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INFORMATION FOR AUTHORS

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Guide to Authors

MH Samorita Medical College Journal provides rapid publication (bienial 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.

The manuscripts should be submitted addressing Editor-in-Chief.

The Journal of MH Samorita Medical College only accepts manuscripts submitted as triplicate hard copy with a soft copy.

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 (**International or National)** or any other publisher.

The submitting (Corresponding) author is responsible for ensuring that the submitting article has been signed by all the co-authors. 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 board officially establishes the date of receipt. Further correspondence and proofs are 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 papers should be addressed to Editor-in-Chief (MH Samorita Med Col J)

The cover letter

Cover letter is expected to be submitted along with manuscript. Use the cover letter to explain why the paper should be published in the Journal of MH Samorita Medical College. The cover letter should include the corresponding author's full address, telephone/ fax numbers and e-mail address.

Ethical aspects

- Ethical aspect of the study is considered very carefully 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 would be blackened out.

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 MH Samorita Medical College Journal (MHSMCJ) 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.

Article Types

Four types of manuscripts may be submitted.

Editorials: It should preferably cover a single topic of common 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 and its volume should **not exceed 5000 words** or equivalent space including title, summary/abstract, main body, references, table(s) and figure(s).

Review Articles: Submissions of reviews 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) and should **not exceed 5000 words**. It should be focused and must be up to date.

Case Reports: This should cover uncommon and/or interesting cases and should **not exceed 1000** words or equivalent space.

Review Process

All manuscripts are initially screened by editor and sent to selective reviewers. Reviewers are requested to return comments to editor within 3 weeks. On the basis of reviewers' comments the editorial board decides whether the articles are accepted or send for re-review the manuscripts. The MH Samorita Med Coll J editorial board tries to publish the manuscript as early as possible fulfilling all the rigorous standard journal needs.

I. Preparing a Manuscript for Submission to MH Samorita Med Coll J

Editors and reviewers spend many hours reading and working on manuscripts, and therefore appreciate receiving manuscripts that are easy to read and edit. The following information provides guidance in preparing manuscripts for the journal.

I A. 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 :

- Title page
- Abstract
- Main body/Text: Introduction, Materials and Methods, Results, Discussion and conclusion (For an original article/ Systematic review)
- Acknowledgement
- References
- 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. General Principles

- The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Materials and Methods, Results, and Discussion(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.
- Authors need to work closely with editors in developing or using the publication formats and should submit supplementary electronic material for peer review.
- Double-spacing all portions of the manuscript— including the title page, abstract, text, acknowledg- ments, 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. 2. Title Page

The title page should have the following information:

- The title should be brief, relevant and self explanatory. It should reflect the content of the article and should include all information that will make electronic retrieval of the article easy. Subtitles should not be used unless they are essential.
- Title should not be phrased as questions.
- The names of the authors should appear below the title that should include full names of all authors **(no initial).**

Example: Md MA Hamid **(correct form);** Hamid MA **(incorrect).**

The affiliations and full addresses of all authors should be mentioned in the title page.

- 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.
- 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.
- Source(s) of support in the form of grants, equipment, drugs, or all of these.

I A. 3. Abstract

Original Article: Structured abstracts are essential for original research. Structured abstract includes introduction, objective(s), materials and methods, results and conclusion. Should be limited to 250 words. The abstract should provide the introduction of the study and blinded state and should mention the study's purpose, basic procedures including selection of study subjects or laboratory animals, main findings (giving specific effect sizes and their statistical significance, if possible) and the principal conclusion. Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion that many readers read, it should accurately reflect the content of the article; so, authors need to be careful about that.

Review Article: is expected to contain background, objective(s), main information and conclusion in brief form. Without any subheading the content should be described in a single paragraph.

Case Study: needs to have background, case summary and conclusion. The content should be described in a single paragraph.

Do not put references in the abstract.

I A. 4. Main body

I A. 4 a) Original article

The body of the text should be divided into the following sections: i) Introduction, ii) Materials and methods, iii) Results, iii) Discussion and iv) Conclusion.

i) Introduction

Should not exceed **500 words**. This section includes background of the problem (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. Only pertinent primary references should be provided and no data or conclusions should be included from the work to be reported. **Justificatio**n of the study and its **objective(s)** should be mentioned at the end of this section. All information given in this section must have references that to be listed in the reference section.

ii) Materials and methods

The Methods section should be written in such way that another researcher can replicate the study. The type of study (study design), study period, sampling technique, sample size, study population, data collection technique and tool as well as data handling, processing and data analysis should be briefly mentioned in this section.

ii a) Selection and Description of Participants

Describe selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility (inclusion) 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 etc. 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.

ii b) Technical Information

- Describe methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results.
- Cite references to established methods, including statistical methods. 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.
- For a systematic review article include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

ii c) Statistics

- Describe statistical methods with enough detail to enable a know- ledgeable 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).
- Cite references for the design of the study and statistical methods (standard for the work) when possible.
- Define statistical terms, abbreviations, and most symbols.
- Specify the computer software used.

iii) Results

Results should be described in past tense.

- Present results in logical sequence in the text, tables, figures and illustrations, giving the main or most important findings first. Maintain the sequence of results with the specific objectives selected earlier.
- Do not repeat all the data in the tables or illustrations in the text; emphasize or summarize only the most important observations.
- When data are summarized in the result 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 (relevant to objectives) and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in figures (graphs/ charts) and tables. **Example:** Age range of the studied respondents should be appeared **either in table or in figure**.
- Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

iv) Discussion

The discussion must be described in **past tense.** This section should reflect the author's comments on the results.

- Emphasize the new and important aspects of the study and the conclusions that follow 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 those findings.
- Compare and contrast the results with other relevant studies and potential argument for discrepancy and consistency should be given here.
- 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, 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.

v) Conclusion

It should be described in **present tense**. Conclusion should be the main message and the authors' impression from the results of the study. The article should be concluded briefly (**not more than 100 words**). Recommendation(s) can also be included in this section which should not exceed 30 words.

I A. 4 b) Review article

For a systematic review or meta-analysis the body of text should be divided into the following sections (Like an original article): i) Introduction, ii). Materials and methods, iii) Findings/Results, iii a) Main information about the topic, iv) Discussion and v) Conclusion. For a general review article section No. ii (Materials and methods) and iii (Findings/Results) iv) (Discussion) are not relevant. So, for a general review article section No. i). Introduction, iii a). Main Information about the Topic and v). Conclusion are required.

i) **Introduction**: should not exceed **500 words**. This section will include background of the topic. At the end of the review, why the author want to publish the topic on the article ie., the objective should be mentioned.

ii) **Material and methods**: How the review was done, what sorts of articles were searched, how they were searched, the total number of articles reviewed should be mentioned here. This section is not required for a general review article.

iii) **Results/findings**: The findings on the topic after reviewing the articles should be compiled, analysed and described here like an original research article. This section is not required for a general review article.

iii a) **Main Information about the Topic**: The main information about the topic should be described and discussed elaborately with the help of published literatures in this section but the subtitles should be relevant to the topic(Title) for a general review article. This section may not be required for a systematic review or meta-analysis.

iv) **Conclusion:** The article should be concluded briefly (**not more than 100 words**).

I A. 4 c) Case Report

The body of the text should be divided into the following sections: i) Introduction, ii) Case Report (Description of the case), iii) Discussion and iv) Conclusion.

i) **Introduction**: A brief description should be given on the topic of the case with the help of published literatures.

ii) **Case Report**

- The findings (history, clinical examination and investigations) should be described here.
- Management (if any) can also be given.

iii) **Discussion**

- The discussion should be started by briefly summarizing the main findings of the case reported, then possible explanations for those findings should be explored.
- The findings of the case should be compared with other relevant studies and potential argument for discrepancy and consistency should be given here.

iv) **Conclusion**

- The article should be concluded briefly (**not more than 100 words**).
- The main findings of the reported case should be emphasized which the readers can consider as a clue to suspect a diagnosis for a rare case in future.

I A. 5. Acknowledgement

Acknowledge advisor(s) and/or any one who helped the researcher(s)

- Technically
- Intellectually
- Financially

I A. 6. References

I A. 6 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.
- Abstracts should not be used 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.
- Citing a "personal communication" should be avoided 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. 6 b) Reference Style and Format

➢ **Reference Style**

Author should follow **Vancouver style**.

- R**eference list** should appear at the end of the article and should be numbered consecutively in the order as they are cited in the text, which is done by **superscript** (single press of 'ctrl shift +') in numerical form **(citation number).**
- When **multiple references** are cited at a given place in the text, use a **hyphen** to join the first and last numbers that are **inclusive**. Use **commas** (without spaces) to separate **non-inclusive** numbers in a multiple citation.

  Example: 2,3,4,5,7,10,12 are abbreviated to **(2-5,7,10,12**).
- **Do not** use a hyphen if there is no citation numbers in between 2 numbers that support your statement.

  Example: 1-2 (**in correct form).** 1,2**(correct form)**
- As a general rule, citation numbers in the text should be placed **outside full stops and commas**, inside colons and semicolons (applicable for any part of the document).

  Example: Masud Alam,1 Selim Khan[2]

  Example: Over the past decades public health relevance of mental health condition 'in children and adolescents has been of growing concern'.[1-3,5,6]
- 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.

➢ **Reference Format**

1. Citing a Book

The essential details required are (in order):

1.1 Name/s of author/s, editor/s, compiler/s or the institution responsible.

- Where there are **6 or less authors** you must list **all authors**.
- Where there are **7 or more author**s, only the **first 6 are listed** and **add "et al"** (after a **comma**).
- Put a comma and 1 space between each name. The last author must have a full-stop after their initial(s).

  Format: surname (**1 space**) initial/s (**no spaces or punctuation between initials**) (**full-stop OR if further names comma, 1 space**)

  Example: Smith AK, Jones BC, Bloggs TC, Ashe PT, Fauci AS, Wilson JD, et al.
- **When author/s is/are editor/s :**Follow the same methods used with authors but use the word **"editor"** or **"editors"** in full after the name/s. The word editor or editors must be in small letter. (**Do NOT** confuse with "ed."used for edition.)

  Example: Millares M, editor. Applied drug information: strategies for information management. Vancouver (WA): Applied Therapeutics Inc; 1998.

Sponsored by institution, corporation or other organization (including PAMPHLET)

E**xample**: Australian Pharmaceutical Advisory Council. Integrated best practice model for medication management in residential aged care facilities. Canberra: Australian Government Publishing Service; 1997.

1.2. Title of publication and subtitle if any

- Italics or underlining should be avoided.
- Only the first word of the titles (and words that normally begin with a capital letter) should be started with capital letter (except proper noun).

Format: title (**full-stop, 1 space**)

Example: Harrison's principles of internal medicine.

Example: Physical pharmacy: physical chemical principles in the pharmaceutical sciences.

Example: Pharmacy in Australia: the national experience.

1.3. Edition (other than the first)

Number of edition **other than first one** should be mentioned as **2nd, 3rd,10th ed.**

Example: Blenkinsopp A, Paxton P. Symptoms in the pharmacy: a guide to the management of common illness. 3rd ed. Oxford: Blackwell Science; 1998.

1.4. Place of publication (if there is more than one place listed, use the first one)

- The place name should be written in full.
- If the place **name is not well known**, add a comma, 1 space and the state or the country for clarification. For places in the USA, add after the place names the 2 letter postal code for the state. This must be in upper case. eg. Hartford (CN): (where CN=Connecticut).

Format: place of publication (**colon, 1 space**)

Example: Hartford (CN):

Example: Texas (NSW):

Example: Kyoto (Japan):

1.5. Publisher

The publisher's name should be spelled out in full.

Format: publisher (**semi-colon, 1 space**)

Example: Australian Government Publishing Service;

Example: Raven Press;

Example: Williams & Wilkins;

1.6. Year of publication

Format: year (full-stop, add 1 space if page numbers follow).

Example: 1999.

Example: 2000. p. 12-5.

1.7. Page numbers (if applicable).

- Abbreviate the word "page" to "p.".

Note: do not repeat digits unnecessarily

Format: p (**full-stop, 1 space**) page numbers (**full-stop**).

Example: p. 122-9 (**correct**); p. 122-129 (**incorrect**).

Example: p. 1129-57 (**correct**); p. 1129-157 (**incorrect**).

Example of citing a book: Lodish H, Baltimore D, Berk A, Zipursky SL, Matsudaira P, Darnell J. Molecular cell biology. 3rd ed. New York: Scientific American; 1995.

(*Name/s. Title. Edition(other than first). Place of publication: Publisher; year of publication. p. Page no*)

2. Citing a Chapter in an Edited Book (to which a number of authors have contributed)

- Name/s of author of the chapter
- Title of chapter followed by, In:
- Editor
- Title of book
- Series title and number (if part of a series)
- Edition (if not the first edition)
- Place of publication (if there is more than one place listed, use the first named)
- Publisher
- Year of publication
- Page numbers

(*Title of Chapter. In: Editor(s). Title of book and number. Edition (other than first). Place of publication: Publisher; year of publication. p. Page no*)

Example of citing a chapter in an edited book:

Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk (CN): Appleton and Lange; 1995. p. 361-80.

3. Citing a Journal Article from a Print source

The essential details required are (in order):

- **Name/s of author/s of the article.**
  See step 1 of "Citing a book" for full details.
- **Title of article.**
  See step 2 of "Citing a book" for full details.

Example: Validation of an immunoassay for measurement of plasma total homocysteine.

- **Name of journal (abbreviated).**

- Abbreviate the name of the journal according to the style used in Medline.
- A list of abbreviations can be found at: http://w**ww.ncbi.nlm.nih.gov/entrez/query.fcgi?db=journals**

  Note: No punctuation marks are used in the abbreviated journal name.

Format: journal title abbreviation (1 space)

Example: Bang J Psychiatry

- **Year of publication (month or day should be omitted).**

Format: year (**semi-colon, one space**)

Example: 1996; 12(5): 127-33.

- **Volume number (and issue/part)**

  Format: volume number (**colon, one space**)

Example: 1996; 12(5): 127-33. Or
1996; 18: 1237-8.

- **Page numbers**

Note: Do not repeat digits unnecessarily

Format: page numbers (full-stop)

Example: 5310-5.

Example of citing a journal: Russell FD, Coppell AL, Davenport AP. In vitro enzymatic processing of radiolabelled big ET-1 in human kidney as a food ingredient. Biochem Pharmacol 1998; 55(5): 697-701.

Name(s). Title. Name of the Journal Year of publication; Volume Number (Session/Issue Number): Page Number.

- **No author given in article**

  Example: Coffee drinking and cancer of the pancreas [editorial]. BMJ 1981; 283: 628.

- **Journals with parts and/or supplements**

Examples

- **Volume with supplement**

  Environ Health Perspect 1994; 102Suppl 1: 275-82.

- **Issue with supplement**

  SeminOncol 1996: 23(1 Suppl 2): 89-97.

- **Volume with part**

  Ann ClinBiochem 1995; 32(Pt 3): 303-6.

4. Citing a Journal Article from Internet and Other Electronic Sources

This includes software and internet sources such as web sites, electronic journals and databases.

The **basic form** of the citations **follow the principles listed for print sources** (see above).

In the case of sources that may be subject to alteration it is important to acknowledge the **Date The Information Was Cited.** This is particularly true for web sites that may disappear or permit changes to be made and for CD-ROMS that are updated during the year.

4.1. Citing a Journal Article from the Internet

Note: Follow the same procedure for citing print journals as for electronic journals regarding date, volume pages and journal title

Format: Author/s (full-stop after last author, 1 space) **Title of article** (full-stop, 1 space)

Abbreviated title of electronic journal (1 space) **[serial online]** (1 space) **Publication year** (1space) **month(s)** - if available (1 space) **[cited year month (abbreviated) day]** - in square brackets (semi colon, 1 space) **Volume number** (no space) **Issue number** if applicable in round brackets (colon) **Page numbers or number of screens** in square brackets (full-stop, 1 space) **Available from** (colon, 1 space) URL:**URL address underlined**

Examples:

- Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 Jan-Mar [cited 1999 Dec 25]; 1(1):[24 screens]. Available from:URL: http://www/cdc/gov/ncidoc /EID/eid.htm
- Garfinkel PE, Lin E, Goering P. Should amenorrhoea be necessary for the diagnosis of anorexia nervosa? Br J Psych [serial online] 1996 [cited 1999 Aug 17]; 168(4):500-6. Available from: URL:http://biomed. niss.ac.uk

4.2. Citing a Journal Article from WWW site

(If the author is not documented, the title becomes the first element of the reference.)

Format: Author (full-stop after last author, 1 space) **Title** (full-stop, 1 space) **[Online]** (full stop, 1 space) **Publication Year** (1 space) **[cited year month (abbreviated) day]** (semi colon) **Number of screens in square brackets or pages** (full-stop, 1 space) **Available from** (colon, 1 space)

URL: (no space) **URL address underlined**

Note: The number of screens is not necessary. Put a semi colon and 1 space after the cited date if no pages or screen numbers are listed.

When the date is approximated, indicate that by following the date with a question mark and inserting the statement in square brackets. Eg. [2001?]

Examples: National Organization for Rare Diseases [Online]. 1999 Aug 16 [cited 1999 Aug 21]; Available from: URL:http://www.rare diseases.org/

Royal College of General Practitioners.The primary health care team.[Online]. 1998 [cited 1999 Aug 22];[10 screens]. Available from:URL: http:// ww. rcgp.org.uk/informat/publicat/rcf0021.htmZand J. The natural pharmacy: herbal medicine for depression [Online]. [1999?] [cited 2001 Aug 23];[15 screens]. Available from:

URL:http://www.healthy.net/asp/templates/Article.asp?PageType=Article&Id=920

Important Points For Reference List

- For **online material**, please cite the **URL**, together with the **date you accessed** the website
- **Online journal** articles can be cited using the Digital Object Identifier **(DOI)** number

Samples of Reference List

A list of references contains details of those works cited in the text.

The references are listed in the same numerical order as they appear in the body of the text

1. Getzen TE. Health economics: fundamentals and flow of funds. New York (NY): John Wiley & Sons; 1997.
2. Millares M, editor. Applied drug information: strategies for information management. Vancouver, WA: Applied Therapeutics, Inc.; 1998.
3. Australian Government Publishing Service. Style manual for authors, editors and printers. 5th ed. Canberra: Australian Government Publishing Service; 1994.
4. Australian Pharmaceutical Advisory Council. Integrated best practice model for medication management in residential aged care facilities. Canberra: Australian Government Publishing Service; 1997.
5. Bennett GL, Horuk R. Iodination of chemokines for use in receptor binding analysis. In: Horuk R, editor. Chemokine receptors. New York (NY): Academic Press; 1997. p. 134-48. (Methods in enzymology; vol 288).
6. Coffee drinking and cancer of the pancreas [editorial]. BMJ 1981;283:628.
7. Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 Jan-Mar [cited 1996 Jue 5]; 1(1):[24 screens]. Available from: URL:http:// www. cdc.gov/ ncidoc/EID/eid.htm

I A. 7. Conflict of interest

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations.

It is important to be consistent when you are referencing.

I A. 8. Tables and Illustrations (Figures)

I A. 8 a) Tables

- In tables, capture information concisely and display it efficiently.
- Use tables /fig that are relevant to the study.
- Try to limit the number of tables/figures.
- 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. 8 b) 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).

- Review the images of such files on a computer screen before submitting them to be sure that 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 colour, MH Samorita Med Coll J accept coloured illustration when it seems essential. This Journal publish illustrations in colour only if the author pays the additional cost. Authors should consult the editorial board of the journal about requirements for figures submitted in electronic formats.

I A. 8 c) Legends for Illustrations (Figures)

- Type or print the 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. 9. 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. 10. 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 should be used in parenthesis on first mention followed by the use of abbreviation in parenthesis unless the abbreviation is a standard and well established one like 'WHO'.

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- 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.
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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.

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If you have submitted mentioning document (1, 2, 3) above, when you first submit your article but if there is change in the authorship or related then you have to re-submit it.

- **General outline for article presentation and format**
- Double spacing
- Font size should be 12 in arial
- Margins 5 cm from above and 2.5 cm from rest sides.
- Title page contains all the desired information
- Running title provided (not more than 40 characters)
- Headings in title case (not ALL CAPITALS, not underlined)
- References cited in superscript in the text without brackets after with/without comma (,) or full stop (.)
- References according to the journal's instructions – abide by the rules of Vancouver Style.
- **Language and grammar**
- Uniformity in the language
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- Numerals from 1 to 10 spelt out
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- **Tables and figures**
- No repetition of data in tables/graphs and in text
- Actual numbers from which graphs drawn, provided
- Figures necessary should be of good quality (colour)
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- Labels pasted on back of the photographs (no names written)
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- Patients' privacy maintained (if not, written permission enclosed)
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- **Title**
- Complete title of the article
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- Not more than 200 words for case reports and 250 words for original articles
- Structured abstract (Including introduction, methods, results and conclusion) provided for an original article and (Introduction, case report and conclusion) for case reports.
- Key words provided – arrange them in alphabetical order (three – five)
- **Introduction**
- Word limit 150 -200 words
- Pertinent information only
- **Material and Methods**
- Study Design
- Duration and place of study
- Ethical approval
- Patient consent
- Statistical analysis and software used.
- **Result**
- Clearly present the data
- Avoid data redundancy
- **Discussion**
- Avoid unnecessary explanation of someone else' work unless it is very relevant to the study
- Provide and discuss with the literatures to support the study with references.
- Mention about limitation of the study
- **Conclusion**
- Give your conclusion
- Any recommendation
- **Acknowledgement**
- Acknowledge any person or institution who have helped for the study
- **Reference**
- Abide by the Vancouver style
- Use reference at the end of the sentence after the full stop with superscript
- **Legends**
- Tables
- Figures

Editorial

Rational Use of Drugs in Medical Practice

Rational use of drugs is an essential element in achieving quality of health and medical care for patients and the community as a whole.[1] WHO defined -"Rational use of drugs requires those patients receiving medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and the lowest cost to them and their community".[2]

Irrational use of drugs can be described as follows: a) Multi-drug use or polypharmacy b) Overuse of injections c) Incorrect prescribing as well as inappropriate use by consumer like inappropriate self-medication, often of prescription-only medicines, non-adherence to dosing regimes d) Inappropriate use of antimicrobials, involves the wrong drug for a specific condition.[3]

Irrational use of medicines is a major problem worldwide. WHO estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately and that half of all patients fail to take them correctly.[4] Conversely, about one-third of the world's population lacks access to essential medicines. It is a serious problem in developing countries where 50 - 90% of drug purchases are made in the private sector.[5]

In Bangladesh, in Primary Health Care centres 55% prescribed antibiotics are in suspected infection and 37% prescribed antibiotics are to please patients in absence of proper indication. [6] In tertiary care hospital 39% antibiotics are purchased without prescription and 30-40% total cost of medicine is contributed by antimicrobials.[7]

Factors contributing to irrational use of drugs include[1] i) Patients: drug misinformation, misleading beliefs, ii) Prescribers: lack of education and training, inappropriate role models, failure to prescribe in accordance with clinical guidelines, competition *iii)* Workplace: heavy patient load, lack of adequate lab capacity, insufficient staffing iv) Drug Supply System: unreliable suppliers, drug shortages, non essential drugs available, limited budgets, expired drugs supplied v) Chemists Shops: profit motives, competition *vi)* Industry: promotional activities, incentives.[1]

Some important consequences of irrational use of drugs: a) Reduction in the quality of drug therapy- this can lead to increased morbidity and mortality b) Waste of resources- reduces availability of other vital drugs and increases costs c) Increased risk of unwanted effect- adverse drug reactions and toxicity d) Antimicrobial resistance- reduces the effectiveness of established treatment and increases the complexity and the cost of treatment e) Psychosocial impacts -patients may believe that there is "a pill for every ill".[8]

To improve the situation "Good prescribing practice" is an essential part of rational drug use.[9] To promote rational use of drugs/medicines WHO advocates 12 key interventions as follows [4]

1. A mandated multi-disciplinary national body to coordinate medicine use policies
2. Clinical guidelines
3. Essential medicines list based on treatment of choice
4. Drugs and therapeutics committees in districts and hospitals
5. Problem-based pharmacotherapy training in undergraduate curricula
6. Continuing in-service medical education as a licensure requirement
7. Supervision, audit and feedback
8. Independent information on medicines
9. Public education about medicines
10. Avoidance of perverse financial incentives
11. Appropriate and enforced regulation
12. Sufficient government expenditure to ensure availability of medicines and staff.

Institutions, health professionals and patients, all have roles to play in promoting rational use of drugs. Effective regulation, clear clinical guidance, supportive incentive structures, training, education and management are key components of an effective policy in this area.[10] It is hoped that programmes in

rational use of drugs can be initiated and implemented widely at different centers in our country.

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Comparing Principle-oriented and Information-oriented Approach in Teaching-Learning of Human Genetics: 'A Profile of Selected Stakeholders'

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Abstract

Introduction: *The specific genes that seem to contribute to specific disorders, the practitioner must understand and be able to explain to patients – which of these reports have clinical significance and which are merely unsubstantiated claims. To achieve the goal of gaining adequate knowledge on Genetics the field of education has to be focused.*

Objectives: *To identify the approaches taken by stakeholders regarding the use of 'principle' and 'information' in presenting Genetics.*

Materials and Methods: *The present study is a cross-sectional descriptive study with qualitative and quantitative component carried out in the department of Anatomy, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Stakeholders of Genetics (30 in number) were enrolled into this study. A questionnaire based survey was conducted among them to assess the feelings, 0pinion, experience and performance of stakeholders regarding 'Principle-oriented approach' and 'Information-oriented approach' in teaching-learning Genetics.*

Results: *Among the findings of the questionnaire-based survey 74% of the participants either clearly understood or somewhat understood the issue of 'Principle' and 'Information' before participating in the survey. They agreed that Genetics can interrelate 'Information' from different aspects of basic Genetics and thus memorizing/understanding of every information is strengthened from different perspectives. Among the participants 97% agreed that while teaching-learning Genetics one should develop the habit of emphasizing 'Principles'. They thought that in our country, the practice of using 'Principles' in explaining genetic 'Information' is either 'rare' or 'not frequent'. A few (23%) of the participants felt that in Genetics textbooks, differentiation between 'Principle-oriented texts' and 'Information-oriented texts' is 'very difficult'. Majority (93%) of the participants believed that most stakeholders of our country would require organized training for successful incorporation of 'Principles' in teaching-learning Genetics. Majority of them agreed that it is also important to take 'Principle-oriented approach' in some part of assessment of medical students. Most (83%) of the participants believed that most of the stakeholders of our country would require organized training for successful incorporation of 'Principles' in teaching-learning Genetics. All of them agreed that they would be happy to attend short training courses on incorporation of 'Principles' in teaching Genetics. Majority (76%) of stakeholders could distinguish 'Principle-oriented text' from 'Information oriented text' in a single statement whereas 67% could do it in paragraph. 'Information oriented text' could be picked by 90% stakeholders on the basis of 'Principle-oriented text' on Genetics and 92% could create 'Principle oriented text' on the basis of given 'Information oriented text'. Most of the stakeholders (92%) could create 'Principle-oriented text' or 'Information-oriented text' from a given 'Principle oriented illustrations' on Genetics and 83% could create the same from a given paragraph.*

Conclusion: *This study has produced a basic profile of the 'Principle and Information-oriented' issue in teaching-learning genetics. This result will provide baseline understanding on which further studies can be designed.*

Key Words: *Principle, Information, Text, Illustration, Stakeholder.*

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Introduction

Genetics is the branch of science concerned with genes, heredity, and variation in living organisms. Genetic disorders differ from other areas of medicine in that it so often involves families, rather than only individuals. The patients are often healthy, but concerned about the risk of developing or transmitting a disorder.[1]

According to Skirton et al[2] as the effect of gene variation on the complex or common diseases increases, so knowledge of Genetics is needed by health professionals to practice. Erickson[3] pointed out, 'At times, teachers express a concern over the tension between a heavy curriculum load and the time to teach for deeper conceptual understanding and the transfer of knowledge'. We must have to go through an acceptable and easy way to make it understandable because students are more likely to enjoy learning when they are able to be successful; they are more likely to be successful if they are learning in a way that is natural to them. Brady[4] stated 'what students need is a "master" organizer-a mental filing system or map they understand-that displays the general layout of the mind and its system for integrating knowledge'. Today's challenge for medical educators is to provide continuing education that supports excellence in clinical practice while finding new approaches to make learning more stimulating, motivating, and entertaining[5]. Here, a way that can be helpful for learning Genetics is "generalisation" which means taking one or a few facts and making a broader, more universal statement. In this research the concept considered for generalisation is termed as "principle" and the fields to which it is applicable are termed as "information". When student learns to analyse information they are able to gain a deeper understanding of ideas. Brain research has shown that information in our brain is organised in schematic structures.[6] These structures are made up of interconnected bits of information and serve as a framework for the knowledge we require. When a learner's knowledge is connected it is much more likely that they will apply the prior knowledge to a wide variety of new situations. They will acquire new information in a way that is more accessible and will be better able to relate it to previously acquired knowledge.

Materials and Methods

This was a cross-sectional, descriptive type of study with qualitative and quantitative data. Here, a questionnaire-based survey was administered among stakeholders of Genetics. This questionnaire-based survey was designed to assess the opinion, experience of Bangladeshi stakeholders regarding 'Principle-oriented' and 'Information-oriented' approaches in teaching-learning and assessment of Genetics as well as to analyze how the concepts of these approaches work in the understanding of students in terms of their performance in dealing with 'Principle-oriented' and 'Information-oriented' texts and illustrations. Bangladeshi stakeholders of Genetics (anatomists, educationists, geneticists, clinicians and residents of MS Anatomy Residency Programme of BSMMU) were selected from institutions situated in Dhaka. The stakeholders available over the phone were invited to participate in a survey on 'Principle-oriented and Information-oriented approach towards Genetics' and 45 were committed to come, ultimately 27 came to participate in the survey and 3 were approached at home. So, a total of 30 (thirty) stakeholders were approached. Here, purposive (judgment) sampling was done. The questionnaire had three sections. Section-A asked for personal professional information of the participants. Section-B enquired about their feelings, experience and opinion regarding 'Principle-oriented' and 'Information-oriented' approaches towards teaching-learning and assessment of Genetics. Section-C involved an exercise to assess the performance of the participants to deal with different aspects of 'Principle-oriented' and 'Information-oriented' approaches in teaching-learning Genetics. The selected portions of the chapters dealing with Genetics in two textbooks were covered in constructing the questionnaire. However, both direct and modified texts and illustrations were used to construct both text-based and illustration-based questions. The participants were gathered in the Seminar Room of the Faculty of Basic Science and Para clinical Science, Block-B, 4th floor, BSMMU. Before the survey, instructions to the participating stakeholders were provided through a PowerPoint presentation by the researcher. The instructions were also supplemented with a printed copy of those. The whole session was conducted in the form of workshop which lasted for five hours.

Result

This section describes the results of the survey. Table 1 shows the status of the participating stakeholders. They were with the designations of Professor, Associate Professor, Assistant Professor and Resident from professional fields of Anatomy, Biotechnology and Genetic Engineering, Biochemistry and Molecular Biology, Medical

Education and Clinical discipline with the educational qualifications of MPhil, MS, MMEd, PhD and MBBS.

Table 2 presents about prior exposure and opinion of stakeholders in the survey to the 'Principle-Information' issue. Here, about 74% of the participants either clearly understood (37%) or somewhat understood (37%) the issue of 'Principle' and 'Information' before participating in the survey. Table 3 reveals the comments of the stakeholders of the survey regarding different aspects of 'Principle-oriented' and 'Information-oriented' approaches. Majority (70%) participants agreed and 24% tended to agree that genetics can interrelate 'Information' from different aspects of basic genetics and thus memorising/understanding every information is strengthened from different perspectives. The respondents either agreed (73%) or tended to agree (24%) that while teaching-learning Genetics one should develop the habit of emphasising 'Principles'. About 70% participants thought that, in our country the practice of using 'Principles' in explaining genetic 'Information' is generally either rare (30%) or is not frequent (40%). Majority of the participants (86%) either agreed (63%) or tended to agree (23%) that incorporation of 'Principles' in teaching-learning Genetics is not a passive process, and it has to be addressed with specially premeditated attention. Most of the participants (93%) either felt that in Genetics textbooks, differentiation between 'Principle-oriented texts' and 'Information-oriented texts' is 'very difficult' (23%) or is 'difficult' (70%). Similar were their feeling about differentiating illustrations dealing with one or more 'Principle' from illustrations dealing with only 'Information'. In this case 23% considered it as very difficult while 67% found it 'difficult'. The majority (70%) of the participants agreed and 23% tended to agree that 'Principle-oriented approach' can be used categorically in some parts of assessment of medical students. Table 4 presents the comments of the stakeholders regarding training on incorporation of 'Principles' in teaching Genetics. Most of the participants (83%) believed that most stakeholders of our country would require organized training for successful incorporation of 'Principles' in teaching-learning Genetics. Moreover, almost all of them either agreed (77%) or tended to agree (20%) that most Bangladeshi stakeholders would be interested in attending short training sessions on incorporation of 'Principles' in teaching-learning Genetics. All of the participants seemed to be happy to attend short training sessions on the incorporation of 'Principles' in teaching-learning Genetics (93% agreed and 7% tended to agree). Table 5 reveals the performance of the stakeholders in distinguishing 'Principle-oriented texts' from 'Information-oriented text' in collections of texts on Genetics. Here, 77% participants could distinguish those in single statement and 67% in paragraph and 87% could distinguish those in illustration based single statement. Table 6 reveals the performance of stakeholders in picking 'Information-oriented text' on the basis of given 'Principle-oriented text' on Genetics and here 90% participants has picked. Table 7 shows the performance of the stakeholders in creating 'Principle-oriented text' on the basis of given 'Information-oriented text' on Genetics and here 93% could create. Table 8 presents the performance of the stakeholders in creating 'Principle-oriented text' or 'Information-oriented text' on the basis of principle oriented illustrations on Genetics and here 87% could create. Table 9 presents the performance of the stakeholders in creating 'Principle-oriented text' on the basis of a paragraph and here 83% could create.

Table 1. Information on different aspects of the stakeholders participating in the survey (N=30)

Status of stakeholders	No. of participants
Educational qualification	
MPhil	10
MS	7
MMEd	2
PhD	2
MBBS	9
Designation	
Professor	5
Associate Professor	6
Assistant Professor	14
Resident	5
Professional field	
Anatomy	15
Biotechnology and Genetic Engineering	3
Biochemistry and Molecular Biology	4
Medical Education	4
Clinical discipline	4

Table 2. Prior exposure and opinion of stakeholders to the Principle-Information issue (N=30)

Statement	Frequency of opinion (response) regarding the statement				
	Completely unknown to me No.(%)	Somewhat known to me No.(%)	Somewhat understood by me No.(%)	Clearly understood by me No. (%)	(Undecided) No.(%)
Before this survey, the issue of 'Principle' and 'Information' was	3 (10%)	5 (17%)	11 (37%)	11 (37%)	0 (0%)

Table 3. Comments of the stakeholders regarding different aspects of 'Principle-oriented' and 'Information-oriented' approaches (N=30)

Statement	Frequency of opinion (response) regarding each statement				
	Disagree	Tend to disagree	Tend to agree	Agree	(Undecided)
A 'Principle' can interrelate 'Information' from the different aspect of Genetics. Thus memorizing / understanding of every information is strengthened from different perspectives.	1 (3%)	0 (0%)	7 (24%)	21 (70%)*	1 (3%)
While teaching-learning Genetics one should develop the habit of emphasizing 'Principle'	0 (0%)	0 (0%)	7 (24%)	22 (73%)*	1 (3%)
In our country, the practice of using 'Principle' in explaining genetic 'Information'	Rare 9 (30%)	Infrequent 12 (40%)	Frequent 6 (20%)	Very frequent 0 (0%)	(Undecided) 3 (10%)
Incorporation of genetic 'Principles' in teaching/learning is not a passive process; it has to be addressed with specially premeditated attentions.	Disagree 1 (3%)	Tend to disagree 0 (0%)	Tend to agree 7 (23%)	Agree 19 (63%)	(Undecided) 3 (10%)
In Genetics textbooks, differentiation between 'Principle-oriented texts' and 'Information-oriented texts'	Very difficult 7 (23%)	Difficult 21 (70%)	Easy 2 (7%)	Very easy 0 (0%)	(Undecided) 0 (0%)
In textbooks of Genetics, differentiation of illustrations (figures) dealing with one or more 'Principle' from illustrations dealing with only 'Information'	Very difficult 7 (23%)	Difficult 20 (67%)	Easy 0(0%)	Very easy 0 (0%)	(Undecided) 3 (10%)
It is also important to use 'Principle-oriented approach' categorically in some part of the assessment of medical students.	0 (0%)	0(0%)	7 (23%)	21 (70%)	2(7%)

Table 4. Comments of the stakeholders regarding training on incorporation of Principles in teaching Genetics (N=30)

Statement	Frequency of opinion (response) regarding each statement				
	Disagree	Tend to disagree	Tend to agree	Agree	(Undecided)
Most of the stakeholders of our country would require organised training for successful incorporation of 'Principles' in teaching genetics	0 (0%)	0 (0%)	3 (10%)	25 (83%)	2 (7%)
Most of the stakeholders of our country would be interested in attending short training sessions on incorporation of 'Principles' in teaching-learning genetics	1 (3%)	0 (0%)	6 (20%)	23 (77%)	0 (0%)
The participants would be happy to attend a short training session on incorporation of "Principles" in teaching-learning genetics	0 (0%)	0 (0%)	2 (7%)	28 (93%)	0 (0%)

Table 5. Performance of the stakeholders in distinguishing 'Principle-oriented text' from 'Information-oriented text' in collections of texts on Genetics (N=30)

Given material	No. of questions	Range of score	Mean±SD (%)†	No. of stakeholders	Percent
'Text-based question' of questionnaire					
-Single-statement	40	24-37	30.53±3.09	23	76.7
-Paragraph (1 paragraph containing 10 sentences)	1	4-10	6.70±1.55	20	66.7
'Illustration-based question' of questionnaire					
-Single-statement (each question containing 3 illustrations and each illustration having one statement)	3	5-9	7.90±0.99	26	86.7

Table 6. Performance of stakeholders in picking 'Information-oriented text' on the basis of given 'Principle-oriented text' on Genetics (N=30)

Given material	No. of questions	Range of score	Mean±SD (%)†	No. of stakeholders	Percent
Picking information oriented text on the basis of Principle-oriented text: One 'Principle-oriented text' and four 'Information-oriented text' per question	3	3-6	5.43±0.81	27	90.0

Table 7. Performance of the stakeholders in creating 'Principle-oriented text' on the basis of given 'Information-oriented text' on Genetics (N=30)

Given material	No. of questions	Range of score	Mean±SD (%)†	No. of stakeholders	Percent
Creating 'Principle-oriented text' on the basis of Information-oriented text.	4	2-4	3.70±0.74	28	93.3

Table 8. Performance of the stakeholders in creating 'Principle-oriented text' or 'Information-oriented text' on the basis of given 'illustrations having Principle-oriented aspects' on Genetics (N=30)

Given material	No. of questions	Range of score	Mean±SD (%)†	No. of stakeholders	Percent
Creating 'Principle-oriented text' or 'Information-oriented text' from 'Principle-oriented illustration'	2	03	2.63±0.85	26	86.7

Table 9. Performance of the stakeholders in creating 'Principle-oriented text' or 'Information orientated text' on the basis of given paragraph on Genetics (N=30)

Given material	No. of questions	Range of score	Mean±SD (%)†	No. of stakeholders	Percent
Creating 'Principle-oriented text' or 'Information-oriented text' from Paragraph	2	06	5.03±1.51	25	83.3

Discussion

It is encouraging to assume from the survey results that the stakeholders of Bangladesh are interested in the 'Principle-oriented approach' in teaching-learning Genetics. The participants of the survey either agreed (73%) or tended to agree (24%) that one should develop the habit of emphasizing 'Principles' while teaching-learning Genetics.

Millar et al[7] indicate that information and the skill of managing information are always important in understanding complex subjects. However, most of the participants also felt that the practice of using 'Principles' in explaining genetic 'information' is either rare (30%) or not frequent (40%). McCoy and Kellerlin-Geller[8] mentioned that teachers' goal is to increase student comprehension and retention through instructional modifications rather than tolerating the loss of instructional time. More than 80% of the participants in the survey either agreed (63%) or tended to agree (23%) that incorporation of genetic 'Principles' in teaching needs a premeditated attention. 'Overt identification of concepts and their characteristics and the deliberate use of graphic organizers reduce the reading comprehension demands placed on students with low abilities'.[8] According to the others -classroom teachers must take responsibilities for identifying concepts within the curriculum, 'an explicit and overt act'.[7, 8] The majority of the participants felt that in Genetics textbooks, differentiation between 'Principle-oriented texts' and 'Information-oriented texts' is either 'very difficult' (23%) or 'difficult' (70%). Research by McCoy and Kellerlin-Geller[8] indicates that only high achieving students ever arrive at a full understanding of the underlying concepts and principles from the content presented in texts. This shortcoming among textbooks leaves the responsibilities for drawing these connections to either the teacher or the students themselves. It is also encouraging that more than 90% of the participants agreed for a categorical 'Principle-oriented approach' in assessment. Majority (93%) of the participants agreed about the requirement of training for successful incorporation of 'Principles' in teaching Genetics. The process of learning how to address the concepts is as important as the concept themselves. Learning how to learn and using understanding to explain and make connections are more useful long-term lessons than is memorization.[5] Almost all (98%) of the participants either agreed or tended to agree to undergo such trainings. Finally, majority of the stakeholders scored positively in identifying 'Principle' and 'Information' oriented texts and illustrations. Similarly, they also performed positively, in creation of 'Principle-oriented' and 'Information-oriented' texts on the basis of given 'Information and Principle oriented' illustrations and paragraph.

Conclusion

From the result of this study it can be concluded that the stakeholders of this country are in favour of emphasizing 'Principles' in teaching Genetics and incorporation of 'Principle and Information oriented' approach in teaching as well as assessing students about Genetics.

This study has produced a basic profile of the 'Principle-Information' issue in the teaching-learning and assessment of Genetics in regards to opinion, experience and performance of stakeholders.

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Prescribing pattern of Antihypertensive Drugs for Adults and their Comorbidities at Medicine and Cardiology Outpatient Department of a Teaching Hospital in Bangladesh

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Abstract

Introduction: *Hypertension is a major health problem and the most common cardiovascular disease. Drugs play an important role in protecting, maintaining and restoring health of hypertensive patients. The purpose of treating hypertension is to prevent complications and to improve patient survival. Accordingly, appropriate drug therapy is very important for patients.*

Materials and methods: *This retrospective observational study was carried out in outpatient department of medicine and cardiology units in a teaching hospital from May to October 2017. Their prescriptions were collected and assessed. The studied patients were 238, all were adult hypertensive of different age and sex with or without co-morbidity and treated with at least one antihypertensive drug. Data were tabulated manually according to key variables and analyzed in a computer.*

Results: *Total 238 hypertensive patients of both sex with different co-morbidities were included in this study. Out of 238 patients 129 (54%) received monotherapy and 109 (46%) received combined therapy. The agent most commonly used in monotherapy was angiotensin receptor blocker (ARB) (52%) then beta blocker (BB) (21%), calcium channel blocker (CCB) (19%), angiotensin converting enzyme inhibitor (ACEI) (5%) and diuretics (0.8%). The combination therapy comprises 2 drugs (33%) and three drugs (13%). In double therapy ARB+ CCB was the most common combination followed by beta blocker with ARB, CCB with beta blocker and beta blocker with ACEI. In triple therapy CCB+ARB+beta blocker and CCB+beta blocker+diuretics were used.*

Conclusion: *From the finding of this study it can be concluded that monotherapy is preferred than combination for treating hypertension in adults. Combination therapy is common with co-morbidity.*

Key words: *prescribing pattern, hypertension, drugs, co-morbidities.*

(MH Samorita Med Coll J 2018; 1(2): 50-54)

Introduction

High blood pressure is a major health problem and the most common cardiovascular disease throughout the world. It results in high morbidity and mortality in world population.[1,2] Worldwide, the prevalence of hypertension has been estimated to be as much as 1 billion individuals and approximately 7.1 million deaths per year may be attributable to hypertension.[3]

In the Non Communicable Disease (NCD) risk factor survey conducted in Bangladesh in 2010, the overall prevalence of hypertension was estimated to be 17.9% for the whole country (19.9% in urban and 15.9% in rural areas) among the population aged 25 years and above. [4] The various reason for hypertension are socio-economic, behavioral, sedentary life style, nutritional and poor health maintenance.[5,6] The poor control of hypertension leads to further progression of cardiovascular complications like ischemic heart disease, heart failure, stroke and chronic renal insufficiency with shortened expectancy of life.[7] In this context, the use

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of established antihypertensives assume paramount importance.[7]

Drugs play an important role in protecting, maintaining and restoring health. [8] A prescription-based survey is considered to be one of the most effective methods to assess and evaluate the prescribing attitude of physicians. [9] A large number of antihypertensive drugs alone or in various combinations are available and physicians need to choose the most appropriate drug for a particular patient. The standard treatment guidelines and drug utilization studies at regular intervals help physicians to prescribe drugs rationally.

Antihypertensive drugs belonging to different classes are available such as angiotensin converting enzyme inhibitors (ACEI), beta blockers (BB), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), diuretics, alpha-adrenergic blockers and central sympatholytics. Choice of drugs for particular patient changes at short intervals because of factors like efficacy, side effects, cost and development of newer drugs. Recommendations of various expert groups regarding the choice of drugs are available as treatment guidelines to reduce practice variability, cost and improve rational pharmacotherapy.[10] Implementation of these guidelines has been shown to be effective in raising the quality of antihypertensive therapy. [10]

The purpose of treating hypertension is to prevent complications and to improve patient survival and the selection of antihypertensives should be based on safety, efficacy and freedom of adverse effects. Accordingly, appropriate drug therapy can ensure immense therapeutic benefit in patients with essential hypertension with least adverse effects. [7]

The study of prescription pattern reflects the physicians' attitude towards the disease and role of drugs in its treatment and their therapeutic knowledge.[11] Moreover, it also helps in monitoring evaluation and necessary modification in prescribing practices to achieve a better medical care. [6]

The study of prescribing pattern in fact a part of medical audit involving monitoring and evaluation of various prescription of medical practitioners to ensure rationality in medical care.[7] Therefore, this study was performed to evaluate the pattern, extent and frequency of antihypertensive drugs used in the treatment of hypertension in adults.

Materials and Methods

It was a retrospective observational study of six months duration undertaken in outpatient department (OPD) of medicine and cardiology units of MH Samorita Hospital and Medical College. Duration of study was 6 months from May'2017 to October '2017. Before data collection permission was taken from the Institutional head. The studied patients were 238 in number, all were adult hypertensive of different age and sex visiting OPD and treated with at least one antihypertensive drug with or without co-morbidity. Data collected from prescription given to studied patients and outdoor medical officers and senior staff nurses who recorded everything about therapy of hypertensive patients. Parameters noted were 1) Sex of the studied patients, 2) Co-morbidities, 3) Types of therapy with or without co-morbidity, 4) Classes of drugs used in different types of therapy. Data analysis was done manually using PC (personal computer). Results are expressed as percentage and displayed in tables and figures.

Results

Total 238 hypertensive adults of both sexes with or without co morbidities were included in this study in which 121 (50.8%) were male and 117(49.2%) were female (figure 1). Among them 79 patients (33%) had no co-morbidity and 159 patients (67%) had co-morbidities like diabetes in 72 (45%), coronary artery disease in 40 (25%), bronchial asthma in 09 (06%) and 38 (24%) patients had other co-morbidities including chronic kidney disease, hyperthyroidism, benign enlarged prostate etc. (Figure 2).

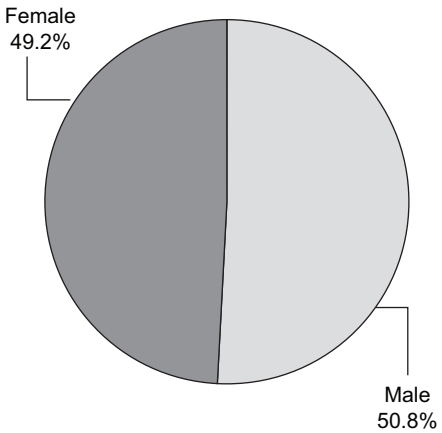

Fig. 1: *Pie chart showing distribution of patient's sex (N=238)*

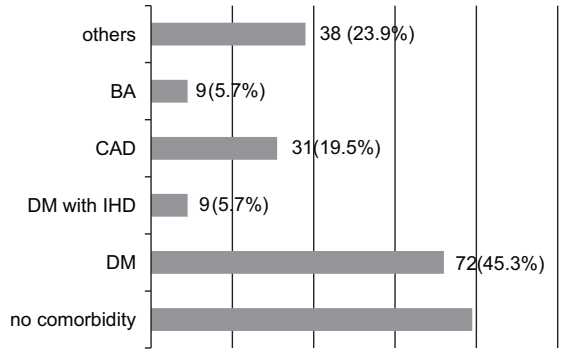

Fig. 2: *Co-morbidity with hypertension in studied patients (N=159)*

(BA=bronchial asthma, CAD=coronary artery disease, DM=diabetes mellitus, IHD=ischemic heart disease, others= chronic kidney disease, hyperthyroidism, benign enlarged prostate)

Monotherapy was given in 129(54.2%) patients, 79 (33%) patients received double and 30 (12.6%) received triple therapy (Table 1). Considering co-morbidity with type of therapy 62 (48%) patients having monotherapy had co-morbidity and the rest 67(52%) had no co-morbidity. But in case of double therapy 68 (86%) patients had co-morbidity. In triple therapy 97% patients had co-morbidity.

Regarding the use of monotherapy, angiotensin receptor blocker (ARB) was most commonly used drugs (52.7%) followed by beta blocker (BB) (21.7%), then calcium channel blocker (CCB) (19.4%). Use of angiotensin converting enzyme inhibitor (ACEI) was 5.4% and diuretics was 0.8% (Table 2).

In double therapy CCB+ARB were the most commonly prescribed drugs (33%) followed by BB+ARB (29%) then CCB+BB and BB+ACEI comprising 25% and 12.6% respectively (Table 3). In triple drug therapy CCB+ARB+BB were mostly prescribed drugs, comprising 73% followed by CCB+BB +diuretics which was 26.7% (Table 4).

Table 1. Types of therapy used for hypertension in studied patients with and without co-morbidity (N=238).

Types of therapy	Hypertension without co-morbidity 79 (33%)	Hypertension with co-morbidity 159 (67%)	Total
Monotherapy	67 (52%)	62 (48%)	129 (54.2%)
Double therapy	11 (14%)	68 (86%)	79 (33.2%)
Triple therapy	01 (3%)	29 (97%)	30 (12.6%)

Table 2. Different classes of drugs used in studied patients as monotherapy (N=129)

Class of drugs	Number	Percent
Angiotensin receptor blocker (ARB)	68	52.7
Beta blocker (BB)	28	21.7
Calcium channel blocker (CCB)	25	19.4
Angiotensin converting enzyme inhibitor (ACEI)	07	5.4
Diuretics	01	0.8

Table 3. Different classes of drugs used in studied patients as double therapy (N=79)

Class of drugs	Number	Percent
Calcium channel blocker (CCB) + Beta blocker (BB)	20	25
Calcium channel blocker (CCB) + Angiotensin receptor blocker (ARB)	26	33
Angiotensin receptor blocker (ARB) + Beta blocker (BB)	23	29
Angiotensin converting enzyme inhibitor (ACEI) + Beta blocker (BB)	10	12.6

Table 4. Different classes of drugs used for studied patients as triple therapy (N=30)

Class of drugs	Number	Percent
Calcium channel blocker (CCB) + Angiotensin receptor blocker (ARB) + Beta blocker (BB)	22	73.3
Calcium channel blocker (CCB) + Beta blocker (BB) + diuretics	08	26.7

Discussion

Hypertension (HTN) is an increasingly important medical and public health problem.[5] A prescription based survey is considered to be one of the most effective methods to assess and evaluate the prescribing attitude of physician and dispensing practice of pharmacist.[10] In the present study hypertensive patients were categorized based on type of drug therapy using different classes of drugs along with various common co-morbidities.

In this study, hypertension was more common among male than in female and same observation was found by Konwar et al.[12] Regarding co-morbidity DM was the commonest (45.3%) and it was supported by Preethi et al.[13] In the present study monotherapy was prescribed more (54%) than combination therapy (46%) which was also observed by Konwar and Rajasekhar et al.[12,14] But in other studies Kale et al [7] and Tiwari et al [15] found combination therapy is more commonly prescribed antihypertensive than monotherapy.

In this study, among the monotherapy angiotensin receptor blocker (ARB) was the most commonly prescribed drug for hypertensive patients comprising 52.8% followed by beta blocker, CCB and ACEIs. This finding is not related to others where Rajasekhar et al[14] Tiwari et al [15], Konwar et al[12] and Kale et al[7] found that CCB is the most commonly prescribed drug as monotherapy. It may be due to less adverse effects caused by CCB. Probably because of less cost ARB was prescribed in this study.

Among double therapy, the present study reveals that ARB + CCB was the most commonly prescribed double therapy followed by ARB+BB, BB+CCB and BB+ACEI in descending order. Regarding double therapy Rajasekhar et al [14] found ARB+CCB followed by BB+CCB which is consistent with the present study. In another study by Kale et al [7] diuretics +ARB was the most commonly prescribed combination. Konwar et al [12] found CCB+diuretics and Tiwari et al[15] found BB+CCB as most frequently used combination antihypertensives. Rate of co-morbidities were very high (86%) among the patients with double therapy.

Among triple therapy the most common combination was CCB+ARB+BB then CCB+BB+diuretics. Triple therapy were mostly used with patients having comorbidity (97%) and this observation are supported by others.[14,15]

Conclusion

From the result of the present study it can be concluded that monotherapy is commonly prescribed antihypertensive drug in adults. Angiotensin Receptor Blocker (ARB) is the commonest prescribed antihypertensive in both mono and combination therapy. Among combination therapy ARB+CCB and ARB+CCB+BB are most commonly prescribed double and triple therapy respectively. Large scale studies are recommended to give additional insight into prescribing pattern of antihypertensive in adults.

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Morphometric Study of Length and Breadth of Dorsal Articular facet of Fully Ossified Dry Human Left Calcaneus

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Abstract

Introduction: *The calcaneus is a weight bearing tarsal bone. It belongs to proximal row and form the posterior pillar of two longitudinal arches of foot. In the upper surface calcaneus forms talocalcaneal joint with talus which maintains eversion and inversion of foot and named as subtalar joint.*

Objectives:*The objective of this study was to determine the morphometry of length and breadth of dorsal articular facet from various anatomical landmarks of fully ossified dry human left calcaneus.*

Materials and methods: *A cross sectional study was done on one hundred and fifty five(155) fully ossified dry Bangladeshi human left calcaneus at the Department of Anatomy, Sir Salimullah Medical College, Dhaka, Bangladesh from January 2014 to June 2015. Morphometric measurement of calcanei was done on studied bones. Data was analysed manually using a personal computer and unpaired students 't' test was used for statistical significance.*

Results: *The mean (±SD) value of length and breadth of dorsal articular facet of calcaneus were greater in male than in female which was statistically significant ($p<0.01$).*

Conclusion: *From the result of the present study it can be concluded that the mean (±SD) value of length and breadth of dorsal articular facet of calcaneus is greater in male than that in female.*

Key words: *Dorsal articular facet, morphometry.*

(MH Samorita Med Coll J 2018; 1(2): 55-58)

Introduction

Calcaneus, the heel bone, is the largest of the tarsal bones. It articulates with the talus above and cuboid in front[1]. It is a rectangular block of bone characterized by sustenticulum tali, a shelf that projects from the upper border of its medial surface[2].

Calcaneus has six surfaces i.e. dorsal, plantar, lateral, medial, anterior, and posterior[3]. Its smooth anterior articular end contrast with its larger, rough posterior aspect. The dorsal surface bears centrally a large articular facet. The plantar surface is rough, the lateral surface is flat, the medial surface is hollowed.[4]

Since calcaneus bone is located at the rear portion of foot, it is most vital in bearing weight of body. Approximately 50% of body weight is distributed through subtalar joint to calcaneus, with remaining 50% transmitted across metatarsal heads. Calcaneus supports leg and helps in easy walking and standing. Functions like rotating and bending foot are possible on calcaneus.[5]

In the upper surface calcaneus forms talocalcaneal joint with talus. There are three facets over the upper side of talocalcaneal joint: anterior talar facet, middle and posterior. The middle third of the superior surface of calcaneus carries posterior talar facet for articulation with the body of talus.[6]

Importance of dorsal articular facet is the formation of talocalcaneal joint which maintains eversion and inversion of foot and named as subtalar joint. The subtalar joint has three important functions: helping walking, pivoting our body on our feet, shock

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absorption as our feet hit the ground. Problems associated with subtalar joint are arthritis, flat foot, cavus foot, tarsal coalition.[7] Knowledge of talar facets of calcaneum is essential for orthopaedic surgeons who perform 'Lengthening-distraction wedge calcaneal osteotomy and interposition bone graft' to correct deformities in pes planus.[8]

No citable published research works on calcaneus in our country has been found. So, further work on calcaneus is needed. We need our own standard baseline data. Morphometric measurements of length and breadth of dorsal articular facet of calcaneus that form the subtalar joint will be helpful data for comparing with male and female calcaneus that will make a guideline for anatomists, anthropologists, forensic scientists, sports medicine physicians, orthopaedic, plastic surgeons and radiologists.[6]

Materials and methods

It was a cross sectional study conducted from January 2014 to June 2015. One hundred and fifty five (155) dry left sided adult human calcaneus were collected from medical students of Sir Salimullah Medical College (SSMC), Dhaka and Dhaka National Medical College.

Though calcaneus is an irregular bone, length and breadth of dorsal articular facet of calcaneus bone was measured with the help of flexible metalic wire and then the straight measurements of that values were considered.

For the measurement of length of dorsal articular facet (DAFL) of calcaneus one dot was given on anterior most point of posterior articular facet of calcaneus and another dot was given on posterior most point of posterior articular facet of calcaneus. The distance between two dots was measured with flexible metallic wire which is represented by DAFL[9]. Then the wire was straightened and measured with digital slide caliper. (Fig-1)

For the measurement of breadth of dorsal articular facet (DAFB) of calcaneus one dot was given on the lateral most point of posterior articular facet of calcaneus and another dot was given on the medial most point of posterior articular facet of calcaneus. The distance between two dots was measured with flexible metallic wire which is represented by DAFB[9]. Then the wire was straightened and measured with digital slide calipers (Fig-2). Data was analysed manually using a PC. Unpaired students 't' test was used to find out statistical significance.

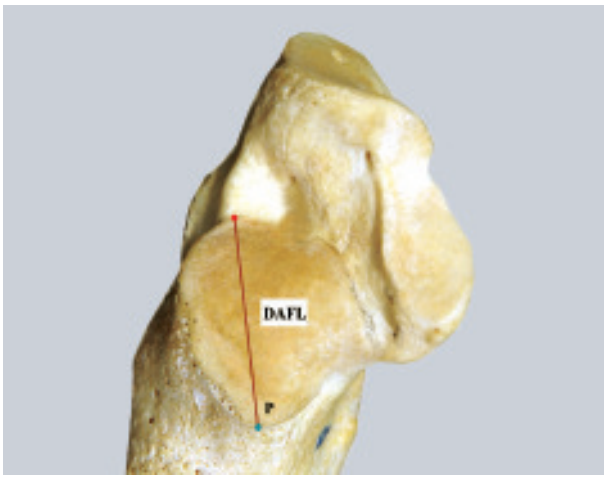

Fig. 1: *Studied calcaneus showing dorsal articular facet length measured by flexible metallic wire. P represents posterior articular facet.*

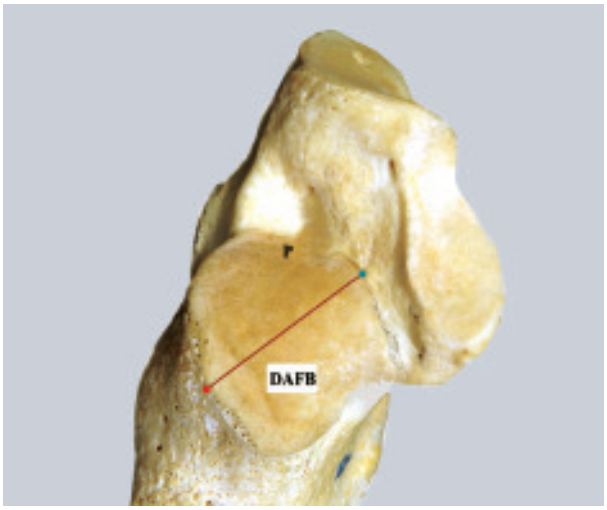

Fig. 2: *Studied calcaneus showing dorsal articular facet breadth measured by flexible metallic wire. P represents posterior articular facet.*

Ethical clearance

This study was carried out after approval of research protocol by Institutional Ethical Committee (IEC) of Sir Salimullah Medical College, Dhaka.

Results

The mean (±SD) dorsal articular facet length of left calcaneus was 30.92 ± 2.71 mm in male and 28.72 ± 2.90 mm in female. The dorsal articular facet length in male was significantly higher than that in female; $p<0.01$ (Table 1). The mean (±SD) dorsal articular facet breadth of left calcaneus was 21.32 (± 2.39) mm in male and 19.99 (± 2.43) mm in female. The breadth

of dorsal articular facet of left calcaneus in male was also significantly higher than that in female; p<0.01 (Table 2).

Table 1. Dorsal articular facet length of studied left calcaneus in male and female (N=155)

Sex	Dorsal articular facet length Mean ± SD in mm (Range in mm)
Male (n=80)	30.92 ± 2.71 (17.36-39.33)
Female (n=75)	28.72 ± 2.90 (21.33-35.89)
P value	0.000**

Table 2. Dorsal articular facet breadth of studied left calcaneus in male and female (N=155)

Sex	Dorsal articular facet Breadth Mean ± SD in mm (Range in mm)
Male (n=80)	21.32 ± 2.39 (16.34-26.11)
Female (n=75)	19.99 ± 2.43 (15.28-29.93)
P value	0.000**

Comparison between sex was done by unpaired Student's 't' test
**= P value < 0.01, significant at 1% level of significance (two tailed)
N= sample size

Discussion

In the present study mean (±SD) dorsal articular facet length and breadth were found greater in male than that in female and was statistically significant (p<0.01). Dorsal articular facet length of calcaneus of present study is consistent with Sakaue K[10] who carried out study on Japanese people. This study was performed on 143 calcanei of both sides. The mean (±SD) dorsal articular facet length was 29.3±2.1 mm in male and 26.0±1.5 mm in female. There was statistically significant difference (p=0.001) when compared between male and female. The values of present study also are in consistence with Kim D and others[9] who worked on 104 calcanei. They reported 26.3±2.4 mm in male and 23.9±2.4 mm in female of dorsal articular facet length of calcaneus. Statistically significant difference (p<0.05) was found when compared between male and female (male>female calcanei).

The values of present study was dissimilar to the findings reported by Ari I., Kafa IM,[11] who carried out study on Turkish people. This study was conducted in 2009 on 160 male calcanei and found dorsal articular facet length 21.4±1.45 which is dissimilar with present study. This dissimilarity might be due to different ethnic and racial variation.

The dorsal articular facet mean breadth of calcanei in the present study is consistent with Sakaue K[10] who carried out study on Japanese people. No conclusion could be inferred regarding this similarity. In that study the mean (±SD) dorsal articular facet breadth was 21.5±1.5 mm in male and 19.4±1.7 mm in female. There was statistically significant difference (p=0.001) when compared between male and female (male>female).

This study was dissimilar to the findings reported by Ari I and Kafa IM[11] on Turkish population which was conducted on 160 male calcanei. The dorsal articular facet breadth of calcanei was 15.6±.10 mm.

This study findings are also dissimilar to the findings of the study done by Intron F et al.[12] who worked on Italian people. They reported that dorsal articular facet breadth was 26.0±2.2 mm in male and 23.2±2.3 mm in female. These dissimilarities might be due to different ethnic and racial variation.

Conclusion

From the result of the present study it can be concluded that the mean (±SD) value of length and breadth of dorsal articular facet of calcanei are greater in male than that in female.

The present study was an attempt to construct data on length and breadth of dorsal articular facet of left sided human calcanei which will serve as a reference value in the field of anatomy, diagnostic procedures and planning treatment in orthopaedic surgery.

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Relationship between Specific HLA-DRB1*03 allele with Acute and Chronic Hepatitis B virus Infection, in a Tertiary Care Hospital in Bangladesh

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Abstract

Introduction: *Host gene variants may influence the natural history of hepatitis B virus (HBV) infection. The human leukocyte antigen (HLA) system, the major histocompatibility complex (MHC) in humans, is one of the most important host factors that are correlated with the clinical course of HBV infection.* ***Objective:*** *To assess the rigorous relationship between specific DRB1*03 allele of HLA gene with outcome of acute and chronic hepatitis B virus (HBV) infected Bangladeshi patients.*

Method: *This cross sectional study was carried out in the Department of Virology, Bangabandhu Sheikh Mujib Medical University (BSMMU) during the period of July 2012 to June 2013. Evaluation of HLA DRB1*03 allele distribution among 30 acute hepatitis B infected (HBV) patients was compared with 30 chronic hepatitis B infected (HBV) Bangladeshi patients. HLA DRB1*03 allele distribution was detected by conventional PCR followed by agarose gel electrophoresis. HLA DRB1*03 allele was defined molecularly using commercial low-resolution DRB1*allele polymerase chain reaction sequence specific priming kit.*

Result: *A total of 60 serologically pre-diagnosed patients with male female ratio 1:1, including 30 acute hepatitis B and 30 chronic hepatitis B infected (HBV) Bangladeshi patients were evaluated. The study revealed that HLA DRB1*03 allele among chronic hepatitis B infected patients was 3 times more frequent compared to acute hepatitis B (30% vs 10%; RR=2.99, X^2 test=4.5; P< 0.05).*

Conclusion: *The present study reveals that HLA DRB1*03 allele is more frequent in chronic hepatitis B infected patients compared to acute hepatitis B infected patients in Bangladesh. These results suggest that HLA genes could affect susceptibility and clearance of HBV infection in Bangladeshi patients.*

Keywords: *Chronic hepatitis B infection; HLA, DRB1*allele; Agarose Gel Electrophoresis; PCR, ALT.*

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Introduction

Hepatitis B infection is an inflammatory illness of the liver caused by hepatitis B virus (HBV). It is a potentially severe disease accounting for over 400 million chronic HBV patients and nearly 1.2 million deaths every year.[1] Even though 2–10% of HBV-infected individuals develop chronic complications, the clinical outcomes vary, with 15–40% chronic HBV patients are at higher risk of developing cirrhosis of liver and hepatocellular carcinoma (HCC) during their lifetime.[2] Age at the time of infection is the best determinant of chronicity. Up to 90% of infants of highly infectious HBsAg and HBeAg positive mothers become chronic HBV carriers as compared with approximately 30% of children infected after the neonatal period but before the age of 5 years.[3,4] By contrast, only 1–5% of adults become chronically infected after clinically overt acute hepatitis. Most carriers infected at birth or in the first few years of life present with HBeAg positive chronic hepatitis with normal ALT and this clinical condition is likely to be maintained up to adulthood by a proportion of the patients.[5-7] Many of these patients enter the immunoactive phase and develop HBeAg positive

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chronic hepatitis with elevated ALT levels only after 10–30 years of infection[7]. By contrast, patients who acquire HBV infection in the late childhood, during adolescence or adulthood and become chronic carriers usually present in the immunoactive phase with active liver disease.[8] The age of adult patients at the time of initial presentation with HBeAg positive chronic hepatitis B is between 24 and 36 years.[8] Acute HBV infection is generally subclinical and anicteric in neonates and children.[8] By contrast, in adults approx. 30–50% develop icteric hepatitis[3]. Some determinants for HBeAg seroconversion have been reported, including sex, age, biochemical activity and more recently HBV genotypes. Older carriers and female are more likely to clear HBeAg.[9,10] Spontaneous HBeAg seroconversion within 1 year occurs in over 50% of patients with serum ALT levels greater than five times the upper limit of normal (ULN) as compared to 10% of those with ALT levels less than five times the ULN [11]. Frequently, acute exacerbation of hepatitis, reflecting immune mediated lysis of HBV infected hepatocytes, with ALT elevations greater than ten times the ULN and more than twice the baseline value and with HBV DNA levels rising before and falling during the flare, precede HBeAg to anti-HBe seroconversion and usually lasts for 2–4 months[12]. Although, the exact mechanism is not fully understood, the reason for this difference in response to HBV virus is believed to be attributed to a complex web of inter-related factors, such as host genetic,viral, and environmental factors.[13]Since the outcome of any infection depends mainly on the host immune response, a number of studies have investigated and reported that several variations in the human leukocyte antigens (HLAs) class I and class II genes are involved in HBV persistence or clearance.[14-16] HLAs belong to the major histocompatibility complex (MHC) genes that are located on chromosome 6p21. MHC class II molecules play an important role in the defense against infections and are involved in presenting antigen to $CD4^+$ T cells thereby augmenting antibody production and cytotoxic T cell activation[17]. Such molecules are encoded by three different loci namely HLA-DR, DQ, and DP. These genes are highly polymorphic; thus enabling them to present a wide range of antigens[18-20]. Although genetic variants in several human leukocyte antigen (HLA) loci have been shown to be associated with Chronic hepatitis B, none of the associations has been proved to be conclusive[21,22]. The mechanism of susceptibility to chronic persistent HBV infection is not well clarified. Since the outcome of HBV infection mainly depends on the host immune response and HLA is an integral component of the immune response, plays an important role in immunological reaction to HBV infection.[23] The highly polymorphic HLA gene has been considered as an appropriate for biological candidate for susceptibility gene that is associated with the development and the progression of chronic HBV infection. Indeed previous studies have highlighted that HLA-DR polymorphism influences individual immune responses thus affecting the outcome of diseases and that many different *HLA* alleles play a role in HBV infection however, this relationship between *HLA-DR* polymorphisms and HBV infection is not universal for all investigated populations.[23] As for Caucasians and Koreans *HLADRB1*1301-02* has been found to be associated with acute self-limited hepatitis B.[24-27] For Taiwanese people, *HLA-DRB1*0406* is associated with recovery from HBV infection in the Han Chinese, as is *HLA-DRB1*4001* in indigenous Taiwanese people.[17] Han Chinese with HLA-DR12 (especially one of its alleles, *DRB1*1201*) or HLA-*DRB1*1101/1104* are able to resist HBV infection, while those with *HLA-DR9*, *DQ9*, *HLA-DRB1*0301*, *HLA-DQB1*0301* and *DRB1*10* are susceptible to chronic HBV infection.[28-30]

Overall, the complicated natural history of hepatitis B infection makes it necessary to find clinical and genetic markers to help predict individuals at higher risk to develop chronic hepatitis B and worse outcomes such as cirrhosis of liver and hepatocellular carcinoma.The HLA system is an integral component of the host immune response. The highly polymorphic HLA genes are key factors in the activation of the immune response against HBV infection through their enormous capacity of attracting and binding viral peptides[28]. HLA gene variations are associated not only with susceptibility or resistance to hepatitis B infection but also with spontaneous HBV clearance, disease progression, efficacy of antiviral treatment and response to hepatitis B vaccines[28]. Furthermore, specific HLA allele variants may have different impact on clinical

outcomes of chronic HBV infections among different ethnic subjects[28]. However, there are no such study in Bangladesh yet. The aim of this study was to find out the relationship of specific HLA DRB1*03 allele with outcome of acute and chronic hepatitis B infected (HBV) Bangladeshi patients.

Materials and methods

This cross sectional study was carried out among hepatitis B infected adult patients attending the in-patient and out-patient departments of Hepatology and Gastroenterology of Bangabandhu Sheikh Mujib Medical University (BSMMU), a tertiary care hospital in Dhaka, Bangladesh. The study period was from July 2012 to June 2013. Participants were selected by non probability purposive sampling method from two different groups: 30 acute hepatitis B infected patients (HBsAg positive for <6 months, Anti HBcIgM positive and anti-HBsAg negative) and 30 chronic hepatitis B infected patients (HBsAg positive for >6 months, Anti HBc total positive Anti-HBcIgM negative and anti-HBsAg negative). A detailed evaluation of patients' history, identified clinical variables, disease severity, age at onset, initial clinical manifestations were recorded in pre-designed data collection sheets after taking informed written consent of studied patients. Blood samples were collected from selected patients for virological tests and HLA typing and all laboratory tests were performed at the Department of Virology, BSMMU.

Primer and reagents

For PCR reaction, the primer (forward and reverse) of the HLA DRB1*03 allele and ² actin gene (House keeping gene,forward and reverse) were selected as control (Table 1)

Detection of DRB1*03 allele

DNA extraction

All non-coagulated ethylene-diamine-tetraacetic acid blood samples were stored at -20^{0}C before DNA extraction.Genomic DNA was extracted from peripheral blood by using classical phenol/ chloroform DNA extraction method using Red Cell Lysis Buffer containing sucrose, Tris, Mgcl2,Triton x, Pk buffer, Pk solution etc[31]

DNA quantitation

DNA concentration was measured in ng/µl by Thermonanodrop Spectrophotometer (2000C) 260 nm wave length.

DNA amplification

Preparation of master mix: 13 µl reaction volume-containing :- 50 nanogram/microlite (ng/µl) of DNA, 0.1 microliter Taq polymerase, 1.25 microliter 10X PCR buffer, 0.25 microliter dNTPs, 0.5 microliter each primers (forward primer 0.5 microliter and reverse primer 0.5 microliter) of the HLA DRB1* allele and rest molecular grade water.

Polymerase chain reaction (PCR)

The thermal cycler programmed for 47 amplification cycles was performed consisting of initial denaturation at 94^{o}C for 4 minutes, then further denaturation at 94^{0}C for 45 seconds, annealing at 55^{o}C for 60 seconds, elongation at 72°C for 30 seconds and final extension at 72^{o}C for 5 minutes. After amplification amplicons were processed for gel documentation or kept at 4^0 C till tested (specific primers with low-resolution Single Specific Primer-Polymerase Chain Reaction (SSP-PCR) with NYSTECHNIK Semiquantitative PCR matchine,

Table 1: The following HLA DRB1*03 oligonucleotide primers and Beta actin House keeping gene were used

Oligonucleotide primer genes	Amplicon Size (bps)	Primer sequences of (5'-3') HLA DRB1* Allele
DRB1*03 (52)	151 bps	Forward- TACTTCCATAACCAGGAGGAGA
DRB1*03 (32)		Reverse- TGCAGTAGTTGTCCACCCG
Beta actin (52)	56 bps	Forward- CCAGCTCACCATGGATGATG
(House keeping gene)		Reverse- ATGCCGGAGCCGTTGTC
Beta actin (32)		

* (Genome Diagnostic Pvt.Ltd, India).

Genome Diagnostic Pvt.Ltd, India).Detection of PCR products by agarose gel electrophoresis The amplified PCR products were detected by agarose gel electrophoresis. For detection of DRB1*03 allele 3% agarose gel was used, for detection of ß actin (Housekeeping gene) 4% agarose gel was used. Agarose gel mixed with 100ml TBE (Tris, Boric acid, Ehylene-diaminetetraacetic acid) containing 6µl of ethidium bromide electrophoresed for170 Volt for 35 minutes. DNA bands were identified according to their molecular size by comparing with 100 bp DNA ladder. 100 bp DNA size standard (Bio-Rad, USA) was used as marker to measure the molecular size of the amplified products. Samples showing the presence of specific DNA band corresponding to 197 bps were considered positive for presence of HLA DRB1*03 allele and specific DNA band corresponding to 56bp band were considered positive band for presence of ß actin -gene used as house keeping gene. If the pooled DNA template result was negative following gel electrophoresis, the sample was considered negative for HLA DRB1* alllele. Only the presence of the amplified product with correct size was interpreted as a test positive. The DNA bands were visualized using Wealtec Dolphin view Gel Imaging System (Wealtec Bioscience Co, Ltd., USA).

All non-coagulated ethylene-diamine-tetraacetic acid blood samples were stored at -20^{0}C before DNA extraction.The genomic DNA was extracted using classical phenol/chloroform DNA extraction method, then DNA concentration was measured in ng/µl by Thermonanodrop Spectrophotometer (2000C) 260 nm wave length after that Low-resolution Single Specific Primer-Polymerase Chain Reaction (SSP-PCR) was performed with NYSTECHNIK Semiquantitative PCR matchine.The amplified PCR products were detected by agarose gel electrophoresis. If the pooled DNA template result was negative following gel electrophoresis, the sample was considered negative for HLA DRB1* gene. Hundred bp DNA size standard (Bio-Rad, USA) was used as marker to measure the molecular size of the amplified products. Only the presence of the amplified product with correct size was interpreted as a test positive. The DNA bands were visualized using Wealtec Dolphin view Gel Imaging System (Wealtec Bioscience Co, Ltd., USA).

Statistical Method Allele frequencies of HLA-DRB1*allele was calculated by direct count. Allele Frequency (AF) for the study group (Acute and Chronic hepatitis B) was compared using Chi-square test. Relative risk frequencies (RR) were calculated.

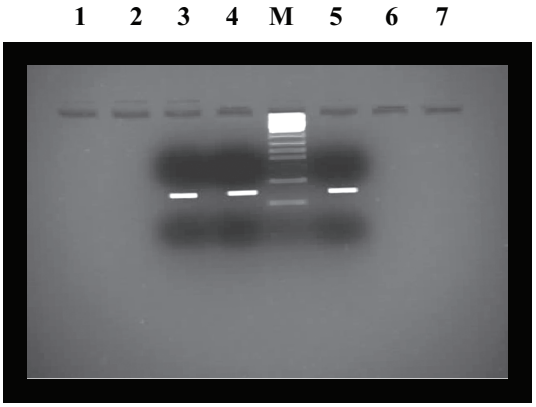

Fig. 1: *In agarose gel electrophoresis positive band of HLA DRB1*03 allele in acute hepatitis B infected patients.*

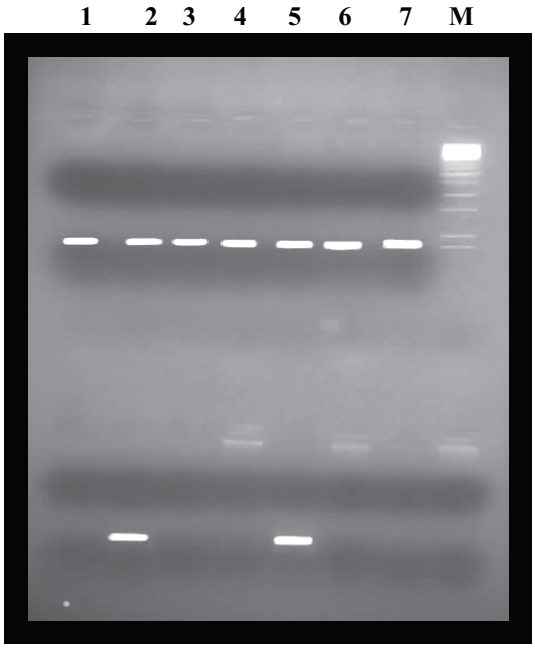

Fig. 2: *In agarose gel electrophoresis positive band of HLA DRB1*03 allele in chronic hepatitis B infected patients.*

Mann – Whitney U test was done. Statistical analysis was performed using SPSS 17.0 software, and p value < 0.05 considered as statistical significance.

Results

In this study, during one-year period, blood samples were collected from 30 acute hepatitis B and 30 chronic hepatitis B infected patients, age ranged from 18 to 55 years with (mean ± SD) 31.6 ± 8.84 year. The mean age of acute hepatitis B and Chronic hepatitis B were 32.9±10.06 and 28.7 ± 6.55 years respectively; male female ratio was 1:1 (Table 2). The mean ALT level of acute hepatitis B and Chronic hepatitis B were 227.26 ± 18.15 IU/L and 159.73 ± 25.15 IU/L respectively (Table 2) In Table 3, the

Table 2: Distribution of Clinical and Virological Characteristics of Studied Patients (N=60).

Variables	Acute hepatitis B n=30	Chronic hepatitis B n=30
Age (Years)mean ± SD	32.9 ± 10.06	28.7 ± 6.55
Sex (F:M)	15 : 15	15 : 15
ALT (IU/L)mean ± SD	227.26 ± 90.1	159.73 ± 46.8

Mann – Whitney U test was done for ALT. P< 0.05 indicates statistical significance.

Table 3: Distribution of HLA DRB1*03 Allele among studied Acute and Chronic hepatitis B (CHB) Patients (N=60).

Hepatits B Infection	HLA DRB1 *03 Genes	Relative Risk (RR) test	Chi - Square Test (X^2 test)	P value*
Acute Hepatits B Infection (n=30)	03 (10)	2.99	4.5	< 0.05
Chronic hepatits B Infection (n=30)	09 (30)			

Figures in the parenthesis indicate percentages. Relative Risk (RR) value 2.99, and Chi-Square value 4.5, P< 0.05.

comparison of HLA DRB1*03 genes between acute hepatits B and chronic hepatits B groups revealed that the risk of frequency of HLA DRB1*03 was three times higher (30%) in chronic hepatits B than in acute hepatits B (10%) which is statistically significant (RR=2.99; X^2 test= 4.5 P< 0.05).

Discussion

Perinatal infection or horizontal infection early in childhood are the main routes of hepatitis B transmission in high endemic areas such as South-East Asia, Africa, Pacific Islands whereas in low endemic regions, such as Western countries, hepatitis B is primarily a disease of adolescents and adults as a result of high risk sexual activity and injectable drug use.[8]

HBV infection is a dynamic process, and the outcome of HBV infection varies due to differences in host responses. Some people with chronic HBV infection remain asymptomatic even after many decades of infection with slow disease progression, whereas, others rapidly progress to cirrhosis and hepatocellular carcinoma. A strong genetic component like HLA gene expression seems to be a major driving force affecting the course of viral hepatitis.[32]

The factors that determine the outcome of chronic hepatitis B infection in individual patients are poorly understood. These may be classified into three categories, virological factors, immunological factors and host genetic factors.[33] Virological factors include viral load, viral genotype and mutations in the viral genome. The HLA genotype has been thought to be an important genetic factor for the predication of the susceptibility of individuals to hepatitis B infection and prognosis of disease in certain populations.[32,34] The association of individuals to hepatitis B infection and disease progression varies since multiple factors such as geography and ethnicity, affect this association.[35-38]

Most genetic studies involving hepatitis B virus susceptibility have focused on its correlations with HLA Class I and Class II. Different HLA Class II alleles are reported to be important in persistence or clearance of hepatitis B virus in various studies throughout the world[39,40]. In present study, the frequency of HLA DRB1*03 gene distribution was three times higher among chronic hepatitis B than acute hepatitis B (Chronic hepatitis B vs Acute hepatitis B, 30% vs 10%, RR=2.99; X^2 test= 4.5 P<0.05). Previous studies observed that HLA DRB1*03 was associated with persistant hepatitis B infection among Chinese and Caucasians[41-43] while in a study from Korea, HLA-DRB1*0301, HLADQA1*0501 and HLADQB1*0301 were closely correlated with susceptibility to chronic hepatitis B[44]. A study from India observed that HLA DRB1*03 was associated with self limited course of acute hepatitis B.[45] In study from China showed that HLA-DRB1*03 and HLA-DRB1*07 were related to susceptibility to chronic hepatitis B virus infection, and DRB1*15 was negatively related to persistence to chronic hepatitis B virus infection among people of Northwestern China.[42] In another study from China, found that

allele frequencies of HLA-DRB1*0301 among chronic hepatitis B group were markedly higher than the normal control group and there was a significant correlation between them.[41] In a study from North eastern Brazil, demonestrated that HLA-DRB1*08 and HLA-DRB1*09 alleles are more susceptible to intensification of hepatitis B infection[46].

Above mentioned data suggest that there is a complexity of genetic susceptibility to HBV infection. It may vary in different populations in different ethnic group in different countries. HLA DRB1* gene expression may be useful in understanding the molecular pathogenesis of different stages of viral hepatitis B in adults.

Conclusion

On the basis of result of the present study it can be concluded that HLA DRB1*03 is more frequent among chronic hepatitis B than in acute hepatitis B infected Bangladeshi patients. So, HLADRB1* 03 should be detected in patients of hepatitis B infection, specially the chronic one which may help the physician to plan further management of those patients. Large and carefully designed studies are necessary to determine the role of *HLA-DR* polymorphisms in the outcome of hepatitis B infection.

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Conflict of interest: We do not have any potential conflict of interest.

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Review Article

Chikungunya in Children: An Update

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Abstract

Chikungunya, caused by "Chikungunya virus,"(CHIKV) is an arbovirus disease transmitted by the bite of infected mosquitoes belonging to the genus Aedes*. Chikungunya fever epidemics have been reported from several countries around the world. Following the bite of an infected* Aedes *mosquito, CHIKV is injected into the dermis and locally targets connective tissue, epithelial cells and fibroblasts where viral replication takes place. In addition, during the viremic phase (≤5–7 days), circulating monocytes are responsible for dissemination into the bloodstream. Secondary infection sites include muscles and joints where fibroblasts are the main target cells. The rate of asymptomatic infection among children varies from 35 to 40% (according to different outbreak reports). The incubation period ranges from 3 to 12 days (usually 3-7 days). Children may have a different clinical presentation than adults. Chikungunya should be suspected when a child presents with high-grade fever of acute onset, rash and/or arthralgia and/or edema not otherwise explained by a different infectious cause. Headache, throat discomfort, abdominal pain, and constipation may also be evident. Conjunctival suffusion, persistent conjunctivitis, cervical, or sometimes generalized lymphadenopathy may be present. Vomiting, diarrhoea, mental confusion, signs of meningeal irritation are frequent presentations in chidren. A chikungunya diagnosis becomes more likely if the child has visited or lived in an endemic/epidemic area. It is also important to keep in mind that cases may appear in places where chikungunya is not endemic. For laboratory confirmation of chikungunya, virological and serological tests are necessary. During the first 5 days of infection, the virus can be found in the blood by reverse transcriptase polymerase chain reaction. In samples obtained later, enzyme-linked immunosorbent assays may confirm the presence of IgM and/or IgG anti-chikungunya antibodies. Chikungunya and dengue viruses transmitted by the same mosquitoes. Patients with suspected chikungunya should be managed as dengue until dengue has been ruled out. Treatment of Chikungunya fever is symptomatic and supportive. Adequate fluid intake must be ensured. Paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDS) may be used for symptom relief. Aspirin, steroid and antibiotic should be avoided . Patients with Chikungunya fever should be advised to avoid being bitten by mosquitoes as the disease can be transmitted to others. Educating the community and public health officials, vector control measures such as elimination of breeding sites and spraying of insecticides should be initiated at the individual and community levels.*

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Introduction

Chikungunya is an arthropod-borne viral disease caused by the chikungunya virus (CHIKV).[1] First described during an outbreak in southern Tanzania in 1952, the virus derives its name from the Makonde language and means "to become contorted" or "that which bends up." [2] This description refers to the hallmark of the disease in adults—ie., severe incapacitating arthralgia, leading to an inability to stand or walk.

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Epidemiology

CHIKV is a single-stranded RNA virus (genus *Alphavirus*, family Togaviridae) transmitted to humans by *Aedes* mosquito bites. In recent years, anthropophilic *Aedes aegypti* and *Aedes albopictus* have been identified as the main vectors. [2] Originally, native to Southeast Asia, *A. albopictus* (also called tiger mosquito) has adapted to cooler climates and thereby propagated worldwide.[2]

Between 1950s and 2000s, CHIKV has caused numerous outbreaks, mainly in Africa, Asia and the Pacific regions.[1,3] Since 2004 reemergence on the east coast of Africa (along with its subsequent spread to

the neighboring islands of the Indian Ocean, India, Southeast Asia and Pacific), CHIKV has caused 2–3 million autochthonous cases and thousands of imported cases, worldwide.[1] This figure includes at least 3 small outbreaks in Europe: 1 in northern Italy in 2007 and 2 in France in 2010 and 2014. In all 3 outbreaks, the index case was a traveler returning from India and/or Cameroon. Subsequent autochthonous transmission of CHIKV occurred by means of local *A. albopictus.* In December 2013, chikungunya was reported for the first time in Americas, with initial cases appearing in Saint Martin, an island in the northeast Caribbean. One year later (ie, in December, 2014), the Pan American Health Organization reported chikungunya in 49 countries or territories—including the Caribbean, Central, South and North American regions—with a total burden of 975,678 suspected and 18,892 laboratory-confirmed cases.[4] These outbreaks highlight the significant risk of a chikungunya pandemic and the possibility of endemicity being established in countries with temperate climates.

Historically, after first detection of chikungunya in 1952 in the Makonde Plateau in Africa [5,6] the virus was known to be maintained in the sylvatic cycle of wild primates and mosquitoes such as *Aedes taylori*. [7,8] Later in 1958, it was detected in urban Asia such as Thailand mainly transmitted by *Aedes aegypti*.[9-11] In India, where both *Aedes aegypti* and *Aedes albopictus* are known to exist and are widely prevalent during the post monsoon season, CHIKV was first detected in 1963 in West Bengal. Following that several epidemics occurred in Chennai, Pondicherry, Vellore, Visakhapatnam, Rajmundry, Kakinada, Nagpur and Barsi between 1964 and 1973.[12] Again its reemergence occurred in India affecting several South Indian states. [12,13] The outbreak started in 2005 from the coastal regions of Andhra Pradesh and Karnataka. [14,15] More than 1.3 million people were estimated to be affected by CHIKV across 150 districts of 8 states in India. [15] Despite the number estimated, the actual disease burden was thought to be much higher because of potential underestimation due to lack of accurate reporting. [16]

From the onset of the outbreak in April 1, 2017, to Sept 7, 2017, the Ministry of Health and Family Welfare, Bangladesh reported 984 cases confirmed by real-time PCR assay and more than 13176 clinically confirmed cases in 17 of 64 districts.[17] A major outbreak has been observed in the capital, Dhaka.[17,18] This was the 3rd outbreak of Chikungunyia in Bangladesh.

The 1st one was in Poba upozilla in Rajshahi district affecting 32 people in 2008 and the 2nd outbreak was in Shathiya upazilla of Pabna in 2009.[19]

Chikungunya fever epidemics display cyclical and seasonal trends. There is an inter-epidemic period of 4-8 years (sometimes as long as 20 years). Outbreaks are most likely to occur in post-monsoon period when the vector density is very high. Human beings serve as the reservoir for Chikungunya virus during epidemic periods. During inter-epidemic periods, a number of vertebrates have been identified as reservoirs which include monkeys, rodents, birds, and other vertebrates.[20]

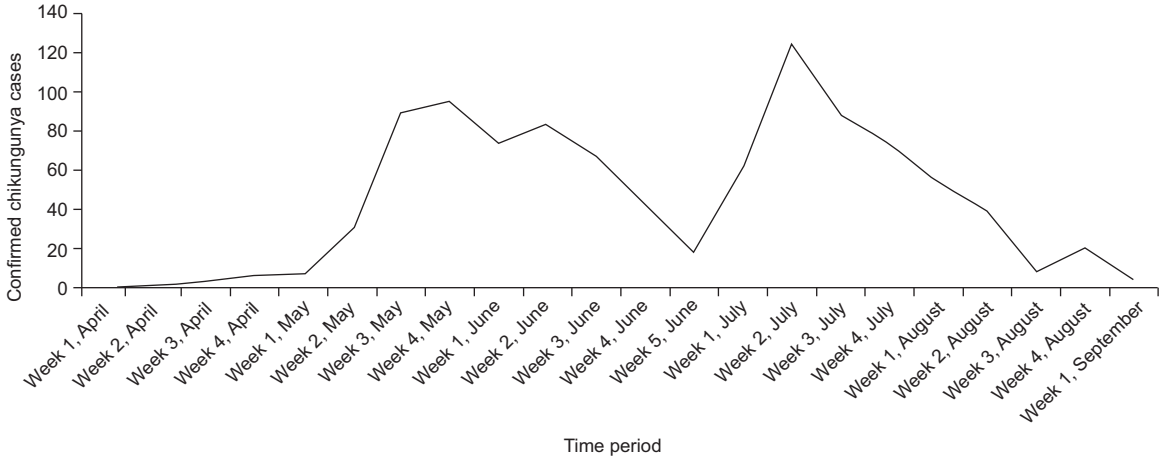

Fig. 1: *Chikungunya outbreak (cases confirmed by PCR) in 17 districts of Bangladesh.*

Aedes aegypti is the main vector of transmission of Chikungunya in Bangladesh. However, Aedes albopictus has also been found to be playing a part in some areas.[20] Aedes mosquitoes breed in clean water collections in containers, tanks, disposables, junk material in domestic and peri-domestic situations besides natural habitats like tree holes, plantations etc. Like Dengue its transmission is also related to rainfall and temperature.[20]

Transmission

The virus is transmitted from human to human by the bites of infected female mosquitoes. Most commonly, the mosquitoes involved are Aedes aegypti and Aedes albopictus, two species which can also transmit other mosquito-borne viruses, including dengue. These mosquitoes can be found biting throughout daylight hours, though there may be peaks of activity in the early morning and late afternoon. [21] After the bite of an infected mosquito, onset of illness occurs usually between 4 and 8 days but can range from 2 to 12 days.[21]

Pathogenesis

During an epidemic, human being serves as the Chikungunya virus reservoir; during inter-epidemic periods, several vertebrates, such as monkeys, rodents, birds, have been implied as the reservoir. [22] Following the bite of an infected *Aedes* mosquito, CHIKV is injected into the dermis and locally targets connective tissue, epithelial cells and fibroblasts, where viral replication takes place and enter into blood stream.[2] In addition, during the viraemic phase (d"5–7 days), circulating monocytes are responsible for dissemination into the bloodstream. Secondary infection sites include muscles and joints where fibroblasts are the main target cells. CHIKV may also be identified in the epithelial and endothelial cells of many organs particularly in the liver, spleen and brain. [2] Adaptive immunity against CHIKV develops after the first week when viral replication has been limited by innate immunity.[2] CHIKV-specific immunoglobulins protect against infection, but both B and T cells may contribute to pathogenesis and long-term joint disease.[23]

Diagnosis

Clinical Manifestations

The rate of asymptomatic infection among children varies according to different outbreak reports (range 35-40%).[2]

A. Manifestations in Older Children

Fever

Fever is typically high-grade in children. Febrile seizures commonly occur within the age range of 6 months to 6 years.[2] The fever varies from low grade to high grade, lasting usually for 24 to 48 hours. In some patients fever rises abruptly, reaching 39-40^{0}C, with chills and rigor. It has no diurnal variation.[20]

Mucocuteneous Manifestations

Skin lesions are less common, particularly in those younger than 2 years of age.[24,25] The skin lesions most frequently reported are pigmentary changes and maculopapular rash in the centrofacial area. The rash usually is present for 5 days, followed by hyperpigmentation in some cases. [2] Infants younger than 6 months may exhibit extensive bullous skin lesions with blistering covering up to 35% of the body surface area.[20,26] Stomatitis and oral ulcers are also observed.[20]

Hemorrhagic Manifestations

Hemorrhagic manifestations are uncommon in Chikungunya fever (Observed in approximately 10% of pediatric cases). [2] When present, these manifestations include epistaxis, bleeding from the gums (gingival bleeding), subconjunctival bleed, petechial/purpuric rash and positive Hess test (Tourniquet test). [2,27-30]

Unlike dengue fever, when present, they are mild and more frequently encountered in Asian compared to African patients. [27-30]

Musculoskeletal Manifestations

Myalgia, arthralgia and arthritis are present in 30% and 50% of affected children.[24]

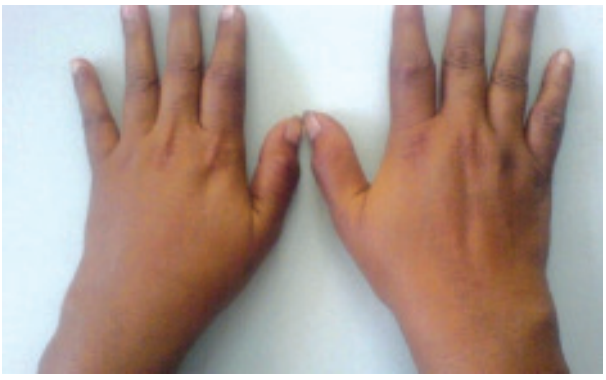

Fig.1 : *Symmetrical inflammatory polyarthritis of the small joints of the hands and tenosynovitis of the wrist joints*

The joint symptoms usually start with arthralgia or arthritis. Involvement is symmetric and often ankles wrists and small joints of the hands are the worst affected. Migratory polyarthritis with effusions may also be seen. [20]

Neurological Manifestations

Central nervous system (CNS) involvement potentially is more significant than previously documented, especially in children. During the chikungunya outbreak in La Réunion, 25% of children developed neurological symptoms, whereas in India 14% of all children presented with suspected CNS infection had chikungunya.[31,32] Among those, a high proportion (40–50%) had severe manifestations, including status epilepticus, complex seizures and encephalitis.

Two years after acute infection, cerebral disorders (including attention and memory difficulties) were reported in approximately 75% of CHIKV-infected subjects and sensorineural disorders (including blurred vision and hearing difficulties) in nearly 50%.[2] These findings indicate that chikungunya in children is not a benign or nonfatal infection but may result in long-term sequelae.[2]

Ocular manifestations

Nodular episcleritis, acute iridocyclitis, uveitis, and neuroretinitis have been documented as unusual ocular manifestations of Chikungunya fever. [33-35]

A. Chikungunya Fever in Neonates and Infants

Neonates

Mothers afflicted with Chikungunya fever in the perinatal period ("4 days to +1 days) can transmit Chikungunya fever to neonates by vertical transmission.[20,24] Neonatal Chikungunya fever is associated with fever, poor feeding, pain, distal edema, various skin manifestations, seizures, meningoencephalitis, and echocardiographic abnormalities in the newborn.[20, 24,29] No neonates/ infants are found to be infected with chikungunya virus through breast feeding. [20]

Infants

Chikungunya fever in infants manifests with certain differences. [24] Fever is commonly present; associated constitutional symptoms include lethargy or irritability and excessive cry. Acrocyanosis may be prominent; symmetrical superficial vesicobullous lesions, erythematous asymmetrical macules, and patches, which later progressed to morbiliform rashes, have also been described. The face and oral cavity are usually spared. [24, 36]

Laboratory Investigations[20]

Routine Investigations

- CBC
  - o Leucopenia (Decreased WBC)
  - o Thrombocytopenia: rare
  - o ESR: Usually Elevated
- C-Reactive Protein: Increased during the Acute Phase and may remain elevated

  for a week
- SGPT: Elevated

Specific Investigations

At least one of the following tests in the acute phase:

- Virus isolation by Cell Culture
- Presence of viral RNA by real Time RT-PCR (Within 5 days of onset of Illness)
- Presence of viral specific IgM antibody in single serum sample collected within 5 to 28 days of onset Fever
- Four-fold Rise of IgG antibody in samples collected at least three weeks apart (1st sample after 7 days)

Preferred Specimen: 1) Blood or Serum 2) CSF (if neurological features present)

Note[2]

Chikungunya should be suspected when a child presents with high-grade fever of acute onset, rash and/or arthralgia and/or edema not otherwise explained by a different infectious cause. A chikungunya diagnosis becomes more likely if the child has visited or lived in an endemic/epidemic area.

For laboratory confirmation of chikungunya, virological and serological tests are necessary. During the first 5 days of infection, the virus can be found in the blood by reverse transcriptase polymerase chain reaction. In samples obtained later, enzyme-linked immunosorbent assays may confirm the presence of IgM and/or IgG anti-chikungunya antibodies.

IgM antibodies appear between days 2 and 7 after onset of disease, whereas IgG antibodies frequently are detected after the first week of illness. IgM antibodies peak at 3–5 weeks after onset of symptoms and then decline 2 months later but still may persist for years. IgG antibodies are believed to be detectable lifelong.

Case definition[20]

Chikungunya Fever should be suspected when a person develops sudden onset of fever, joint manifestations and rash.

Cases are to be categorized as:

a) Possible case: a patient meeting only clinical criteria

b) Probable case: a patient meeting both the clinical and epidemiological criteria

c) Confirmed case: a patient meeting the laboratory criteria, irrespective of the clinical presentation

Criteria for Identifying Chikungunya Infection[20]

Clinical criteria

- acute onset of fever >38.5°C
- severe arthralgia/arthritis not explained by other medical conditions

Epidemiological criteria

- Residing or having visited epidemic/endemic areas
- having reported transmission within 15 days prior to the onset of symptoms

Laboratory Criteria: At least one of the following tests in the acute phase:

- Virus isolation by Cell Culture
- Presence of viral RNA by real Time RT-PCR (Within 5 days of onset of Illness)
- Presence of viral specific IgM antibody in single serum sample collected within 5 to 28 days of onset Fever
- Four-fold Rise of IgG antibody in samples collected at least three weeks apart (1st sample after 7 days)

Clinical Classification of Chikungunya Fever[20]

Chikungunya fever is classified in to three categories based on severity of clinical presentation.

Mild

- Low grade fever
- Mild artharlgia
- Mild focal myalgia
- General weakness
- Skin rash/itching

Moderate

- Low to high grade persistent fever
- Moderate arthralgia /arthritis
- Generalized myalgia
- Retro-orbital pain
- Oliguria
- Hypotension
- Mild bleeding

Severe

- Persistent high grade fever
- Severe arthralgia/Arthritis
- Persistent vomiting / Diarrhoea
- Altered sensorium
- Bleeding (GI bleeding due to use of drugs e.g. analgesics)
- Shock due to persistent vomiting and/or diarrhoea

Differential Diagnoses

Diseases considered as differential diagnoses: [20]

(1) **Dengue fever:** Severe back pain with purpuras or active bleeding might suggest dengue fever. Confirmatory laboratory diagnosis is possible.

(2) **Reactive Arthritis:** Any arthritis that follows a febrile gastrointestinal or genitourinary infection (triggering microbes) is considered as reactive acute inflammatory arthritis if it lasts less than six months. The hallmark feature is enthesitis where collagenous structures such as tendons and ligaments insert into bone are involved. Oral mucosal ulcers are seen.

(3) **Serum sickness illness:** Polyarthritis may be associated with a serum sickness type reaction caused by vaccine, medication or other viral infections

(4) **Rickettsial disease:** Can present with fever, rash and joint pains. Confirmed by serology.

(5) **Rheumatic fever:** Presents with fleeting (migratory) polyarthritis predominantly affecting the large joints. Modified Jones criteria should be the basis for diagnosis. Raised ASO titre and a history of recurrent sore throat are other points to be noted.

(6) **Malaria:** Patient can present with high fever and may also complain of joint pain. Periodicity of fever and alteration of consciousness / seizures should direct a diagnosis of malaria

(7) **Leptospirosis:** Severe myalgia localized to calf muscles with conjunctival congestion/ or subconjunctival haemorrhage with or without oliguria or jaundice in a person with history of skin contact to contaminated water would suggest Leptospirosis.

According to some other author[2] the differential diagnoses of febrile children with recent travel to, or residency in, tropical areas should include malaria, dengue, typhoid fever, influenza, hepatitis, leptospirosis and rickettsial infection. In addition, in areas where these viruses are present, infection with West Nile virus and other viruses belonging to the group of Flavivirus, Togavirus, Bunyavirus and Reoviruses should be considered, particularly if there is CNS involvement.[2]

Among the diseases listed, dengue is the infection most mimicking to chikungunya. In this regard, clinical signs including arthralgia and rash cannot reliably be used to distinguish between dengue and chikungunya.[31] However, rash appears earlier in the course of chikungunya than it does with dengue. Furthermore, thrombocytopenia more frequently is seen in patients with dengue; however, up to 50% of children with chikungunya also have mild thrombocytopenia.[37]

Clinical and laboratory features of Chikungunya compared to Dengue viral infections[20]

Features	Chikungunya	Dengue
Fever (>39°C)	+++	++
Arthralgia	+++	+/-
Arthritis	+	-
Headache	++	++
Rash	++	+
Myalgia	+	++
Hemorrhage	+/-	++
Shock	-	+
Lymphopenia	+++	++
Neutropenia	+	+
Thrombocytopenia	+	+++
Hemoconcentration HCT	-	++

Principles of Management

Treatment of Chikungunya fever is symptomatic and supportive. Adequate fluid intake must be ensured. Paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDS) may be used for symptom relief. Aspirin should be avoided due to its effect on platelets.[22]

Mild and moderate cases can be managed at home. Severe cases should be managed at hospital.

Home Management[20]

- Consume plenty of water with electrolytes e.g., dub water, fruit juice etc.
- Give paracetamol to children with the dose of 50-60 mg per kg body weight per day in divided doses.
- Adequate rest in a warm environment
- Cold compresses may help in reducing joint damage. Heat may increase/worsen joint pain and is therefore best to avoid during acute stage.
- Refrain from exertion. Mild forms of exercise and physiotherapy are recommended in recovering persons.
- Avoid self medication with aspirin or NSAIDs.
- Antihistamines can be used for itching.

Criteria for hospital admission[20]

1. If the child is hemo-dynamically unstable (frequent syncopal attacks, hypotension with a systolic BP falls or a pulse pressure less than 30 mmHg).
2. Oliguria
3. Altered sensorium
4. Bleeding manifestations
5. Children not responding or having persistent joint pain or disabling arthritis even after three days of symptomatic treatment
6. Infants (below one year of age)

C. Hospital management[20]

Following Admission

- Assess for dehydration and institute proper rehydration therapy. (Normal Saline for older children, & baby saline for infants)
- Give paracetamol to children with the dose of 50-60 mg per kg body weight per day in divided doses.

- Refrain from exertion.
- Antibiotics can be used to treat secondary bacterial infection.
- Antihistamines can be used for itching.
- Cold compresses may help in reducing joint damage.
- Mild forms of exercise and physiotherapy are recommended for patients with joint manifestation in recovery phase.
- Cutaneous manifestations can be treated with topical or systemic drugs, and neuropsychiatric problems with specialist care
- For ophthalmic symptoms ophthalmologists should be consulted.
- Aspirin or NSAIDs should be avoided during first 10 days. NSAIDs can be used in Chikungunya only when Dengue fever is excluded.
- Steroid has no role in acute stage.

  Published evidence does not support the use of corticosteroids, antibiotics, or antiviral drugs in the management of Chikungunya fever, and indiscriminate use of these agents can be hazardous. Electrolyte imbalance, pre-renal acute renal failure, and bleeding manifestations should be watched carefully and managed accordingly. [38]

Prevention

- Personal protection against mosquito bites is essential. In hospitals chikungunya affected viremic patients should be nursed in screened wards or under mosquito nets.[39] Patients with Chikungunya fever should be advised to avoid being bitten by mosquitoes as the disease can be transmitted to others. [22]
- Educating the community and public health officials, vector control measures such as elimination of breeding sites of Aedes mosquito by removal of water containing receptacles and spraying of insecticides[22,39] should be initiated at the individual and community levels.
- During outbreaks, insecticides and space spraying may also be used.
- Insect repellents containing *N*,*N*-diethyl-3-methylbenzamide, IR3535 (3-[*N*-acetyl-*N*-butyl]-aminopropionic acid ethyl ester) or icaridin (1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester) should be applied to exposed skin for personal protection. In addition, insecticide-treated mosquito nets are vital for infants and children who sleep during the daytime. [2]

Active involvement of community and public health authorities with regard to hygiene and mosquito control measures is essential. Integrated vector management measures to reduce or interrupt transmission of the disease must be pursued.

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Case Report

Acute Pancreatitis in 3rd Trimester of Pregnancy- A Case Report

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Abstract

Acute pancreatitis during pregnancy is a rare event with wide variation in its incidence. Pancreatitis in pregnancy has the same aetiology as those in general population. This reported a case of 19 years old primigravid female at 31 weeks of gestation, presented with sudden severe upper abdominal pain with radiation to back, nausea and vomiting for the last 24 hours. She was toxic with fever and severe dehydration. There was tenderness all over the abdomen more on epigastric region. Serum amylase and lipase were raised. Abdominal ultrasonogram (USG) could not visualize the pancreas due to obstruction by bowel gas shadows and revealed the gall bladder with normal features. Patient was managed conservatively with multidisciplinary approach and was discharged after 11 days in a stable condition. Regular follow up was done till 37 weeks of gastation and emergency caesarean delivery was done in view of non-reassuring foetal heart rate at 37 weeks of gestation. A female baby was delivered with good APGAR score. Early diagnosis of acute pancreatitis in pregnancy and good supportive care by a multidisciplinary team are crucial to ensure good maternal and foetal outcomes.

Key words: *Acute pancreatitis, Pregnancy, Good APGAR.*

(MH Samorita Med Coll J 2018; 1(2): 74-78)

Introduction

Acute pancreatitis is a rare and serious complication during pregnancy, estimated to occur in 1/1000 to 1/10000 pregnancies[1]. More than 50% of cases are diagnosed in third trimester of pregnancy demonstrating that acute pancreatitis is more common with advancing gestational age[2]. The most frequent aetiology of acute pancreatitis in pregnancy is biliary, caused by gall stones or sludge[3]. Other causes include idiopathic, hyperlipidemia and alcohol abuse[3] .The recent advances in clinical gastroenterology have improved the early diagnosis and effective management of acute pancreatitis[4]. With early recognition and better supportive treatment of acute pancreatitis as well as improvements in maternal and perinatal care, maternal and perinatal mortality dramatically appears to be decreased over the past two decades[5].

Case report

A 19-year-old, primi gravid lady at her 31 weeks of pregnancy was admitted with sudden severe upper abdominal pain since previous day. She also complained of severe nausea and vomiting for several times for the same duration. On admission she was febrile and severely dehydrated. Her pulse rate was 100 beats/ min, BP 120/80 mm of Hg, respiratory rate 22 breaths/min. Abdominal examination revealed tenderness all over the abdomen, more on epigastric region with radiation to back. Symphysio-fundal height was 30cm and uterus was contracted. Foetal heart rate was 150-155 beats/min and regular. There was no vaginal bleeding or watery discharge. On the day of admission, the blood tests showed raised levels of serum amylase, serum lipase and triglyceride. There were also electrolyte imbalance and hypo albuminemia.

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Table 1. Investigations on admission

Investigations	Result	Reference value
Hb%	11.0 gm/dl	
ESR	30mm in 1st hour	
Neutrophils	82%	
S. Amylase	903 U/L	Up to 220 (U/L)
S. Lipase	3234 U/L	73- 393
S. Triglyceride	180mg/dl	Â150 mg/dl
S. Calcium	6 mg/dl	9-11 mg/dl
Sodium	135.8 mmol/L	136-145 mmol/L
Potassium	3.11 mmol/L	3.5-5.1 mmol/L
Chloride	113.9 mmol/L	96-107 mmol/L
Creatinine	0.7 mg/dl	0.6- 1.2 mg/dl
Total Bilirubin	0.6 mg/dl	d•1.0 mg/dl
S. Albumin	25 gm/L	36- 53 gm/L
S. Troponin-I	Â0.01ng/ml	Â0.01ng/ml

Abdominal ultrasonogram (USG) revealed a normal gall bladder with smooth wall, no intraluminal biliary sludge or calculus. The pancreas could not be visualized due to obstruction by bowel gas shadows. Both kidneys were normal in size, shape and position with well-defined cortex and medulla. No mass or calculi were detected. Foetal USG revealed 31 weeks single live pregnancy, amniotic fluid index (AFI)- 12.4 cm, expected fetal weight (EFW)-1786 (±261) gm. Placenta anterior in position and away from internal os with no features of placental separation.

Initially patient was kept nil per oral and nasogastric suction was given. Hydration and nutrition were maintained by intravenous fluids. The patient was given parenteral analgesics, antipyretic, antispasmodics, antibiotics and tocolytics. A regular foetal and maternal vital monitoring were started with maintenance of intake-output chart.

In spite of those above treatment patient's condition was worsening. Patient was having severe abdominal pain with gradual abdominal distention. Intensive monitoring and care were needed and patient was shifted to the intensive care unit (ICU) where she was managed by a multidisciplinary team involving obstetrician, medicine specialist, surgeon and intensivist. She was kept nil per oral; nasogastric suction was given two hourly and hydration was maintained by intravenous fluids. Parenteral antiulcerant, antispasmodic, analgesics (inj. Pethidine hydrochloride: 4-7 mg/ hour), tocolytics (inj. Mgso4: 8 drops/ min), antipyretics, antiemetic were given. For electrolyte imbalance inj. KCL, inj. 10% calcium gluconate were also given. With those above

Table 2. Subsequent investigations

Tests		Day3	Day 5	Day 7	Reference values
S. Amylase		96	85	81	25-125 U/L
S. Lipase		114	90	90	73-393 U/L
Calcium		6.5	7.0	8.3	9.11mg/dl
Potassium		2.4	3.1	3.6	3.1-5.1 mmol/L
Magnesium		0.7	0.92	1.0	0.8-1.0 mmol/L
S. Albumin		25	26	28	36-53 gm/L
S. Urea			23		
HCT		22			38-48%
Prothrombin time:Control		12 sec			
Patient		14 sec			
	Ratio	1.16			
	Index	1.16			

treatments along with close maternal and foetal monitoring the patient was improving gradually.

After 48 hours oral feeding was started but patient's symptoms were detoriorating and decision was taken to keep the patient nil per oral for the next 48 hours. On 5th day after admission, Serum amylase dropped from 903.97 U/L to 85 U/L, serum lipase from 3234.0U/L to 90.0 U/L and electrolyte imbalance was corrected. On the same day again oral feeding was started and patient was shifted back to the antenatal ward. Patient became completely asymptomatic after 11 days and discharged with advice. Regular follow up was done till 37 weeks and emergency caesarean delivery was done in view of non-reassuring foetal heart rate at 37 weeks of gestation. A healthy female baby was delivered with APGAR score 7/10 at 1st min, 9/10 at 5th min and birth weight was 3.1 kg. After 6 weeks of caesarean section re- evaluation was done, the lab results were completely normal with no clinical signs of pancreatitis. The abdominal ultrasound (USG) showed a normal pancreas and gallbladder.

Discussion

Acute pancreatitis (AP) in pregnancy is very rare. The spectrum of acute pancreatitis in pregnancy ranges from mild pancreatitis to severe pancreatitis associated with necrosis, abscesses, pseudo cysts and multi organ dysfunction syndromes.[6] Pancreatitis in pregnancy may also be associated with haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome or preeclampsia leading to high foetal mortality or preterm delivery[7]. Gallstone is the most common etiological factor.[3] The relaxant effect of progesterone in pregnancy leading to atony of the biliary tract, bile stasis in the duodenum and slow empting of gall bladder may be a contributing factor. The second most common causative agent is hyperlipidaemia specifically hyper-triglyceridemia.[8] Lipids and lipoproteins (including triglycerides) levels are increased during pregnancy, which increase three fold during the third trimester of pregnancy[4]. Pregnancy itself can be a cause due to the physiological changes such as increasing weight, increased triglycerides, and increased levels of estrogen. However, primary diseases were absent in most cases (57.89%).[9] Apart from being pregnant, the reported case did not have other risk factors.

The most common clinical presentations of acute pancreatitis are abdominal pain (89.47%) and vomiting (68.42%)[9]. Other sign and symptoms include low grade fever, anorexia, nausea, vomiting, decreased bowel sounds, abdominal distension[4].The pain may radiate to back, can be exacerbated by meals or by lying down, and can be relieved by leaning forward.[5] Other than abdominal distention this reported case had all the signs and symptoms of acute pancreatitis.

The diagnosis of acute pancreatitis in pregnancy according to the revised Atlanta classification requires two of the three following features: 1) abdominal pain consistent with acute pancreatitis, 2) serum lipase and amylase activity increased at least three times than the higher normal serum level, 3) characteristic imaging findings of acute pancreatitis on ultrasonogram (USG), magnetic resonance imaging (MRI) or computed tomography (CT).[10] It is important to mention that if the clinical and laboratory examinations strongly suggest the presence of acute pancreatic inflammation, the diagnostic imaging is not necessary at first hours. This reported case had a typical abdominal pain consistent with acute pancreatitis, increased amylase level up to four-fold and increased lipase level up to eight fold.

Even though no clear protocol has been developed for the diagnosis of acute pancreatitis in pregnancy, studies show that the three-fold increase of amylase and lipase levels are the good predictors[11]. When taking into account the sensitivity and the specificity, lipase levels seem to correlate better with AP diagnosis than amylase levels (94% and 96% versus 83% and 88%)[12]. In this reported case lipase level has increased more than the amylase level. Diagnosis of acute pancreatitis (AP) in this lady was established mainly by clinical presentation, blood markers.

Abdominal ultrasound is the first line imaging technique, followed by magnetic resonance imaging (MRI), if the first one fails to deliver the necessary results[13]. But due to lack of MRI facility, MRI was not performed in this reported case. Computed tomography (CT), endoscopic ultrasound (EUS) and magnetic resonance cholangio-pancreatography are the other available diagnostic tools for diagnosing a biliary etiology for acute pancreatitis.[14]

The severity of AP is established using Ranson and Balthazar criteria or the Atlanta classification.[15] This case was diagnosed as mild acute pancreatitis (MAP) according to Ranson's criteria. Mild acute

pancreatitis (MAP), is the most common form, has no organ failure or local or systemic complications and resolves in the first week. Severe acute pancreatitis (SAP) is defined by persistent organ failure, that is, organ failure for more than 48 hours. Local complications include peripancreatic fluid collection and peripancreatic or pancreatic necrosis[10]. There are authors who recommend the diagnosis of severe AP based solely on the presence of peripancreatic fluid or peripancreatic or pancreatic necrosis.[15] Researches concerning fetal outcome state the following: in case of MAP, fetal loss is due to miscarriages and preterm labour, while in case of SAP, the concerns are fetal death and stillbirth.[16]

Management of acute pancreatitis (AP) in pregnancy is a controversial issue since the initial treatment is similar to the non-pregnant patient but the subsequent management might differ due to the risk of foetal disturbances or teratogenesis. Therefore, it is important to approach the patient by a team of different specialties such as obstetrician, gastroenterologist, surgeon and radiologist.[17]

The initial treatment focuses on diminishing the pancreatic exocrine secretion, restoring the third space fluid sequestration, and supporting the patient by providing necessary nutrition, oxygen, analgesics and monitoring the vital signs of mother and fetus[17]. The initial management of acute pancreatitis is restricted in aggressive intravenous hydration by 250 – 500ml/hour of isotonic crystalloid solution, preferably lactated Ringer's solution, unless cardiovascular, renal or other co-morbidities exist.[18]

Mild acute pancreatitis usually resolves within the first seven days and do not need extra nutritional support since the patient can take food orally immediately as long as the nausea, vomiting and abdominal pain subsides.[18,19] Low fat diet can be started within 3–5 days.[20]

In severe acute pancreatitis (SAP), treatments should include enteral feeding by either naso-jejunal or post pyloric feeding and may require parenteral feeding. Total Parenteral Nutrition (TPN) feeding has a risk of infections and metabolic derangement, whereas enteral feeding is physiological and helps gut to maintain gut immunity.[19]

The role of using antibiotics in acute pancreatitis is controversial[21,22] .The latest recommendations on the use of antibiotics support that there is no benefit from their administration:1) in mild acute pancreatitis, 2) in normal common bile duct size and without evidence for cholangitis, 3) as routine use of prophylactic antibiotics in patients with severe acute pancreatitis, 4) and/or sterile necrosis.[16,18] The same applies for the routine administration of antifungal agents along with antibiotics.[16] However, the indications of use of therapeutic antibiotics are extra pancreatitic infection (such as cholangitis, catheter-acquired infections, bacteremia, urinary tract infections, and pneumonia) and infected necrosis.[18]

The timing of pregnancy termination for patients with acute pancreatitis has long been an issue for obstetricians. Indications for pregnancy termination include full-term gestation, deteriorated condition after 24-48 hours of treatment, no improvement of paralytic ileus, still birth, fetal malformation, and severe pancreatitis.[23]

As per the recommended way of delivery, the Caesarean section is to be avoided if possible, and the vaginal birth should be encouraged, in order to limit the risk of super infection. Even so, no matter the delivery mode, a multidisciplinary team consisting of a gastroenterologist, a surgeon and an obstetrician should be gathered.

Conclusion

Acute pancreatitis in pregnancy is a complicated evolving disease and the pregnant woman supports two lives thus remains a challenging clinical problem to manage. For successful management early diagnosis and classification of severity of acute pancreatitis at presentation is an essential step. A multidisciplinary approach and supportive treatment with intensive maternal and fetal monitoring can result in good perinatal outcome.

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Abstract from Current Literature

(MH Samorita Med Coll J 2018; 1(2): 79-81)

THE ROLE OF BIPHOSPHONATES IN THE MANAGEMENT OF THALASSEMIA-INDUCED OSTEOPOROSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Tsartsalis AN, Lambrou GI[2], Tsartsalis D, Savvidis C, Karantza M, Terpos E, Kanaka-Gantenbein C[3], Chrousos GP, Kattamis A

Hormones (Athens). 2018 Jun;17(2):153-166. doi: 10.1007/s42000-018-0019-3. Epub 2018 May 2.

Thalassemia Major (TM) is a clinical entity with a high prevalence of low bone mass. The aim of the present study was to perform a meta-analysis of all available data on the role of bisphosphonates (BPs) in the therapy of thalassemia major-induced osteoporosis. The PRISMA recommendations for reporting systematic reviews and meta-analyses were used to guide the present study. We searched PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) through March 31, 2017 for articles related to thalassemia and BPs. To meta-analytically synthesize the primary endpoint, we used the standardized mean difference (SMD) after Hedges's g transformation under the scenario of a random effects model. Heterogeneity across studies was examined using the I^2 statistic. Nine randomized controlled trials (RCTs) containing original data were included in this review. Three studies were performed in Italy, one in Australia, three in Greece, one in Cyprus, and one in China. The BPs investigated included zoledronate, alendronate, pamidronate, clodronate, and neridronate. Zoledronate and alendronate showed a tendency to perform best as compared to neridronate and the placebo effect with respect to femoral neck, lumbar spine, total hip, and total body in terms of bone mass density (g/cm^2). BPs and in particular, zolendronate, were quite effective in the treatment of osteoporosis. These findings suggested that bisphosphonates are still a front-line treatment of osteoporosis in TM. However, to draw more meaningful and significant conclusions for the use and efficacy of BP in TM, larger and more complete RCTs should be conducted.

KEYWORDS: Bisphosphonates; Bone mineral density; Osteoporosis; Zolendronic acid; ²-thalassemia

PARACETAMOL (ACETAMINOPHEN) FOR PATENT DUCTUS ARTERIOSUS IN PRETERM OR LOW BIRTH WEIGHT INFANTS.

Ohlsson A, Shah PS

Cochrane Database Syst Rev. 2018 Apr 6;4:CD010061. doi: 10.1002/14651858.CD010061.pub3.

Background: In preterm newborns, the ductus arteriosus frequently fails to close and the infants require medical or surgical closure of the patent ductus arteriosus (PDA). A PDA can be treated surgically; or medically with one of two prostaglandin inhibitors, indomethacin or ibuprofen. Case reports suggest that paracetamol may be an alternative for the closure of a PDA. An association between prenatal or postnatal exposure to paracetamol and later development of autism or autism spectrum disorder has been reported.

Objectives: To determine the effectiveness and safety of intravenous or oral paracetamol compared with placebo or no intervention, intravenous indomethacin, intravenous or oral ibuprofen, or with other cyclo-oxygenase inhibitors for treatment of an echocardiographically diagnosed PDA in preterm or low birth weight infants.

Search Methods: We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 10), MEDLINE via PubMed (1966 to 6 November 2017), Embase (1980 to 6 November 2017), and CINAHL (1982 to 6 November 2017). We searched clinical trial databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials (RCT) and quasi-randomised trials.

Selection Criteria: We included RCTs in which paracetamol was compared to no intervention, placebo or other agents used for closure of PDA irrespective of dose, duration and mode of administration in preterm (≤34 weeks' postmenstrual age) infants. We both reviewed the search results and made a final selection of potentially eligible articles by discussion. We included studies of both prophylactic and therapeutic use of paracetamol.

Data Collection And Analysis: We performed data collection and analyses in accordance with the methods of the Cochrane Neonatal Review Group. We used the GRADE approach to assess the quality of evidence for the following outcomes when data were available: failure of ductal closure after the first course of treatment; neurodevelopmental impairment; all-cause mortality during initial hospital stay (death); gastrointestinal bleed or stools positive for occult blood; and serum levels of creatinine after treatment (μmol/L).

Main Results: We included eight studies that reported on 916 infants. One of these studies compared paracetamol to both ibuprofen and indomethacin. Five studies compared treatment of PDA with paracetamol versus ibuprofen and enrolled 559 infants. There was no significant difference between paracetamol and ibuprofen for failure of ductal closure after the first course of drug administration (typical risk ratio (RR) 0.95, 95% confidence interval (CI) 0.75 to 1.21; typical risk difference (RD) -0.02, 95% CI -0.09 to 0.09); I^2 = 0% for RR and RD; moderate quality of evidence. Four studies (n = 537) reported on gastrointestinal bleed which was lower in the paracetamol group versus the ibuprofen group (typical RR 0.28, 95% CI 0.12 to 0.69; typical RD -0.06, 95% CI -0.09 to -0.02); I^2 = 0% for RR and RD; number needed to treat for an additional beneficial outcome (NNTB) 17 (95% CI 11 to 50); moderate quality of evidence. The serum levels of creatinine were lower in the paracetamol group compared with the ibuprofen group in four studies (moderate quality of evidence), as were serum bilirubin levels following treatment in two studies (n = 290). Platelet counts and daily urine output were higher in the paracetamol group compared with the ibuprofen group. One study reported on long-term follow-up to 18 to 24 months of age following treatment with paracetamol versus ibuprofen. There were no significant differences in the neurological outcomes at 18 to 24 months (n = 61); (low quality of evidence).Two studies compared prophylactic administration of paracetamol for a PDA with placebo or no intervention in 80 infants. Paracetamol resulted in a lower rate of failure of ductal closure after 4 to 5 days of treatment compared to placebo or no intervention which was of borderline significance for typical RR 0.49 (95% CI 0.24 to 1.00; P = 0.05); but significant for typical RD -0.21 (95% CI -0.41 to -0.02); I^2 = 0 % for RR and RD; NNTB 5 (95% CI 2 to 50); (low quality of evidence).Two studies (n = 277) compared paracetamol with indomethacin. There was no significant difference in the failure to close a PDA (typical RR 0.96, 95% CI 0.55 to 1.65; I^2 = 11%; typical RD -0.01, 95% CI -0.09 to 0.08; I^2 = 17%) (low quality of evidence). Serum creatinine levels were significantly lower in the paracetamol group compared with the indomethacin group and platelet counts and daily urine output were significantly higher in the paracetamol group.

Authors' Conclusions: Moderate-quality evidence according to GRADE suggests that paracetamol is as effective as ibuprofen; low-quality evidence suggests paracetamol to be more effective than placebo or no intervention; and low-quality evidence suggests paracetamol as effective as indomethacin in closing a PDA. There was no difference in neurodevelopmental outcome in children exposed to paracetamol compared to ibuprofen; however the quality of evidence is low and comes from only one study. In view of concerns raised regarding neurodevelopmental outcomes following prenatal and postnatal exposure to paracetamol, long-term follow-up to at least 18 to 24 months' postnatal age must be incorporated in any studies of paracetamol in the newborn population. At least 19 ongoing trials have been registered. Such trials are required before any recommendations for the possible routine use of paracetamol in the newborn population can be made.

CLINICOPATHOLOGICAL, GENOMIC AND IMMUNOLOGICAL FACTORS IN COLORECTAL CANCER PROGNOSIS

Marks KM, West NP, Morris E, Quirke P

BJS 2018; 105: e99-e109

Background: Numerous factors affect the prognosis of colorectal cancer (CRC), many of which have long been identified, such as patient demographics and the multidisciplinary team. In more recent years, molecular and immunological biomarkers have been shown to have a significant influence on patient outcomes. Whilst some of these biomarkers still require ongoing validation, if proven to be worthwhile they may change our understanding and future management of CRC. The aim of this review was to identify the key prognosticators of CRC, including new molecular and immunological

biomarkers, and outline how these might fit into the whole wider context for patients.

Method: Relevant references were identified through keyword searches of PubMed and Embase Ovid SP databases.

Results: In recent years there have been numerous studies outlining molecular markers of prognosis in CRC. In particular, the Immunoscore® has been shown to hold strong prognostic value. Other molecular biomarkers are useful in guiding treatment decisions, such as mutation testing of genes in the epidermal growth factor receptor pathway. However, epidemiological studies continue to show that patient demographics are fundamental in predicting outcomes.

Conclusion: Current strategies for managing CRC are strongly dependent on clinicopathological staging, although molecular testing is increasingly being implemented into routine clinical practice. As immunological biomarkers are further validated, their testing may also become routine. To obtain clinically useful information from new biomarkers, it is important to implement them into a model that includes all underlying fundamental factors, as this will enable the best possible outcomes and deliver true precision medicine.

GROWTH RATES OF PULMONARY METAS-TASES AFTER LIVER TRANS-PLANTATION FOR UNRESECTABLE COLORECTAL LIVER METASTASES.

Grut H, Solberg S, Seierstad T, Revheim ME, Egge TS, Larsen SG et al.

BJS 2018; 105: 295-301

Background: The previously reported SECA study demonstrated a dramatic 5 year survival improvement in patients with unresectable colorectal liver metastases (CLM) treated with liver transplantation (LT) compared with chemotherapy. The objective of this study was to assess whether immunosuppressive therapy accelerates the growth of pulmonary metastases in patients transplanted for unresectable CLM.

Method: Chest CT scans from 11 patients in the SECA study resected for 18 pulmonary metastases were reviewed retrospectively. Tumour diameter, volume and CT characteristics were registered and tumour volume doubling time was calculated. Findings in the SECA group were compared with those of a control group consisting of 12 patients with non transplanted rectal cancer resected for 26 pulmonary metastases. Disease free survival (DFS) and overall survival (OS) after first pulmonary resection were determined.

Results: Median doubling time based on tumour diameter and volume in the SECA and control groups were 125 and 130 days (P = 0·658) and 110 and 129 days (P = 0·632) respectively. The metastases in both groups were distributed to all lung lobes and were mostly peripheral. Median DFS after LT in the SECA group and after primary pelvic surgery in the control group was 17 (range 6–42) and 18 (2–57) months respectively (P = 0·532). In the SECA group, estimated 5 year DFS and OS rates after first pulmonary resection were 39 and 51 per cent respectively.

Conclusion: Patients treated by LT for unresectable CLM have a good prognosis following resection of pulmonary metastases. Doubling time did not appear to be worse with the immunosuppression used after LT.

Notes and News

(MH Samorita Med Coll J 2018; 1(2): 82)

Bangladesh has a unique health system under Ministry of Health and family Welfare starting from tertiary level hospitals at different medical colleges, different specialized Institutes in the capital to union sub-centre and community clinics at grass-root level. But the service coverage is not adequate for the people of the densely populated country, Bangladesh. Privatization of health care service is very important for our country. With this point in view, MH Samorita Medical college was established in the year 2010 with affiliation to Samorita Hospital at Panthopath, Dhaka. Later this Medical College and Hospital was shifted to its own new building at Tejgaon, love Road in 1st July' 2014. This 500 bedded hospital is a well equipped hospital delivering both general and specialized services, including ICU, NICU, HDU, CCU, Cath lab, CT scan, Dialysis unit etc.

The following students obtained **honours** in respective subjects against their names

Name	Course	Batch	Type of Exam.	Year	Subject
Mohammad Reyajul Aalam	MBBS	MH-05	3rd Professional	May 2018	Pharmacology
Anima Karki	MBBS	MH-05	3rd Professional	May 2018	Pharmacology