, **, ††, ‡‡, §§, — —, ¶¶, etc.
- Identify statistical measures of variations, such as standard deviation and standard error of the mean.
- Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

I. A. 11. Illustrations (Figures)

- Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. In addition to requiring a version of the figures suitable for printing, (for example, JPEG / GIF)
- Authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 _ 173 mm (5 _ 7 inches)
- Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication.
- Photographs of potentially identifiable people must be accompanied by written permission to use the photograph. Figures should be numbered consecutively according to the order in which they have been cited in the text.
- If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce the figure. Permission is required irrespective of

authorship or publisher except for documents in the public domain.

- For illustrations in color, JBCPS accept coloured illustration but when it seems essential. This Journal publish illustrations in color only if the author pays the additional cost. Authors should consult the journal about requirements for figures submitted in electronic formats.

I. A. 12. Legends for Illustrations (Figures)

- Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations.
- When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

I. A. 13. Units of Measurement

- Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.
- Authors should report laboratory information in both local and International System of Units (SI).
- Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

I. A. 14. Abbreviations and Symbols

- Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers.
- Avoid abbreviations in the title of the manuscript.
- The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

I. B. Sending the Manuscript to the Journal

- If a paper version of the manuscript is submitted, send the required number of copies of the manuscript and figures; they are all needed for peer review and editing, and the editorial office staff cannot be expected to make the required copies.
- Manuscripts must be accompanied by a cover letter, conflicts of interest form, authorship and declaration, proforma of which is available in JBCPS web site.

Editing and peer review: All submitted manuscripts are subject to scrutiny by the Editor in-chief or any member of the Editorial Board. Manuscripts containing materials without sufficient scientific value and of a priority issue, or not fulfilling the requirement for publication may be rejected or it may be sent back to the author(s) for resubmission with necessary modifications to suit one of the submission categories. Manuscripts fulfilling the requirements and found suitable for consideration are sent for peer review. Submissions, found suitable for publication by the reviewer, may need revision/ modifications before being finally accepted. Editorial Board finally decides upon the publishability of the reviewed and revised/modified submission. Proof of accepted manuscript may be sent to the authors, and should be corrected and returned to the editorial office within one week. No addition to the manuscript at this stage will be accepted. All accepted manuscripts are edited according to the Journal's style.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

Check Lists

Final checklists before you submit your revised article for the possible publication in the Journal of Bangladesh College of Physicians and Surgeons:

1. Forwarding/Cover letter and declaration form
2. Authorship and conflicts of interest form
3. Manuscript
 - o Sample of the above documents is available in the following links: <http://www.bcpsbd.org> (registration required for download)
 - o If you have submitted mention document (1, 2, 3) above, when you first submitted your article then you don't need to re-submit but if there is change in the authorship or related then you have to re-submit it.
- General outline for article presentation and format
 - Δ Double spacing
 - Δ Font size should be 12 in arial
 - Δ Margins 5 cm from above and 2.5 cm from rest sides.

- Δ Title page contains all the desired information (vide supra)
- Δ Running title provided (not more than 40 characters)
- Δ Headings in title case (not ALL CAPITALS, not underlined)
- Δ References cited in superscript in the text without brackets after with/without comma (,) or full stop (.)
- Δ References according to the journal's instructions – abide by the rules of Vancouver system. Use this link to get into the detail of Vancouver system.

- **Language and grammar**

- Δ Uniformity in the language
- Δ Abbreviations spelt out in full for the first time
- Δ Numerals from 1 to 10 spelt out
- Δ Numerals at the beginning of the sentence spelt out

- **Tables and figures**

- Δ No repetition of data in tables/graphs and in text
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- Δ Figures necessary and of good quality (colour)
- Δ Table and figure numbers in Arabic letters (not Roman)
- Δ Labels pasted on back of the photographs (no names written)
- Δ Figure legends provided (not more than 40 words)
- Δ Patients' privacy maintained (if not, written permission enclosed)
- Δ Credit note for borrowed figures/tables provided
- Δ Each table/figure in separate page

If you have any specific queries please use at www.bcps.com

Manuscript Format for Research Article

- **Title**

- Δ Complete title of your article
- Δ Complete author information
- Δ Mention conflict of interest if any

- **Abstract**
 - Δ Do not use subheadings in the abstract
 - Δ Give full title of the manuscript in the Abstract page
 - Δ Not more than 200 words for case reports and 250 words for original articles
 - Δ Structured abstract (Including introduction, methods, results and discussion, conclusion) provided for an original article and (Introduction, results and discussion , conclusion) for case reports.
 - Δ Key words provided – arrange them in alphabetical order (three – five)
- **Introduction**
 - Δ Word limit 150 -200 words
 - Δ Pertinent information only
- **Material and Methods**
 - Δ Study Design
 - Δ Duration and place of study
 - Δ Ethical approval
 - Δ Patient consent
 - Δ Statistical analysis and software used.
- **Result**
 - Δ Clearly present the data
 - Δ Avoid data redundancy
 - Δ Use table information at the end of the sentence before full stop between the small bracket

- **Discussion**
 - Δ Avoid unnecessary explanation of someone else work unless it is very relevant to the study
 - Δ Provide and discuss with the literatures to support the study
 - Δ Mention about limitation of your study
- **Conclusion**
 - Δ Give your conclusion
 - Δ Any recommendation
- **Acknowledgement**
 - Δ Acknowledge any person or institute who have helped for the study
- **Reference**
 - Δ Abide by the Vancouver style
 - Δ Use reference at the end of the sentence after the full stop with superscript
- **Legends**
 - Δ Table
 - Δ Figures

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MERS-CoV: Current Global Status and Threats for Bangladesh

While writing this editorial the first case of “Middle East Respiratory Syndrome corona virus”(MERS-CoV) is already detected in Bangladesh in a person returning from middle east. MERS-CoV is a novel corona virus first reported on 24th September, 2012 on proMed –mail by Egyptian virologist Dr. Ali Mohammad Jaki in Jeddah. He isolated and identified a new corona virus from a 60 year old male patient with acute pneumonia and renal failure¹. Until 23rd May 2013, MERS-CoV had frequently been referred to as a SARS like virus.²

As of 11th June, 2014, 699 laboratory confirmed cases of human infections with MERS-CoV have been reported to WHO, including at least 209 deaths. Overall 63.5% of cases reported (n=695) are male and the median age is 47 years old. To date, the affected countries in the Middle East include Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia (KSA), United Arab Emirates (UAE) and Yemen; in Africa: Algeria, Egypt and Tunisia; In Europe: France, Germany, Greece, Italy, The Netherlands and the United Kingdom; in Asia: Malaysia, Philippines and Bangladesh and in North America: the United States of America.³

Bangladesh reported its first laboratory confirmed case on 15th June, 2014 in a 50 year old patient who had travelled to Abu Dhabi recently. All cases in newly affected countries have a history of residence in or travel to the Middle East or contacts with travellers returning from these areas. The infection has occurred in the community (sporadic cases with unknown exposure), in families (contact with infected family members) and in health care facilities (patients and health care workers from whence the majority of cases are reported)

The incubation period of MERS-CoV is estimated to be up to two weeks, but likely shorter in most cases, however more data are required to refine the estimate. There is an increasing trend of severe cases of MERS-CoV infections in older patients with comorbidity and milder cases in their contacts. Most of the cases recently reported from KSA reflect infection acquired through

human to human transmission in health care settings and there is no evidence of sustained human to human transmission in the community.³

Most confirmed cases have presented with or later developed severe lower respiratory tract infection. The most frequently reported symptoms were fever, cough and breathlessness and complicated by ARDS, renal insufficiency and shock.⁴ Of the first 47 cases in Saudi Arabia 89% required management in intensive care and 72% required mechanical ventilation. If anyone develops lower respiratory infections within 14 days after returning from the Middle East, must seek medical attention. Laboratory confirmation of MERS-CoV infections to date largely been by real-time reverse transcription polymerase chain reaction (RT-PCR).⁵

There is no current treatment or vaccination available for MERS-CoV. Interferon alpha 3b and ribavirin may work primarily by reducing inflammation of lungs and promoting healing by altering the host response rather than directly targeting the virus.

Preventive measures are extremely important which includes use of personal protective equipment (mask, gown, gloves by health care workers and exposed people), hand hygiene, influenza vaccination, patient isolation in a single bed negative pressure room.

Hajj and Umrah draws some of the largest crowds in the world, and the large crowds bring some health and safety risk. The virus can spread from person to person when people are touching or very near each other, thus pilgrims in crowd may be at risk. About ten thousand Muslims of Bangladesh travel to Saudi Arabia each year to perform Hajj. So we should pay attention to our health when travelling in the Arabian Peninsula.

Actions to take before Umrah or Hajj or travel to Middle East

- pilgrims with pre-existing major medical conditions (e.g. chronic diseases such as diabetes, chronic lung disease, immunodeficiency) are

advised about the increased risk of MERS-CoV infection and high risk person are prohibited.

- Pilgrims are to be educated about on **general travel health precautions**.
- Medical staff accompanying pilgrims should be up to date on MERS-CoV information and guidance

Actions to take during Umra or Hajj or travel to Middle East

- Travellers who develop a significant acute respiratory illness with fever and cough (severe enough to interfere with usual daily activities) should be advised to:
- Minimize their contact with others to keep from infecting them;
- Cover their mouth and nose with a tissue when coughing or sneezing and discard the tissue in the trash after use and wash hands afterwards, or, if this is not possible, to cough or sneeze into upper sleeves of their clothing, but not their hands. And report to the medical staff accompanying the group or to the local health services.

Actions to take after Umra or Hajj or travel to Middle East

- Returning pilgrims should be advised that if they develop a significant acute respiratory illness with fever and cough during the two weeks after their return, they should seek medical attention and immediately notify their local health authority.
- Persons who have had close contact with a pilgrim or traveller with a significant acute respiratory illness with fever and cough and who themselves develop such an illness should be advised to report to local health authorities to be monitored for MERS-CoV.
- Practitioners and facilities should be alerted to the possibility of MERS-CoV infection in returning pilgrims with acute respiratory illness

Enhancing infection prevention and control awareness and implementation measures is critical to prevent possible spread of MERS-CoV infections in health care facilities. Health care facilities that provide care for patients suspected or confirmed to be infected with MERS-CoV infections should take appropriate measures to decrease the risk of transmission to other patients, health care worker and visitors. Bangladesh should maintain high level of vigilance as we have large number traveller or workers returning from the Middle East.

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Prof. HAM Nazmul Ahasan

Professor and Head, Dept. of Medicine

Dhaka Medical College

&

Editor-in-Chief, Journal of Bangladesh College of Physicians & Surgeons.

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Association of Hyperuricaemia with Perinatal Outcome in Pregnancy Induced Hypertension

S AKTER^a, S SULTANA^b, SR DABEE^c

Summary:

The high serum uric acid concentration correlates with the degree of severity of the pregnancy induced hypertension (PIH) and perinatal outcome. In this context, maternal serum uric acid level is reported to be one of the prognostic factor for determination of perinatal outcome. Based on the existing data, the present prospective study was undertaken in the Department of Obstetrics and Gynaecology, BIRDEM Academy, from January to December, 2010. Out of 120 women, 60 suffering from PIH (severe preeclampsia and eclampsia) served as group I and 60 normotensive women at third trimester of pregnancy served as group II.

This study showed that mean (\pm SD) serum uric acid was significantly elevated in group I PIH patients (7.21 ± 1.81

mg/dl) compared to group II normotensive pregnancy (4.40 ± 0.84 mg/dl).

In group I PIH patients, 39 (86%) had adverse perinatal outcome (preterm, IUGR, stillbirth), and 6 (13.3%) term and healthy deliveries when serum uric acid level was >6 mg/dl.

Current study showed that there was positive and statistically significant relationship between diastolic blood pressure and hyperuricaemia in group I PIH patients ($r = +0.359$, $P < 0.01$).

This study also showed that in group I PIH patients, when serum uric acid increased, birth weight significantly decreased ($r = 0.279$, $P < 0.05$).

Key words: Fetal outcome, Hyperuricaemia, PIH.

(*J Bangladesh Coll Phys Surg 2014; 32: 124-129*)

Introduction:

Many clinical and biochemical parameters have been used to detect pregnancy induced hypertension (PIH) and to assess its severity. Unfortunately most of the available parameters till date are neither specific nor always sensitive. In preeclamptic patients with mild pathologic lesions documented by renal biopsy, serum uric acid (SUA) was elevated¹. In more severe cases with azotemia, SUA was higher². The pathogenesis of hyperuricaemia in PIH has not yet been determined. Chesely and Williams stated that in PIH there was impaired glomerular filtrate rate (GFR) and an increased tubular reabsorption of uric acid, leading to impaired uric acid clearance³. But Pollak and Nettles reported that decreased uric acid clearance was the result of

enhanced tubular reabsorption or inhibited tubular secretion or both¹.

Hypertensive disorders during pregnancy increases the maternal and infant risk. The greatest impact is associated with pregnancy specific syndrome⁴. Preeclampsia, conventionally diagnosed by gestational onset of hypertension and proteinuria, has increased perinatal mortality by five fold and kills 50,000 women yearly worldwide^{4,5}. Gestational hypertension without proteinuria has much less of an adverse effect on maternal or fetal outcome, whereas the major risk from hypertension that antedates pregnancy is the superimposition of preeclampsia⁶.

Elevated uric acid is another component of the preeclampsia syndrome that was recognized many years ago⁷. It is one of the most consistent and earliest detectable changes in preeclampsia and has been cited as a better predictor of fetal risk than blood pressure^{8,9}. Despite these findings, uric acid assessment in the evaluation of PIH has fallen into disfavour. A recent publication reported that the utility of measuring serum uric acid levels in PIH is limited¹⁰.

a. Dr. Saida Akter, Private Practice, 52/7 East Raja Bazar (2nd floor), Dhaka.

b. Dr. Sharmin Sultana, Medical Officer, 200 Bedded Hospital, Narayanganj.

c. Dr. Seema Rani Dabee, Junior Consultant, 20 Bedded Hospital, Amin Bazar, Savar.

Address of Correspondence: Dr. Saida Akter, 52/7 East Raja Bazar (2nd floor), Dhaka 1215, Phone: 0171 1824 262.

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Association of elevated serum uric acid with development of hypertension is established outside of pregnancy, less is known about whether women who begin pregnancy with elevated serum uric acid have an increased risk of developing hypertensive disease during pregnancy or vice versa. In healthy pregnancies, uric acid decreases from an average of 4.2 mg/dl pregnancy to 3.1 ± 1.1 mg/dl in the first trimester, and slowly increases during gestation to an average of 5.1 ± 1.2 mg/dl from 35 weeks of gestation to term^{11,12}. It has been reported that gestational hypertension with hyperuricaemia or preeclampsia with hyperuricaemia defines a more severe form of hypertensive disease, with increased risk of adverse fetal outcome including preterm birth and small for gestational age (SGA) compared to women with gestational hypertension or preeclampsia without hyperuricaemia¹³.

Hyperuricaemia has received much attention and debate recently with regard to its utility as a marker for preeclampsia and as a predictor of adverse maternal and fetal outcome¹⁴. Stander and Cadden in 1945 were the first to demonstrate a high correlation between the severity of PIH and concentration of serum uric acid level. Serum uric acid level is one of the parameter used in early diagnosis of PIH. Hyperuricemia in PIH is a result of primarily of decreased renal clearance of uric acid, a decrease that exceeds the reduction in glomerular filtration rate and creatinine clearance³.

In women with PIH, hyperuricemia was associated with shorter gestations and smaller birth weight centiles and increased risk of preterm birth and small for gestational age (SGA) infants. Hyperuricemia increased the risk of these outcomes in the presence and absence of proteinuria. Risk was also increased in a small group of women with hyperuricemia and proteinuria without hypertension. Women with only hypertension and hyperuricemia have similar or greater risk as women with only hypertension and proteinuria. Those with hypertension, proteinuria and hyperuricemia have greater risk than those with hypertension and proteinuria alone. The risk of these outcomes increased with increasing uric acid¹³.

In the light of evidences from different studies, in the present study we tried to find out whether raised serum uric acid has an adverse effect on perinatal outcome in severe preeclampsia and eclampsia. We also tried to

find out if serum uric acid concentration can be used as a screening test for the prediction of perinatal prognosis.

Materials and Methods:

This prospective study was carried out in the Department of Obstetrics and Gynaecology, Bangladesh Institute of Research and Rehabilitation, Endocrine and Metabolic Disorders Hospital (BIRDEM), and Dhaka Medical College Hospital (DMCH), Dhaka, during January and December, 2010.

The study population consisted of 60 women suffering from PIH (severe preeclampsia, eclampsia) (Group I) and 60 normotensive women (Group II) attending Department of Obstetrics and Gynaecology, BIRDEM and Dhaka Medical College Hospital (DMCH).

Inclusion Criteria: Third trimester pregnant women suffering from PIH (preeclampsia and eclampsia) (Group I) and normotensive (Group II). **Exclusion criteria:** Patients with known chronic renal disease, patients suffering from diabetes mellitus, diagnosed patients of hepatic dysfunction, and patients suffering from gout.

Ethical consideration: Permission was obtained from Ethical Review Committee of BIRDEM. Before inclusion in the study, informed written consents was obtained from each patient.

Data processing: Data of each individual participants was recorded on a predesigned data collection sheet, and appropriate statistical analyses were done using computerbased software (SPSS).

Collection of blood sample: Two milliliter of random venous blood was collected from antecubital vein of the pregnancy induced hypertension and normotensive subjects taking all aseptic precautions. Blood was drawn single time from each subject and submitted within half an hour to the laboratory for analysis.

Laboratory method: Estimation of serum uric acid concentration was done by enzymatic colorimetric method.

Dependent or outcome variables: Preterm, stillbirth, IUGR, and term and healthy babies. **Independent variables:** Hypertension and serum uric acid.

Results:

Table I shows characteristics of the study population. Both mean (\pm SD) systolic and diastolic blood pressure

was significantly high ($P<0.001$) in group I (159.17 ± 12.53 and 107.73 ± 8.80 mmHg) compared to group II (107.00 ± 9.26 and 68.67 ± 7.69 mmHg). Mean (\pm SD) serum uric acid was also significantly high in group I (7.21 ± 1.81 mg/dl) compared to group II (4.40 ± 0.84 mg/dl). Serum uric acid was normal (≤ 6 mg/dl) in 15 (25%) and 54 (90%), and raised (>6 mg/dl) in 45 (75%) and 6 (10%) women in group I and group II, respectively.

Table II shows pregnancy outcome. There were 13 (21.7%) and 53 (88.3%) term and vaginal deliveries, 24 (40%) and 3 (5%) preterm deliveries, 9 (15%) and 2 (3.3%) IUGRs, and 14 (23.3%) and 2 (3.3%) stillbirth in group I and group II, respectively. In group II

significantly high ($P<0.001$) number of deliveries were term and vaginal. Mean (\pm SD) birth weight was significantly low ($P<0.001$) in group II (2.28 ± 0.19 kg) compared to group I (2.75 ± 0.26 kg). Birth weight was significantly ($P<0.001$) low (<2.5 kg) in 50 (83.3%) babies of group I compared to 7 (11.7%) babies of group II, and vaginal <2.5 kg in 10 (16.7%) and 53 (88.3%), in group I and group II, respectively

Table III shows association between hyperuricaemia (serum uric acid >6 mg/dl) and fetal outcome in group I women. Serum uric acid level was ≤ 6 mg/dl in 15 (25%) and >6 mg/dl in 45 (75%) group I women. Fetal outcome was term and healthy in 7 (46.7%) and 6 (13.3%), preterm in 4 (26.7%) and 20 (44.4%), IUGR

Table-I

<i>Characteristics of the study subjects</i>					
Variables	Group I (n=60)		Group II (n=60)		P value
Systolic blood pressure (mmHg)					
Mean \pm SD	159.17 \pm 12.53		107.00 \pm 9.26		0.0001***
Diastolic blood pressure (mmHg)					
Mean \pm SD	107.73 \pm 8.80		68.67 \pm 7.69		0.0001***
Serum uric acid (mg/dl)					
Mean \pm SD	7.21 \pm 1.81		4.40 \pm 0.84		0.0001***
	No.	(%)	No.	(%)	
≤ 6	15	(25.0)	54	(90.0)	0.0001***
>6	45	(75.0)	6	(10.0)	

Unpaired Student's 't' test/Chi square test, *** = significant ($P<0.001$)

Table-II

<i>Fetal outcome</i>					
Variables	Group I (n=60)		Group II (n=60)		P value
	No.	(%)	No.	(%)	
Fetal outcome					0.0001***
Term and healthy	13	(21.7)	53	(88.3)	
Preterm	24	(40.0)	3	(5.0)	
IUGR	9	(15.0)	2	(3.3)	
Stillborn	14	(23.3)	2	(3.3)	
Birth weight (kg)					0.0001***
<2.5	50	(83.3)	7	(11.7)	
≥ 2.5	10	(16.7)	53	(88.3)	
Mean \pm SD	2.28 \pm 0.19	2.75 \pm 0.26	0.0001***		

Chi square test/Unpaired Student's 't' test, *** = significant ($P<0.001$)

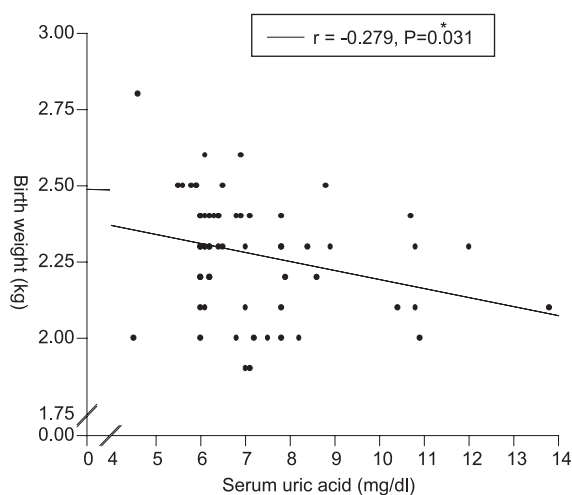
Table-III*Association between serum uric acid level and fetal outcome in group I subjects*

Variables	Serum uric acid level (mg/dl)				P value
	≤6 (n=15)		>6 (n=45)		
	No.	(%)	No.	(%)	
Fetal outcome					0.056 ^{ns}
Term and healthy	7	(46.7)	6	(13.3)	
Preterm	4	(26.7)	20	(44.4)	
IUGR	2	(13.3)	7	(15.6)	
Stillborn	2	(13.3)	12	(26.7)	
Normal/adverse outcome					0.007 ^{**}
Term and normal	7	(46.7)	6	(13.3)	
Adverse (preterm, IUGR, stillborn)	8	(53.3)	39	(86.7)	

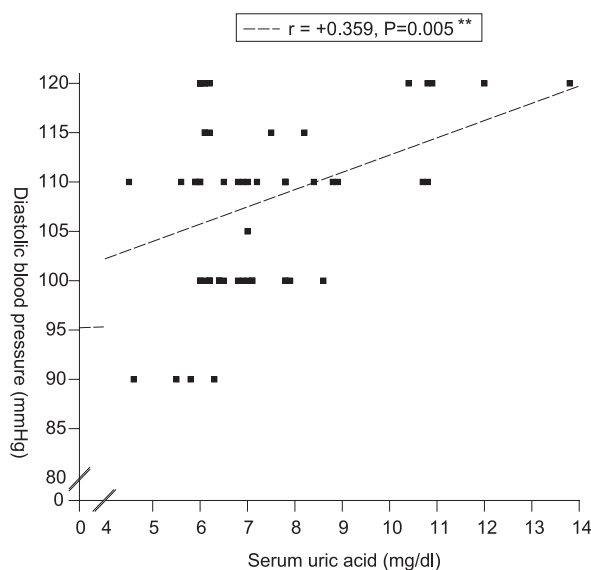
Chi square test, ns = not significant ** = significant (P<0.01)

in 2 (13.3%) and 7 (15.6%), and stillborn in 2 (13.3%) and 12 (26.7%) in women with serum uric acid level ≤6 mg/dl and >6 mg/dl, respectively. When fetal outcome was grouped into term and healthy, and adverse (preterm, IUGR, stillborn), hyperuricaemia showed significant (P<0.01) association. Term and vaginal deliveries were achieved in 7 (46.7%) and 6 (13.3%), and adverse (preterm, IUGR, stillbirth) in 8 (53.3%) and 39 (86.7%) when serum uric acid level was ≤6 mg/dl and >6 mg/dl, respectively.

Fig. 1 shows negative and statistically significant relation ($r = -0.0279$, $P < 0.05$) between serum uric acid

**Fig-1:** Relationship between serum uric acid and birth weight of group-I babies

level and birth weight of group I babies. Fig. 2 shows positive and statistically significant relationship between serum uric acid and diastolic blood pressure ($r = +0.359$, $P < 0.01$) in group I women.

**Fig-2:** Relationship between serum uric acid and diastolic blood pressure in group-I subjects**Discussion:**

Perinatal complications are correlated with hypertensive disorders of pregnancy. In this context, the maternal serum uric acid level is found to be one of the prognostic

factor in determining perinatal outcome. This study showed that serum uric acid was significantly elevated ($P<0.001$) in group I PIH patients compared to group II normotensive pregnant women. Mean (\pm SD) and median serum uric acid level of group I (severe preeclampsia, eclampsia) was 7.21 ± 1.81 and 6.50 mg/dl, and in group II (normotensive pregnant women) was 4.40 ± 0.84 and 4.10 mg/dl, respectively.

Status of serum uric acid of the study subjects showed that serum uric acid was ≥ 6 mg/dl in 15 (25%) of group I and 54 (90%) of group II subjects, and was >6 mg/dl in 45 (75%) of group I and 6 (10%) of group II subjects ($P<0.001$).

Association of serum uric acid level with fetal outcome in group I showed that, out of 15 babies whose mothers had serum uric acid level ≥ 6 mg/dl, 7 (46.7%) babies achieved term and vaginal delivery, and 8 (53.3%) had adverse outcome (preterm, IUGR, stillborn), and out of 45 babies whose mothers had serum uric acid level >6 mg/dl, 6 (13.3%) babies achieved term and vaginal delivery while 39 (86.7%) had adverse outcome. Serum uric acid level of mothers showed significant association with fetal outcome ($P<0.01$). Maximum number of adverse outcomes belonged to serum uric acid level >6 mg/dl compared to ≥ 6 mg/dl. Similar observation was made by Yassae¹⁵.

Current study showed that both systolic (159.17 ± 12.53 vs 107.00 ± 9.26 mmHg) and diastolic (107.83 ± 8.80 vs 68.67 ± 7.69 mmHg) blood pressure were significantly high in group I than group II. Positive and statistically significant relationship between serum uric acid and diastolic blood pressure in group I was also observed. Redman *et al.*, Varma and Mustaphi *et al.* also reported similar findings^{16 18}.

The present study showed that mean birth weight of babies was significantly lower ($P<0.001$) in group I (mean \pm SD 2.28 ± 0.19 , median 2.30 kg) compared to group II (mean \pm SD 2.75 ± 0.26 , median 2.70 kg). Relationship between serum uric acid level of mothers and fetal birth weight in group I showed that when serum uric acid level increased, birth weight significantly decreased ($r = 0.279$, $P<0.05$). This was supported by the findings of Roberts *et al.*¹³ They examined fetal growth adjusted for gestational age, hyperuricemia with pregnancies who had neither PIH nor high serum uric acid, the risk of an infant having birth weight ≤ 10 th or

≤ 5 th centile was significantly higher in the hyperuricemic group. This finding apparently and weakly supported the current correlation between birth weight and hyperuricemia.

Although this study showed adverse perinatal outcomes were more in hyperuricemia, supported by many previous studies, another study carried out by Lim *et al.* showed as a diagnostic test, serum uric acid was neither sensitive nor specific when used to diagnose preeclampsia in the setting of new hypertension¹⁰. There was one obvious limitation to this study, the women were socioeconomically diverse, data came from tertiary center, which may have limited generalizability.

Despite the fact that hyperuricemia is not a conventionally used diagnostic criteria for PIH and nor typically considered as useful aid to management, several observations have suggested that the presence of hyperuricemia may identify a form of PIH with increased risk¹³.

Meanwhile, this study showed that hyperuricemia with maternal hypertension was associated with perinatal morbidity and mortality, and premature intervention of pregnancy. Therefore, estimation of serum uric acid does help to identify fetus at risk of developing adverse perinatal consequences and to assess severity of the disease. Laboratory investigations of serum uric acid is simple and can be easily performed in any laboratory.

In this study, the relationships we observed were examined prospectively and tests performed to determine whether the information positively and effectively affected perinatal outcome. It is quite likely based on prior studies that uric acid may be used in the complex decision making for delivery, the cornerstone of management of women with PIH. This has been supported by Odendaal and Pienaar.¹⁹ An important question to be resolved is whether, as suggested by our data in this study, the adverse perinatal outcomes were associated with likely presence of concomitantly increased uric acid. Finally, this finding encourages a reevaluation of the current classification of PIH in relation to pregnancy outcome using serum uric acid and other markers of pathophysiology.

Conclusion:

There have been some conflicting and significant reports in the literature regarding usefulness of serum uric acid estimation in women with PIH. The present study was

carried out as an attempt to critically reappraise the association of hyperuricemia with adverse perinatal consequences by this simple biochemical test. From this study, it appears that there was significant and positive relationship between hyperuricemia and adverse perinatal outcome. In normal pregnancy, serum uric acid usually reduces in early and mid pregnancy and rises to normal level in late pregnancy. It is appropriate and useful to estimate the serum uric acid level in women at increased risk to obtain satisfactory pregnancy outcome and ensure appropriate management of pregnancy complicated by pregnancy induced hypertension.

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Haematological Changes in Peripheral Blood of HIV – Infected Persons with Correlation to CD4 Cell Count

MM RAHMAN^a, S GITI^b, MS ISLAM^c, MM RAHMAN^d

Summary:

Objective: Aims at recognizing the haematological abnormalities in peripheral blood associated with HIV infection and to correlate the haematological abnormalities with CD4 cell count to highlight these manifestations with disease progression.

Methodology: Observational cross sectional study.

Setting: Department of Haematology, Armed Forces Institute of Pathology (AFIP), Dhaka Cantonment.

Patients: Two hundred four (204) HIV – infected patients receiving antiretroviral therapy aged from three years to 65 years. There were 132 male and 72 female patients.

Results: Anaemia was found in 103 (50.5%) cases. Leucopenia and thrombocytopenia were observed in ten (4.9%) and seven (3.4%) cases respectively. Lymphopenia

was found in 12 (5.9%) cases. In 50 (24.5%) cases Erythrocyte Sedimentation Rate (ESR) was > 20 mm at the end of 1st hour. Flow cytometric analysis for CD4 cell count showed < 200 cells/cmm in 65 (31.8%) cases, in between 200 cells/cmm and 499 cells/cmm in 117 (57.4%) cases and > 500 cells/cmm in 22 (10.8%) cases.

Conclusion: Haematological abnormalities are common in HIV – infected patients and responsible for significant morbidity and mortality in these patients. These abnormalities are more frequent with disease progression. The present study revealed a significant increase in the number of anaemia, leucopenia, lymphopenia and thrombocytopenia with decreasing CD4 cell count.

Keywords: CD4 cell count, Haematological abnormalities, HIV, Peripheral blood.

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Introduction:

Acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 and human immunodeficiency virus (HIV) was identified in 1983¹. Globally the phenomenon of HIV/AIDS is best viewed as a pandemic affecting nearly all the countries of the world². The first case of HIV/AIDS in Bangladesh was detected in 1989. Since then 1495 cases of HIV/AIDS have been reported (as of December 2008). However, UNAIDS estimates that the number of people living with HIV in the country may be as high as 12000, which is within

the range of the low estimate by UNICEF's State of the World's Children Report 2009³.

Peripheral blood changes commonly seen in human immunodeficiency virus – infected individuals and disease associated with HIV may reflect disease elsewhere in the body, may result from treatment for that disease, may reflect an attempt to attack the HIV itself, or may seem to be isolated haematological disorders⁴.

The CD4+ lymphocyte is the primary target of HIV infection and leads to progressive impairment of cellular function, characterized by a gradual decline in peripheral blood CD4+ lymphocyte levels⁵.

This study aims at recognizing the haematological abnormalities associated with HIV infection, to correlate the haematological abnormalities with CD4 cell count and to highlight these manifestations with disease progression.

Materials and Methods:

This observation cross - sectional study was carried out at Armed Forces Institute of Pathology (AFIP) in the department of haematology during a period of eight months from June 2012 to January 2013. A total of 204 HIV – infected patients on antiretroviral therapy (AZT)

- Lt Col (Dr) Md. Mizanur Rahman, Classified Specialist in Pathology, Armed Forces Institute Pathology (AFIP), Dhaka Cantonment.
- Col (Dr) Susane Giti, Classified Specialist in Pathology, AFIP, Dhaka Cantonment.
- Maj Gen (Dr) Md. Saiful Islam, Commandant and Classified Specialist in Pathology, AFIP, Dhaka Cantonment.
- Dr. Md. Mostafizur Rahman, Assistant Professor, Department of Statistic, Engineering University School and College, Polasi, Dhaka

Address of correspondence: Lt Col (Dr) Md Mizanur Rahman, Classified Specialist in Pathology (Haematology), AFIP, Dhaka Cantonment, e-mail: mizan142004@yahoo.com Mobile: 01726990942.

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irrespective of age and sex from a Non-government Organization (NGO) were included in this study. All the patients were brought to AFIP by a representative of that NGO for blood sampling. Ethical issues were properly addressed and also cleared by the ethical committee of Directorate General of Medical Services (DGMS) of Bangladesh Armed Forces. About two ml venous blood in EDTA bottle was taken for complete haemogram and CD4 cell count. Complete haemogram was performed by automated haematology analyzer Sysmex XT 1800i. Before running the specimen, the analyzer was calibrated by low, normal and high control supplied by the manufacturer. Erythrocyte Sedimentation Rate (ESR) was done by Westergren method. CD4 lymphocyte count was done by Partec Flow Cytometer (cyFlow), an automated multicolour system that performs both analysis and sorting using dual lasers 488 nm air cooled argon-ion blue and 532 nm green diode solid state laser. Cells are treated with monoclonal antibody Men-41 which recognizes the human CD4 antigen. As a cell passes through the flow chamber, it is intersected by a laser beam. Forward light scatter is proportional to the cell size and side scatter is related to cell granularity which allows separation of WBCs based on size and granularity. Analysis of CD4 – PE fluorescence signal helps in delineating subpopulation. Data was analyzed by cell quest software.

Statistical tests included mean, standard deviation, ANOVA (analysis of variance), chi-square test (χ^2). The data was entered in Microsoft Office 2010 Excel worksheet and statistical analysis was done using Statistical Package for Social Sciences Software (SPSS) version 21. Descriptive statistics were applied: p – value less than 0.05 was considered statistically significant.

Results:

During the study period, 204 HIV – infected patients were referred to the haematology department, AFIP and included in this study. The age ranged from three years to 65 years. Mean age was 35.3 ± 9.5 years. The majority of 91 (40.6%) cases were in the age group of 31 – 40 years followed by 55 (27.0%) cases in 21 to 30 years age group. There were 132 (64.7%) males and 72 (35.3%) females in this study with male to female ration 1.8: 1. Table – I shows the demographic data of the patients.

Table-I

Demographic data of the patients as per age and sex (n = 204)

Age (in years)	Sex
Range: 3 – 65	Male: 132 (64.7%)
Mean: 35.3	Female: 72 (35.3%)
	M : F= 1.8 : 1

M = Male; F = Female.

In this study haematological parameters that have been included were haemoglobin (Hb) level, RBC count, haematocrit (Hct), absolute values (MCV, MCH, MCHC), RDW, ESR, TLC, absolute neutrophil, lymphocyte, monocyte and eosinophil count, platelet count and CD4 count. Out of 204 patients, 17 (8.3%) cases had haemoglobin level equal to or less than 10.0 g/dl, 60 (29.4%) cases had haemoglobin level in between 10.1 g/dl and 12.0 g/dl and 127 (62.3%) cases had more than 12.0 g/dl. In case of haematocrit, 19 (9.3%) cases had Hct equal to or less than 0.30 L/L, 85 (41.7%) cases had in between 0.31 L/L and 0.36 L/L and 100 (49.0%) cases had more than > 0.36 L/L. Out of 204 cases, 154 (75.5%) cases had Erythrocyte Sedimentation rate (ESR) less than 20 mm in the 1st hour and 50 (24.5%) cases had more than 20 mm in the 1st hour. RBC count ranged from $2.9 \times 10^{12}/L$ to $5.2 \times 10^{12}/L$ in case of female and in case of male it was from $3.2 \times 10^{12}/L$ to $4.7 \times 10^{12}/L$. In 24 (11.8%) cases RBC count was equal to or less than $3.0 \times 10^{12}/L$, 79 (38.7%) cases had in between $3.1 \times 10^{12}/L$ and $4.0 \times 10^{12}/L$ and 101 (49.5%) cases had more than $4.0 \times 10^{12}/L$.

Mean Corpuscular Volume (MCV) ranged from 62.6 fl to 124.5 fl. Nineteen cases (9.3%) had MCV equal to or less than 76 fl, 104 (51.0%) cases had in between 76 fl and 96 fl and 81 (39.7%) cases had more than 96 fl. Mean Corpuscular Haemoglobin (MCH) ranged from 18.2 picograms to 43.7 picograms. Seventy eight (38.2%) cases had MCH within normal range (29 ± 2.5 pg), 45 (22.1) cases had MCH equal to or less than 27.0 pg and 83 (40.7%) cases had more than 32 pg. Mean Corpuscular Haemoglobin Concentration (MCHC) ranged from 29.1 g/dl to 36.9 g/dl. Out of 204 cases, 20 (9.8%) cases had MCHC equal to or less than 31.5 g/dl, 97 (47.5%) cases had MCHC in between 31.5 g/dl and 34.5 g/dl and 87 (42.6%) cases had more than 34.5 g/dl. Red Cell Distribution Width – Co-efficient of Variation (RDW - CV) ranged from 10.3% to 35.2%. In 10 (4.9%) cases, RDW – CV was equal to or less

than 11.6%, 124 (60.8%) cases had in between 11.6% and 14%, 70 (34.3%) cases had more than 14%.

Total Leucocyte Count (TLC) in this study ranged from $2.1 \times 10^9/L$ to $15.4 \times 10^9/L$. Ten (4.9%) cases had leucopenia ($< 4.0 \times 10^9/L$), 19 (9.3%) had leucocytosis and 175 (85.8%) cases had leucocyte count within normal range. Absolute neutrophil count ranged from $9.0 \times 10^9/L$ to $13.9 \times 10^9/L$. Neutropenia ($< 2.0 \times 10^9/L$) was found in 20 (9.8%), 18 (8.8) cases had neutrophilia ($> 7.0 \times 10^9/L$) and 166 (81.4%) cases had absolute neutrophil count in between $2.0 \times 10^9/L$ and $7.0 \times 10^9/L$. Absolute lymphocyte count ranged from $0.6 \times 10^9/L$ to $6.5 \times 10^9/L$. The majority of 133 (65.2%) cases had absolute lymphocyte count within the normal range (from $1.0 \times 10^9/L$ to $3.0 \times 10^9/L$), 12 (5.9%) cases had lymphopenia ($< 1.0 \times 10^9/L$) and 59 (28.9%) cases had lymphocytosis ($> 3.0 \times 10^9/L$). Absolute monocyte count ranged from $0.1 \times 10^9/L$ to $2.0 \times 10^9/L$. Only one (0.5%) case had monocytopenia ($< 0.2 \times 10^9/L$), seven (3.4%) cases had monocytosis ($> 1.0 \times 10^9/L$) and rest of the 196 (96.1%) cases had absolute monocyte count within the normal range ($0.2 \times 10^9/L$) to $1.0 \times 10^9/L$). In this study, 68

(33.3%) cases had eosinophilia ($> 0.5 \times 10^9/L$), absolute eosinophil count ranged from $0.03 \times 10^9/L$ to $0.5 \times 10^9/L$. Eosinopenia was not found in this study. Platelet count ranged from $60.0 \times 10^9/L$ to $573 \times 10^9/L$. Only seven (3.4%) cases had thrombocytopenia ($< 150 \times 10^9/L$), 189 (92.7%) cases had platelet count in between $150 \times 10^9/L$ and $400 \times 10^9/L$, eight (3.9%) cases had thrombocytosis ($> 400 \times 10^9/L$). CD4 lymphocyte count was in between 52 cells/cmm and 908 cells/cmm in this study. Out of 204 cases 65 (31.9%) had CD4 count less than 200 cells/cmm, 117 (57.3%) cases had CD4 count in between 200 cells/cmm and 499 cells/cmm and 22 (10.8%) cases had more than 500 cells/cmm. Table – II shows the pattern of haematological parameters in HIV – infected persons in this study.

Common haematological abnormalities found in this study were anaemia, raised ESR, leucopenia, leucocytosis, neutropenia, neutrophilia, lymphopenia, lymphocytosis, monocytopenia, monocytosis, eosinophilia, thrombocytopenia, thrombocytosis and low CD4 lymphocyte count. Table – III shows the frequency and percent of these findings.

Table-II

Pattern of haematological parameters in HIV- infected persons (n=204)			
Parameters	Range	Mean \pm 2SD	P - value
ESR (mm in 1 st hour)	6 – 17 (M)	19 \pm 28	P < 0.001
	5 – 50 (F)	20 \pm 28	P < 0.0001
Hb (g/dl)	9.0 – 17.2 (M)	12.5 \pm 3.6	P > 0.0001
	7.8 – 15.2 (F)	11.6 \pm 3.0	P > 0.0001
RBC count ($\times 10^{12}/L$)	3.2 – 4.7 (M)	4.0 \pm 1.6	P > 0.0001
	2.9 – 5.2 (F)	3.8 \pm 1.6	P > 0.001
Hct (L/L)	0.27 – 0.47 (M)	0.37 \pm 0.10	P > 0.0001
	0.27 – 0.45 (F)	0.35 \pm 0.08	P > 0.001
MCV (fl)	62.6 – 124.5	93.1 \pm 28.4	P < 0.001
MCH (pg)	18.2 – 43.7	37.8 \pm 11.2	P < 0.0001
MCHC (g/dl)	29.1 – 36.9	34.1 \pm 4.0	P < 0.001
RDW – CV (%)	10.3 – 35.2	14.1 \pm 5.4	P < 0.001
TLC ($\times 10^9/L$)	2.1 – 15.4	7.6 \pm 5.0	P < 0.0003
ANC ($\times 10^9/L$)	0.9 – 13.9	4.1 \pm 4.0	P < 0.0001
ALC ($\times 10^9/L$)	0.6 – 6.5	2.4 \pm 2.0	P < 0.0001
AMC ($\times 10^9/L$)	0.1 – 2.0	0.6 \pm 0.4	P < 0.0001
AEC ($\times 10^9/L$)	0.03 – 5.0	0.5 \pm 0.8	P < 0.0001
PLC ($\times 10^9/L$)	60 – 573	265 \pm 152	P < 0.0001
CD4(/cmm)	52 - 908	278 \pm 214	P > 0.0001

M = Male; F = Female; RDW – CV = Red Cell Distribution Width; TLC = Total Leucocyte count; ANC = Absolute Neutrophil count; ALC = Absolute Lymphocyte count; AMC = Absolute Monocyte count; AEC = Absolute Eosinophil count; PLT = Platelet. Z test was done to analyze the data.

Table-III*Common haematological abnormalities in HIV- infected persons (n=204)*

Findings	Frequency	Percentage (%)
Anaemia	103	50.5
ESR (> 20 mm in 1 st hour)	50	24.5
Leucopenia	10	4.9
Leucocytosis	19	9.3
Neutropenia	20	9.8
Neutrophilia	18	8.8
Lymphopenia	12	5.9
Lymphocytosis	59	28.9
Monocytopenia	01	0.5
Monocytosis	07	3.4
Eosinophilia	68	33.3
Thrombocytopenia	07	3.4
Thrombocytosis	0865	3.931.9
CD4 count (< 200/cmm)		
CD4 count (200/cmm to 499/cmm)	117	57.4
CD4 count (>500/cmm)	22	10.8

Table-IV*Comparison of number of anaemia cases in present study with others*

Authors	No of anaemia cases	Total cases	Percentage (%)
Parinitha et al	210	250	84.0
Karcher et al Tripathi et al	17561	19774	89.082.4
Sitalakshmi et al	27	42	64.2
Kalousti et al	34	40	85.0
Present study	103	204	50.5

Table-V*Comparison of morphological patterns of blood picture in present study with other studies*

Patterns of blood picture	Parinitha et al		Khandekar et al		Tripathi et al		Present study	
	No	%	No	%	No	%	No	%
Normocytic normochromic blood picture	101	48.1		13	17.6	101	49.5	
Normocytic normochromic anaemia	29	13.7	68	48.7	54	79.9	28	13.7
Microcytic hypochromic anaemia	18	8.6	15	10.7	04	5.4	10	4.9
Macrocytic anaemia	15	7.2	32	29.9	03	4.1	30	14.
Anaemia of Chronic Disorder	-	-	-	-	-	-	35	17.2
Dimorphic anaemia	47	22.4	25	17.9		-	-	-
Total	210	100	140	100	74	100	204	100

Table-VI*Comparison of haematological parameters in patients with different CD4 counts*

Parameters	CD4 > 500 cells/cmm (n= 22)	CD4 200 – 400 cells/cmm (n= 117)	CD4 < 200 cells/cmm (n= 65)	Statistical test	p – value
Anaemia (No of cases)	09 (41.0%)	39 (33.3%)	55 (84.6%)	$\chi^2= 45.28$	$P < 0.0001$
Total leucocyte count (mean±SD)	8.1 ± 2.8	7.8 ± 2.4	7.0 ± 2.5	F= 5.0	$P < 0.01$
Leucopenia (No of cases)	01 (4.5%)	02 (1.7%)	07 (10.8%)	$4\chi^2= 8.68$	$P < 0.01$
Absolute lymphocyte count (mean±SD)	3.0 ± 1.3	2.7 ± 0.9	1.8 ± 0.9	F= 0.04	$P > 0.05$
Lymphopenia (No of cases)	00 (00%)	00 (00%)	12 (18.5%)	$\chi^2= 94.8$	$P < 0.001$
Platelet count (mean±SD)	265 ± 78	267 ± 68	254 ± 95	F= 2.54	$P > 0.05$
Thrombocytopenia (No of cases)	01(4.5%)	01 (0.9%)	05 (7.7%)	$\chi^2= 5.99$	$P= 0.05$
ESR (mean±SD)	22 ± 13	17 ± 12	22 ± 16	F= 1.79	$P > 0.05$

χ^2 = chi square test, F = analysis of variance (ANOVA) test.

Discussion:

Haematological abnormalities frequently encountered in HIV-infected individuals are anaemia, granulocyte disorders, thrombocytopenia, lymphomas, coagulopathies and vascular malignancies like Kaposi sarcoma. Although in the majority of cases, haematologic abnormalities are detected in middle or advanced stages of HIV infection, some of these like anaemia and thrombocytopenia have been reported to occur in early stages of HIV infection⁶.

The origin of haematological disorders in HIV infection remain incompletely understood, but has been attributed to dysfunctional haematopoiesis in bone marrow caused by several factors. These include severe nutritional stress in advanced stages of HIV infection, suppression of marrow by invading opportunistic infections or neoplasm, chronic disease associated changes and toxic effects of antiretroviral compounds (or other medications used to combat the complications of HIV disease). The possibility of HIV directly infecting the haematopoietic precursor cells and inhibiting their differentiation and development to mature cells, has been an attractive hypothesis for the origin of HIV associated dysfunctional haematopoiesis, but to date it remains, to a great extent, an incompletely understood phenomenon⁷.

In the present study, haemoglobin level ranged from 7.8 g/dl to 17.2 g/dl with the mean being 12.5 g/dl. The majority (50.5%) of cases in this study had anaemia

with haemoglobin level less than the lower limit of their respective age and sex. Parinitha SS et al reported haemoglobin ranged from 3.3 g/dl to 19.3 g/dl with the mean being 10.2⁸. Kaloutsis et al reported haemoglobin in the range of 3.8 g/dl to 17.3 g/dl and a mean of 10.8⁹. However Tracy et al¹⁰ reported mean closer to the present study of 11.4 g/dl. Mean haematocrit in this study was 0.37 L/L. Tripathiet al¹¹ reported a mean haematocrit of 0.28 L/L. A better haemoglobin and haematocrit level in this study may be due to inclusion of cases with early HIV infection and good treatment response. Mean RDW – CV was 14.1% in the present study. A closer observation was made by Schneider et al¹². Mean RBC count was $4.1 \times 10^{12}/L$ in this study with standard deviation of 0.81. A similar observation was made by Parinitha SS et al⁸. Tripathi et al reported a mean RBC count of $3.1 \times 10^{12}/L$ and a standard deviation of 0.36 among 55 AIDS patients¹¹. In this study, mean MCV, MCH and MCHC were 93.1 fl, 37.8 pg and 34.1 g/dl with standard deviation of 14.2 fl, 5.6 pg and 2.0 g/dl respectively. Parinitha SS et al reported findings close to this study⁸. Tripathi et al reported a mean MCV, MCH and MCHC of 81.8 fl, 27.6 pg and 32.5 g/dl¹¹. Erythrocyte Sedimentation Rate (ESR) ranged from 5 mm in 1st hour to 70 mm in 1st hour with mean and standard deviation were 19.5 and 14.1 respectively in this study. The majority of 154 (75.5%) cases had ESR less than 20 mm in 1st hour. Thirty 34 (16.7%) cases had ESR equal to or more than 40 mm in

1st hour. Raised ESR found in HIV – infected persons may be related to chronic nature of HIV infection⁸.

In the present study, anaemia was observed in 103 (50.5%) cases. Paranitha et al⁸ reported anaemia in 84.0% (210/250) Kaloutsi et al reported anaemia in 85% (34/40)⁹, Karcher et al reported anaemia in 89% (175/197) of cases¹³ and Tripathi et al in 82.4% (61/74) of cases¹¹. However Sitalakshmi et al¹⁴ reported anaemia in 64.2% (27/42) of cases which closer compared to the present study. This difference in anaemia in different study may be due to variation in large sample size and treatment response. Table – IV shows a comparison of number of anaemia cases in the present study with other studies.

Macrocytosis without anaemia was found in 81 (39.7%) cases. Treatment with reverse transcriptase inhibitors will cause macrocytosis because they interfere with DNA production, which may lead to megaloblastic changes. Most patients with HIV who are being treated with reverse transcriptase inhibitors will display macrocytosis without anaemia. This indicates medications compliance by the patient, and no treatment is necessary¹⁵. The most common type of anaemia was anaemia of chronic disorder (ACD) observed in 35/103 (34.0%) cases, followed by macrocytic anaemia in 30/103 (29.1%) cases. Table – V shows the comparison of morphological patterns of blood picture in the present studies with other studies.

Mean Total Leucocyte Count (TLC) was $4.1 \times 10^9/L$. Paranitha et al⁸ reported mean of TLC $5.8 \times 10^9/L$, Kaloutsi et al⁹ reported a mean of $5.2 \times 10^9/L$. The majority of 175 (85.8%) cases had normal total leucocyte count. Patwardhan et al¹⁶ reported in 75.6% (378/500) of cases almost similar observation. Leucopenia was seen in 10 (4.9%) and leucocytosis 19 (9.3%) cases. Neutropenia and neutrophilia were found in 20 (9.8%) and 18 (8.8%) cases respectively. In 12 (5.9%) cases, lymphopenia and 59 (28.9%) cases, lymphocytosis was observed in this study. Paranitha et al⁸ reported lymphopenia in 163 (65.2%) cases out of 250 cases, Tracy et al¹² in 70% (14/20) and Tripathi et al¹¹ in 25.6% (19/74) of cases. In the present study, monocytopenia was seen in one (0.5%) cases and monocytosis was found in seven (3.4%) cases. Eosinophilia was observed in 68 (33.3%) cases in this

study. Paranitha et al⁸ observed eosinophilia in 54 (21.6%) cases and Khandekar et al¹⁷ in 16 (11.4%) cases out of 140 cases. Thrombocytopenia was observed in seven (3.4%) cases in this study. Paranitha et al⁸ reported thrombocytopenia in 45 (18%) cases, Patwardhan et al¹⁶ in 65/500 (13%) cases and Castello C et al⁵ in 121/925 (13%) cases. However, Karcher et al¹³ reported thrombocytopenia in 88/196 (45%) cases, much higher compared to the present study.

CD4 lymphocyte count is essential for assessment of immune status in HIV – infected persons as the pathogenesis of AIDS is largely attributed to a decrease in absolute CD4 cell count. CD4 cell counts are the criterion for categorizing HIV-related clinical conditions by CDC classification system for HIV infection¹⁸. Patients in the present study were divided into three groups based on absolute CD4 lymphocyte count.

Haematological parameters were compared in these three groups. The number of cases with anaemia, leucopenia, lymphopenia and thrombocytopenia increased with reducing CD4 cell counts. Mean total leucocyte count, mean absolute lymphocyte count was lower with reducing CD4 cell count. These parameters showed significant difference (p value < 0.05) between three groups with differing CD4 cell count. This indicates higher occurrence of anaemia, leucopenia, lymphopenia and thrombocytopenia with progression of disease. These haematological findings almost correlate with Paranitha et al⁸. Table – VI shows the comparison of haematological parameters in patients with different CD4 cell counts.

Conclusion:

Haematological manifestations are common in HIV – infected patients. Anaemia is the most common manifestation and the most frequent form is anaemia of chronic disorder followed by macrocytic anaemia. A proportion of patients also show leucopenia and thrombocytopenia. Incidence of anaemia, leucopenia and thrombocytopenia correlates with disease progression. The present study also showed significant correlation of absolute lymphocyte count with CD4 cell count. Thus absolute lymphocyte count can be used as a predictor of CD4 count and also to assess the stage of the disease in centres where CD4 count evaluation is not available.

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Death Audit –An Experience In Medicine Ward

MF ABEDIN^a, MJ ABEDIN^b, AFMH UDDIN^c, MI MUJUMDAR^d,
RS CHOWDHURY^e, AK SAHA^f, MA FAIZ^g

Summary:

Background: In industrialized countries, the audit has become an integral part of medical care. The experience in developing countries yet inadequate. This is the first formal death audit in medicine ward in Bangladesh. This study had been carried out to find out relation between some factors like age, sex, causes, diurnal variation, duration of hospital stay with death & errors in certification process
Methods: It was a cross sectional study conducted at the Medicine Department of Sir Salimullah Medical College (SSMC) and Mitford Hospital from March 2010 to August 2010. Information of consecutive 100 deaths in medicine department were collected in a pre designed clinical data sheet within half an hour of every occurrence. Necessary data was collected from hospital case records (admission register, case files and death certificates) using structured check-list. Patients who were brought dead excluded from the study.
Result: Among 100 deaths, 48% were male(n=48) and 52% were female(n=52). The age range was 15-85 years. The highest incidence of death(24%) occurred in 56-65 years group. Within this group 66.7% were male and 33.3% were female. First day(within 24 hour of admission) death accounted for 46%(n=46) of all death, by the second day 23%(n=23) of all death occurred. Before the 5th day

88%(n=88) of all death occurred. Only 7% of all death occurred after 10th day. During office period that means 8 AM to 3 PM only (n=23) 23% of death occurred, rest of the death(77%, n=77) occurred after office period. Among the 77% of death that occurred after official hour. 62.3% of death occurred during 9 PM to 8 AM. During data collection we observed almost 100% of our existing death certificates had both major and minor errors. The highest underlying cause of death was cerebrovascular disease that were 29%(n=29) of total death, infectious disease contributes 20%, chronic liver disease 13%, malignancy 7%, poisoning 6%, cor pulmonale were 5%, others were 20%.
Conclusion: Death certificate is an important tool of death audit, whereas most of our death certificate had both major and minor error. Measures should be taken to improve our death certificate. In our hospital maximum death occurred during 9 pm to 8 am. To reduce hospital mortality we should ensure facilities of health care during this vulnerable time.

Key Words: Poisoning, Cor pulmonale, Major error, minor error.

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Introduction:

Audit in medical practice is defined as the systematic and critical analysis of the quality of medical care, including the procedures used for diagnosis and

treatment, the use of resources and the resulting outcome and quality of life for the patient¹.

The audit involves a criticism of current practice. However this is well appreciated that audit is not fault finding but it encourages thoughtful planning which leads to valid information collection and subsequently to informed decision making².

The review of causes of morbidity and mortality in health care facilities is an important exercise with far reaching implications. This form of clinical audit gives a picture of the prevailing disease pattern in the particular community and at the same time looks out for any change in the disease pattern over time³.

In ancient years, audit has become an acquired concept in the context of obstetric and other health care in both industrialized and developing countries. Death audit is in practice in United Kingdom, South Africa, and Malaysia since 1952, 1998 and early 80's respectively⁴.

Recently Bangladesh has started maternal, neonatal and child death audit^{5, 6}. Death audit in other health sector especially in medicine department is not started yet.

- Dr. Md. Forhad Abedin, Bangabandhu Sheikh Mujib Medical University, Dhaka.
- Dr. Md. Joynal Abedin, Honorary Medical officer, Department of Medicine, Sir Salimullah Medical College & Mitford Hospital, Dhaka.
- Dr. A F M Helal Uddin, Assistant Professor, Department of Medicine, Sir Salimullah Medical College & Mitford Hospital, Dhaka.
- Dr. Md. Ishaq Mujumdar, Assistant Professor, Department of Medicine, Sir Salimullah Medical College & Mitford Hospital, Dhaka.
- Dr. Ranajit Sen Chowdhury, Assistant Professor, Department of Medicine, Sir Salimullah Medical College & Mitford Hospital, Dhaka.
- Prof. Anup Kumar Saha, Professor, Department of Medicine, Sir Salimullah Medical College & Mitford Hospital, Dhaka.
- Prof. Md Abul Faiz, Professor, Department of Medicine, Sir Salimullah Medical College & Mitford Hospital, Dhaka.

Address of Correspondence: Dr. Md. Forhad Abedin, Bangabandhu Sheikh Mujib Medical University, Dhaka, Email: fabedin75@gmail.com. Mobile:01716741473

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Recently Directorate General of Health Services provided a circular to maintain death audit in every department of health sector (Public health-2/ESD-01/information/2008/454). Death audit is important because it gives an understanding to what happens and why. This helps to go beyond rates and ratios to determine the inciting factors and to take measures how deaths could have been avoided⁷.

This study was designed to find out relation between some factors like age, sex, causes, diurnal variation, duration of hospital stay with death pattern in adult medicine units, in a tertiary health facility and major error in death certification as described by WHO like mechanism of death listed without an underlying cause, improper sequencing of events and competing cause of death, minor errors like abbreviation, absence of time intervals and mechanism of death followed by underlying legitimate cause of death⁸.

Methodology:

This was a cross-sectional study carried out in medicine department of Mitford hospital, Dhaka from March 2010 to August 2010. During this period a total of 100 consecutive deaths except those who were brought dead included in this study. Death certificate play a important role to make successful death audit. Our existing death certificate which is supplied by the government of Bangladesh was not adequate enough to fulfill the format of cause of death section based on the recommendation of the World Health Organization. More over our doctor are not trained enough for appropriate fulfillment of death certificate. Major errors are mechanism of death

listed without an underlying cause, Improper sequencing, Competing cause and minor errors are using abbreviations, absence of time intervals, mechanism of death followed by underlying legitimate cause of death. Definition of major & minor errors in death certificate are shown in Table(I). Ethical clearance was obtained from the concerned authority to conduct the research work. We used purposive non probability sampling for collection of cases. Our inclusion criteria was all death during study period & exclusion criteria was Brought dead. We developed a network with nurses, interneer and midlevel doctors so that one of us could reach the hospital within half an hour of a death. After taking permission from hospital authority necessary data were collected from hospital case records, admission register, case files A checklist was designed to record profile of patients, time of admission, diagnosis at the time of admission, time of death and cause of death. Data were analyzed by SPSS where necessary.

Results:

During the study period a total 13,123 (Male-5249, 40%; Female-7874,60%) patients were admitted in the medicine department of Sir Salimullah Medical College (SSMC) and Mitford Hospital. Among them consecutive 100 deaths in medicine ward were analyzed under death audit. Among 100 deaths 48% were male(n=48) and 52% were female(n=52). The age range was 15-85 years. The highest incidence of death occurred in 56-65 years group. This group represents 24% of total death. Within this group 66.7%(N=16) were male and 33.3%(N=8) were female. As shown in table (II).

Table-I

Definition of major & minor errors in death certificate

MAJOR ERROR	
Type of error	Definition
Mechanism of death listed without an underlying cause	Mechanism or nonspecific condition as the underlying cause of death
Improper sequencing	Sequence of event does not make same underlying cause of death not listed on the lowest completed line of part-I
Competing cause	Two or more casually unrelated etiologically specific disease listed in part-I
MINOR ERRORS	
Abbreviations	Abbreviation used in identifying the disease
Absence of time intervals	No time interval listed in part –I or part –II
<i>Mechanism of death followed by underlying legitimate cause of death</i>	<i>Use of mechanism but qualified by an etiologically specific cause of death</i>

Table-II

Age-sex distribution of the study population(=100)

Age(years)	Male	Female	Total
15-25	6	8	14
26-35	3	5	8
36-45	4	8	12
46-55	8	9	17
56-65	16	8	24
66-75	6	10	16
76-85	4	3	7
>85	1	1	2
Total	48	52	100

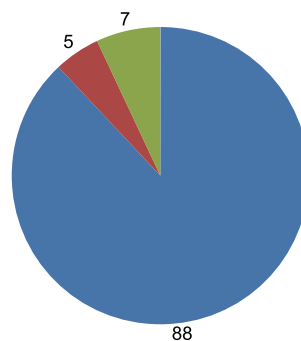
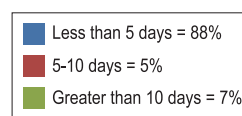
Table-III*Distribution of cases by cause of death and sex*

Cause of death	Male	Female	Total	Percentage
Cerebrovascular disease	15	14	29	29
Chronic liver disease	7	6	13	13
Infectious disease	6	14	20	20
Chronic kidney disease	2	2	4	4
Ischemic Heart disease	4	0	4	4
Poisoning	3	3	6	6
Malignancy	3	4	7	7
Cor Pulmonale	3	2	5	5
Diabetic Keto acidosis	3	1	4	4
Hypoglycaemia	0	1	1	1
Undiagnosed	2	3	5	5
Others	0	2	2	2

First day (within 24 hour of admission) death accounted for 46% (n=46) of all death, by the second day 23% (n=23) of all death occurred. Before the 5th day 88% (n=88) of all death occurred. Only 7% of all death occurred after 10th day. Fig (I) shows the grouped duration of study and end point (Died).

During working hour (Regular hospital work hours) that means 8 AM to 3 PM only (n=23) 23% of death occurred, rest of the deaths (77% ,n=77) occurred after (regular hospital work hours) working hour period. Among the 77% of death that occurred after official hour. 62.3% of death occurred during 9 PM to 8 AM. as shown in Fig(II).

In the present study , during data collection we observed almost 100% of our existing death certificate had major

**Fig.-1:** Distribution of death according to duration of Hospital stay.

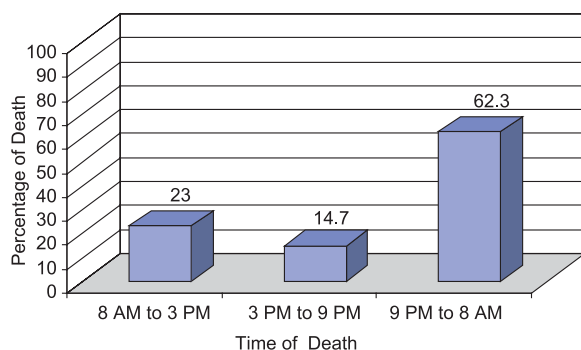


Fig.-2: Diurnal variation of death

error in a form of mechanism of death listed without an underlying cause, improper sequencing and had 100% minor error in the form of abbreviation , absence of time interval .

According to the audit, the highest underlying cause of death was non communicable disease that comprises substantial amount of death and rest of the causes are due to communicable diseases and few are undiagnosed causes as shown in fig(III). It also shows that there is no significant variation between male and female in non communicable disease. Among the non communicable disease, Cerebrovascular disease that were 29%(n=29) of total deaths. Among the cerebrovascular deaths, as

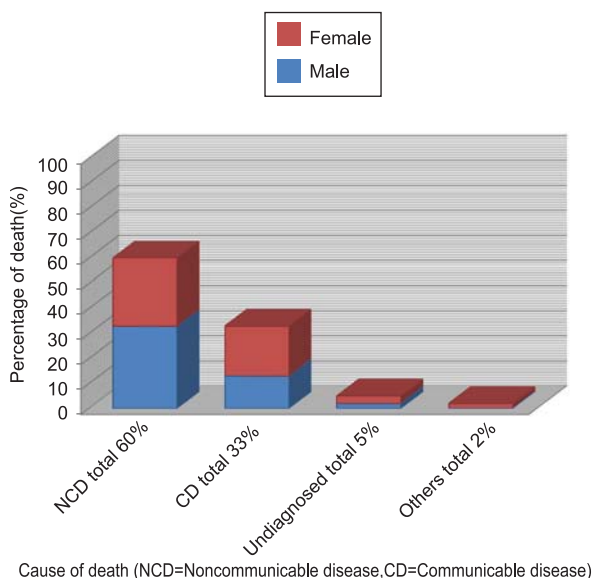


Fig.-3: Distribution of death by Non communicable (NCD) and Communicable Disease(CD) between male and female

co-morbidity Hypertension was responsible for 79.3% cases and Diabetes Mellitus was responsible for 20.7% cases. As an underlying cause of death infectious disease contributes 20%, chronic liver disease 13%, malignancy 7%, poisoning 6%, cor pulmonale were 5%. Table(III) shows the underlying cause of death among the study population.

Discussion :

In our death audit 88% of all death occurred within 5th day of admission which is consistent with another study conducted in tertiary hospital KADUNA Nigeria⁹. Where 65% of death occurred within 5th day of admission .It is our limitation that we don't know whether the disease pattern and severity is similar or not in two hospital. The similarity of result between two study is due to almost similar socioeconomic background in perspective of health care facilities in two countries. First day death contributes a significant portion of a hospital mortality rate even though the hospital can do little to prevent them. Lack of ICU facilities and intensive care contributes the most . In absence of ICU facilities, close monitoring of seriously ill patient by better utilization of hospital resources both human and logistics can substitute the ICU facilities as it is present in snake bite clinic in Chittagong Medical College Hospital, Chittagong and in malaria ward in Bikaner, INDIA¹⁰ .

In this study 62.3% of death occurred during 9 pm to 8 am which is consistent with another study conducted in Germany from 1987 to 1991¹¹.In our country availability of health care provider and facilities are minimum during this period. To reduce mortality we can ensure optimum number of health care provider and arrange optimum health care facilities during this period.

In our study 100% of death certificate had major error. In a study conducted in Canada major error were found in 32.9% cases⁸. High incidence of error in death certification was probably due to error from death certificate which was supplied by the government of Bangladesh. Our existing death certificate has only one part where as standard death certificate by WHO consist of two parts. First part contains immediate cause , and underlying cause sequentially which is absent in our death certificate. There is no part two in our death certificate which indicates the contributory factors of death. There is no space for approximate time interval

between onset and death in our existing death certificate. There is also lack of knowledge about the process of death certification among the young doctors. There should be more structured and organized teaching to reduce the error in death certification .

In this study the underlying cause of most death resulted from cerebrovascular disease (29%). High number of death due to stroke with risk factor like hypertension, diabetes mellitus provides the hint of non-communicable disease as emerging health problem. In one study conducted in Bangladesh at 2010 found that 66% of death was due to non communicable disease in adult population¹². In the health bulletin of DGHS 2010 the common cause death has been found due to poisoning in Upazilla hospital¹³.

Although the audit has become an integral part of medical care in industrialized countries, the experience in developing countries yet very rudimentary. However Government of Bangladesh has taken initiatives to establish perinatal death audit in different hospital since 2004. A decrease in overall mortality rates was recorded after introduction of perinatal mortality audit in LAMB Hospital of Bangladesh (a NGO)⁵. This glorious example should be an eye opening for the professionals , hospital managers and the planners for introducing death audit in a 'non blaming' atmosphere.

Conclusion:

Death certificate is an important tool of death audit, whereas most of our death certificate had both major and minor errors. Measures should be taken to improve our death certificate. In our hospital maximum death occurred during 9 pm to 8 am. To reduce hospital mortality we should ensure facilities of health care during this vulnerable time. Regarding the cause of death, most of the death occurred due to non communicable disease which is about 60% of all death and rest of the causes are due to communicable disease(infectious disease and Chronic liver disease) and few are undiagnosed causes. Although there is no significant variation between male and female in non communicable disease female are more prominent feature of communicable disease which about 20% compared to 13% of male. Among the non communicable causes the most important causes are cerebrovascular disease and among the communicable disease Infectious disease are the leading cause of death then Chronic liver disease is

the second most important cause of death. So measure should be taken to better prevention of non communicable disease and concomitantly communicable disease should be prevented and treated as early as possible.

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Study of Polycystic Ovaries (PCO) in Mymensingh Medical College Hospital, Bangladesh

K NAHAR^a, H YASMIN^b, L PRAMANIK^c

Summary:

Background information: Polycystic ovaries (PCO) and their clinical expression (polycystic ovary syndrome) are conditions characterized by menstrual abnormality, clinical and biochemical features of hyperandrogenism. It is the killer of womanhood. Woman of any ethnic background can present with PCOS.

Objectives: To find out demographic characteristics such as age, BMI, clinical presentations like hirsutism, menstrual cycle pattern and fertility status and the hormonal changes like LH/FSH ratio and serum testosterone level.

Study design: A descriptive cross sectional study for 1 year from December 2009 to November 2010.

Study setting: Outdoor Department of obstetrics and gynaecology and center for Nuclear Medicine and Ultrasonography (CNMU) Mymensingh Medical College Hospital, Mymensingh.

Introduction:

Polycystic ovary syndrome is the most frequently encountered endocrinopathy in women of reproductive age. It is associated with significant morbidity in terms of both reproductive and non-reproductive events¹.

The condition was first described in 1935 by Stein and Leventhal as a syndrome manifested by amenorrhoea, hirsutism and obesity associated with enlarged polycystic ovary².

According to Rotterdam Criteria a refined definition of PCOS was the presence of two out of the following three criteria.

1. Oligomenorrhoea/or anovulation.
2. Hyperandrogenism (clinical and/or biochemical).

a. Prof. (Dr.) Kamrun Nahar, Professor & Head Dept. of Gyane & Obs, Green Life Medical College & Hospital, Green Road, Dhaka.

b. Dr. Halima Yasmin, Medical Officer, Upazilla Health Complex, Phulpur, Mymensingh.

c. Dr. Lita Pramanik, Consultant, Eshorganj Upazilla Health Complex, Mymensingh.

Address of Correspondence: Prof. (Dr.) Kamrun Nahar, E-mail: run@btcl.net.bd Mobile No: 0088-01711689778

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Result: Total 55 patients were evaluated. Most common age was 20-29 years (72.7%) with mean age 23.55 years and mean BMI 27.12 kg/m². Clinical presentations were in this study hirsutism in 36.4%, irregular menstrual cycle in 63.6% and subfertility in 56.3%. Laboratory findings revealed testosterone level was more than normal range in 58% case, LH/FSH ratio was increased (more than 1:1) in 58.2% cases, 26 cases had both increased testosterone level and increased LH/FSH ratio. 17 cases had testosterone level within normal range and LH/FSH ratio less than 1:1.

Conclusion: There are significant relationship between irregular menstrual cycle pattern and hormonal changes such as testosterone level and LH/FSH ratio. There are also significant relationship between BMI and hirsutism with increased testosterone level.

Keywords: Polycystic ovary, irregular menstrual cycle, Hirsutism, subfertility LH/FSH ratio, testosterone level.

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3. Polycystic ovaries with the exclusion of other aetiologies³.

Polycystic ovaries are seen at ultrasound in 20-25% women of reproductive age while PCOS occurs at least 4-6% of the population. The prevalence of polycystic ovary syndrome seems to be rising because of the current epidemic of obesity³.

Women of any ethnic background can present with PCOS. 4% to 4.7% of white women and 3.4% of African American women had PCOS⁴.

The aetiology of PCO is uncertain. There is some evidence of autosomal transmission related to strong familiar clustering. It also represents a complex trait in which a small number of major genes interact with environmental and other genetic factor to account for the heterogeneity⁵.

Family study has revealed that about 50% of first degree relatives have PCOS suggesting a dominant mode of inheritance⁶.

Although USG finding of PCO present in women but of them 66% notice abnormal menstrual pattern⁷. The menstrual cycle abnormality ranges from amenorrhoea, oligomenorrhoea to menorrhagia. Patient with PCOS

may experience endometrial hyperplasia. About 15% to 30% of women with PCOS may have regular cycle in spite of anovulation⁴.

Infertility is a common problem in women with PCOS. The syndrome accounts for 90-95% of women who attend infertility clinics⁸. The chance of pregnancy with PCOS women using fertility treatment is very good⁹.

The prevalence of obesity is high in patient with PCOS. The rate of obesity in PCOS population ranges from 38% to 87%. The cause of obesity in PCOS is not fully known. The obesity of PCOS is of the android type (central type). There is an increased waist to hip ratio associated with hyperandrogenemia, insulin resistance, glucose intolerance and dyslipidemia¹⁰.

Excessive hair growth is the most distinction and visible feature of PCOS. The hair growth usually are seen on the face, upper lip, chin and lower abdomen as an extension of pubic hair towards the umbilicus. Women with PCOS may experience increase skin oiliness secondary to excessive stimulation of the pilosebaceous unit. Acanthosis nigricans appears as symmetrical darkness that appears commonly on the nape of the neck¹¹.

PCOS are most often diagnosed by means of laboratory studies. The ratio of the LH to the FSH level is useful in the diagnosis. The ratio of LH to FSH is greater than 1:1, as tested on day 3 of the menstrual cycle. This change in LH to FSH ratio is enough to disrupt ovulation¹².

Serum level of androgens including androstenedione, testosterone and dehydro-epiandrosterone sulfate may be elevated. The free testosterone level is thought to be the best means¹³. Total testosterone ranges are 6-86 ng/dl. Free testosterone refers to the amount of testosterone that is unbound and actually active and its ranges from 0.7-3.6 ng/dl. Women with PCOS often have an increased level of both total testosterone and free testosterone¹².

According to the Rotterdam criteria the ultrasonic feature of PCO are defined and include either 12 or more follicles, measuring 2-9 mm in diameter and increased ovarian volume $>10\text{cm}^3$. It is essential that the ultrasound scans is performed at a time of ovaries quiescence such as during the early follicular phase of the menstrual cycle¹⁴.

Material and Methods:

It is Descriptive cross-sectional study conducted in the outdoor Department of Obstetrics & Gynecology and Center for Nuclear Medicine and Ultrasonography (CNMU) Mymensingh Medical College Hospital, Mymensingh for one year duration from December 2009 to November 2010. The present study includes the women of reproductive age (15 years to 45 years) who sonographically show PCO, excluding the woman with other medical disorders like ovarian tumour, hypothyroidism and hyperprolactinoma. Purposive sampling technique was followed for selection of sample.

Measurement of LH, FSH and Testosterone Level: 5ml venous blood was collected from each subject with all aseptic precaution using sterile disposable plastic syringe by antecubital venipuncture and poured into a clean glass test tube. The collected blood was allowed to clot at room temperature. Serum was separated and taken in other three plastic test tube. Each test tube is leveled separately for LH, FSH and testosterone. Antibody of LH, FSH and testosterone were added to these serum and mixed well. Then these test tube are kept for 2 hours at 37⁰ C temperature. After that I¹²⁵ were added to these test tube and incubated at 4⁰-7⁰ C temperature. Duration of incubation time was different for each hormone. After that incubation time the serum was kept in room temperature for 30 minutes. Then 500 microliter precipitating solution was added in each test tube and mixed well. These test tube were kept in centrifuge machine and centrifuge it at 3500 Rpm. Precipitant were appeared at the bottom test tube. The level of these hormones were measured from these Precipitant.

Transabdominal ultrasonography was performed with 3.5MHz curvilinear electronic probe in the Center for Nuclear Medicine and Ultrasonography (CNMU), MMCH to all the women of this study in full bladder. The diagnosis of PCO was done by ovarian volume ($e^{10}\text{cm}^3$), stromal echotexture and follicular number (>10).

Data were collected using a structured questionnaire containing all the variables of interest. Collected data were processed and analyzed using computer based software SPSS (Statistical Package for Social Sciences) version 12. A probability value of <0.05 was considered significant. The summarized data were presented in the form of tables and graphs with due interpretation.

Results:

Fifty five (55) women with PCO were selected from outdoor department of Obs and Gynae MMCH having USG report from Centre for Nuclear Medicine and Ultrasonography MMCH during the period of December 2009 to November 2010. All cases were evaluated clinically (age, BMI, hirsutism, menstrual cycle pattern and fertility status). Hormonal level (LH/FSH ratio and total testosterone level) were done for all cases.

The findings and related interpretation are presented in tables and figures according to the objectives of the study.

Table-I: Respondents by age: Regarding age distribution of the respondents in the study group it was observed that most of the women were within 20-29 years (72.7%).

Table-I*Respondents by age.*

Age (Years)	Numbers	Percentage
15-19	09	16.4
20-24	22	40.0
25-29	18	32.7
30-34	05	9.1
>35	01	1.8
Total	55	100.0

Mean \pm SD of age distribution was 23.55 \pm 4.62 years.

Table-II: Respondents on the basis of BMI: Most of the respondents 26 (47.3%) were over weight (BMI 25.1-30kg/m²), 12(21.8%) were obese having BMI more than 30kg/m² & 17(30.9%) cases had normal BMI. Mean \pm SD of BMI was 27.12 \pm 3.52 kg/m².

Table-II*Respondents on the basis of BMI.*

BMI (kg/m ²)	Numbers	Percentage
20.0-25	17	30.9
25.1-30.0	26	47.3
>30.1	12	21.8
Total	55	100.00

Table-III: Respondents by hirsutism: Hirsutism was present in 20 (36.4%) cases and absent in 35 (63.6%) cases.

Table-III*Respondents by hirsutism.*

Hirsutism	Numbers	Percentage
Present	20	36.4
Absent	35	63.6
Total	55	100.00

Table-IV: Respondents by menstrual cycle pattern: 31 (56.3%) women were presented with oligomenorrhoea and 03 (5.5%) women had amenorrhoea. Here 35(63.6%) women had irregular menstrual cycle. On the other hand 20 (36.4%) women had regular menstrual cycle.

Table-IV*Respondents by menstrual cycle pattern.*

Menstrual cyclepattern	Numbers	Percentage
Regular	20	36.4
Oligomenorrhoea	31	56.3
Amenorrhoea	03	5.5
Menorrhagia	01	1.8
Total	55	100.00

Table-V: Respondents by fertility status: Regarding fertility status of the women, primary subfertility was found in 28 (50.8%) cases and secondary subfertility was found in 03 (5.5%) cases. Total subfertility cases were 31 (56.3%). Satisfactory fertility was present in 9 (16.4%) cases. Fertility status of 15 (27.3%) respondents was not concerned as they were unmarried.

Table-V*Respondents by fertility status.*

Fertility status	Numbers	Percentage
Fertile	09	16.4
Primary subfertility	28	50.8
Secondary subfertility	03	5.5
Not concern	15	27.3
Total	55	100.00

Fig-1: The testosterone level & LH/ FSH ratio of the respondents: 26 women had LH/FSH ratio more than 1:1 and testosterone level more than normal limit. 17 women had LH/ FSH ratio at or less than 1:1 and testosterone level within normal limit.

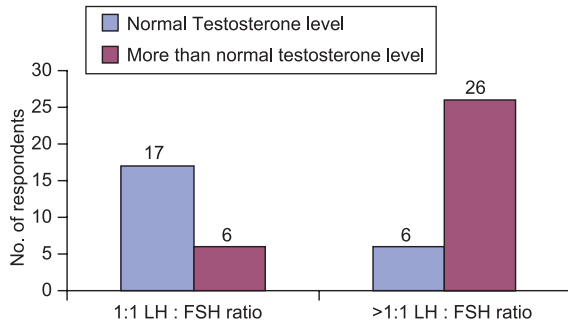


Fig-1: The testosterone level & LH/ FSH ratio of the respondents.

Table -VI: Relationship between menstrual cycle pattern with levels of testosterone (N=54):

In case of menstrual cycle pattern, 29 (53.8%) women with oligomenorrhoea and 2 (3.7%) women with amenorrhoea had increased testosterone level. The relationship between menstrual cycle pattern and

testosterone level was also statistically significant ($X^2 = 39.31$, $df = 2$, p value < 0.05).

Table-VII: Relationship between BMI, hirsutism and fertility status with levels of testosterone (N=55): 27 (49%) women with increased BMI ($> 25 \text{ kg/m}^2$) had increased testosterone level. The overall relationship between BMI and level of testosterone was statistically significant. 16(29%) women with hirsutism had increased testosterone level. The relationship between the present or absent of hirsutism with testosterone levels were statistically significant ($X^2 = 6.149$, $df = 1$, p value < 0.05). 15(27.5%) women with primary subfertility and 1(1.8%) women with secondary subfertility had increased testosterone level. Fertility status with testosterone level were statistically non-significant.

Table-VIII: Relationship between menstrual cycle pattern with LH/FSH ratio (N=54): For menstrual cycle pattern, 25(46.4%) women with oligomenorrhoea and 2(3.6%) women with amenorrhoea had LH/FSH ratio more than 1:1. The relationship between menstrual cycle pattern and LH/FSH ratio was statistically significant ($X^2 = 16.96$, $df = 2$, p value < 0.05).

Table-IX: Relationship between BMI, hirsutism and fertility status with LH/FSH ratio (N=55): Though more

Table-VI

Relationship between menstrual cycle pattern with levels of testosterone (N=54).				
Menstrual Cycle Pattern	Testosterone (n %)		X^2 (df)	p-value
	Normal	> Normal		
Regular	19 (35.2)	1 (1.8)	39.31 (2)	0.000
Oligomenorrhoea	2 (3.7)	29 (53.8)		
Amenorrhoea	1 (1.8)	2 (3.7)		
Total= 54 (100%)	22 (40.7)	32 (59.3)		

Table-VII

Relationship between BMI, hirsutism and fertility status with levels of testosterone (N=55).					
Clinical Characteristics	Testosterone (n %)		X^2 (df)	p-value	
	Normal	> Normal			
BMI	Normal				
	20-25 kg/m^2	12 (22.0)	05 (09.0)	8.371 (1)	0.004
	$> 25 \text{ kg/m}^2$	11 (20.0)	27 (49.0)		
	Total=55(100%)	23 (42.0)	32 (58.0)		
Hirsutism	Present	4 (7.0)	16 (29.0)	6.149 (1)	0.013
	Absent	19 (34.54)	16 (29.46)		
	Total= 55(100%)	23 (41.54)	32 (58.46)		
Fertilitystatus	Primary subinfertility	13 (23.6)	15 (27.5)	1.76 (2)	0.424
	Secondary subfertility	2 (3.6)	1 (1.8)		
	Others	8 (14.5)	16 (29.0)		
	Total= 55 (100%)	23 (41.7)	32 (58.3)		

Table-VIII*Relationship between menstrual cycle pattern with LH/FSH ratio (N=54).*

Menstrual cycle pattern	LH: FSH (n %)		X ² (df)	p-value
	≤1:1	>1:1		
Regular	15 (27.8)	05 (9.3)	16.96 (2)	0.001
Oligomenorrhoea	6 (11.1)	25 (46.4)		
Amenorrhoea	1 (1.8)	2 (3.6)		
Total= 54(100%)	22(40.7)	32 (59.3)		

Table-IX*Relationship between BMI, hirsutism and fertility status with LH/FSH ratio (N=55).*

Clinical Characteristics	LH: FSH (n %)		X ² (df)	p-value	
	≤1:1	> 1:1			
BMI	20-25 kg/m ²	09 (16.4)	08 (14.5)	1.251 (1)	0.263
	>25 kg/m ²	14 (25.5)	24 (43.6)		
	Total=55(100%)	23 (41.9)	32 (58.1)		
Hirsutism	Present	5 (9.0)	15 (27.0)	3.654 (1)	0.056
	Absent	18 (33.0)	17 (31.0)		
	Total= 55(100%)	23 (42.0)	32 (58.0)		
Fertility status	Primary subfertility	12 (22.0)	16 (29.2)	.958 (2)	0.505
	Secondary subfertility	2 (3.6)	1 (1.8)		
	Others	9 (16.4)	15 (27.0)		
	Total=55 (100%)	23 (42.0)	32 (58.0)		

than 40% women had increased BMI and increased LH/FSH ratio, but statistically the relationship between BMI and LH/FSH ratio was not significant. 15(27%) women with hirsutism and 16(29.2%) women with primary subfertility had increased LH/FSH ratio. The relationship between the present or absent of hirsutism and fertility status of the women with LH/FSH ratio were also statistically non-significant.

Discussion:

Polycystic ovaries are seen by USG finding in 20-25% women of reproductive age. PCOS occur in at least 5% women of the population. Polycystic ovaries can be diagnosed in patient of any age from menarche. Typically women in their 20s present with polycystic ovary syndrome¹⁵. In present study among 55 women, 72.7% were within the age of 20-29 years. The mean age was 23.55 years. In another study, the mean ± SD

of age distribution was 21.9 ± 3.06 ¹⁶, which is nearer to present study. A recent study showed that the common age of PCO women were 21-25 years¹⁷. This result is also close to the present study.

In the present study, thirty eight out of the fifty five women were overweight and obese with mean BMI of 27.12 ± 3.52 kg/m². In another study mean BMI was 27.1 kg/m²¹⁷. Mean BMI of PCO women were 28.98 kg/m² in an Indian study¹⁶. Both the results are nearer to present study.

In the present study hirsutism was present in 36.4% cases. In a study at BSMMU 50% women had hirsutism¹⁷. The percentage was more than the present study because asymptomatic women with PCO were included. The presence of hirsutism was significant among women with PCO than without PCO in an Indian study¹⁸.

The common presentation of the women having PCO was menstrual disturbance⁷. In the present study out of 55 women, 35 (63.6%) women attended in outdoor department with irregular menstrual cycle.

Among them 56.3% women had oligomenorrhoea. The study at BSMMU showed that women with PCOS had oligomenorrhoea in 28% cases¹⁷. The percentage was less than the present study. In a study in Iraq, oligomenorrhoea was prevalent in 43.93% women, nearer to the present study¹⁹.

56.3% women with PCO attended in outdoor department due to subfertility (both primary and secondary) during the study time period. Among them about 28 (50.8%) women had primary subfertility and 3(5.5%) women had secondary subfertility. In the study of BSMMU, primary subfertility was found in 90% cases and secondary subfertility was found in 10% cases¹⁷. According to a literature, 16-25% of normal ovulatory women have polycystic ovaries without evidence of the syndrome, a subgroup of women with PCO (up to 30%) may have PCOS¹. In present study out of 55 women, 60% women had PCOS and 40% women had only PCO, not similar to the literature review.

In the present study, 58.2% women with PCO had LH/FSH ratio more than 1:1. Increased testosterone level was found in 58% women with PCO. In an Indian study, 55.55% women had increased LH/FSH ratio and 64.44% women had increased testosterone level which is closed to present study¹⁶. 53.8% women with oligomenorrhoea and 3.7% women with amenorrhoea had increase testosterone level in present study. The result is significant. In another study 73% girl with irregular menstrual cycle (oligomenorrhoea and amenorrhoea) had the highest androgen level, nearer to present study¹⁷.

In the present study 49% cases with increased testosterone level were over weight and obese (BMI>25kg/m²) and 20% cases with normal testosterone level were overweight and obese. The result is significant. Increased testosterone levels among overweight and obese women were found in 59.18% cases in another study¹⁶. The result of the present study is nearer to this study.

In the present study hirsutism was present in 36.4% cases. In relation with hirsutism and testosterone level,

29% women with increase testosterone level had hirsutism whereas 7% women with normal testosterone level had hirsutism. The result is significant. In an Indian study, 44.2% women with hirsutism had significantly high testosterone level¹⁶. The result is more than the present study.

In the present study 27.5% women with primary subfertility and 1.8% women with secondary subfertility had increased testosterone level. The result is not significant. Other study showed 36% subfertile women with PCO and 28% subfertile women without PCO had increased testosterone level²¹. So their result supports present study.

In the relation between menstrual cycle pattern and LH/FSH ratio, 46.4% women with oligomenorrhoea and 3.6% women with amenorrhoea had increase LH/FSH ratio in present study and 11.1% women with oligomenorrhoea and 1.8% women with amenorrhoea had LH/FSH ratio at or less than 1:1. The result is significant. Study in Iraq about correlation between LH/FSH ratio and disease manifestation showed no significant correlation between menstrual cycle pattern and LH/FSH ratio²⁰.

In present study 43.6% obese and overweight women had > 1:1 LH/FSH ratio. On the other hand 25.5% obese and overweight women had at or less than 1:1 LH/FSH ratio. The result is not significant. In a study in Iraq, they also found that there was no significant correlation between BMI and LH/FSH ratio²⁰. This result has similarity to present result.

About the correlation between hirsutism and LH/FSH ratio, 27% women with hirsutism had increased LH/FSH ratio and 9% women with hirsutism had LH/FSH ratio at or below 1:1. The result is not significant. Statistical correlation between LH/FSH ratio and hirsutism was not significant in a study in Iraq²⁰.

In the present study, 29.2% women with primary subfertility and 1.8% women with secondary subfertility had LH/FSH ratio more than 1:1. Whereas 22% women with primary subfertility and 3.6% women with secondary subfertility had LH/FSH ratio at or less than 1:1. The result was not significant. Another study had increased LH/FSH ratio in 60% subfertile women with PCO and 70% women without PCO²¹. So their result supports the present study.

The required size was not possible to collect because of limitation of time and financial constrains. All the facts and figures mentioned here may considerably vary from those of large series covering wide range of time.

Conclusion:

Irregular menstruation, increased BMI, hirsutism and subfertility are the common presentation of women with PCOS. There are significant relationship between irregular menstrual cycle pattern and hormonal changes such as testosterone level and LH/FSH ratio. There are also significant relationship between BMI and hirsutism with increased testosterone level. Common future outcome of PCOS are type 2 diabetes mellitus, hypertension, cardiovascular disease and endometrial carcinoma. Early diagnosis and proper preventive management of these patients with PCO will reduce reproductive and non reproductive morbidity.

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A Comparative Study between Single Dose of Ceftriaxone, Metronidazole and Gentamicine as a Prophylaxis versus Conventional Dose Antibiotic in Hysterectomy in BSMMU

SA MUNMUN^a, R ARA^b, S CHOWDHURY^c, MMA SARKAR^d, SB CHOWDHURY^e,
N PARVIN^f, R SULTANA^g, S ISLAM^h

Summary:

A prospective study was done in the Department of Obstetrics & Gynaecology, BSMMU, Dhaka from January 2006 to December 2006. Hundred cases were studied during this period. The patients admitted for hysterectomy operation were divided into group A and group B. In group A 50 patients received prophylactic injectable 1 gm ceftriaxone, 500 mg metronidazole and 80 mg gentamicine one hour before operation. In group B 50 patients received conventional antibiotic comprising ciprofloxacin for 7 days (both I.V and Oral), metronidazole for 5 days (both I.V and oral) and gentamicine for 3 days (I.V/I.M). After fulfilling the inclusion and exclusion criteria the patients were randomly assigned to receive either parenteral loading dose of 1 gm Ceftriaxone, 500 mg Metronidazole and 80 mg Gentamicine (Group-A) pre-operatively or conventional dose of antibiotic (Group-B). Relevant careful clinical records and data were kept on predesigned proforma. Incidence of post-operative complications, operative time and hospital stay were recorded for each patient. Data was analyzed using SPSS program with the consultation of the statistician. Because of nature of the analysis, only chi-square (X²) test was applied. Most of

the patients (64% in Group-A and 67% in Group-B) were from low socio-economic class. Significant number of patients were anaemic (Hb% between 50-55%) and duration of operation was within 60-89 minutes in most of the cases. There were 3(6%) post operative wound infection in Group-A and 2(4%) post operative wound infection in Group-B after abdominal hysterectomy. 1 patient of Group-A and 1 patient of Group-B developed wound infection after vaginal hysterectomy operation. So, there was no significant difference in post-operative wound infection between Group-A and Group-B. Length of post-operative hospital stays in both groups were within 5-9 days (Group-A 90% and Group-B 92%). The study demonstrates that there is no significant difference regarding surgical outcome between Group-A and Group-B. Moreover the patient of Group-A needs antibiotic cost only Tk. 220 and Group-B needs of about Tk. 640, so that it saves about Tk. 420 which supports the economic benefits for Group-A and cost effectiveness.

Key Words: Hysterectomy, Antibiotics, Parenteral, Prophylaxis, Conventional

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Introduction:

The prevention of infection in surgical patient undergoing operation is a major challenge. The use of antibiotic

prophylaxis has been shown to prevent post surgical wound infection. When employed rationally, significant reduction in the mortality and morbidity and saving in resources can be achieved¹. Most of the patients who undergo major operation in public hospital are of low socio-economic group with poor nutritional status and the chance of cross infection in hospital is more. Better outcome after major surgical procedure mainly depends upon the nutritional status of the patient, type of surgical wounds maintenance of strict asepsis during operation, post operative care etc. In hospital there is more chance of cross infection due to overcrowding. So usually we treat the patient with conventional parenteral antibiotic therapy followed by oral Ciprofloxacin for 7 days, Metronidazole for 5 days and parenteral Gentamicine for 3 days to prevent infection.

But to reduce the expenditure of patient and minimize the side effects of conventional long time antibiotic therapy, single dose preoperative antibiotic as a prophylaxis can be tried alternatively to control the infection.

- Dr. Salma Akter Munmun, Medical Officer, Department of Obs & Gynae, Bangabandhu Sheikh Mujib Medical University.
- Dr. Rowson Ara, Medical Officer, Department of Obs & Gynae, Bangabandhu Sheikh Mujib Medical University.
- Dr. Shiuly Chowdhury, Assistant Professor, Department of Obs & Gynae, Bangabandhu Sheikh Mujib Medical University.
- Dr. Mst. Manjumun Ara Sarkar, Register, Department of Gynae Oncology, NICRH, Mohakhali, Dhaka
- Prof. Saleha Begum Chowdhury, Department of Obs & Gynae, Bangabandhu Sheikh Mujib Medical University.
- Dr. Nahida Parvin, Medical Officer, Department of Obs and Gynae, Bangabandhu Sheikh Mujib Medical University.
- Dr. Rabeya Sultana, Assistant Professor, Department of Obs & Gynae, City Medical College, Gazipur
- Dr. Sabiha Islam, Medical Officer, Department of Obs and Gynae, Bangabandhu Sheikh Mujib Medical University

Address of Correspondence: Dr. Salma Akter Munmun, Mailing address: Room no. 827, Block-C, Department of Obs & Gynae, Bangabandhu Sheikh Mujib Medical University, Phone: +8801715000137, E-mail: salma.a.munmun@gmail.com

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It has been learnt from the different study that proper aseptic technique alone could reduce but not completely eliminate the bacterial contamination of the surgical field². Therefore, the need for antibiotics as supplement to aseptic technique became more widely accepted specially in a situation like our overcrowded hospital.

Different study showed that broad spectrum antibiotics and administration of more than one dose were more efficacious³.

The effective use of prophylactic antibiotic depends upon the appropriate timing of their administration. Parenteral antibiotic in sufficient doses generally should be given within 1 hour before the operation which help to achieve the therapeutic drug level both in the blood and related tissue during the operation⁴. The antibiotics used must have better tissue penetration, prolong half life and should cover most of the polymicrobes involves in per and post operative infection. Ceftriaxone, Metronidazole and Gentamicine when administered together as a prophylaxis can fulfill the above criteria of a good antibiotic.

Materials and Methods:

Prospective type of comparative study was done in the Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from January 2006 to December 2006. All patients who were admitted for hysterectomy were included. Patient with impaired renal function, patient with hypersensitivity to penicillin group of drugs and patient with previous history of infection or any focus of infection in the body preoperatively were excluded from the study. After taking history, clinical examination was done by the investigator. Pre-operative anaesthetic check up was done for surgical fitness. When the patient was found to be fit for operation, one hour prior to surgery single dose of parenteral triple antibiotic was given to one study group (Group-A) and conventional dose antibiotic to another study group (Group-B). Patients were randomly assigned to receive parenteral one dose of 1 gm Ceftriaxone, 500 gm Metronidazole and 80 mg Gentamicine (Group-A) or conventional dose of Ciprofloxacin for 7 days, Metronidazole for 5 days and Gentamicine for 3 days (Group-B). From both the group required information were recorded in the preformed check list. Prospective analysis was done by Frequency Test to get the percentage. Statistical analysis was done by chi-square test for measuring the association in order to answer the research questions. All the data were entered into the template of SPSS software after necessary screening and both qualitative and quantitative analysis were performed accordingly.

Results:

This comparative study was conducted to determine whether only single dose of Ceftriaxone, Metronidazole & Gentamicine prophylaxis in hysterectomy operation is effective in controlling post operative wound infection.

Wound infection was observed in four patients (8.5%) of Group-A & three patients (6.25%) of Group-B. There was no significant difference ($p > 0.05$) in terms of wound infections in both abdominal hysterectomy and vaginal hysterectomy.

The study findings show that only single dose of 1 gm Ceftriaxone, 500 mg Metronidazole and 80 mg Gentamicine is as effective as conventional dose. Moreover prophylactic dose group patient is benefited due to their easy drug administration, fewer prick, fewer side effect and cost effectiveness.

Study showed that to decrease post operative wound infection needs appropriate aseptic surgical technique and improvement of patients nutritional status and anaemic condition.

Figure 1: Bar diagram showing number of patients in different hysterectomy group (Total 100 patients were taken into trail).

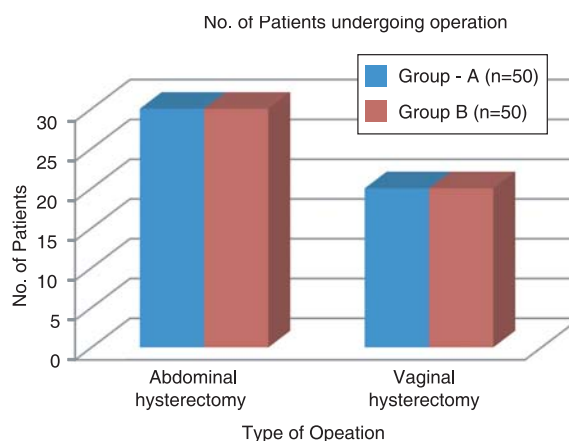


Fig-1:

Table-I

Age distribution of both groups (n=95)

Age Group	Group-A (n=47)	Group-B (n=48)
25-34	13 (28%)	12 (25%)
35-44	20 (43%)	21 (44%)
45-54	10 (21%)	9 (19%)
55-64	4 (8%)	6 (12%)

$\chi^2=0.5066$, $p > 0.50$ (Not significant)

It is seen that about 50% of the patients are in 35-44 years age group. There is no difference in age between the two groups of patients.

Table-II*Socio-economic condition*

	Group-A (n=47)	Group-B (n=48)
Low	30 (64%)	32 (67%)
Middle	14 (30%)	13 (27%)
High	3 (6%)	3 (6%)

$X^2=0.0919$, $df=2$, $p>0.50$ (Not significant)

Low= $<$ Tk. 10,000/- to 15,000/- per month

Middle= $>$ Tk. 15,000/- to Tk. 30,000/- per month

High= $>$ Tk. 30, 000/- per month

Most of the patients are of the low income group. Only 6% is of high income group.

Table-III*Analysis of risk factors for infection in study group.*

Observed association of different variables among 7 (seven) patients of both group who experienced infection.

No. of patients	Age	Weight (lbs)	Socio-economic condition	Hemoglobin	Duration of operation in min
1	52	180	Low	50	120
2	45	120	Low	50	80
3	43	130	Low	60	80
4	52	130	Low	52	90
5	57	72	Low	55	90
6	54	110	Low	50	90
7	49	120	Low	60	90

All patients were of low socio-economic status. Hb% was within 50-55%, weight was between 72-180 lbs, duration of operation was 80-120 minutes.

Discussion:

The present study was designed to compare the efficacy of only single dose of Ceftriaxone, Metronidazole and Gentamicine versus conventional multi-dose regimen in hysterectomy operation to prevent post operative wound infection which revealed no significant difference between the groups. Hysterectomy is one of the most frequently performed major operation in gynaecology⁵. Many randomized trial were performed worldwide to find out the effectiveness of antibiotic prophylaxis in high risk patient⁶. Appropriate choice of prophylactic antibiotics require an understanding of the polymicrobial nature of the endogenous microflora each site⁴. There was no trial of antibiotic prophylaxis in low risk group worldwide i.e

the patient with aseptic surgery. They recommended the use of prophylactic antibiotic in high risk patients who have prosthetic implant, colorectal surgery etc. and also in those in whom the development of an infection might be associated with a catastrophic end result⁷. A study done by Naz (2001) showed single dose offers patients compliance. Patients of control group complaint of many side effects, like nausea, vomiting, dizziness, constipation etc. with conventional treatment which did not occur with that of the single dose prophylactic antibiotic. Most of the complaints were due to the use of metronidazol. Single dose prophylaxis also decrease the workload of the hospital staff⁸.

In this study at the time of randomization, the general characteristic of the patient in both groups showed no significant difference (table I & II). So it is concluded that this comparative study was carried out in matched groups of patients so that it didn't influence the outcome.

The prophylactic use of antimicrobial agents to reduce post operative wound infection has been frequently advocated. The objective of pre-operative prophylaxis is to prevent post-operative infections which are the primary cause of morbidity and mortality in patient undergoing surgery today⁹. Investigators demonstrated that proper aseptic technique alone could decrease but not completely eliminate bacterial contamination of the surgical field. Therefore the need for antibiotics to supplement aseptic technique becomes more widely accepted¹⁰.

Risk of infection may also depends on age, general condition, duration of operation, amount of blood loss during surgery and number of blood transfusion required⁹.

Hoplin L (2000) showed that multiple dose regimen for prophylaxis appears to offer no added benefit over single dose regimen¹¹. This present study findings matched with the findings of Hoplin.

Some studies also showed administration of intermittent intramuscular injection produces lower blood levels and retarded entry of antibiotics into the wound fluid^{12,13}.

In the present study single parenteral dose of 1 gm Ceftriaxone, 500 mg Metronidazole and 80 mg Gentamicine Intravenous were given stat in Group-A. There were 3(6%) post operative wound infection in Group-A and 2(4%) in Group-B. 1 patient of Group-A and 1 patient of Group-B developed wound infection after vaginal hysterectomy operation. So, there was no significant difference in post operative wound infection between Group-A and Group-B in respect of vaginal

hysterectomy. In the both study group, significant number of patients were anaemic (Hb% between 50-55%) and duration of operation was within 60-89 minutes in most of the cases (in Group-A 51% and in Group-B 58%). Most of the patients (64% in Group-A and 67% in Group-B) were from low socio-economic class, it is the most striking feature that indicates poor nutritional status of the patient. So, it is seen that patients general condition i.e. Hb% and nutritional status have marked influence on post operative wound infection, which is supported by other studies⁴.

Begum A. (1981) has shown in her study that post operative wound infection is more common in those patients who need prolong time for operation. In this study there was no significant difference of operation time found between two groups. So it has no influence on the result of the present study¹⁴.

In both group of study there was no significant difference regarding intra operative adhesion and type of suture materials used in skin closure.

The study demonstrate that there is no significant difference in post operative wound infection, or post operative hospital stay between Group-A & Group-B.

This study clearly demonstrated that there is no significant difference in abdominal wound infection in both groups ($p > 0.05$). Considering vaginal hysterectomy there is also no significant difference ($p > 0.05$). So, it is shown that only loading dose is as effective as conventional multi regimen.

Moreover the patient with Group-A needs antibiotic cost only 220 tk. and Group-B needs of about 640 tk. that saves about 420 tk. which support the economic benefits for Group-A.

Single dose offers patients compliance. Side effects like nausea, vomiting, dry mouth, metallic taste etc is more in Group B patients. This study result suggests that these side effects were less in Group A patients.

There is no significant difference in morbidity between prophylactic antibiotic & routine conventional antibiotic in hysterectomy operation. To reduce post operative wound infection as a whole it needs aseptic surgical technique and improvement of patients general condition. Single dose prophylaxis is effective for most procedures and results in decreased toxicity and antimicrobial resistance¹⁵.

Conclusion:

Single dose antibiotic prophylaxis offers patients compliance, cost effectiveness and minimum side effect

but conventional antibiotic offers less patient compliance with expensive treatment cost and probability of more side effects. Postoperative wound infection not only depends upon antibiotic use but also on many other factors like age, nutritional status, hygienic condition, anaemic status and duration of operation, blood loss during operation and amount of blood transfusion.

The findings of this study demonstrated that administration of prophylactic antibiotic rather than conventional antibiotic at hysterectomy operation is not associated with significant difference in post-operative morbidities.

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Personalized Medicine in Cancer

MM RAHMAN

Summary:

Current and emerging biomedical science efforts are driven by determining how to improve clinical outcomes for patients. High-throughput technology has revolutionized the area of translational research, confirming the high complexity and heterogeneity of common diseases, particularly cancer. Therefore, moving from 'classic' single-gene-based molecular investigation to molecular network research might result in discovering clinical implications faster and more efficiently. Molecular characterization of tumour cells enables refinement of classifications for many cancers and can sometimes guide treatment. Malignant diseases are no longer classified only by tumour site and histology but are separated into various homogenous molecular subtypes, distinguished by a presumed key molecular

alteration. Therapies for patients with cancer have changed gradually over the past decade, moving away from the administration of broadly acting cytotoxic drugs towards the use of more-specific therapies that are targeted to each tumour. To facilitate this shift, tests need to be developed to identify those individuals who require therapy and those who are most likely to benefit from certain therapies. In particular, tests that predict the clinical outcome for patients on the basis of the genes expressed by their tumours are likely to increasingly affect patient management, heralding a new era of personalized medicine. In this review a brief discussion on definition and molecular aspects of personalized medicine and its practical application for the management of common solid cancers are highlighted.

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Personalized oncology

The term “personalized medicine” has gained widespread acceptance in the healthcare field and particularly in oncology, where it most often refers to a vision of cancer management in which treatment is tailored to individual patients based on the molecular profile of their tumour.^{1,2} In that sense, the term is neither an accurate reflection of what constitutes a person – the molecular profile of his or her tumour – nor of our capacity to personalize medicine, since for the moment, we can only choose among the existing therapies the one that best matches the tumour characteristics. The rapid advances currently underway in “-omics” research, new high through put molecular analyses and next-generation sequencing, are improving our understanding of cancer biology and have allowed us to develop new agents specifically designed to disrupt the molecular pathways that are critical to disease initiation and tumour-cell proliferation. Here again at best we can hope to identify molecular subgroups of

patients in whom the tumour may be susceptible to therapy. But targeted therapy necessarily implies that there are subgroups of patients whose genetic and biological profiles place them outside the target. Given what we already know about the highly complex mechanisms that drive the disease, the goal of personalised medicine cannot possibly be to develop one treatment for each individual person's cancer.³ Personalized oncology includes the concepts that each individual solid tumor and hematologic malignancy in each person is unique in cause, rate of progression and responsiveness to surgery, chemotherapy and radiation therapy⁴.

In the past, personalized oncology relied on nonspecific clinical signs. However, emerging genomic and proteomic technologies are now allowing for the subclassification of diseases on an individual basis. For example, expanded knowledge of the molecular basis of cancer has shown that significant differences in gene sequence and/or expression patterns can guide therapy for a variety of solid tumors such as breast cancer (*HER2* test-ing), colorectal cancer (*KRAS* and *BRAF* test-ing), lung cancer (*EGF* receptor gene [*EGFR*] testing) and melanoma (*BRAF* testing), as well as for malignant lymphoma and both lymphoid and nonlymphoid leukemias⁵.

Address of Correspondence: Prof. Md. Mizanur Rahman, Professor and Head, Department of Surgical Oncology, National Institute of Cancer Research and Hospital, Mohakhali, Dhaka-1212, Bangladesh. E Mail: mizannicrh@gmail.com

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Definition of personalized medicine:

Individualized treatment vs. treatment for a sub-patient group-

Personalized medicine has been defined in many ways. According to the U.S. National Institutes of Health (NIH), personalized medicine is “an emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease”⁶. The U.S. Food and Drug Administration defined personalized medicine as “the best medical outcomes by choosing treatments that work well with a person’s genomic profile or with certain characteristics in the person’s blood proteins or cell surface proteins”. The President’s Council of Advisors on Science and Technology (PCAST) described personalized medicine as “tailoring of medical treatment to the individual characteristics of each patient”⁷.

It is important to recognize that personalized medicine does not literally mean individuality. The idea of personalized medicine has often been exaggerated, as suggested in a headline in Newsweek (June 10, 2005) “Medicine Tailored Just for You.” In fact, a new treatment regimen is assessed on a group of carefully selected patients but not individuals⁸. As such, PCAST reports that personalized medicine is “the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment”⁹. If a new treatment works effectively on a sub-patient group, a preventive intervention can then be furnished to those who will benefit, avoiding adverse drug effects and sparing expense for those who will not.

Why Personalized Medicine?

The wide-ranging impacts and myriad opportunities provided by personalized medicine can be summarized in reference to its four major attributes⁷.

Personalized

Personalized medicine integrates personal genetic or protein profiles to strengthen healthcare at a more personalized level, particularly with the aid of recently emerging “-omic” technologies such as nutritional genomics, pharmacogenomics, proteomics, and metabolomics¹⁰. Personalized medicine targets what has a positive effect on a patient’s disease and then develops safe and effective treatments for that specific

disease. In fact, genetic biomarkers that may be specifically associated with a disease state are the foundation of personalized medicine. Knowledge of a patient’s genetic profile leads to the proper medication or therapy so that physicians can manage a patient’s disease or predisposition towards it using the proper dose or treatment regimen⁶.

Preventative

Personalized medicine pursues not reaction but prevention. With the ability to forecast disease risk or presence before clinical symptoms appear, personalized medicine offers the opportunity to act on the disease through early intervention. In lieu of reacting to advanced stages of a disease, preventive intervention can be life-saving in many cases. For example, females with genetic mutations in the BRCA1 or BRCA2 genes have a higher chance of developing breast cancer compared to those in the general female population¹¹. An accurate test of these breast cancer susceptibility genes can guide surveillance and preventive treatment based on objective risk measurements such as increased frequency of mammography, prophylactic surgery, and chemoprevention.

Predictive

Personalized medicine enables physicians to select optimal therapies and avoid adverse drug reactions. Molecular diagnostic devices using predictive biomarkers provide valuable information regarding genetically defined subgroups of patients who would benefit from a specific therapy. For example, Oncotype DX® (Genomic Health, Redwood City, USA) uses a 16-gene signature to determine whether women with certain types of breast cancer are likely to benefit from chemotherapy^{12,13}.

MammaPrint (Agendia, Amsterdam, the Netherlands) uses a 70-gene expression profile to assess the risk of distant metastasis in patients with early-stage breast cancer. These complex diagnostic tests can be used to classify patients into subgroups to inform physicians whether patients would be treated successfully with hormone therapy alone or may require more aggressive chemotherapy treatment.

Participatory

Personalized medicine would lead to an increase in patient adherence to treatment¹⁴. When personalized

healthcare assures its effectiveness and can minimize adverse treatment effects sparing the expenses, patients will be more likely and willing to comply with their treatments.

Implications of heterogeneity in cancer

Every type of human cancer is comprised of biological subsets that differ in clinical behaviour and response to treatment¹⁵, and there are many important examples of treatment regimens that produce better results in some tumour subtypes than others. Notable examples of tumour subtypes that must be recognized to optimize treatment include oestrogen receptor or HER2 (also known as ERBB2)-positive breast cancer. More recent examples are non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-activating mutations; colorectal cancer with KRAS mutations¹⁶; or malignant gliomas with hypermethylation of the methyl guanine methyl transferase (*MGMT*) gene¹⁷. In each case, knowledge of the molecular profile of the tumour is necessary to guide selection of therapy for the patient. Expanding knowledge of tumour biology and tumour–host interactions has moved the field of cancer therapeutics in several new directions, including the following: Development of targeted therapies designed to interrupt molecular pathways known to be critical for cell growth and survival; for example, imatinib treatment for chronic myeloid leukaemia and gastrointestinal stromal tumours. Development of single-gene or multigene expression signatures of response or resistance to particular drug treatments (for example, HER2 and oestrogen receptor) to identify patients with breast cancer who are likely to benefit from adjuvant paclitaxel treatment, or ERCC1 expression as a marker of resistance to platinum-based chemotherapy. Development of vaccine therapies and other immunological approaches that are highly specific to each individual tumour¹⁸.

Genomics in personalized medicine

In 2011, the National Cancer Institute of Health, USA, defined “personalized medicine” as a form of healthcare that considers information about a person’s genes, proteins and environment to prevent, diagnose and treat disease. The reason the word “personalized” has been added is that technology has brought us much closer to exquisite precision in disease diagnosis and treatment. In this context, it is clear that genomics will play a pivotal

(though not exclusive) role in the development of personalized medicine¹⁹. While genetics refers to the study of single genes, genomics includes information about the complex interplay between many genomic markers contained not only in genes but also in intergenic regions with environmental and epigenetic variables, although the distinction between the two is more quantitative than qualitative.

Molecular characterization of tumour cells enables refinement of classifications for many cancers and can sometimes guide treatment²⁰. Malignant diseases are no longer classified only by tumour site and histology but are separated into various homogenous molecular subtypes, distinguished by a presumed key molecular alteration. For example, in lung cancer, tumours with mutations in *ALK* (reported in 4% of cases) or *EGFR* (noted in <10% of adenocarcinomas) have specific clinical presentations and targeted treatments. Moreover, the precise sequence of the mutation can predict outcome, and mutation frequencies vary greatly across ethnic groups. Rare cancers can also be fragmented into subtypes. Gastrointestinal stromal tumours comprise at least ten different subtypes, which need distinct treatments for advanced or adjuvant phases²¹. Complexity grows with recognition that heterogeneity can arise within one tumour and patient. Complex branched evolution of mutations is taking place, from primary tumour cells to metastatic cells²².

One important special feature of biology is its diversity, its variation. That is why personalized medicine is significant. Personalized medicine refers to the right treatment for the right individual at the right time in the health-care world and has the potential to diminish the incidence of drug adverse reactions, eliminate invalid therapy, improve the efficacy of treatments, ultimately, achieve optimal health outcomes. During recent years, most people seem to agree that personalized medicine is the trend of the future. Owing to the accomplishment of the Human Genome Project (HGP), personalized medicine is looming in the horizon and modern medicine moves towards a new individualized health-care model with biological–psychological–social–environmental–spiritual characteristics that reflect the thinking of patient-centred care²³.

Since the early 1990s, knowledge of the genetic basis of cancer, coupled with rapid development of new

technologies, has led to an increased understanding of the heterogeneity of cancer and an ability to develop new therapies targeting specific molecular pathways that may be driving a particular tumour's growth. Consequently, the concept of personalized therapy has evolved from selection of a treatment based on the various toxicity profiles of relatively equivalent therapies to selection of a specific treatment based on the genetic and molecular aspects particular to an individual patient's cancer²⁴.

Application of personalized medicine in some common cancers:

Breast Cancer:

The clinical course of breast cancer varies tremendously between patients. While some of this variability is explained by traditional clinico-pathological factors (including patient age, tumor stage, histological grade and estrogen receptor status), molecular profiling studies have defined breast cancer subtypes with distinct clinical outcomes. The genetic heterogeneity seen in breast cancer has important clinical implications.

It has long been recognized that the clinical course of breast cancer varies tremendously between patients. Traditional clinicopathological variables, including tumor stage, grade and estrogen receptor status, have been used for decades by clinicians to help prognosticate and guide treatment of their patients. In the last 30 years or so, a range of molecular biology technologies, including gene expression profiling, have been used to define molecular subgroups of breast cancer with distinct clinical outcomes. These studies have identified recurrent somatic abnormalities, including gene mutations, copy number aberrations and translocations, the most important of which has been the ERBB2 amplification present in 15 to 20% of breast cancers²⁵.

Recent next-generation sequencing studies:

Whole-genome sequencing studies have reported tens of thousands of somatic mutations in different cancers. The degree of genetic heterogeneity within tumors from individual patients in both space and over time is increasingly well characterized²⁶. In one early report using whole-genome sequencing, Shah et al. examined paired, metachronous tumors from a single patient with advanced invasive lobular carcinoma of the breast, and found 19 non-synonymous mutations present in

metastatic tumors that were not evident in the primary tumor diagnosed nine years earlier²⁷.

In the largest breast cancer series reported to date, the METABRIC study group performed an integrated analysis of copy number and gene expression in discovery and validation sets each containing approximately 1,000 primary breast tumors, with long-term clinical follow-up²⁸. Inherited genetic variants (single nucleotide polymorphisms (SNPs) and copy number variants (CNVs)), and acquired somatic CNAs were associated with altered gene expression in approximately 40% of genes. Importantly, analysis of the combined DNA-RNA profiles revealed 10 different sub-groups with distinct clinical outcomes, which reproduced in the validation cohort. These included subgroups not previously identified by first-generation gene expression profiling studies, in particular with seven distinct subtypes of ER positive disease and a separation of triple negative cancers into at least two subtypes²⁹. Indeed, there is increasing evidence that diagnosis of "triple negative" breast cancer does not describe a single biological entity with distinct natural history. Rather, it refers to a wide range of cancers with great genetic diversity, which can be further classified into multiple subtypes³⁰. In one study, the functional heterogeneity observed within the stem-cell-like compartment of triple-negative breast cancers revealed a 31-gene signature which was associated with the development of metastatic disease.

Stephens et al. analyzed the genomes of 100 tumors for copy number alterations and mutations in coding exons of protein-coding genes. The authors found correlations among the number of somatic mutations, the age at which cancer was diagnosed and tumor histological grade. New driver mutations were found in nine cancer genes including: AKT2, ARID1B, CASP8, CDKN1B, AP3K1, MAP3K13, NCOR1, SMARCD1 and TBX³¹. Banerji et al. focused on the use of whole exome sequencing to identify patterns of mutation and translocation from 103 breast cancers from a range of subtypes³². The authors confirmed the presence of PIK3CA, TP53, AKT1, GATA3 and MAP3K1 mutations, but also identified a recurrent MAGI3-AKT3 fusion found most commonly in ER/PR-negative, HER2-negative breast cancers. Functional experiments showed that this fusion gene caused constitutive activation of AKT kinase which was

amenable to therapy with a selective, small-molecular AKT inhibitor^{32,33}.

Scopes of targeted therapy

One of the most well-known examples of a targeted therapy in cancer is trastuzumab for the treatment of breast cancer, which started in 1999. The Her2 protein is overexpressed in 18%–23% of breast cancers and is associated with increased disease recurrence and poor prognosis. Treatment of breast cancer with the Her2-targeted antibody trastuzumab has been directed using fluorescence *in situ* hybridization (fish) to profile amplification of the *ERBB2* gene (which encodes her2), or immunohistochemistry (ihc) to profile her2 protein expression³⁴. In combination with chemotherapy, trastuzumab has improved progression-free and overall survival in patients with both operable early-stage and metastatic breast cancer⁹, representing a significant benefit for 18%–23% of the 20,000 Canadian women diagnosed with breast cancer annually²⁴.

Colorectal Cancer:

Although Colorectal Cancer (CRC) is highly treatable if diagnosed and surgically removed at an early stage, 5-year survival is <10% in patients with unresectable metastatic disease³⁵. Approximately 40–50% of CRC patients develop metastatic disease, and 80–90% of these have unresectable metastases most of which are in the liver. Amongst patients with metastatic disease, 50% present with a synchronous primary tumour and secondary lesion, whereas the rest develop metachronous metastases. Surgical resection represents the only potentially curative therapy for metastatic CRC. Resection of hepatic metastases from CRC has yielded 5-year survival rates ranging from 35 to 55% although these values are strongly dependent upon pre- and postsurgical variables such as the number of lesions, lesion diameter and clear resection margins³⁶. Similarly, 5-year survival rates after resection of lung metastases from CRC ranged from 20% up to 60% in large series³⁷.

It is unfortunate that surgical resection is not suitable for the vast majority of CRC patients with metastatic disease, and the only treatment option to prolong survival is systemic therapy directed at the disseminated metastatic colonies. For several decades, 5-fluorouracil (5-FU)/leucovorin (LV)-based therapy was the mainstay of treatment of metastatic CRC with median survival of about 11 months [16]. In the past decade, the outcome

of patients with metastatic CRC has improved considerably with the advent of combination regimens of oxaliplatin or irinotecan and 5-FU/LV³⁸. The addition of irinotecan to a bolus or infusional regimen of 5-FU in combination with LV in the firstline setting has resulted in a median survival of 15–23 months³⁹. Irrespective of the first-line chemotherapy regimen, an overall survival (OS) exceeding 2 years is currently achieved when patients, especially those presenting with liver metastases, are exposed to all available active cytotoxic drugs against CRC⁴⁰.

Because these compounds act on selective molecules, their efficacy is limited if indiscriminately administered to all patients, but they significantly affect OS and disease-free survival when treatment selection is driven by molecular profiles. Indeed, it has recently been demonstrated that molecular stratification must be adopted to select the most appropriate targeted agent for individual patients. Most of the targeted inhibitors in development or in clinical use are molecules with high affinity for growth factor receptors, such as fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), mast/stem cell growth factor receptor (KIT) and epidermal growth factor receptor (EGFR). The recent introduction of monoclonal antibodies that bind to vascular endothelial growth factor (VEGF) and to EGFR into the combination chemotherapy regimens currently used in metastatic CRC has been shown to be effective and has further widened the treatment options^{41,42}.

Several biomarkers with both prognostic and predictive value have been described over the past decade. In the present review, we focus on the latest progress within the genomic and proteomic fields, with regard to predictive biomarkers for individualized therapy in sporadic CRC.

Genetic macro-classification and response to chemotherapy:

Three major genetic and epigenetic alterations that drive CRC tumorigenesis have been identified: microsatellite instability (MSI), chromosomal instability (CIN) and CpG island methylator phenotype (CIMP). These alterations have mainly been used as markers for defining CRC prognosis, but recent data have demonstrated their correlation with treatment response.

The MSI-positive subgroup accounts for 10–15% of all CRC cases and is characterized by a better prognosis than the microsatellite stable (MSS) group. Conflicting data have been reported for both FOLFOX and 5-FU-based chemotherapy response in MSI-positive patients. Overall, 65–70% of CRCs show a CIN pattern. Mutations of KRAS, P53, SMAD and APC genes are often present in this group of tumours. CIN involves DNA copy number variation (CNV) that has been identified in more than 80% of CRC patients, most of whom are MSS^{43,44}. Changes in DNA copy number determine variations in gene expression that is associated with prognosis and response to adjuvant therapy. Thus, CNV represents a potential predictive marker of response to chemotherapy. CIN is also associated with multidrug resistance and could contribute to the low response rate of CRC patients to taxanes (paclitaxel and docetaxel)⁴⁵.

A large subpopulation of CRC cases, designated as CIN-/MSI- and partially overlapping with the MSI subgroup, contain a high degree of hypermethylation known as CIMP. This post-translational alteration may alter the up- or down regulation of gene expression events that alter the survival of genetically aberrant clones and promote their expansion. Generally CIMP tumours present few P53 mutations, a high rate of BRAF and KRAS mutations, frequent hypermethylation of MLH1 gene and a strong association with MSI-High (MSI-H)⁴⁶. Inconsistent results regarding the correlation between CIMP positivity and CRC responsiveness to 5-FU treatment have been reported. Therefore, more accurate investigations are needed to clarify these results.

For decades, the misleading assumption that all patients with tumours originating from the same primary organ had to be considered and treated as a homogeneous population has profoundly hindered the development of unique therapeutic strategies that can dramatically improve outcome and OS at the individual patient level. The possibility of identifying which patients are most suitable for each chemotherapeutic agent would maximize efficacy and spare unnecessary toxicity. The discovery of the impact of KRAS mutation on the efficacy of antibodies targeting EGFR in metastatic CRC has provided evidence that subgroups of patients may benefit from differential therapy.

The recent development of sophisticated technologies that allow accurate and incisive investigation has led to a better understanding of the molecular alterations on which cancer development and progression are based. Moreover, recent discoveries of alterations in gene and protein expression/activity in tumour cells have generated valuable new hypotheses to explain therapeutic failure and success as well as drug resistance⁴².

Gastric Cancer:

Despite optimization of surgery, radiotherapy, and cytotoxic chemotherapy, survival of advanced gastric cancer is poor. Five years after this multimodal treatment, 40% of Western patients with stage II or III disease are alive. In metastatic stage IV, mean survival is only 10 months. Most promise to improve this poor survival is provided by biologically targeted agents. The concept is exciting. Suppression of deregulated signaling pathways which play a central role in cell proliferation, survival, apoptosis, and angiogenesis may be a highly effective approach against cancer. Over the last decade, several agents targeting key components of important do on-stream signaling have been developed and approved by the Food and Drug Administration (FDA) for a series of cancers. Inhibition of signaling cascades may suppress cancer cell proliferation and survival. However, for most solid tumors, clinical efficacy measured by overall survival benefit is modest⁴⁷.

From Basic Science Discovery to Clinical Practice

The discovery of the epidermal growth factor (EGF) and its receptor (EGFR) in 1962 and 1978, respectively, opened the way for a new era of molecular oncology⁴⁸. However, successful translation of these basic research findings into the clinic has occurred only during the last decade and mostly for only one type of cancer, i.e., breast cancer. The ErbB family consists of four closely related type 1 transmembrane tyrosine kinase receptors: EGFR (or HER1), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4). Each receptor comprises an extracellular domain at which ligand binding occurs, an α -helical transmembrane segment, and an intracellular protein tyrosine kinase domain. Ligand binding to these EGF family receptors phosphorylates and activates a complex intracellular signaling pathways network that controls a range of cellular processes including proliferation, angiogenesis,

cell cycle, survival, and apoptosis⁴⁹. HER2 amplification and overexpression plays a central role in initiation, progression, and metastasis of some common cancers, including breast cancer and gastric cancer. HER2 status has been recognized as an important prognostic factor. Patients with breast cancer or gastric cancer an HER2-positive disease have significantly worse survival than those with HER2-negative tumors^{49,50}.

Thus, this pivotal receptor is a potential therapeutic target. Trastuzumab binding inhibits HER2 signaling pathway activity in tumor cells overexpressing HER2. Phase III trials confirming preclinical and clinical data for the safety and efficacy of trastuzumab independently of robust clinicopathologic factors in both metastatic and adjuvant setting have led to the establishment of this antibody as standard treatment for HER2-positive breast cancer. However, there has been no such evidence for any other cancer.

Changing Treatment of Gastric Cancer

Now, for the first time, positive results of a phase III trial for the efficacy of trastuzumab are reported for gastric cancer. Van Cutsem and colleagues have presented the results of the ToGA study in the 2009 ASCO Annual Meeting, May 29–June 2, in Orlando, FL.⁵¹ In this randomized controlled multicenter trial, 594 patients were randomized 1:1 at sites in Europe, Latin America, and Asia. All these patients had HER2-positive gastroesophageal and gastric adenocarcinoma (locally advanced, recurrent or metastatic). They were randomized to receive trastuzumab (Herceptin) and chemotherapy (5-fluorouracil or capecitabine and cisplatin) for six cycles or chemotherapy alone. Trastuzumab was given until disease progression.

Addition of trastuzumab to chemotherapy improved oncological outcomes. Median overall survival was significantly longer (13.5 months) in the experimental arm (trastuzumab plus chemotherapy) than in the standard arm. Overall response rate was significantly increased by 13% in the trastuzumab arm ($P = 0.0017$). Safety profile and adverse effects data showed that trastuzumab-based regimen was a well-tolerated treatment; there was no difference in symptomatic congestive heart failure between arms, and asymptomatic left ventricular ejection fraction decreases were reported as 4.6% in the experimental arm and 1.1% in the chemotherapy arm.

The rate of 22% for HER2-positive gastric cancer is similar to the HER2-positive breast cancer rate. Second, the investigators correctly decided to use overall survival as primary endpoint and not progression-free survival (PFS). Indeed, the objectivity of PFS to assess response, efficacy, and clinical utility of an experimental targeted agent has become questionable. Cancer heterogeneity is one of the major biological arguments against the use of PFS to measure therapy efficacy. Although several targeted agents have been approved by the FDA based on significant improvement of PFS, more current evidence suggests that some cancer cell populations, initially rare within the tumor, refuse to die under treatment. Therefore, a nonprogressive disease assessment by imaging techniques (no tumor size increase) does not reflect overall response. Sensitive cancer cells are killed, but resistant cells proliferate, developing a uniform tumor consisting of resistant cells. These cancer cells have the ability of metastasis, which results in no overall survival benefit⁴⁷.

Perspectives for Overcoming Resistance:

Resistance to molecular targeting therapy is currently the cause of treatment failure in cancer. Despite trastuzumab-containing treatment a substantial proportion of HER2-positive breast cancer patients either recur in the adjuvant setting or progress after initial response and die of the disease. Similarly, the absolute additional response rate to trastuzumab among HER2-positive advanced gastric cancer in the ToGA study is small: 12.8%. Given that HER2-positive accounts for approximately 25%, only 3.12% of all gastric cancer patients can benefit from trastuzumab treatment.

How could this intrinsic or acquired resistance be overcome? Research strategies are focused on the development of both novel drugs and molecular markers beyond HER2 expression for tailoring the best treatment to individual patients. There are two main directions: first, better understand of ErbB signaling pathways and trastuzumab mechanisms of actions and resistance; second, exploring the role of other signaling pathways including Wnt/bcatenin, TGF- β /SMADs, and other pathways involved in

cancer may lead to understanding of intracellular signaling pathways network in various cancer types. The first, more realistic, approach has already led to clinical applications. Improved insights into the biology of the

ErbB family have led to additional active anti-HER2 therapies. New strategies against HER2 include ErbB tyrosine kinase inhibitors (TKIs), heat shock protein 90 inhibitors, ErbB dimerization inhibitors, and antibody–chemotherapy conjugates. All of these approaches have shown substantial clinical activity in patients who have progressed on trastuzumab treatment.³ TKIs-based targeting of HER2, preventing signal transduction of both the Ras–RAF1 MAPK and PI3K–Akt pathways, led to an increase in apoptosis and a decrease in cellular proliferation^{47,49}.

Multitargeting, Signaling Pathways Network-Based Therapy

Although still in its infancy, the second approach to predict complex signaling pathways interactions, including ErbB signaling, if successful, might revolutionize treatment of gastric cancer, breast cancer, and other solid tumors. Given the current strong evidence that multiple genetic alterations and several signaling pathways are dysregulated in solid cancers, one of the most rational approaches is to inhibit these pathways. Combining targeted agents and considering crosstalk between pathways and bypass of targeted agents as well as predictors of response might lead to highly effective therapies⁵². However, there are many challenges. Cancer heterogeneity is reflected by variation in deregulated pathways among patients with the same tumor, tumor–node–metastasis (TNM) staging, and clinicopathologic factors. At present there is no standard method to identify either which pathways are dysregulated or how they interact in individual patients. The new era of personalized medicine provides major promises. One approach is to integrate personal genomics and clinicopathologic and treatment data into sophisticated in silico models to predict genotype–phenotype map in cancer. Rapid advances in molecular systems biology and future cheaper whole-genome

cancer data scans are innovative exciting developments towards the development of novel response predictors and a new generation of multitargeted agents⁵³. The new era of personalized cancer care is here, but multiple challenges including major funding requirements and reliable data analysis make the translation of personalized research approaches into clinical medical practice difficult.

HER2 status should now be included in diagnostic makeup of patients with advanced gastric cancer. Addition of trastuzumab to chemotherapy improves overall survival and is a new standard treatment for patients with locally advanced, recurrent or metastatic HER2-positive disease. Although this efficacy is likely in the adjuvant setting, an evidence-based decision on trastuzumab use in early gastric cancer requires the completion of new adjuvant phase III trials.

Resistance to current therapies is a major challenge. Lapatinib and other novel antibodies or TKIs tested in clinical trials for HER2-positive breast cancer might also prove effective in trastuzumab-resistant HER2-positive gastric cancer. However, such ErbB-based approaches have less application in HER2-negative disease, which accounts for the majority of patients with gastric cancer or breast cancer. Understanding genotypic–phenotypic cancer diversity and signaling feedback loops as well as developing reliable methods to screen for identifying dysregulated signaling pathways in individual patients is a rational and exciting approach. If successful, such comprehensive approaches using molecular systems biology and future whole-genome cancer data scans may result in the discovery of novel multitargeted therapies tailored to individual patients on the basis of novel predictors of response to combined therapies⁴⁷. Table-1 shows commercially available kits for personalized medicine practice the common available drugs are also mentioned.

Table-I

List of Commercially Available Tests (few) Used for Personalized Medicine in Cancer

Test	Cancer Type	Test Type	Predicts response to
HerceptTest	Breast	Her 2 overexpression	Trastuzumab
KRAS Mutation Kit	CRC	KRAS mutation	Panitumumab; Cetuximab
CYP450 Test	Breast	CYP2D6, CYP2C19 genotype	Tamoxifen
EGFR Amplification Test	CRC	EGFR amplification	Cetuximab, Panitumumab
EGFR Amplification Test	NSCLC	EGFR amplification	Gefitinib, Erlotinib
BCR-ABL Mutation Analysis Test	CML	T3151 mutation	Imatinib
ALK Gene Rearrangement Test	NSCLC	ALK gene arrangement	Erlotinib

CRC-Colorectal cancer, NSCLC- Non-small cell lung cancer, CML- chronic myeloid leukaemia

Future perspective :

Molecular systems approaches allow progress towards understanding how intracellular signal-ing pathways networks operate and how interactions among heterogeneous cancer cells within an individual primary tumor and its associated metastases govern the oncological outcomes. This comprehensive understanding of how a solid tumor functions as a whole biological system, including the primary tumor, its associated metas-tases and their relationships with multiple host variables, such as heritable causal mutations, envi-ronmental exposure and lifestyle, can be achieved by systems approaches, revealing the fundamental importance of systems medicine. Therefore, such sophisticated network-based approaches represent a major hope for the development of novel robust biomarkers and effective biologics.

In the real world, the principles and rules of comparative effectiveness research and the stage of FDA approval should be considered at an early preclinical development stage of designing such molecular systems-based markers and drugs, giv-ing particular emphasis to the integration of clin-ical data. Novel, network-based targets should prove their potential superiority over the current standard cancer diagnostics and therapeutics in clinical trials.

Conclusion:

Personalized medicine is receiving a large amount of growing attention for its tremendous potential with new opportunities. The ultimate promise of personalized medicine depends on the discovery of the personal genetic causes of disease. The remarkable advent of current high-through put technologies in combination with improved knowledge of the molecular basis of malignancy provides a solid base for identifying novel molecular targets. Genomic sequencing and its interpretation will have to be further developed and standardized for routine clinical practice to develop efficient and effective methods for discovering and verifying new biomarkers and enabling personalized medicine technologies. Medical educational institutions should prepare the next generation of physicians to use and interpret personal genetic information appropriately and responsibly. Though for a developing country like Bangladesh it will not be easy to adopt a higher and expensive technology, but for the sake of cancer patients

and better outcome we will have to run in parallel with the developed countries.

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Kaposi's Sarcoma in HIV Positive Male

MEH KHAN^a, M PARVAG^b, M ALAM^c, S SHAHRIAR^d, A SERAJI^e, MS BARI^f

Summary:

Kaposi's sarcoma is a vascular tumor usually involves skin, mucous membrane and other organs. HIV associated Kaposi's sarcoma is very rarely reported in Bangladesh. The reporting case was presented with a recurrent, ulcerated, firm nodule on left groin along with multiple blackish flat or raised lesions on different parts of body. According to previous histopathological report this case

was operated as a case of recurrent fibrous histiocytoma and this time the diagnosis was confirmed histologically and by immunohistochemistry as Kaposi's sarcoma. Later, it was found that the patient is serologically positive for HIV.

Key Words: HIV infection, Kaposi's sarcoma.

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Introduction:

Kaposi's sarcoma is the most common neoplasm of an AIDS patient.¹ It is a vascular tumor that composed of spindle – shaped cells which express markers for endothelial cells and smooth muscle cells.^{1,2} This rare condition comes to the forefront because of its increased association with HIV infected patient.³ In Bangladesh Kaposi's sarcoma has been very rarely reported. We are reporting Kaposi's sarcoma in an HIV positive male of Bangladesh.

Case Report:

A 28 years old married male presented with a recurrent, dark colored, ulcerated nodule with serous discharge on left groin for about three months which first appeared about four and half months back. At that time the lesion was excised and biopsied locally and histopathology report was fibrous histiocytoma. But the patient presented with local recurrence within one and half month. He also complained of multiple dark colored, flat, raised lesions on different part of body. His first lesion started about five months back on his left arm. Initially all the lesions were small, reddish and macular. With time, lesions were increasing in size and became blackish in color. He worked as a cleaner at Saudi Arab for about five years. There was no history of trauma, fever, significant weight loss or blood transfusion. He did not give any history of sexual exposure.

On examination, there was a firm nodule with ulcerated blackish to pinkish surface about 2cm×1.5 cm size on left groin. There were multiple (about 36) plaques on both upper arms, right forearm, front and back of chest, back of trunk, upper part of medial aspect of left thigh, right leg and on hard palate. There was generalized lymphadenopathy. Lymph nodes were discrete, firm and non tender. There was no perianal or intra rectal abnormality. All other general and systemic examinations were normal. Previous histopathology report of this lesion was recurrent fibrous histiocytoma.

- a. Dr. Mohammad Emrul Hasan Khan, Assistant Registrar, Burn Plastic & Reconstructive Surgery Dept. Shaheed Suhrawardi Medical College Hospital.
- b. Dr. Masum Parvag, Medical Officer, Plastic & Reconstructive Surgery Dept. Shaheed Suhrawardi Medical College Hospital
- c. Dr. Mahabub Alam, Assistant Registrar, Burn Plastic & Reconstructive Surgery Dept. Shaheed Suhrawardi Medical College Hospital.
- d. Dr. Shaon Shahriar, Assistant Registrar, Burn Plastic & Reconstructive Surgery Dept. Shaheed Suhrawardi Medical College Hospital.
- e. Dr. Ahmad Seraji, Assistant Professor, Burn Plastic & Reconstructive Surgery Dept. Shaheed Suhrawardi Medical College Hospital
- f. Prof. Dr. Md. Shahidul Bari, Professor & Head of the Dept. Burn Plastic & Reconstructive Surgery Dept. Shaheed Suhrawardi Medical College Hospital.

Address of Correspondence: Dr. Mohammad Emrul Hasan Khan, Assistant Registrar, Department of Burn, Plastic & Reconstructive Surgery, Shaheed Suhrawardi Medical College Hospital, Sher – E – Bangla Nagar, Dhaka, Bangladesh. Tel.: +8801713242529, E-mail address: dremrul@gmail.com

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Fig-1: Groin Lesion (Pre operative)



Fig-2: Groin Lesion (Post operative)

His laboratory investigations e.g complete blood count, random blood sugar, serum creatinine, chest X ray were within normal limit. So that wide local excision of the groin lesion was performed and histopathologically the lesion was diagnosed as Kaposi's sarcoma. To confirm the diagnosis immunohistochemistry was done and report was compatible with Kaposi's sarcoma. FNAC of lymph nodes of cervical and axillary revealed reactive lymphadenitis. As the tumor is rare but its presence is strongly associated with HIV, so serology for HIV was done and found positive. His CD4 cell count was 90cells/ μ l of blood. On screenings it was found that his wife was also HIV positive but his son was negative.



Fig-3: Lesions on Back



Fig-4: Lesions on Front of chest & Right Arm

For the better management of AIDS, the patient was referred to Infectious Disease Hospital.

Discussion:

In 1872 Moriz Kaposi 1st described Kaposi's sarcoma.^{4,5} There are four epidemiological forms of Kaposi's sarcoma - 1) Chronic / classic Kaposi's sarcoma, 2) Lymphadenopathic / endemic Kaposi's sarcoma, 3) Transplant associated Kaposi's sarcoma, 4) HIV related / Epidemic Kaposi's sarcoma.^{4,5} Morphologically it has 3 stages 1) Patches, 2) Raised Plaques, 3) Nodular.⁴

Kaposi's sarcoma may be seen any time during the course of HIV infection.⁶ The lesions can arise early before the immune system is compromised or in advance

stage of HIV infection.³ In this case there was no other clinical feature of immunosuppression at presentation, but after diagnosis it was found that his CD4 cell count is 90 cells/ μ l of blood which indicates immunosuppression.

The presentation and natural course of Kaposi's sarcoma vary widely.^{4,6} HIV associated Kaposi's sarcoma has no site predilection in comparison to the classic variety, where lesions are common on the lower extremities.^{3,5,6} Patient with HIV associated Kaposi's sarcoma usually present with skin lesion on upper half of body but some patient may present with gastrointestinal tract or lymphnode involvement.^{5,6,7} This presenting case has about 35 skin lesions mostly on upper half of body.

HIV associated Kaposi's sarcoma can affect the skin, GIT, lymph node and lung.⁷ But usual causes of death in HIV associated Kaposi's sarcoma are opportunistic infection and systemic involvement of HIV especially of the pulmonary system.^{4,5,7,8}

In 1994 Human Herpes Virus-8 (Kaposi's sarcoma associated Herpes Virus – KSHV) was identified in cutaneous Kaposi's sarcoma.^{4,9} It is transmitted sexually and Kaposi's sarcoma is more common among homosexual or bisexual HIV patient.^{4,7,8} But recent publication also reported its occurrence in heterosexual male.^{7,10} The reported case is an HIV positive heterosexual male.

Kaposi's sarcoma in an HIV infected patient is the indication to start antiretroviral therapy.⁶ HAART forms the mainstay of treatment which has significantly changed the morbidity and mortality associated with Kaposi's sarcoma.⁷ In case of few skin lesions with no systemic involvement local treatment like wide excision, radiotherapy or intra-lesional chemotherapy may be used.^{6,11} But in case of visceral involvement or extensive Kaposi's sarcoma HAART along with doxorubicin or Paclitaxel can be used as systemic therapy or immunotherapy with interleukin 2 or interferon may use.^{6,7,11}

Chance of becoming infected with HIV at operation of HIV patient has been assumed about 1 in 130000 cases.¹¹ So to prevent transmission, preoperative screening has been advocated, but in the context of our country pre operative screening in all patients is not practically possible or feasible, if not he had some features to assume as HIV positive patient. As an

alternative it is better to practice a policy of universal precaution, such as at least safer handling of sharp & pointed instruments and double gloving.

In this reporting case, patient did not show the typical profile of an HIV infected patient and so that pre operative screening for HIV was not done. After the post operative histopathological study, clinical diagnosis of HIV infection came in front.

Conclusion:

The surgical team operated on this patient was under greater risk of transmission of HIV. So we encourage for the adaption of a high standard of precaution measures in all patients. BCPS started basic surgical skill training where universal precaution and safe sharp instrument handling are important parts. But that should be trained to all doctors and all staffs working in the operation theatres.

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Beckwith–Wiedemann Syndrome

F MOHSIN^a, R ISLAM^b, T BEGUM^c, K AZAD^d, N NAHAR^e

Summary :

Beckwith–Wiedemann syndrome (BWS) is a disorder of growth regulation characterized by macrosomia, macroglossia and developmental abnormalities with a predisposition to tumour development. The diagnosis of Beckwith-Wiedemann syndrome may be missed because of variable or incomplete clinical expression. Here we present a case of a newborn delivered at BIRDEM (Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic

Disorders) General Hospital, presenting with macrosomia, macroglossia and hypoglycaemia. The baby also had umbilical hernia and asymmetry of limbs. The case is presented in order to create further awareness and to highlight the peculiarity of management of this rare disorder.

Keywords: Beckwith–Wiedemann Syndrome, Developmental abnormalities.

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Introduction:

Beckwith–Wiedemann syndrome (BWS) is a disorder of growth regulation exhibiting somatic overgrowth and a predisposition to embryonal tumors.¹ It was also known as EMG (Exomphalos, Macroglossia, Gigantism) syndrome which was recognized independently by Beckwith in 1963 and Wiedemann in 1964.^{2,3} The diagnosis of Beckwith-Wiedemann syndrome may be missed because of variable or incomplete clinical expression. Recognition of such patients is important, however, because they have the potential for development of neoplasia.⁴ Here we present a case recently seen at BIRDEM General Hospital in order to create further awareness and highlight peculiarity of management as may be applicable in a setting as ours.

Case Report:

A male newborn was delivered by caesarian section at 35 weeks pregnancy. There was no history of

consanguinity. Mother was 27 years old, primigravida with gestational diabetes mellitus, had pregnancy induced hypertension and polyhydramnios.

Physical examination revealed an active baby with the following anthropometric measurements, weight 3.2kg (>90th centile), length 51 cm (>90th centile), head circumference 34 cm (>3rd centile). The baby had impressively large tongue protruding out of the oral cavity (Figure 1). Initially he had mild tachypnoea and respiratory distress and was diagnosed as a case of preterm, infant of diabetic mother (IDM) with macrosomia, macroglossia and transient tachypnea of newborn (TTN). The tachypnea and respiratory distress was resolved by 24 hours.



Fig-1: Newborn with Beckwith-Wiedemann syndrome showing macroglossia

- Dr. Fauzia Mohsin, Associate Professor, Department of Paediatrics, BIRDEM General Hospital and Ibrahim Medical College, Dhaka, Bangladesh
- Dr. Rubaiya Islam, Senior Medical Officer, Department of Paediatrics, BIRDEM general Hospital
- Prof. Tahmina Begum, Professor and Head, Department of Paediatrics, BIRDEM General Hospital and Ibrahim Medical College
- Prof. Kishwar Azad, Senior Honorary Consultant, Department of Paediatrics, BIRDEM General Hospital and Ibrahim Medical College
- Prof. Nazmun Nahar, Department of Paediatrics, BIRDEM General Hospital and Ibrahim Medical College

Address of Correspondence: Dr. Fauzia Mohsin, Department of Paediatrics, BIRDEM General Hospital and Ibrahim Medical College, Tel: 880-1713063141 (Mobile), Email: fauzia_mohsin@yahoo.com

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Initially the baby was given oxygen, kept nothing per oral and 10% dextrose in aqua was started. According to protocol for IDM babies capillary blood glucose as well as formal blood glucose was monitored and baby was normoglycaemic initially. Nasogastric feeding was

started from day 2 along with intravenous fluid. In spite of these, the baby developed repeated hypoglycemia from day 2 (RBS 1.9 mmol/L). Then the strength of dextrose was increased to 12.5% and as hypoglycaemia persisted, injectable hydrocortisone was added from day 3 and continued for 3 days. The blood glucose became normal from day 4 onwards. An ultrasound scan of abdomen was done which was normal. Echocardiography showed small atrial septal defect (secundum type), Thyroid function test was normal.

A regular monitoring of blood glucose was continued. The baby again developed hypoglycaemia from day 9. A blood sample was sent at the time of hypoglycaemia (Blood glucose 1.8 mmol/L) for further evaluation which revealed : serum Insulin-11.80 iU/ml (normal value: 2.1-22iU/ml),serum cortisol-190.70nmol/l (normal value: 116-690 nmol/l) and growth hormone-7ng/ml (normal value: 0.05-3ng/ml). His blood pH, serum ammonia and lactate were normal, urine was negative for ketone and reducing substance thus excluding metabolic disorders like galactosemia, glycogen storage disorders etc. In non-hyperinsulinaemic hypoglycaemia, at a blood sample sent at the time of hypoglycaemia which is also known as critical sample, the insulin level should be undetectable or very low (less than 5 iU/ml and no higher than 10iU/ml) and cortisol and growth hormone level high. But in hyperinsulinaemic hypoglycaemia, at hypoglycaemic state, plasma insulin is > 5-10iU/ml and insulin (iU/ml): glucose (mg/dL) is > 0.3-0.5.^{5,6} Therefore the results were consistent with that of hyperinsulinaemic hypoglycaemia with an inadequate cortisol response. Persistent hypoglycemia was managed with tablet hydrocortisone for 2 weeks and as the baby maintained normal blood glucose level, hydrocortisone was tapered over next 2 weeks and then stopped. For macroglossia, oral and maxillofacial surgeon was consulted who advised for follow up.

On follow up at six weeks of age, his blood glucose levels were normal and basal serum cortisol level was 395nmol/L, which was normal for his age. The baby was healthy but macroglossia persisted and baby had developed umbilical hernia and mild asymmetry of limbs with right sided hemihypertrophy (Figure 2) which were not apparently evident at birth. On follow up at 4 month of age, the baby was maintaining normal blood glucose. The macroglossia persisted but was not progressing,

umbilical hernia and asymmetry of both limbs were more prominent. His weight and length still went parallel to the 90th centile. Development was age appropriate. Serum α -fetoprotein level and follow up ultrasound scan of abdomen were done which were normal.



Fig.-2: Baby with Beckwith-Wiedemann syndrome at 6 week showing macroglossia, umbilical hernia and mild asymmetry of limbs

Discussion:

Beckwith-Wiedemann syndrome (BWS) is clinically and genetically a heterogeneous disorder with an incidence of 1 in 13,700 live births with an equal sex distribution.⁷ The phenotype of BWS is likely to result from an imbalance of a number of critical genes at chromosome 11p15.⁸ In BWS, 85% of cases are sporadic and 15% are autosomal dominant.⁷ The risk of recurrence in a family depends on genetic cause of BWS in the proband. Recent reports suggested that assisted reproductive technology (ART) may increase the risk of imprinting disorders and BWS in particular.^{9,10} ART may favour imprinting alteration at the centromere of chromosome 11p15 during the pre-implantation phase of embryonic development.

Elliott and Maher¹¹ identified clinical features for postnatal diagnosis of BWS. Three major features are: anterior abdominal wall defect, macroglossia, pre-or postnatal overgrowth. The minor features are: ear lobe creases, fissures or pits, facial naevus flammeus, hypoglycaemia, nephromegaly, hemihypertrophy. Postnatal diagnosis is based on either three major features, or two major and three minor features.¹¹ Based on clinical features our patient fulfilled the criteria for diagnosis of BWS. Of the transient hyperinsulinaemic states, infants of diabetic mothers (IDM) are the most

common. Although an infant of diabetic mother (IDM), our patient had persistent hypoglycaemia. Persistent hypoglycaemia due to hyperinsulinaemic state can be caused by genetic forms of hyperinsulinism which includes focal and diffuse SUR1 and Kir 6.2 defect, glutamate dehydrogenase defect, glucokinase deficiency. It can also be due to Beck-Wiedemann syndrome, islet cell tumour and factitious hyperinsulinaemia.^{5,6} There was no consanguinity or family history in our patient. Genetic study was not possible in our present context but of the above mentioned conditions, macroglossia and hemihypertrophy was typical of BWS. Reish et al¹² made it possible by ultrasound and cytogenetic analysis of the fetus and both parents to diagnose this condition prenatally. Constant ultrasound findings include fetal overgrowth, polyhydramnios, enlarged placenta and specifically a distended abdomen. These signs usually develop after twenty two weeks of gestation.¹²

Macroglossia is the most frequent manifestation of BWS. Like many other physical abnormalities of BWS, it tends to regress with increasing age. Macroglossia may cause feeding problems, speech problems, and/or obstructive apnoea and surgical tongue reduction may be required in severe cases.¹¹ Cardiac malformations are found in about 20% of children with BWS. Approximately half manifest cardiomegaly that resolve spontaneously.¹³ Overgrowth in BWS is most marked in the first few years and is associated with an advanced bone age. It tends to slow down in late childhood and adult heights are generally in the normal range.¹ Hemihypertrophy occurs in upto 25% of cases. It is usually evident at birth and often becomes more marked as the child grows. Mild asymmetry may require physiotherapy and conservative orthopedic management. In more severe cases surgical intervention may be performed at puberty.¹¹ Hemihypertrophy is also seen in other conditions such as Klippel-Trenaunay-Weber syndrome associated with port-wine stain or capillary malformations in the skin and neurofibromatosis. Even isolated hemihyperplasia is associated with an increased risk of embryonal tumour, mainly wilms' tumour and hepatoblastoma.¹⁴

Hypoglycaemia is reported in 30-50% of babies with BWS, likely to be caused by islet cell hyperplasia and hyperinsulinaemia.^{8,13,15} Often hypoglycemia is transient, asymptomatic and resolve within the first few days of life. In about 5% of children, the hypoglycemia

can be persistent and extend beyond the neonatal period, requiring either continuous feeding, medical therapy, or, in rare cases, partial pancreatectomy. In this group of children, the hypoglycemia can be severe, causing significant brain damage even death.^{8,13,15} Our patient had repeated hypoglycemia from second day which was managed with nasogastric feeding, intravenous dextrose and injectable hydrocortisone as per standard protocol¹⁶ and hypoglycaemia resolved. But the baby again developed hypoglycemia from day 9. Hierarchical approach to manage persistent hypoglycaemia due to hyperinsulinism has been outlined by Aynsley-Green et al¹⁷ which starts with adequate carbohydrate (oral or intravenous), followed by oral agents such as diazoxide, chlorthiazide and Nifedipine, then use of parental agent such as glucagon and octreotide and finally pancreatic surgery if all medical management fails.¹⁷ There are also reports of successful treatment of hypoglycaemia with diazoxide, cortisol or glucagon as monotherapy.¹⁸ As diazoxide was not available and there was inadequate cortisol response, our patient was managed with tablet hydrocortisone.

BWS must be followed for the neoplasia that may present in 7.5% of patients, most common is wilms' tumor, especially in patients with hemihypertrophy. Other tumors are adrenal carcinoma, hepatoblastoma, neuroblastoma and rhabdomyosarcoma.^{14,19} Most of the tumors associated with BWS occur within first 8-10 years of life with very few being reported beyond this age. Given the importance of early diagnosis, all children with BWS should be screened for cancer. An abdominal ultrasound every 3 months until at least eight years of age and a blood test to measure alpha-fetoprotein (AFP) every 3 months until at least four years of age are recommended.^{1,14,19} AFP level should be interpreted with a normal curve established specifically for BWS as AFP can be higher in patients with BWS than in healthy infant and children.²⁰

In most patients with BWS, the long term survival is favourable.²¹ Therefore screening for hypoglycaemia and its management is of paramount importance to prevent cognitive impairment. Supportive medical and surgical strategies and cancer screening is important. Genetic counseling regarding etiology and recurrence risk for BWS is most accurate if data from a complete diagnostic evaluation are available, including current molecular testing.

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Double Aneuploidy - A Rare Condition : Report of Two Cases

S HABIB^a, SG BANU^b, SMS ISLAM^c, CA KAWSER^d

Summary:

The chance of two chromosome abnormalities occurring in one conceptus is rare. Here we report two cases of double aneuploidy with karyotype 48,XXY,+21 and 48,XXY,+21. The diagnosis was confirmed by cytogenetic analysis using peripheral blood followed by Giemsa banding technique. Clinically both the children had most of the phenotypic features of Trisomy 21. However phenotypic features of XYY

were not present but the child with XYY had undescended right testis. The purpose of this communication is to report such rare disorders discovered as the result of the evaluation for Trisomy 21.

Key words: Cytogenetics, double aneuploidy, Trisomy 21, sex chromosomes.

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Introduction:

Chromosomal disorders are of two types: numerical and structural. Numerical disorders include aneuploidy in which the addition or loss of one, or rarely two chromosomes occur. The most common autosomal aneuploidy trisomy 21 (Down syndrome) is compatible with survival.¹ The incidence of Trisomy 21 is 1 in 700 births in the Western population and 1 in 920 births in the Indian population.² Other commonly seen sex chromosomal aneuploidies are Turner syndrome, Klinefelter syndrome and its variants, poly X syndromes and poly Y syndromes. Incidence of 47, XYY was reported to be 1/840 live births.³ The incidence of Klinefelter syndrome (47,XXY) is 1 per 1000 live male births.¹

The co-occurrence of two numerical chromosomal abnormalities in same individual (double aneuploidy) is relatively rare with 3% to 7% of fetuses with cytogenetic abnormalities having double aneuploidy.^{4,5,6} The incidence of 48,XXY,+21 in the general population is 0.4 to 0.9 per 10,000 male births.^{7,8} In 1959, the first case with autosomal and sex chromosomal anomalies, 48,XXY,+21, was presented by Ford et al.⁹ The case of 48,XXY,+21's are rare with clinical data

limited to only 29 reported cases.^{9,10} To our knowledge these are the first two reported cases of double aneuploidy in Bangladeshi patients.

Case Report:

Case 1:

A 23-month old male child was evaluated for recurrent infections like respiratory tract infection, dental caries, angular stomatitis and skin rashes. There was also developmental delay. He was the third child of his family. He had one brother and one sister who were healthy. His weight was 11kg. The features of Trisomy 21 were obvious, that included flat facial profile, depressed nasal bridge, and upward slant of eyes and protruded tongue. The genitalia were those of a normal, immature male. Echocardiography showed atrial septal defect (ASD).

Cytogenetic study was performed on peripheral blood leucocytes culture using Giemsa banding technique in the department of Pathology, Bangabandhu Sheikh Mujib Medical University. Thirty metaphase spreads were analyzed at 400 band level of bands for chromosomal analysis and was reported according to ISCN nomenclature 1995. The karyo-type of the case was determined as 48, XYY, +21 (Fig. 1). The diagnosis of double aneuploidy involving chromosome 21 and Y was made. Parental chromosomal analyses could not be carried out.

Case 2:

A 9-month old boy, product of a nonconsanguineous marriage born to a 40- years-old mother was the third offspring delivered without any complication. His weight and head circumference were 7600gm and 41cm respectively. He had history of repeated convulsion. Chromosomal analysis performed because of facial dysmorphic features and developmental delay. At physical examination the patient was hypotonic with flat facial profile, flat nose, bilateral epicanthal folds, enlarged tongue

- Dr. Saequa Habib, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University
- Dr. Sultana Gulshana Banu, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University
- S M Shahedul Islam, Scientific Officer, Department of Pathology, Bangabandhu Sheikh Mujib Medical University
- Professor Choudhury Ali Kawser, Chairman, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University

Address of Correspondence: Dr. Sultana Gulshana Banu, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Mobile: 01552493970, Email:risalat_march@yahoo.com

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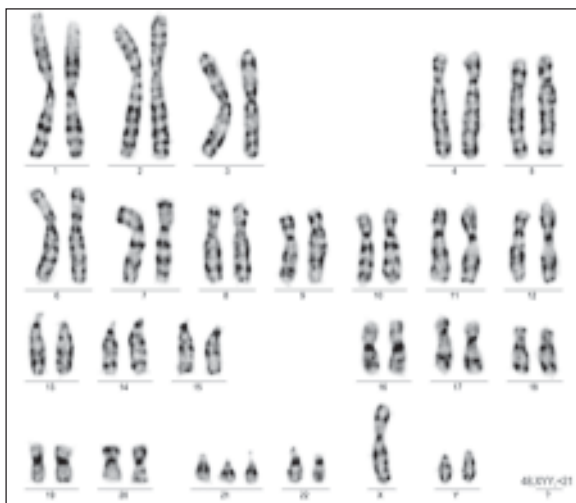


Fig-1: Photomicrograph of a karyotype of a child having Trisomy 21 and XYY syndrome (Giemsa stain x 100)

and short neck. Simian crease was also observed. He had also right sided undescended testis. Electroencephalogram suggested epileptic encephalopathy. Ultrasonogram of brain showed dilated lateral ventricle with a 0.8cm cyst in caudothalamic groove.

Cytogenetic study was performed on peripheral blood leucocytes culture using Giemsa banding showed trisomy 21 with XXY. In each of the 30 metaphases 48, XXY, +21 was found. Based on this, diagnosis of double aneuploidy involving chromosome 21 and X was made (Fig 2). Parental chromosomal analyses could not be carried out. on peripheral blood

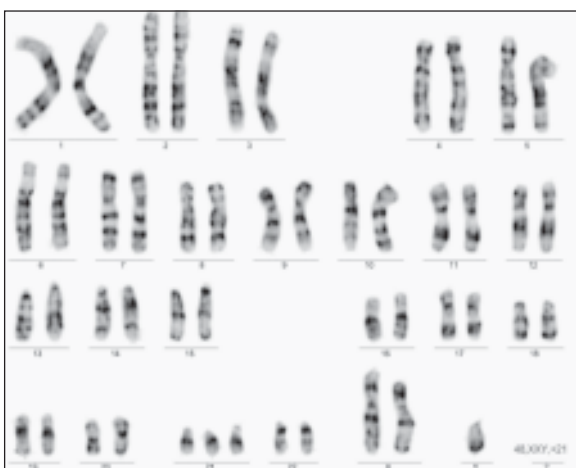


Fig-2: Photomicrograph of a karyotype of a child having Trisomy 21 and Klinefelter (XXY) syndrome (Giemsa stain x 100)

Discussion:

Aneuploidy is defined as an abnormal number of chromosomes. Double aneuploidy, the existence of two numerical chromosomal abnormalities in the same individual, is relatively rare. It can involve both autosomal (chromosome 13, 18 or 21) and sex chromosomes and each may manifest either as a monosomy or trisomy or even tetra- or pentasomy. Data collected from the National Down syndrome Cytogenetic Register (NDSCR) in England and Wales and from the literature indicate that the frequencies of all nonmosaic double aneuploidies, except for 48,XXY,+21, are lower than expected, probably because of strong intrauterine selection against such pregnancies.¹⁰ Furthermore, double aneuploidy involving both autosomal and sex chromosomes is seldom described.

The clinical presentations of double aneuploidy are variable depending on the predominating aneuploidy or a combination effect of both. In patients with double aneuploidies phenotype is more commonly determined by autosomal aneuploidies. Compatible with the literature; the clinical phenotype of Trisomy 21 in our patients was dominant as expected.^{11, 12, 13} In our first case the phenotypic features of XYY were not present. An XYY sex chromosome complement, without any abnormal phenotypical effect, may be found in the general population.¹⁴ But patients may characteristically have long stature, large teeth, prominent glabella, asymmetric and long ears and fingers, dull mentality, relative weakness, poor fine coordination and learning disabilities. Behavioral problems like hyperactivity and anger onset may be prominent at childhood or adolescence which may be found at a later age.¹¹ In patients with Klinefelter syndrome, the diagnosis is often made later in life, and they have a tall stature, absent or decreased facial and pubic hair, small hyalinized testes, a small penis, and feminine distribution of adipose tissue, including gynecomastia.¹⁵ Signs that are sometimes noted in infants with Klinefelter syndrome are an underdeveloped phallus and scrotum, valviform hypospadias, hyperpigmentation of scrotal raphe, and small or ectopic testis.⁷ In our second case patient with Trisomy 21-Klinefelter syndrome, the Trisomy 21 syndrome phenotype predominates, with Klinefelter syndrome manifesting as undescended testis. According to the Trisomy 21-Klinefelter case reports neonates and

infants younger than 10 months show few or no signs of Klinefelter syndrome.⁷ These characteristics begin developing as the child ages.

Trisomy 21 and numeric sex chromosomal anomalies are common chromosomal disorders caused by parental nondisjunction during gametogenesis. Classical trisomy 21 results from maternal meiotic nondisjunction. Y chromosome of XYY is always paternal and it occurs by nondisjunction at meiosis II or mitosis after fertilization.^{10,11,13} Nondisjunction in cases of double trisomy has been found to be entirely maternal in origin, entirely paternal in origin, and both maternal and paternal in origin.⁷ In such cases in which the additional chromosomes originate from different parents, the two errors may be coincidental and unrelated to a genetically determined nondisjunction.

Abnormal separation of chromosomes may occur in older individuals because of dysfunction of structures related to chromosome separation, such as the spindle apparatus and kinetochore.⁷ Caron et al¹⁶ found 1 case of 48, XXY, +21 in 24,901 amniocenteses performed for advanced maternal age (e³⁵ years), which is a 3.8-fold increase over the expected rate. Among 28 reports of 48, XXY, +21, which include 36 cases with known parental ages, Kovaleva and Mutton¹⁰ found that the risk for 48, XXY, +21 was age dependent, with a mean maternal age of 33 years and a mean paternal age of 38 years. This finding is supported by the older parental ages in our second case.

If routine chromosomal study is not done in patients with classical features of Trisomy 21 then cases with double aneuploidy remain largely undiagnosed. Conventional chromosomal study is sufficient for detection of double aneuploidy.

Conclusion:

The occurrence of double trisomy is exceptional. Due to rarity and scanty published data the incidence, phenotype and recurrence risk are difficult to determine.

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Rhizomelic Chondrodysplasia Punctata (RCDP) in a Newborn

BK RAHA^a, ZSM HAQUE^b, N JAHAN^c, M BEGUM^d, M HASAN^e, AWS ROB^f, T FARHANA^g,
S YASMIN^h, SKA HASNATⁱ, Z ISLAM^j

Summary:

A female newborn baby presented with the features of Rhizomelic chondrodysplasia Punctata (RCDP) characterized by rhizomelic shortening with contracture of lower extremities, ichthyosis, microcephaly, dysmorphic facial features including a depressed nasal bridge, hypoplastic midface, full cheeks & low set ear, breathing difficulties and anthropometric measures below the expected indexes for her age. The patient also presented congenital heart disease, a less common manifestation of the syndrome. Radiological features include epiphyseal stippling &

multiple calcification in the epiphyseal cartilage, metaphyseal flaring and clefts in vertebral bodies. It is a rare autosomal recessively inherited skeletal dysplasia. The prognosis is bad and death usually occurs within the first year of age. We report a case of neonatal RCDP which was diagnosed based on the typical clinical and radiological features.

Keywords: *Ichthyosis, Punctate calcification, Rhizomelic shortening*

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Introduction:

Rhizomelic chondrodysplasia punctata is a rare autosomal recessive peroxisome disorder characterized by shortened long bones in the arms and legs, abnormalities of the spine, stippled or dotted appearance to the cartilage, seizures, recurrent respiratory tract infections, ichthyosis, cataract, and profound mental retardation^{1,2}. It affects fewer than 1 in 100,000 people worldwide.²

The diagnosis of RCDP1 is based on clinical findings and confirmed by biochemical or molecular genetic

testing. Biochemical tests of peroxisome function include: red blood cell concentration of plasmalogens (deficient), plasma concentration of phytanic acid (elevated), and plasma concentration of very long chain fatty acids (normal) in cultured fibroblasts which has consistently predicted the PEX7 receptor defect in RCDP1². RCDP Types 2 and 3 and their specific enzyme defect are diagnosed based on deficient enzyme activity in fibroblasts. Radiological features include Punctate epiphyseal calcification, metaphyseal flaring and coronal clefts in the vertebral bodies².

Management is supportive and limited by the multiple handicaps present at birth and poor outcome. The characteristic stippling or dotted cartilage will disappear as the child ages². Cataract extraction may restore some vision. Physical therapy is recommended to improve contractures and orthopedic procedures may improve function in some cases. Genetic counseling may be necessary for individuals who have been determined to be carriers. Monitoring of growth and development, regular assessments for seizure control, vision, hearing, contractures, and orthopedic complications are required in these children on follow up.

The RCDP has a very poor prognosis. The majority of children do not survive beyond the first decade of life and a proportion die in the neonatal period. In a review of 69 children with RCDP diagnosed by the Peroxisomal Diseases Laboratory at the Kennedy Krieger Institute, 60% of children survived the first year and 39% the second; a few survived beyond age ten years². Most deaths were secondary to respiratory complications. Clinical experience suggests that neonatal deaths have

- a. Dr. Biplob Kumar Raha, Assistant Professor of Neonatology, Ad-din Medical College Hospital, Dhaka.
- b. Prof. ZSM Haque, Professor of Neonatology, Ad-din Medical College Hospital, Dhaka.
- c. Dr. N Jahan, Assistant Professor of Neonatology, Ad-din Medical College Hospital, Dhaka.
- d. Dr. M Begum, Assistant Professor of Neonatology, Ad-din Medical College Hospital, Dhaka.
- e. Dr. M Hasan, Associate Professor of Neonatology, Ad-din Medical College Hospital, Dhaka.
- f. Dr. AWS Rob, Assistant Professor of Neonatology, Ad-din Medical College Hospital, Dhaka.
- g. Dr. T Farhana, Indoor Medical Officer of Neonatology, Ad-din Medical College Hospital, Dhaka.
- h. Dr. S Yasmin, Indoor Medical Officer of Neonatology, Ad-din Medical College Hospital, Dhaka.
- i. Dr. SKA Hasnat, Indoor Medical Officer of Neonatology, Ad-din Medical College Hospital, Dhaka.
- j. Dr. Z Islam, Indoor Medical Officer of Neonatology, Ad-din Medical College Hospital, Dhaka.

Address of Correspondence: Dr. Biplob Kumar Raha, Assistant Professor, Dept. of Neonatology, Ad-din Medical College Hospital, 2, Boro Moghbazar, Dhaka-1217, Mobile no: 01716942580, E-mail: biplob_raha@yahoo.com

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been associated with congenital heart disease or pulmonary hypoplasia³.

Case Report:

A one hour old female baby, inborn, 1st issue of a consanguinous parents, delivered by LUCS at 40 weeks of gestation on 01/08/2013 was admitted in the neonatal Intensive Care Unit of Ad-din Medical College Hospital, Dhaka with respiratory distress, rhizomelic shortening and joint contracture. Mother was 26 years old and was on regular antenatal check up. There was no history of any maternal disease or teratogen exposure during the antenatal period. She was neither hypertensive nor diabetic. There was no family history of such deformity of limbs.

Clinically the baby was tachypnic and had dysmorphic facial features including a depressed nasal bridge, hypoplastic midface, full cheeks & low set ear. Her OFC was 32 cm (<3rd centile) and length was 40 cm (<5th centile). Her upper segment to lower segment ratio was 1.8:1. So, she was disproportionately short infant and microcephalic. Her birth weight was 2900 gm. She had symmetrical rhizomelic shortening of all 4 limbs, with contracture of knee and ankle joints (Figure-1). Her respiratory rate was 68/min and regular, breath sound was equal on both side, heart rate was 150 beats/min, 1st and 2nd heart sounds were normal, pansystolic murmur was heard over the precordium mostly marked on the left lower sternal border. She had a short neck and a barrel-shaped chest. Her abdomen was soft with no organomegaly. She had a ichthyotic rash in the neck area. Erythema and maculo-papular skin rashes were also noted in the face,



Fig.-1: Phenotypic features of RCPD

trunk and lower limb on day 2. Provisionally we diagnosed a case of Achondroplasia with congenital heart disease.

Routine laboratory tests like full blood count, serum electrolyte, serum calcium were done which showed normal findings. On Skeletal survey there was a) epiphyseal stippling, b) multiple calcification in the epiphyseal cartilage, c) Clefts in vertebral bodies (Figure-2) d) metaphyseal flaring (Figure-3). Cranial



Fig.-2: A) Epiphyseal stippling B) multiple calcification in the epiphyseal cartilage C) Cleft in second lumbar vertebrae



Fig.-3: Upper limb radiograph showing metaphyseal flaring

ultrasonography, and abdominal ultrasonography were normal. Chest X-ray showed cardiomegaly and Doppler echocardiography revealed small ventricular septal defect with persistent patent foramen ovale. Based on clinical and radiological findings, a diagnosis of rhizomelic chondrodysplasia punctata was made. Biochemical tests and genetic assay to identify the mutations in the PEX7 gene was not undertaken owing to financial constraints. Genetic counseling was given to the parents. Child is receiving regular physiotherapy and currently under follow up.

Discussion:

Chondrodysplasia punctata (CDP) is characterized by shortened bones, punctated or dot-like calcification deposits in the cartilage, and abnormal peroxisomes¹. There are various types of chondrodysplasia punctata; autosomal recessive forms (RCDP types 1, 2 and 3), X-linked dominant form (Conradi-Hünermann-Happle syndrome), an X-linked recessive brachy-telephalangic type and Sheffield type⁴. Several milder forms of CDP, tibia-metacarpal type and humero-metacarpal type, have also been described^{5,6}. Within these variations, there are different syndromes characterized by distinct anomalies, severity, modes of transmission and radiological features. There are patients with CDP, in which known etiologies have been exhaustively investigated, and none has been found⁷.

RCDP is characterized by rhizomelic shortening of the extremities, congenital contractures, dysmorphic facial features (including a depressed nasal bridge, hypertelorism, hypoplastic midface, anteverted nostrils, full cheeks), bilateral congenital cataract, short stature or dwarfism, microcephaly, abnormal hair loss, seizure, recurrent respiratory tract infections, ichthyosis and severe growth and mental deficiency^{1,2,4}. Radiological features include punctate epiphyseal calcification, metaphyseal flaring and clefts in vertebral bodies². All these classical radiological findings were present in the present case. Other malformations observed in individuals with RCDP1 include cleft palate, congenital heart disease and ureteropelvic junction (UPJ) obstruction². In the present case, congenital heart disease was found.

RCDP1 is the most frequent form of RCDP⁸. RCDP1 involves mutations in the PEX7 gene, which encodes enzymes responsible for peroxisome function^{9,10}. RCDP

Types 2 and 3 are phenotypically similar to RCDP Type 1, but result from deficiencies of the specific peroxisomal enzymes dihydroxyacetone phosphate acyltransferase and alkyl dihydroxyacetone phosphate synthase respectively². Genetic assay to identify the mutations in the PEX7 gene and biochemical tests was not undertaken owing to financial constraints. Other causes of calcific epiphyseal stippling include maternal exposure to warfarin in early gestation, and infants of mothers with presumed vitamin K deficiency and with autoimmune disease¹¹, several peroxisomal disorders including Zellweger syndrome spectrum, Smith Lemli Opitz syndrome¹², Trisomy 18 and 21¹³.

White AL et al.¹⁴ delineate the natural history of RCP through systematic analysis of 35 previously unreported individuals (as well as review of 62 literature cases with respect to survival and cause of death). Rhizomelia and punctate calcifications have been noted on ultrasound examination as early as 18 to 19 weeks^{15,16}, analysis of DNA extracted from fetal cells obtained by amniocentesis or chorionic villus sampling, assay of plasmalogen biosynthesis in cultured chorionic villi obtained by CVS or in cultured amniocytes obtained by amniocentesis, preimplantation genetic diagnosis (PGD)². In the present case, ultrasound was done at 22 weeks of gestation which showed rhizomelia and congenital heart disease. An association with fetal ascites and polyhydramnios has been reported¹⁷. In the present case, polyhydramnios was found.

Routine brain imaging was normal or has shown cerebral and cerebellar atrophy with enlargement of the ventricles and CSF spaces¹⁸. MR imaging and MR spectroscopy have shown delayed myelinization, signal abnormalities in supratentorial white matter, decreased choline-to-creatine ratios, and increased levels of mobile lipids, thought to reflect the deficiency of plasmalogens, which are substantial components of myelin^{19,20}. Computerized tomography (CT) scan was done in the present case at the age of 22 days which showed enlargement of the ventricles with cerebral atrophy. Radiologic and MRI evidence of multilevel cervical stenosis with or without compression of the spinal cord has been observed²¹.

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A Young Male with Abdominal Distension and Per Rectal Bleeding

R AFROJ^a, AZMM HOSSAIN^b, MAU KHAN^c, SMS ALAM^d

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A 32 years old previously healthy male developed abdominal distension, abdominal pain and per rectal bleeding after having been sexually assaulted by his associates followed by forcible insertion of something per anus two days back. Initially pain was felt in the lower abdomen which was constant and dull aching. Later on spreads throughout the abdomen and pain became severe, colicky non radiating. He had no history of fever and vomiting. Blood pressure was 100/70 mm hg, pulse rate was 88/min and temperature was 98.4°F.

Abdomen was moderately distended. There was a hard, elongated intraabdominal mass over the lower abdomen extending from symphysis pubis to left side of the umbilicus, about 12 cm in length and 4 cm in breadth, ill defined borders, surface was smooth, mildly tender, moves from side to side but not from above downwards. It was free from surrounding structures. Lower limit could not be reached. Bowel sound was increased. Plain X-ray abdomen revealed an elongated radio opaque shadow in the lower abdomen and pelvis.

Rectal foreign body may presents with features of intestinal obstruction or Perforation.

- Dr. Roksana Afroj, Medical Officer, Casualty Department, Dhaka Medical College Hospital, Dhaka.
- Dr. A.Z.M. Mostaque Hossain, Professor of Surgery, Dhaka Medical College Hospital, Dhaka.
- Dr. Mohammad Ashraf Uddin Khan, Junior Officer, Casualty Department, Dhaka Medical College Hospital, Dhaka.
- Dr. S.M. Syeed-Ul-Alam, Assistant Registrar, Casualty Block-I, Dhaka Medical College Hospital, Dhaka.

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LETTER TO THE EDITOR

(*J Bangladesh Coll Phys Surg 2014; 32: 179-181*)

To

Editor-in-Chief

Journal of Bangladesh College of Physicians and Surgeons.

Sir,

At First, we would like to thank to the editor for publishing the case report on 'Cholecystocutaneous fistula following drainage of parietal abscess' in your journal on January' 2014 issue. we have gone through this article and found the content is very interesting and informative. However, we like share some of my observations and comments.

A patient with Cholecystocutaneous fistula may give history of discharge of stones or granular sludge through the cutaneous opening¹. But in the reported case the patient did not mention history of such type of discharge, although USG showed sludge in the gallbladder lumen.

While investigating the patient, sonogram revealed linear tract communicating with a cavity. But it was not mentioned whether the cavity was parietal or intra abdominal. If contrast CT scan² would have been done it could show the exact location of the cavity together with its possible communication with a intra abdominal viscus.

Exploratory laparotomy should have been the procedure of choice as the sinus tract communicated with a intra abdominal viscus. But it was planned for exploration and excision biopsy of the sinus tract only.

Finally, we thank the authors for presenting this case report on rare Cholecystocutaneous fistula and enriching our knowledge.

1. Dr. Tapan Kumar Saha

Associate Professor, Department of Surgery, Dhaka Medical College, Dhaka.

2. Dr. H.A. Nazmul Hakim

Assistant Professor, Department of Surgery, Dhaka Medical College, Dhaka.

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2. R. Pezzilli, B. Barakat, R. Coninaldesi and M. Cavazzab. 'Spontaneous Choleaystocutaneous Fistile' case reports in Gastroenterology, Vol.-4. No-1, 2010. pp. 356-360.

To

Editor – in – Chief

Journal of Bangladesh College of Physicians and Surgeons.

Subject: Responding to readers comment regarding the case report on "Cholecystocutaneous fistula following drainage of parietal abscess" published in vol . 32, No. 1; Page 37-40; January 2014.

Sir,

First of all we express our deep gratitude to you and all concerned for publishing our case report in the Journal of Bangladesh College of Physicians and Surgeons.

We are also thankful to our two honorable readers for going through the case report and making comments. We are very happy to see that it has generated lot of enthusiasm and queries among the readers. We shall try to address to the issues raised by the learned readers.

I have tried to give the answers of their questions.

1. Our patient had developed an intervening abscess cavity in the parietes from where seropurulent materials were discharged recurrently. Cholecystectomy revealed that the gall bladder was containing pus and some necrotic debris. In our opinion a simple, straight tract probably may discharge stones or biliary sludge if any, in a case of cholecystocutaneous fistula.
2. Sinogram (not sonogram) revealed a linear tract communicating with a cavity but could not accurately locate it. We agree with you that a contrast CT scan would have been the preferred next step for further evaluation but as the patient had financial constraint we decided to operate on the basis of USG and contrast X ray finding.
3. None of our preoperative investigations could delineate certainly, the presence of a fistula communicating with an intra-abdominal viscus. A negative laparotomy could not be justified in that case. Our initial step was to explore the tract keeping in mind that laparotomy may be needed. Operative findings guided us in that way which led to complete excision of sinus tract along with cholecystectomy.

Regards.

Dr. Md. Abdullah-Al-Amin

Professor & Head, Dept. of Surgery & MISC,
BIRDEM & Ibrahim Medical College,
Dhaka, Bangladesh.

To

Editor in chief

Bangladesh College of Physicians and Surgeons

Sir,

I had gone through the original article of the valuable journal, volume 32, No1 Journal 2014 title with “Clinicopathological profile of Wilms’ tumor in children” by M.Majumder et al with keen interest and have few observations.

The article was well written and the contents and illustrations were nice.

Wilms’ tumor is the most common abdominal tumor of childhood¹ Early stage and favorable histology has excellent outcome after treatment. Most Wilms’ tumors are unilateral, only about 6% are bilateral presentation and it is termed as stage V, It is the exceptional stage.²

Regarding diagnosis now the recommendation is not to do biopsy unless unresectable and bilateral.³In current COG renal tumor protocol children who present with bilateral renal masses receive two cycles of chemotherapy without biopsy. Biopsy is reserved for those who do not show volume reduction.²

Bilateral Wilms’ tumors are not usually hereditary.⁴ Many bilateral tumors are present at the time Wilms tumor is first diagnosed (i.e., synchronous), but a second Wilms’ tumor may also develop later in the remaining kidney of 1% to 3% of children treated successfully for Wilms’ tumor. The incidence of such metachronous bilateral Wilms’ tumors is much higher in children whose original Wilms’ tumor was diagnosed before age 12 months and/or whose resected kidney contains nephrogenic rests. Periodic abdominal ultrasound is recommended for early detection of metachronous bilateral Wilms’ tumor as follows:^{5,6}

- Children with nephrogenic rests in the resected kidney (if younger than 48 months at initial diagnosis)—every 3 months for 6 years.
- Children with nephrogenic rests in the resected kidney (if older than 48 months at initial diagnosis)—every 3 months for 4 years.
- Other patients—every 3 months for 2 years, then yearly for an additional 1 to 3 years.

Another important point to note that neuroblastoma may be confused with nephroblastoma. Neuroblastoma is the extra-renal mass. Nephroblastoma is renal origin. Previously it can be distinguished by IVU. Now a days MRI is sufficient.⁷

In our country most of the patients present in stage III and abdominal radiotherapy is needed. For local control and to prevent metastasis radiotherapy should be started early within 9-10 days after surgery. This is an exception as because in other malignant cases it is prohibited due to risk of wound dehiscence. Now common consensus is that radiotherapy should be started on 9th post operative day. In stage V when there is both lungs metastasis radiotherapy can be given as lung bath. If pulmonary nodule disappears after giving chemotherapy, radiotherapy can be omitted²

Absence of anaplasia is a good prognostic factor, Anaplasia correlates best with responsiveness to therapy rather than to aggressiveness. It is most consistently associated with poor prognosis when it is diffusely distributed and when identified at advanced stages. These tumors are more resistant to the chemotherapy traditionally used in children with favorable-histology Wilms’ tumor.⁸

The tumor is chemosensitive. In early stage most of the cases are treated with Vincristine, Doxorubicin, Actinomycin D. In unfavorable group and stage IV Carboplatin, Etoposide, Ifosfamide combination can be used. It is very toxic combination and response is only 30%.²

This article only covers the clinicopathological profile of Wilms’ tumor. For a better overview of the disease - diagnostic procedure, treatment modalities and available treatment facilities in our country and outcome of treatment may be included in this article, so that the physicians can acquire knowledge about it at a glance.

1. Professor Dr .Md. Moarraf Hossen

Professor and Head
Department of Radiotherapy
Dhaka Medical College and Hospital

2. Dr. Aliya Shahnaz

Assistant Professor,
Department of Radiotherapy,
Dhaka Medical College and Hospital

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Author's Reply

To

Editor in chief

Bangladesh College Of Physicians and Surgeons

Sir

We thank Professor Dr .Md. Moarraf Hossen & Dr. Aliya Shahnaz for their interest & valuable observations on the original article.¹ I totally agree that this article only covers the clinicopathological profile of Wilms' tumor. For a better overview of the disease - diagnostic procedure, treatment modalities and available treatment

facilities in our country and outcome of treatment should be included in this article. My study period was short & it was only designed for the clinicopathological profile . As a part of limitation of the study I have stated that this study raised the necessity of further large scale work on the issue.

Regarding anaplasia as you mentioned that Anaplasia correlates best with responsiveness to therapy rather than to aggressiveness. It is most consistently associated with poor prognosis when it is diffusely distributed and when identified at advanced stages. These tumors are more resistant to the chemotherapy traditionally used in children with favorable-histology Wilms' tumor.² It also said that focalanaplasia is a comparable to favourable histology.²

But later the 5th NWTS results showed that the prognosis for patients with stage IAH is worse than that for patients with stage I favourable histology.³ Novel treatment strategies are needed to improve outcomes for patients with Anaplastic Histology, especially those with stage III to V disease.³

Dr. Monika Mazumder

Registrar

Department of Paediatrics

Rangpur Medical College Hospital, Rangpur

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FROM THE DESK OF EDITOR in CHIEF

(J Bangladesh Coll Phys Surg 2014; 32: 182)

Dear Fellows

You would be glad to know that we are inching closer to our goal of achieving an International standard for our very own JBCPS. A little bit more support from the fellows is all we seek. We like to urge you to submit your papers through our online portal and instead of sending original articles abroad, the editorial committee requests you to submit quality papers for publication in JBCPS. You already know that we have been able to

cut down on the backlog, so a timely publication is our goal.

Your support will obviously take us the few steps left from reaching our destination.

Professor HAM Nazmul Ahasan

Editor-in-Chief

Journal of Bangladesh College of Physicians
and Surgeons

The following fellows who died on April to July, 2014

Dr. (Major) Sanjita Biswas

Dr. (Major) Sanjita Biswas died on 14th May, 2014. He passed fellowship in Paediatrics in January-2014, from Bangladesh College of Physicians and Surgeons (BCPS).

Professor S.N.Samad Choudhury

Professor S.N.Samad Choudhury died on 18th May, 2014. He won fellowship without examination in Anaesthesiology, 1983 from Bangladesh College of Physicians and Surgeons (BCPS).

Professor Ameena Majid

Professor Ameena Majid died on 7th June, 2014. He passed fellowship in Obst. and Gynae in January-1984, from Bangladesh College of Physicians and Surgeons (BCPS).

Professor Emeritus A.K.M Kafiluddin

Professor Emeritus A.K.M Kafiluddin died on 13th June, 2014. He won fellowship without examination in Medicine, 1974 from Bangladesh College of Physicians and Surgeons (BCPS).

Professor Ahmed Hossain

Professor Ahmed Hossain died on 25th June, 2014. He won Honorary fellowship in Radiology & imaging 2005 from Bangladesh College of Physicians and Surgeons (BCPS).

Dr. Mohammed Shafiqul Islam

Dr. Mohammed Shafiqul Islam died on 11th July, 2014. He passed fellowship in Otolaryngology in July, 2009, from Bangladesh College of Physicians and Surgeons (BCPS).

Dr. Razia Sultana

Dr. Razia Sultana died on 12th July, 2014. She passed fellowship in Obst. and Gynae in January-2005, from Bangladesh College of Physicians and Surgeons (BCPS).