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Journal of Bangladesh College of Physicians and Surgeons (JBCPS)

INFORMATION FOR AUTHORS

MANUSCRIPT PREPARATION AND SUBMISSION

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Five types of manuscripts may be submitted:

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All manuscripts are initially screened by editor and sent to selective reviewer. Decisions will be made as
rapidly as possible, and the journal strives to return reviewers’ comments to authors within 3 weeks. The editorial board will re-review manuscripts that are accepted pending revision. The JBCPS editorial board will try to publish the manuscript as early as possible fulfilling all the rigorous standard journal needs.

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

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

Preparation:
1. Manuscript should be written in English and typed on one side of A4 (290 x 210cm) size white paper.
2. Margin should be 5 cm for the header and 2.5 cm for the remainder.
3. Style should be that of modified Vancouver.
4. Each of the following section should begin on separate page:
   o Title page
   o Summary/abstract
   o Text
   o Acknowledgement
   o References
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Pages should be numbered consecutively at the upper right hand corner of each page beginning with the title page

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• The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called “IMRAD” structure is a direct reflection of the process of scientific discovery.
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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.

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The title page should have the following information:

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- Structured abstracts are essential for original research and systematic reviews. Structured abstract means introduction, methods, results and conclusion in abstract

- Should be limited to 250 words

- The abstract should provide the introduction of the study and blinded state and should state the study’s purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), principal conclusions. It should emphasize new and important aspects of the study or observations. Articles on clinical trials should contain abstracts that include the items that the CONSORT group has identified as essential (http://www.consort-statement.org).

- Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that they accurately reflect the content of the article.
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• Provide a context or background for the study (that is, the nature of the problem and its significance). It should be very specific, identify the specific knowledge in the aspect, reasoning and what the study aim to answer.

• State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question.

• Both the main and secondary objectives should be clear.

• Provide only directly pertinent primary references, and do not include data or conclusions from the work being reported.

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

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

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

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

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• Do not repeat in detail data or other information given in the Introduction or the Results section.
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• Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly as such.

I. A. 9. References
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• 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.
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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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2. Authorship and conflicts of interest form
3. Manuscript
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• Language and grammar
  - Uniformity in the language
  - Abbreviations spelt out in full for the first time
  - Numerals from 1 to 10 spelt out
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  - Complete author information
  - Mention conflict of interest if any
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  - Do not use subheadings in the abstract
  - Give full title of the manuscript in the Abstract page
  - Not more than 200 words for case reports and 250 words for original articles
  - Structured abstract (Including introduction, methods, results and discussion, conclusion) provided for an original article and (Introduction, results and discussion, 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
  - Use table information at the end of the sentence before full stop between the small bracket

• **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
  - Mention about limitation of your study

• **Conclusion**
  - Give your conclusion
  - Any recommendation

• **Acknowledgement**
  - Acknowledge any person or institute 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**
  - Table
  - Figures

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EDITORIAL

Changing Pattern of Gastric Surgery

Though it has been said for pong period that Peptic Ulcer disease may occur in any age group irrespective of sex, it has been proclaimed that this is the commonest affection of Stomach and Duodenum. Surgery related to peptic ulcer disease is mainly based on Combating the short term and long term complications of such. Surgeons were busy with managing the three Life threatening complications like perforation, haematemesis and gastric outlet obstruction. The epidemiology of peptic ulcer disease reflects the prevalence of *H pylori* infection in different populations. The timely discovery of H2 blocker agents and Proton pump inhibitor made it possible to treat the most of the disease effectively by non surgical means. Later on, the concentration on eradication of *H pylori* by medical means make it easier for the surgeon to manage the other diseases of stomach and so on.

Carcinoma of the stomach and other malignant diseases of the stomach clearly prevails in middle aged to elderly persons. It was one of the life threatening disease process from ancient and still prevails. Geographical distribution of malignant disease of the stomach is a great concern and the peoples resides in and around Japan are the worst sufferers. On the contrary Japanese management protocol based on “Tier” removal made it gold standard for rest of the world.

As the affluence persons of the world are increasing day by day and many of them are suffering from Obesity related problem, there are increasing concern on weight reduction by surgical means. Earlier days most of this surgery were open procedure and significant number of morbidity and mortality in relation to those made those unpopular for the common people.

**Surgical treatment for Stomach Diseases**

There are a varieties of surgery for benign disease of the stomach. For repair of peptic ulcer perforation, most of the procedures are direct repair of the stomach. In addition lower partial resection, antrectomy, Emergency vagotomy-gastrojejunostomy are rarely performed. For haematemesis and melaena most of the patient are treated by non surgical means and endoscopic coagulation of blood vessel. However in case of deemed necessary, open lower partial gastrectomy or under running of bleeding vessel is a therapeutic choice. For Gastric outlet obstruction following scarred Duedenal or Pyloric ulcer a bypass procedure is practiced throughout the world, still today. A time tested procedure of Bilateral truncal vagotomy and gastrojejunostomy is still the choice of the surgeons mostly. A modification of selective or highly selective vagotomy or pylorus sparing vagotomy is also been popular in some parts of the world. Gastro-jejunostomy can be modified by pyloroplasty or antrectomy in some cases as well.

Surgery for gastric cancer remarkably changed based on its clear idea of knowledge of lymphatic distribution. The lymph nodes draining the stomach has a clear understanding and Contrast enhanced CT scan or MR scan made it possible to clearly define the lymphatic drainage of the stomach. Its based on tier like distribution and mapping of these lymph nodes made it possible to predict the clearance of the local metastasis.

Laparoscopic procedure in stomach has revolutionalized the approach to surgery easier, better and safe handling thereafter. In addition discovery of endostapler and endovascular control made it more soft handling and a better outcome.

A small modification of palliative surgery for stomach is insertion PEJ catheter for advanced malignancy and also patients having prolonged parenteral nutrition. It is a combined procedure for surgeons and gastroenterologist as a team and in same sitting to insert the catheter safely. Generation of changes in Gastric Surgery

First generation:—1. Repair of perforation
   1. Gagotomy- gastrojejunostomy
   2. Antrectomy for haematemesis.

A. Second Generation:—1. Lower partial gastrectomy
   1. Total Gastrectomy.
   2. Roux-n- Y anastomoses.
   3. Trans thoracic gastrectomy
B. Third Generation:—1. Vertical Banded gastroplasty
   1. Radical gastric dissection
   2. PEJ insertion.
C. Fourth generation:—1. Laparoscopic Gastroplasty
   1. Robotic assisted gastroplasty.

Recent studies demonstrated increasing feasibility for non-surgical palliation of unresectable gastrointestinal cancers as well as gastric outlet obstruction. Diagnostic laparoscopy was introduced as the final staging investigation in GI cancer patients who do not have advanced disease after radiological staging and therefore seem candidates for surgical resection. The aim of Diagnostic laparoscopy is to detect peritoneal, superficial liver, or lymph node metastasis and locally advanced disease those may be missed on radiological staging and thus could avoid a non-therapeutic laparotomy.

The obesity epidemic and its associated diseases threaten to over burden global healthcare resources. Bariatric surgery is the only intervention that gives long standing improved or resolution of obesity related conditions and also survival benefits. It is highly cost effective. In the US and some European countries, the number of operations performed has now surpassed cholecystectomy.

The three commonly performed procedures for morbid obesity are laparoscopic Roux-en-Y gastric bypass, laparoscopic adjustable gastric band and sleeve gastrectomy.

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References:
**Summary:**
The objective of this study is to evaluate the efficacy and safety of vildagliptin compared to sulphonylurea (SU) in Type 2 Diabetes during Fasting in Ramadan. This was a prospective, observational cohort study, which enrolled patients from Bangladesh. Patients aged ≥18 years with T2DM and HbA1c ≤8.5% were treated with vildagliptin or SU as add-on to metformin or as monotherapy for 16 weeks. The primary outcome of interest was to compare the proportion of patients with ≥1 hypoglycemic event(s) (HE) during fasting between the vildagliptin and SU groups. Changes in HbA1c, body weight and treatment adherence were also measured. Of the 100 patients enrolled, 97 completed the study and 3 patients discontinued prematurely. Patients experiencing ≥1 HE(s) were fewer in the vildagliptin group compared with SU group (4.3% vs. 8.2%; p = 0.678). The reduction in HbA1c was 0.1% with vildagliptin from a baseline of 7.1%, however, there was no change with SU from a baseline of 7.2% (between-treatment difference: "0.1%; p = 0.600). A gain of 0.35kg and 0.08 kg was seen with vildagliptin and SU treatment, respectively. Overall, the incidence of adverse events was similar between the vildagliptin and SU groups (23.4% vs. 20.4%) with no new safety signals.

The treatment with vildagliptin was associated with fewer hypoglycemic events compared with SU and was well tolerated in Muslim T2DM patients fasting during Ramadan. **Keywords:** DPP-4 inhibitor, Hypoglycemia, Ramadan, Type 2 Diabetes Mellitus, Vildagliptin, Sulphonylurea.

**Efficacy and Safety of Vildagliptin Compared to Sulphonylurea in Patients with Type 2 Diabetes during Fasting in Ramadan**

MF PATHAN\(^a\), MF AMIN\(^b\), F AFSANA\(^c\), MSA RAHIM\(^d\), MJA SARKER\(^e\), TM ALI\(^f\), M MM RAHMAN\(^g\), F HASAN\(^h\)

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**Introduction:**
Ramadan is a holy month (the ninth month of the Islamic calendar) for the Muslims worldwide and fasting from pre-dawn to after sunset is widely practiced\(^1\). Depending on the geographical location and time of the year, fasting can last from 11 to 20 hours a day. As fasting should not create excessive hardships, certain individuals who are ill are exempted from fasting. However, a majority of Muslim patients with type 2 diabetes mellitus (T2DM) do not consider themselves ill, and are ardent about their Ramadan fasting, despite the complications such as hyperglycemia and hypoglycemia, diabetic ketoacidosis, dehydration, and thrombosis.\(^2,3\) The Population-based Epidemiology of Diabetes and Ramadan (EPIDIAR) study showed that there was a 7.5-fold increase in the risk of severe hypoglycemic events (HEs) and a 5-fold increase in hospitalization due to hypoglycemia in fasting patients with T2DM.\(^4\) Therefore, the risk of hypoglycemia is to be taken into account while choosing or maintaining an antidiabetic agent during Ramadan.

Current Ramadan guidelines (South Asian guidelines for the management of endocrine disorders in Ramadan) recommend individual assessments, investigations, counseling, as well as necessary changes in lifestyle, diet, and medication for patients fasting during
Ramadan. There is no consensus about the most appropriate oral antihyperglycemic agent(s) for patients with T2DM during Ramadan, as there is limited data assessing the efficacy and safety of these agents during Ramadan. Sulphonylureas (SUs) and glinides are widely used as antihyperglycemic agents due to their well-established clinical profile and low cost; however, they are associated with an increased risk of hypoglycemia and weight gain.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are important substitutes for SUs in patients with T2DM during fasting owing to their glucose-dependent mechanism of action, efficacy, and tolerability. Vildagliptin is a potent and selective DPP-4 inhibitor that improves glycemic control by increasing the a- and b-cell responsiveness to glucose. It significantly reduces the risk of hypoglycemia compared with sulphonylurea.

The Vildagliptin Experience compared with Sulphonyl Ureas Observed (VIRTUE) study was conducted in 12 countries of the Middle East and Asia including Bangladesh. The results of the study showed that treatment with vildagliptin was associated with significantly fewer patients experiencing hypoglycemia compared with SUs in fasting Muslim patients with T2DM. As there is a dearth of literature on patients with T2DM fasting during Ramadan in Bangladesh, the present study assessed the proportion of patients with ≥1 HE (Hypoglycemic Event) receiving vildagliptin or SU as add-on to metformin or as monotherapy during fasting in Ramadan.

Methods:

Study design and patient population
This was a prospective, observational cohort study, which included patients aged ≥18 years with duration of T2DM for more than 12 months before the start of Ramadan fasting (HbA1c ≤8.5% measured within 6 weeks before the study entry). Patients were treated with vildagliptin or SUs as add-on to metformin or as monotherapy for at least 4 weeks, but not more than 3 years before fasting commenced.

Patients were excluded if they had contraindications to the study medication or if they required three or more oral antidiabetic drugs or insulin therapy at the time of the study entry. During the observational period of approximately 16 weeks, data from at least two routine clinic visits were recorded for each patient at baseline (6 weeks before the start of fasting) and at the end of the study (within 6 weeks after the end of fasting). At both the visits, HbA1c was estimated. Patients were provided a diary/log book during their fasting period and were asked to record the diabetes treatment time points, blood glucose measurements and hypoglycemia symptoms. This data was used to assess patient adherence to prescribed dosages and timing of doses while fasting. Information was collected from Patient log book supplied which included total day of fasting or missing of fasting, daily anti-diabetic agent intake, hypo or any other adverse events, confirmed hypoglycemia and how they overcome.

Data collection was also permitted during the observational period if the patient made an interim visit during the fasting period. A written informed consent for the collection and use of data was obtained from all the participants, and the study was conducted in accordance with the guidelines for Good Pharmacoepidemiological Practices, national requirements and regulations, in line with the ethical principles laid down in the Declaration of Helsinki. Ethical clearance for the study was received from BADAS Ethical Review Committee.

Study outcome assessments
The primary objective was to assess the proportion of patients who experienced at least one HE during the fasting period. HEs were categorized by investigators as mild or grade 1, defined as any reported symptoms by the patient and/or any blood glucose measurement <3.9 mmol/L (70 mg/dL), and severe or grade 2, defined as the need for third-party assistance. Secondary objectives included assessment of changes in body weight and HbA1c from pre-fasting baseline to the study endpoint and treatment adherence (proportion of patients who did not miss more than 20% of the prescribed medication doses during Ramadan). Overall safety was assessed by monitoring and recording adverse events (AEs) and serious AE (SAEs). Hypoglycemia-related symptoms or any other AEs were recorded by the patient in the paper diary or log book. If a patient did not record HEs or glucose readings, the number of HEs experienced was recorded by the physician at the end of observational period, as recalled by the patient.

Statistical analysis
For the primary assessment variable, based on 90% power and a two-sided significance level of 0.05, a sample size of 35 patients per group would be sufficient to detect a 40% difference between the proportions of patients experiencing ≥1 HE(s), tested with a two-group continuity corrected chi-squared test. The change in
HbA1c from baseline was computed and summarized. The difference estimate is based on the published incidences of HEs for patients receiving SU (60%) and vildagliptin (d°20%)\textsuperscript{12}. The primary study variable was analyzed using a two-sided Fisher’s exact test performed on data from all patients who received at least one dose of the study medication at the beginning of Ramadan and had at least one efficacy assessment after the start of fasting (primary analysis set, [PAS]). Apart from HbA1c assessments, other assessments were performed on the safety population, consisting of all patients who received at least one dose of the study medication at the beginning of Ramadan and had at least one safety assessment. HbA1c and body weight data were analyzed using the last observation carried forward approach. Data were analyzed by DATAMAP GmbH, Freiburg, Germany using SAS\textsuperscript{®}, Release 9.3 (SAS Institute Inc., Cary, NC).

**Results:**

Of the 100 patients enrolled from Bangladesh, 97 patients completed the study and three patients discontinued prematurely. A total of 50 patients were treated with vildagliptin and 49 patients were treated with an SU. One patient was neither treated with vildagliptin nor with an SU, and therefore was excluded from the study. In the vildagliptin group, three (6.0%) patients were excluded from the PAS and safety set due to withdrawal before the start of Ramadan. The key demographics and clinical background characteristics were broadly similar in both vildagliptin and SU groups except for body weight and body mass index (BMI) (Table I). The mean age of patients was 50.3 years, 55.2% were male, mean body weight was 69.1 kg, and mean BMI was 26.7 kg/m\textsuperscript{2}. The mean baseline HbA1c was 7.1% in the vildagliptin group and 7.2% in the SU group. The mean weight of patients in the vildagliptin group was higher (71.5 kg) compared with patients in the SU group (66.8 kg), which led to the difference in BMI as well.

A majority of the patients were receiving metformin in combination with the study medication: 97.9% (n=46/47) in the vildagliptin group and 83.7% (n=41/49) in the SU group. Median daily dose of vildagliptin was 100 mg and of SUs were: glimepiride 1 mg (n=24), gliclazide 70 mg (n=20), glipizide 7.5 mg (n=2) and glibenclamide 5 mg (n = 1). In both the treatment groups, the mean exposure during Ramadan (vildagliptin, 30 days; SU, 30 days) and the mean number of days fasting (vildagliptin, 27.9 days; SU, 29.4 days) were similar.

**Frequency of HEs**

Numerically fewer patients experienced \( \geq 1 \) HE(s) with vildagliptin (n = 2/47, 4.3%) compared with those receiving SUs (n = 4/49, 8.2%), resulting in a 50.0% relative risk reduction (odds ratio [OR] = 0.5; 95% CI: 0.087, 2.869; \( p = 0.678 \); Table III). All the patients experiencing hypoglycemia during fasting reported a single HE in both the groups. No patient reported a grade 2 HE.

**Table-I**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vildagliptin = 47</th>
<th>Sulphonylurea = 49</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49.8 (10.0)</td>
<td>50.7 (10.1)</td>
<td>50.3 (10.0)</td>
</tr>
<tr>
<td>&lt;65, n (%)</td>
<td>45 (95.7)</td>
<td>47 (95.9)</td>
<td>92 (95.8)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>14 (29.8)</td>
<td>39 (79.6)</td>
<td>53 (55.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71.5 (12.4)</td>
<td>66.8 (9.2)</td>
<td>69.1 (11.1)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1 (3.8)</td>
<td>25.4 (3.1)</td>
<td>26.7 (3.7)</td>
</tr>
<tr>
<td>Duration of T2DM, years</td>
<td>5.9 (5.0)</td>
<td>4.5 (3.2)</td>
<td>5.2 (4.2)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.1 (0.7)</td>
<td>7.2 (0.8)</td>
<td>7.1 (0.8)</td>
</tr>
<tr>
<td>Diabetes medication changed for fasting during Ramadan, n (%)</td>
<td>43 (91.5)</td>
<td>40 (81.6)</td>
<td>83 (86.5)</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless indicated otherwise. BMI, body mass index; HbA1c, hemoglobin A1c; SD, standard deviation; T2DM, type 2 diabetes mellitus.
At the end of the study, the mean HbA1c level decreased by 0.1% in the vildagliptin group from a pre-fasting baseline of 7.1%; however, no change was seen in the SU group from a pre-fasting baseline of 7.2% (between-treatment difference; p = 0.600; Table IV). Weight changes from pre- to post-Ramadan were 0.35 kg with vildagliptin versus 0.08 kg with SUs, with a mean between-treatment difference of 0.27 kg, which was not significant (p = 0.528).

### Treatment adherence

Treatment adherence was high in both the treatment groups (~98.0%): 46 patients (97.9%) in the vildagliptin group and 48 patients (98.0%) in the SU group. The number of doses (mean±SD) missed during the fasting period was similar between the two groups with 1.4±4.6 and 1.0±3.2 in the vildagliptin group and the SU group, respectively.

### Safety and tolerability

A total of 12 patients (25.5%) in the vildagliptin group and ten patients (16.3%) in the SU group experienced AEs after the beginning of Ramadan fasting. Pyrexia (n = 4; 8.5%) was the most common AE in the vildagliptin group and hypoglycemia (n = 4; 8.2%) in the SU group (Table II). The majority of AEs were mild in severity. There were no SAEs and no deaths reported in both the groups and no patient discontinued the study due to AEs.

### Discussion:

To our knowledge, this is a first prospective observational study conducted in Bangladesh in patients with T2DM fasting during Ramadan. The results of this observational study showed that there is a 50% less risk for HEs in patients treated with vildagliptin compared with SUs. The present findings are consistent with the findings from the previous studies conducted on Muslims with T2DM fasting during Ramadan, which showed that the incidence of HEs was significantly lower in the vildagliptin group than in the SU group during Ramadan.12, 13

The present results are also comparable with the results from other studies that used other DPP-4 inhibitor sitagliptin. In a study conducted in Egypt, Israel, Jordan, Lebanon, Saudi Arabia, and the UAE, the risk of symptomatic HE was significantly decreased with sitagliptin compared with SU (OR = 0.51; 95% CI 0.34, 0.75).14 These results are also supported with the overall VIRTUE study findings, in which vildagliptin showed reduction in HEs compared with SU (5.4% vs. 19.8%, respectively).11
In the present study, a small increase in the mean body weight from baseline was observed in both the vildagliptin and SU groups, which was statistically not significant, as people of Bangladesh take food with more calorie value because of their dietary habit during Ramadan period. A slight improvement in mean HbA1c was observed during the study period for the vildagliptin group, whereas in the SU group, the mean HbA1c increased slightly. The improvement in HbA1c was smaller compared with the findings from the VECTOR study which may be due to low HbA1c at baseline compared with baseline HbA1c in the VECTOR study. Although hypoglycemia is a significant barrier to treatment adherence, the self-reported adherence in the present study was high in both the treatment groups (98%). The present results are also comparable with the results from overall VIRTUE study.

Interestingly, higher median daily dose of vildagliptin (100 mg daily) was compared with the lower median daily dose of SUs (glimperide 1 mg [n=24], glipizide 10 mg [n=20], glibenclamide 5 mg [n=1]). This could explain the lower incidence of HEs in the SU group. Higher frequency of HEs is expected with high doses of SUs compared with present median dose. Despite comparing with a very low dose of SU, vildagliptin therapy had numerically fewer HEs in this study.

Overall, the incidence rate of AE was similar between the vildagliptin and SU groups (23.4% vs. 20.4%) with no new safety signals. There were certain limitations of this study, such as small sample size, lack of diet, eating patterns, and exercise data. Being an observational study, there are certain inherent limitations and bias associated with it. Owing to the non-interventional nature of the study, the reported HEs did not require mandatory confirmation with blood glucose measurements, which can potentially under or overestimate the number of HEs due to subjectivity in perceiving symptoms of hypoglycemia. Other factors that limit inference of the results are varied eating practices among different cultures during Ramadan (two to four meals) and of recording of HEs in the diary due to recall bias. Despite the above-mentioned limitations, this study has enabled collection of data from a patient group in a real-lifesetting which could complement the findings of randomized, interventional clinical trials.

Patients with T2DM who wish to fast during Ramadan should be well prepared to make fasting as safe as possible. Medical counseling is important for diabetic patients concerning the potential risks if they decide to fast. Any modification in medication, if required, should be done before the start of Ramadan fasting in order to provide a stable glycemic control.

**Conclusion:**
Vildagliptin therapy was associated with numerically fewer patients experiencing hypoglycemia compared with SU therapy in fasting Muslim patients with T2DM from Bangladesh. Our findings suggest that vildagliptin is a suitable treatment option, particularly to reduce the risk of hypoglycemia during the long daytime fasting periods during Ramadan in Muslim patients with T2DM.

**Acknowledgment:**
The authors acknowledge all investigators at the participating centers and all patients for their commitment to the study that was supported by Novartis Pharma AG, Basel, Switzerland. Vasundhara Pathak, Novartis Healthcare Private Limited, India, provided the medical writing and editorial assistance for the manuscript. All authors participated in the development and reviewing of the manuscript and took full responsibility for the contents of the article. The study was funded by the Novartis Pharma Bangladesh.

**References:**


Summary:
Background: Anaemia is common among general population in developing Asian countries. Iron deficiency anaemia (IDA) is the commonest type of anaemia. It is usually due to chronic gastrointestinal blood loss. The standard of care for these patients with IDA includes evaluation of the Gastrointestinal (GI) tract for bleeding lesions. Iron deficiency anaemia is considered as an alarm sign for the presence of possible GI malignancies, and inadequate evaluation of patients with IDA may delay the diagnosis of GI tumors especially colorectal cancer.

Objective: To identify the gastrointestinal lesions endoscopically in patients with iron deficiency anaemia. To determine the usefulness of endoscopic procedures (both upper and lower GI) in diagnosis of underlying cause of iron deficiency.

Method: This cross-sectional study was conducted to evaluate Iron deficiency anaemia in patients with or without GI symptoms during the period of July 2010 to December 2010 in the department of Gastroenterology, BIRDEM General Hospital. Sixty eight adult eligible patients with iron deficiency anaemia were taken as per inclusion criteria. All study subjects were underwent endoscopy and colonoscopic procedure after adequate preparation along with examination of their stool. Data were collected through face-to-face interview, observation and document review. Data were recorded and analyzed.

Results: Majority of patients were 55 to 64 years age group (33.8%). Mean age ± SD of this study subject was 54.00 ±11.792 with maximum and minimum age 86 and 27 years respectively. More than half of the patients were female (51.5%) and rests were male 33 (48.5%). Among the study subjects, 70.58% patients had GI symptoms, 29.42% had non-GI symptoms. On stool examination, 17.64% patients had ova/cyst of helminthes; 82.36% were normal. Stool OBT revealed 11.8% positive and 88.2% negative. On upper GI endoscopy 32.4% had normal findings, 67.6% had some lesions. Majority of these lesions were ulcers and erosions (30.9%), malignancy (ca stomach) was 4.41%; others (which includes congestive gastropathy, reflux oesophagitis, vascular ectasias and helminthiasis) were 32.4%. On colonoscopy, 30.88% patients had normal colon; 69.12% had lesions. Among the lesions, most common lesion was hemorrhoids (36.76%); ca colon was 5.88% and others (includes ulcers, polyps, vascular ectasias and helminthes) were 26.47%.

Patients with normal upper GI endoscopy- 50% had GI symptoms and 50% had non-GI symptoms whereas patients having lesions on upper GI endoscopy 80.4% had GI symptoms and 19.6% had non-GI symptoms. This difference was statistically significant (p<0.05).

Patients with normal colonoscopy- 42.9% had GI symptoms and 57.1% had non-GI symptoms. On the other hand, patients having lesions on colonoscopy 70.6% had GI symptoms and 29.4% had non-GI symptoms. This was also statistically significant.

Conclusion: Majority of the study population had lesions on endoscopy (both upper GI endoscopy and colonoscopy) including malignant lesions. Study showed that lesions are more common in patients with GI symptoms than those without GI symptoms (non-GI symptoms). Therefore, Routine endoscopic (both upper and lower GI) procedures is valuable in evaluating patients with iron deficiency anaemia- for diagnostic as well as therapeutic purposes. Effective treatment of patients with IDA is predicated on the identification of a specific lesion.

Introduction:
Anaemia is common among general population in developing Asian countries. Iron deficiency anaemia (IDA) is the commonest usually due to chronic gastrointestinal (GI) blood loss when there is no obvious source of bleeding.
The standard of care for these patients with IDA includes evaluation of the Gastrointestinal (GI) tract for bleeding lesions. Iron deficiency anemia is considered as an alarm sign for the presence of possible GI malignancies, and inadequate evaluation of patients with IDA may delay the diagnosis of GI tumors especially colorectal cancer.

In 20% of patients with IDA a routine upper and lower GI endoscopy may not ascertain GI cause during hospital admission. The available literature, in heterogeneous groups including old age patients and postmenopausal women with IDA, has shown GI lesions in 40 – 70%. Studies have shown that increasing age, male gender, ferritin level, prior NSAIDs use, positive fecal occult blood test were factors predictors of endoscopic lesions in patients with IDA with and without GI symptoms. Studies have concluded that prevalence of endoscopic lesions in patients with IDA without GI symptoms is between 48 – 71%, however there is a sparse data related to factors predicting GI lesions in this group.

Important implications for recognition of iron deficiency anaemia include diagnosis and treatment of underlying causes, most of which are identifiable by means of conventional upper gastrointestinal endoscopy and colonoscopy. However it remains unresolved which procedure should be done first. Many studies have concluded that on evaluation of Gastrointestinal Tract for IDA; most of the lesions were in lower GI Tract and have recommended that evaluation for IDA should be started with lower GI examination.

There is scanty data to predict the nature and site of GI lesions in IDA patients without gastrointestinal symptoms. Therefore there is a need for studies especially from developing Asian countries, which may establish endoscopic findings and their predictors in this group.

Primary aim of the study was to identify gastrointestinal lesions diagnosed endoscopically in patients with iron deficiency anemia with or without gastrointestinal symptoms.

Method:
This cross-sectional analytic study was conducted to evaluate Iron deficiency anaemia in patients with or without GI symptoms and their socio-demographic characteristics and attributes associated with GI symptoms. The total period of study was from July 2010 to December 2010. The study was undertaken at the department of Gastrointestinal, Hepatobiliary and Pancreatic disorders (GHPD), BIRDEM. Eligible subjects with iron deficiency anaemia with or without GI symptoms were included: patients admitted in various units of GHPD department, Referred patients from different departments for endoscopy and colonoscopy like Internal medicine, Endocrinology, Nephrology, Surgery and other departments of BIRDEM hospital and Patients seen at gastroenterology outdoor were enrolled after informed consent. All study subjects were underwent endoscopy and colonoscopic procedures after adequate preparation along with examination of their stool. Iron deficiency anemia was defined as hemoglobin concentration < 12.5 g/dl for men (normal range, 13.5 to 17.5) and < 10.6 g/dl for women (normal range, 11.6 to 15.8); With at least one of the following laboratory values consistent with iron deficiency:

- serum iron <45 µg/dl (normal range 50 to 150) with a transferrin saturation <10 percent (normal range 16 to 60 percent),
- serum total iron binding capacity (TIBC) of >400 µg/dl (Normal range 250 – 400)
- Serum ferritin concentration < 20 ng/ml for men (normal range 20 to 450) and < 10 ng/ml for women (normal range, 10 to 250).
- PBF –microcytic hypochromic anaemia

Estimated sample size was 81. But as in this study purposive sampling technique was used due to the time constraint, 68 samples were taken. After ethical clearance, data were collected by face to face interview using a semi structured questionnaire and from procedures results review. Data were analyzed by SPSS software, cross tabulation, chi square test and independent sample tests.

Result:
Iron deficiency anaemia is a common and also a serious health problem especially in developing countries. It is often associated with gastrointestinal (GI) lesions. A hospital based cross-sectional study was carried out to
identify predictors of GI lesions diagnosed endoscopically in patients with iron deficiency anaemia with or without GI symptoms at the department of Gastrointestinal, Hepatobiliary and Pancreatic disorders (GHPD), BIRDEM. Total 68 adult male and female were selected purposively. Data were collected through face-to-face interview, observation and document review. Majority of patients were 55 to 64 years age group (33.8%). Only 2.9% patients were in age group 25 to 34 years which got lowest position. Mean age ± SD of this study subject was 54.00 ±11.792 with maximum and minimum age 86 and 27 years respectively. In this study, more than half of the patients were female (51.5%) and rests were male 33 (48.5%). Among the study subjects, 70.58% patients had GI symptoms, 29.42% had non-GI symptoms. On stool examination, 17.64% patients had ova/cyst of helminthes; 82.36% were normal. Stool OBT revealed 11.8% positive and 88.2% negative. On upper GI endoscopy 32.4% had normal upper GIT, 67.6% had lesions. Majority of these lesions were ulcers and erosions (30.9%), malignancy (ca stomach) was 4.41%; others (which includes congestive gastropathy, reflux oesophagitis, vascular ectasias and helminthiasis) were 32.4%. On colonoscopy, 30.88% patients were normal colon; 69.12% had lesions. Among the lesions, most common lesion was hemorrhoids (36.76%); ca colon was 5.88% and others (includes ulcers, polyp, vascular ectasias and helminthes) were 26.47%.

Patients with normal upper GI endoscopy- 50% had GI symptoms and 50% had non-GI symptoms whereas patients having lesions on upper GI endoscopy 80.4% had GI symptoms and 19.6% had non-GI symptoms. This difference was statistically significant (p<0.05).

Patients with normal colonoscopy- 42.9% had GI symptoms and 57.1% had non-GI symptoms. On the other hand, patients having lesions on colonoscopy 70.6% had GI symptoms and 29.4% had non-GI symptoms. This was also statistically significant.

Significant (malignant) lesions on upper GI endoscopy were 4.41% and on colonoscopy was 5.88%. Cross tabulation was done between anaemia and GI symptoms, it was not significant. T test of biochemical analysis and GI symptoms was done, it was also not significant.

<table>
<thead>
<tr>
<th>Table-I</th>
<th>Age group of the respondents (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (in Years)</td>
<td>Frequency (n)</td>
</tr>
<tr>
<td>25-34</td>
<td>02</td>
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<tr>
<td>35-44</td>
<td>11</td>
</tr>
<tr>
<td>45-54</td>
<td>19</td>
</tr>
<tr>
<td>55-64</td>
<td>23</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>54.00 ±11.792</td>
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</table>

<table>
<thead>
<tr>
<th>Table-II</th>
<th>Frequency of GI symptoms among the study subjects (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI symptoms</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31.25%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10.41%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.33%</td>
</tr>
<tr>
<td>Heart Burn</td>
<td>16.33%</td>
</tr>
<tr>
<td>Loose motion</td>
<td>12.5%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8.33%</td>
</tr>
<tr>
<td>Mucus per rectum</td>
<td>12.5%</td>
</tr>
<tr>
<td>Total</td>
<td>100.0%</td>
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<table>
<thead>
<tr>
<th>Table-III</th>
<th>Non GI Symptoms among the study subjects (N=68)</th>
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</thead>
<tbody>
<tr>
<td>Non GI symptoms</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Light Headedness</td>
<td>10.0%</td>
</tr>
<tr>
<td>Leg swelling</td>
<td>15.0%</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>20.0%</td>
</tr>
<tr>
<td>G. weakness</td>
<td>40.0%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>6.0%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>4.0%</td>
</tr>
<tr>
<td>Palpitation</td>
<td>5.0%</td>
</tr>
<tr>
<td>Total</td>
<td>100.0%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Table-IV</th>
<th>GIT status of the patients (N=68)</th>
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</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Frequency (n)</td>
</tr>
<tr>
<td>GI Symptom</td>
<td>48</td>
</tr>
<tr>
<td>Non-GI Symptoms</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
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</table>
Table-V

Findings of Endoscopy and Colonoscopy procedures (N=68)

<table>
<thead>
<tr>
<th>Findings</th>
<th>Endoscopy</th>
<th>Colonoscopy</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>22(32.4%)</td>
<td>21 (30.88%)</td>
</tr>
<tr>
<td>Lesions</td>
<td>6 (67.60%)</td>
<td>47(69.12%)</td>
</tr>
</tbody>
</table>

Table-VI

Chi-square test of endoscopic findings with symptoms (N=68)

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>GI symptoms</th>
<th>Non-GI symptoms</th>
<th>x²</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>11(50%)</td>
<td>11(50%)</td>
<td>6.640</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>Positive findings</td>
<td>37(80.4%)</td>
<td>9(19.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P value <0.05, df = 1, x² = 6.64.

Table-VII

Chi-square test of colonoscopy findings and symptoms (N=68)

<table>
<thead>
<tr>
<th>Colonoscopy findings</th>
<th>GI symptoms</th>
<th>Non-GI symptoms</th>
<th>x²</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>09(42.9%)</td>
<td>12(57.1%)</td>
<td>11.25</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Positive findings</td>
<td>39(70.6%)</td>
<td>08(29.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P value <0.05, df = 1, x² = 11.25

Discussion:
Iron deficiency anaemia due to chronic blood loss is usually silent and becomes evident when patients become symptomatic. Studies in patients with IDA without gastrointestinal symptoms are few. It is difficult to conclude what is usual pattern of diseases and factors which can predict the endoscopic outcome in IDA patients without gastrointestinal symptoms\(^{11}\).
In this study the respondents aged 25-80 years were selected. The mean ± SD of age of the respondents was 54 ±11.79 years and 33.8% respondents were of 55 to 64 age group. Maximum and minimum age were 86 and 27 years where range was 59 years.

More than half of the patients were female 35(51.5%) and rests were male 33 (48.5%). Data was mostly collected at working hours which might be the reason for presence of high proportion of female in the sample unit.

Less than one third of the subjects had severe anemia (23.53%). Most of the subjects had moderate anemia (41.18%) followed by mild anemia (35.29%). In a normal population, 2.5% of the population would be expected to be below this threshold12. Hence, iron deficiency anaemia would be considered a public health problem only when the prevalence of haemoglobin concentration exceeds 5.0% of the population14.

Among the study subjects 32.4% had normal upper GIT at endoscopy, 30.9% had ulcers and erosions, 36.8% had other findings such as congestive gastropathy, Ca stomach, reflux oesophagitis and vascular ectasia.

A study done by Majid et al. showed that 10% of patients had colonic involvement while 61% had bleeding and non bleeding causes in upper gastrointestinal tract. Lesions involving both the tracts were present in one patient. Result of this cohort favors that endoscopic evaluation of the upper gastrointestinal tract first15.

Normal colonoscopy finding were observed in 30.88% study subjects, 36.76% respondents were suffering from hemorrhoids and 32.35% patients were presented with other GI findings such as Ulcer, Ca colon, Polyp and Vascular ectasia.

Among the study subjects, most of the patients found negative OBT finding (88.2%). Rest had positive (11.8%).

In this study, among the patients having normal endoscopic findings- 50.0% had GI symptoms and rest 50.0% had non-GI symptoms. Respondents with positive findings at endoscopy - 80.4% had GI symptom and 19.6% had non-GI symptoms. These differences were statistically significant (p<0.05).

Among the patients with normal colonoscopy finding, 42.9% had GI symptoms and 57.1% had non-GI symptoms. Among the patients with Positive findings 70.6% had GI symptoms and 29.4% had non GI symptoms. This difference was statistically significant (p<0.05).

Study by Jame et al.,Capurso et al. showed that more than half (70.58%) of the respondents having GI lesions on endoscopy had gastrointestinal symptom and rests had no such symptoms16. The study also showed Hemoglobin, ferritin, female gender and history of NSAIDs have been associated with endoscopic lesions in patients with IDA having gastrointestinal symptoms. In the current study there was no correlation with the factors described in patients with GI symptoms.

Available data in patients with IDA having gastrointestinal symptoms revealed the prevalence of endoscopic lesions is up to 70% while in asymptomatic IDA patients the cause (bleeding and non-bleeding) was found in 85% and bleeding related lesions were found in 37- 44%. In another study it was found that 53% of patients with bleeding related cause for IDA and overall cause of IDA (bleeding and non bleeding lesions) was 71% on upper and lower GI endoscopy17.

A prospective study on patients with iron deficiency anaemia found an upper GIT lesion in 49% of cases and a lower GIT lesion in 32% of cases18.

Finally, our study demonstrated that endoscopic procedures (both Upper GI endoscopy and Colonoscopy) is valuable in identifying the cause of iron deficiency anaemia in patients with IDA whether they have GI symptom or not. So GIT evaluation is important for every patient with iron deficiency anaemia.

Our study also demonstrated those endoscopic lesions (both upper and lower GI) are more common in patients having GI symptom than those without. But, the sample size of this study was small to draw any reasonable conclusions.

**Conclusion:**

Essentially any lesion, in any site of the gastrointestinal tract, can bleed in an occult or obscure fashion. The most common manifestation of occult bleeding is iron deficiency anemia. While gastrointestinal tract malignancy is a crucial consideration in this group of patients. In our study, majority of the study population had lesions on endoscopy (both upper GI endoscopy and colonoscopy) including malignant lesions. Study showed that lesions are more common in patients with IDA.
GI symptoms than those without GI symptoms (non-GI symptoms). In this study, the most common upper GIT lesion on endoscopy was ulcers and erosions followed by congestive gastropathy, Ca stomach, reflux oesophagitis, and vascular ectasia. The most common colonoscopic finding was hemorrhoids followed by other lesions including ulcers, ca colon, polyp, and vascular ectasia. Therefore, Routine endoscopic (both upper and lower GI) procedures is valuable in evaluating patients with iron deficiency anemia for diagnostic as well as therapeutic purposes. Effective treatment of patients with IDA is predicated on the identification of a specific lesion. Further research is expected to shed light on the role of endoscopy or colonoscopy, in particular to investigate whether these modalities improve outcomes.

**Limitations of the study**

Although optimum care had been tried by the researcher in every step of this study, still some limitations existed:

- The study was conducted in a selected institution. So the study population might not represent the whole community.
- Probability sampling technique could not be employed to recruit the study unit; they were selected purposively due to time constraints. As a result, there might be some selection bias.
- In spite of maximum effort by the researcher due to time and resource limitation sample size was small; a larger sample size would have given a better result.

**Recommendations:**

This hospital-based cross-sectional study provides information about iron deficiency anemia and GI symptoms and factors associated with it among adults.

Following recommendations are made based on the study findings:

- When planning therapeutic approaches for IDA patients, GI lesions always should be taken into consideration and identification and treatment of it should be an integral part of IDA management protocol.
- IDA patients, particularly those who are without GI symptom, should be routinely screened for GI lesion.
- In this study, small intestine distal to 2nd part of duodenum was not visualized. Lesion in that part causing IDA could not be detected. So, those study subjects who have normal GIT on endoscopy may have lesions in the small intestine. Therefore, evaluation of small intestine by enteroscopy or capsule endoscopy may indentify lesions in those with apparently normal GIT.
- Primary care physicians should be informed that only blood transfusion or iron supplement is not the treatment of iron deficiency anemia, rather underlying cause should be found out and treated accordingly.
- Further in-depth research should be conducted to clarify the association between GI symptoms and IDA.

**References:**


Evaluation of Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL), as an Early Biomarker and Prognostic Factor of Contrast Induced Acute Kidney Injury (CI-AKI) following Cardiac Catheterization

A NESSA\textsuperscript{a}, MAH FAKIR\textsuperscript{a}, M MOSTAFI\textsuperscript{a}, M AHMED\textsuperscript{b}

Summary:

Acute kidney injury (AKI) usually detected by s. creatinine, which rises after 48 hrs of insult causes delay in diagnosis and to take preventive or therapeutic measures. Hence amongst many neutrophil gelatinase associated lipocalin (NGAL) is emerging as early, sensitive, and most promising biomarker of AKI both in urine and plasma.

This prospective cross sectional observational study was carried out in Combined Military Hospital (CMH) Dhaka from October 2011 to March 2012. A total of willing 100 adult patients undergoing elective coronary angiogram (CAG) with normal kidney function were included in this study. Our study defined contrast induced AKI (CI-AKI) as rise of serum creatinine by $\geq 25\%$ or $e"0.5 \text{ mg/dl from}\text{ baseline after exposure to contrast media and urine NGAL } e"100 \text{ ng/ml was taken as cut off value to predict AKI as calculated by ROC curve. The main outcome measures were urine NGAL at 4 hrs and serum creatinine at 48 hrs after CAG. Significant elevation of urine NGAL was noted in 9 patients after 4 hrs of CAG, of them 8 (8\%) patients developed raised s. creatinine (AKI) after 48 hrs. Patient demographics and procedural factors were although statistically significant in few instances but none was predictive of AKI.}

Keywords: NGAL, Biomarker, CI-AKI, Cardiac catheterization.

Introduction:

The incidence of acute kidney injury (AKI) has reached epidemic proportions worldwide, affecting about 7\% of hospitalized patients. In the critical care settings, the prevalence of AKI requiring dialysis is about 6\% with a mortality rate exceeding 60\%.\textsuperscript{1,2} A significant increase in morbidity and mortality associated with AKI has been demonstrated in a wide variety of clinical situations including exposure to radio contrast dye, cardiopulmonary bypass, mechanical ventilation, sepsis etc. The early diagnosis of AKI currently depends on detection of reduced kidney function by the rise in serum creatinine concentration which is a delayed and unreliable measure in acute setting.

The search for early specific simple AKI biomarker is an area of intense contemporary research to permit more timely diagnosis of AKI, prediction of injury severity and safety assessment during drug development. Amongst many promising new biomarkers of AKI, NGAL is emerging as excellent biomarker both in urine and plasma, which significantly (more than tenfold) increase within 2-4 hrs of both ischaemic and nephrotoxic AKI in animal models.\textsuperscript{3,4}

NGAL also known as lipocalin 2 or Lcn is a 25 KDa protein initially identified bound to gelatinase in specific granules of the neutrophil. It is synthesized during a narrow window of granulocyte maturation in the bone marrow\textsuperscript{5} but also may be induced in epithelial cells in the settings of inflammation and malignancy.\textsuperscript{6}

Till to date, there is no study regarding NGAL carried out in Bangladesh in any clinical or preclinical settings. So it is imperative to study the significance of NGAL as simple, specific, cheap and early predictors of AKI in various clinical settings. This study will add and strengthen the data already available in the western literature or to have a reference data in this regard home and abroad.
Materials and methods:
This was a prospective cross sectional observational study carried out in combined military hospital (CMH), Dhaka after getting ethical clearance from directorate general of medical services (DGMS) of Bangladesh armed forces between the period of October 2011 to March 2012. A total of willing one hundred patients of both sexes undergoing coronary angiogram for diagnostic or therapeutic procedure were included in the study. Those with known kidney disease as understood by raised serum creatinine or e-GFR <60 ml/min/1.73 m2, peripheral vascular disease, severe chest infection, urinary tract infection, history of contrast allergy or contrast administration within last one month, who developed shock during the procedure and who were receiving aminoglycosides, NSAIDs were excluded from the study.

Demographic characteristics, baseline investigations reports, procedural factors were recorded in a preformed data sheet for each patient. Low osmolar, nonionic radiocontrast agent iohexol (Imiro-350) was used for all patients. Urinary NGAL and s creatinine tests were done in the following sequence-

t₀ - baseline (just before procedure).
t₁ - 4 hrs after the procedure.
t₂ - 48 hrs after the procedure.

Urinary NGAL samples were analyzed by human NGAL rapid ELISA kit(037). Lot no: NR-1006 FCE: BIOPORTO Diagnostics, Denmark.

The rise of serum creatinine from baseline by either ≥ 0.5 mg/dl (≥44.2micromol/L) or ≥25% occurring 48 hrs of contrast administration was defined as CI-AKI.7

The data collected were tabulated and analyzed using SPSS (statistical package for the social sciences) package version 13 software. Quantitative data were expressed as mean & standard deviation (X ±SD) and analyzed by applying student’s t- test (paired and unpaired) for comparing two groups of variables .Qualitative data were expressed as number and percentage (no & %) and analyzed by applying chi-square test. Results were considered as significant at p<0.05.

Results and observations:
The receiver operating characteristics curve at different cut off values in relation to s. creatinine were evaluated. With a cut-off value of 100 ng /ml, the 4 hr u-NGAL revealed the highest sensitivity and specificity (100% and 98.91% respectively) in predicting AKI with area under the curve (AUC) 0.995.(Fig-1)

Fig.-1: ROC curve at different cut off values of u-NGAL in relation to serum creatinine

There was a sharp rise of mean urine NGAL (150±29.52 ng/ml) at 4 hrs time point in AKI group, whereas there is no significant change in non- AKI group (21.16±18.55) (Fig.-2) and it was statistically significant (p=0.0001). But at 48 hrs the level of uNGAL in AKI group although still higher than baseline but dropped below the cut off value (100 ng/ml).

Fig.-2: u NGAL vs time
Patients having no AKI (rise of serum creatinine <25% or rise <0.5 mg/dl) (n=92) and AKI (rise of serum creatinine ≥25% or rise ≥0.5 mg/dl) (n=8) mean baseline and at 4 hrs s. creatinine didn’t differ significantly (Fig-3). But at 48 hrs, the mean change of serum creatinine in AKI group (1.59±0.19) was statistically significant (p=0.0001) than non AKI group (1.08±0.15).

**Table-I**

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Marker</th>
<th>No AKI</th>
<th>AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>u-NGAL</td>
<td>91</td>
<td>08</td>
</tr>
<tr>
<td>48</td>
<td>s. creatinine</td>
<td>92</td>
<td>08</td>
</tr>
</tbody>
</table>

Prediction of AKI basing on raised u-NGAL (>100 ng/ml) and s. creatinine (≥25% or ≥0.5 mg/dl from base line)

**Table-II**

*Comparison of patients characteristics with CI-AKI and Non-AKI as predicted by uNGAL (>100ng/ml) at 4 hrs time point (n=100).*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Non-AKI(n=91)</th>
<th>AKI(n=09)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>51.76±8.98</td>
<td>61.38±11.01</td>
<td>(0.005)a</td>
</tr>
<tr>
<td>Range</td>
<td>(30-75)</td>
<td>(36-70)</td>
<td></td>
</tr>
<tr>
<td>Sex(M/F)</td>
<td>72/19</td>
<td>7/2</td>
<td>(0.01)b</td>
</tr>
<tr>
<td>DM(+/−)</td>
<td>23/68</td>
<td>8/1</td>
<td>(0.0001)b</td>
</tr>
<tr>
<td>HTN(+/−)</td>
<td>50/41</td>
<td>7/2</td>
<td>(0.069ns)b</td>
</tr>
<tr>
<td>Hb% (gm/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>12.16±1.64</td>
<td>12.01±1.08</td>
<td>(0.515 ns)a</td>
</tr>
<tr>
<td>Range</td>
<td>(10.80-14.70)</td>
<td>(10.2-13.80)</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>67.37±6.88</td>
<td>69.88±5.65</td>
<td>(0.306 ns)a</td>
</tr>
<tr>
<td>Range</td>
<td>(50-80)</td>
<td>(60-77)</td>
<td></td>
</tr>
<tr>
<td>e-GFR(ml/min/1.73m²) (CG method)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>80.87±15.63</td>
<td>76.76±13.67</td>
<td>(0.474 ns)a</td>
</tr>
<tr>
<td>Range</td>
<td>(60.00-152.77)</td>
<td>(60.30-93.55)</td>
<td></td>
</tr>
<tr>
<td>Vol of Contrast media (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>89.67±42.77</td>
<td>125.00±23.15</td>
<td>(0.024)a</td>
</tr>
<tr>
<td>Range</td>
<td>(50.00-300.00)</td>
<td>(100.00-150.00)</td>
<td></td>
</tr>
<tr>
<td>Dose of Iodine (gm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>31.39±14.97</td>
<td>43.75±8.10</td>
<td>(0.024)a</td>
</tr>
<tr>
<td>Range</td>
<td>(17.50-105.00)</td>
<td>(35.00-52.50)</td>
<td></td>
</tr>
<tr>
<td>Duration of procedure (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>45.27±14.25</td>
<td>58.13±5.30</td>
<td>(0.013)a</td>
</tr>
<tr>
<td>Range</td>
<td>(30.00-90.00)</td>
<td>(45.27±14.25)</td>
<td>0.0137(45.00 60.00)</td>
</tr>
</tbody>
</table>

*aUnpaired Student’s ‘t’ test
*bChi square test
*ns = Not significant
CG method=Cockroft Galt formula.
at different time points (0, 4, 48 hrs) revealed at 04 hrs, 09 patients (9%) had significantly raised u-NGAL (suspected AKI) whereas no patient had significantly raised s. creatinine at that time point. But at 48 hrs, 08 of them had also raised s. creatinine and confirming AKI. One patient with clinically significant uNGAL at 04 hrs but normal s. creatinine at 48 hrs considered as false positive. (Table-1)

When the demographic features and procedural factors were compared between patients with non-AKI and AKI groups it was found that mean age of the patient in AKI group was significantly higher than non- AKI group (61.38±11.01 yrs vs 51.76±8.98 yrs). Seven (07) male and two (02) female patients had significantly high u-NGAL at 4 hrs after contrast exposure, which is also statistically significant (p value=0.01). 08(eight) patients were diabetic and 01(one) was non-diabetic in high NGAL group whereas 23 diabetic patients and 68 non-diabetic patients had normal u-NGAL and this finding is statistically significant (p=0.0001). 07 patients with AKI were hypertensive and 02 had normal BP in AKI group whereas 42 out of 92 had no history of hypertension in normal u-NGAL (non-AKI) group, which has no statistical significance (p=0.069ns). Mean e-GFR was 76.76±13.67 ml/min/1.73m² in suspected AKI (high NGAL) group compared to 80.87±15.63 in patients with non AKI group. Mean volume of contrast media (CM) in AKI group was 125.00±23.15 ml whereas it was 89.67±42.77 ml in non AKI group (p=0.024). Mean duration of procedure in AKI & non AKI group were 58.13±5.30 and 45.27±14.25 min respectively (p=0.013*). Both pre angiogram urine NGAL and 4 hrs post angiogram urine NGAL were significantly positively correlated with the volume of contrast, duration of the procedure and 48 hrs post angiogram serum creatinine level but had significant negative correlation with HTN, Hb%, body wt and e-GFR level.

Mean duration of AKI (n=09) was 5.25±0.71 days and mean hospital stay after CAG of this group of patients was 6.25±1.16 days compared to 3.70±1.44 days in non AKI group. The difference was statistically significant (P=0.0001). No patient required renal replacement therapy or dialysis and there was no case of mortality in study subjects because of the procedure itself or its complication (AKI).

Discussion:

The incidence of both acute kidney injury (AKI) and chronic kidney disease (CKD) is reaching epidemic proportions. In both situations, early intervention can significantly improve the prognosis. However the paucity of early predictive non invasive biomarkers has impaired our ability to institute potentially effective therapies for these common clinical conditions in a timely manner. A troponin like biomarker of AKI that is easily measured, unaffected by other biological variables and capable of both early detection and risk stratification would represent a tremendous advance in clinical medicine. NGAL is now being evaluated as a novel biomarkers in human AKI in different clinical setting including exposure to radio-contrast dye, cardiopulmonary bypass, mechanical ventilation, sepsis etc. In this study, NGAL is evaluated as an early biomarker of AKI in patients following administration of contrast dye during cardiac catheterization.

Table-III

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Non-AKI (n=91)</th>
<th>AKI (n=09)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of AKI (days)</td>
<td>(uNGAL&lt;100ng/ml)</td>
<td>(uNGAL &gt;100ng/ml)</td>
<td></td>
</tr>
<tr>
<td>Hospital Stay after CAG(days)</td>
<td>3.70±1.44</td>
<td>6.25±1.16</td>
<td>0.0001</td>
</tr>
<tr>
<td>mean±SD (Range)</td>
<td>2.00-3.00</td>
<td>4.00-7.00</td>
<td></td>
</tr>
<tr>
<td>Dialysis requirement</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*Unpaired student’s ‘t’ test

Evaluation of Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) A Nessa et al.
Here Urine NGAL & serum creatinine level is measured just before (t₀), 4 hrs (t₁) and 48 hrs (t₂) after contrast administration and AKI was defined as rise of serum creatinine ≥0.5 mg/dl or 25% from baseline and the cut off value of uNGAL indicating AKI as 100ng/ml as proved by receiver operating characteristic (ROC) curve analysis also.

The diagnostic performance of NGAL varied considerably among different studies depending on the clinical setting at the assay being used. ROC analyses are frequently used to determine the discriminatory ability of a diagnostic test at a different cut off values to predict AKI. The area under the ROC (AUC-ROC) is a measure of the ability of a test to separate patients with the diagnosis from unaffected individuals.

The AUC – ROC for NGAL in the diagnosis of AKI across different studies has varied between 0.61 (a poor test) and 0.998 (a magnificent test).

The predictive performance of NGAL also depends on the severity of AKI as classified by RIFLE criteria. Despite these numerous potential variables, a meta analysis revealed an overall AUC of 0.78 for prediction of AKI when NGAL measured within 6 hrs of initiation of CPB and AKI was defined as a >50% increase in serum creatinine.

Several studies in which patients developed AKI have demonstrated the use of NGAL in the early diagnosis of AKI and proposed cut off value for optimum utility of the test ranging from 100-270 ng/ml reported an optimum value of 104 ng/ml which is close to the value (95th centile of 107 ng/ml) proposed by M.Rachel Cullen.

For patients receiving iodinated contrast media, the development of contrast induced AKI (CI-AKI) is associated with adverse in-hospital outcomes and increased risk of death. In 439 patients with CKD (S.creatinine>158 mmol/L) undergoing percutaneous coronary revascularization, 37% of patient developed CI-AKI as defined by an increase in s. creatinine e°25%. The in-hospital mortality for the AKI group was three times higher than those without AKI (14.9% vs. 4.9%), with an almost two fold increase in one year mortality.

In this study, 9 patients had significantly raised uNGAL at 4 hrs of CAG. Eight of them were diabetic (8 out of total 31 diabetic patients). This agreed with Malyszako et al who concluded that diabetic patients are more vulnerable and prone to develop contrast nephropathy. Toprak reported that the most important and well established patient- related risk factors for CIN are CKD particularly CKD combined with diabetes mellitus and advanced age.

Comparing patients who developed CIN (CI-AKI) and those who did not develop AKI it was found in this study that volume of contrast was significantly higher in those who developed AKI. This agreed with Morabito et al who concluded that contrast media volume is a strong modifiable risk factor for AKI. This was also in agreement with Sanaei-Ardekani et al who reviewed 931 cases of coronary angiography and found increased CIN with increased volume of contrast.

CI AKI has been associated with longer hospital stays and requirement for renal replacement therapy in 1-4% of patients depending on the presence or absence of underling renal impairment or the type of contrast used (high or low osmolar vs. iso-osmolar contrast media).

In this study mean duration of hospital stay in patient (n=09) with CIN was 6.25±1.16 days in comparison to 3.70±1.44 days in no AKI group and the difference is statistically significant. The rise of s. creatinine was subtle and reversible with volume expansion only. No patient of this study required dialysis or there was no case of mortality.

In a retrospective study of 7586 patients undergoing percutaneous coronary intervention, CI-AKI was associated with baseline renal impairment, the presence of acute myocardial infarction, haemodynamic instability and the volume of contrast administered. In contrary to this study Morabito et al reported that lower levels of basal haemoglobin appeared to be related to a higher risk of CI-AKI. Baseline eGFR was significantly lower in patients who developed CI-AKI as also found by Ling et al.

This study has got several strengths. First, we prospectively recruited a relatively homogenous cohort of adult subjects without any preexisting renal pathology whom the only obvious etiology for AKI would be the result of contrast administration. Second, the study design allowed for the precise temporal definition of altered urine NGAL concentration and a direct comparison with subsequent changes in serum creatinine. Results of this study clearly indicate that...
urine NGAL is a powerful early biomarker of AKI that precedes the increase in serum creatinine by several hours to days. The magnitude of rise supports the notion that urine NGAL is a highly discriminatory biomarker with a wide dynamic range and cut off values that allow for easy risk stratification. Third, use of urinary sample have certain advantages like noninvasive nature of sample collections and the reduced number of interfering proteins although leucocyturia can be a confounding variables. Fourth the results obtained using the ARCHITECT® Platform were independent of changes in urinary concentration and were equally applicable after correction for urine creatinine measurements.

The excellent performance of uNGAL in this study can probably be attributed to the exclusion of patients with co morbidities (e.g. known kidney diseases) and tend to the fact that we studied a homogenous population undergoing routine CAG. Similar to several previous investigations we didn’t normalize u-NGAL for urinary creatinine excretion but this approach did not seem to affect the performance of the test in this study.23

Despite the optimism in the field, there are important limitations that exist in the published AKI biomarker literature that must be acknowledged. First, majority of studies reported were from single centers. Second, most studies like this study didn’t include patients with CKD. Third, only a few studies have investigated biomarkers for the prediction of AKI severity, morbidity and mortality. Fourth, biomarker combinations are likely to improve clinician’s ability to predict AKI and its outcomes and these studies are only beginning to surface.

Finally, and perhaps most importantly the definition of AKI in the published studies was based largely on elevations of serum creatinine, which raises the challenge of using a flawed outcome variable to analyze the performance of a novel assay. This definition of AKI set up the biomarkers assay for lack of accuracy due to either false positive or false negative results. Indeed a recent multicenter pooled analysis of published data on 2322 critically ill children and adults revealed the surprising finding that approximately 20% of patients display early elevations in NGAL concentration but never develop increase in serum creatinine.24

Importantly this subgroup of NGAL positive -creatinine negative subjects encountered a substantial increase in adverse clinical outcome including mortality, dialysis requirement, ICU Stay and overall hospital stay. In this study, we found, one patient had raised uNGAL at 4 hrs but his serum creatinine was all through normal. Thus early NGAL measurements can identify patients with subclinical AKI, who have an increased risk of adverse outcomes even in the absence of diagnostic increase in serum creatinine and should alert clinicians to the need for close clinical monitoring of kidney function and facilitate timely initiation of renal protective therapies. Since the gold standard for true AKI (tissue biopsy) is highly unlikely to be feasible in humans and the current absence of gold standard criteria of AKI and universally accepted cut off value, a level of uncertainty will remain for near future.

Conclusion:
NGAL has entered the final phases of the biomarker development process, facilitated by the development of commercial tools for its measurements in larger populations with different settings. Till to-date including in this study, urinary NGAL represent novel, sensitive, specific and highly predictive early biomarker of AKI when compared to other conventional biomarkers. In this study, a significant rise in urine NGAL was demonstrated 04 hours after contrast administration which significantly correlated with the rise in serum creatinine 48 hours after contrast. Thus rise of urine NGAL (>100 ng/ml) can be used as early predictor of contrast induced acute kidney injury. If current prospective multicentre studies with well defined patient cohorts measuring NGAL levels using standardized laboratory platforms provide promising result, NGAL may qualify as ‘Troponin’ of not only in contrast induced but in all types of AKI, which will definitely prove to be useful in facilitating early diagnosis, guiding targeted intervention and monitoring disease progression and resolution.

Acknowledgement:
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References:


Antimicrobial Efficacy of Mineral Trioxide Aggregate against Therapy Resistant Endodontic Microorganisms

MLA BANUa, AKM BASHARb, MR HOWLADERc, MS ALAMd, MA HUSSAINe

Introduction:
Success of endodontic treatment and re treatment depends on elimination of bacteria and their substrate from the root canal. Intra-canal medicaments have been long used to control the pulpal and periapical infection in adjunct with biomechanical preparation. Therefore importance of antimicrobial medicaments in root canal therapy can not be over looked, because asepsis and sterilization in root canal environment can not be accomplished only by biomechanical preparation. So there has been a continuous search for new endodontic medicaments that present an ideal combination of good mechanical, physiochemical and biological properties. Calcium hydroxide which has been used as an root canal medicament, sometimes found to be resistant in failed endodontic cases, especially in presence of certain resistant microorganism like Enterococci faecalis, E.coli etc. Because of relative inefficient activity of calcium hydroxide, concerning the treatment of persistent infection cases, new endodontic materials search has been even more incessant.

Mineral Trioxide Aggregate or MTA is a new promising material, have shown a significant improvement over other materials in endodontics. Perforation, pathological

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incomplete root formation, periapical surgery, resorption etc. are often associated with failed or resistant endodontic cases, in which situation MTA has been proven as most effective repairing restorative material. But regarding these situations, the antimicrobial efficacy of MTA especially against resistant microorganisms has not been clarified yet. Therefore the objective of this study is to evaluation of antimicrobial efficacy of Mineral Trioxide Aggregate on resistant endodontic microorganisms.

Furthermore the antimicrobial efficacy of MTA was also compared with that of calcium hydroxide.

Materials and Methods:
The prospective comparative study was done in the Department of Conservative Dentistry and Endodontics, and the Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University Hospital from January 2006 to December 2007. *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (BTCC 17), *Candida albicans* (BTCC 493) and *Enterococcus faecalis* (clinically isolated) were collected and preserved in crio vial with 20% glycerin broth and stored in liquid nitrogen at -196°C temperature. Mueller Hinton agar media was poured in sterilized Petri Dishes and left till the media turned into gel form. Prepared potato dextrose media was collected and preserved in the same manner. All the Prepared dishes were stored in refrigerator at 4°C until use. Immediately before inoculation, all the media containing plates were dried in dryer to make moisture free.

From the collected microbial specimens, using a sterilized swab, a lawn of single microbiological strain other than *Candida albicans* were taken and spreaded over a sterilized Mueller Hinton Plate. *Candida albicans* was spreaded over a sterilized potato dextrose agar media. All the plates were incubated for 24 hours at 37°C in incubator. Different microbiological strains were sub-cultured in different plates. A standard microbiological suspension was prepared compare with 0.5 McFarland Scale. (0.5 McFarland Scale = \(1.5 \times 10^8\) CFU). The dried media in Petri dish was then inoculated with the prepared standard suspension of 0.5 McFarland Scale by sterile swab stick (Fig.-1).

Now two standard holes of 3 mm diameter and 4 mm depth were prepared on each individual micro organism inoculated plate with a copper puncher (Fig.-2). Mineral trioxide aggregate paste (Pro root MTA, Dentsply, Tulsa, USA) or MTA paste was made in a creamy consistency. One prepared hole in inoculated media was then completely filled immediately by MTA following its preparation (Fig.-3). Calcium hydroxide paste was directly poured into another hole from its tube with the help of a needle supplied by manufacturer (Fig.-4). All the micro organism inoculated plates were maintained at room temperature for 1 hour to allow pre diffusion of the materials, and then incubated at 37°C for 24 hours.
After 24 hours, plates were taken out of the incubator and observed for formation of zones of microbial inhibition. The zones were then measured with a millimeter ruler with accuracy of 0.5mm (Fig.-5). Data were posted on respective data sheets. Tests were replicated for thirty times on each sample.

After completion of the procedure, data were collected and posted on data sheets. The statistical analysis was done for the test of significance.

Data were processed and analyzed using one way ANOVA with multiple comparisons facilitated by Post-Hoc Games-Howell Test. Here p value < 0.05 was considered significant.

Results:
Both MTA and Ca (OH)\textsubscript{2} were found to produce zone of inhibition against \textit{Staphylococcus aureus} (ATCC 25923), \textit{Pseudomonas aeruginosa} (ATCC 27853), \textit{Bacillus subtilis} (BTCC 17), and \textit{Candida albicans} (BTCC 493). (Fig 8) MTA showed highest activity against \textit{S. aureus} and lowest activity against \textit{P. aeruginosa} which was similar to the activity range of Ca (OH)\textsubscript{2} against the mentioned organisms. But both of them failed to produce any activity against \textit{E. coli} and \textit{E. faecalis}. MTA was found to produce a lower efficacy than Ca (OH)\textsubscript{2} while comparing the zone of inhibition between them and statistically it was significant.

The findings of the study derived from data analysis are documented in tabular form (Table I- Table IV).

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Zone of inhibition produced around holes (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTA</td>
</tr>
<tr>
<td>\textit{S. aureus}</td>
<td>14.65</td>
</tr>
<tr>
<td>\textit{P. aeruginosa}</td>
<td>8.20</td>
</tr>
<tr>
<td>\textit{E. coli}</td>
<td>0</td>
</tr>
<tr>
<td>\textit{E. faecalis}</td>
<td>0</td>
</tr>
<tr>
<td>\textit{B. subtilis}</td>
<td>10.70</td>
</tr>
<tr>
<td>\textit{Candida albicans}</td>
<td>12.27</td>
</tr>
</tbody>
</table>

* Means of thirty times assays.
Table II

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Zone of inhibition produced around holes (mm)</th>
<th>p-value #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTA (n = 180)</td>
<td>Calcium hydroxide (n = 180)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>14.65 ± 0.53</td>
<td>24.48 ± 0.61</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>8.20 ± 0.25</td>
<td>12.20 ± 0.25</td>
</tr>
<tr>
<td>E. coli</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B. subtilis</td>
<td>10.70 ± 0.70</td>
<td>15.83 ± 0.69</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>12.27 ± 0.45</td>
<td>15.73 ± 0.69</td>
</tr>
</tbody>
</table>

# Data were analysed using Student’s t-Test and were presented as mean ± SD.

Table III

<table>
<thead>
<tr>
<th>Comparing organisms</th>
<th>Mean difference in zone of inhibition (mm)</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus vs. P. aeruginosa</td>
<td>6.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S. aureus vs. B. subtilis</td>
<td>3.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S. aureus vs. C. albicans</td>
<td>2.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P. aeruginosa vs. B. subtilis</td>
<td>-2.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P. aeruginosa vs. C. albicans</td>
<td>-4.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B. subtilis vs. C. albicans</td>
<td>1.57</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

# Data were analysed using ANOVA statistics with multiple comparison facilitated by Post Hoc Games Howell Test; * The mean difference is significant at 0.05 level.

Table IV

<table>
<thead>
<tr>
<th>Zone of inhibition (mm)</th>
<th>Group</th>
<th>p-value #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MTA (n = 180)</td>
<td>Calcium hydroxide (n = 180)</td>
</tr>
<tr>
<td></td>
<td>7.64±5.76</td>
<td>11.38±8.89</td>
</tr>
</tbody>
</table>

# Data were analyzed using Student’s t-Test Test and were presented as mean ± SD.

Table I shows that both MTA and Calcium hydroxide produced highest zone of inhibition against S. aureus but failed to produce any zone of inhibition against E. coli and E. faecalis.

Table II shows that in the culture media containing microorganisms like S. aureus, P. aeruginosa, B. subtilis and Candida albicans, the zone of inhibitions produced around the holes of MTA was observed to be significantly smaller than those produced around calcium hydroxide suggesting that the efficacy of calcium hydroxide is better than that of MTA on the four organisms (p < 0.001 in each case). However, neither calcium hydroxide nor MTA was found effective on E. coli and E. faecalis as no zone of inhibition was found to be produced in the media containing culture of these two organisms.
Table III demonstrates that antimicrobial efficacy of MTA was significantly better on *S. aureus* than that on *P. aeruginosa, B. subtilis* and *Candida albicans*, \((p < 0.001)\). Again the efficacy of MTA was evident to be better on *B. subtilis* and *Candida albicans* compared to that on *P. aeruginosa* \((p < 0.001)\) with *B. subtilis* being more sensitive to MTA than *Candida albicans* \((p < 0.001)\).

Table IV compares the zone inhibitions produced around the holes in culture plates of irrespective of different microorganisms. The zone of inhibition produced around holes containing MTA was observed to be significantly smaller \((7.64 \pm 5.76)\) compared to that produced around holes containing calcium hydroxide \((11.38 \pm 8.89 \text{ mm})\) irrespective of microorganisms \((p < 0.001)\).

**Discussion:**

In the present study both Mineral Trioxide Aggregate (MTA) and Calcium Hydroxide showed antimicrobial activity against *S. aureus, P. aeruginosa, B. subtilis* and *C. albicans*. The findings are similar to the findings of Sipert et al.\(^8\) who using similar methodology observed in vitro antimicrobial activity of MTA and calcium hydroxide based sealers (i.e. sealapex, fill canal, and Portland cements) against those organisms.

The reason for antimicrobial activity of MTA has been explained by the study of Duarte et al.\(^9\) who demonstrated that the antimicrobial activity is seem to be related with elevated pH. Furthermore MTA contains calcium oxide, which when mixed with water; forms calcium hydroxide and induces an increase in pH by dissociation of calcium and hydroxide ions. An increase in pH level (pH 12.5), creates an unfavorable environment for microbial growth\(^10\) because high pH is considered as bactericidal. Hydroxyl ions kill bacterial cells by damaging the cytoplasmic membrane, protein denaturation and damaging the DNA. Torabinejad et al.\(^11\) observed an initial pH of 10.2 for MTA, rising to 12.5 in 3 h. The antimicrobial activity of calcium hydroxide may also be related to ionization with subsequent release of hydroxyl ions and an increase in pH levels (pH 12.5). The antimicrobial activity of MTA-based materials against *Candida albicans* observed in the present study can also be explained by the sensitivity of this strain to high pH. Al-Nazhan and Al-Judai\(^12\), demonstrated that at a stable concentration of 50 mg/ml, white MTA was able to eliminate *C. Albicans* in vitro for up to three days.

Present study findings solely contradict with the study findings of Filho et al.\(^10\) who observed in vitro antimicrobial activity of Endodontic sealers, MTA based cements and Portland cement. They showed that all above mentioned organisms including *E.coli* and *E. faecalis* also inhibited by those materials. However, the difference between our study and the study of Filho et al.\(^10\) may be due to using double layered agar plates and different concentration of microorganisms.

In the present study *E. coli* and *E. faecalis* were found to be resistant against the anti microbial activity of MTA and calcium hydroxide. Using agar diffusion method, Sipert et al.\(^8\) while observing in vitro antimicrobial activity for sealapex, fill canal, Pro Root MTA, and Portland cements found no antimicrobial activity of MTA and Portland cement against *E. coli*. Ribeiro et al.\(^13\) in an anaerobic condition, observed in vitro antimicrobial activities for MTA, calcium hydroxide and Portland cement; but found no antimicrobial activity against *E. coli* and *E. faecalis*. Miyagak et al.\(^14\) also showed MTA and calcium hydroxide containing sealer have no antimicrobial effect against *E.coi*, *E. faecalis* etc with same methodology. Studies have shown that *E. faecalis* got killed only at a pH greater than 10-12 due to an inbuilt proton pump which enables it to survive in such alkaline environments.\(^15\) The materials may also need direct contact with the bacteria for acting.

While comparing the antimicrobial activity of MTA and calcium hydroxide, although the mechanism of action of antimicrobial activity of MTA and calcium hydroxide is more or less same, in the present study, Mineral Trioxide Aggregate showed an antimicrobial activity lower than calcium hydroxide. This result is similar with previous study\(^8,10,13,16\) This variation in antimicrobial activity between MTA and Ca(OH)\(_2\) may be due to different diffusion and dissociation capabilities of two materials. Some substances have difficulty in dissociating and diffusing in agar (semi-solid medium), not expressing their real antimicrobial effect.\(^17\) A material that diffuses more easily will probably provide larger zones of microbial growth inhibition\(^18\). However, great care was taken to keep the plates for 1 h at room temperature to allow the diffusion the agents through the agar and then incubated.

Although used by many authors, differences in agar medium, diffusion capacity of inhibitory agents, bacterial
strains and cellular density, as well as anaerobic atmosphere may interfere with formation of inhibition zones around materials used in antimicrobial testing. However, there is not a consensus regarding a gold standard test for the appraisal of antimicrobial testing of cements and other solutions used in dental therapy.

**Conclusion:**

According to the study findings, it can be concluded that MTA, though it was found effective against *Staphylococcus Aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Candida albicans*; but it showed a lower efficacy than Ca(OH)$_2$. On the other hand both MTA and Ca (OH)$_2$ found inactive against *E.coli* and *E. faecalis*. So considering all these findings it can be recommended that for achieving asepsis in endodontic infection, Ca(OH)$_2$ is preferable and should be used but continuing search should carry on to find out more effective material even against *E.coli* and *E. faecalis*.

**References:**

Recent Advancement on Current Trend in the Management of Endocrine Emergency in Critically Ill Patient

HS FERDOUSa, F AFSANAb, NK QURESHIC, RSB ROUFd, AA PARVEZd, AS MIRD

Summary:
Endocrine emergencies represent a group of potentially life-threatening conditions that are frequently overlooked, resulting in delays in both diagnosis and treatment, factors that further contribute to their already high associated mortality rates. Although endocrine emergencies are often encountered in patients with a known endocrinopathy, the emergency may be the initial presentation in previously undiagnosed individuals. If these endocrine disorders are not rapidly identified or if specific treatment is delayed, significant complications or even death may occur. Careful evaluation of clinical history and a high degree of suspicion are the corner stone to diagnose such problems. Aggressive management of the patient is equally important as the complications are devastating and can prove highly fatal.

The present article is an attempt to review some of the common endocrine emergencies in intensive care unit and the challenges associated with their diagnosis and management.

Keywords: Endocrine emergencies, Critically ill, Evaluation, Management.

Introduction:
Diabetic and endocrine emergencies are traditionally treated by the acute medical admitting team or ICU staff. Most will see diabetic emergencies on a regular basis, as they are common and diabetes is increasing in prevalence. Diabetic emergencies are usually easily treated and the patients discharged. However, it is vital not to become complacent as these disorders can lead to death. It is particularly important to follow local guideline and to involve the diabetes team both during and after each episode. The other endocrine emergencies are less common, but in some ways more important simply because of their rarity. A high level of suspicion is often required to make a diagnosis, although some, such as acute adrenal insufficiency, myxoedema coma, are usually obvious. In some instances treatment must be started before the diagnosis can be confirmed.

Hypoglycemia:
Common causes of hypoglycemia in the ICU setting include sepsis, severe hepatic dysfunction, renal failure, and adrenal insufficiency. Administration of excessive exogenous insulin is another common cause. Uncommon causes include pancreatic islet-cell tumors, various nonpancreatic neoplasms (e.g., hepatoma, sarcoma, lymphoma, leukemia, and carcinoid tumors) that secrete insulin-like factors, hereditary fructose intolerance, and glycogen storage disease. Certain drugs (e.g., ethanol, sulfonylurea agents, adrenergic blocking agents, pentamidine, quinidine, and disopyramide) can potentially cause hypoglycemia.1

Clinical presentation:
The clinical findings of hypoglycemia are mainly either manifestations of the resulting hyperadrenergic state or the effects of neuroglycopenia. The latter include: headache, visual disturbances, confusion, behavioral changes, delirium, stupor, coma, or seizures. Among the hyperadrenergic manifestations are tremulousness,
anxiety, diaphoresis, palpitations, tachycardia, nausea, vomiting, and weakness.1,3 These signs and symptoms can be absent or blunted in patients taking α-adrenergic blocking agents. In most cases the etiology is apparent or the episode represents an isolated event.

**Laboratory investigations**

Hypoglycaemia is arbitrarily defined as blood glucose level < 3.9mmol/dl. However, serial glucose monitoring is very essential to diagnose and treat any such episode in the ICU.

**Therapeutic management**

In case of severe hypoglycemia or patients on long acting OAD or insulin even with less severe hypoglycemia require hospitalization. Treatment with I/V glucose and patient education regarding prevention of further hypoglycemia is the cornerstone of management.5 Initial treatment consists of IV injection of concentrated dextrose (usually 50 mL of 50% dextrose solution). Whatever caused the hypoglycemia is likely to still be present and the hypoglycemia is expected to recur once the dextrose administered has been metabolized. Therefore, a continuous IV infusion of dextrose should be started. The final aspect of acute management is to provide for serial blood or serum glucose testing to detect possible recurrences and tailor the rate of ongoing dextrose administration.

**Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS)**

Diabetic ketoacidosis (DKA) and the hyperglycemic hyperosmolar state (HHS) appear as 2 extremes in the spectrum of diabetic decompensation.4 They remain the most serious acute metabolic complications of diabetes mellitus and are still associated with excess mortality. Because the approach to the diagnosis and treatment of these hyperglycemic crises are similar, we have opted to address them together.

**Pathophysiology:**

**Precipitating factors**

Infection remains the most important precipitating factor in the development of DKA and HHS. In 20%–25% of cases, infections are the first manifestations of previously undiagnosed diabetes mellitus.5 Omissions or inadequate insulin doses are frequent precipitating factors, particularly for DKA.6 Other precipitating factors, especially for HHS, are silent myocardial infarction, cerebrovascular accident, mesenteric ischemia, acute pancreatitis, and use of medications such as steroids, thiazide diuretics, calcium channel blockers, propranolol, and phenytoin.7 In 2%–10% of cases of DKA, no obvious precipitating factor can be identified.5

**Diagnosis and Clinical presentation**

A definitive diagnosis of DKA or HHS must be confirmed through laboratory investigation. The clinical presentation can provide helpful information for the preliminary bedside diagnosis.8 DKA usually occurs in younger, lean patients with type 1 diabetes and develops within a day or so, whereas HHS is more likely to occur in older, obese patients with type 2 diabetes and can take days or weeks to fully develop. In addition, HHS usually occurs in elderly diabetic patients, often those with decreased renal function who do not have access to water.9 In both conditions, abdominal pain with nausea and vomiting can develop owing to acidosis per se or to decreased mesenteric perfusion and can be mistaken for an acute surgical abdomen. Kussmaul–Kien respiration (rapid and deep respiration) with breath acetone is typical of DKA but is absent in HHS. DKA and HHS are usually accompanied by hypothermia, a normal or elevated temperature may indicate underlying infection.

**Laboratory findings**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water, mL/kg</td>
<td>100(7L)</td>
<td>100-200(10.5L)</td>
</tr>
<tr>
<td>Sodium, mmol/kg</td>
<td>7-10(490-700)</td>
<td>5-13(350-910)</td>
</tr>
<tr>
<td>Potassium, mmol/kg</td>
<td>3-5(210-300)</td>
<td>5-15(350-1050)</td>
</tr>
<tr>
<td>Chloride, mmol/kg</td>
<td>3-5(210-350)</td>
<td>3-7(210-490)</td>
</tr>
<tr>
<td>Phosphate, mmol/kg</td>
<td>1-1.5(70-105)</td>
<td>1-2(70-140)</td>
</tr>
<tr>
<td>Magnesium, mmol/kg</td>
<td>1-2(70-140)</td>
<td>1-2(70-140)</td>
</tr>
<tr>
<td>Calcium, mmol/kg</td>
<td>1-2(70-140)</td>
<td>1-2(70-140)</td>
</tr>
</tbody>
</table>
The success of treatment of DKA and HHS depends on adequate correction of dehydration, hyperglycemia, ketoacidosis and electrolyte deficits 24 (Fig. 1). Any comorbid precipitating event should be identified and treated appropriately.

### Table-II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose level, mmol/L</td>
<td>4.2–6.4</td>
<td>&gt;=14</td>
<td>&gt;=34</td>
</tr>
<tr>
<td>Arterial pH*</td>
<td>7.35-7.45</td>
<td>&lt;=7.30</td>
<td>&gt;7.30</td>
</tr>
<tr>
<td>Serum bicarbonate level, mmol/L</td>
<td>22-28</td>
<td>d’15</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Effective serum osmolality, mmol/kg</td>
<td>275-295</td>
<td>&lt;=320</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Anion gap, † mmol/L</td>
<td>&lt;12</td>
<td>&gt;12</td>
<td>Variable</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Negative</td>
<td>Moderate to high</td>
<td>None or trace</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Negative</td>
<td>Moderate to high</td>
<td>None or trace</td>
</tr>
</tbody>
</table>

*If venous pH is used, a correction of 0.03 must be made.20
†Calculation: Na+ – (Cl– + HCO3

### Thyrotoxic Crisis:

The thyrotoxic crisis, or thyroid storm, is a life threatening exacerbation of the hyperthyroid state characterized by decompensation of one or more organ systems.12 Usually it complicates Graves disease, but sometimes it occurs in association with toxic nodular...
goiter. There is no clear cut off value of circulating thyroid hormones (TH) defining the thyroid storm, since the results of laboratory tests show, in most cases, similar serum levels of TH to those observed in uncomplicated thyrotoxicosis. Nevertheless, the rapid recognition of the thyrotoxic crisis and the institution of immediate drug therapy is important in limiting the morbidity and mortality associated with this condition.

Pathogenesis:
The thyrotoxic crisis typically occurs in patients in whom preexisting hyperthyroidism has not been diagnosed or has been treated insufficiently. The crisis has an abrupt onset, and is almost always evoked by a precipitating factor. How such precipitating events result in an accentuation of thyrotoxicosis is unclear. The magnitude and the steepness of the hormone increase may be more important than the absolute values of circulating TH’s levels. Other possible mechanisms explaining the progression from uncomplicated thyrotoxicosis to thyroid storm include an increase of tissue iodothyronine levels or an enhancement of the cellular response to TH.

It is known that TH increase cellular adrenoceptor expression or modify postreceptor pathways leading to a tissue hypersensitivity to catecholamines.

Clinical presentation:
The clinical picture of the thyroid storm is characterized by four main features: (1) Fever, sinus tachycardia or a variety of supraventricular arrhythmias (paroxysmal atrial tachycardia, atrial flutter and atrial fibrillation), often accompanied by various degrees of congestive heart failure, central nervous system symptoms (agitation, restlessness, confusion, delirium and coma), and finally (4) gastrointestinal symptoms, in particular vomiting, diarrhea, intestinal obstruction. Unexplained jaundice is suggestive for thyroid storm, but is a poor prognostic sign. Dehydration with electrolytes imbalance is another frequent feature. Other typical symptoms and signs of thyrotoxicosis may complete the clinical presentation (goiter, ophthalmopathy, tremor, hyperreflexia, Plummer’s nail, systolic hypertension). Younger patients often present sympathetic related symptoms, while older one frequently show cardiovascular dysfunctions. Atypical presentations, such as normothermic crisis, hepatic failure or apathetic storm (extreme weakness) have been reported.

Diagnosis:
Thyroid storm is not an entity distinct from thyrotoxicosis, but rather one end of a spectrum of severity of hyperthyroidism. Since it is difficult in most emergency departments to obtain rapid confirmatory laboratory or nuclear medicine tests, the diagnosis of thyrotoxic crises is often made on the basis of clinical findings alone, even if the symptoms and signs may not be specific. Furthermore, low levels of thyroid stimulating hormone (TSH) and high levels of free triiodothyronine (T3) and free L-thyroxine (T4) are characteristic, but as yet stated, not helpful in distinguishing uncomplicated thyrotoxicosis from thyroid storm.

Management:
Patients with thyroid storm should be treated in the ICU. This allows close cardiac and neurologic monitoring and early recognition of dehydration, cardiac dysrhythmias, heart failure, and respiratory failure. The use of pharmacologic agents to inhibit thyroid hormone synthesis is the primary specific treatment of thyroid storm. Lugol’s iodine solution is administered as adjunctive therapy to block release of this stored hormone. Other iodine containing agents, such as the oral radiocontrast agent sodium ipodate, oral potassium iodide solution, or IV sodium iodide, can also be used for this purpose. It is important not to administer any of these iodine containing preparations until at least 1 h after propylthiouracil has been started. If iodine is given first, it will augment thyroid hormone synthesis. β-Adrenergic blocking drug (propranolol) is routinely administered to patients with thyroid storm. It blunts the cardiovascular effects of thyrotoxicosis, including tachycardia and hypertension. If there are relative contraindications to propranolol, a cardioselective β-blocker (eg, metoprolol) may be employed. Propranolol, sodium ipodate, and corticosteroids are known to inhibit conversion of T4
to T3 in peripheral tissues. Routine hydrocortisone administration has been recommended in thyroid storm because of the possibility of coexisting adrenal insufficiency.1,33

**Acute adrenal insufficiency:**
Cortisol is the predominant corticosteroid secreted from the adrenal cortex in humans.

With severe infection, trauma, burns, illness, or surgery, there is an increase in cortisol production by as much as a factor of six that is roughly proportional to the severity of the illness.34-37 Stimulation of the hypothalamic–pituitary–adrenal axis in this context is caused by elevated levels of circulating cytokines, among other factors.38 Adrenal responsiveness to exogenous corticotropin is normally maintained during acute illness.39-40 In addition, during critical illness, levels of corticosteroid-binding globulin decrease rapidly,41 leading to increased levels of circulating free corticosteroids. Levels of free cortisol may also increase at sites of inflammation owing to the cleavage of corticosteroid-binding globulin by neutrophil elastase, an effect that liberates cortisol.42 In addition to having systemic actions, inflammatory cytokines can increase tissue cortisol levels through changes in peripheral cortisol metabolism43 and can increase the affinity of glucocorticoid receptors for cortisol.44 These changes in cortisol action appear to be important adaptive mechanisms regulating the inflammatory response.45 During severe illness, many factors can impair the normal corticosteroid response. These factors include preexisting conditions affecting the hypothalamic–pituitary–adrenal axis,45 but corticosteroid insufficiency can also occur during the course of acute illness. Responses involving corticotropin-releasing hormone and corticotrophin can be impaired by head injury, central nervous system depressants, or pituitary infarction.45

**Management:**
Since adrenal insufficiency appears to be common in patients with septic shock, treatment should be initiated at the time of diagnostic testing and can be stopped if results do not indicate the presence of adrenal insufficiency.

In patients in whom improved outcomes are seen, high doses of corticosteroids may be required to overcome tissue specific resistance to corticosteroids.55

Supraphysiologic doses of glucocorticoids in patients with critical illness outside the situations in which benefit has been proved are not indicated.

**Table-III**

<table>
<thead>
<tr>
<th><strong>Features Suggesting Corticosteroid Insufficiency.</strong></th>
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<tbody>
<tr>
<td><strong>Symptoms</strong></td>
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<tr>
<td>Weakness and fatigue</td>
</tr>
<tr>
<td>Anorexia, nausea, vomiting</td>
</tr>
<tr>
<td>Abdominal pain</td>
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<tr>
<td>Myalgia or arthralgia</td>
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<tr>
<td>Postural dizziness</td>
</tr>
<tr>
<td>Craving for salt</td>
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<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Memory impairment Depression</td>
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<tr>
<td><strong>Findings on physical examination</strong></td>
</tr>
<tr>
<td>Increased pigmentation</td>
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<tr>
<td>Hypotension (postural)</td>
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<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Decreased body hair</td>
</tr>
<tr>
<td>Vitiligo</td>
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<tr>
<td>Features of hypopituitarism</td>
</tr>
<tr>
<td>Amenorrhea</td>
</tr>
<tr>
<td>Intolerance of cold</td>
</tr>
<tr>
<td><strong>Clinical problems</strong></td>
</tr>
<tr>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td>Hyperdynamic (common)</td>
</tr>
<tr>
<td>Hypodynamic (rare)</td>
</tr>
<tr>
<td>Ongoing inflammation with no obvious source</td>
</tr>
<tr>
<td>Multiple organ dysfunction</td>
</tr>
<tr>
<td>Hypoglycemia</td>
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<tr>
<td><strong>Laboratory findings</strong></td>
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<tr>
<td>Hyponatremia</td>
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<tr>
<td>Hyperkalemia</td>
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<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Eosinophilia</td>
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<tr>
<td>Elevated thyrotropin levels</td>
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</table>
Myxedema coma:
Myxedema coma is a severe and life threatening form of decompensated hypothyroidism with an underlying precipitating factor. The mortality rates may be as high as 25–60% even with best possible treatment\textsuperscript{66-60}. It presents as central nervous system dysfunction, defective thermoregulation, and cardiopulmonary decompensation.

Etiology:
Myxedema most commonly develops in patients with neglected, inadequately treated, or undiagnosed hypothyroidism. Multiple factors appear to precipitate myxedema coma, including gastrointestinal bleeding; infection; metabolic disturbances such as acidosis, hypoxemia, and hypercapnia; stroke; and cardiovascular compromise (Table 5).
Table IV

<table>
<thead>
<tr>
<th>Common Precipitating Factors of Myxedema Coma$^{61}$</th>
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<tbody>
<tr>
<td>Stroke</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Gastrointestinal bleeding</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Drugs</td>
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<tr>
<td>Anesthetics</td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Sedatives</td>
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<tr>
<td>Metabolic disturbances</td>
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<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Hypoxemia</td>
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<tr>
<td>Acidosis</td>
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<tr>
<td>Hypercapnia</td>
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Table V

<table>
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<tr>
<th>Clinical and laboratory features of myxedema coma</th>
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<tr>
<td><strong>Respiratory:</strong></td>
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<tr>
<td>Hypoxia</td>
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<tr>
<td>Hypercarbia</td>
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<tr>
<td>Myxedema of larynx</td>
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<tr>
<td>Pleural effusion</td>
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<tr>
<td>Pneumonia (precipitating factor)</td>
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<tr>
<td><strong>Cardiovascular:</strong></td>
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<tr>
<td>Bradycardia and hypotension</td>
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<tr>
<td>Cardiomegaly</td>
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<tr>
<td>Low cardiac output</td>
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<tr>
<td>Pericardial effusion</td>
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<tr>
<td>Bundle</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
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<tr>
<td>Bundle branch blocks and arrhythmias Nonspecific ECG finding</td>
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<tr>
<td><strong>Neuropsychiatric:</strong></td>
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<tr>
<td>Confusion and obtundation</td>
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<tr>
<td>Lethargy</td>
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<tr>
<td>Coma</td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Poor cognitive function</td>
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<tr>
<td>Depression and psychosis</td>
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<tr>
<td><strong>Renal and water metabolism:</strong></td>
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<tr>
<td>Anasarca and hyponatremia</td>
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<tr>
<td>Bladder atony</td>
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<tr>
<td>Urine sodium normal or increased</td>
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<tr>
<td>Urine osmolality &gt; serum osmolality</td>
</tr>
<tr>
<td><strong>Gastrointestinal:</strong></td>
</tr>
<tr>
<td>Anorexia and nausea</td>
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<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Paralytic ileus</td>
</tr>
<tr>
<td>Toxic megacolon</td>
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<tr>
<td>Gastric atony</td>
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<tr>
<td>Neurogenic oropharyngeal dysphagia</td>
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</tbody>
</table>

**Treatment of Myxedema Coma:**
Treatment should be prompt and multidimensional with attention to the following principles:

(a) intensive care treatment with ventilator support, central venous pressure monitoring, and pulmonary capillary wedge pressure if feasible in patients with cardiac disease,
(b) appropriate fluid management and correction of hypotension and dyselectrolytemia,
(c) aggressive management of precipitating factors and steroid supplementation if required,
(d) thyroid hormone replacement.$^{61}$

**Pituitary apoplexy:**
Pituitary apoplexy is an uncommon event heralded by abrupt onset of severe headache, restriction of visual fields, deterioration of visual acuity, and weakness of ocular motility frequently coupled with clinical indications of decreased endocrine function.
Hemorrhage into or necrosis of a preexisting sellar mass, usually a pituitary macroadenoma, produces an expansion of sellar contents. Compression of adjacent structures elicits the variable expression of symptoms referable to displacement of the optic nerves and chiasm and impingement of the third, fourth, and sixth cranial nerves. Damage to or destruction of the anterior pituitary leads to multiple acute and/or chronic hormone deficiencies in many patients.63

Signs and symptoms of pituitary apoplexy
- Headache (frontal or retroorbital)
- Restriction of visual fields
- Decrease in visual acuity
- Ophthalmoplegia
- Nausea
- Vomiting
- Vertigo
- Meningismus
- Decreased level of consciousness
- Facial pain or altered or impaired facial sensation
- Epilepsy
- Fever
- Hemiparesis
- Horner syndrome

TREATMENT
The pituitary gland remains capable of secreting adequate amounts of hormones when as little as 10% of residual tissue remains; however, a dearth or absence of sufficient hormone can lead to adrenal crisis. The definitive treatment for pituitary apoplexy is surgery for decompression of constricted cavernous and/or suprasellar structures, especially in cases in which visual acuity or field defects, decreased level of consciousness, or progressive deterioration of visual or oculomotor abilities are present. A significant visual compromise, diminished level of consciousness, and declining visual status are clear indications for operative intervention.64 Extensive intracavernous extension or invasion limit the opportunity for complete tumor removal. Medical management includes close monitoring of endocrine, neurological, and ophthalmological function, hormone administration, and support with intravenous fluids and electrolytes.

Conclusion:
Endocrine emergencies are life threatening as well as uncommon. Timely diagnosis is the greatest challenge for the physician and intensivist. Prompt recognition and management is mandatory to avoid their dreadful consequences. A brief clinical history, suspicion through experienced clinical eye can be helpful to manage the patient before it brings fatal complications. Laboratory investigation helps the confirmation of the clinical suspicion to become a diagnosis but that is also time consuming and very difficult for health facilities in a country like Bangladesh.

Reference:


Chronic Granulomatous Disease: A Rare Hereditary Immuno-deficiency Disorder in a Young Boy with Its Adverse Consequences

MM RASHIDA, A NIGARB, MR HASSANC

Introduction:
Chronic granulomatous disease (CGD) is a rare inherited primary immunodeficiency, first described in the 1950s, in which defective phagocyte killing renders patients susceptible to severe, recurrent life-threatening bacterial and fungal infections1,2. Inheritance is usually X-linked (XL), but can be autosomal recessive (AR). Defects in components of nicotinamide adenine dinucleotide phosphate-oxidase leave phagocytes unable to generate reactive oxygen radicles necessary to eliminate ingested organisms3-8. Patients are particularly susceptible to fungal infection, typically from Aspergillus species, but also catalase positive bacteria including Staphylococcus aureus and Burkholderia cepacia. Most patients present with infections, typically lymph node abscesses, but also recurrent respiratory infection, deep-seated abscesses and septicemia9,10. Since the 1960s, improved tests mean that CGD can be diagnosed easily and accurately11. More recently, the use of prophylactic antibiotics and anti-fungal agents appears to have reduced morbidity and mortality, but CGD remains a life-threatening condition12-16. However, little is known of the clinical course, complications and risk of death. Here, I report a case of chronic granulomatous disease with its clinical features, diagnostic works, management perspectives and adverse outcomes that will help our clinicians for early diagnosis and treatment of CGD in their clinical practice.

Case Report:
A 12 yrs’ young boy, a student of class five was admitted to National Institute of Diseases of Chest and Hospital...
NIDCH on December 2012 with the complaints of severe breathlessness for 1 month and productive cough for same duration. On admission, his breathlessness was so severe that he couldn’t speak in sentences and was sweaty. Sputum was muco-purulent, frothy and profuse. He had fever as well. On query, it was seen that he had been suffering from cough and breathlessness from his early childhood when he was only at three. Since then, he had repeated attack of cough and fever that was treated with different antibiotics by different internists and pulmonologists. He was treated with anti-TB drugs at least two times before, though there was no evidence of sputum microscopy and culture for acid-fast Bacilli (AFB) positive. Previous X-ray chest revealed non-homogeneous opacities at different places of lungs with ring-like and reticular opacities throughout his lung fields. Interestingly, it was seen in serial chest x-rays that the opacities and shadows are changing in locations and textures. This patient hadn’t suffered from chronic diarrhea, abdominal pain, serious skin infection or joint pain. He had parents and two sisters in his family and all were healthy.

On examination, the patient was dyspneic, cyanosed, and sweaty with puffy face and prominent accessory muscles of respiration. He was in sitting posture with a nasal canula on his face with oxygen cylinder beside his table. He was non-anemic, non-edematous, but had early clubbing. His respiratory rate was 34/min; Oxygen saturation was 88%; temperature was 102°F, Pulse 112/ min, Blood pressure 110/75 mm of Hg. There was prominent scalene and supra-clavicular and suprasternal recession. Trechea was central, chest was expanded and breath sound was diminished vesicular with ronchi and crepitations in both lung fields.

Total white cell was 12,500/cu mm and of them, neutrophils were 88%. ESR was 76 mm in 1st hr and hemoglobin was 12 gm/dl. Random blood sugar was 110 mg/dl, serum creatinin 1.2 mg/dl, billirubin 1.1 mg/dl. Ultrasonography of abdomen was normal. Chest radiograph revealed opacity in right middle and lower zone with multiple rings like opacities in both lung fields. Computer tomographic scan of chest revealed ground glass opacities in right lower and part of its middle with bilateral reticular and reticulo-nodular opacities. Sputum culture was done at times. Different organisms was identifies, mostly pseudoMonas aueroginosa, Klbiellaspp, Enterococcus, Coagulase negative Staphylococcus spp, Serratiaemarcescens etc. Sputum AFB microscopy And AFB culture was done this time and for three occasions previously and it was never seen positive. There was a fine needle aspiration cytology (FNAC) done previously in 2003 from an opacity in mid-lung of right side and that cytology revealed non-caseating chronic granulomatous lesions. At that time, he was sent abroad for further evaluation and a Nitroblu-tetrazolium test (NBT) was done which was found positive. Since then, he was taking sulfamethoxazole-trimethoprim 960 mg and fluconazole 50 mg daily as prophylaxis. In spite of all these efforts, he developed recurrent episodes of fever

Fig-1 A & B: CT scan of Chest done in 2005 shows homogeneous opacities more marked in left side with bilateral reticular opacities
and productive cough with increasing breathlessness. He used to take different antibiotics in each episode. Now patient can’t walk meters without breathlessness, defecate in a chair-bound toilet in bed room, had to take oxygen 3 liter/min for at least 15 hrs at home and frequently in demand for salbutamol and ipratropium nebulization. Regularly he was taking salmeterol and fluticasone inhaler twice daily, nebulized N-acetylcysteine twice daily, nutitionalsuppliments as required. Prophylactic sulphamethoxazole-trimethoprime 960mg and itraconazole 100mg daily was prescribed to prevent infection and warfarin 5mg daily to prevent thrombo-embolism was prescribed. He was taking yearly prophylactic pneumococcal vaccine and influenza vaccine.

This acute episode of pulmonary infection was treated with per-enteral hydrocortisone thrice daily, parenteral colistin thrice daily, parenteralvancomycin twice daily, nebulized tobramycin twice daily and nebulized N-acetylcysteine thrice daily with high flow oxygen and bronchodilatormebulizations for 10 days. In spite of all these medications, patient had persistent low-grade fever at evening along with cough and breathlessness at the same time. So, lastly he was put on anti-TB treatment empirically for two weeks and observed improvement with the regime. Then patient was discharged with anti-TB, prophylactic antibiotics and Bronchodilators.

Discussion:

Chronic granulomatous disease (CGD) (also known as Bridges–Good syndrome, and Quie syndrome) is a diverse group of hereditary diseases in which certain cells of the immune system have difficulty forming the reactive oxygen compounds (most importantly, the superoxide radical) used to kill certain ingested pathogens. This leads to the formation of granulomata in many organs. Most cases of chronic granulomatous disease are transmitted as a mutation on the X chromosome and are thus called an “X-linked trait”. The affected gene on the X chromosome codes for the gp91 protein 91-PHOX. CGD can also be transmitted in an autosomal recessive fashion (via CYBA and NCF1) and affects other PHOX proteins. The type of mutation that causes both types of CGD is varied and may be deletions, frame-shift, nonsense, and missense.
Patients with the X-linked recessive form of the disease appear to have a more serious clinical phenotype than patients with the autosomal recessive forms of the disease, based on the fact that they are diagnosed significantly earlier (mean, 3.01 years of age versus 7.81 years of age, respectively), have a significantly higher prevalence of perirectal abscess (17% versus 7%), suppurative adenitis (59% versus 32%), bacteremia/ fungemia (21% versus 10%), gastric obstruction (19% versus 5%), and urinary tract obstruction (11% versus 3%), and a higher mortality (21.2% versus 8.6%). Though no genetic analysis was done in our patient, it was likely to be of X-linked assumed from his family tree, he had no extra-pulmonary illness; but clinical course was aggressive like XL form.

The nitroblue-tetrazolium (NBT) test is the original and most widely-known test for chronic granulomatous disease. It is positive in CGD, meaning that it does not turn blue. The higher the blue score, the better the cell is at producing reactive oxygen species. This test depends upon the direct reduction of NBT by superoxide free radical to form an insoluble formazan. This test is simple to perform and gives rapid results, but only tells whether or not there is a problem with the PHOX enzymes, not how much they are affected. A similar test uses dihydrorhodamine (DHR) where whole blood is stained with DHR, incubated, and stimulated to produce superoxide radicals which reduce DHR to rhodamin in cells with normal function. An advanced test called the cytochrome C reduction assay tells physicians how much superoxide a patient’s phagocytes can produce. Once the diagnosis of CGD is established, a genetic analysis may be used to determine exactly which mutation is the underlying cause.

Gene therapy is currently being studied as a possible treatment for chronic granulomatous disease. CGD is well-suited for gene therapy since it is caused by a mutation in single gene which only affects one body system (the hematopoietic system). Viruses have been used to deliver a normal gp91 gene to rats with a mutation in this gene, and subsequently the phagocytes in these rats were able to produce oxygen radicals.

In 2006, two human patients with X-linked chronic granulomatous disease underwent gene therapy and blood cell precursor stem cell transplantation to their bone marrow. Both patients recovered from their CGD, clearing pre-existing infections and demonstrating increased oxidase activity in their neutrophils. However, long-term complications and efficacy of this therapy are unknown.

Chronic granulomatous disease was first described as ‘fatal granulomatous disease of childhood’ since then advances in the management and treatment of these patients have led to an improvement in life expectancy. However, many still have a chronic disease, which results in prolonged episodes of hospital admission and debilitation. As CGD is a multi-faceted disease with a wide spectrum of disease severity, it may present to a variety of specialists and it is vital to raise awareness of this condition so that appropriate treatment can be instituted promptly.

References:


Retrograde Jejunogastric Intussusception (RJGI): A Life-Threatening Complication after Gastric Bypass Surgery

I FARUK\textsuperscript{a}, SF KABIR\textsuperscript{b}, SM ALAM\textsuperscript{c}, KABMAA HASAN\textsuperscript{d}

Summary:
Retrograde jejunogastric intussusception (RJGI) after gastric bypass surgery is a rare but potentially life threatening complication. This complication may develop after simple gastrojejunostomy, after lower partial resection of stomach with gastrojejunostomy (Billroth-II gastric surgery) or after Roux-en-Y gastric bypass. Among the three anatomic type of jejunogastric intussusception (JGI), type-II is the commonest variety. The acute form is a surgical emergency. Mortality rate is very high. Little is known about the mechanism but many literatures indicate abnormal motility may be a cause. A 50 year old male presented to us with a three month history of repeated vomiting and one day of upper mid-abdominal pain. He had a history of gastric bypass for pyloric stenosis 12 years back. Diagnosis was confirmed by upper GI endoscopy. At laparotomy type II retrograde jejunogastric intussusception was identified. En-block resection of affected segment of jejunum and lower part of the stomach was done followed by Roux-en-Y reconstruction. RJGI is a rare complication of gastric bypass surgery. Early diagnosis is imperative. High index of suspicion is therefore important. Barium meal X-ray, ultra sonogram, enhanced CT scan occasionally be diagnostic, but endoscopy is certainly diagnostic in experienced hand. Laparotomy is mandatory. Surgical options include simple reduction, en-block resection and/or plication.

Key word – intussusception, jejunogastric, retrograde.


Introduction:
Retrograde jejunogastric intussusception (RJGI) after gastric bypass surgery is a rare but potentially life threatening complication.\textsuperscript{1,2} This complication may develop after simple gastrojejunostomy, after lower partial gastrectomy with gastrojejunostomy (Billroth-II gastric surgery) or after Roux-en-Y gastric bypass. There are three anatomic types of jejunogastric intussusception that may develop as complication of the gastrojejunal anastomosis.\textsuperscript{3} In Type I, the afferent loop alone may intussuscept into the stomach. In Type II, the efferent loop may undergo retrograde intussusception and either stops short of or pass through the gastrojejunostomy stoma and in Type III, both afferent and efferent loops together may intussuscept into the stomach. Type II is the commonest variety. Little is known about the mechanism but many literatures suggest abnormal motility may be a cause. JGI can occur at any time after the gastric operation.\textsuperscript{4} Presentation may be acute or chronic. The acute form is a surgical emergency. Mortality may be high (10 to 50\%) if not treated promptly.\textsuperscript{3,5} Barium meal X-ray, ultra sonogram, enhanced CT scan occasionally be diagnostic, but endoscopy is certainly diagnostic in experienced hand.\textsuperscript{6} A case report of retrograde jejunogastric intussusception 12 years after vagotomy and gastrojejunostomy for pyloric stenosis is presented here.

Case Report:
A 50 year old male presented to us with a three month history of repeated bilious vomiting and one day of upper mid-abdominal pain. He had a history of vagotomy and gastrojejunostomy for pyloric stenosis 12 years back. The gastrojejunostomy was performed in conventional posterior, short loop, isoperistaltic and retro-colic fashion. The patient had been relatively asymptomatic since that procedure. Initial diagnosis was acute abdomen. After one day of fluid resuscitation his physical condition became hemodynamically stable, but pain was persistent and poorly relieved by pethidine. Nausea and vomiting were associated symptoms. His vital signs showed a heart rate of 100 beats per minute. Abdominal examination showed a diffuse tender epigastric lump, but no signs of generalized peritonitis. White blood cell count was 9500, serum amylase was 472 U/L. USG of whole abdomen showed distended bowels with huge fluid collection in the stomach? gastric outlet obstruction (Fig.-1).
Endoscopy of upper GIT was done and findings are shown in fig.-2, the pertinent finding was lumen of oesophagus and stomach contains huge amount of (1.5 L) brown color, foul smelling fluid. After aspiration, loops of jejunum became visible within the lumen of the stomach which was protruded through the gastrojejunostomy stoma. Part of the loop was blackish in color.

Then the diagnosis was made retrograde jejunogastric intussusception (RJGI). The decision of urgent laparotomy was taken. Figure-3 shows the findings at laparotomy. On exploration, type II retrograde jejunogastric intussusception was identified. The afferent loop (bilio-pancreatic limb) was markedly dilated. There was jejuno-jejunal intussusception about ten cm. distal to the previous gastrojejunostomy site, which in turn intussuscepts into the gastric lumen through the stoma and causing obstruction to the afferent loop also. After gastrotomy through the anterior wall, the interior of stomach was inspected. The intussusceptum consisted of jejunum. Part of jejunum was necrotic. No lead point was found. Gastric wall appeared normal. En-block resection was done (affected part of jejunum along with lower part of the stomach including the stoma was excised). Duodenal stump was closed and the small bowel was reconstructed by creating a side to side, posterior, retro-colic anastomosis between the Roux limb and gastric remnants using the linear cutter stapler. About 10cm distal to this anastomosis, the bilio-pancreatic limb was anastomosed with the jejunum in end to side manner by hand swing. A naso-gastric tube was kept inside the gastric remnants. The patient did well in the post-operative period and was discharged on 12th post-operative day.

**Fig.-1:** (a) Distended bowels, (b) Fluid collection in the stomach

**Fig.-2:** (a) Loops of jejunum inside the stomach, (b) Part of jejunal loop became gangrenous inside the stomach
Fig.-3: (a) Distended stomach, (b) Jejuno-jejunal intussusception, (c) Jejunal loop after gastrotomy, (d) Division of stomach by linear cutter, (e) Resected specimen
Discussion:
Intussusception is a rare event in adult. Among the post-operative complications of gastrectomy or gastrojejunostomy retrograde jejunogastric intussusception (RJGI) is rare complication. RJGI was first described by Bozzi in 1914. This complication has been observed, either after simple gastroenterostomy or after partial resection with Billroth-II or R-Y reconstruction and may occur after several years of gastric surgery. According to Shackman, three anatomic types of jejunogastric intussusception may occur as complication of the anastomosis. Type II is the commonest variety. This rare complication following gastric bypass surgery has the potential of bowel obstruction, strangulation, gangrene, perforation, subsequent sepsis and death.

Intussusception causes about 1% of small bowel obstructions in the adult patient and most of the cases, it has been associated with a definable bowel lesion. Most intussusceptions are antegrade type. But following gastric bypass surgery, the intussusceptions are more often retrograde and are not associated with a bowel lesion or lead point. The mechanism of jejunogastric intussusception is poorly understood. Suggested underlying causes include - a long afferent loop, jejunal spasm with abnormal motility, increased motility of efferent loop, adhesions leading to intussusception of a more mobile segment into fixed segment, widening of upper jejunum, causes of increased intra-abdominal pressure like vomiting, pregnancy and labor, dilated atonic stomach and retrograde peristalsis. Mechanical causes are also been suggested, among them are adhesions to the mesocolon, a sucking action of the stomach where the stoma is narrow, too large a stoma, jejunal stenosis with obstruction facilitating antiperistalsis and other technical imperfections are important. Once the process has been started, however, its dynamics are easily understood. The point of initial invagination may be at, proximal to or distal to the gastroenterostomy stoma. As peristalsis (afferent loop) or antiperistalsis (efferent loop) continues, more jejunum is pushed into the stoma. In acute type, the neck is tight so the chance of strangulation of the intussuscepted loop is more.

The presentation of RJGI is of two typical patterns, either as an acute and fulminating process or as a chronic and intermittently recurrent one. In acute form the common presentation is upper abdominal pain, bilious vomiting, hematemesis and epigastric lump. Visible peristalsis and upper abdominal rigidity are often present. The usual pre-operative diagnosis has been high intestinal obstruction, acute pancreatitis or acute abdomen. It should be pointed out that a sudden onset of epigastric pain, vomiting, subsequent hematemesis and a palpable epigastric lump in a patient with a previous gastric surgery are thought as the classical triad of jejunogastric intussusception. Except hematemesis all other features were present in our case. In chronic recurrent form symptoms are vague, transient often confusing and subside spontaneously. Repeated episodes are usually accompanied with nausea and vomiting.

Early diagnosis is imperative. A history of gastric surgery is an important clue. Plain X-ray abdomen usually not helpful, mild to moderate elevation of serum amylase is a non-specific finding as in our case. Barium meal X-ray is very helpful. The oval or round filling defect in the stomach with its base at the site of gastroenterostomy stoma and a uniform pattern of curved lines suggestive of jejunal mucosa is quite pathognomonic of JGI. Ultrasonography can show intragastric tubular images with or without peristalsis. Enhanced computed tomography (CT) of abdomen is one of the most reliable method of diagnosis. Findings of a dilated stomach with an intragastric filling by bowel loops suggestive of JGI. Edward described CT with contrast carries an accuracy of up to 80%. However endoscopy performed by someone familiar with this rare complication, is certainly diagnostic as in the present case.

Laparotomy is mandatory. Although definitive, corrective and preventive measures have not yet been established. Surgical options include simple reduction, en-blocked resection with RY reconstruction and/or plication.

Conclusion:
After gastric bypass surgery, retrograde jejunogastric intussusception is a rare but potentially life threatening complication. This complication may occur after several years of gastric surgery. In acute form common presenting symptoms are acute upper abdominal pain, bilious vomiting, haematemesis and epigastric lump. Endoscopy appears to be the most effective diagnostic
tool. Laparotomy is mandatory. Surgical options remain controversial. High mortality is due to delay in diagnosis and poor preparation of patient. Early diagnosis with a high index of suspicion and prompt treatment are therefore important.

References:
Haemophagocytic lymphohistiocytosis in Adult- A Case Report and Literature Review

SF HOSSAIN*a, NK QURESHI*b, Z MAHMUD*c, MI HOSSAIN*d

Summary:
Haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes that commonly appears in infancy, although it has been seen in all age groups. The disease may be inherited or acquired due to infections, collagen vascular diseases and malignancies. The pathological hallmark of the syndrome is uncontrolled activation of T lymphocytes and macrophages, together with an impaired cytotoxic function of NK cells and CD8+ T lymphocytes, resulting into massive cytokine release (e.g., interferon γ, TNF α, interleukin[IL]-6, 8,10,12,18 etc) from these cells and overwhelming inflammation. Lymphocytes and macrophages, sometimes with haemophagocytic activity accumulate in bone marrow, spleen, liver, or lymph nodes.

Introduction:
Haemophagocytic lymphohistiocytosis (HLH) is a rare and frequently fatal syndrome of pathological immune activation, characterized by unregulated histiocyte proliferation and hypercytokinemia.1 It comprises two different conditions, a primary or genetic 2 and a secondary or acquired form3 which may be difficult to distinguish one from another. The primary autosomal recessive form, also known as familial haemophagocytic lymphohistiocytosis (FHLH), is usually seen among children though adult cases have been reported.4 FHLH were first reported among in two siblings in 1952 5 and has an estimated incidence of 1 case per 50,000 live-born children.6 This variety is a fatal disease with a median survival less than 2 months after diagnosis if untreated, and it typically has its onset during infancy or early childhood.7 Despite its name, family history is often negative since the disease is recessive and its onset may be triggered by infections as well.8 Secondary (sHLH) or acquired HLH was first established as a distinct clinicopathological entity by Risdall in 1979 25 which is more common among adults and typically occurs after strong immunological triggers that may occur with a variety of viral, bacterial, fungal, parasitic infections, collagen-vascular diseases, 9-12 and malignancies, particularly T-cell lymphomas.13-16 Considering association, infection is important in both sporadic and familial cases. HLH may often mimic infectious illnesses, such as overwhelming bacterial sepsis and leptospirosis;17 and may also obscure the diagnosis of a precipitating, treatable infectious illness (as reported for visceral leishmaniasis).18 We report a case of HLH in adult in order to illustrate the spectrum of clinical features and to emphasis the importance of prompt diagnosis and initiation of therapy.

Case Report:
A 65-years-old male, known patient of hypertension, diabetes mellitus, coronary artery disease (triple vessel disease with left main), had CABG (one month past) was admitted into Medicine department of United...
Hospital Limited in June 2013 with complaints of drowsiness for 1 day with a recent history of high grade intermittent fever and generalized erythroderma for preceding 6 days. He had no history of headache, convulsion, vomiting, diarrhoea, sore throat, cough, urinary complaints, trauma, documented hypoglycemia, recent change of medication or recent travel. Along with medications of prevailing chronic co-morbidities, he got injectable ceftriaxone 2 gram/day for 4 days prior to admission.

Clinical examination revealed- GCS as 11, core temperature- 104°F, blood pressure as 140/70 mmHg, pulse as 120 bpm, generalized erythroderma distributed more in face, neck and trunk than limbs, congested conjunctiva, healthy sternotomy wound, no lymphadenopathy, no organomegaly and no sign of meningeal irritation with normal deep tendon and planter reflexes.

Initial investigations revealed pancytopenia ( Hb%-11.1 mg/dl, WBC-3.2×10^3/µl with neutrophil 82%, PLplatelet-107×10^3/µl), Hyponatremia (Na-123 mmol/L), raised ALT (128 U/L) and AST (86 U/L)), hypoalbuminaemia (22gm/L), rasied FDP [70 (mg/dl)] and D-dimer [58360 (µg/L)]. Other parameters as PT [13 second (sample)], INR [1.15], APTT-[32.9 (second)], serum procalcitonin [0.9ng/ml], renal function test, urine R/E were normal. ICT for malaria, Dengue, Chlamydia and Viral markers (HBsAg, Anti HCV, CMV IgM-IgG, CMV-PCR, EBV-Ab, HIV 1& 2) were negative. USG of abdomen showed mild hepatomegaly and chest x-ray detected no radiological abnormality. His blood and urine culture both aerobic and anaerobic detected no organism.

During in-hospital course of illness, the patient received empirically injectable broad spectrum antibiotics (including meropenem) along with injectable antiviral (acyclovir) and antifungal (fluconazole) for febrile neutropenia. Despite of supportive treatment with multiple PRBCs, platelet apheresis and G-CSF, pancytopenia worsened progressively ( Hb: 11.1 to 8.9 gm/dl; WBC: 3.2 to 0.6 ×10^3/µl ; neutrophil 82% to 32.8 %; platelet 107 to 74×10^3/µl). Serum bilirubin increased from 0.68 to 2.9 mg/dl, ALT: 128 to 144 U/L and AST: 86 to 111 U/L and patient continued to remain febrile with fluctuating level of conciousness. CT & MRI of brain showed mild cerebral atrophy and CSF analysis revealed mononuclear pleocytosis with elevated protein content.

At this stage with precaution and supportive care, bone marrow aspiration was done which revealed as hypocellularity (Fig.-1) with severely depressed erythropoiesis, granulopoiesis. Megakaryocyte were reduce, lymphocytes and plasma cells were prominent with increased number of histocytes and also showed marked haemophagocytosis (Fig.-2)- altogether suggestive of Haemophagocytic syndrome / Haemophagocytic lymphohistocytosis (HLH). Further studies which revealed elevated serum Ferritin (4541µg/L), Hypofibrinogenaemia(1.07 gm/L) supported the diagnosis of HLH.

**Fig.-1:** Low power view of the bone marrow smear of the patient showing hypocellularity.

**Fig.-2:** High power view of the bone marrow smear of the patient showing several macrophages laden with cell debris (arrow)
Patient fulfilled five of eight diagnostic criteria of HLH including fever, cytopenia, high ferritin, hypofibrinogenaemia and typical bone marrow findings. Therefore treatment according to HLH-2004 protocol was initiated with Etoposide, Dexamethasone, CyclosporineA on the 7th day after admission. Patient remained static during initial three days of chemotherapy but subsequently patient clinical and biochemical parameters deteriorated with all continued supportive treatments. (progressive pancytopenia: as Hb: 9.8 to 9.3 gm/dl; WBC: 0.6 to 0.03 ×10³/µl; neutrophil 32.8 % to 23.5 %; platelet 74 to 22.4×10³/µl). Repeated blood and urine cultures were sterile. Repeat serology did not identify any significant viral titre. The clinical condition of the patient further deteriorated with circulatory & respiratory insufficiency requiring ionotropic support and mechanical ventilation. Despite continued specific and supportive therapy, the patient succumbed to the illness within 12 days of admission and after 5 days of start of chemotherapy.

Discussion:
HLH encompasses a heterogeneous class of rare but potentially fatal disorders characterized by multi-system inflammation, that occurs due to prolonged and intense activation of antigen-presenting cells (macrophages, histiocytes) and CD8+ T-cells, and excessive proliferation and ectopic migration of T-cells resulting into consumption and apoptosis of various hematologic cell lines. The primary form (FHLH) is an inflammatory disease which is similar to secondary one on the basis of symptoms. Age of onset of this variety is less than one year of age in 70% of cases but it can rarely be observed in the first two weeks of life. In rare cases, it may occur in adults as well. Although several types of gene mutations e.g.; PRF 1, UNC 13D, STX 11, RAB27A, STXB2, SH2D1A, XIAP, LYST etc. have been identified in patients with primary HLH, they all lead to the common phenotype of impaired cytotoxic function by NK and T cells, and a predisposition to develop HLH.

Acquired (secondary) forms of HLH may develop as a result of strong immunological activation of the immune system, which may be caused by a severe infections, rheumatological disorders and malignancies. It generally occurs among older children and adults who present without a family history or known genetic cause. Leading triggering agents of infection-associated haemophagocytic syndrome (IAHS) are viruses of the herpes group, especially EBV and CMV. The patients in the original report by Risdull et al. were mostly associated with viral infection following organ transplantation. Subsequently its association was established with many viruses as well as a number of bacteria, fungi, mycobacteria and parasite and the term Viral Associated Haemophagocytic Syndrome (VAHS) was redesigned as Infection Associated Haemophagocytic Syndrome (IAHS). A review of published cases in children with IAHS reported that more than half of them were from Far East and Ebstein Barr Virus (EBV) was the triggering virus in 74% of the children. Fardet et al. reported Human Herpes virus 8 associated HLH among HIV-infected patients. Malignancy associated acquired HLH (MAHS), with lymphoma being the commonest trigger, is well known entity in adults but rare in children. In a recent review of patients with lymphoma associated haemophagocytic syndrome (LAHS) in Japan showed that EBV genome was detected from more than 80% of T/NK cell lymphoma but rarely from B cell lymphoma. Macrophage-activation syndrome (MAS) is a special form of HLH which occurs both in children and adults with autoimmune diseases, and most commonly seen in association with systemic onset juvenile rheumatoid arthritis (sJRA) or adult onset Still’s disease and rarely found with systemic lupus erythematosus or other entities. Clinical picture and laboratory findings are similar to HLH. Patients of sJRA were found to have low NK cell function and perforin expression compared to other form of rheumatoid arthritis. MAS is a grave disorder with a mortality of about 10-20%. It has been suggested by some rheumatologists that MAS be classified as a form of secondary HLH. Categorizing patients as having either “primary” or “secondary” HLH at diagnosis is of limited value. Without a known genetic defect or family history, it is often not possible to make an initial diagnosis of “primary” or “secondary” HLH. Furthermore, a careful search for underlying disease triggers should be performed in all patients. However, Recurrence of HLH, in the absence of autoimmune disease or malignancy, is generally considered to be good evidence that a patient has primary HLH. Despite attempts to differentiate primary from secondary HLH, the clinical presentation
is highly overlapping, hence initial treatment should not be delayed or altered based on these categories.\textsuperscript{19} The clinical picture of HLH is nonspecific and differentiation of HLH from sepsis with disseminated intra vascular coagulation (DIC) can be difficult. Generally, the onset of HLH is acute or subacute, with persistent high-grade fever (e$^\circ$38.5$^\circ$ C and e$^\circ$7 days), anorexia, and weight loss.\textsuperscript{35, 36, 37} Enlargement of the spleen and liver are often seen in HLH. Rash, jaundice, edema, lymphadenopathy, and cerebro-meningeal symptoms (meningitis, seizures, gait and balance problems, etc) can also be present.\textsuperscript{35, 36, 37} Life-threatening multi organ failure is frequently seen in full-pictured HLH.\textsuperscript{36, 37} The fever often fluctuates with complete remission and recurrence. Patients may have a variety of skin manifestations, including generalized maculopapular erythematous rashes, generalized erythroderma, edema, panniculitis, morbilliform erythema, petechiae, and purpura.\textsuperscript{5, 39} The incidence of skin manifestations ranges from 6%-65% with highly pleomorphic presentations.\textsuperscript{4, 40, 7} Some patients may present with features suggestive of Kawasaki disease, including erythematous rashes, conjunctivitis, red lips, and enlarged cervical lymph nodes.\textsuperscript{41} The patient in our case report presented with prolonged fever with generalized erythroderma.

Patients may develop pulmonary dysfunction which is an ominous sign. In a review of the radiographic abnormalities in 25 patients, 17 had acute respiratory failure with alveolar or interstitial opacities, with fatal outcomes in 88% of those cases.\textsuperscript{42} Our patient developed acute respiratory failure and needed ICU support including mechanical ventilation.

More than one-third of patients will present with neurologic symptoms, including seizures, meningismus, altered level of consciousness, cranial nerve palsy, psychomotor retardation, ataxia, irritability, or hypotonia.\textsuperscript{43} Patient may have even only neurological manifestations.\textsuperscript{44, 45} The cerebrospinal fluid (CSF) is abnormal in >50% of HLH patients with findings of pleocytosis, elevated protein, and/or haemophagocytosis.\textsuperscript{43} MRI findings are variable, including discrete lesions, leptomeningeal enhancement, or global edema, and images correlate with neurologic symptoms.\textsuperscript{46} Retinal hemorrhages, swelling of the optic disc and infiltration of the choroid have been reported in infants with HLH.\textsuperscript{47, 48, 49} Diffuse peripheral neuropathy with pain and weakness secondary to myelin destruction by macrophages may also occur.\textsuperscript{50, 51}

The workup for HLH includes a complete and differential blood count, renal function tests, liver function tests, fasting triglycerides, international normalized ratio, partial thromboplastin time, fibrinogen, and ferritin. The most characteristic laboratory findings in HLH are cytopenia affecting e$^2$ cell lineages in peripheral blood and hyperferritinemia, often “sky high” >10,000 µg/L.\textsuperscript{35, 36, 38, 52} Anemia and thrombocytopenia occur in > 80% of patients at the time of presentation\textsuperscript{53, 54} that depends on combination of haemophagocytosis, hypersplenism and massive cytokine release by activated macrophages (e.g., INF à, TNF-á).\textsuperscript{36, 37} Thrombocytopenia is almost always present and can lead to severe bleeding, especially in the presence of coagulopathy (e.g., low fibrinogen level). Current case had pancytopenia. Hepatic manifestations of HLH include a moderate increase in serum transaminases, pronounced cholestasis, raised serum bilirubin, decreased serum albumin and coagulation factors deficiency.\textsuperscript{55} Most patients have variable evidence of hepatitis at presentation.\textsuperscript{53, 4, 54} Autopsy evaluation study of the liver has shown chronic persistent hepatitis with peri-portal lymphocytic infiltration in 22 of 27 patients with HLH.\textsuperscript{56} Our reported case had transaminitis. Hypertriglyceridemia, hypofibrinogenemia, elevated serum lactate dehydrogenase, hyponatremia are frequently seen in HLH.\textsuperscript{35, 36} Elevated VLDL and decreased HDL may also be present.\textsuperscript{35} Nearly 95% of patients have features of disseminated intravascular coagulation and are at high risk for acute bleeding & associated with high (>70%) mortality when present.\textsuperscript{57} Elevated ferritin levels (>10,000 µg/L) are reported to be 90% sensitive and 96 % specific for HLH in children,\textsuperscript{57} although this has not been validated in adults.

Investigations for secondary triggers of HLH include investigations for viral infections (particularly EBV, HSV, HIV and CMV) and for malignancies as clinically indicated. A search for these etiologic agents was performed in our patient. He was found to be negative for EBV,HSV, HIV, CMV virus. However it should be emphasized that with the possible exception of leishmaniasis, anti-infectious therapy alone is not sufficient to control HLH. A lumbar puncture is also recommended as part of a diagnostic workup, and more than half of patients will have a moderate pleocytosis and/or increased protein content, even in the absence of neurological symptoms. The caution with lumbar puncture must be taken with regard to a possibly increased intracranial pressure.\textsuperscript{20} All patients should have a bone marrow aspiration. However, frank haemophagocytosis may not be
observed early in the course of the disease, and serial marrow aspirates may be helpful. 58, 59 Haemophagocytosis might be found in the first bone marrow aspiration of a FHLH patient but the absence of it will not rule out this diagnosis. As a result, if the bone marrow is not conclusive, material should be obtained from other organs e.g.; liver, spleen, and lymph nodes 60, 56 and occasionally the central nervous system 61, 62 skin 63 and serial aspirates over time may also be helpful.58, 59 In our case, the bone marrow aspiration was performed and it revealed haemophagocytosis. Activated macrophages may engulf erythrocytes, leukocytes, and platelets, their precursors, and cellular fragments. These cells appear “stuffed” with other blood cells. Haemophagocytosis may be present in the liver and infiltration of the hepatic portal tracts with lymphocytes is also common.60, 56 Although haemophagocytosis in bone marrow is associated with HLH, the morphologic phenomenon may also be induced by more common events, including blood transfusions, infection, autoimmune disease, and other forms of bone marrow failure or causes of red blood cell destruction.64-66 Despite the nomenclature of HLH, diagnosis should never be made or excluded solely on the presence or absence of haemophagocytosis. Infiltration of bone marrow or liver by activated macrophages, along with global clinical evaluation, may distinguish HLH from other causes of haemophagocytosis. Two highly sensitive diagnostic parameters are low natural killer (NK) cell activity, 67-71 and a hypercytokinemia, in particular elevated alpha chain of the soluble interleukin-2 receptor (sIL-2r) levels (sCD25) 71, 72 in serum and in the CSF.72, 73 NK cell activity helps to differentiate between reactive form of HLH from familial type. In patients with FHL, NK cell number is normal, but the activity is persistently decreased or absent. Patients with acquired HLH may have low NK cell number; NK cell function is decreased with active disease, but usually reverts to normal after treatment. 29 The laboratory work-up should involve perforin expression by NK cell by using flow cytometry. Patients lacking perforin expression should be analyzed for the PRFI gene mutation, Molecular studies for HLH include mutations in perforin (PRF), Munc 13-4 (UNC13D), syntaxin 11 (STX11), and others can be done at specialized centers.

To assist with the rapid diagnosis of HLH, the Histiocyte Society has developed a set of diagnostic guidelines that encompass both clinical and laboratory findings 35 which are summarized in Table 1.

| Table-I

**Revised Diagnostic Guidelines for HLH**

The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled

1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (At least five criteria)

A. Initial diagnostic criteria (to be evaluated in all patients with HLH)

- Fever
- Splenomegaly
- Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
  - Haemoglobin <90 g/L (in infants <4 weeks: haemoglobin<100 g/L)
  - Platelet < 100 × 10^9/L
  - Neutrophils <1.0 × 10^9/L
- Hypertriglyceridemia and/or hypofibrinogenemia:
  - Fasting triglycerides ≥3.0 mmol/L (i.e. ≥265 mg/dL)
  - Fibrinogen ≤1.5 g/L
- Haemophagocytosis in the bone marrow or spleen or lymph nodes
- No evidence of malignancy

B. New diagnostic criteria

- Low or absent NK-cell activity (according to local laboratory references)
- Ferritin ≥500 µg/L
- Soluble CD25 (i.e. soluble IL-2 receptor) ≥2400 U/ml

**N.B:** In the absence of a family history or specific molecular diagnosis, at least five diagnostic criteria are needed for a diagnosis of HLH.
In the absence of a family history or specific molecular diagnosis, an assemblage of at least five of the eight diagnostic criteria are needed for a diagnosis of HLH and initiation of therapy [35]. At the end after ruling out other diagnoses and considering the fact that our patient had five criteria for HLH (fever, pancytopenia, hyperferritinemia, hypofibrinogenemia and Haemophagocytosis in bone marrow), we decided that HLH is the most probable diagnosis. It is important to consider the fact that none of these eight criteria are specific for HLH diagnosis and might be found in sepsis, SIRS and MODS.74-76 For example the etiology of hypertriglyceridemia in these states can be multifactorial such as insulin resistance 77, 78 and inhibition of lipoprotein lipase activity.79, 80 High level of serum ferritin has also been associated with inflammatory states and is frequently seen in toxic patients due to the up regulation of hemoxygenase- 1 (heat shock protein).81, 82 Ferritin is also an anti-apoptotic agent in ischemia-reperfusion injury 83 Elevated soluble IL-2 receptor (CD25) is also observed in sepsis, SIRS and can be a predictive marker in neonatal sepsis.84, 85 Similar to HLH disease, NK-cell activity is also decreased in sepsis and thermal injury.86

The therapy of any form of HLH should focus on: (1) suppression of the life-threatening hyper-inflammatory status by destruction of activated CD8+ T lymphocytes and macrophages, and (2) treatment of any existing HLH triggers. 35,36,52 In cases of FHL, an additional aim is correction of the underlying immune defect. 35,36,88,89 The first prospective international treatment protocol for HLH (HLH-94) was introduced in 1994.91 The experience gained from this protocol and other studies have led to the development of a new treatment protocol, HLH-2004 (including etoposide, dexamethasone and CyA).35 Current international HLH 2004 protocol is designed for all patients with newly diagnosed HLH, with or without evidence of familial or genetic disease, and regardless of suspected or documented infection.35 The protocol represents systemic chemo-immunotherapy including dexamethasone, cyclosporine A, etoposide and, in selected patients, intrathecal therapy with methotrexate. Corticosteroids show cytotoxic effect and inhibit expression on cytokines. Cyclosporine A prevents T-lymphocyte activation. Etoposide is an anti-neoplastic agent highly effective in monocytic and histiocytic disorders. Intrathecal methotrexate is used only in patients with persistently abnormal cerebrospinal fluid or progressive neurological symptoms and CNS reactivation.35

In genetic HLH the ultimate aim must be hematopoietic stem cell transplantation (HSCT) to replace congenitally defective immune system with normal functioning immune effectors cells of healthy donors. However, in the vast majority of FHL cases immuno-chemotherapy with HLH-94 or HLH-2004 protocols is temporarily effective in the control of disease, and the outcome of FHL is uniformly fatal unless the patient undergoes allogeneic stem cell transplantation (allo-SCT). 35,89,90 Treatment of sHLH is not standardized so far and remains highly variable across the centers. Obviously, if possible, treatment of any existing trigger of HLH is a must. Front line treatment of infection associated HLH and MAS (particularly of milder grades) usually involves corticosteroids (as in HLH-94 and HLH-2004 protocols) with or without intravenous immunoglobulin (IVIG), which may be sufficient to control hyperinflammation.36 After improvement of complete blood count and resolution of coagulopathy, steroids are slowly tapered down to avoid relapses.36,92 Patients with viral-associated haemophagocytic syndrome should receive appropriate anti–viral therapy such as ganciclovir for CMV. Other interventions include supportive therapy with antimicrobial prophylaxis and intravenous immunoglobulins (IVIg). 93,35 Emmenegger and others had evidence that IVIG is effective in the treatment of HLH. 94,95 A key finding of their analysis was that efficacy of IVIG was satisfactory if administered at the beginning (within hours) of the macrophage activation process. Rituximab, an anti–CD20 monoclonal antibody, has been used to suppress EBV– infected B cells in HLH.96 The utility of biological response modifiers, such as TNF-á inhibitors, IL-1 inhibitors, IL-6 inhibitors, or anti-CD52 antibodies remains unclear. Available case reports have conflicting results, and at present time there is no consensus on recommendations in respect to this group of drugs in HLH.97-101 Finally, anecdotal reports have also shown the efficacy of allo-SCT in refractory or recurrent sHLH (e.g., EBV-HLH, M-HLH).102-107 Acquired HLH, even when treated in a timely manner, can be fatal and deaths being reported among patients treated with massive doses of steroids.92 However, corticosteroid resistant non-responders may benefit from second-line therapies, such as CyA.87 If there is
no response to aforementioned drugs, use of the HLH-2004 protocol including etoposide is recommended. In summary, patients with sHLH could be started on therapy without etoposide, as long as treatment adjustments are made rapidly in refractory cases. Initial treatment is given for eight weeks, and patients with persistent disease or an underlying genetic abnormality (primary HLH) should go on to continuation therapy as a bridge to allogeneic stem cell transplantation. In patients with poor performance status and multi–organ dysfunction, palliation is reasonable.

Although symptoms and laboratory features improve within 2 to 3 weeks, in some cases cytopenia may persist. In these cases bone marrow examination should be repeated to differentiate between non-response and myelosuppression due to etoposide. If there is no response, then unlikely to have benefit with medical treatment. There is no established salvage regimen. Isolated patient has responded to daclizumab, alemtuzumab or to stem cell transplantation. Hasegawa et al reported remission of HLH after syngenic bone marrow transplantation.

Despite treatment, the prognosis of both familial and acquired forms of HLH is usually poor and is rapidly fatal in untreated cases. The CNS disease can cause relapses and may results into irreversible disability. Since HLH can be rapidly fatal without specific intervention, it is recommended that treatment be started when there is a high clinical suspicion, even when results of some diagnostic studies are still pending.

**Conclusion:**

HLH is a life-threatening hyper-inflammatory syndrome which remains difficult to diagnose and can be easily overlooked or misdiagnosed. The clinical features can mimic the multi-system involvement seen in severe sepsis or malignancy. The presenting features are so indistinct that unless definitive criteria are actively sought, many cases may go unrecognized or be recorded as sepsis. Early establishment of the diagnosis is very important for timely commencement of the treatment, before overwhelming disease activity makes irreversible damage and a response to treatment becomes less likely. Despite treatment, the prognosis of both familial and acquired forms of HLH is usually poor and is rapidly fatal in untreated cases.

**References:**


Medication Bezoar Causing acute Gastric Outlet Obstruction: A Case Report

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Summary:
Medication bezoars are rare and are composed of medications and/or medication vehicles. Rarely, medication bezoars can cause serious problems due to complications such as perforation, obstruction, haemorrhage. A 60 years old woman presented with 10 days history of epigastric pain, weakness and postprandial non-bilious vomiting. Her abdominal ultrasonography showed strong post acoustic shadow noted within 1st part of duodenum possibly foreign body. Upper gastrointestinal endoscopy was performed and a bezoar of tablet of aluminum hydroxide was extracted. The patient had uneventful recovery.

Introduction:
Medication bezoars are unusual entities. Medications reported to cause bezoars include aluminum hydroxide gel, enteric-coated aspirin, sucralfate, guar gum, cholestyramine, enteral feeding formulas, psyllium preparations, nifedipine XL, and mepronamate. These patients often present with signs and symptoms consistent with an obstruction of the gastrointestinal tract and represent an even greater diagnostic challenge due to the rarity of this complication. To date, treatment of medication bezoars involves mainly physical manipulation of the bezoar through lavage, endoscopic removal, or, in most cases, surgical removal. Herein, a 60 years old lady who presented with acute gastric outlet obstruction and had an uneventful recovery after endoscopic extraction of medication bezoar.

Presentation of the case
A 60 years old woman presented with 10 days history of epigastric pain, weakness and postprandial non-bilious vomiting. Pain did not radiate, and was not associated with jaundice, fever or bowel alteration. The patient did not have chest-pain, respiratory difficulties or sweating. She had no contributing factors such as gastric surgery, psychiatric illness, diabetes mellitus but had a history of open cholecystectomy and cholecystolithotomy. The patient had a history of mild dyspeptic upper abdominal pain for which she had taken anti-ulcer drugs on occasions. She took omeprazole capsule and aluminum hydroxide tablet as medication for her complaints before admission. No oral medication was given after admission to our hospital till diagnosis. On physical examination, she appeared ill, mildly anaemic, non icteric, dehydrated with tachycardia with low blood pressure. Her abdomen was soft but mildly tender over the epigastric area. No organomegaly or mass was detected on examination. The rest of her examination was unremarkable. Laboratory test results did not show any notable abnormality except mild hyponatraemia.

Abdominal X-ray film was also unremarkable. Abdominal ultrasonography showed strong post acoustic shadow noted within 1st part of duodenum (Fig.1) possibly foreign body. After sufficient fluid resuscitation and gastric lavage, an upper gastrointestinal endoscopy (UGE) was performed to evaluate the cause of gastric outlet obstruction. A greenish solid impacted foreign body of tablet was detected in the first portion of the duodenum with complete obstruction (Fig. 2). The solid bezoar is extracted with biopsy forceps and dormia basket, after removal it was revealed that the bezoar was formed

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Acute gastric outlet obstruction is relatively uncommon and mostly due to foreign bodies related to food impaction, with meat being the most frequent culprit. The diagnostic approach to acute gastric outlet obstruction is similar to other cause of GOO. However, therapeutic options differ for each patient. The diagnosis should be made in prompt time to prevent life threatening complications due obstruction and/or effect of medication forming bezoar.

Keywords: Medication bezoar, gastric outlet obstruction, endoscopy.

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Discussion: Bezoars are foreign bodies in the gastrointestinal tract that increase in size by the accretion of nonabsorbable food or fibers. Interestingly, the term “bezoar” is derived from Arabic *badzehr* or from Persian *pâd-zahr*, both meaning counterpoison or antidote\(^3,4\). Bezoars are commonly found in domestic animals, and for centuries were used as charms or emollients to treat maladies as diverse as vertigo, epilepsy, and leprosy\(^5\). Although the prevalence of bezoars in humans is low, if treatment is not administered, associated mortality rates may be as high as 30% primarily because of gastrointestinal bleeding, obstruction, or perforation\(^3\). The first description of a postmortem human bezoar was by Swain in 1854\(^6\). The pathologic report of bezoars in humans was largely unrecognized, however, until 1939, when DeBakey and Ochsner reported 311 cases\(^7\).

Gastric bezoars are usually formed by indigestible plant material (phytobezoars), ingested hair (trichobezoars), conglomerations of medications or medication vehicles (pharmacobezoars), or the combination of any of the above\(^8\).

Medication bezoars occur within the digestive tract and are composed of medications and/or medication vehicles. Rarely, however, is bezoar formation solely due to a medication. In nearly all reported cases the patient had one or more significant risk factors that contributed to bezoar formation. They most often occur in patients with a previous history of a gastric operation and are detected in up to 20% of patients who have undergone gastric antrectomy. Reduction of gastric acidity, poor gastric mixing, psychiatric illness, coeliac...
disease and metabolic disorders such as uraemia have also been implicated as contributory factors\textsuperscript{5,9}. Medications reported to cause bezoars include aluminum hydroxide gel, enteric-coated aspirin, sucralfate, guar gum, cholestryramine, enteral feeding formulas, psyllium preparations, nifedipine XL, and meprobamate\textsuperscript{1}. Bowel hypoactivity, dehydration, and concomitant use of anticholinergics and narcotics appear to contribute to the propensity for bezoar formation by aluminum hydroxide gel and Isocal\textsuperscript{1}. The hygroscopic properties of psyllium and guar gum appear to contribute to their propensity to form bezoars. Insolubility of the carrying vehicle of enteric-coated aspirin and nifedipine is the setting in which these medications form bezoars\textsuperscript{1}. In our case, tablet of aluminum hydroxide to cause the bezoar. The exact method by which medications bezoars form is dependent on the particular type or combination of medications involved. Bezoar formation may be associated with significant complications for the patient due to the presence of the bezoar and because of the effects of the medication within the bezoar.

Gastric outlet obstruction (GOO) is a well known condition in Gastrointestinal practice. But acute gastric outlet obstruction is relatively uncommon. In general, most upper gastrointestinal tract obstructions are due to foreign bodies related to food impaction, with meat being the most frequent culprit\textsuperscript{10}. Anybody presented with features of acute gastric outlet obstruction, a meticulous history of ingestion including drugs and others are very important especially in children, mentally retarded and old patient and in those who had previous abdominal operations. The diagnostic approach is similar to the other causes of the GOO. Upper gastrointestinal endoscopy, is not only an investigating tool but also a good option for therapeutic approach for acute gastric outlet obstruction. Ultrasonography and computerized tomography may be done. Treatment of medication bezoars depends largely on the location, cause and complications of the bezoar. To date, treatment modalities includes endoscopic removal involves fragmenting the larger bezoar by water flushes, direct suction, large polypectomy snare, biopsy forceps, electrosurgical knife, mechanical or extracorporeal lithotripsy and Nd:YAG laser\textsuperscript{11}. Small bezoar may be amenable to nasogastric lavage or suction, a clear liquid diet, and the use of prokinetic agents\textsuperscript{12}. Dissolution trials with cola and acetylcysteine may also be used\textsuperscript{11}. A recently described technique from China incorporates a laser mini-explosive technique through an endoscope; in 100 patients, the cure rate was 100\%\textsuperscript{13}. Operative intervention may be needed if endoscopic therapy fails or if there is a complication related to the bezoar such as perforation or bleeding. However, GOO due to bezoars requires early surgery as it rarely improves with conservative therapy. If surgical intervention is required, bezoar removal is commonly done by gastroscopy. For this, either a laparotomy or laparoscopy can be used. Different reports have been published for laparoscopic removal. This technique is usually preferred because of its less postoperative pain and better cosmetic results. However, the longer operating time, higher costs and retrieval problems are the disadvantages of laparoscopy\textsuperscript{14}. For the presented case, endoscopic removal were done and found bezoar of tablet of aluminum hydroxide.

**Conclusion:**

High index of suspicion should be there to identify the medication bezoar as a cause of acute gastric outlet obstruction. The diagnosis should be made in prompt time to prevent life threatening complications due obstruction and/or effect of medication forming bezoar. Surgical intervention is required if conservative treatment or endoscopy fails or complication such as perforation or bleeding.

**Reference:**

7. DeBakey M, Ochsner A. Bezoars and concretions: a comprehensive review of the literature with analysis of
303 collected cases and a presentation of 8 additional cases. Surgery 1939;5:132-160.


A 21-year-old male presented with spastic quadriparesis, developed gradually over months. He had no pain or restricted movement of neck. Other than features of upper-motor-neuron-lesion of all four limbs, physical examination revealed, multiple Café-au-lait macules (>2cm in diameter) [Fig. 1], bilateral axillary freckles [Fig. 2], multiple subcutaneous neurofibroma [Fig. 3] scoliosis, and a tender soft tissue mass at right lower chest. Chest x-ray postero-anterior view showed scoliosis, extrathoracic soft tissue shadow with invasion of the pleural space, consistent with plexiform neurofibroma, rib notching and “twisted-ribbon” ribs [Fig. 4]. Based on clinical and radiological findings, he was diagnosed as neurofibromatosis type 1. MRI of spine revealed multiple neurofibromas, at cervical and dorsal levels. He was offered neurosurgical management. But he decided for treatment at local health-facility, and was lost to follow-up.
Discussion:

von Recklinghausen’s disease or Neurofibromatosis type 1, is an autosomal dominant disorder, first described in 1882 by Frederich von Recklinghausen. It is a relatively common inherited condition (worldwide incidence of ~1 per 2500 to 3000 individuals, irrespective of age, gender or ethnicity), caused by a germ-line-inactivating mutation in the \( NF1 \) gene on chromosome 17q11.2, having high predisposition to develop benign and malignant tumours, and associated with increased mortality and morbidity. The disease manifestation is usually apparent from birth, with varying features of multi-organ involvement, especially the nervous system.\(^1\,^2\)

Common non-malignant features are café-au-lait macules (earliest clinical manifestation, develops within first 2 years), intertriginous freckles or Crowe’s sign (small, usually found in axillary and inguinal region, but may also be present in areaswhere skinfolds are in apposition, including the neck, above the eyelids and under the breasts in women), Lisch nodules (benign melanocytic hamartomas of the iris that is pathognomonic for \( NF1 \), do not impair vision or cause any medical problems, best detected on slit-lamp examination), neurofibromas (benign Schwann-cell tumours, with four subtypes: cutaneous, subcutaneous, nodular or diffuse plexiform, and spinal, result in discomfort or disfigurement, sometimes both sensory and motor deficits), plexiform neurofibromas (arise from multiple nerve fascicles, typically manifest at birth, can continue to grow during adolescence and early adulthood, can extend into surrounding structures, causing substantial pain and bone destruction, have a lifetime risk of malignant transformation), skeletal dysplasia (short stature, osteopenia, scoliosis, sphenoid dysplasia, congenital tibial dysplasia, pseudoarthrosis), cardiovascular abnormalities, ranging from congenital heart disease (cardiovascular anomaly, pulmonary artery stenosis) to vasculopathy (renal and cerebral artery stenosis, aortic coarctation, arteriovenous malformations) and hypertension, and neurocognitive deficits.\(^1\,^2\) Associated malignant tumors with varying lifetime risk include glioma of the optic pathway, malignant peripheral nerve-sheath tumour, gastrointestinal stromal tumour, breast cancer, leukaemia, phaeochromocytoma, duodenal carcinoid tumour, rhabdomyosarcoma etc.\(^1\)

Diagnosis of neurofibromatosis type 1 is most commonly made using established clinical criteria (National Institute of Health consensus criteria).\(^1\,^2\) Two or more of the following clinical features are sufficient to establish a diagnosis of neurofibromatosis type 1: (1) six or more café-au-lait macules (>0·5 cm at largest diameter in a prepubertal child or >1·5 cm in post-pubertal individuals), (2) axillary freckling or freckling in inguinal regions, (3) two or more neurofibromas of any type or one or more plexiform neurofibromas, (4) two or more Lisch nodules, (5) a distinctive osseous lesion, (6) an optic pathway glioma, and (7) A first-degree relative with neurofibromatosis type 1 diagnosed by the above criteria.\(^3\) \( NF1 \) genetic testing is reserved for unusual presentations or reproductive decision-making.\(^1\)

Routine and cheap investigations like chest radiograph can be very important in diagnosis. Kyphoscoliosis, a hallmark of neurofibromatosis, can easily be visualized,
if not evident physically.\textsuperscript{4} In chest radiographs, ribs appear notched, due to erosion by neurofibromas in intercostals nerves in the neurovascular grooves,\textsuperscript{4} whereas “twisted-ribbon” ribs reflect mesodermal bone dysplasia.\textsuperscript{5} Plexiform neurofibromas are poorly delineated diffusely infiltrating multiple masses that arise along the axis of the major nerves, better viewed with CT or MRI.\textsuperscript{5}

A multidisciplinary approach to care throughout the lifetime of the patient has been suggested for the appropriate management of neurofibromatosis type 1. With the enhancing knowledge on the disorder, swift implementation of newer effective treatments is also becoming possible.\textsuperscript{1} Prompt diagnosis is important to provide optimum care. But because of the varying clinical presentation, patients can present to different medical and surgical specialists and symptoms might not be recognized. So clinicians must beware of the diverse features of this disorder, both clinical and radiological, and be vigilant to detect the disorder early.

References:
To
to the

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

Sir,

I would like to thank you for publishing the article ‘Influence of Number of Parity on Bone Mineral Density among Postmenopausal Women’. I have gone through it and found the content nice. I would like to share some of my observations and comments.

Osteoporosis and osteopenia among postmenopausal Bangladeshi women are common problem. Low bone mass is the important. Genetic factors play a significant role in determining bone mass. Others are controllable lifestyle factors such as diet and physical activity, environmental factors such as pregnancy and period of lactation. Amenorrhea (cessation of menstrual periods) after the onset of puberty, before menopause, and after menopause is a very serious threat to bone health.

Teen pregnant mother that have not yet reached peak bone mass, the 30 g of calcium required for the fetal skeleton competes with the calcium demands for the teen’s mineral accretion. It remains controversial whether peak bone mass is compromised in women who experience teen pregnancies.

Several changes occur during pregnancy and lactation that can affect bone mass, including changes in reproductive hormones and in hormones that affect calcium metabolism. Since fetal and infant bone growth during pregnancy and lactation depends on calcium transfer from the mother, there is possibility that pregnancy and lactation affect risk for bone mineral loss later in life. Intestinal calcium absorption increases during pregnancy to meet many of the fetal calcium needs, but maternal bone losses may occur in the last months of pregnancy. Bone mass may increase due to greater estrogen level in the third trimester of pregnancy. The mother’s skeleton also loses bone during breastfeeding, but this loss is largely restored during weaning, as ovulation and menses are re-established. This bone loss and its subsequent restoration appear to be independent of lifestyle behaviors, including dietary calcium intake and physical activity patterns.

4. Some studies indicate that neither extended lactation nor multiple pregnancies are associated with subsequent osteoporosis, whether measured by BMD levels or by assessment of fracture risk. In contrast some studies report, the risk of hip fracture in women has been found to decrease by 5-10 percent with each additional child, and there is no apparent association between the duration of lactation and fracture risk. Some researchers’ belief that, pregnancy and lactation in healthy adult women do not appear to cause lasting harm to the skeleton. Sadat Ali et al., in their study found that, increased parity protects women from osteoporosis and the severity of the disease. In a study, women with more than 10 pregnancies and extended lactation had BMD levels similar to those in women who have not been pregnant. Cumming RG et al. observed that, parity does not have positive correlation to increased risk of fracture. A number of confounding variables influence the effect of parity on BMD, which may contribute to the divergent results in the studies.

Because of the lack of evidence of the potential effects of parity on bone mineral density, the significance of the observed changes in BMD in every bone site and parity remains unclear. Therefore, further well designed observational studies with large sample size should be carried out to confirm these results. Overall I think the article is updated, informative. I would like to thank the authors for their hard work on time demanding common problem.

References:


**Author’s Reply**

Thank you madam for careful reading and criticism about my article. There are lot of studies done in different countries to see the relation between parity and bone mineral density. Ozdemir et al, Gurey et al, Hreshchysyn et al, Ghannam NN shows negative correlation between parity and numbers of pregnancy. Karlsson C et al, Sadat Ali, Cumming R G et al found no relation. Hoffman et al shows BMD increase in subsequent pregnancy. The results of this study were automatically generated in machine and subsequent analysis shows negative correlation. Other confounding variables also influence the effect of parity on BMD. I also strongly agree that further well designed study with larger sample size should be carried out.

**Dr. Irin Parveen Alam**

Assistant Prof. (Gynae)
Sir Salimullah Medical College & Mitford Hospital.
Dear Fellows,

It gives me immense pleasure and honor to address you as the new editor-in-chief of yours esteemed journal of Bangladesh College of Physicians and Surgeons. I express my earnest gratitude to all concerns to bestow this prestigious responsibility on me. Journal of BCPS has been a leading journal of the country through many years and has served with highest impact in enhancing medical education and research in our community. It represents our works and views globally as well. I sincerely look forward to enrich our journal further in all aspects with your kind support and active participation. All members of the editorial board will devote as a team to upgrade our beloved journal to higher international standards.

Your co-operation and Almighty’s blessings are my only strength.

Thank you.

Prof. Khan Abul Kalam Azad
Editor-in-Chief
Journal of BCPS