IRON DEFICIENCY ANAEMIA
CURRENT CONCEPTS

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IRON DEFICIENCY ANAEMIA: CURRENT CONCEPTS

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# List of Abbreviations

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<tr>
<td>6-PGDH</td>
<td>6-Phosphogluconate dehydrogenase</td>
</tr>
<tr>
<td>ALAS2</td>
<td>ALA-synthetase 2</td>
</tr>
<tr>
<td>ABCB7</td>
<td>ATP-binding cassette subfamily B7 genes</td>
</tr>
<tr>
<td>Bmpr1a</td>
<td>Bone morphogenetic protein receptor type 1a</td>
</tr>
<tr>
<td>DMT1</td>
<td>Divalent metal iron transporter 1</td>
</tr>
<tr>
<td>DCytb</td>
<td>Duodenal cytochrome b</td>
</tr>
<tr>
<td>FTH1</td>
<td>Ferritin heavy polypeptide 1</td>
</tr>
<tr>
<td>FTL</td>
<td>Ferritin light polypeptide</td>
</tr>
<tr>
<td>G6PDH</td>
<td>Glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>GRLX5</td>
<td>Glutaredoxin 5</td>
</tr>
<tr>
<td>HCP1</td>
<td>Haem carrier protein 1</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>Haematoxylin and eosin</td>
</tr>
<tr>
<td>Hfe</td>
<td>Haemochromatosis</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Hjv</td>
<td>Hemojuvelin</td>
</tr>
<tr>
<td>IF gamma</td>
<td>Interferon gamma</td>
</tr>
<tr>
<td>IL1</td>
<td>Interleukin 1</td>
</tr>
<tr>
<td>IL6</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>IRP1</td>
<td>Iron regulatory protein 1</td>
</tr>
<tr>
<td>IRP2</td>
<td>Iron regulatory protein 2</td>
</tr>
<tr>
<td>JAK/STAT</td>
<td>Janus kinase/signal transducer and activator of transcription</td>
</tr>
<tr>
<td>MCH</td>
<td>Mean corpuscular haemoglobin</td>
</tr>
<tr>
<td>MCHC</td>
<td>Mean corpuscular haemoglobin concentration</td>
</tr>
<tr>
<td>MCV</td>
<td>Mean corpuscular volume</td>
</tr>
<tr>
<td>PCV</td>
<td>Packed cell volume</td>
</tr>
<tr>
<td>rhEPO</td>
<td>Recombinant human erythropoietin</td>
</tr>
<tr>
<td>RDW</td>
<td>Red cell distribution width</td>
</tr>
<tr>
<td>EP</td>
<td>Erythrocyte protoporphyrin</td>
</tr>
<tr>
<td>RARS</td>
<td>Refractory anaemia with ring sideroblast</td>
</tr>
<tr>
<td>IRE</td>
<td>Iron responsive elements</td>
</tr>
<tr>
<td>sTfR</td>
<td>Serum transferrin receptor</td>
</tr>
<tr>
<td>SI-LfR</td>
<td>Small intestine lactoferrin receptor</td>
</tr>
<tr>
<td>TIBC</td>
<td>Total iron binding capacity</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>Tumour necrosis factor alpha</td>
</tr>
<tr>
<td>UIBC</td>
<td>Unsaturated iron binding capacity</td>
</tr>
<tr>
<td>ZPP</td>
<td>Zinc protoporphyrin</td>
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With the advent of spectacular advances and recent break throughs in various facets of diseases including molecular aspects, genetics epigenomics immunology, and revolutionary changes in diagnostic armamentarium, we were prompted to review the global public health problem of iron deficiency anaemia. This millennium has witnessed amazing strides that have inundated medical literature by colossal breathtaking advances contributing to enhanced comprehension of molecular profiles and mechanisms of hematologic diseases. As Hematology is a discipline that alliances pathology, molecular genetics and medicine, we have endeavoured to incorporate a wide field in the interest of integration. Despite nay because of the accelerating pace of the advances in the cutting edge technology and molecular profile of diseases, in the opinion of the authors the subject of iron deficiency anaemia has not received the attention it truly deserves. In this context, we are primarily concerned with the welfare of the patients and their families and the main focus of our efforts is for successful therapeutic outcomes. As pathologists, we felt deeply committed to deliver useful information in its best light in any way possible. Hence, we have selected an excellent showcase which will hopefully pave the way for students and residents for continued studies of this very consuming global problem of iron deficiency anaemia. Much of what is embodied herein may demand rethinking in future as hematology analogous to Medicine is changing incessantly. We are deeply indebted to the numerous esteemed experts whose publications were freely consulted and quoted and needless to reiterate that this has infused in us enormous confidence in the preparation of this book. Our heartfelt thanks to Puan Adibah, Chief in charge of publications in USIM for her
unstinted cooperation in processing this publication. Any expression of special thanks to Associate Professor Rosline Hassan and Dr. Prashanta Kumar Das will be insufficient to convey our sincere gratitude for their remarkable and ungrudging help for sparing their precious time for reviewing this piece of work. Admittedly it is well nigh impossible for a book of this nature to be wholly free from human errors, and particularly typographical errors. Nevertheless we hope that readers will find it useful, interesting, illuminating and inspiring. We would also appreciate feedback from the readers for further enhancement of the book.
CHAPTER 1: Introduction

The impetus for presentation of this micro-review is to re-look at the common problem of iron deficiency anaemia with particular reference to current concepts of its pathogenesis, historical perspective and impact on health in human population. Hence this warrants a critical appraisal of the subject. It is appropriate therefore to look into its historical perspective in addition to clearly defining the concept of iron deficiency anaemia as a significant public health problem. It calls for an apt definition of iron deficiency anaemia as it is generally conceived today.

There has been a paradigm shift from the early terminology and concept of nutritional anaemia which was defined by World Health Organisation (WHO) in 1968. It was referred to as a condition in which the haemoglobin content of the blood is lower than normal as a result of deficiency of one or more essential nutrients regardless of the cause of the deficiency. WHO studies in determining the cause of anaemia concluded that iron deficiency which was present in 40% to 90% of pregnant women is the most common cause of nutritional anaemia. This particular shift in emphasis in the concept of iron deficiency was further confirmed by Baker and Demayer (1979). Nutritional anaemia assumed great significance as a large component of global anaemia prevalence and iron deficiency anaemia is now being considered as the most common cause of nutritional anaemia. World Health Organization (WHO) in 1989 stated clearly that iron deficiency is by far the commonest cause of nutritional anaemia; it may be associated with folate deficiency especially during pregnancy (WHO/UNICEF/ICCIDD, 2007).

According to the current definition, anaemia is a condition when the haemoglobin concentration is less than 13.0g/dl in males or less than 11.5g/dl in females (Walter, 1994). It obviously causes a decline
APPENDIX 1

Kinetic approach in the management of patient with anaemia

Anaemia

Reticulocytes count

Low

Reduced RBC production

- Nutritional deficiency (e.g., iron, B12, folate)
- aplastic anaemia
- pure red cell aplasia
- Myelodysplastic syndrome (MDS)
- bone marrow infiltration
- drugs

Raised

Blood loss

- Trauma
- malaena
- haematemesis
- menorrhagia
- peptic ulcer
- malignancy
- excessive blood donation
- hemodilysis

Increased RBC destruction

- hereditary spherocytosis
- thalassaemia
- haemoglobinopathies
- autoimmune haemolytic anaemia
- thrombotic thrombocytopenic purpura (TTP)
- haemolytic uraemic Syndrome (HUS)
- malaria
APPENDIX 2

Morphological approach in the management of patient with anaemia

- **Anaemia**
  - **MCV**
    - Low
    - Normal
    - Raised
      - **Reticulocyte**
        - Raised
        - Normal / low
          - Thalassaemia Major
          - other thalasaemia Syndromes eg; S-β thal, E-β thal
        - IDA
        - lead poisoning
        - thalassaemia trait
        - sideroblastic anaemia
        - ACD
        - enzyme disorders eg; G6PD def
        - immune disorders eg; AIHA
        - MAHA
        - infection induced hemolysis
        - megaloblastic anaemia ie; B12 & folate deficiency
        - MDS
        - LGL
        - alcoholic
        - liver disease
        - hypothyroidism
        - membrane disorders eg; HS, HE
        - haemoglobinopathies eg HbSS, HbSC
        - Congenital AA
        - Diamondblackfan, Fanconi's anaemia
        - Acquired AA
        - BM infiltration by malignancies
        - aplastic crisis with underlying hemolysis eg; HS, sickle cell disease
        - hypersplenism
        - ACD

**MCV** = Mean Cell Volume
**ACD** = Anaemia of Chronic Disease
**G6PD** = Glucose - 6 - Phosphate Dehydrogenase
**AIHA** = Autoimmune Hemolytic Anaemia
**MAHA** = Microangiopathic Hemolytic Anaemia
**MSD** = Myelodysplastic Syndrome
**LGL** = Large Granular Lymphocyte Leukaemia
**HS** = Hereditary Spherocytosis
**HE** = Hereditary Elliptocytosis
**AA** = Aplastic Anaemia
Appendix

Diagnostic approach to children with pallor

![Diagram]

- **Anaemia**
  - **Raised Reticulocyte count**
    - **MCV**
      - **Low**
        - Thalassaemia major
        - other thalassaemia syndrome eg; S-β thal, E-β thal
      - **Normal**
      - **Raised**
        - enzyme disorders eg; G6PD def
        - immune disorders eg; AIHA
        - MAHA
        - infection induced hemolysis
  - **Normal or Low Reticulocyte count**
    - **MCV**
      - **Low**
        - IDA
        - lead poisoning
        - thalassaemia trait
        - sideroblastic anaemia
        - ACD
      - **Normal**
      - **Raised**
        - megaloblastic anaemia eg; B12 and folate deficiency

- **MCV** = Mean Cell Volume
- **ACD** = Anaemia of Chronic Disease
- **G6PD** = Glucose - 6 - Phosphate Dehydrogenase
- **AIHA** = Autoimmune Hemolytic Anaemia
- **MAHA** = Microangiopathic Hemolytic Anaemia
- **HS** = Hereditary Spherocytosis
- **HE** = Hereditary Elliptocytosis
- **AA** = Aplastic Anaemia

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BIODATA

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He has been actively engaged in research both as a research worker and supervisor for post-graduate students (MSc and PhD). He is the recipient of Sir David Galloway Memorial Award from Singapore Academy of Medicine for his work on Rhinosporidiosis. Currently, he also teaches post-graduate students in Surgical Sciences in UKM. He was an examiner for Primary FRCS of the Royal College of Surgeons, Ireland and FRCPA of Royal Australasian College of pathologists. He is an examiner for post graduate. He was a research collaborator with Professor Warwick Armstrong of California University on Nasopharyngeal carcinoma. He has more than 120 research publications in local and international peer reviewed journals. He is the principal author of a book on Dysfunctional Uterine Bleeding with Professors Dr Sivaachanna and Professor Dato' Dr. Nik Nasri as co-authors. He has also co-authored with Dr. Noor Fadzilah Zulkifli for this book on Iron Deficiency Anemia.
IRON DEFICIENCY ANAEMIA: CURRENT CONCEPTS

This book was written with the aim of presenting the subject of iron deficiency anemia oriented primarily towards the academic needs of students of medicine and trainees; it provides an easy access to current knowledge of the subject. This book attempted to cover comprehensively many facets including the epidemiology, normal iron homeostasis in human body, aetiology, pathology, differential diagnosis, and diagnostic investigations; in addition management, prevention and clinical approach to a patient with suspected iron deficiency anaemia have also been alluded to. Hopefully this book will serve useful for all interested in iron deficiency anemia including researchers.

“This book is an extensive compilation of the author on iron deficiency anaemia. Iron deficiency anaemia is a very common haematological disorder and has been a public health problem in this region. It gives an invaluable understanding about the disease and it is a useful reference for researchers, graduates and public. I wish to recommend it to all who are interested in this area.”

Assoc. Professor Dr. Rosline Hassan, Head, Department of Haematology, School of Medical Sciences, USM

“The contents of this book have been outlined under clear and distinct headings and the matter has been presented in a lucid and easily understandable manner suitable for local environment. Although the disease is an old entity, the authors have searched through the recent developments including Molecular Biology to unravel the mystery of the mechanism. Several line diagrams and tables incorporated in the manuscript are appropriate and helpful in better understanding. The colour plates of blood films are of good quality and appropriate. The reference is extensive and the indexing is easier.

I am certain that the book will be popular and beneficial for the undergraduate and post graduate students in Pathology and Medicine. The Clinicians will find it an easy readable reference”.

Dr. Prashanta Kumar Das (M.D., FRCPath), Consultant Pathologist, Hospital Lam Wah Ee, Penang (Formerly Professor of Pathology in School of Medical Sciences, USM)