“In nothing do men nearly approach the Gods than in giving health to men.”

– Cicero
Theme: ANAEMIA

Front cover
Electron micrographs showing peripheral blood pictures of normal cells & that of different types of Anaemia.

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Around onethird of the total world population are anaemic in whom the hematocrit is <41% (haemoglobin is <13.5 gm/dl.) in males or <37% (haemoglobin <12 gm/dl) in females, and half of them, which constitutes around 600 million peoples are iron deficient, which is the most common cause of anaemia worldwide. The most important cause of Iron Deficiency Anaemia is blood loss and the commonest site is Gastrointestinal Tract. Besides, there are many other causes congenital or acquired according to pathophysiology i.e. diminished production or accelerated loss of RBCs or as per mean cell volume (red blood cell size). Microcytic anaemias are iron deficiency anaemia, thalassemias and anaemia of chronic diseases whereas macrocytic anaemias are due to megaloblastic (Folate or B₁₂ deficiency) or nonmegaloblastic like myelodysplasia and use of antiretroviral drugs.

Hemolytic anaemias may be due to intrinsic defects of RBC, like membrane, enzyme system and haemoglobin, most of which are hereditary like Spherocytosis, Sickle Cell Disease, Paroxysmal Nocturnal Haemoglobinuria (PNH) and G6 PD deficiency or due to extrinsic factors like autoimmunity, drugs or microangiopathic hemolytic anaemias like TTP, HUS, DIC, Vasculitis and hypersplenism. In injury or abnormal expression of haematopoietic stemcells, the bone marrow becomes hypoplastic giving rise to pancytopenia and aplastic anaemia.

Evaluation of anaemia includes a detailed laboratory workup including PBS, Reticulocyte count, tests of Iron supply and storage and Bone marrow examination besides a detailed history including nutritional history, drug and alcohol history and family history of anaemia and physical examination including evidence of infection, blood in the stool, lymphadenopathy, spleenomegaly or purpura.

Treatment is initiated in mild to moderate anaemia only after a specific diagnosis is made and in acute setting where the anaemia is severe, red cell transfusion is required before workup. Therapeutic options have expanded after blood component therapy, recombinant EPO, IV iron therapy and targetted genetic therapy.
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In India anemia is one of the commonest presenting symptom in patients of rural as well as urban population. The most affected are the women, especially during pregnancy, lactation and perimenopausal problems and also the children, particularly in rural sectors, suffering from parasitic diseases. As per Lancet, it is prevalent as 53.3% among women in reproductive age and 69.5% in children below 5yrs of age in India.

Anemia has been traditionally defined as low haemoglobin level in the blood below the lower extreme of the normal range for the given age and sex of an individual. Obviously anemia is the symptom, not the diagnosis. It is always a manifestation for an underlying disorder and sometimes is the only window open for clinician to look through at a disease which is otherwise subclinical and occult.

History and symptomatology should alert a clinician to look for anemia in the patient. It is a well known symptom that starts due to tissue hypoxia when haemoglobin falls below 7gm%. However this is not a hard and fast rule. A patient of cardiopulmonary problem for example, can present with anemia at a higher level (<10 gm%).

The main symptoms are weakness, drowsiness, fatigue, mild reeling of the head and seeing spots as complaints by the patient. More serious symptoms may include angina, syncope and dyspnoea on exertion. Sometimes probing questions to the patients brings out complains regarding melena, epistaxis, hematemesis and menorrhagia. Jaundice, weight loss, severe bone or chest pain as well as gloves and stocking type of paraesthesia may suggest the cause of anemia.

The basic laboratory investigations include haemoglobin (Hb), ESR, TRBC, TWBC, DC and comment on peripheral smear, would point towards the probable causes of anemia. If the anemia is normochromic and normocytic, then the causes could be anemia of chronic disease, haemolytic anemia or anemia of acute haemorrhage. If the anemia is hypochromic and microcytic, then the causes may be Vit B12 or folate deficiency. Commonly iron deficiency anemia may be due to parasitic diseases, nutritional deficiencies or also due to chronic blood loss in GI pathology.

Keeping the above outline in the mind, a clinician advises laboratory evaluation for peripheral blood smear, red blood cell count, red cell indices, haemoglobin, haemotocrit, reticulocyte count, platelet count, white blood cell count, and blood in stool and urine (overt or occult). If the diagnosis of the cause is still not clear one can go for serum iron level, total iron binding capacity (TIBC), serum ferritin level and Hb electrophoresis.

One of the most sophisticated complete blood count (CBC) machine is the laser based automated blood cell counter. This machine measures and calculate Hb, RBC count, MCV (a measure of RBC Size), MCH (a measure of Hb content in individual RBC) and MCHC (a measure of the Hb level in individual RBC).

The diagnostic criteria for anemia in men is Hb< 14 gm/dl and for women is Hb < 12 gm/dl. In infants, normal values vary with age.

First the hematocrit and Hb are done to get the MCV. If MCV is high (i.e. macrocytic on peripheral smear), reticulocyte count, serum B12 and serum folate are usually done to consider megaloblastic anaemia. If MCV is low (i.e. microcytic on peripheral smear), then serum iron and total iron binding capacity (TIBC) are done. If these values are less, then serum ferritin
and bone marrow investigations are performed. In case of normal value, one must go for Hb electrophoresis to investigate for haemoglobinopathies. If MCV is normal, then along with peripheral smear serum iron, TIBC, reticulocyte count, haptoglobin, and Coomb’s test are done. RBC indices can help indicate the mechanism of anemia. The reticulocyte count is expressed as the percentage of reticulocytes (Normal range- 0.5 to 1.5%) or absolute reticulocyte count (Normal range -50,000 to 150000/îl). Higher values of reticulocytes indicate excessive production (reticulocytosis). In the presence of anemia, reticulocytosis suggests excess RBC destruction. Low no of reticulocytes in the presence of anemia indicate decreased RBC Production (e.g. Hypoplastic / aplastic anaemia)

Bone marrow aspiration and biopsy which are technically easy and safe provide direct observation and assessment of RBC precursors. The presence of abnormal maturation of blood cells and the amount, distribution and cellular pattern of iron content can be assessed. More analytical laboratory methods include cytogenetic and molecular analysis on marrow aspirated materials, and also flow cytometry which can be taken up in cases of lymphoproliferative and myeloproliferative states to define immune phenotype.

Anemia being one of the commonest presenting symptoms, a clinician who may either be a general duty medical officer in the periphery, or in an urban well developed referral centre, should be able to carry out the basic clinical and laboratory investigations to evaluate a possible cause of anaemia. Further sophisticated investigations would need better equipped laboratories. A systematic but focused approach to the laboratory evaluation of anaemia leads to an expedient and precise diagnosis. One should always think in terms of ‘common causes occur commonly’ and go for further investigation only when the basic causes are ruled out.

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Members are requested to enroll more colleagues as members of IMA and join AMS and CGP in large nos for formation of local branches and extra academic activities.
Anaemia In Pregnancy – The Indian Scenario

Maya Padhi¹, Prabhat Kumar Padhi²

Introduction:

Anaemia is a major public health problem in the developing countries in general and amongst the economically weaker sections of the population in particular. It is the commonest medical disorder complicating pregnancy and is of especial concern in this group of women due to its potential adverse effects on the mother and the foetus.

Definition of Anaemia:

The WHO defines anaemia in pregnant women as aHb level below 11 gm%. The degree of anaemia is graded according to the Hb level as follows-

- Mild - 10.0-10.9 GM%
- Moderate - 7.0-10.0 gm%
- Severe - 4-6.9 gm%
- Very severe - < 4gm%

The Centre for Disease Control and Prevention (1990) recommends that the Hb level of pregnant women should not be allowed to fall below 10.5 gm% in the 2nd trimester taking into account the physiological changes of pregnancy (1).

WHO has classified the world into different anaemia prevalence zones depending on the incidence of anaemia in these areas –

- High prevalence - >40%
- Medium prevalence - 15-39%
- Low prevalence - 5-14.9%
- Not a problem - <5%

Magnitude of the problem:

Anaemia is derived from the Greek word ‘anaimia’ = without blood. It is estimated by the WHO that 2 billion people globally suffer from anaemia or iron deficiency (2). Precise data on the prevalence of anaemia is not available but a rough estimate would be that about 500 million women between 15 to 49 years of age worldwide are anaemic.(2). In developing countries, the prevalence of anaemia in pregnant women varies from 50-90% in different countries and in different sectors of the same country. In developed countries, the incidence is much lower at 18-20%. Throughout Africa, about 50% of pregnant women are anaemic, the incidence being the greatest in Western Africa and least in South Africa. The incidence in Latin America hovers around a mean of 40% while it is significantly higher in the Caribbeans where the average incidence is 60%. Sub-Saharan Africa and South Asia has the highest prevalence of anaemia in pregnant women. (3).

Legend for Figure - I

Prevalence of Anemia among Women in India, INFHS-3, 2005-06
In India, the incidence of anaemia is stated to be 40-80% (4). According to WHO, 13 million out of the 22 million pregnant women population suffer from anaemia in varying degrees. While anaemia is common in India, the prevalence is highest in the Eastern states, especially Bihar, Jharkhand, Orissa, Bengal and Assam (Fig.I, II). More importantly, there is a high incidence of severe anaemia in several developing countries. In a steering committee report from India, 13% women were reported with anaemia less than 5gm% and 34% had Hb levels less than 8gm% (5). India is among the countries with highest prevalence of anaemia in the world. As India is a population billionaire, the country accounts for the largest number of anaemic persons in the world (Table 1). The magnitude of reduction in the prevalence of anaemia during nineties in India is lower than that in neighbouring South and South East Asian countries.

The incidence of anaemia ranges between 20-30% in the middle income groups and between 60-80% in the lower income groups. Anemia antedates pregnancy, being overwhelmingly prevalent in the adolescent group. (Fig. III) In geographical areas where malaria and helminthic infestations are endemic, the incidence of anaemia rises to almost 90%. Anaemia contributes directly to 20% of maternal deaths and is contributory in another 20% of maternal deaths by way of obstetric haemorrhages, sepsis, obstructed labour and other causes(6). The figures of anaemia related maternal deaths reflect only the tip of the proverbial iceberg as maternal morbidity is not usually quantified. For every woman dying of an anaemia related cause, there are several women who survive only to suffer from long term sequelae.

Table 1:

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence of</th>
<th>Iron Deficiency</th>
<th>Anaemia in South Asia (%)</th>
<th>Maternal deaths from anaemia/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
<td>Women</td>
<td>Pregnant women</td>
<td>Maternal deaths</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>65</td>
<td>61</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>55</td>
<td>36</td>
<td>74</td>
<td>2800</td>
</tr>
<tr>
<td>Bhutan</td>
<td>81</td>
<td>55</td>
<td>58</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>INDIA</td>
<td>75</td>
<td>51</td>
<td>87</td>
<td>22000</td>
</tr>
<tr>
<td>Nepal</td>
<td>65</td>
<td>62</td>
<td>63</td>
<td>760</td>
</tr>
<tr>
<td>Pakistan</td>
<td>56</td>
<td>59</td>
<td>-</td>
<td>-</td>
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<tr>
<td>S.A region total</td>
<td></td>
<td></td>
<td>25,560</td>
<td></td>
</tr>
<tr>
<td>World total</td>
<td></td>
<td></td>
<td>25,560</td>
<td></td>
</tr>
</tbody>
</table>


Figure - II

Legend for Figure - II
Anemia among pregnant women state wise.
(Source: RCH Survey, 2002)
Changes in Maternal Blood Physiology in Pregnancy:

Pregnancy imposes significant demands on erythropoiesis. Intravascular blood volume expansion starts at 8-10 weeks of pregnancy and reaches a maximum in the late 2nd trimester of pregnancy. The circulating blood volume increases by about 30-40% during pregnancy to accommodate the increased demand created by the uteroplacental circulation, the general vasodilatation and the increase in maternal body tissue mass. The rise in plasma volume of 45% exceeds that of the red cell mass of 25% leading to haemodilution and drop in the maternal Hb levels by approximately 2 gm%. This drop is most evident in the second trimester. There is a drop in the PCV but no alteration in MCV and MCHC values indicating physiological dilution of pregnancy. The serum iron level falls during pregnancy but the iron binding capacity increases by almost 33% allowing greater storage.

The Hb level is high in the foetus – 18 gm/dl. The foetus maintains this in spite of maternal anaemia. This indicates that the foetus draws its iron and other nutritional requirements from the mother, irrespective of the anaemic status of the latter. However, the iron reserves are poorer in neonates of anaemic mothers and they tend to suffer from anaemia later in infancy.

Risk Factors for Anaemia in Pregnancy:

Risk factors for anaemia in pregnancy in India include the following

- a) Age<20 or >30 years
- b) Parity>2
- c) Birth spacing <2 years
- d) Low socioeconomic status, faulty dietary habits
- e) Illiteracy, unemployment, ignorance
- f) Anaemic status in the pre-pregnant state
- g) Caloric intake < 80%
- h) BMI <18.5
- i) Vegetarian diet
- j) Worm infestation
- k) Chronic illness (Malaria, TB etc)
- l) Increased demand as in multiple pregnancy

Why is Anaemia Common in Pregnancy?:

The anaemia of pregnancy is multifactorial. Though nutritional anaemia is the commonest, especially in the developing countries, other reasons for anaemia should not be overlooked. Various aetiological factors for the development of anaemia in pregnancy include the following:

a) Increased demand of iron in pregnancy:

A total of about 1000 mg of iron is required to meet the increased demands of pregnancy (expanded red cell mass = 500 mg + foetoplacental unit = 300 mg + growing uterus =200). As a result of amenorrhoea, there is a saving of 150-200 mg of iron and, therefore, the net requirement of extra iron in pregnancy is 800 mg. Diet alone cannot provide this extra iron and the iron stores get depleted. However, if the iron stores are already depleted, iron deficiency anaemia (IDA) manifests. The daily iron requirement is increased to 3.0 mg/day in early pregnancy and this requirement is almost doubled in the later part of pregnancy and lactation. Normally, only about 10% of the ingested iron is absorbed, but during pregnancy, this is enhanced to 20%.

b) Deficient Iron Stores:

20% of the total iron stores in the adult female resides in the stores – the reticuloendothelial system consisting of liver, spleen and bone marrow. Majority of women in child bearing age have deficient iron stores because of blood loss from menstruation. Thus, most women enter pregnancy with an already depleted iron store. Menorrhagia in the child bearing age and
repeated child bearing in the multigravida further compound the problem. In an iron deficient woman, it may take a year for haemoglobin to regain its pre-pregnancy status, but iron supplementation restores the levels much faster (8).

c) Deficient Iron Intake and Other Haemopoietic Factors:

Deficient intake of iron and other haemopoietic factors during pregnancy is common in Indian women due to poverty, ignorance, illiteracy, absorption disorders etc. Folic acid and other micronutrient deficiency is also commonly associated with iron deficiency. Deficient iron stores in infancy, childhood, adolescence and during child bearing years perpetuate anaemia during pregnancy and beyond. Vit. B12 deficiency, though uncommon, is sometimes seen in strict vegetarians (9).

d) Chronic Blood Loss:

Chronic blood loss also contributes to the anaemia. Malaria, several endemic pockets of which are found in India, causes anaemia by haemolysis. Ankylostomiasis, trichuriasis, amoebiasis and schistosomiasis cause blood loss directly leading to iron deficiency anaemia. These conditions are very common in India.

e) Infections:

Chronic and recurrent infections or inflammations (eg. TB, UTI) cause anaemia by impairing haematopoiesis.

f) Other Causes:

Besides nutritional anaemia, several other causes of anaemia may be present. Certain areas are endemic for Thalassaemia, Sickle cell trait, G6PD deficiency and this should be kept in mind when dealing with populations in these areas. These conditions (except the rare condition of Thalassaemia major) are usually associated with iron deficiency anaemia. Aplastic anaemia complicating pregnancy, though rare, is potentially fatal for the mother and the foetus.

Effect of Pregnancy on Anaemia:

Pregnancy worsens the anaemic state because of the following factors:-

a) Physiological haemodilution of pregnancy causes a drop in the maternal Hb levels.
b) Maternal nutrition in the first trimester is affected because of the poor appetite and insufficient intake by the mother.
c) Increased demand is placed on iron reserves by the growing maternal tissues and the growing foetus.
d) Due to blood loss during and after delivery and due to the increased demands on iron stores entailed by lactation, the mother loses iron from her body in the intra- and post-partum periods.
e) Unless iron supplementation is provided, the iron deprivation of the mother as a result of these factors is likely to aggravate her already existing anaemia.

Effect of Anaemia on Pregnancy:

Anaemia directly and indirectly aggravates several pregnancy related complications such as :-

a) Pre-eclampsia
b) Congestive cardiac failure
c) Increased risk of infections due to depressed immune system
d) Antepartum haemorrhage
e) Post partum haemorrhage
f) Intra uterine foetal growth restriction
g) Preterm labour and delivery
h) Uterine inertia and maternal exhaustion in labour
i) Puerperal sepsis
j) Obstetric shock
k) Delayed wound healing and recovery.
l) Thromboembolic complications
m) Subinvolution of uterus
n) Failure of lactation

Pre-existing anaemia causes a woman to succumb to pregnancy complications more easily. The foetus, though acting as a parasite in situations of iron deficiency, also suffers from the adverse effects of maternal anaemia. There is a 3-fold risk of low birth weight babies and a 2-fold risk of prematurity. Besides, anaemia and iron deficiency in pregnancy are associated with large placental weight and a high ratio of placental weight to birth weight, both of which are predictors of adult hypertension (10).
Types of Anaemia in Pregnancy:

Though iron deficiency is the major cause of anaemia in pregnancy, other aetiological factors may be present which should be kept in mind. The various causes of anaemia in pregnancy are-

I) Nutritional anaemias—Iron, folic acid and Vit. B12 are the principal micronutrients necessary for the prevention of anaemia. Proteins and Vit. C act as facilitators:

   a) Iron deficiency—Iron deficiency is the most commonly recognized nutritional deficit either in the developed or the developing world. The daily iron requirement in the latter half of pregnancy increases to 6.3 mg/day. Iron deficiency is not synonymous with iron deficiency anaemia as the latter denotes a depletion of body stores of iron and a consequent inability to meet the iron demands of the body. Most women in India are already in a precarious state of iron balance during their reproductive years due to various causes such as poor nutrition, menorrhagia, intrauterine devices (which increases mean blood loss during menstruation by 30-50%) etc. Hence, their body is unable to meet the extra demand for iron during pregnancy and this predisposes them to anaemia with its consequent adverse effects.

   b) Folic acid deficiency—Folic acid is necessary for the maturation of red blood cells. It also plays an important role in cell division and is an intermediary in the metabolism of amino acids. Its stores in the body are limited. The liver stores about 6-10 gms. The daily requirement of folic acid is 300-500 mg and this is met from folates in foods like potatoes, spinach, bananas, asparagus, broccoli, dark green vegetables etc. However, the folates present in the foods are heat labile and light sensitive and are, thus, easily destroyed by cooking. Large amounts of additional folates are required in pregnancy, especially in multiple pregnancy. Folic acid deficiency is associated with increased risk of foetal neural tube defect and abruption placentae. Folic acid supplementation is recommended in pre-pregnancy counseling and in the first half of pregnancy.

   c) Vit. B12 deficiency—This deficiency is rare in pregnancy. It is mainly seen in vegetarians and in women suffering from malabsorption syndrome or autoimmune disease. The normal pre-pregnant value of serum Vit. B12 (140-820 pg/ml) falls during pregnancy. Vit. B12 and folic acid deficiency either together or singly give rise to megaloblastic anaemia. This condition can be diagnosed by peripheral smear examination. The Hb level is <10 gm/dl and >4% of the polychromas are hypersegmented (>5 lobes). Macrocyes with diameter exceeding 12 microns must be present. Residual nuclear inclusions called Howell-Jolly bodies are demonstrable. There is presence of nucleated RBCs with premature haemoglobinization. Treatment includes nutritious diet, folic acid and Vit. B12 supplementation.

II) Haemoglobinopathies—Haemoglobinopathies account for less than 3% of all cases of anaemia. In these cases, abnormalities in the haemoglobin constitute the underlying cause of rapid destruction of red blood cells resulting in anaemia. This condition is common in the Mediterranean regions and to a lesser extent in South East Asia and in Afro-Americans. Some of the major haemoglobinopathies encountered in clinical practice are briefly reviewed here.

   a) Beta Thalassaemia Minor—This disease is transmitted by autosomal recessive gene. The lifespan of RBCs is shortened from 120 to 40 days. During pregnancy, the Hb level falls to 8.0-10.0 gm/dl. The major foetal hazard is a 1:4 risk of beta thalassaemia major in the offspring if both the parents are affected by beta thalassaemia minor. The obstetric outcome does not differ from that of the general population. There is an increase in the incidence of mild anaemia and a doubtful increase in the incidence of neural tube defects consequent to relative folate deficiency. (11). Prenatal counseling should be offered to couples when both the partners are carriers of betathalassaemia gene.

   b) Beta Thalassaemia Major—Women with this condition have a high mortality and morbidity. In spite of this, more than 100 pregnancies have been reported in women with beta thalassaemia major. Most of these women are subfertile due to late onset of menarche, primary or secondary amenorrhoea, chronic anovulation consequent to multiple endocrinopathies due to iron deposition. There is a high incidence of early pregnancy losses, IUGR and prematurity. Cardiac failure due to myocardial haemosiderosis may occur. Hypersplenic crisis manifesting as anaemia, leucopenia
and thrombocytopenia occurs in the last weeks of pregnancy. The iron chelating agents used during pregnancy have terratogenic effects such as retarded bone ossification, vertebral aplasia and bifurcation or fusion of ribs.

c) Alpha Thalassaemia Minor - Women with alpha thalassaemia trait are asymptomatic but their peripheral smears show microcytic hypochromic anaemia with low MCV, the anaemia not responding to iron supplements. In alpha thalassaemia, the adverse effects of pregnancy are due to accumulation of abnormal haemoglobins like HbH and Bart's Hb. The pregnancy is well tolerated in the carrier state. However, profound foetal and neonatal adverse effects may be associated.

d) Sickle Cell Trait - This is the heterozygous form of the disease and not enough abnormal Hb is available for sickling to occur. The morbidity is low. The importance lies in the detection of the disease in the offspring in case both the parents are heterozygous. Genetic counseling should be offered to these couples.

e) Sickle Cell Disease - This is the homozygous state of the disease and is far more serious clinically. It is not uncommon for women with sickle cell disease to become pregnant. Pregnancy predisposes to sickle cell crisis. Infections of the lungs and urinary tract are common. Obstetric complications include abortion, pre-eclampsia, eclampsia, prematurity and intra uterine foetal loss. Maternal mortality is 5-10% and perinatal loss is high. With improved obstetric and neonatal care, the neonatal mortality ranges from 0-10% (12). Such pregnant women should have frequent antenatal check-ups, should be adequately hydrated and should receive daily folic acid supplements. Long term oral penicillin therapy may be considered to prevent infection. Patients in labour should receive I.V fluids and oxygen mask supplementation. Continuous foetal monitoring is advisable to detect foetal hypoxia at the earliest.

f) Other Haemoglobinopathies - Combinations of thalassaemia with sickle cell disease may manifest as severe forms of anaemia. Their genetic transmission to the progeny is an important consideration requiring prenatal genetic counseling.

g) Other Haemolytic Anaemias - Anaemias can also result from an abnormal fragility of RBCs due to conditions like spherocytosis, elliptocytosis, G6PD deficiency, paroxysmal nocturnal haemoglobinuria. In tropical countries like India, malaria is a well known cause of chronic haemolysis leading to persistent anaemia.

h) Chronic Renal Disease - This is associated with persistent anaemia.

III) Haemorrhagic Causes - Chronic anaemia may result from chronic blood loss like bleeding piles, menorrhagia antedating pregnancy, pregnancies in quick succession that does not allow a woman to recover from the blood loss sustained during delivery and puerperium.

IV) Parasitic Infestations - Parasitic infestations with hookworm, roundworm, Tinea solium, Trichuris trichuria, Enterobius vermicularis and protozoan infection with Entamoeba histolytica and Giardia lamblia are common causes of anaemia in tropical countries like India due to minute blood losses and associated malabsorption (13).

V) Aplastic Anaemia - This condition is rare in pregnancy, only 82 cases having been described in world literature till date. A study from Bangalore stated that the maternal mortality in their study was 33% while foetal wastage was 50%. Blood component therapy forms the mainstay of therapy (14). Treatment with cyclosporine may be undertaken if remission does not occur after delivery. Bone marrow transplant is the last resort.

Since a detailed discussion of the various types of anaemias in pregnancy is outside the scope of this article, we will restrict ourselves to a deliberation on the nutritional anaemias of pregnancy and particularly to iron deficiency anaemia.

Stages of Development of Iron Deficiency Anaemia:

Progression to iron deficiency anaemia occurs through 3 stages -

a) 1st Stage: Negative iron balance. In this stage, the demand for iron exceeds the body's ability to absorb iron from the diet. Causes include blood loss, pregnancy, inadequate dietary iron intake. During this stage, iron stores start decreasing. As long as iron stores can be mobilized, the TIBC, red cell protoporphyrin and red cell morphology remain normal.
b) 2nd Stage: Iron deficient erythropoiesis. In this stage, the iron stores become depleted as seen from falling serum ferritin levels. TIBC and red cell protoporphyrin levels increase correspondingly. As long as the serum iron levels remain within the normal range, Hb synthesis is unaffected, despite the decreasing iron stores. Once the transferrin saturation falls to 15-20%, Hb synthesis becomes impaired. This is the period of iron deficient erythropoiesis. Peripheral smear examination at this stage reveals microcytic, hypochromic cells along with reticulocytes. In due course of time, the haemoglobin and hematocrit levels begin to fall.

c) 3rd Stage: Iron deficient anaemia--Peripheral smear at this stage shows marked hypochromia, microcytosis, poikilocytes and target cells. Erythroid marrow, which was initially depressed, now becomes hyperproloferative.

Clinical Manifestations:

Anaemia in pregnancy can be easily diagnosed. Symptoms include easy fatiguability, decreased work and exercise tolerance, shortness of breath, palpitations, swelling of feet, generalized swelling. Clinical evaluation of the patient reveals facial, conjunctival, tongue and palmar pallor. Parietal and pedal oedema may be present. Enlarged liver and spleen, generalized lymphadenopathy, sternal tenderness should be looked for. Haemic murmur is a common cardiac sign. Basal crepitations are suggestive of cardiac failure.

Screening for Anaemia:

The Hb level forms the first line screening test for anaemia. It should be done at the first antenatal visit and should be repeated in each trimester and after delivery. It draws attention to the presence or absence of anaemia. If the Hb level is below 9.5 gm/dl, further investigations are called for.

a) CBC with indices - Haematocrit measurement is an acceptable and recommended method for anaemia evaluation but has no advantage over Hb estimation. MCV and MCH are the most sensitive indices of iron deficiency. A reduced MCV with near normal Hb levels should alert one to the possibility of thalassaemia.

b) Peripheral smear - In IDA, the blood picture shows microcytosis, hypochromia, anisocytosis, poikilocytosis and reticulocytes in patients undergoing treatment. Megaloblastic anaemias due to folic acid deficiency shows a blood picture of macrocytosis, hypersegmented neutrophils and fully haemoglobinized RBCs. In haemolytic anaemias, the blood picture shows polychromatic cells, stippled cells and target cells, typical of sickle cell disease. Attention should also be given to the presence of malarial parasites in the peripheral blood. Thus, a detailed peripheral smear examination can yield information about the degree of anaemia as well as the underlying cause.

c) Other specialized tests - (Table 2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Iron</td>
<td>100 mg/dl</td>
</tr>
<tr>
<td>Serum total iron binding capacity</td>
<td>300-350 mg/dl</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>40-340 ng/ml</td>
</tr>
<tr>
<td>Serum folic acid</td>
<td>5-15 ng/ml</td>
</tr>
<tr>
<td>SerumVit B₁₂</td>
<td>140-820 pg/ml</td>
</tr>
</tbody>
</table>

Management of Anaemia

I) General management:

a) Preconceptional advice – Ideally, anaemia should be corrected before embarking on the journey of pregnancy. Folic acid supplement should be given periconceptionally.

b) Dietary advice - Balanced diet should be taken in pregnancy to meet the extra demands of the condition.

c) Elimination of intestinal parasites should be done either prior to pregnancy or after the first trimester.

d) Screening tests to determine the degree and type of anaemia.
II) **Definitive Therapy**

**a) Oral iron therapy** – This forms the mainstay of treatment of IDA. It is effective both for prevention and treatment of anaemia. The ferrous form of iron is better than the ferric form. Several iron salts are available commercially but vary only minimally in their efficacy. The commonly available iron preparations are ferrous sulphate, ferrous fumarate, ferrous gluconate, ferrous succinate, ferrous ascorbate, ferrous glycine sulphate, iron polymaltose complex and carbonyl iron. They differ in their elemental iron content, their bioavailability and in their side effects. Oral iron tablets should not be taken along with antacids or foods containing phytates or phosphates like milk and cereals. Prophylactic dose of iron is 100 mg of elemental iron along with 500 mcg of folic acid per day. Therapeutic dose constitutes 100 mg of elemental iron along with 500 mcg of folic acid twice daily till Hb reaches normal level and for a further period of 12 weeks in the same dosage to replenish iron stores. Following this, the prophylactic dose may be continued as maintenance.

**b) Parenteral iron therapy** – This form of iron administration is traditionally reserved for the following category of women –

- Poor tolerance to oral iron therapy
- Poor absorption of iron as in chronic diarrhoea, ulcerative colitis, inflammatory bowel disease
- Non-compliance
- Poor response to iron therapy
- Women near term with severe anaemia
- Presence of concurrent diseases like CRF
- The advantages of parenteral iron preparations include elimination of the risk of non-compliance and saving critical time in non-responders. Parenteral iron preparations include iron sucrose complex, iron dextran complex, iron sorbitol citric acid complex, ferric sodium gluconate.

Iron sucrose complex is the most commonly used preparation at present and has largely replaced the earlier iron-dextran and iron-sorbitol complexes. This preparation does not need a test dose and does not cause anaphylactic reactions. It can be given as a single dose of 200-300mg, the dosage not exceeding 600 mg in a week. The entire dose can be given as a diluted bolus over 5 minutes or can be given mixed in 100ml of normal saline. The total dose of iron required to be infused can be calculated by one of several formulas;

- **a)** Wt. of patient in Kg×Hb deficit in gm/dl×2.21+1000
- **b)** Wt. of patient in lbs×Hb deficit in %×0.3+50% of TDI
- **c)** 200 mg of elemental iron raises Hb level by 1 gm%.

**Indian Governmental Strategies**

India was one of the first countries to recognize the importance of iron supplementation in the prevention and treatment of IDA. Accordingly, the National Nutritional Anaemia Control Programme (NNACP) was initiated in 1970. This involved the free supply of iron + folic acid tablets through governmental health channels in the second and third trimester and during lactation. The Ministry of Health and Family Welfare, Government of India in 1987 recommended the intake of 100 mg of elemental iron with 500 mcg of folic acid per day for a minimum of 100 days in the second half of pregnancy as prophylaxis. Though this programme has been in effect for several decades, the results have not been as expected. After more than 20 years of IFA supplementation, NFHS II (1998-1999) reported a drop in anaemia prevalence from 80-90% to 49.7%. However, this finding was not substantiated by other studies. The Healthcare and Research Association for Adolescents, Noida and the Nutrition Foundation of India, N.Delhi (Sept. 2001-April 2003) which surveyed the same districts as studied by NFHS II found a prevalence rate of 84% with 9.2% belonging to the severe anaemia category.(15). This was further corroborated by several ICMR studies which showed a prevalence rate of anaemia of 84.2% (16). Also, the most recent study of NFHS III (2005-2006) has reported a rise of anaemia prevalence from 49.4% to 59.4%. The current anaemia scenario conclusively proves that the IFA programme has been a failure.

**The Way Forward**

It is now clear that the IFA programme has failed to yield the expected results. Though the benefits of iron supplementation are universally acknowledged, its implementation has remained largely unsuccessful.
The causes for this phenomenon are varied. Probably, the single most important reason for the failure of this programme is non-compliance by the pregnant women. Reasons cited are GI symptoms (nausea, constipation, diarrhea), belief that the baby would increase in size causing difficult delivery, sensation of ‘heat in the body’, advice from family members and neighbours. On the side of the health care providers, partial population coverage, inadequate dosing, short and erratic supply of drugs, lack of effective health education and supervision appear to be the major factors. Defective absorption due to malabsorption and intestinal infestations are also a major contributing factor.

It is now quite evident that a major shift in policy and strategies is necessary to eradicate this eminently preventable scourge of iron deficiency anaemia in pregnancy. Some of the different methods that may merit consideration are as follows:

a) Intravenous iron supplementation – Several western studies have demonstrated the efficacy of treating iron deficiency anaemia with intravenous iron sucrose complex in a variety of settings including pregnancy. There is irrefutable evidence that compared to oral iron, IV iron sucrose supplementation results in rapid resolution of IDA(17,18). The side effects are minimal, anaphylactic reactions are virtually unknown, and being administered intravenously, the problem of non-compliance is circumvented. This mode of administration can be given in the outdoor, no admission being required. Some studies have recorded an appreciable rise in the Hb levels with two sittings of IV iron-sucrose complex of dosage 200-300 mg. This method of iron supplementation through health care centres may prove to be the most effective way to combat IDA in the future.

b) Screening of all pregnant women for anaemia using a reliable Hb estimation method.

c) Oral iron-folic acid supplementation for all non-anaemic pregnant women at the recommended dosage of 100 mg of FeSO4 + 500 mcg of folic acid. In pregnant anaemic women, the dosage should be increased to two tablets daily.

d) Encouraging intake of iron-rich foods such as pulses, cereals, jaggery, beetroot, green leafy vegetables, legumes, dry beans, liver, egg, fish. Best cooking practices like use of iron vessels for cooking and preservation of water used for cooking of rice and vegetables should be routinely advised.

e) Hospital admission and intensive personalized cares for pregnant women with severe anaemia.

f) Supervision of intake of the required dosage of the drug by designated personnel in line with the DOTS programme may be considered. This can be rendered more feasible by making the dosage interval weekly or twice weekly.

g) Iron fortification – This is probably the most practical, sustainable, and cost-effective long-term solution to control iron deficiency anaemia at the national level. The iron compound and type of fortification should be chosen on the basis of the fortification vehicle, the iron requirement of the target population and the iron bioavailability of the local diet. Foods most used for iron fortification in different countries include staple cereal flour, sugar (Guatemala), curry powder (South Africa), soy sauce (China), fish sauce (Vietnam), and maize flour (Kenya).(19)

h) Biofortification–The iron content of rice can be increased two- to three-fold by introducing the ferritin gene from soy bean into it. The iron uptake from the soil can be increased by introduction of a ferric reductase gene into plant root system. Phytase from Aspergillus fumigates can lower the phytic acid content of rice.

Conclusion:
The correction of anaemia should start from childhood and adolescence so that women with adequate iron stores can enter the pregnancy state. IDA, though achievable, seems a distant goal at present. Better organization of primary health services, strengthening of the supplementation programmes, nutritional education, maternal education and development of suitable fortificants are required. A paradigm shift in the treatment and prevention of IDA via implementation of parenteral iron preparations may provide a step in
the right direction. However, the significant cost and logistical factors are to be considered, especially since the target population is predominantly rural-based. Effective implementation of the Tenth Plan strategies by governmental and non-governmental organizations including channeling of available resources will go a long way in eradicating IDA in pregnancy.

References

Anaemia in the ICU
Arata Kumar Swain¹, Basant Kumar Pradhan²

INTRODUCTION:
Anaemia is a common clinical problem in ICU. Almost universal by the end of first week after admission (1). However, these results can be misleading because it is based on Hemoglobin concentration in blood as a marker of Anaemia. In ICU in critical illness it is a distinct entity although it is similar in many aspects to the anaemia of chronic diseases, inflammation appears to be a measure factor. There are three major categories of anaemia: 1- Hypoproliferative anaemia secondary to marrow production defects. 2- Ineffective erythropoiesis caused by red cells maturation defects. 3- Decreased survival of red blood cells secondary to blood loss, hemolysis. Majority of anaemia cases in ICU (75%) are hypoproliferative type. This article presents the current knowledge on defining various parameters of anaemia in ICU, etiopathogenesis its relation to tissue oxygenation and overall highlights the common practice of transfusing red blood cells to correct anaemia which is an arbitrary intervention in critical care medicine.

DEFINITION:
Anaemia is defined as “decrease in oxygen carrying capacity of blood which is a function of total volume of circulating red blood cells.” This parameter can be measured by chromium tagged erythrocytes, (normal values shown in Table-1, but the methodology is not readily available in the clinical setting. Therefore an clinical alternative definition of anaemia that is based on hematocrit and hemoglobin concentration in blood. This practice is problematic in critically ill patient, the problem with the clinical definition of anaemia is the influence of plasma volume on the hematocrit and hemoglobin concentration, as plasma volumes change frequently as a result of 1- They are hemodynamically unstable due to fluid shifts between extra vascular compartment and intravascular compartment. 2- Hypoalbuminemia, is common in critical ill patient, this shifts fluids out of compartment. 3- I.V fluids, increases plasma volume and diuretics which are frequently used in ICU. Therefore hematocrit and hemoglobin are unreliable markers of anaemia in critically ill patient. (2, 3).

Table:-1-Reference Ranges for Red Cell Parameters In Adults

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell Count</td>
<td>Males: 4.6-6.2x10¹²/lit</td>
</tr>
<tr>
<td>Mean Cell Volume (MCV)</td>
<td>Females: same</td>
</tr>
<tr>
<td>Reticulocyte Count</td>
<td>Males: 25-75x10⁹/lit</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Males: 40-54%</td>
</tr>
<tr>
<td>Red Blood Cell Volume</td>
<td>Males: 26 mL/kg</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Males: 14-18 g/dl</td>
</tr>
<tr>
<td>Age</td>
<td>Normal value are 0.5 g/DL lower in blacks.</td>
</tr>
</tbody>
</table>

Common etiology and pathogenesis of anemia in ICU.

There are two established common causes of anaemia in ICU are 1- Systemic inflammation 2- Repeated phlebotomy and blood loss. Failure of erythropoiesis can also occur without this two predisposing condition if the energy needs of erythropoiesis is not satisfied. An Adult has six trillion (6x10²¹) RBC per litre of blood (Table 1) using a blood volume of 5 liters the average turn over of circulating RBC is 1% per day, which means that (0.01x 30 trillion) 300 billion RBCs must be produce daily to maintain a constant pool of circulating erythrocytes. Failure to meet the energy requirements of this effort could lead to failure of erythropoiesis and subsequent anemia.
This daily production of RBCs (which takes place in the cavities of the axial skeleton in adults) is regulated by erythropoietin, a hormone produced in the peritubular capillary endothelium in the kidney that stimulates erythropoiesis in marrow cavities. The cells that manufacture erythropoietin can respond to decreases in the arterial O2 content (either hemoglobin or arterial pO2) by increasing the secretion of erythropoietin. The subsequent actions of erythropoietin on marrow erythropoiesis would then help to correct the deficit in the O2 content of blood. Interruption of the erythropoietin regulatory system is considered one of the major mechanisms for ICU-acquired anemia.

**INFLAMMATION AND ANEMIA**

Inflammatory cytokines (e.g., tumor necrosis factor) have several effects that can promote anemia, including inhibition of erythropoietin release from the kidneys, reduced marrow responsiveness to erythropoietin, iron sequestration in macrophages, and increased destruction of RBCs. The anemia associated with inflammation has the same characteristics as the anemia of chronic disease: i.e., a decrease in iron, total iron binding capacity, and transferring levels in plasma, combined with increased ferritin levels in plasma and iron sequestration in reticuloendothelial cells. This is the most common pattern observed in the anemia that develops in ICU patients, so inflammatory cytokines are believed to play a major role in ICU-acquired anemia.

**Phlebotomy and Anemia**

The volume of blood withdrawn from ICU patients to perform laboratory tests averages 40ml to 70ml daily. Cumulative increases in this phlebotomy volume can reach 500 ml (1 unit of whole blood) after one week, and this volume can augment the severity of anemia from other causes (by removing iron that is needed for erythrocyte production), or can itself become a source of anemia if allowed to continue.

The daily phlebotomy volume is at least 4 times higher in ICU patients than in other hospitalized patients, and the difference is not entirely due to increased diagnostic testing in ICU patients. Blood samples for laboratory analysis are usually withdrawn through indwelling vascular catheters, and the initial aliquot of blood (usually 5 ml) withdrawn through the catheter is discarded because it contains fluid from the catheter lumen instead of the bloodstream. Summary of cascade of events contributing to anaemia in the critical ill is shown in figure -1.

**Figure-1.-Summary of cascade of events contributing to anaemia in the critical ill.**

- Critical illness ▼
  - Blood turn over
  - Blood Loss
  - Decrease Production ▼
  - Immune activation ▼
  - Decrease Iron in circulation ▼
  - Decrease erythropoiesis

**Anemia and Oxygen Transport:**

The uptake of oxygen into peripheral tissues (VO2) is using the equation shown below (where Q is cardiac output, Hb is hemoglobin concentration in blood, and SaO2 – SvO2 is the arteriovenous oxyhemoglobin saturation difference).

\[ VO_2 = Q \times 13.4 \times Hb \times (SaO_2 - SvO_2) \]  
(Eq.1)

The oxygen transport system operates to maintain a constant VO2 in the face of changes in any of the variables in (Eq. 1). In the case of anemia, VO2 remains constant because the decrease in hemoglobin (Hb) is accompanied by increases in both cardiac output (Q) and peripheral O2 extraction (SaO2 – SvO2). These compensatory responses to anemia are described next.

**Cardiac Output:**

The influence of anemia on circulatory blood flow is the hematocrit is the principal determinant of blood viscosity, and thus a decrease in hematocrit will decrease the viscosity of blood. According to the Hagen-Poiseuille equation shown below, a decrease in viscosity (u) will result in an increase in circulatory blood flow (Q) as long as the pressure gradient along the circulation (“P) and the dimensions of the blood vessels (r for radius and L for length) remain constant.

\[ Q = DP \times \frac{pr^4}{8mL} \]  
(Eq.2)
A decrease in blood viscosity augments cardiac stroke output by reducing ventricular afterload.

Anemia can also be accompanied by activation of the sympathetic nervous system (4) which will augment cardiac output by increases in both myocardial contractility and heart rate.

However, this response is not prominent, and thus tachycardia is not a prominent finding in anemia at least at rest.

When considering the isolated effects of anemia on cardiac output the blood volume should be normal or unchanged (this condition is referred to as **isovolemic anemia**). The changes in cardiac output associated with progressive, isovolemic anemia are shown in Figure -2. Note that the increase in cardiac output is proportionally much greater than the decrease in hematocrit. This response is attributed to the flow dependency of blood viscosity; i.e., an increase in blood flow (cardiac output) will decrease blood viscosity. Thus, anemia decreases blood viscosity, which then increases cardiac output, which then decreases blood viscosity, and so on. Ketchup is another fluid with a flow-dependent viscosity, so if you can picture what happens when you pour ketchup (the flow is sluggish at first, then increases as you continue to pour), you will get the idea.

**Peripheral Oxygen Extraction**

In addition to the global changes in cardiac output, anemia can preferentially increase flow in the cardiac and cerebral circulations, and decrease flow in the splanchnic circulation. This will have a protective effect on myocardial and cerebral metabolism in the presence of anemia.

### Peripheral Oxygen Extraction

The effects of progressive isovolemic anemia on systemic oxygen transport is (8) the initial decrease in hematocrit is accompanied by a decrease in systemic oxygen delivery (DO2), and this is counterbalanced by an increase in O2 extraction (SaO2 – SvO2). The reciprocal changes in DO2 and O2 extraction keep the VO2 constant (VO2 = DO2 x O2 extraction). However, when the hematocrit falls below 10%, the increase in O2 extraction is no longer able to match the decreasing DO2, and the VO2 begins to fall. The decrease in VO2 is a sign of dysoxia (defined in as oxygen-limited aerobic metabolism), and it is accompanied by an increase in lactate production. The point at which the VO2 begins to fall is thus the threshold for tissue dysoxia, and it usually occurs when the O2 extraction reaches a maximum level of 50 to 60%. This means that an O2 extraction (SaO2 – SvO2) that is 50% or higher is a sign of inadequate tissue oxygenation.

Thus, because of the compensatory changes in cardiac output and peripheral O2 extraction, progressive anemia will not impair tissue oxygenation until the hemoglobin and hematocrit reach dangerously low levels. The hematocrit had to fall below 10% (corresponding to a hemoglobin concentration of 3g/dL) before tissue oxygenation is compromised. The experimental animals in this study were anesthetized and breathing pure oxygen (which could favor tolerance to severe anemia), but similar results have been reported in awake animals breathing room air (9). The lowest hemoglobin or hematocrit that is capable of supporting tissue oxygenation in humans is not known, but one study by Weiskopf RB, Viel and Feiner et al, of isovolemic anemia in healthy adults showed that hemoglobin levels of 5g/dL had no deleterious effects on tissue oxygenation (10).

### Paradoxical Effect

Isovolemic anemia can have a paradoxical effect that increases tissue oxygenation. Which is from an animal study that evaluated the effects of isovolemic anemia on skin flaps using a specialized oxygen
electrode to measure the PO2 in subcutaneous tissues below the skin. (11). As indicated in the graph, reductions in hematocrit were associated with increases in the subcutaneous PO2 in both normal and ischemic skin regions. Furthermore, the increase in tissue PO2 persisted until the hematocrit fell to 10 to 15% (which is about the same hematocrit where tissue oxygenation became compromised in the study). The improvement in tissue oxygenation can be explained if the cardiac output response to anemia is so exaggerated that the oxygen delivery increases despite the decrease in serum hemoglobin. Anemia can preferentially increase flow in certain regional circulations, as mentioned earlier, and the skin may be one of these regions. In fact, the beneficial effects of isovolemic anemia on blood flow to the skin has led to the use of isovolemic anemia as a clinical tool for promoting the viability of skin flaps.

CONCLUSIONS:

Anemia is almost universal in patients who spend more than a few days in the ICU and about half of ICU patients with anemia are given one or more transfusions of concentrated erythrocytes (packed red blood cells) to correct the problem. This practice of transfusing red blood cells to correct anemia is one of the most fickle and arbitrary interventions in critical care medicine. Few ICUs employ practice guidelines to standardize transfusion therapy, and in most cases blood transfusions are given without documented evidence of need or benefit. A single most important point is to remember that anemia is well tolerated as long as intravascular volume is maintained, hemoglobin level has to drop to 3gm/dl to demonstrate evidence of impaired tissue oxygenation because (as indicated in the introductory quote) anemia does not compromise tissue oxygenation as long as the intravascular volume (and hence cardiac output) is maintained. The important role of blood volume in supporting tissue oxygenation is often overlooked, even by the American Red Cross, whose popular slogan, blood saves lives, deserves a more accurate update, blood volume saves the life.

REFERENCE

ABSTRACT:
Anaemia – in the perioperative period is always associated with excess morbidity and mortality. Blood transfusion has been a longstanding strategy for managing perioperative anaemia. In developing countries like us collection of allogeneic blood has always been a problem. Moreover blood transfusion carries risks of infection, renal insult, and transfusion related acute lung injury [TRALI]. Further, data suggest that perioperative mortality and length of hospital stay are worsened with liberal use of transfusion. Other alternatives to blood transfusion include supplementation of iron [both Oral & IV] and erythropoiesis-stimulating agents (ESAs). Though ESAs reduce the need for perioperative blood transfusion but increased risk of thrombotic events cannot be ruled out.

INTRODUCTION
Anemia is commonly unrecognized and overlooked by physicians and surgeons because it often exhibits very non-specific symptoms or no symptoms at all. Detection of anemia is often overshadowed by the myriad of other concerns that need to be addressed when preparing a patient for surgery.1

Consequences of Anemia
Anemia should be viewed as a significant clinical condition, rather than simply an abnormal laboratory value.6 In surgical patients, anemia has been linked to increased postoperative morbidity and mortality.2 Several studies have shown that patients with preoperative anemia have a higher incidence of allogeneic blood transfusion compounding the problems from anemia which may include a longer hospital stay and an increased likelihood of death after surgery.2,7,8 Patients who are transfused after surgery as a result of anemia are more likely to develop postoperative infection, require longer periods of mechanical ventilation, and have a greater risk of mortality.9,10

Causes of Preoperative Anemia
❖ Blood loss [Acute or Chronic]
❖ Nutritional deficiency
❖ Renal insufficiency
❖ Malignant diseases
❖ Long standing illnesses (like tuberculosis)

Additionally, some patients may be more susceptible to perioperative anemia than others. Studies have shown that female patients, those with smaller body surface area, and African American patients are at increased risk.1, 11

Untreated bleeding episodes, along with the frequent phlebotomies that are a standard part of postoperative procedure, cause blood loss and can contribute to anemia during surgery and recovery.5 Postoperative inflammatory response can additionally lead to blunted erythropoietic response and diminished iron availability, resulting in anemia.1

BLOOD TRANSFUSION- is this the only option?
The use of allogeneic blood transfusion to manage anemia and blood loss is a concept that originated several centuries ago and has changed little over the years.

Blood collection challenges
In developing countries like us blood collection has historically lagged demand, resulting in a blood supply is never sufficient to meet transfusion needs. Unless practices are changed to increase blood donation, these unmet transfusion needs may grow.

Safety of blood transfusion
The safety of the blood supply has improved markedly. Sophisticated testing and public demand have
led to a dramatic decline in the risk of transfusion-related transmission of HIV, hepatitis C virus, and hepatitis B virus. Despite this progress, the risk of transfusion-related acute lung injury (TRALI) has persisted in recent years. TRALI is characterized by acute onset of non-cardiogenic pulmonary edema within 6 hours of blood product transfusion. Believed to be immune-mediated, TRALI is thought to occur as antibodies to human leukocyte antigens develop, inducing capillary leak syndrome.

**Stored blood – duration and its outcomes**

An interesting factor in the relation between transfusion and outcomes is the shelf life of the blood being transfused. A recent study of patients who received red blood cell transfusions during cardiac surgery found that those who received “older blood” (stored for > 14 days) had significantly higher rates of sepsis, prolonged intubation, renal failure, in-hospital mortality, and 1-year mortality compared with those who received “newer blood” (stored for < 14 days). These differing outcomes are generally attributed to the so-called storage defect. As blood gets older, it loses components such as 2, 3-DPG and adenosine diphosphate, its red cells lose deformability, and it undergoes buildup of cytokines and free hemoglobin. Increased demand for newer blood in light of the storage defect could further intensify pressures on the blood supply.

**MANAGEMENT OF PERIOPERATIVE ANEMIA**

**Preoperative screening for Anaemia**

The evaluation should include history of bleeding diatheses, previous transfusions, and symptoms of anemia. History of use of certain drugs like, aspirin, clopidogrel and anticoagulants should be reviewed with an eye toward any that may predispose to perioperative bleeding and anemia. In physical examination evaluation of pallor and petechiae is key, as is attentiveness to symptoms of anemia such as shortness of breath and fatigue.

Quantitatively, anaemia is defined as hemoglobin level less than 13g/dl in males and less than 12g/dl in females. But there is debate with regard the threshold for intervening and the target prior to surgery. An Hb level of below 10g/dl is regarded the minimum for intervening. There is also debate around the transfusion Hb threshold. Practice guidelines from the American Society of Anaesthetists suggest definitely at 6g/dl and not at 10g/dl. Within the range 6g/dl and 10g/dl decisions will be taken based on circumstances (co-morbidity, organ ischemia, intravascular volume, ongoing bleeding, risks of inadequate oxygenation).

If anaemia is associated with other hematologic abnormalities, hematologist may be consulted and bone marrow study may be considered. If no other abnormality exists then management may be planned according to red cell indices as in Figure -1.

**Clinical care pathway for identifying and evaluating anaemia in patients undergoing elective surgery**

**Management options**

Once the cause of anaemia is established, treatment can be planned accordingly. Broadly it is of two types – Pharmacological and Technological. The former include iron supplements and erythropoiesis stimulating agents [ESAs]. Among other pharmacologic options are thrombin, collagen, fibrin glue, tranexamic acid, and aminocaproic acid, but these agents are less well studied than the first two. Technological options include preoperative autologous blood donation, cell salvage, and acute normovolemic hemodilution. In addition to these options, careful management of anticoagulant and antiplatelet medications should be practiced, including discontinuation or substitution of drugs that could hamper clotting perioperatively.

**PHARMACOLOGICAL MANAGEMENT**

**Iron supplementation**

Oral iron is available in five preparations: ferrous ascorbate, ferrous sulfate, ferrous gluconate,
ferrous fumarate, and iron polysaccharide. Gastrointestinal side effects may limit these preparations’ tolerability. Iron supplements with a high elemental value will require fewer pills and fewer doses, reducing the risk or frequency of side effects.

**Intravenous (IV) iron preparations** are much safer now than they were years ago, when anaphylactic reactions were a concern. The ones generally used in the perioperative setting are iron sucrose and iron gluconate. Unlike the older IV preparations, the use of iron sucrose and iron gluconate often requires a second dose. The effect on hemoglobin levels usually occurs starting at 1 week, with the maximum effect achieved at 2 weeks. Hypotension, arthralgia, abdominal discomfort, and back pain are potential side effects of IV iron.

**Erythropoiesis-stimulating agents**

Erythropoiesis-stimulating agents (ESAs) include epoetin alfa (erythropoietin), and the more recently introduced darbepoetin alfa. The preoperative dosing schedule for epoetin alfa is usually three weekly doses (plus a fourth dose on the day of surgery) if the surgery is scheduled 3 or more weeks in advance. However, daily dosing can be used effectively if the preoperative period is less than 3 weeks, provided that it is continued until 4 days after surgery. Oral iron is necessary throughout the course of epoetin alfa therapy.

**TECHNOLOGICAL OPTIONS AND OTHER STRATEGIES**

**Autologous blood donation:**

In cases of elective surgery, autologous blood donation can be used to protect against disease transmission and overcome the challenge of blood type compatibility. Preoperative autologous donation of blood has been a prevalent practice, but its use is declining. One reason is that waste is high (approximately 50% at Cleveland Clinic), which makes this practice more costly than is often realized. Also, autologous blood donation increases the likelihood that the patient will be anemic on the day of surgery, so that he or she may still need allogeneic blood after all, defeating the initial purpose. Despite these limitations, preoperative autologous blood donation remains a useful option for a subset of patients with multiple antibodies for whom donor blood may be difficult to obtain.

**Cell salvage**

Cell salvage is an innovative technology that recovers the patient’s own blood (after being shed from the surgical incision) for transfusion after filtering and washing. It is particularly well suited to procedures that involve massive blood loss. Cell salvage requires technical expertise, however, and involves costs associated with both the machine and disposables.

**Restricted postoperative phlebotomy**

Phlebotomy accounts for a significant amount of blood loss, especially in intensive care patients with arterial lines. The equivalent of 30% of total blood transfused has been reported to be lost to phlebotomy during an intensive care unit stay.36 Triggers for transfusion cannot be assigned universally based on blood loss from phlebotomy but must consider the patient’s hemodynamic status, cardiac reserve, and other clinical characteristics.

**Component therapy**

As there is always a high demand-supply ratio for blood, component therapy is an option to be promoted. It reduces the risks involved in transfusion and also helps meeting the demand for blood. Only drawback being expenditure and expertise, but in long run it can be managed effectively.

**CONCLUSION**

Anemia is associated with increased morbidity and mortality in the perioperative setting. Perioperative blood transfusion is one method of raising hemoglobin levels in anemic surgical patients, but it increases perioperative morbidity in the form of acute transfusion reactions, immunosuppression, postoperative infection, and longer hospital stays. Moreover, blood collection continues to lag blood demand. Medical alternatives — all of which can be used in the perioperative setting—include iron supplementation, vitamin B12, and ESAs in select patient groups.

**REFERENCES**


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Anaesthesia in Patient with Sickle Cell Disease

B. Sriramka¹, B.K Naik², R. Panda²

Introduction:

Sickle cell disease is a congenital haemoglobinopathy characterized by deformed red blood cells, acute episodic attacks of pain and pulmonary compromise, widespread organ damage, leading to early death. Since the time it was first discovered by Dresbach¹ in 1904 and the first surgery reported in these ‘peculiar’ patients by Washburn RE² almost a century ago; there have been tremendous advances in biochemical and molecular field complimented with improved grasp of the clinical squeal of the disease and numerous anesthetic case reports, reviews, and studies³⁻⁷. Yet despite this fairly extensive perioperative literature, there remains considerable uncertainty over the extent and nature of postoperative complications.

In India the Hemoglobin S (HbS) was first detected in Vedoid tribe in Nilgiri hills of Tamilnadu and subsequently discovered in other states. Sickle gene frequency is between 5% to 40%, distributed in 3 different geographic zones and Orissa falls into the high prevalence zone (21-40%). They are distributed in both the tribal and nontribal populations, mainly in the Kuilta, Agharia, Gouda castes⁸.

A single amino acid substitution, valine for glutamate, at position 6 on the α chain is responsible for the condition. Sickle cell disease is inherited as an autosomal recessive disorder following a predictable Mendelian pattern. Thus heterozygote (HbAS) parents will have a 25% chance of producing either a normal (HbAA) or sickle cell disease (HbSS) and a 50% chance of producing another heterozygote (HbSA, trait) child. When lysine is substituted for glutamate, also at position 6 of the α chain, hemoglobin C is produced. HbSC disease produces similar pathophysiology but with fewer and often less severe clinical problems. Patients may also be double heterozygotes for SCD and α thalassemia, producing HbStα disease. If they are coded to produce no normal α chains (α0) the disease is similar in severity to SCD. If they are coded to produce normal α chains in diminished quantities, they have a milder form of the disease.

Pathophysiology:

The key to understanding the pathophysiology lies in the fact that sickling is a molecular disease of ‘sickle cells’ which produce a vicious cycle and “sticky cells” which leads to an inflammatory response. A single amino acid substitution creates an allosteric abnormality of the hemoglobin molecule rendering it unstable as well as less soluble when deoxygenated. Deoxygenated HbS is 50 times less soluble in blood than deoxygenated HbA. Red blood cells with HbSS begin sickling when the oxygen saturation falls below 85% and it comes out of solution forming long crystals called “tactoids” which distort the red cell and cause it to become crescent shaped. Initially this is reversible with oxygenation but repeated sickling in the low oxygen tension of the microcirculation causes membrane damage. The cell wall then becomes brittle and is then susceptible to premature destruction resulting in a lifespan of only 10-20 days as opposed to a normal 120 days. The structural change and associated increase in blood viscosity promotes venous stasis. A vicious cycle is initiated with local blood vessel obstruction leading to tissue hypoxia producing further deoxygenation which promotes further sickling. This leads to cell death and tissue infarction at the site of obstruction. This is termed as sickle cell crisis.

Many episodes of sickling occur spontaneously although certain factors may increase the risk. Apart from hypoxia, acidosis (irrespective of the prevailing oxygen tension) is important and is the principle reason for most sickling occurring in the venous circulation. Infections (bacterial or viral) are potent inducers. Hypothermia and dehydration are also important.
causing venous stasis and hypoxia via vasoconstriction. Decreased cardiac output and hypovolemia lead to increased transit time through the hypoxic environment of the capillary bed, also increasing the sickling process.

Historically, it was felt that this red cell pathophysiology was essentially solely responsible for SCD related problems. However, the interactions between red cells, platelets, leukocytes, thrombin, and endothelial cells along with disturbances of nitric oxide (NO) biology are now known to be at least equally important in this complex pathophysiology\(^9\). There is reasonable evidence that there is decreased production and increased scavenging of NO in SCD patients\(^11\). Through complex mediators this results in endothelial dysfunction, enhanced platelet aggregation, coagulation dysfunction, enhanced leukocyte endothelial adhesion, susceptibility to oxidant mediated injuries, and both acute and chronic pulmonary hypertension. Administration of inhaled NO has been shown to be beneficial in some patients suffering vasoocclusive crisis including stroke and acute chest syndrome (ACS)\(^12\). The consequence of sickling and endothelial inflammation results in adhesion and occlusion of the microvasculature. As the cells sickle and reform the intricate balance of iron metabolism, ion transport, and cellular hydration is disturbed which alters the red cell membrane making them sticky.

Thus the HbS red cell is unstable, sticky and insoluble resulting in early red cell destruction, sickling, and endothelial damage. It is this pathology that results in the acute crisis as well as the long-term chronic problems in these patients. The common complications seen in individuals with sickle cell disease are summarized by the mnemonic “HBSS PAIN CRISIS”: From Georgia Comprehensive Sickle Cell Web Site www.scinfo.org/prod05.htm. The episode commences from about 6 months of age after the reduction in fetal haemoglobin (HbF) which initially acts as a protective mechanism. Some sufferers are fortunate to maintain a higher than normal HbF production throughout their lives which improves their condition.

Figure 1: complications in sickle cell patients

ANESTHETIC MANAGEMENT

Preoperative Preparation:

Historically, perioperative mortality rates as high as 10% and morbidity rates as high as 50% have been reported. More recent studies have reported a mortality of around 1%. Sickle cell disease causes such wide spread organ damage, that it is difficult to give a single critical pathway for standardized preoperative care, which will apply, to all patients. The aim is to prevent a sickle cell crisis whilst providing anaesthesia. Attempts should be made to improve the patient’s condition preoperatively and to avoid hypoxia, acidosis, hypotension, dehydration and hypothermia perioperatively. Together the hematologist, anesthesiologist and surgeon can assess the patient’s perioperative risk and determine any special requirements.

In general the patient should be admitted to the hospital the day before surgery to permit assessment by hematologist, anesthesiology, and surgery. A thorough investigation is useful to complement the history and examination. The mere presence of anemia however does not always imply sickle cell disease. Further investigations should include blood microscopy to check for sickle cells, Howell Jolly bodies and sideroblasts; and “Sickledex” test. Urea and electrolyte to assess renal function, and liver function tests for unconjugated bilirubin to access haemolytic anemia. ECG to look for evidence of cardiac damage and finally chest X-ray to assess lung fields and cardiac size.

An elective surgical procedure should not proceed in a sickle cell patient with an ongoing infection such as urinary tract infection or respiratory tract infection since these could lead to a painful crisis, ACS, or CVA.
Intravenous fluids should be administered while the patient is fasting. While the recommendation of an infusion rate of one and a half times maintenance fluid requirement of a balanced salt solution is frequently made, there is no evidence that excessive hydration is beneficial. The goal of intravenous fluid therapy is to prevent dehydration throughout the perioperative period.

The role of preoperative transfusion continues to be somewhat controversial. Earlier hematologists and anesthesiologists provided aggressive transfusion practices with target Hb of 10 mg/dl and HbS concentration of 30% or less. The National Institutes of Health 2002 publication on “The Management of Sickle Cell Disease” recommends: “In patients with SCD-SS and SCD-S α Thalassemia, simple transfusion to achieve hemoglobin of 10g/dl should be performed before all but the lowest risk procedures.” Transfusion provides improved oxygen carrying capacity and dilutes the percentage of sickle cells with RBCs containing HbA. Very high-risk patients may require the more aggressive transfusion approach. This should be decided in concert with the hematologist. However, this increases the risk of transfusion related complications. The hemoglobin should not be permitted to rise above 11g/dl, since this can increase blood viscosity, delay transit time, promote sickling and precipitate a stroke. In our institution only very low risk patients having low risk procedures avoid transfusion.

Preoperative physiotherapy and breathing exercises decrease the incidence of postoperative atelectasis and lung collapse.

Premedication: If premedication is planned anxiolytics are preferable to opiates which may depress the respiration.

Intraoperative Management:

No particular anesthetic or technique has proven to be more or less advantageous for sickle cell disease patients. The general recommendations are:

Preoxygenate for 2-3 minutes. Hypotension on induction should be avoided by careful titration of induction agents.

If there is any doubt about the airway a rapid sequence induction with intubation should be performed. Except for the shortest procedures ventilation should be controlled to ensure oxygenation and normocarbia (normal CO₂ level). A 30-50% inspired oxygen level is advisable.

Close monitoring of anaesthesia should prevent hypoxia, cardiovascular depression or acidosis developing. Clinical observation can be usefully supplemented by pulse oximetry, blood pressure measurement, ECG and end tidal CO₂ monitoring when available.

Replace fluid loss promptly. A central venous pressure line may help monitor fluid replacement. Monitor urinary output.

Temperature loss should be measured and minimized. Creating a warm ambient temperature is important. Cover all exposed parts of the body. Pre-warm bags of fluids using a bowl of water warmed to body temperature if a blood warmer is not available. Inspired gases can be partly warmed using a condenser humidifier such as a “Humidivent”.

Venous stasis should be minimized. This may be a particular problem in the prone (face down) position when compression of the inferior vena cava may occur. Pay attention to the placement of supports. The use of tourniquets is controversial. Previously contraindicated, an increasing number of reports have shown no evidence of sickling with the use of tourniquets when there is an absolute need for a bloodless field. It is of no importance in sickle cell trait, contrary to popular opinion.

Historically regional anesthesia has been avoided but they may have advantages over general anaesthesia and should be considered whenever possible. Benefits include: Peripheral vasodilation secondary to sympathetic block. This improves blood flow to the extremities thereby limiting the possible devastating consequences of vasoconstriction. The Analgesia is improved in the early postoperative phase and may help to prevent the increased oxygen demand imposed by pain and shivering. Skeletal abnormalities arising from the consequences of sickle cell disease may make intubation difficult. This potential problem is avoided with local anaesthesia. However, there are disadvantages, however. Regional blocks may cause hypotension and hypoperfusion. Prevent these with
adequate fluid loading and a careful technique. Use small doses of vasoconstrictors only if absolutely necessary. Do not mix adrenaline with the local anesthetic as it may exacerbate a crisis. Suffice it to say that the technique of anesthesia is likely much less important than the meticulous attention to detail in the areas of preoperative preparation, perfusion, temperature control, and oxygenation.

The wisdom of the use of a tourniquet in patients with sickle cell disease has been debated. If one chooses to use a tourniquet the extremity should be carefully exsanguinated prior to inflation.

**Postoperative Management:**

The immediate postoperative period is a critical time for patients with sickle cell disease. Vaso-occlusive crises are among the most frequent and include painful crisis, acute chest syndrome and stroke. Hypoventilation resulting from general anaesthesia can easily result in a sickling crisis. The risk can be reduced by:

- Careful monitoring of vital signs and conscious level. Ensure a clear airway, and where possible, postoperative oxygen therapy.

Neuromuscular function must be fully returned to normal before extubation is contemplated. Unless a nerve stimulator is available test this by checking if the patient can perform a sustained head lift (5 seconds) or a strong hand grip on command. Ventilation should be continued until these are apparent.

Extubation should be preceded by 2 - 3 minutes of breathing 100% oxygen and supplementary oxygen should be continued postoperatively. This will help to overcome the effects of any residual depressant effects of general anaesthesia, any shunt present in the lungs and will compensate for the increased oxygen demand resulting from pain or shivering. Regular chest physiotherapy should be available with the aim of preventing a chest infection.

Adequate analgesia is essential but must be balanced against the problems of hypoventilation with the use of opiates. Titrate the dose carefully. Regional and local blocks are useful. Non-steroidal anti-inflammatory drugs can be used unless renal function is impaired.

Maintenance of intravenous fluids is essential until the patient is able to eat and drink.

**Emergency Anaesthesia**

The same guidelines should be followed as detailed above. Although less time for preoperative assessment will be available, prepare the patient as thoroughly as possible in the time available.

**Sickle Trait (HBSA)**

By definition HbSA patients have at least 50% HbA. Under physiologic conditions problems are very rare. While intracellular polymerization begins below oxygen saturations of 85% in HbSS this does not occur in HbSA until saturations are below 40%. Thus it is generally accepted that patients with sickle trait do not require transfusions. However attention to hydration, perfusion, ventilation, and temperature control is prudent as always.

**Sickle Hb C Disease (HBSC)**

In general patients with both HbS and HbC (HbSC or S-C disease) have less frequent and usually milder vaso-occlusive episodes. Transfusion appears to be beneficial in HbSC disease patients undergoing abdominal procedures but is not necessary in minor procedures. Because these patients are usually only mildly anemic partial exchange transfusions may be required to keep hemoglobin levels to less than 12 g/dl.

**Specific Procedures**

**Adenotonsillectomy**

Early functional hyposplenism is associated with hypertrophy of other lymphoid tissue, hence adenotonsillar hypertrophy is common. Tonsillectomy has also been found to reduce the incidence of complications associated with *S. pneumoniae* in SCD patients, because of the harboring of the organism in tonsillar tissue. Obstructive sleep apnea (OSA) secondary to adenotonsillar hypertrophy is common in children with SCD. Halvorson et al. found postoperative complications after adenotonsillectomy are increased if the HbS is greater than 40% and in patients younger than 4 years of age. These postoperative complications are increased in the presence of OSA. They recommended that children should be transfused preoperatively for elective tonsillectomy, to an HbS of less than 40%. Chest problems after adenotonsillectomy are thought to be linked to postoperative pain, hypoventilation, atelectasis and subsequent hypoxia.
Aggressive respiratory therapy, bronchodilators and incentive spirometry help to decrease these pulmonary complications. Although the association between hypoxemia because of OSA and vaso-occlusive events is not established Kirkham et al. found that those children with a high proportion of their sleep study with saturation readings less than 90% were at significantly increased risk of future CNS events. However, intermittent dips in saturation, or previous adenotonsillectomy had no effect on risk.

**Cholecystectomy and Splenectomy**

Splenectomy is performed for sequestration crises and may be performed in early childhood. Cholecystectomy is the most common surgical procedure performed in SCD patients. The National Preoperative Transfusion Study recommends preoperative transfusions to lower incidence of sickle cell events. Emergency cholecystectomy is associated with a high morbidity and should be avoided if possible. It should be noted that it may be difficult differentiating between sickle cell crisis and acute calculous biliary tract disease in the SCD patient. Between laparoscopic and open cholecystectomy, Delatte et al. found that laparoscopic surgery did not decrease the risk of developing ACS though associated with longer time and anesthetic exposure. The operative risks of laparoscopic cholecystectomy are now thought to be acceptable and are outweighed by the risks of complications from gallstones.

**Orthopedic Surgery**

Orthopedic disease affects the majority of SCD patients, of which aseptic necrosis of the hip is most common, occurring in up to 50% of patients. Sickle cell-related events have been found to occur in 17% of orthopedic cases. The orthopedic report of the National Sickle Cell Surgery Study Group supports the use of conservative preoperative transfusion to bring the haemoglobin concentration to between 9 and 11 gm/dl. Use of arterial tourniquets is controversial in SCD. In patients with SCD, circulatory stasis, hypoxia and acidosis beneath and distal to the tourniquet cuff are ideal conditions for the induction of red cell sickling. However if all their use is contemplated than careful exsanguinations of the limb before tourniquet ination, and optimum acid–base balance and oxygenation should be allowed for uneventful procedures with a mean tourniquet time not exceeding over 1 h. The risks of precipitating a sickle crisis with a tourniquet during surgery in patients with SCD should be balanced against the benet of operating in a bloodless eld.

**Neurosurgery**

SCD patients with neurosurgical problems require consideration of preoperative medications and angiography, transfusion therapy and anesthetic technique. The rest problem is the need for contrast medium. These are able to induce sickling by osmotic shrinkage of RBCs; however modern day contrast are isotonic media have little effect on RBC and reducing the HbS to less than 40% before angiography has also been shown to reduce the problems of sickling secondary to contrast medium. Among the drugs used in neurosurgery mannitol and fursemide, used for brain volume reduction, cause increased tonicity and may present an increased risk though barbiturates and steroids have been found to be safe in SCD. Urea is thought to be the osmotic agent of choice because it does not produce sickling when mixed with sickle cell blood in vitro. This may be because it crosses the red cell membrane freely, producing no osmotic gradient between the intra- and extracellular spaces. The fluid restriction often imposed on patients undergoing craniotomy may be dangerous in the SCD population and a spinal catheter or ventriculostomy is a good alternative method to reduce intracranial volume. Other than this, the principles mentioned earlier such as careful positioning and avoidance of hypothermia should be adhered to. Theoretically hypothermia, for its cerebral protective effects, should be avoided in these patients.

**Cardiac surgery**

The issues relating to the need for contrast media for radiological studies have been mentioned earlier. Open-heart surgery using hypothermic cardiopulmonary bypass clearly creates all the conditions that precipitate sickling. Many different methods have been employed to avoid the potentially lethal complications of SCD. Correction of anemia prior to surgery, partial exchange transfusion, use of blood prime, avoidance of hypoxia and acidosis, and the avoidance of aortic cross-clamping, hypothermia, cardioplegia and topical cooling have all been recommended for open-heart surgery on these patients. The majority of previously reported cases requiring cardiopulmonary bypass recommend
the use of pre- or intraoperative exchange transfusions to reduce the circulating concentration of HbS. Exchange can be carried out either in the preoperative period, or on initiation of cardiopulmonary bypass. Again hypothermia should be avoided. It should not be forgotten in these patients undergoing cardiac surgery, the need for care in avoiding precipitating factors of sickle crises throughout the perioperative period and not just during cardiopulmonary bypass.

**Pregnancy and cesarean delivery**

Pregnancy for women with SCD is still characterized by a high rate of complications, particularly for homozygous SCD. The rate of Cesarean delivery in the SCD population is generally higher than in the whole population. No consensus exists concerning the anesthetic care of parturients with SCD. Regional anesthesia could be beneficial for SCD patients by inducing vasodilation and enhanced blood flow in the anesthetized area, and by providing optimal pain control. Interestingly, epidural analgesia has been described to treat the unusual occurrence of a vaso-occlusive crisis during labour. However, general anesthesia may be the most appropriate choice in some circumstances, including fetal bradycardia. One approach could be the early insertion of an epidural catheter to reduce the need for general anesthesia in such a high-risk population.

Blood transfusion therapy should be made available for medical and obstetrical complications to include increasing hypoxemia, progressive anemia, acute chest syndrome, twin pregnancy, splenic sequestration syndrome, preeclampsia, septicemia, or prior to general anesthesia and surgery keeping in mind the complications attributing to blood transfusion therapy. Excellent prenatal monitoring and aggressive intervention should be instituted when problems arise for the successful management of the pregnant patient with sickle cell disease. Prenatal diagnosis and cord blood screening should be made available for the infant. Appropriate pediatric referral and prophylactic penicillin is recommended for the infant with sickle cell disease.

**Conclusion :**

SCD is a relatively common multisystem disease with life-threatening complications (such as stroke and ACS), in the perioperative period, and is of great relevance to the anesthetist. A structured multidisciplinary approach is of great help in the perioperative management of these patients. New treatments are being researched, although an attention to detail of basic measures such as avoidance of perioperative dehydration, adequate analgesia and active mobilization forms the backbone of the anesthetist’s role in the care of these patients.

**References :**

8. Patel DK. Epidemiology and clinical aspects of Sickle cell disease in India.
9. Hebbel RP, Vercelloti GM. The endothelial biology of sickle cell disease. J Lab Clin Med 1997; 129: 288–93.
INTRODUCTION

Anemia is common in patients with heart failure and defines a group of patients at very high risk for death and cardiovascular complications. Over the past decade, there has been increasing recognition of the importance of anemia in the pathophysiology, treatment and prognosis of heart failure. There is an emerging appreciation that, targeting anemia may serve as a potential treatment strategy for patients with chronic heart failure. (1)

DEFINITION

Determining the impact of anemia on heart failure and its prevalence requires a proper definition. Differences in prevalence of anemia in different published studies reflect the differences in the definition of anemia that is followed.

Some investigations follow the historical definition of anemia put forward by WHO in the context of nutritional anemia over 4 decades ago. Anemia is defined as Hb concentrations less than 13 g/dl for men or less than 12 g/dl for women. (2) But it suffers from the lack of rigorous clinical validation particularly in the setting of heart failure, and its appropriateness and clinical applicability continues to be debated. National kidney foundation defines anemia as Hb less than 13.5 g/dl for men or less than 12 g/dl for women. Other investigators prefer to use a more conservative definition eg. <12 g/dl for men & <11 g/dl for women.

PREVALENCE

Anemia is prevalent in patients with heart failure regardless of the clinical setting, although the exact rates vary widely.

A recent meta-analysis analyzed a total of 153,180 patients with heart failure reported in 34 published studies from 2001 to 2007 and estimated the prevalence of anemia to be 37.2%. (3)

This finding is consistent with the finding from the latest prospective STAMINA–HFP (Study of Anemia in Heart Failure Population) Registry, which identified a prevalence of 34% in a cohort of 1076 unselected outpatients with chronic heart failure (based in WHO criteria).

INCIDENCE

Large clinical trials are better poised to record incidences of anemia – because of their prospective design and close follow-up as compared to registry studies. Determining the incidence of anemia in heart failure can be biased because of the exclusion of subjects with significant anemia or pre-existing renal insufficiency.

The SOLVD (Studies of Lest Ventricular Dysfunction) Trial found a 9.6% 1 yr. incidence of new-on set anemia. (4) More recent large trials such as COMET and Val–HeFT observed 1 yr. incidence rates of 14.2% and 16.9% respectively. (5)(6) The incidence of real–world new onset anemia may even be higher with upto 20% over a 6month follow–up period in 1070 ambulatory patients with chronic heart failure. (7)

The true incidence can be influenced by dilutional anemia as a result of hypervolemia in congested patients, which may resolve after stabilization. (8)

ETIOLOGY

There are many potential underlying causes of anemia in the setting of heart failure. The main causes of anemia in heart failure include –

• Nutritional deficiencies: Male absorption, Impaired metabolism
• Acute Blood Loss: GI Bleeding (Not common)
• Intrinsic renal disease – Insufficient erythropoietin production or response.
• Haemo dilution from volume expansion.

Most patients present with normocytic anemia with similar mean corpuscular volume across the spectrum of Hb levels.
These findings suggest that there is relatively low prevalence of significant iron deficiency, even though the presence of functional or subclinical iron deficiency can’t be excluded. However, recent demonstration of potential benefits of iron infusion in improving functional capacity in patients with heart failure, suggest that relative iron deficiency may be present.

FACTORS CONTRIBUTING TO ANEMIA IN HF:

Heart Failure Disease Severity

The presence of anemia is tightly linked to clinical disease severity of heart failure. Posthoc analysis of the data from clinical trials have provided a host of factors, other than NYHA class as predictors of incidence of anemia including more advanced age, higher dose of diuretics or the use of spironolactone and digoxin, elevated serum creatinine and potassium as well as serum sodium and body mass index, which are all suggestive of worsening heart failure severity. Patients with higher plasma levels of natriuretic peptide demonstrated higher likelihood of presenting with anemia than those with lower levels of plasma natriuretic peptide.(9)

Demographic Data

Advancing age is an important contributor to the severity of anemia. Although gender plays an important role in the overall population, the prevalence and clinical consequences appeared to be similar in several reports in heart failure cohorts.(10)

Preserved Vs. Impaired Ejection Fraction

Several observational studies have found similar prevalence in preserved and impaired LVEF. Analysis of CHARM data, revealed that the prevalence of anemia was similar between those with preserved LVEF and reduced LVEF 27% and 25% respectively eventhough a weak inverse relation of Hb with LVEF was observed.(11) This data was supported by finding from Val-HEFT (restricted to impaired LVEF) study, in which relationship between Hb and LVEF was less apparent. Meanwhile another study reported, the prevalence of diastolic dysfunction to be proportional to the presence and severity of anemia.(12)

Diabetes Mellitus

Consistent across different observational cohorts, patients with a history of diabetes mellitus demonstrated greater prevalence of anemia than non diabetic patients.(10)

Renal Insufficiency

Intrinsic renal disease leading to reduced EPO production has been one of the predominant contributes to the developed of renal function (GFR < 60ml/min/1.73m2) was associated with a 3-fold higher likelihood of developing anemia . In an analysis of CHARM program with a 26% prevalence of anemic patients, more than half had stage III to IV chronic kidney disease compared with less than a their of non-anemic patients. The degree of anemia was directly proportional to the degree of renal dysfunction with every 10- point decrease of GFR below 60ml/Min/1.73m2 being associated with a decrease of Hb by 0.290g/dl.(10)

Haemodilution

Haemodilution & dilutional anemia are unique features of heart failure, resulting due to hypervolumic state. A single center report described a 46% prevalence of dilutional anemia, a substantial proportion of whom demonstrated resolution of their anemic status with standard heart failure treatment.(8)

Chronic Inflammation

Presence of anemia in association with higher levels of CRP, suggest a role of inflammation & inflammatory bio-markers as a cause of anemia in this settings, although few studies have analyzed this relationship.

PATHOPHYSIOLOGY OF ANEMIA IN HEART FAILURE

Despite the increasing importance of anemia in HF little is known about the pathophysiology of anemia in HF and mechanism by which anemia may worsen HF.

As compared to patients with heart failure who don’t have anemia, patients who are anemic are more likely to be older, have diabetes, and CKD. These patients are also more likely to have worse HF as indicatd by higher NYHA – class, lower exercise capacity, worse quality of life scores, greater peripheral oedema, lower blood pressure, higher use of diuretic and other cardiovascular medications, and worse neurohormonal and inflammatory profile. Renal
dysfunction, diabetes, peripheral oedema, high BNP, and CRP, low weight and low diastolic blood pressure were found to be independently associated with the likelihood of anemia in Val –HEFT (Valsartan Heart Failure trial) database.(13)

POTENTIAL CAUSES OF ANEMIA DURING HEART FAILURE

Haematinic Abnormalities: Serum vitamin B12 and folic acid, levels are low in only a minority of anemic patients with HF. Gastrointestinal function is often abnormal in patients with HF and this can lead to malabsorption causing iron and other nutritional deficiencies. Moreover, aspirin-induced gastrointestinal bleeding could also cause iron deficiency. Lacking standard criteria, the reported prevalence of iron deficiency has varied greatly from 5% to 21%. One study reported a prevalence of 43% for low serum iron (< 8 m mol/L) or ferritin (<30 mg/L), but microcytic anemia was seen only in 6% of subjects with anemia with HF.(14)

Similarly in another study, depleted iron store in bone marrow was found in 73% of subjects despite normal serum iron, ferritin and erythropoietin. These findings may be explained by diversion of iron from the bone marrow to other reticulo-endothelial stores where it is not available for erythropoiesis even though serum iron and ferritin are normal or increased.

Chronic Kidney Disease and Impaired Erythropoietin Production

Although there is extensive evidence for inadequate erythropoietin production in CKD, the mechanisms remain unclear. Tubulointerstitial fibrosis, tubular loss and vascular obliteration are probably the most important factors that contribute to a decrease in erythropoietin producing cells. In HF, the RBF is decreased and approximately 50% of patients with HF have some renal dysfunction.(15) These findings lead to the suggestion that decreased renal erythropoietin production is the cause of anemia in HF.

Although some studies report correlation between RBF and erythropoietin secretion, recent study found no such correlation and erythropoietin levels were often increased in portion to the seventy of HF but lower than expected to the degree of anemia, suggesting a blunted erythropoietin response.

According to a study by belonje and colleagues,(16) erythropoietin levels were lower than expected in the majority of subjects (79%), whereas, 12% had levels as expected and 9% had erythropoietin levels higher than expected. High levels of erythropoietin at base line and 6 months, as well as higher observed to predicted ratio erythropoietin to Hb level were independently related to increased risk for mortality.

Higher erythropoietin production may be explained by higher levels of AngII, in HF, which reduces RBF. At the same time AngII induced decrease in GFR causes an increase in proximal tubular sodium re-absorption that increases oxygen demand. The factors stimulate erythropoietin production by reducing oxygen delivery at the level of erythropoietin producing cells (Specialised peritubular fibroblasts that are situated within the cortex and outer medulla), by activating hypoxia-inducible-factor 1 (HIF 1), which in turn induces transcription of the erythropoietin gene.

Several factors may explain the finding that erythropoietin response is blunted and the levels are inappropriately low to the degree of anemia in HF. TNF–α and its soluble receptors (sTNF –R1 and sTNF –R2), IL6, circulating neutrophils and CRP are increased in patients with HF.

IL6 and TNFa in particular inhibit erythropoietin productions in the kidney by activating GATA –2 and NF –KB. Therefore, erythropoietin levels may be lower than expected. Additionally these cytokines also directly inhibit the differentiation and proliferation of erythroid progenitor cells in the bone marrow. Furthermore, IL-6 downregulates the expression of ferroportin, preventing the release of iron from body stores.

Anemia and Renin- Angiotensin system

Angiotensin system appears to be closely involved in the control of erythropoiesis. As mentioned earlier, Ang II decreases PO2 by reducing renal blood flow erythropoietin production. Ang II also directly stimulates bone marrow erythroid progenitor cells. ACE inhibitors and ARBs cause a modest reduction of Hb by decreasing erythropoietin and by preventing the breakdown of the haematopoiesis inhibitor N – acetyl - seryl – asparty1 –lysil – proline (ACSDKP).
Haemodilation

Anemia might be caused by hemodilution commonly seen in patients with HF. Androne and colleagues found that nearly half the subjects who were clinically euvolemic referred for cardiac transplant had haemodilution induced pseudoanemia.

Anemia of Chronic disease

Although multiple mechanisms could cause anemia in patients with HF, a treatable cause of anemia is often not identified in majority of patients. A vast majority of these patients may have anemia of chronic disease. In a study comprising 148 well characterized subject with stable HF and anemia. A specific cause of anemia including CKD, iron, folic acid, Vit B12 deficiency and β-thalassemia was found in 43% of subjects. A substantial proportion of remaining 57% of subjects were found to have pro-inflammatory cytokine activation, inadequate erythropoietin production, or defective iron utilization despite adequate iron stores, suggesting anemia of chronic disease.

IMPACT OF ANEMIA ON MORBIDITY & MORTALITY ASSOCIATION WITH HF

Over last decade, numerous well-conducted studies have demonstrated strong relationships between anemia and survival in populations with HF. Regardless of the definition used, anemia consistently portents a poor prognosis. The reported estimates of association between anemia and mortality vary from non-significant to robust with most point estimates indicating a 24% to 94% increase in the risk of death for patients with anemia. On a per 1 gm/dL basis, the reported point estimates range from a 2% increase in 1 year mortality with a 1 gm/dL decline to a 16% improved survival with a 1 gm/dL improvement in Hb. As expected, patients with anemia are more likely to be more symptomatic. In a quality of life - questionnaire based evaluation of impact of anemia on HF-related morbidity, the adjusted changes in quality of life score was proportional to change in Hb level (STAMINA - HF registry).
These findings concur with prior reports in Val-HeFT, regarding higher Minnesota Living with HF Questionnaire scores with more advanced heart failure symptoms.

Analysis of several randomized trial cohorts have also shown that anemia increases the risk of repeated HF hospitalization, which dramatically increases the cost of therapy and negatively affects patient’s quality of life.

TREATMENT OF ANEMIA IN HF

Concurrent with the treatment of heart failure, several studies have demonstrated that correction of anemia leads to better outcome in terms of morbidity & mortality, HF-hospitalization in better QOL-outcomes.

Two broad approaches have evolved with respect to correction of anemia by iron- supplementation and the second approach involves stimulating erythropoietin by EPO.

A. TREATMENT WITH IRON IN PATIENTS WITH HF

Supplementation with iron in HF with or without anemia is based on the premise that, there is relative or absolute iron deficiency in patients with HF. Iron-containing protein are responsible for O2 transport in blood (Hb) and O2 utilization in skeletal muscles (Cytochrome). Hence Iron deficiency influences negatively aerobic capacity and HF outcomes.

Several investigators have reported on the effects of iron supplementation in patients with or without anemia.

Given that reduced absorptive capacity due to abnormal iron-metabolism at the level of GI tract play a role in iron deficiency state in HF, all these trials utilised parenteral route for iron supplementation.

In a prospective, uncontrolled study by Bolger al (19) administration of intravenous iron in anemic HF patients showed improvement in Hb, Serum Ferritin, Sr iron & T.Sat, NYHA-Class, Minnesota living with Heart Failure (MLWHF) score and mean 6-min walk distance.

In another placebo-controlled RCT by Toblli et al (20), in patients receiving weekly iron-sucrose, intravenously for 5 weeks there was significant reduction of NT- Pro BNP, compared with placebo. Similarly there was improvement in exercise tolerance in patients receiving iron-sucrose in FERRIC-HF trial.(21)

Similar results were reported with iron supplementation with feromic carboxy maltose (FCM). Interestingly the results were similar in patients with and without anaemic.

So in conclusion, there are accumulating data indicating short term administration of intravenous iron is associated with improved symptoms and quality of life of patients with heart failure.

(B) TREATMENT WITH ERYTHROPOECTION STIMULATING AGENTS (ESA)

Based on data from iron-supplementation studies, stimulating erythropoiesis by ESA seems to be conceptually tempting.

The effect of anemia correction in HF - by this method has been studied in several controlled and uncontrolled trials. Result from these trials are mixed and at present the role of ESA in treating anemia in HF is controversial. As continued evidences accure for improvement of anemia with these agents, some trials at the same time failed to show any improvement in HF outcomes. Although smaller trials showed both improvement in anemia and HF outcomes with ESA treatment, some of the larger trials like STAMINA-HeFT (darbopoetin-alpha) did not demonstrate significant improvement in exercise duration, quality of life or NYHA functional class by treating anemia to a higher target Hb. The Reduction of Events with Darbopoetin-alpha in Heart failure (RED-HF) trials is an ongoing multicenter study on this issue. Pending its results, in the light of current evidences the role of ESA, in treatment of anemia in heart failure is uncertain.

FUTURE DIRECTIONS IN MANAGEMENT OF ANEMIA IN HF:

In consistencies, controversies and lack of information are the hurdles in the treatment of anemia in HF. The outcomes of anemia in patients with HF are encouraging, but it is not clear if the benefit is from iron or ESA. Mortality, strokes, progression or resurgence of cancer and marginal improvement in quality of life have curbed the enthusiasm for treatment...
of anemia in HF. Absence of clearly defined targets of Hb and lack of standardized performance measure tools complicate the issue of anemia management in HF. Future works need to address these issues.

As regards 'end point', one approach used successfully in A-HeFT (African-American Heart Failure Trial) is the incorporation of a composite score using surrogate measures of disease severity (exercise testing, quality of life questionnaires, and/or global assessments) that are relevant to the anticipated physiologic effects of the agent under investigation, in combination with the occurrence of morbidity and mortality events. This approach seems promising and likely to remove heterogeneity in outcome measures.

Several promising therapeutic concepts are emerging. One such agent in the continuous erythropoietin receptor activator - a pegylated recombinant human erythropoietin with larger half life than the most recent erythropoietin congener, darbopoietin alpha.

Hematide is another investigational synthetic pegylated erythropoietin mimetic peptide with a peptide sequence that is different from that of natural or recombinant erythropoietin. However, it stimulates erythropoietin receptor in the same manner as native or recombinant erythropoietin. Haematide holds interesting future prospects in determining CV outcomes.

Hypoxia inducible factor-1 (HIF-1) alpha stimulates production of erythropoietin in conditions of hypoxia but is degraded by prolyl hydroxylase (PH) inhibitors. A novel strategy to increase the native erythropoietin production is the use of stabilizers of HIF that inhibit the PH activity. The oral PH inhibitors allow HIF-1 stabilization despite normoxia and result in stimulation of erythropoietin. These agents are currently under clinical trials.

In view of difficulty in accurately diagnosing iron deficiency due to acute phase nature of iron parameters, a low dose oral iron absorption test showing increment in iron levels after 2 hours of administration of 10 mg. ferrous sulfate solution has been considered helpful in demonstrating the value of oral iron administration. This seems an interesting prospect for future use.

Inflammation plays an important role in pathogenesis of heart failure. Hepcidin, secreted by liver in response to IL-6, downregulates the expression of ferroportein thereby decreasing iron absorption from the duodenum. Thus, inflammation, via hepcidin can perpetuate iron deficiency and has to be considered as a target of anemia therapy.

ESA hyporesponsiveness remains a common problem in therapy for anemia. With evidence of harm from high ESA dose, it is worthwhile to investigate the possibility of decreasing ESA usage by recognizing and treating the factors related to ESA resistance.

Aggressive intravenous iron therapy without ESA is emerging as a new concept with encouraging results. Few trials have already analysed this approach and data are encouraging. In FERRIC-HF study, although there was no significant difference in change in haemoglobin level in the treatment group compared with placebo, there was improvement in ferritin level & functional class. Similar results were obtained in Fair-HF trial also. Encouraging results from these studies, with improvement in cytokines, suggest that iron therapy alone may be preferred for treatment of anemia in HF, although large RCTs with attention to safety data will be necessary before such a recommendation is made.

Although recent evidences from multiple RTCs appropriately suggest caution in using ESA for treatment of anemia, it will be interesting to see if lower doses of these agents to lower individualised targets make a difference.

CONCLUSION:

The explosion of academic investigation and exponential increase in the acquisition of knowledge relevant to the pathogenesis and potential treatment options have clearly identified anemia as an important clinical factor to consider in HF and have provided novel insight into the complex pathophysiology of HF, but some important questions are still unanswered, such as the optimal means to evaluate the cause of anemia in clinical settings and identification of patients most likely to derive clinical benefit from treatment. Ongoing studies with ESA and intravenous iron preparations in the population with HF and with novel agents in other anemic populations may provide important data for clinical decision making over the next few years.
INTRODUCTION:

Anemia is defined as a condition resulting from an unusually low number of red blood cells or too little hemoglobin in the red blood cells. There are many causes of anemia which include increased blood loss; nutritional deficiencies, particularly that of folate, iron, and/or Vitamin B₁₂ and increased destruction of RBCs. The common causes of anemia in developing countries include nutritional deficiency, intestinal parasitic infection and malaria. Although the most common type is iron-deficiency anemia in which the red blood cells are reduced in size and number, and hemoglobin levels are low, the impact of inadequate nutrient intake is amplified by intestinal worms and malaria infections which interfere with nutrient uptake and aggravate anaemia further.

PARASITIC CAUSES OF ANEMIA:

Intestinal Parasites:

Intestinal worms occur throughout the developing world, but are most commonly seen in the people of low socioeconomic group. Its consequences on health and development are enormous. Apart from permanent organ damage, poor physical growth, poor intellectual development and impaired cognitive function, it causes anaemia and huge numbers of deaths (Crompton et al., 2002). The intestinal parasites causing anemia include hookworms, tapeworms, trichuris trichura, etc.

a. Hookworm- The most common culprit is the hookworm, an intestinal parasite of humans that usually causes mild diarrhea or cramps. Heavy infestations can create serious health problems, including anemia.

Hookworm infection is caused by the blood-feeding nematode parasites. One of the most common species is Ancylostoma duodenale, found in southern Europe, northern Africa, northern Asia, and parts of South America, and the second species is Necator americanus, which was widespread in the southeastern United States. Infections occur mostly in tropical and subtropical climates and are estimated to infect over a billion people or, about one-sixth of the world’s population and is concentrated mostly among the world’s poorest communities. Together, the hookworms

Eggs of hookworm: 60×40 µm in size, oval in shape, shell is thin and colorless. Content is 2-8 cells.

Adult hookworm: look like an odd piece thread and are about 1 cm. They are white or light pinkish when living. & is slightly larger than &. The male’s posterior end is expanded to form a copulatory bursa.
infect an estimated 576-740 million individuals today of which 80 million are severely infected. The morbidity associated with severe infection includes intestinal blood loss, anemia, and protein malnutrition. While half of the estimated 10 million pregnant women in Africa alone infected with Schistosomiasis suffer from anaemia (King et al., 2004), an estimated 44.3 million of the developing world’s 124.3 million pregnant women harbored hookworm infection alone (WHO, 1994) out of which more than 10% were suffering from worm infections severe enough to adversely affect pregnancy outcomes. The total burden of disease has been estimated to be 450 million episodes annually and is responsible for 18 percent of all childhood deaths in sub-Saharan Africa, equivalent to 800,000 deaths each year.

Amongst the hookworm species, Necator can be transmitted only through penetration of the skin whereas Ancylostoma can be transmitted percutaneously, orally, and maybe transplacentally. Infection occurs generally by direct contact with contaminated soil, while walking barefoot or by accidentally swallowing contaminated food and drinks. The incubation period can vary between a few weeks to many months and is largely dependent on the number of hookworm parasites with which an individual is infected [1]. Hookworms feed on the blood, while tapeworms rob nutrients. Hookworm infection is generally considered to be asymptomatic, but Norman Stoll has described in 1962, that hookworm is an extremely dangerous infection because its damage is “silent and insidious” [2]. There are general symptoms that an individual may experience soon after infection. Ground-itch, an allergic reaction at the site of parasitic penetration and entry, is common in patients infected with N. americanus [3]. Additionally, cough and pneumonitis may result as the larvae begin to break into the alveoli and travel up the trachea. Once the larvae reach the small intestine of the host and begin to mature, the infected individual may suffer from diarrhea and other gastrointestinal discomfort. However, the “silent and insidious” symptoms referred to by Stoll are really only related to chronic, heavy-intensity hookworm infections. Major morbidity associated with hookworm is caused by intestinal blood loss, iron deficiency anemia, and protein malnutrition [4]. They result mainly from adult hookworms in the small intestine ingesting blood, rupturing erythrocytes, and degrading hemoglobin in the host [5]. This long-term blood loss can manifest itself physically through facial and peripheral edema. Eosinophilia and pica caused by iron deficiency anemia are also experienced by some hookworm-infected patients [6].

Diagnosis of hookworm infection relies mainly on the recovery of the eggs from the stools. The egg is unsegmented or in an early segmentation stage when passed, but sometimes when specimens have been allowed to stand at room temperature for a long period of time, a larva may be observed within the egg. It is rare that eggs hatch and that free larvae are found in the stool. If, however, this occur, the free larvae has to be distinguished from the larva of Strongyloides. This can be done based on the length of the buccal cavity, the space between the oral opening and the esophagus: hookworm rhabditiform larvae have long buccal cavities whereas Strongyloides rhabditiform larvae have short buccal cavities [8].

Recent research has focused on the development of DNA-based tools for diagnosis of infection, specific identification of hookworm, and analysis of genetic variability within hookworm populations [9]. Because hookworm eggs are often indistinguishable from other parasitic eggs, PCR assays could serve as a molecular approach for accurate diagnosis of hookworm in the feces [11].

The most common treatment for hookworm are Benzimidazoles (BZAs), specifically albendazole and mebendazole. BZAs kill adult worms by binding to the nematode’s beta-tubulin and subsequently inhibiting microtubule polymerization within the parasite [12]. In certain circumstances, levamisole and pyrantel pamoate may be used [13]. The 2008 study by Keiser and Utzinger, “Efficacy of Current Drugs Against Soil-Transmitted Helminth Infections: Systematic Review and Meta-analysis,” examined the relative efficacies of different drug treatments. They found that the efficacy of single-dose treatments for Hookworm infections were as follows: 72% for albendazole, 15% for mebendazole, and 31% for pyrantel pamoate [14]. This substantiates prior claims that albendazole is much more effective than mebendazole for Hookworm infections. Also noteworthy is that the World Health
Organization recommends anthelmintic treatment in pregnant women after the first trimester [15]. It is also recommended that if the patient also suffers from anemia ferrous sulfate (200mg) be administered three times daily at the same time as anthelmintic treatment; this should be continued until hemoglobin values return to normal which could take up to 3 months [16].

b. **Trichuris trichuria** – It was discovered by Linnaeus in 1771. It is commonly called whipworm because it resembles the handle and lash of whip (trichuris means hair tail, trichocephalus means hairhead). It is often found in association with Ascaris. The adult worms live in the large intestine of man, particularly the caecum and also in appendix. Human infection with T. trichiura is called trichuriasis.

*Trichuris trichiura*: typical *T. trichiura* eggs; egg measures 50-55 by 22-24- µm and has a brown, smooth shell, with bipolar prominences (plugs) and contains a single-cell ovum

Light infection are generally asymptomatic. In moderate infection clinical manifestations are usually abdominal pain, anorexia, diarrhea and constipation. In heavy infection, bloody diarrhea, emaciation and prolapse of the anus may occur. Anaemia and eosinophilia may occur to variable extent.

Diagnosis of trichuriasis in particular of heavy infections, is readily made by examination of saline preparation of stool for characteristic barrel-like bile-stained eggs. Adults may occasionally be present in the stool.

A single dose of albendazole 400 mg or mebendazole 100 mg is effective in mild to moderate infections but heavier infections require 03 days treatment.

c. **Schistosomiasis** - it is a parasitic disease caused by blood flukes (trematodes) of the genus *Schistosoma*.

After malaria and intestinal helminthiasis, schistosomiasis is the third most devastating tropical disease in the world, being a major source of morbidity and mortality for developing countries in Africa, South America, the Caribbean, the Middle East, and Asia.

*Egg of schistosoma spp* - oval and measures 70-170 by 40-70 µm with spine

Trichuriasis is worldwide in distribution, but the prevalence and intensity of infection is higher in tropics and subtropics. Because of similar soil (environmental) requirements for development of their eggs, infections of *A. lumbricoides* and *T. trichuris* often coexist. Trichuris infections are more frequently observed in older children because of longer life span of the adult parasites.

Transmission occurs through ingestion of food contaminated (vegetables etc.) or water by infective ova. After ingestion, the eggs hatch in the small intestine and the larvae penetrate the villi of small intestine and develop there. After about a week, the larvae leave small intestine leaving behind bleeding points and migrate to large intestine where they develop into adult worms.

More than 207 million people, 85% of who live in Africa, are infected with schistosomiasis[20] and an estimated 700 million people are at risk of infection in 76 countries where the disease is considered endemic, as their agricultural work, domestic chores, and recreational activities expose them to infested
Most human schistosomiasis is caused by *S. haematobium*, *S. mansoni*, and *S. japonicum*. Schistosomiasis is due to immunologic reactions to *Schistosoma* eggs trapped in tissues. Antigens released from the egg stimulate a granulomatous reaction involving T cells, macrophages, and eosinophils that results in clinical disease. Symptoms and signs depend on the number and location of eggs trapped in the tissues. Eggs can end up in the skin, brain, muscle, adrenal glands, and eyes. As the eggs penetrate the urinary system, they can find their way to the female genital region and form granulomas in the uterus, fallopian tube, and ovaries. Today, 120 million people are symptomatic with schistosomiasis, with 20 million having severe clinical disease.

Proposed mechanisms of schistosomiasis-mediated anemia include (a) Loss of iron from the body as blood is passed in either the stools (*Schistosoma japonicum* and *Schistosoma mansoni*) or in the urine (*Schistosoma haematobium*). This is thought to occur when eggs pass through the intestinal wall into the lumen of the gut (*S. mansoni* and *S. japonicum*) and when eggs inflame and irritate the bladder and urethra (*S. haematobium*). Blood loss might be exacerbated by intestinal polyps in the case of *S. japonicum* and *S. mansoni*, which might be sufficient to decrease the hemoglobin concentration if iron stores are already depleted because of either hookworm infection or insufficient dietary intake to meet ongoing losses. (b) Individuals with splenomegaly are anemic because sequestration of RBCs in the spleen reduces the effective circulating mass of RBCs and/or increases the rate of hemolysis in a hypertrophic spleen. (c) Autoimmune hemolysis is a process of immunemediated RBC destruction. RBCs are identified for premature destruction before the end of their usual lifespan (120 days) because interaction of antibodies with the RBC membrane ‘marks’ them for early destruction. In this case, RBCs are identified and destroyed primarily by phagocytes in the spleen and liver. (d) Anemia of inflammation and chronic disease. Anemia of inflammation (also known as anemia of either infection or chronic disease) involves pro-inflammatory cytokine mediators that are produced in response to infections, cancer and autoimmune diseases such as arthritis. Tumor necrosis factor α (TNF-α) disrupts RBC production and longevity by decreasing the production of erythropoietin and impairing the erythropoietic response of the bone marrow. IL-6 causes upregulation of hepcidin, which decreases iron absorption in the gut and alters iron metabolism by causing sequestration of iron into storage forms such as ferritin in the reticuloendothelial system, which decreases bioavailability. In addition, pro-inflammatory cytokines cause anorexia (decreased appetite), which might reduce the overall intake of iron and other important micronutrients.

The drug of choice for treating all species of schistosomes is praziquantel. Cure rates of 65-90% have been described after a single treatment with praziquantel. In individuals not cured, the drug causes egg excretion to be reduced by 90%.

**Malaria:**

Yet another culprit, malaria is a global health problem causing disease on a vast scale. Four species of the malarial parasite infect man. The severity of hematologic disease is related to the ability of the parasites to invade and grow in different red cell populations as well as the intrinsic growth rate of the parasite.

1. *Plasmodium spp*

P. vivax and P. ovale have a strong preference to infect only young red cells (reticulocytes), thereby limiting parasitemia levels to approximately 1 to 2 percent. Anemia due to hemolysis does occur and may be severe, but there is no peripheral sequestration of parasitized red cells. P. malariae invades red cells of
all ages, but parasite multiplication during each cycle is relatively low. Infection results in limited parasitemia (<1 to 2 percent) and mild symptoms. *P. falciparum* can invade red cells of all ages, including cells as early as orthochromatic erythroblasts, multiplies 10-fold within each 24 hour cycle, and expresses clonally variant antigens on the surface of infected red cells, which are receptors for ligands on the surface of endothelial cells, red cells, and platelets. These variant antigens enable late blood-stage infected red cells to sequester in post-capillary venules. Parasitemia is often high, occasionally exceeding 50 percent, and the potential for severe anemia, systemic disease, and death is considerable. *P. knowlesi* was originally described as a malarial infection of macaque monkeys. Morphologically it resembles *P. malariae* and it appears that it causes significant and sometimes severe human infection, previously misdiagnosed as *P. malariae*, in Borneo, Malaysia, and in other areas of Southeast Asia. It has even been reported in travelers returning from those locations.

The majority of malarial infections are associated with some degree of anemia, the severity of which depends upon patient-specific characteristics (eg, age, innate and acquired resistance, comorbid features) as well as parasite-specific characteristics (eg, species, adhesive, and drug-resistance phenotype). Malarial anemia is capable of causing severe morbidity and mortality especially in children and pregnant women infected with *Plasmodium falciparum*.

In areas of Africa with stable malaria transmission, malaria infection during pregnancy is estimated to cause 400,000 cases of severe maternal anaemia and from 75,000 - 200,000 infant deaths each year (Steketee, 2001).

**COMPLICATIONS OF ANEMIA**

Most cases of anemia are mild, including those that occur as a result of chronic disease. Nevertheless, even mild anemia can reduce oxygen transport in the blood, causing fatigue and a diminished physical capacity. Moderate-to-severe iron-deficiency anemia is known to reduce endurance. Some studies indicate that even iron deficiency without anemia can produce a subtle but still lower capacity for exercise. Because a reduction in red blood cells decreases the ability to absorb oxygen from the lungs, serious problems can occur in prolonged and severe anemia that is not treated. Anemia can lead to secondary organ dysfunction or damage, including heart arrhythmia and heart failure.

Pregnant women with significant anemia may have an increased risk for poor pregnancy outcomes, particularly if they are anemic in the first trimester. Anemia causes intrauterine growth retardation, prematurity and low birth weight. In anaemic women, the risk of dying during pregnancy or child birth is up to 3.5 times higher than in non-anaemic women (Brabin et al., 2001).

In children, severe anemia can impair growth and motor and mental development. Children may exhibit a shortened attention span and decreased alertness. Children with severe iron-deficiency anemia may also have an increased risk for stroke.

Anemia is common in older people and can have significantly more severe complications than anemia in younger adults. Effects of anemia in the elderly include decreased strength and increased risk for falls. Anemia may have adverse effects on the heart and increase the severity of cardiac conditions, including reducing survival rates from heart failure and heart attacks. Even mild anemia may possibly lead to cognitive impairment or worsen existing dementia.

**CONCLUSION**

Since parasitic infection are a major cause of anemia which is responsible for patients morbidity and mortality, timely treatment with antiparasite medication along with nutritional therapy must be done.

**REFERENCES**


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Members of IMA, Odisha who have not received their copy of “OMJ 2011” are requested to collect it from State HQ Office, Cuttack
Anaemia in the Elderly

Srikrushna Mahapatra

The geriatric population as per UN agreement is defined as population aged 60 years and above.(1) The phenomenon of population aging (an increase in the median age of population) is already a major social and health challenge in the developed and developing countries. Govt. of India adopted ‘National Policy on Older Population ‘ in January 1999. The policy defines ‘senior citizen’ or ‘elderly’ as a person who is of age 60 yrs. or above. Between 2000 and 2030 the number of older adults worldwide is expected to rise from 420 to 974 millions, 59% of that would be living in developing countries of Africa, Asia, Latin America, the caribbeans and oceania. (2) In India, the elderly population accounted for 7.4% of total population as per 2001 census. It is projected to rise to 12.4% of the population by the year 2026. Further, the life expectancy at birth during 2002-06 was 64.2 for females as against 62.6 years for males. At the age of 60 average remaining length of life was found to be about 18 years (16.7 for males and 18.9 for females), and that at 70 years was less than 12 years (10.9 for males and 12.4 for females). (3) Numerically the magnitude of elderly population has risen from 12.1 million in 1901 to approximately 77 million in the census 2001. According to official projections the number of elderly persons will rise to approximately 140 million by 2021. (3)

The elderly people suffer from a variety of problems which have been now drawing the attention of the public and the government. Economic hardship (due to reduction of income on retirement/incapacity to work) affects standards of living, the problem could be accentuated by bereavement of spouse. Human aging is characterized by progressive decline in homeostatic reserve of every organ system. The decline of each organ system appears to occur independently of the changes in other organ system and is influenced by diet, environment, personal habits and genetic factors. (2) The common aging problems are senile cataract, nerve deafness, musculoskeletal changes affecting locomotion, poor reflexes making elderly more accident prone, enlargement of prostate in males, dementia etc.; unfortunately anemia is the problem which is less identified though it has far reaching consequences.

The WHO definition of anemia is a hemoglobin concentration less than 13 gms/dl in men and less than 12 gms/dl in women, as established in 1968. In general hemoglobin levels are lower in older people than younger people. The reason for this is not completely understood. (4) It is unclear whether hemoglobin falls in older people because this is a feature of normal aging or whether this is always pathological, even if the underlying condition cannot be identified. Older people who suffer from chronic ailments might be expected to be anemic just as younger people are. However it is not always appreciated that older persons who suffer from other medical problem (e.g., cognitive ailments) have a worse prognosis if they are also anemic. (4)

In a recent public health report published by the World Bank, anemia was ignored(!) in most developing countries even though it is one of the most prevalent public health problems and has serious consequences for national development. (5) Anemia of any degree is recognized as a significant independent contributor to morbidity, mortality and frailty in older patients. Although anemia has often been considered a normal consequence of aging, the pathophysiology of such age related decline in erythropoesis is obscure. As aging population is likely to rise to an unprecedented number in 21st century, anemia in elderly has become a major target of research interest. (6) Iron deficiency causes at least 50% of all anemias and almost a million deaths a year; three quarters of which occur in Africa and South–East Asia.

WHO estimates that two billion people worldwide are anemic. A severe public health problem exists when anemia prevalence is more than 40% in any age group (5). In India anemia affects an estimated 50%...
of all population, overall 52% of women have some form of anemia, rural population having more than that of urban population.(7).

It has been reported that even mild degrees of anemia in men and women 65 years and older have been associated with significant morbidity including frailty, decreased bone density, decreased skeletal muscle strength and density, decreased physical performance and increased mortality.(8)

Frailty is a poorly defined syndrome in the elderly population and includes weight loss, impaired mobility, generalized weakness and poor balance. Some studies have shown elevated proinflammatory markers associated with development of frailty. Furthermore, anemia is associated with an increased in nearly all markers of frailty in elderly population. (9)

Age-related changes in erythropoiesis are

1. Alternations intrinsic to erythroid progenitor or hematopoetic stem cells and/or the local hematopoetic environment.
2. Alternations in humoral control mechanisms particularly related to the secretion of Erythropoietin and possible deterioration of hypoxia sensing mechanisms (8).

The impact of aging on erythropoiesis (8):

1. Decreased marrow cellularity in the elderly with a concomitant rise in adipose tissue in bone marrow.
2. Decreased red cell uptake with oral but not intravenous iron in elderly.
3. Decreased BFU-E (Bone Forming Unit-Erythroid) and CFU-E (Colony Forming Unit-Erythroid) frequencies.
5. Downregulation of genes involved in chromatin regulation and DNA repair.
6. Decreased circulating CD34+ cells in the elderly.
7. Increased serum stem cell factor levels in the elderly.

In adults, erythropoietin is produced primarily in the kidneys and acts on the erythroid progenitors to prevent cell death. Basal erythropoietin levels are approximately 10-20 mU/ml. (10)

Deviated oxygen tension in blood is the strongest stimulator of erythropoietin production. It has been observed that erythropoietin levels are decreased in unexplained anemia of the elderly and elderly with malnutrition. Elderly with hypertension and diabetes mellitus also present with decreased erythropoietin levels. (11)

Unexplained anemia is defined as 1) absence of renal disease, 2) absence of iron deficiency, 3) absence of folate and vitamin B12 deficiency, 4) absence of anemia of chronic inflammation (ACI). (8)

Hypoxia Induced Factors (HIF) are transcription factors which control (stimulate) erythropoietin gene expression. There are three main isoforms of HIF α (HIF-1α, HIF 2α, HIF 3α). Under normoxic conditions HIF α is hydroxylated and ineffective, while in hypoxic conditions it is not hydroxylated, rapidly enters nucleus and binds to HIF 1α. This heterodimeric complex binds to hypoxia-responsive element (HRE) at the 3′ enhancer region of erythropoietin gene for de novo transcription of the gene. (12)

There are in vitro and animal model data suggestive of altered HIF response to hypoxia in aging. However, it is not known whether there are age-related changes in response to hypoxia that affect erythropoiesis in man.

The changes in endocrine function with aging are diverse and include decreased testosterone and growth hormone levels. The exact mechanism of how androgens induce erythropoiesis is not known. The effect of growth hormone on erythropoiesis appears to be mediated through insulin like growth factor -1, and include inhibition of apoptosis and potentiation of effects of erythropoietin and other cytokines. Growth hormone may increase erythropoietin levels by increased synthesis of erythropoietin in liver. (8)

Anemia of chronic inflammation (ACI), also known as anemia of chronic disease (ACD) or simply anemia of inflammation (AI), is characterized by a normocytic, normochromic anemia with slightly shortened red cell survival, reduced erythropoietin levels and a blunted response to erythropoietin. On a biochemical basis it is classically characterized by low serum iron, low iron binding capacity in the setting of an elevated serum ferritin. (6)

Aging and the development of age-related comorbidities has been associated with raised proinflammatory cytokines such as TNFα, IL-6,
IL-1, Macrophage inhibitory factor (MIF) and acute phase proteins.(13) It has also been reported that elderly subjects are consistently found to have increased levels of IL-6. Both IL-6 and IL-1 lead to an increased hepatic synthesis of Hepcidin.(14)

Hepcidin was initially isolated from plasma ultrafiltrate by Krause et al. and named Liver Expressed Antimicrobial Peptide (LEAP-1) as it exhibited antimicrobial properties.(15) Later it was isolated from human urine and named Hepcidin by Park et al after its hepatic origin and bactericidal effect in vivo.(16)

The human hepcidin gene is located in chromosome 19 and encodes for a precursor protein of 84 amino acid (a.a). This pre-prohepcidin undergoes enzymatic cleavage to a 64 a.a products prohepcidin before it enters endoplasmic reticulum from cytoplasm. Then a 39 a.a sequence is removed by a furin like protein to produce the 25 a.a mature hepcidin.(16) There are two other hepcidins which contain 20 and 22 a.a, but believed to be degraded product of hepcidin. The five N-terminal amino acid sequence are absolutely required for the bioactivity of hepcidin.(17) Hepcidin binds to the transmembrane iron exporter protein Ferroportin which is present on macrophages, basolateral side of enterocytes and hepatocytes. Hepcidin induces internalization and degradation of ferroportin. By diminishing the effective number of iron exporters on the membrane of enterocytes or macrophages, it suppresses iron absorption and release respectively. At present four putative upstream regulatory pathways are thought to control hepcidin production.(18).

1. iron store related regulation
2. erythropoetic activity driven regulation
3. inflammation related regulation
4. a mandatory signaling pathway.

HIFs as described before induce erythropoietin production. Iron store regulation involves the circulating amount of transferrin bound to iron that competes with HFE (Hemochromatosis Iron Protein) in binding to TIR 1 (transferring receptor) hereby promoting TIR 1/HFE complex as an inducer of hepcidin production. The direct effect of intracellular iron from the labile pool of iron on hepcidin production is not clear yet. The inflammation regulated pathway is mainly induced by IL-6 and is thought to act more dominantly regardless of the activity of other pathways.

Hemojuvelin (HMJ) has an inhibitory effect on SMAD (mother against decapentaplegic homologue – Drosophila)/BMP (Bone morphogenic Protein); both of which act as transcription factors to bind to HAMP (Hepcidin Antimicrobial peptide gene) promoter site and induce transcription of hepcidin gene. The HMJ controlled SMAD/BMP signaling pathway appears to be mandatory for the activity of the store and erythropoietic derived regulation.(18).

Leptin has recently been shown to induce hepcidin via JAK 2/STAT 3 signaling – thus potentially linking obesity to inflammation and iron homeostasis. Low leptin levels have been associated with impaired erythropoietic responsiveness on erythroid precursors and syndrome of frailty in elders.(19)

The third National Health and Nutrition Examination Survey (NHANES III) study showed that the incidence of anemia in men and women older than 65 years was 11% and 12% respectively. Of the anemic patients one third were found to have nutritional deficiency, one third were found to have anemia of inflammation and one third were diagnosed to have unexplained anemia. Interestingly in this study Vitamin D deficiency was associated with anemia independent of sex, age, ethnicity with odds for anemia being increased to 60% in the presence of vitamin D deficiency. Vitamin D deficiency was most prevalent with anemia of inflammation.(20) But the potential efficacy of vitamin D supplementation in AI is yet to be studied.

The pathophysiology of unexplained anemia is poorly understood and it remains primarily a diagnosis of exclusion, some insisting on some form of myelodysplasia(8). It has been postulated that over expression of proinflammatory cytokines is an important determinant of unexplained anemia in the elderly as they induce anemia by suppression of erythroid colony formation (MIF/TNF/IL-1) on the one hand and impairment of iron utilization (IL-6/Hepcidin) on the other.(6)

Measurement of hepcidin along with study of iron status is an important management tool for the elderly because it can establish whether an elderly
has pure iron deficiency anemia or has excess hepcidin which diminishes iron absorption and utilization. However hepcidin measurement could be inaccurate in ELISA or routine antigen-antibody assay techniques as the 20 and 22 a.a isoforms of hepcidin could interfere. The present method of hepcidin isoform measurement is done by SELDITOF-MS (surface enhanced laser desorption / ionosation time of flight mass spectrometry). (21)

CONCLUSION:
Numerically the aging population is greatly on the rise in both developing and developed countries. Anemia is a significant health problem in the elderly but relatively neglected. Iron is a one way substance and could be toxic, its therapeutic use should only be restricted for cases of iron deficiency anemia. Hepcidin and IL-6 estimation hold promise in evaluation of anemia in the elderly. Impact of inflammatory mediators, erythropoietin insensitivity and role of vitamin D in aetiology of anemia are fields under research. Better understanding of the pathophysiology of anemia in elderly will provide clues for better interventions and reduce morbidity, frailty and mortality.

References:
1. http://www.who.int/healthinform/survey/aging defn
3. Situation analysis of the elderly in India’-Central statistics Office, Ministry of Statistic and Programme Implementation, Govt. of India July 2011.
Study of Autoimmune Hemolytic Anemia In Children
Jyotiranjan Champatiray¹, Niranjan Mohanty²

Abstract:
Seven children’s with autoimmune hemolytic Anemia are described. Six had acute and one had insidious onset with positive direct coomb test. Pallor was the main presenting complaint followed by hepatomegaly, fever, splenomegaly, jaundice and haemoglobinuria. Out of 7 cases 5 belonged to primary group and 2 to secondary group. Secondary causes were SLE and Lymphoma. Oral Prednisolone produce remission in all cases but 2 had relapses after initial response. 2 out of 5 primary cases needed steroid in a tapering dose for 16-24 wks, 3 cases responded to a short course of 3-4 wks of steroid with no relapse till yet. Average Blood Transfusion given before diagnosis of AIHA was three. Average time duration to diagnosis of AIHA was two days in our setup.

KEY WORDS:
Autoimmune hemolytic Anemia, Steroid, Blood transfusion.

Introduction:
Autoimmune hemolytic anemia is a condition where antibody directed against autologous red cells most frequently demonstrated by a positive direct combs test¹. As it’s annual incidence is 1:80,000² it is very rarely thought in any case of anemia but it has excellent prognosis if promptly diagnosed and treated. Thus we undertook this study to study the clinicohematological profile and treatment outcome of AIHA in children with brief review of the literatures.³,⁴,⁵,⁶,⁷

Materials & Method:
This is a prospective study involving all patients < 14yrs with positive direct Coomb’s test diagnosed as AIHA during May 2006-09(n-3). Age Sex, clinical presentations of all cases were studied. In all these cases complete blood count, peripheral smear comment, Recticulocyte count, G-6 PD Activity, Liver function test, Renal function test, some special test like sepsis screening, DCT was done. Bone marrow study, x ray chest, ANA, CAT scan Abdomen and thorax, Lymph node biopsy were undertaken to identity the secondary causes. The patients were treated with blood transfusion, steroid IV/ Oral as per the clinical conditions. Number of blood transfusions taken in our unit and by referred hospitals before diagnosis, Average time to diagnosis of AIHA and number of blood transfusion after diagnosis was documented. The patients were put on regular follow up every 4 wks. The dose and duration of therapy was recorded.

Result:
The patients included 4 male and 3 female whose age at the onset of the disease ranged from 5 to 13 yrs. 6 had acute onset and 1 had insidious onset (table No.1). All patient had pallor as presenting complaint followed by hepatomegaly, fever, splenomegaly, Jaundice, hemoglobinuria, lymphadenopathy (fig-1). Out of 7 cases 5 had primary and 2 had secondary causes (Table -2). 4 cases had Hb <5 gm at the time of admission and three had more than five, but less than 10gm/dl. Leucocytosis were seen in 2 cases.

Table -1 Age, Sex and mode of onset of cases

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>10.5 ± 2.76 yr.</td>
</tr>
<tr>
<td>Range</td>
<td>5 - 13 Yr</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
</tr>
<tr>
<td>Mode of onset</td>
<td></td>
</tr>
<tr>
<td>Abrupt</td>
<td>6</td>
</tr>
<tr>
<td>Insidious</td>
<td>1</td>
</tr>
</tbody>
</table>

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Megaloblastic marrow and infective marrow was seen in one case each. Platelet count was normal in all cases (Table-3). Average number of blood transfusion given before diagnosis of AIHA was 3. Average time duration to diagnosis of AIHA was 2 days in our setup. In two cases six Blood Transfusions were given before diagnosis and average one transfusion was needed after treatment with steroid. All patients received packed red cells. Two patients given iv methylprednisolone at a dose of 30mg/kg. five patients received oral steroid at dosed 1-2mg/kg (Table-4). 3 cases responded to short course of steroid (3 - 4 weeks) with no relapse till yet. 2 cases needed steroid in a tapering doses for 16-24 weeks, one out of these 2 cases had relapses, now following a chronic course and was planned for alternate therapy (Table-5). Common adverse effects of long term therapy was cushingoid facies, truncal obesity, striae.

Discussion:

Autoimmune hemolytic Anemia is an uncommon condition in pediatric practice. 71% cases belonged to primary group. Dacie, Dausect etal reported an occurrence of approximately 70% of idiopathic variety. Male female occurrence was 1.3 :1. Buchanan etal in 1976 reported male female ratio of 1.2 to 1.9:1. All the patients had moderate to severe anemia of acute onset, some of theme also had fever, hepatomegaly, Jaundice, Splenomegaly. This spectrum of clinical feature is well recognized in pediatric patient.

Male female occurrence was 1.3 :1. Buchanan etal in 1976 reported male female ratio of 1.2 to 1.9:1. All the patients had moderate to severe anemia of acute onset, some of theme also had fever, hepatomegaly, Jaundice, Splenomegaly. This spectrum of clinical feature is well recognized in pediatric patient.

Table-3 : Haematological findings at the time of diagnosis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>HB (gm/dl)</th>
<th>Rectic count</th>
<th>WBC/mm³</th>
<th>Platelet count*</th>
<th>Peripheral smear comment</th>
<th>Bone marrow study</th>
<th>Coomb’s test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>4.6</td>
<td>7</td>
<td>12,400</td>
<td>Normal</td>
<td>Microcytic erythroid hyperplasia</td>
<td>+Ve</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>5</td>
<td>9</td>
<td>20,500</td>
<td>Normal</td>
<td>Dimorphic anemia</td>
<td>+Ve</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>2</td>
<td>5</td>
<td>22,800</td>
<td>Normal</td>
<td>Neutrophilic Leucocytosis</td>
<td>Infective</td>
<td>+Ve</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>2</td>
<td>8</td>
<td>9,800</td>
<td>Normal</td>
<td>Dimorphic</td>
<td>Megaloblastic</td>
<td>+Ve</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>6,800</td>
<td>Normal</td>
<td>Spherocytosis</td>
<td>Not done</td>
<td>+Ve</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>7,800</td>
<td>Normal</td>
<td>Spherocytosis</td>
<td>Not done</td>
<td>+Ve</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>11,200</td>
<td>Normal</td>
<td>Spherocytosis</td>
<td>Not done</td>
<td>+Ve</td>
</tr>
</tbody>
</table>

* More than 1,00,000/mm³

Table -4. Treatment Profile of the cases

<table>
<thead>
<tr>
<th>No</th>
<th>No of BT given before diagnosis of AIHA</th>
<th>Time to diagnosis of AIHA in our Hospital in days.</th>
<th>Treatment given</th>
<th>No of BT given after Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>2</td>
<td>BT+IV methylprednisolone</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>2</td>
<td>BT+Oral steroid</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1</td>
<td>BT+Antibiotic+IV methylprednisolone</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2</td>
<td>BT+ oral Steroid</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Nil</td>
<td>2</td>
<td>BT+Oral steroid</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Nil</td>
<td>2</td>
<td>BT + Oral Steroid</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>1</td>
<td>BT Oral steroid</td>
<td>1</td>
</tr>
</tbody>
</table>

Table -5- Duration of therapy in Primary AIHA

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Duration</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3-4 wks</td>
<td>3-4 wks</td>
</tr>
<tr>
<td>2</td>
<td>16-24 wks</td>
<td>16-24 wks</td>
</tr>
</tbody>
</table>
within normal limit in autoimmune hemolytic anemia but in acute hemolysis, leukocytosis can be noted, and the usual level is above 30,000/mm³ (Habibi et al 1947). In our series 3 pts had leukocyte count above 20,000/mm³ suggestive of leukocytosis. Bone marrow examination usually reveal erythroid hyperplasia and rarely megaloblastic changes. In our study one case had megaloblastic changes and one had feature of marrow infection which was later diagnosed as lymphoma by lymphnode excisional biopsy. Two cases showed erythroid hyperplasia and bone marrow was not done in two cases. Recticulocytosis was marked in almost all cases and average count was five.

Three out of seven (42.8%) patients presented with severe anemia and heart failure. This is in agreement with the pattern of AIHA because of acute nature of disease in most cases. The same presentation was reported in different studies.5

There is no literature available about the number of transfusion given before a diagnosis AIHA made and exact time taken to a diagnosis of AIHA. In our series average three transfusions given prior to establishment of AIHA with average time duration to diagnosis was two days in our hospital. In two cases six blood transfusions had been given before DAT (Direct Antiglobulin Test) showed positive result. This can be well explained by the facts that poor index of suspicion by treating (general practitioners) physicians because of low incidence, lack of proper lab facility, symptomatic management and delayed reaching to tertiary care centre. Possibility of alloimmunisations due to frequent transfusions also can not be ruled out.

Initially all patients responded to steroid which was similar to response in other series.6 Two patients were given IV methylprednisolone because of the serious general condition. The others were put on oral steroid. Three patients had relapse one had subsequently diagnosed as lymphoma. One case responded to short course of steroid but another case had relapse even after one year in tapering dose of steroid and entered into chronic course so planned for IVIG therapy. IVIG though one modality of treatment, the use was deferred in our series due to non affordability, more often acute nature of disease in our series. One patient who was in chronic course had been put on IVIG and was marked no relapse till yet. 60% primary cases responded to short course steroid (3-4 weeks). Steroid toxicity though marked in 2 cases it subsided after stopping it and changing over to IVIG therapy.

**Conclusion:**

Autoimmune Hemolytic Anemia though uncommon, high index of suspicion of it and workup in any case of acute, sub-acute anemia and early treatment improves the outcome. Blood transfusion without expected rise of hemoglobin and difficulty in grouping due to lysis are early clues to the diagnosis, prompt treatment and need of lesser BT. This study further suggests study of antibodies to different alloantigen in high transfusion cases.

**Bibliography:**

Anatomical Study and Clinical Applications of Neurocutaneous Flaps for Lower Leg Defects

A.P. Patnaik¹, S.P. Mishra²

Introduction

Coverage of the soft tissue defects of the limbs, especially the lower one third of leg and foot has been a difficult problem to tackle. The steps of reconstructive ladder range from simple closure to microvascular flaps. Neurocutaneous flap is a recent concept in reconstructive surgery that utilizes the superficial cutaneous nerve and its vasculature for nourishment of flap.

Many questions still remain unanswered in Neurocutaneous flaps e.g.
1. What is the anatomical basis of these flaps?
2. What are the safe limits of the flap?
3. What structures are really essential for the survival of the flaps (Nerve and the peri/paraneural vasculature, the vein, deep fascia, perforators from the major arteries etc.)
4. Where should be the pivot point?

Material and Methods:

ANATOMICAL STUDY

The anatomical study was conducted in the Department of Anatomy, S.C.B. Medical college Cuttack. Ten cadavers were studied. Dye study done in one fresh cadaver. The main aim was to dissect the superficial cutaneous nerves of the leg and study the course of the nerves and its peri and paraneural vasculature in relation to veins and neurocutaneous perforators. A study of the relationship of cutaneous nerves to the blood supply of the overlying skin was done by doing a dye study. The dye study was done by injecting 40-50ml of Methylene blue (50ml in the Lower limb) in the major supplying artery of the area i.e. popliteal artery for leg. Finer dissection was done under 4x magnifying loupe and photographic documentation was made using+1close up lens.

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Sural nerve between two heads of gastrocnemius with perforators to skin and muscle

ligated so that all the dye injected remains in the vessels of the leg only. 50 cc of Methylene blue was injected in the cannula in the popliteal artery with due care to avoid spillage. The dye injected made the major vessels as well as the perforators more conspicuous. A line was marked in the midline of the calf to a point 2 centimeter behind lateral malleolus. This is the line of the medial sural cutaneous nerve. A sural neurocutaneous flap measuring 10x8 cm was marked on the posterior calf in the middle third of the leg. The pedicle of the flap of 3 cms width was marked in tapering fashion till the lateral malleolus. The cadaver was than made supine and leg kept in mild medial rotation. A vertical line was drawn from the head of fibula to the lateral malleolus and another line on the tibial crest. A longitudinal skin incision was made in between these two lines and skin was dissected off the fascia. The course of the superficial peroneal nerve, its relation to the superficial veins, site at which it becomes suprafascial and presence of perforators were noted. In its lower part special attention was paid to the communication of the vascular network of the nerve to the lateral malleolar network were studied.

The leg was now laterally rotated and a longitudinal incision was made 2 cm posterior to the medial border of the tibia. Skin was dissected from the fascia. The course of the saphenous nerve, its relation to the superficial veins particularly the Great saphenous vein, site at which it becomes suprafascial and presence of perforators were noted.

CLINICAL APPLICATION

The knowledge gained from anatomical study was used in repair of soft tissue defects of the limbs. Patients with defects of the lower leg and heel were assessed for reconstruction of their defects by neurocutaneous flaps. Special emphasis were given on the cause and duration of the lesion, the nature of the defect. Previous history of hypertension, diabetes mellitus, history of peripheral vascular disease, smoking etc. were noted.
On local examination site, size and shape of defect, condition of surrounding area including presence of exposed bone, infections etc were noted. Vascular status of the limb, aesthetic importance of the area and reconstructive demands of the defect were noted. Other than routine investigations the patients underwent X-ray of the area if bony involvement is suspected. Elderly patients and patients with history of trauma underwent a doppler study of the peripheral vessels to look for the presence of artery and its perforators. A wound swab for CIS was carried out in relevant cases, followed by Doppler study.

Retrograde sural neurocutaneous flap:

One the day prior to the surgery, flaps were planned using planning in reverse technique and the upper limit of the flap were based 10cm below joint line.

Operative Technique: The patients were operated under spinal anaesthesia or sciatic block. The flap was approached in prone position. A tourniquet may be used but is not necessary. The dissection starts in the most proximal part of the flap. The incision was deepened till the sub-fascial plane. Lesser saphenous vein and sural nerve are ligated and divided. The deep fascia was anchored to the skin to avoid shearing of the flap. The bleeding in the divided sural neuro vascular bundle gave some idea of the blood supply to the flap. The flap was dissected off the gastrocnemius, ligating the neuromuscular and musculocutaneous perforators encountered. The flap was elevated till the pivot point, which is at least 5 cm above the tip of lateral malleolus. The flap was now insetted into the defect.

The flap can be raised as islanded or as peninsular flap. In its peninsular form designing the flap in a teardrop fashion or tapering in the lower part facilitates better arc of rotation. After marking the skin island, a decision was made regarding the width of the flap base, designed obliquely towards the lateral malleolus, to include maximum number of perforators in the pedicle. Division of the pedicle was done after three weeks.
In case of an island flap, from the proximal most part of the retrograde flap to the pivot point, the skin was elevated. A 3cm wide pedicle consisting of the sural nerve, lesser saphenous vein, fat and fascia was raised till the pivot point. The flap was now rotated into the flap with the pedicle traversing through a skin tunnel or an incision. The pivot should remain at least 4-5 centimeters above the tip of lateral malleolus to include the most constant peroneal perforator in the inter-crusal septum. The donor site if large was skin grafted or closed directly if small. A drain was kept under the flap if there was chance of accumulation of blood. The leg was immobilized in Plaster of Paris cast for two weeks.

The details of postoperative complication and management were recorded. The following points regarding postoperative management (in days) were noted- Primary dressing, Drain removal, Stitch removal, Mobilisation/ Ambulation,& Weight bearing allowed.

After discharge from the hospital the patients were called for follow up to check the stability of the flap. In the follow up aesthetic appearance of the flap, Colour match, Donor site morbidity, Secondary procedure required if any and over all patient satisfaction were recorded.

Results:

Anatomical study:

Sural Nerve:

It begins as a branch from the tibial nerve behind the knee joint. It receives a sural communicating nerve from the peroneal nerve.

A well-defined mesentery of the sural nerve, which connects the sural nerve and the deep fascia in the sub fascial course of the nerve, was found in all the cadavers.

At the mid point of the leg, the nerve becomes supra fascial and is joined by the short saphenous vein. How ever in two cases nerve became supra fascial 6 cm below joint line.

Superficial peroneal nerve

It arises at the neck of fibula deep to the fibers of peroneus longus. It descends between the peroneal muscles and pierces the deep fascia at the junction between the upper two third and the lower one third on the lateral side of the leg. It is divided into medial and lateral branches.

Saphenous Nerve

Saphenous nerve arises from the femoral nerve. It pierces the medial side or knee between sartorius and the gracilis. It runs downwards in front of gracilis.

In the leg it divides into two branches, a larger anterior and a smaller posterior. It supplies the skin over the medial side of leg and medial side of foot up to the ball of big toe.

The anterior branch is in close association with great saphenous vein

Clinical application:

25 retrograde sural neurocutaneous flap were used for reconstruction of lower leg and foot. The constituents of the flap were skin, subcutaneous tissue, deep fascia, the sural neurovascular axis and lesser saphenous vein. 22 of the flaps were islanded on venoneurodepofascial pedicle while three were peninsular.

The width of the pedicle ranged from 3-4cms. The pivot point was 4-6 cm from the lateral malleolus. Flap size ranged from 6x5cm to 11 x9 cm. The proximal limit of the flap ranged from 21 cm to 16 cm from the lateral malleolus.

Operating time ranged from 45 minutes to 90 minutes. Islanding the flap takes almost twice the time of a peninsular flap. None of the flaps were made sensate by neurotisation. Follow up ranged from 18 months to 2 years. Patients tolerated not weight bearing walking 4 weeks after surgery and weight bearing after 8 weeks.

None of the 25 patients had any major complication. Mild flap oedema was noted in all he patients. Only one patient had superficial skin loss at the distal end of the flap which has to be grafted again.

DISCUSSION:

In all the cutaneous nerves studied i.e. sural nerve, superficial peroneal nerve, peri and paraneural vessels accompanied the nerves.

Sural Nerve and Sural neurocutaneous flap:

In this study Sural nerve originated from the tibial nerve at the back of the knee and is joined by
the sural communicating branch from the common peroneal nerve. It lies deep in between the two heads of gastrocnemius muscle.

It is accompanied and supplied by the median superficial sural artery, which is a branch of popliteal artery. It was noted by us that around mid calf the sural nerve becomes supra fascial. This finding is similar to that of the findings of Haertsch (1981) and many other authors who have published articles on this flap (Masquelet et al 1992 and Hasegawa et al 1994). The nerve gives neurocutaneous perforators at regular interval and thus the flap is really safe because of the close proximity of the nerve (with its vessels) and the skin.

While the nerve is in its subfascial course it gives neurocutaneous as well as neuromuscular branches. 2-4 neuromuscular perforators going to the medial head of gastrocnemius were observed. The perforators were quite significant in size. The presence of these perforators will enable harvesting of a myoneurocutaneous flap by including the gastrocnemius muscle in a sural neurocutaneous flap.

In its subfascial course, it was found that the sural nerve had a mesentery like connection going from the nerve to the undersurface of the deep fascia. The neurocutaneous perforators were seen branching out into a plexus on the deep fascia. This finding suggest that, if the flap has to extend above the supra fascial course of the nerve, the nerve must be dug out along with the mesentery or should be harvested along with a cuff of muscle so that the neurocutaneous perforators remain intact. Based on this finding Ayyapan and Chaddha (2002) presented their work where large flaps were raised. The distal limit of the retrograde flap was extending up to 2 cm distal to the popliteal crease. They have called this flap a Supersural flap.

The neurovascular axis was found communicating with the peroneal perforators in the lateral inter muscular septum. The perforators lie in a line approximately 2 cm behind the line joining the head of the fibula to the lateral malleolus. The peroneal perforators were more frequent in the lower part of the leg. The most constant perforator was at around 5 cm from the tip of lateral malleolus. This finding is similar to that of the authors who have carried out anatomical study Haertsch (1981), Masquelet et al (1992), Hasegawa et al (1994), Oberlin, Azoulay & Bhatia (1995), Hollier et al (2002) and Almeida (2002). Hollier et al (2002) and Bhattacharya and Watts (2003) noted that the proximal most perforator is 13 cm from the tip of lateral malleolus. This is true because the lateral inter muscular septum becomes well defined only in the lower third of the leg. In the present study, it was noted that the lower most perforator was seen even at 2 cm above the tip of the lateral malleolus.

24/25 flaps’ did well and in one there was little skin loss at the flap tip which needed skin grafting. The success of this series may be contributory to the fact that, it remained within the zones of safe limit as described by Masquelet at al (1992) and included all the components described above. Venous oedema was encountered in two flaps but did not have any detrimental effect on the flaps and it disappeared in two weeks time.

All the patients complained of loss of sensation on the lateral border of the foot particularly when asked about it. It seems that, they don’t regard it as a major morbidity. The sensation gradually improved with time.

In none of the cases in this series, painful neuroma of the sural nerve was encountered. This is because we have always buried the cut end of the nerve in the gastrocnemius muscle.

In 4/25 cases reconstructed with this flap, the patients had trauma of the lower leg. These cases were assessed by Doppler for the patency and the presence of perforators of the peroneal artery.

Baumeister et al (2003) stated that the complication rate reported by other authors is because the patient group included in respective studies is in young patients of trauma and does not reflect the true complication rate. When they analysed the complication rate in a co-morbid patient group the complication rate raised to 49%. In this series too, the patients are young and most of trauma.

This flap is reported to be safe in cases of diabetes, electric burn and post traumatic patients.

Saphenous Nerve:

In the cadaveric dissections carried out, the saphenous nerve descended in the leg on the medial side of the knee. It supplies the skin over the medial
side of leg and medial side of foot. It divides into anterior and posterior branches.

The great saphenous vein and vasa nervosum which arises from the anterior tibial artery accompanied it as it was described by Ballmer, Hertel, Noetzli and Masquelet (1999). Medial malleolar network anastomoses with the paraneural vessels. A safe pivot point for a retrograde will ideally be the 5 cm mark above the medial malleolus

**Superficial peroneal Nerve:**

This flap is the least popular of the neurocutaneous flaps and reports on this flap are scanty. In the dissections conducted it arises at the neck of fibula deep to the fibers of peroneus longus. It descends between the peroneal muscles and pierces the deep fascia at the junction between the upper two third and the lower two third on the lateral side of the leg. The Branches of the anterior tibial artery supply this nerve. The vascular network around this nerve gives off neurocutaneous perforators supplying the skin over it. The vascular network of the nerve anastomoses with the branches of the lateral malleolar artery and the branch of the lateral malleolus at the level of the lateral malleolus. This forms the vascular basis of the flap.

**SUMMARY & CONCLUSION:**

Sural nerve originated from the tibial nerve at the back of the knee and is accompanied and supplied by sural artery, which is a branch of popliteal artery in 7/10 cadavers.

Sural nerve has a mesenteric connection with the deep fascia in its subfascial course. Neurocutaneous perforators were seen traversing the mesentery. If the retrograde flap is to include this part of the skin then the sural nerve along with mesentery has to be included or a cuff of muscle around the nerve should be included.

The nerve becomes suprafascial around mid calf and is closely associated with lesser saphenous vein. In its lower part, the sural neurovascular axis anastomoses with peroneal perforators. The most constant peroneal perforator is 5 cm above the tip of lateral malleolus.

The flap should include the neurovascular axis, lesser saphenous vein, and deep fascia. The flap is safest in the middle third of leg as the nerve is suprafascial in this region.

A doppler study is helpful in the successful execution of the flap, especially in elderly and post traumatic cases to look for the patency of the peroneal arterial system before surgery.

The complication rate in the series was low (1/25). This may be due to the fact that, the patients were younger and flap was raised in the safest part of the leg i.e. mid third of calf.

The technique is easy and less time consuming and is one of the options for reconstruction of lower leg and foot.

**BIBLIOGRAPHY:**

2. Contribution of the Distally-based Neurocutaneous sural flap for reconstruction of tissue defects of the Lower Third of The Leg: 16 cases Alain Fabre; Michel Levdoux; Bertrand Bauer; Edouard Van Gaver; and Sylvain RIGAL Paris, France: 7–11 November 2005
Sleep Apnea
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Loud, constant snoring can indicate a potentially life-threatening disorder called SLEEP APNEA. The word “apnea” is derived from Greek to mean “without breath.” An estimated 5 in 100 people, typically overweight middle-aged men, suffer from sleep apnea. A person with sleep apnea stops breathing repeatedly while sleeping, anywhere from 10 seconds to 3 minutes.

Although an individual may not recall waking up, sleep is disrupted temporarily. As a result, sleep deprivation, excessive daytime sleepiness occur. If left untreated, sleep apnea can trigger high blood pressure and dangerous heart problems.

Sleep apnea can also occur in children and, in some cases, has been linked to Sudden Infant Death Syndrome (SIDS). In older children, sleep apnea occurs in those children who are overweight or who have unusually large tonsils and adenoids. Children with sleep apnea may snore, squeak, and thrash while sleeping. During the day, a child who suffers from sleep apnea will be sluggish or termed “lazy.” Since snoring is not normal for any child, parents should report this to their physician.

There are three types of sleep apnea: obstructive, central, and mixed. Obstructive sleep apnea (OSA) is the most common and severe form. This type of apnea occurs, when the airway closes and remains obstructed, resulting in blocked airflow. As pressure to breathe increases, the diaphragm and chest muscles stop working. Eventually the decreased level of oxygen in the blood signals the brain to awaken the sleeper to restart breathing. This type of apnea becomes more common with age and is associated with heart disease or a neurological disorder.

Mixed sleep apnea is a combination of central and obstructive sleep apnea. This disorder initially occurs as central sleep apnea, where there is no brain signal to breathe. When the diaphragm suddenly begins moving, the airway is blocked by an obstruction (obstructive sleep apnea). It is not uncommon for a sleep disorder specialist to see all three types of apnea occur in one night.

Physical abnormalities are usually the cause of OSA. Excessive pharyngeal tissue, an overly large tongue, a congenitally small airway or fatty deposits are often found to be the reason. Corrective surgery is a common solution to eliminating obstructive sleep apnea.

There are actually a number of forms of treatment for obstructive sleep apnea, not just surgery. These range from weight loss and other lifestyle changes to several surgical procedures. The most common and still the most effective treatment, is the use of continuous positive airway pressure or CPAP, a device that uses pressurized air delivered through a nasal interface to hold the airway open while the patient sleeps. Combinations of these therapies are also used.

In central sleep apnea, the brain actually fails to signal the muscles to breathe. The airway is clear, but the diaphragm and chest muscles stop working. Eventually the decreased level of oxygen in the blood signals the brain to awaken the sleeper to restart breathing. This type of apnea becomes more common with age and is associated with heart disease or a neurological disorder.

What is Snoring?

Snoring is a noise produced by a sleeping individual in which the soft palate and the uvula vibrate during breathing. It is a sign that, the breathing airway is not completely open. The unpleasant and often annoying sound associated with snoring comes from efforts to force air through the narrowed passageway.

Primary snoring (snoring not caused by apnea) poses no known serious consequences, is not life
threatening and does not cause chronic fatigue in the sleeper. Snoring can, however, cause fatigue and extreme annoyance in other household members, as well as the isolation of a bed partner. It is estimated that as many as 40 percent of adults snore. The majority of snorers are men.

When should I see a Doctor?

If sleep apnea is suspected, scheduling an appointment with a physician is recommended. The physician will take a medical history and a referral for a night in a sleep evaluation laboratory will be required. It is often helpful for the doctor or sleep specialist to interview the bed partner or other members of the household. It is a good idea to complete the Bed Partner Questionnaire and review it with the doctor or sleep specialist.

For a diagnosis of sleep apnea to be made, each abnormal breathing episode must last at least 10 seconds and occur at least 5 times for each hour asleep. Doctors call this the Respiratory Disturbance Index (RDI).

What treatments are available for Sleep Apnea?

Weight loss is often an effective treatment for snoring-related sleep apnea. Even just a few pounds can improve breathing during sleep. Another effective treatment is medication. Some antidepressants and asthma medications have been found to relieve sleep apnea because they are respiratory stimulants.

For severe sleep apnea cases, continuous positive airway pressure or CPAP therapy may be required. Patients receiving this treatment wear a light mask over the nose during sleep. An air compressor forces air through the nose and into the airway. Other sleep apnea patients find relief with oral appliances that prop the airway open by moving the jaw, tongue, and soft palate forward.

In some cases, surgery may be required to correct physical abnormalities. Sleep apnea as the result of enlarged tonsils and/or adenoids in children, can be alleviated with a tonsillectomy and/or adenoidectomy. Another surgical technique called uvulopalatopharyngoplasty (UPPP) removes excess tissue at the back of the throat. For some patients, however, there are negative side effects or apnea symptoms are not resolved.

Somnoplasty is a non-invasive procedure, that uses low power, low temperature radio frequency energy to reduce the tongue. The procedure takes place in the physician’s office under local anesthesia and typically takes less than an hour. Multiple somnoplasty treatments may be required, but snoring and apnea episodes are often alleviated.

A tracheostomy, a procedure in which a tube is inserted into the throat by making an opening in the windpipe, is only used for severe cases of sleep apnea and when other treatments fail. The tube is closed during the day, allowing for normal activities and opened at night, bypassing the obstruction in the throat.

What is Sleep Apnea?

Sleep apnea is a serious, potentially life-threatening condition that is far more common than generally understood. First described in 1965, sleep apnea is a breathing disorder characterized by brief interruptions of breathing during sleep. It owes its name to a Greek word, apnea, meaning “want of breath.” There are two types of sleep apnea: central and obstructive. Central sleep apnea, which is less common, occurs when the brain fails to send the appropriate signals to the breathing muscles to initiate respirations. Obstructive sleep apnea is far more common and occurs when air cannot flow into or out of the person’s nose or mouth although efforts to breathe continue.

In a given night, the number of involuntary breathing pauses or “apneic events” may be as high as 20 to 30 or more per hour. These breathing pauses are almost always accompanied by snoring between apnea episodes, although not everyone who snores has this condition. Sleep apnea can also be characterized by choking sensations. The frequent interruptions of deep, restorative sleep often lead to early morning headaches and excessive daytime sleepiness.

Early recognition and treatment of sleep apnea is important because it may be associated with irregular heartbeat, high blood pressure, heart attack and stroke.

Who gets Sleep Apnea?

Sleep apnea occurs in all age groups and both sexes, but is more common in men (it may be under-diagnosed in women) and possibly young African Americans. It has been estimated that, as many as 18 million Americans have sleep apnea. Four percent of...
middle-aged men and 2 percent of middle-aged women have sleep apnea along with excessive daytime sleepiness. People most likely to have or develop sleep apnea include those who snore loudly and also are overweight or have high blood pressure or have some physical abnormality in the nose, throat or other parts of the upper airway. Sleep apnea seems to run in some families, suggesting a possible genetic basis.

**What causes Sleep Apnea?**

Certain mechanical and structural problems in the airway cause the interruptions in breathing during sleep. In some people, apnea occurs when the throat muscles and tongue relax during sleep and partially block the opening of the airway. When the muscles of the soft palate at the base of the tongue and the uvula relax and sag, the airway becomes blocked, making breathing laboured and noisy and even stopping it altogether. Sleep apnea also can occur in obese people when an excess amount of tissue in the airway causes it to be narrowed. With a narrowed airway, the person continues his or her efforts to breathe, but air cannot easily flow into or out of the nose or mouth. Unknown to the person, this results in heavy snoring, periods of no breathing and frequent arousals, causing abrupt changes from deep sleep to light sleep. Ingestion of alcohol and sleeping pills increases the frequency and duration of breathing pauses in people with sleep apnea.

**How is normal breathing restored during Sleep?**

During the apneic event, the person is unable to breathe in oxygen and to exhale carbon dioxide, resulting in low levels of oxygen and increased levels of carbon dioxide in the blood. The reduction in oxygen and increase in carbon dioxide alert the brain to resume breathing and cause an arousal. With each arousal, a signal is sent from the brain to the upper airway muscles to open the airway; breathing is resumed, often with a loud snort or gasp. Frequent arousals, although necessary for breathing to restart, prevent the patient from getting enough restorative, deep sleep.

**What are the effects of Sleep Apnea?**

Because of the serious disturbances in their normal sleep patterns, people with sleep apnea often feel very sleepy during the day and their concentration and daytime performance suffer. The consequences of sleep apnea range from annoying to life-threatening. They include depression, irritability, sexual dysfunction, learning and memory difficulties, and falling asleep while at work, on the phone or driving. It has been estimated that up to 50 percent of sleep apnea patients have high blood pressure. Although it is not known with certainty, if this is a cause of hypertension or there is effect relationship. It appears that, sleep apnea contributes to high blood pressure. Risk for heart attack and stroke may also increase in those with sleep apnea. In addition, sleep apnea is sometimes implicated in sudden infant death syndrome.

**When should Sleep Apnea be suspected?**

For many sleep apnea patients, their spouses are the first ones to suspect that, something is wrong, usually from their heavy snoring and apparent struggle to breathe. Coworkers or friends of the sleep apnea victim may notice that, the individual falls asleep during the day at inappropriate times, such as while driving a car, working, or talking. The patient often does not know he or she has a problem and may not believe it, when told. It is important that, the person see a doctor for evaluation of the sleep problem.

**How is Sleep Apnea diagnosed?**

In addition to the primary care physician, pulmonologists, neurologists or other physicians with special training in sleep disorders, may be involved in making a definitive diagnosis and initiating treatment. Diagnosis of sleep apnea is not simple, because there can be many different reasons for disturbed sleep. Several tests are available for evaluating a person for sleep apnea.

Polysomnography is a test, that records a variety of body functions during sleep, such as the electrical activity of the brain, eye movement, muscle activity, heart rate, respiratory effort, air flow and blood oxygen levels. These tests are used both to diagnose sleep apnea and to determine its severity.

The Multiple Sleep Latency Test (MSLT) measures the speed of falling asleep. In this test, patients are given several opportunities to fall asleep during the course of a day, when they would normally be awake. For each opportunity, time to fall asleep is measured. People without sleep problems, usually take an average of 10 to 20 minutes to fall asleep. Individuals who fall asleep in less than 5 minutes are likely to
require some treatment for sleep disorders. The MSLT may be useful to measure the degree of excessive daytime sleepiness and to rule out other types of sleep disorders.

Diagnostic tests usually are performed in a sleep center, but new technology may allow some sleep studies to be conducted in the patient’s home.

How is Sleep Apnea treated?

The specific therapy for sleep apnea is tailored to the individual patient, based on medical history, physical examination and the results of polysomnography. Medications are generally not effective in the treatment of sleep apnea. Oxygen administration may safely benefit certain patients, but does not eliminate sleep apnea or prevent daytime sleepiness. Thus, the role of oxygen in the treatment of sleep apnea is controversial and it is difficult to predict which patients will respond well. It is important that, the effectiveness of the selected treatment be verified. This is usually accomplished by polysomnography.

Behavioural therapy

Behavioural changes are an important part of the treatment programme and in mild cases behavioural therapy may be all that is needed. The individual should avoid the use of alcohol, tobacco and sleeping pills, which make the airway more likely to collapse during sleep and prolong the apneic periods. Overweight persons can benefit from losing weight. Even a 10 percent weight loss can reduce the number of apneic events for most patients. In some patients with mild sleep apnea, breathing pauses occur only when they sleep on their backs. In such cases, using pillows and other devices, that help them sleep in a side position is often helpful.

Physical or Mechanical therapy

Nasal continuous positive airway pressure (CPAP) is the most common effective treatment for sleep apnea. In this procedure, the patient wears a mask over the nose during sleep and pressure from an air blower forces air through the nasal passages. The air pressure is adjusted, so that, it is just enough to prevent the throat from collapsing during sleep. The pressure is constant and continuous. Nasal CPAP prevents airway closure while in use, but apnea episodes return when CPAP is stopped or used improperly.

Variations of the CPAP device attempt is necessary to minimize side effects, that sometimes occur, such as nasal irritation and drying, facial skin irritation, abdominal bloating, mask leaks, sore eyes and headaches. Some versions of CPAP vary the pressure to coincide with the person’s breathing pattern and others start with low pressure, slowly increasing it to allow the person to fall asleep before the full prescribed pressure is applied.

Dental appliances, that reposition the lower jaw and the tongue have been helpful to some patients with mild sleep apnea or who snore, but do not have apnea. Possible side effects include damage to teeth, soft tissues and the jaw joint. A dentist or orthodontist is often the one to fit the patient with such a device.

Surgery

Some patients with sleep apnea may need surgery. Although several surgical procedures are used to increase the size of the airway, none of them is completely successful or without risks. More than one procedure may need to be tried before the patient realizes any benefits. Some of the more common procedures include removal of adenoids and tonsils (especially in children), nasal polyps or other growths or other tissue in the airway and correction of structural deformities. Younger patients seem to benefit from these surgical procedures more than older patients.

Uvulopalatopharyngoplasty (UPPP) is a procedure used to remove excess tissue at the back of the throat (tonsils, uvula and part of the soft palate). The success of this technique may range from 30 to 50 percent. The long-term side effects and benefits are not known and it is difficult to predict, which patients will do well with this procedure.

Laser-assisted uvulopalatoplasty (LAUP) is done to eliminate snoring, but has not been shown to be effective in treating sleep apnea. This procedure involves using a laser device to eliminate tissue in the back of the throat. Like UPPP, LAUP may decrease or eliminate snoring, but will not cure sleep apnea itself. Elimination of snoring, the primary symptom of sleep apnea, without influencing the condition may carry the risk of delaying the diagnosis and possible treatment...
of sleep apnea in patients, who elect LAUP. To identify possible underlying sleep apnea, sleep studies are usually required before LAUP is performed.

Tracheotomy is used in persons with severe, life-threatening sleep apnea. In this procedure, a small hole is made in the windpipe and a tube is inserted into the opening. This tube stays closed during waking hours and the person breathes and speaks normally. It is opened during sleep, so that air flows directly into the lungs, bypassing any upper airway obstruction. Although this procedure is highly effective, it is an extreme measure, that is poorly tolerated by patients and rarely used.

Other procedures

Patient in whom sleep apnea is due to deformities of the lower jaw, may benefit from surgical reconstruction. Finally, surgical procedures to treat obesity are sometimes recommended for sleep apnea patients, who are morbidly obese.

National Centre on Sleep Disorders Research (NCSDR)

The National Center on Sleep Disorders Research (NCSDR) is part of the National Heart, Lung, and Blood Institute of the National Institutes of Health.

Self-Remedies and conservative treatments for Sleep Apnea

- Self-Help remedies
- Devices
- Nasal Surgery
- Upper Airway Surgery
- Lower Airway Surgery
- Surgical Bypass of the Airway

Self-Help remedies

These remedies may or may not be applicable to you. They may be reasonable options by themselves or may be combined with other treatments.

Weight Loss

If you are overweight, weight reduction may improve your snoring or sleep apnea. Weight gain deposits fat into and around the soft palate, tongue and neck structures. Weight loss can reduce these fat deposits and enlarge the airway size.

Sleep Positioning Maneuvers

Elevating the head of your bed and avoiding sleeping on your back may be helpful. A common way to train you to not sleep on the back is to place a tennis ball in the middle of your back during sleep. The ball is placed in a sock that is pinned to the back of a sleep shirt or placed in a pocket sewn into the shirt.

Improve amount and regularity of sleep

You should go to sleep and wake up at approximately the same time every day. You should try to get at least 7 1/2 to 8 hours of sleep a night. Snoring and sleep apnea is often worse if you are overtired.

Avoid drugs and habits that worsen airway narrowing

Alcohol and most sleeping pills relax the muscles of the throat and can worsen snoring and sleep apnea. You should avoid alcohol for at least 3 hours prior to bedtime. Smoking can also worsen snoring and sleep apnea, due to swelling of the nasal tissues.

Nasal Dilators

Internal or external devices that dilate your nasal passages may help your snoring.

Devices

Devices must be worn all night and every night in order to control the sleep disorder. Devices may be difficult to use and are not always tolerated. The main advantage of a device is that there are usually minimal risks associated with their use.

CPAP, BiPAP

CPAP (continuous positive airway pressure) is a device that controls apnea and snoring in most patients and is the most common and successful treatment prescribed for sleep apnea. CPAP is an air compressor that blows air through a corrugated tube attached to a mask that is placed over your nose. The mask is held in place by elastic straps around the back of your head. The air blows up your nose and down your throat and prevents the throat from closing up.

BiPAP (Bilevel Positive Airway Pressure) is a similar device that blows a higher pressure for inhaling and a lower pressure for exhaling. BiPAP is generally used for patients who can not tolerate high constant air pressure with CPAP.
Both of these devices currently require a sleep study (polysomnogram) to determine the proper pressure to use. If the pressure is too low, the airway may still collapse and obstruct, and if the pressure is too high, the device may not be tolerated or a different type of apnea (central apnea) may occur.

**Oral appliance**

An adjustable oral appliance is a custom-fit device that is worn over the teeth and pulls the lower jawbone forward. Since the tongue is attached to the jaw, moving the jaw forward will open up the airway and may help snoring or sleep apnea. Once tolerated the entire night, the device can be adjusted until breathing improves.

**Nasal Surgery - Septoplasty**

The goal of surgery is to enlarge the airway and prevent snoring and airway collapse. Surgery is site-specific (performed to enlarge a certain portion of the airway). Due to risks associated with anesthesia or an operation, surgery may not be considered as a first option. The main advantage of surgery is that it may achieve a permanent cure for the problem.

The septum is the divider between the two nasal passages. A deviated (crooked) septum may obstruct the nasal airway. A septoplasty is performed through the nostrils. A small incision is made just inside one nostril and the cartilage and bone of the septum is straightened.

**Turbinate Reduction**

The turbinates within the nose are made of bone surrounded by soft tissue whose function are to warm up and moisturize the air as you breathe. There are three turbinates in each nostril (inferior, middle, and upper). Reduction of the size of an enlarged turbinate can improve the size of the nasal airway. Turbinate reduction may be performed with surgical instruments, lasers, radio-frequency energy, or a cautery unit.

**Removal of Polyps, Endoscopic Sinus Surgery**

When polyps obstruct the nasal airway or sinus infections contribute to nasal obstruction, sinus surgery or removal of the polyps may be necessary. These surgeries are typically performed through the nostrils with magnifying scopes so as to avoid external incisions.

**Upper Airway Surgery**

The goal of surgery is to enlarge the airway and prevent snoring and airway collapse. Surgery is site-specific (performed to enlarge a certain portion of the airway). Due to risks associated with anesthesia or an operation, surgery may not be considered as a first option. The main advantage of surgery is that it may achieve a permanent cure for the problem.

Upper airway surgery is used for narrowing the upper part of the airway involving the soft palate, uvula, tonsils, or adenoids.

**Uvulopalatopharyngoplasty (UPPP)**

An enlarged uvula and elongated soft palate may cause sleep apnea and snoring. Uvulopalatopharyngoplasty, or UPPP, is a surgical procedure performed in the operating room under general anesthesia. The operation is performed either with a laser or standard surgical instruments. The uvula is removed, the lower edge of the soft palate trimmed, tonsils are generally removed (if present), and tissues are trimmed around the tonsils. Stitches are placed and dissolve away in several weeks.

**Laser-Assisted Uvulopalatoplasty (LAUP)**

Laser-assisted uvulopalatoplasty (LAUP) is a surgical procedure for the treatment of habitual loud snoring or obstructive sleep apnea. The procedure involves a progressive removal of the back edge of the palate and size of the uvula. When tonsils are present and are contributing to the snoring, they can be serially vaporized with the laser at the same time. LAUP is most frequently performed with a carbon dioxide (CO₂) laser in the office under local anesthesia. Treatment continues every 4-6 weeks until symptoms improve. Each treatment takes about fifteen minutes. Most patients require between one and 3 treatments.

**Radio-frequency Tissue Ablation of the Palate (Somnoplasty)**

Radio-frequency tissue ablation palatoplasty, also called somnoplasty, delivers radio-frequency waves by a needle electrode placed under the surface of the soft palate and causes contraction of excessive tissues that are causing snoring. Radio-frequency tissue ablation involves a progressive shrinkage of the soft palate and uvula. The procedure is virtually painless when used for the treatment of habitual loud snoring.
The procedure takes about 15 minutes and is performed in the office under local anesthesia. If symptoms persist, the next treatment is performed 4-6 weeks later. Most patients require between 1 and 4 treatments.

**Tonsillectomy and Adenoidectomy**

The tonsils are tissues on the sides of the upper throat and when enlarged may narrow the width of the upper airway. The adenoids are at the back of the nose and may obstruct the nasal airway. Removal of tonsils and adenoids are performed most often in children with snoring or sleep apnea. Since the adenoids usually shrink with age, they only rarely require removal in adults. Tonsillectomies and adenoidectomies are generally performed under general anesthesia in the operating room.

**Lower Airway Surgery**

The goal of surgery is to enlarge the airway and prevent snoring and airway collapse. Surgery is site-specific (performed to enlarge a certain portion of the airway). Due to risks associated with anesthesia or an operation, surgery may not be considered as a first option. The main advantage of surgery is that it may achieve a permanent cure for the problem.

Lower airway surgery is used to narrow the lower part of the airway, located behind the back of the tongue.

**Genioglossus Advancement**

The genioglossus muscle is a muscle that attaches from the back of the tongue to a spot on the back of the chin. The purpose of this operation is to pull the back of the tongue forward, enlarging the air space behind the tongue. Genioglossus advancement is performed in the operating room under general anesthesia through an incision inside the lower lip. A rectangular or circular segment of chin bone (just below the front 4 teeth) is pulled forward and held in place with a titanium screw or plate. The operation produces a minimal change (several millimeters) in the appearance of the chin.

**Hyoid Advancement**

The hyoid bone is a C-shaped bone in the upper neck that sits just above the Adam’s apple. The hyoid bone has muscle attachments to the back of the tongue, as well as the sides of the lower throat. Hyoid advancement is performed in the operating room by making an incision in the neck just above the Adam’s apple. The hyoid bone is moved forward and either attached to the Adam’s apple or to the jawbone. This operation also enlarges the air space behind the tongue.

**Midline Glossectomy, Lingualplasty, and Lingual Tonsillectomy**

When the tongue is enlarged, surgery may be performed to make it smaller. The back of the tongue may be reduced in size by excising a V-shaped portion of the center part of the tongue (midline glossectomy). A more aggressive resection with additional removal of side wedges is termed lingualplasty. When enlarged, the lingual tonsils (tonsil-like tissue on the back part of the tongue) may also be removed with a laser. A temporary tracheostomy is frequently performed along with these operations to avoid breathing difficulty that could result from temporary swelling. By reducing the tongue size, the air space behind the tongue is enlarged.

**Bimaxillary Advancement (Lefort 1 Maxillary Osteotomy with Bilateral Sagittal Split Mandibular Osteotomy)**

The upper and lower jawbones can be moved forward along with all of the teeth in order to pull soft tissue structures forward and make more room for the tongue. The advanced portions of the jawbones are held in place with titanium metal plates and screws. This surgical procedure is performed for patients with a small jaw structure or in those who have failed other “soft tissue” surgeries. The surgery is performed under general anesthesia in the operating room. Orthodontic work prior to or following the advancement procedure may be necessary to maintain proper alignment of the teeth. The degree of change in facial appearance relates to the amount of advancement performed.

**Tongue Base Radio-frequency Tissue Ablation (Somnoplasty)**

When the tongue is enlarged, radio-frequency treatments may be performed to make it smaller. Radio-frequency tongue reduction, also called somnoplasty, is performed by a needle electrode placed under the surface of the tongue that causes contraction of excessive tissues. The procedure takes about 45 minutes and is performed in the office under local anesthesia.
anesthesia. Each treatment results in a progressive shrinkage of the back of the tongue. If symptoms persist, the next treatment is performed about 4 weeks later.

**Tongue Suspension Suture**

A tongue suspension suture (“Repose”) may prevent the tongue from falling back during sleep. A titanium screw is placed at the back of the chin. A permanent stitch attached to this screw is placed through the back of the tongue and is tied so that the tongue is pulled forward. This prevents collapse of the airway during sleep. Tongue suspension suture is performed under general anesthesia in the operating room.

**Surgical Bypass of the Airway**

**Tracheostomy (Tracheotomy)**

The goal of surgery is to enlarge the airway and prevent snoring and airway collapse. Surgery is site-specific (performed to enlarge a certain portion of the airway). Due to risks associated with anesthesia or an operation, surgery may not be considered as a first option. The main advantage of surgery is that it may achieve a permanent cure for the problem.

Instead of enlarging the narrowed portions of the airway, a tracheostomy, also called a tracheotomy, may be performed in order to bypass the narrowed segments or any obstruction associated with sleep apnea. In this operation, an opening is created in the front of the neck to the windpipe (trachea) and a plastic or metal tube is inserted. This tube keeps the tracheostomy from closing up. During sleep, the patient breathes through the tracheostomy tube. While awake, the tracheostomy tube is covered to allow for normal speech and breathing. Tracheostomy is usually performed for severe life-threatening sleep apnea or along with multiple airway reconstructive surgeries.

**Reference:**

The Advent of MR and PET Imaging

Ruchi Bhuyan¹, Sanat Kumar Bhuyan ²

ABSTRACT:
Advancements in imaging took a leap in the last decade, when PET. Only systems were phased out and replaced out and replaced with PET-CT systems. This led to a functional and anatomic image of tissues of high contrast and greater application. Another breakthrough in oncology imaging is expected with the merger of MRI and PET, where imaging of specific body locations with no additional radiation burden and better tissue contrast is achieved.

Key words: CT-Computed Tomography, PET-Positron Emission Tomography, MRI-Magnetic Resonance imaging.

Introduction
An effective management of a cancer patient depends on the correct detection of tumor and staging of disease. A cancer patient undergoes several investigations including different imaging studies, which are later correlated to arrive at a definitive diagnosis. Such processes are usually tedious and time consuming. Moreover, well defined and reproducible landmarks are necessary for correct interpretation of these imaging modalities. Patient positioning also varies in various procedures leading to inconsistencies and errors. Also, there may be problems due to patient movement or motion of internal organs such as heart or bowel peristalsis. To overcome such problems, developments in imaging in oncology led to fusion of PET with CT and more recently PET with MRI.

Review and Discussion
In PET alone imaging, the most often used radiopharmaceutical is 18F-FEG. There is derangement of glucose utilization in cancer cells. Taking advantage of this derangement, FDG mimics the glucose utilization, and photons are emitted from this 18F-FDG. In MR imaging, a scout view is obtained and the imaging field is then defined. In this way combining both of these modalities leads to an anatomic and functional registration of tissues. However, a different support is required to combine MR and PET as both have different detectors.

MR-PET imaging
MR imaging usually takes longer time than a multi-detector CT making the acquisition times for MR and PET become quite similar. Thus, the “simultaneous acquisition” method is usually the preferred option. PET/CT imaging usually involves “sequential acquisition”, which leads to a longer time for MR/PET; thus leading to increased chances of patient movement and motion artifact causing misregistration of the final image. Hence the simultaneous acquisition allows interrogation and measurement of patient’s tissues at exactly the same time.

Simultaneous acquisition
The PET detectors should be able to operate inside the magnetic field without interfering with the MR imaging for a combined MR/PET imaging. These types of detectors have successfully been constructed and are typically based on silicon avalanche photodetectors (APDs). Several animal systems based on this technology have been constructed with one system introducing a PET insert for one of their MR systems in 2007. However, the system was limited to brain only imaging. A recent clinical study comparing PET/CT and MR/PET imaging showed that the image quality was similar for both systems.

Sequential acquisition
A different system design is used in another commercially available MR/PET system. The conventional PET and MRI gantries are placed at some distance from each other in order to minimize interference between the two systems. The two devices use a common patient bed, which can be moved into either imaging gantry. This solution does not require special PET detector, although additional magnetic...
shielding is placed around the PET gantry to minimize the effect on the PMTs. This type of acquisition has the drawback of not allowing simultaneous PET and MR imaging, which prevents imaging of physiological and biochemical processes at the same moment in time by the two modalities. Since the PET and MRI data sets are acquired much longer than CT, the imaging sessions are substantially longer compared to corresponding PET/CT imaging procedures.

Advantages of MR/PET Imaging

The combination yields a simultaneous anatomic and functional registration of the tissues. A higher tissue contrast is obtained, and sophisticated MR imaging techniques such as perfusion and diffusion imaging, and MR spectroscopy, without adding extra radiation to the patient may be incorporated. Moreover, no ionizing radiations are involved in MR imaging so the total absorbed radiation dose to the patient is solely due to the radiopharmaceutical used for PET imaging. This is much more favorable that CT, which has a relatively high radiation burden. It is very likely that this technology will be extended to clinical whole body imaging in the very near future.

Challenges for MR/PET Imaging

There are a number of challenges in combining PET and MRI. The PMTs (photo-multiplier tubes) used in conventional PET detectors are highly sensitive to magnetic fields and cannot be used near the MR magnet. Solid-state detectors are less sensitive to magnetic fields and have been shown to operate relatively undisturbed in strong magnetic fields. These detectors have to constructed without any ferromagnetic materials that would otherwise produce heterogeneity within the magnetic field. Therefore different approaches have been sought to overcome these challenges for a better combined MR/PET systems.

The slices for MR imaging are usually thick slices (5-7 mm in z plane), whereas PET has image slices of 2-4 mm. Another challenge for a combined MR/PET system is the attenuation correction. An additional complication is that not all tissue types are visualized in MRI (e.g. bone). This may require the use of deformable anatomical atlases to generate the correct attenuation coefficients. The conversion of MR Images to attenuation maps is a complex problem and is an area of active research. A number of different approaches are currently being investigated and developed.

Final Considerations

The radiologist or nuclear medicine specialist must be eager to participate in the changing field of combined and correlative imaging in oncology. The detailed anatomic framework required for accurate interpretation of functional images, is of paramount importance in oncology. Such requirements were fulfilled when PET was combined with CT to provide an image of superior quality having both an anatomic and functional registration. Moreover, the combined imaging process saved patients time. Fusion of image by such a process led to improved lesion localization. It may be expected, that with better systems being developed, MR/PET will develop as an imaging modality of choice for oncology patients. The simultaneous acquisition, used in MR/PET, will definitely benefit image registration and reduce artifacts leading to an accurate image.

References

Restrictive Transfusion Policy on Anemia - An Ideal Strategy in Critically Ill Patient

Arata Kumar Swain¹, Prasanna Kumar Mishra²

Introduction

A hematocrit between 20% and 25% was considered an urgent indication for transfusion, but at the turn of this century, maintaining a hematocrit at this level is considered to be “best-practice medicine”.(1)

Anemia is apparently tolerated in most patients, particularly those who are young/relatively healthy, the ICU population must be thought of differently. Anemia in the ICU may be due to acute blood loss, phlebotomy or due to the presence of inflammatory disease. The risks of blood transfusions are many. Nonetheless, Hemoglobin levels at or above 10 g/dl may be important for oxygen delivery to vital organs, especially in critically ill patients with increased oxygen demands.(1) The appropriate transfusion trigger for critically ill patients in this setting remains unknown.

Aim:

This study aims to assess the prevalence of anemia in critically ill patients and studies the association of blood transfusion and mortality in critically ill patients. It also compares restrictive transfusion policy (Hb < 7 g/dl) and liberal transfusion policy (Hb < 10 g/dl).

Materials and Methods

A total of 100 patients were included for three years in the study from 2008 Mach to 2011 March. A matched cohort study was performed. The complete blood count was done every week and patients were followed for 21 days or till death/transfer from the ICU. The following standards were used for case identification:- Hb less than 12g/dl (males). Hb less than 10 g/dl (females) [any single episode during ICU stay].

Inclusion Criteria

All patients admitted in the intensive care unit during the study period in the age group of 15-65 years.

Exclusion Criteria

1. HIV positive patients
2. Hematological malignancies
3. Patients with a known hematological disorder
4. Patients on chemotherapy

Matching and selection of control patients

The study of the association between blood transfusion and mortality, control patients were those who never received blood during ICU stay. They were selected according to the following criteria:

- Age (+5 years)
- Sex
- APACHE ll score on first day of ICU admission (+5 points)
- History of cardiac disease (ischemic heart disease, congestive heart failure)
- History of renal disease (acute or chronic renal failure)
- Clinical diagnosis
- The Chi-square test was used for statistical significance and P<0.05 was considered significant at 95% confidence interval.

Result

The study cohort of 100 patients had an average APACHE score of 16.2. The overall mortality was 46% and the age-wise distribution of mortality was as shown in Table. 1.

1. Out of 100 patients 68 were found to be anemic during the study period. The mean Hb level was 8.72 g/dl. The predominant peripheral smear picture was of microcytic hypochromic type. The others were normocytic normochromic with 3% showing a leukemoid reaction [table 2].
2. Sepsis was the commonest clinical setting associated with anemia. The others being gastrointestinal bleed, chronic renal failure and postoperative blood loss [Table 3].

3. Out of the 100 patients studied, 38 patients were given blood transfusion and matching control patients were identified for 36 patients. The mortality in the transfusion group was 58.33% when compared to 25.0% in the non transfusion group (P 0.005). The attributable mortality was 33.33% with a relative risk of 2.33 [Table 4].

4. The mortality rate in those transfused at Hb<7g/dl was 10% when compared to 70% mortality rate in those transfused at Hb<10 g/dl (P 0.005) [Table 5].

5. The duration of stay in the ICU was doubled in anemic patients [Table 6].

Discussion
The study shown that nearly two-thirds of patients admitted to an ICU have Hb levels less than 10 g/dl. Anemia may be caused by decreased production of RBCs, nutritional deficiencies, inadequate production of RBCs, inadequate endogenous erythropoietin production renal failure and diagnostic blood smpling (3,4).
As anemia progresses in otherwise healthy persons, compensatory mechanisms are recruited and a certain degree of anemia may be tolerated. These mechanisms may not operate efficiently or at all in critically ill patients. Under various preconditions anemia may be associated with increased mortality of the critically ill. The same is true with blood transfusion (5,6).

The complications of blood transfusions include volume overload, febrile reactions and fatal hemolytic reactions which may all contributed to increase mortality. The anemia and blood transfusions study conducted in Western European ICUs also show overall mortality rates were significantly higher in patients who had blood transfusion vs who had not received transfusion (2).

The concept of optimal Hb concentration has been challenged. Wilkerson and colleagues using a paralyzed, anesthetized, normovolemic anemic primate model, noted that compensatory mechanisms for low Hb concentration did not occur until the Hb concentration fell below 7 g/dl.

The study by Hebert et. Al (7) showed that a restrictive transfusion policy (Hb<7 g/dl) has better overall outcomes than when the transfusion trigger was more liberal (Hb<10 g/dl). The decision to transfuse or not must be taken after weighing up the potential consequences of anemia against blood transfusion associated risks. Every single patient’s ability to compensate for anemia is different. The question of whether a potential transfusion is capable of affecting the clinical outcome of a given patient is related to the question whether tissue hypoxia is in fact prevailing at a certain Hb Concentration.

REFERENCES
1. Pearl RG, Pohlman A. Understanding and managing anemia in critically ill patients, Crit Care Nurse Dec 2002; Suppl:1-14

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Parenteral Iron preparations – A Clinical update

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ABSTRACT
Iron deficiency is a common problem occurring in normal people who experience excessive blood loss, as well as in patients with inherited or acquired bleeding disorders. Oral iron replacement is usually adequate for most patients, but intolerance to oral iron, abnormal absorption due to surgery or gastrointestinal disease, significant bleeding, and noncompliance may make oral iron treatment in some patients inadequate. These patients may benefit from parenteral iron therapy which on the other hand provide a faster rate of increase in the haemoglobin levels, faster replenishment of iron stores and with a better patient compliance. New iron formulations continues to evolve in order to improve their tolerance and efficacy. The different parenteral iron preparations used in clinical practice are iron dextran, iron sucrose, iron gluconate, Ferrumoxytol, iron carboxy maltose and iron isomaltoside. These non dextran IV irons have been considered to have a markedly lower serious acute event rate than the older iron dextrans.

KEY WORDS: iron deficiency; iron therapy, parenteral iron

INTRODUCTION
Anemia is a common feature of many disease. In addition, in anaemia associated with inflammatory states, there is sequestration and impaired release of iron from the macrophages of the reticuloendothelial system of the liver, spleen, and bone marrow which is referred to as the reticuloendothelial blockade. Among the various causes of anaemia the prevalence of iron deficiency in patients with chronic kidney diseases is around 25–70%¹. Oral iron therapy for anaemia is sometimes inadequate and impractical due a number of reasons. First and foremost the available oral preparations often have intolerable gastrointestinal toxicity for which the patients may not adhere to the prescribed treatments. Secondly Hepcidin an endogenous agent is produced in the liver during inflammatory states which inhibits iron absorption from the small intestine, further limiting the bioavailability of such oral iron preparations². Thus, intravenous iron is the mainstay of treatment in patients as these can overcome the reticuloendothelial blockade and thereby deliver sufficient amount of iron to be utilized for hemoglobin synthesis and erythropoiesis.

Parenteral iron was first introduced in the early 29th century. Amongst the currently available intravenous iron preparations, the iron dextrans have the advantage of permitting administration of larger doses of iron by slow infusion over several hours, but the risk of anaphylaxis, consequent requirement of a test dose, and other side effects have led to a decline in their use in most developed countries ³. The newer iron formulations such as iron sucrose and iron gluconate are though associated with a lower incidence of allergic reactions as compared to the iron dextrans, can be administered only in small doses because of their dose-related side effects like hypotension ⁴, ⁵. These preparations also cause direct release of some iron into the plasma which can cause the generation of a free or labile iron pool, which is largely responsible for the immunological side effects of iron. Thus an ideal IV iron formulation should have low immunogenicity, stable binding of the iron to its carrier molecule in serum until it is taken up into the reticuloendothelial system for transfer to transferrin or for storage. The objectives of this review are to summarize the available parenteral iron products.

PHARMACOLOGICAL PARAMETERS OF IV IRON PREPARATIONS
Chemical Structure-All the parenteral iron products are composed of small spheroidal complexes of colloids of iron and carbohydrates. Each particle
consists of a core of iron-oxyhydroxy gel surrounded by a shell of carbohydrate that stabilizes the gel, which in turn causes slow release of iron and maintains the particle in a colloidal form. All the different preparations of IV iron have the same chemical structure but differ from each other by the size of the core and the density of the surrounding carbohydrate. The rate of release of iron from the complex (degradation kinetics of the preparation) is inversely proportional to the strength of the complex. Thus stronger the complex the slower is the rate of dissociation and release of iron and thus less potential to saturate transferrin as compared to the weaker complexes of iron.

Metabolic Fate: After injection the iron carbohydrate complex mixes with the plasma and is phagocytosed by the reticuloendothelial system where the carbohydrate shell is degraded and the released iron is either stored as ferritin in the cells or is transported out of the cell by a carrier protein. This then gets bound to the transport protein transferrin which delivers iron to the transferrin receptors on the surface of the erythroid precursors. The resulting internalization of the iron transferrin complex supplies iron for hemoglobin synthesis. All the IV iron preparations release biologically available or labile iron. The rate of labile iron release in each agent is inversely related to the size of its iron core. The clearance of iron from the body is dependent on the body’s need for iron, iron storage status and the demand for body metabolic processes. A small amount of iron is eliminated in the urine.

Route of administration – Though the IM route is a safer alternative to the IV route, intramuscular administration of iron are painful and causes permanent discolouration of the skin and gluteal sarcomas. So the preferred route of administration is either intravenous or by infusion.

Dose calculation - Dose (mg of iron) = [(a-b) x c x 2.4] + 500mg*

Where: a = target haemoglobin (g/dl)
    b = actual haemoglobin (g/dl)
    c = body weight (kg) to a maximum of 90kg

* The additional 500mg is required to replace the iron stores and is applicable to patients with a body weight of 35kg or more.

PARENTERAL IRON PREPARATIONS

1. IRON DEXTRAN

Iron dextran is a colloidal solution of ferric oxyhydroxide complexed with polymerized dextran which became available in the 1950s. Following parenteral administration the full process of release of iron from the dextran complex to its delivery to the bone marrow takes several months. The absolute reticulocyte count increases within 7 days and favourable hemoglobin responses occur within 1–2 weeks of iron dextran administration. Iron dextran is the only parenteral iron product that can also be administered by the intramuscular route. One of the advantages of iron dextran is the ability to infuse the patient’s total iron requirement in a single administration (total-dose infusion). Thus clinicians can conveniently treat patients in a single hospital or clinic visit with this product. However, this method has been associated with anaphylactic reactions and a higher incidence of adverse events. Delayed reactions of hypotension, arthralgias, myalgias, malaise, abdominal pain, nausea, and vomiting have also occurred following total dose infusion. Patients should be monitored for adverse effects for 1 hr after a dose. However with the availability of newer, safer parenteral iron therapy choices the use of this preparation is obsolete at present.

2. SODIUM FERRIC GLUCONATE COMPLEX IN SUCROSE (SFGC)

Sodium ferric gluconate complex in sucrose was approved by the FDA in February 1999. The molecular weight of ferric gluconate is approximately 350,000 daltons. This has replaced iron dextran as the preferred IV iron. But on the other hand it has a fast degradation kinetics which causes faster and direct release of iron from its complex, to the plasma proteins resulting in oversaturation of the transferrin binding sites as compared to other preparations. Hence the free iron released into the plasma after saturation of transferrin may induce acute endothelial cell injury and can cause a transient capillary leak syndrome. Thus the rate of administration should not exceed 12.5 mg/min.

A double-blinded study which has evaluated the adverse drug reactions to sodium ferric gluconate suggests that ferric gluconate can be safely administered to patients who are hypersensitive to iron dextran. Studies have also demonstrated safe
administration of ferric gluconate to patients who had past histories of severe reactions to iron dextran. Doses of 250 mg of ferric gluconate intravenously over 1 hr have been reported to be safe and well tolerated. Thus it has the following advantages:
- No test dose is required
- Can be safely administered as an IV push (12.5 mg/min) or by IV infusion over 1 hour (diluted in 100 mL of 0.9% sodium chloride)
- Can be administered anytime during hemodialysis as it is not dialysable.
- It allows for accurate measurements of iron parameters without interrupting weekly therapy

3. IRON SUCROSE INJECTION

It is an aqueous, complex of polynuclear iron (III)-hydroxide in sucrose with a molecular weight of approximately 34,000 to 60,000 daltons and a proposed structural formula of \([\text{Na}_2\text{Fe}_5\text{O}_8\text{(OH)} \cdot 3\text{(H}_2\text{O})\]n \(\cdot \text{m(C}_{22}\text{H}_{44}\text{O}_{11})\) where: n is the degree of iron polymerization and m is the number of sucrose molecules associated with the iron (III)-hydroxide. It was approved by the FDA in November 2000.

Each ml contains 20 mg elemental iron as iron sucrose in water for injection. The product contains no preservatives. The osmolarity of the injection is 1,250 m osmol/L.

Iron sucrose is dissociated into iron and sucrose by the reticuloendothelial system and iron is transferred from the blood to a bone marrow. It is administered by intravenous injection or infusion and has a medium degradation kinetics with partial uptake of released iron by plasma proteins and to the RES.

- Test dose not required
- Does not over saturate free iron
- Does not cause endothelial injury unlike SFGC
- Significant increase in Hb level
- Non dialysable

The recommended schedule is to administer 100 mg intravenously over 5 min, 1–3 times weekly until 1,000 mg has been administered. The rate of administration should not exceed 20 mg per minute. This preparation is considered to be the safest among all the parenteral preparations of iron. But cases of severe fatal, allergic reactions with collapse has also been reported with this product.

This drug belongs to FDA pregnancy category B which means that it is unknown whether iron sucrose will harm the foetus or pass into the breast milk. So caution must be exercised while prescribing to pregnant and lactating patients.

4. FERUMOXYTOL

Ferumoxytol is a novel, semisynthetic, super paramagnetic iron oxide nanoparticle that is recommended to be administered intravenously. It is in the form of a bioactive iron core encapsulated by a stabilizing low molecular weight carbohydrate shell which is made up of a poly glucose sorbitol carboxy methyl ether. This shell helps to isolate the bioactive iron from plasma until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow where the iron is released from the iron-carbohydrate complex within vesicles in the macrophages and then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to the erythroid precursor cells for final incorporation into hemoglobin.

Chemically Ferumoxytol is \(\text{Fe}_{5874}\text{O}_{8752}\cdot\text{C}_{11719}\text{H}_{18682}\text{O}_{9933}\text{Na}_{414}\) with a molecular weight of 750 kDa. It is a black to reddish brown liquid, which is marketed in single use vials containing a total of 510 mg of elemental iron. It is isotonic with a pH of 6 to 8 and with an osmolality of 270–330 mOsm/kg. The injection is an aqueous colloidal product with the particle size of 17–31 nm in diameter, that is formulated with mannitol and in vitro data suggest that it contains less free iron as compared to the other available IV iron preparations. It is perhaps these physicochemical characteristics that permit the rapid administration of larger doses of ferumoxytol as compared with the currently available intravenous iron preparations. Furthermore, because the molecular weight of ferumoxytol is above the permeability cut off of standard haemodialysis membranes, it is not removed from plasma by dialysis and can therefore be administered any time during the haemodialysis procedure (not dialysable).

5. FERRIC CARBOXYMALTOSE

Ferric carboxymaltose is a novel dextran-free...
iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell, designed for controlled delivery of iron to the cells of the reticuloendothelial system. As it is a strong complex, there is a slow release of iron from the complex, to the iron-binding proteins ferritin and transferrin and hence there is a minimal risk of release of large amounts of ionic iron in the serum, which does not trigger immunogenic reactions.

It can be administered in high doses of up to 1000 mg of iron. Repeated weekly administration of ferric carboxymaltose does not result in accumulation of transferrin iron in patients with iron-deficiency anaemia. It rapidly improves haemoglobin levels and replenishes the depleted iron stores in various populations of patients with iron-deficiency anaemia, including those with inflammatory bowel disease, heavy uterine bleeding, postpartum iron-deficiency anaemia or chronic kidney disease. It was well tolerated in clinical trials. Ferric carboxymaltose is, therefore, an effective option in the treatment of iron-deficiency anaemia in patients for whom oral iron preparations are ineffective or cannot be administered. The incidence of drug-related adverse events in patients receiving intravenous ferric carboxymaltose is generally similar to that in patients receiving oral ferrous sulfate. Rapid intravenous infusion of iron polymaltose is well accepted by patients, reduces costs and saves time compared to conventional protocols and is associated with only minor adverse events, where as the older i.v. iron formulations have their own limitations, including the potential for immunogenic reactions induced by dextran molecules (iron dextran), dose limitations, a slow rate of administration (to prevent acute, labile iron-induced toxicity and vasoactive reactions) and the compulsory requirement for a test dose.

6.IRON ISOMALTOSIDE
This is the newest among all agents which was approved in 2009 and is still undergoing clinical trials. It contains iron in a strongly bound form which enables a controlled and slow release of bioavailable iron to iron binding proteins with minimal free iron. Results from ongoing clinical trials suggest that efficacy was consistent with established guidelines for CKD, no observed serious adverse events and no requirement for a test dose.

SAFETY OF PARENTERAL IRON
1. General-Nausea, abdominal pain, constipation, diarrhoea, injection site reactions (pain, superficial phlebitis), metallic taste, headache, dizziness and rash may occur with all IV preparations with an incidence of 1%-3%. Other effects include urticaria, rashes, itching, nausea and shivering.

2. Allergic and anaphylactic reactions-Anaphylaxis may occur with iron dextran, probably due to preformed dextran antibodies. They usually occur within the first few minutes of administration and are generally characterised by the sudden onset of respiratory difficulty and/or cardiovascular collapse.

However the cause of milder anapylactoid reactions which are a characteristic of all intravenous iron preparations may be due to too much of iron administered too rapidly. According to data from the FDA during 2001-2003, the total number of reported parenteral iron-related adverse drug events was 1141 amongst approximately 30 million doses administered, with 11 deaths amounting to seven with iron dextran, three with iron gluconate and one with iron sucrose.

The absolute rates of life-threatening adverse events were 0.6, 0.9 and 3.3 per million for iron sucrose, sodium ferric gluconate complex, iron dextran respectively. Post-marketing data submitted to regulatory agencies reported hypersensitivity rates for iron sucrose comparable to ferric gluconate at 2.6 episodes per million doses.

3.IV iron and infection—Elemental iron a pro-oxidant is an essential growth factor for bacteria, has been shown to cause sepsis in experimental animals and hence can exacerbate sepsis. So it has been suggested that patients with iron overload are theoretically at an increased risk of infection. Furthermore iron supplement may inhibit the defence mechanisms of polymorphonuclear leukocytes. Nevertheless, despite the absence of definitive clinical data, it seems sensible to avoid IV iron administration in the setting of an acute infection.

4.IV iron and oxidant damage-Following injections of IV iron there is some release of free iron into the circulation. This free iron when comes in contact with the tissues directly causes oxidative damage to the DNA, proteins and lipids and so plays
a role in oxidative stress, subsequent inflammation, and the propensity for accelerated atherogenesis. However, available evidence relating IV iron administration to atherogenesis is indirect, and there is little evidence that IV iron adversely affects survival in patients with dialysis-dependent CKD.

CURRENT RECOMMENDATIONS FOR THERAPY
1. For patients intolerant of iron dextran, ferric gluconate and iron sucrose offer safe and effective alternatives, although their costs are substantially higher and multiple infusions are necessary to totally replete iron stores with these products.

2. For ferric gluconate and iron sucrose, the package insert guidelines should be followed regarding total dose administered per infusion. Exceeding dosages or infusion rates increases the incidence of adverse events.

3. Transferrin saturation and serum ferritin measurements are useful in deciding on the frequency of repeat parenteral iron infusions except in treating “functional iron deficiency.”

4. Appropriate use of parenteral iron will eliminate the necessity for transfusing red blood cells in most patients with iron-deficiency anemia.

5. The novel ferric carboxymaltase designed for administering high doses with minimum side effects is the most promising amongst all.

INDICATIONS OF PARENTERAL IRON
1. Renal causes of anaemia
The primary causative factor in the anaemia associated with renal disease is the decreased production of erythropoietin (EPO). However adequate iron is critical for optimal response to EPO which cannot be achieved by oral supplementation alone.

2. Post operative haemorrhage
Many patients are iron deficient pre operatively due to chronic gastrointestinal or genitourinary blood loss. Parenteral iron therapy may have a role in these patients as iron stores can be replenished rapidly, particularly when there is intolerance or lack of response to oral iron. In many cases the use of oral iron post operatively is adequate. Parenteral iron replenishes depleted iron stores rapidly and has been shown to allow a reduction in post operative blood transfusion.

3. Iron deficiency during pregnancy
Increasing severity of anaemia during pregnancy is associated with a higher risk of pre-eclampsia, pyelonephritis and peripartum bleeding as well as premature delivery, low birth weight and placental insufficiency. The absorption of oral iron is limited in pregnancy and is often associated with gastrointestinal side effects. Parenteral iron is a safer and more cost effective way of treating iron deficiency in pregnancy in those women who are unable to tolerate or who fail to respond to oral iron, than transfusion. But parenteral iron is contraindicated in the first trimester of pregnancy.

4. Postpartum anaemia
Up to 30% of women in the postpartum period are affected by anaemia with a haemoglobin (Hb) level of less than 10 g/dl, and about 10% by more severe anaemia with a Hb of less than 8 g/dl. The main cause for this is iron deficiency secondary to iron supplied to the foetus during pregnancy and blood loss during and after birth. Oral iron is often all that is needed to replenish iron stores during this period. However parenteral iron should be considered before allogenic blood transfusion in severely iron deficient patients.

5. Patients with inflammatory bowel disease (IBD)
15% of patients with IBD are anaemic (Hb less than 10.5 g/dl). This anaemia is a combination of anaemia of chronic disease and iron deficiency. Iron deficiency results mainly from blood loss but iron absorption is also often impaired and cannot be overcome with oral iron which may exacerbate symptoms. Parenteral iron should be considered before allogenic blood transfusion.

6. Chronic blood loss
Occasionally patients with chronic blood loss are dependent on regular blood transfusions as the source of bleeding is not apparent, they are not fit for a corrective procedure. These patients are chronically iron deficient. One unit of blood contains 250 micrograms of available iron and will not replace iron stores even when the haemoglobin is corrected. For this reason all patients with chronic blood loss who
require transfusions should be treated with iron replacement.

**CONTRAINDICATIONS**

The use of parenteral iron is contraindicated in:

1. Non iron deficiency anaemia - haemolytic anaemias, thalassaemia, sickle cell disease.
2. Iron overload or disturbances in utilisation of iron (eg: haemochromatosis, haemosiderosis).
3. History of hypersensitivity to parenteral iron or excipients.
4. History of asthma, eczema or anaphylactic reactions, as these patients are more likely to have allergic reactions.
5. Decompensated liver cirrhosis or hepatitis and any infective states as parenteral iron may exacerbate bacterial or viral infections.
6. Acute renal failure.
7. First trimester of pregnancy.

**SPECIAL PRECAUTIONS DURING THERAPY**

1. In the event of a serious anaphylactic reaction, appropriate facilities for resuscitation and medical support must be available.
2. Mild allergic reactions should be managed by stopping the intravenous iron and administering antihistaminics.
3. Hypotensive episodes may occur if the iron is administered too rapidly. Patients with low iron binding capacity and/or folic acid deficiency are at particular risk.
4. These preparations should only be administered by qualified nursing staff or medical staff and patients to be observed closely during and post infusion.
5. Large doses of iron dextran (5ml or more) have been reported to give a brown colour to serum from a blood sample drawn four hours after administration.

**CONCLUSION**

The availability of new parenteral iron products combined with expanding uses for parenteral iron makes parenteral iron therapy options a practical topic for hematology–oncology physicians. Oral iron is usually a suboptimal choice for iron replacement therapy in many patients from the point of efficacy, safety, and tolerability. Drug cost may also be a consideration in choosing parenteral iron products. Thus parenteral preparations of iron offers patients across the continuum of anaemia, a new paradigm for the treatment.

**REFERENCES**

Cholestatic Liver Disease – Diagnosis & Management

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Cholestasis (showing of bile flow) may be acute or chronic and affect any age group. In infants and children the causes often are congenital or inherited and as a result of improved management some affected children now survive to adulthood. Although jaundice is a hallmark of cholestasis it may be absent, particularly in adults with chronic cholestatic liver disease most of whom are entirely asymptomatic. A detailed history and physical examination are crucial to the diagnosis and noninvasive radiologic tests (ultrasound, computerized tomography scan and magnetic resonance cholangiography) greatly facilitate diagnosis, particularly when the cause is extrahepatic. Only if sufficient portal tracts (> 10) are present on liver biopsy examination, this test can reliably evaluate damage to the small bile ducts. Therapy should address both the cause and the consequences of retained bile acids within the liver and diminished delivery of bile to the gastrointestinal tract. Therapies should address symptoms, mostly pruritus and prevention, particularly osteoporosis and osteomalacia. Portal hypertension can be an early event in chronic cholestatic liver disease, sometimes occurring before the development of cirrhosis. Ursodeoxycholic acid improves the biochemical markers of cholestasis regardless of cause and may delay liver disease progression; only liver transplant is potentially curative.

The term cholestasis is Greek in origin, meaning bile stop page. In its most overt form, cholestasis presents to the clinician as jaundice. However, jaundice is only the tip of the iceberg of cholestatic liver disease. The introduction of screening blood work has allowed us to appreciate that much chronic cholestatic liver disease is anicteric. If symptoms are present, generalized pruritus without a skin rash predominates. Those with no symptoms generally are identified at a time when routine laboratory tests are being performed or during a work-up for another disease when an increase is noted in the level of serum alkaline phosphatase and / or \( \gamma \)-glutamyltranspeptidase (GGT). The early stages of a cholangiopathy caused by, for instance, primary biliary cirrhosis (PBC), may be identified on liver histology in individuals who have entirely normal serum biochemical tests but who test positive for anti mitochondrial antibodies (AMA) 1. Thus, the scope of cholestatic liver disease is much greater than one would at first appreciate.

Approach to Cholestasis

The first approach is always the history, which often is very pertinent in both acute and chronic cholestasis. Jaundice is confined predominantly to those with acute or acute-chronic cholestasis because end-stage chronic disease rarely is seen because liver transplant supervenes. A thorough drug history is imperative. Any medications taken within 6 weeks of presentation may be incriminated and only one dose may be sufficient to initiate disease, but a 1-time medication often is forgotten (eg, a benzodiazepine borrowed from a friend to facilitate sleep on a red-eye airplane ride). It may be impossible to identify the specific agent, such as in a herbal remedy mixture. The liver biopsy specimen in Figure 1 was from a woman whose jaundice resolved once it was realized she was drinking a new herbal tea. Few women consider oral contraceptives a medication, and although they rarely by themselves induce clinical manifestations of cholestasis, except in those who are heterozygotes for MDR3 deficiency, they not infrequently tip the balance from an acute anicteric hepatitis to a severely pruritic, acute cholestatic hepatitis (eg, in a teenager with infectious mononucleosis). MDR3 is the phosphatidylcholine translocator across the hepatocyte canalicular membrane. Similarly, a young

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man wanting to build up his muscle bulk may deny any over-the-counter muscle builders—those containing androgen-like substances may cause cholestasis. Probably the most common in-hospital/intensive care unit consultation request for jaundice is in the postoperative patient who is on TPN and is septic; in this situation it is hard to know whether it is the TPN and/or the sepsis that is causing the cholestasis. Cholestasis secondary to either TPN or sepsis may be prolonged and, albeit rare, may lead to progressive liver disease.

If the surgery has been in the region of the biliary system, inadvertent damage to the bile duct also needs to be considered.

Having exhausted the personal history, the family history also is very pertinent. Jacquemin et al., a French pediatrician, noted that there were many women in the family of a young child with progressive familial intrahepatic cholestasis (type 3) who had suffered from intrahepatic cholestasis of pregnancy (ICP). Genetic testing subsequently revealed that the heterozygote state of the MDR3 mutation responsible for PFIC type 3 may be associated with a number of cholestatic conditions that include ICP, intraductal cholesterol gallstones, and as previously mentioned, the propensity to develop jaundice after estrogen therapy. Another astute clinician traced back to prior generations of a young man with idiopathic ductopenia and found several family members with biliary cirrhosis and/or hepatic tumors. However, to date, no specific genetic mutation for this form of adult-onset ductopenia has been described. These clinical observations serve to remind us of the great value of thorough history taking.

The physical signs of cholestasis are most evident in young children in whom the cholestasis often is congenital and severe. Now that transplantation has become so successful for most of these inherited causes of cholestasis, the grossly disfiguring, long-term physical effects (eg, generalized tuberous xanthomata and green teeth) rarely are seen. The most obvious physical signs of cholestasis are scratch marks and shiny nails secondary to persistent scratching. Chronic cholestasis eventually leads to increased skin pigmentation. Xanthelasma, a common feature of PBC in the past, now is less often.

Abbreviations used in this paper: AMA, antimitochondrial antibodies; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane regulator; ERCP, endoscopic, retrograde cholangiopancreatography; GGT, \( \gamma \)-glutamyltranspeptidase; ICP, intrahepatic cholestasis of pregnancy; MDR3, human multidrug resistance gene-3; MRCP, magnetic resonance cholangiopancreatography; MRP, multidrug resistance proteins; PBC, primary biliary cirrhosis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

Typically, the biochemical markers of chronic cholestasis are an increase in the levels of the bile duct enzymes alkaline phosphatase and/or GGT. Although the serum alkaline phosphatase level may be increased in bone disease, gastrointestinal disease, or during pregnancy, the GGT level is almost specific to the liver. Increased serum levels of these enzymes likely are caused by the damaging effect of high concentrations of bile acids on intracellular and biliary membranes. The measurement of fasting serum bile acids is the most sensitive test for cholestasis, but this test is not generally available. In the early phase of cholestasis, observed particularly well during intrahepatic cholestasis in pregnancy, the serum aminotransferase levels are more likely than the alkaline phosphatase level to be increased. The serum bilirubin level in its conjugated form may not be increased in cholestasis. Gilbert syndrome, which gives rise to an unconjugated hyperbilirubinemia, affects 7% of the adult population and accentuates the hyperbilirubinemia of any underlying liver disease and thus may confuse the picture if the bilirubin is not fractionated. An infiltrative disorder of the liver may be associated with a very similar biochemical pattern to that of cholestasis (eg, amyloidosis, fatty liver and lymphoma). Sometimes serum levels of aminotransferases may be very high (\( > 1000 \text{IU} / \text{L} \)) and fluctuate despite obvious cholestasis this pattern is typical of biliary obstruction caused by intraductal stones. An isolated increase in the serum GGT level may be owing to enzyme induction alone such as after alcohol consumption or in those who need to take anti-epileptics or other drugs that act as enzyme inducers.
Further Investigations in Cholestasis

Ultrasoundography revolutionized the diagnostic work-up of apparent cholestasis because it could clearly distinguish intrahepatic vs extrahepatic biliary tract disease. However, although ultrasound is an excellent technique, it is very technician-and interpreter-dependent, whereas computerized tomography scan is less technician-dependent. For this reason, computerized tomography is frequently the test of first choice, even though it is not as good as ultrasonography at delineating the biliary tree.

If the bile ducts are not dilated in an individual whose history suggests an extrahepatic cause for their cholestasis, clinical judgment should be pursued and another procedure or repeat ultrasound should be performed within the next 2 weeks. This may be seen with very early pancreatic carcinoma or an ampullary carcinoma. In patients who have just passed a common duct stone there nearly always will be stones remaining in the gall bladder, even though the duct system is no longer dilated.

Extrahepatic biliary obstruction may be caused by stones, tumors, cysts, parasites or stricture(s) of the biliary tree. Further work-up of dilated ducts depends on the presumed cause. If in doubt as to whether a therapeutic maneuver will solve the problem, it is probably wise to perform magnetic resonance cholangiography next, if only to avoid an invasive procedure that may not be needed, for example, in a patient with anicteric primary sclerosing cholangitis (PSC).

Visualization of the Bile Ducts: Endoscopic Retrograde Cholangiopancreatography Versus Magnetic Resonance Cholangiopancreatography

The gold standard for visualizing the extrahepatic biliary system is endoscopic retrograde cholangiography, but even in good hands it carries a significant complication rate. Around 3%-5% will develop some degree of pancreatitis. In individuals in whom the need for a therapeutic maneuver is not anticipated, magnetic resonance cholangiopancreatography (MRCP) is the safer option. The sensitivity and specificity of MRCP compared with endoscopic retrograde cholangiopancreatography (ERCP) have been best evaluated in patients with PSC. Although many would argue about which is the best test to delineate the second- and third-generation intrahepatic bile ducts, few would argue that ERCP gives a clearer picture of the pancreatic portion of the biliary tree. The negative predictive value for MRCP is 94% and positive predictive value ranges between 85% and 94% when compared with ERCP.

One situation in which it is far safer to use MRCP than ERCP to delineate the biliary tree is when a portal biliopathy (which may look very similar to PSC) secondary to portal vein thrombosis is present. Intraductal stones also may be seen and these patients not infrequently present with cholangitis. Septic cholangitis with multiple liver abscesses also may be confused with PSC, but the changes resolve completely after appropriate antibiotic therapy. Similarly, viral or parasitic cholangitis, formally a common feature of late-stage acquired immune deficiency syndrome, can look like PSC. The biliary tree may return to normal if successful eradication of the causative infection can be achieved. Now rare in North America, acquired immune deficiency syndrome cholangiopathy remains common in the developing world where a clinical diagnosis is generally all that is available. Autoimmune pancreatitis also is associated with a picture that may be confused radiologically with PSC, although it particularly affects the lower end of the common bile duct-also too may resolve with corticosteroids.

Intrahepatic Cholestasis (Physiology and Pathophysiology)

Both inherited and acquired liver disease may cause intrahepatic cholestasis. It is the identification of the may be genetic causes so prevalent in the pediatric population that has facilitated our understanding of intrahepatic bile flow. Intrahepatic cholestasis may be caused by disease at the subcellular level or by abnormalities of canalicular transport or mortility or from damage to small biliary ductules. Cloning of the canalicular transporters in the early 1990s identified several different mutations that now have been shown to be responsible for many of the inherited cholestatic syndromes of childhood. Antibodies now are available that allow visualization of the distribution of these transporters in liver tissue by using immunohistochemistry.

Bile acids synthesized from cholesterol within hepatocytes are transported across the cell in vesicles...
and shunted along microtubules to the canalicular membrane. Thus, any hepatic injury that damages these intracellular organelles will promote cholestasis—alcohol is the most common of such toxins. At the canalicular membrane bile salts predominately are transported across the canaliculus by the bile salt excretory pump, whereas the phosphotidylcholine necessary for biliary micelle formation is flipped across the canalicular membrane by the MDR3 transporter. Bilirubin and organic anions predominantly are transported by the membrane transporter MRP2, and cholesterol uses yet other transporters to gain access to the bile.

There are other mechanisms that if interrupted may cause cholestasis at the level of the canaliculus. The canaliculus, a tube with a closed end, requires a mechanism that propels its luminal contents distally. This is achieved by intermittent contraction of actin-myosin strands that surround each canaliculus. Paralysis of this actin-myosin network causes marked dilation of canaliculi, described by hepatopathologists as bland cholestasis. Recently studies have identified the absence of villin protein in the liver of some children with gross canalicular abnormalities. The lipid content of the canalicular membrane if altered will change its motility and can cause bland cholestasis (eg, with estrogens). If the tight junctions that bind the 2 opposing canalicular membranes of adjacent hepatocytes are not held in close apposition, this will allow leakage of canalicular contents back into the sinusoid. A missense mutation of the tight junction protein causes just this. However, far less rare causes of leaky tight junctions are distal obstruction and / or ductopenia. Both in children and particularly in adults, the myriad of causes of ductopenia are the most common causes of chronic intrahepatic cholestasis in general gastroenterologic practice.

**Cholestasis in Children**

There are many other inherited causes of cholestasis that fortunately are very rare; such as the zinc-storage disorder described in children of Ojibwe origin. This causes a marked cholestatic jaundice and liver failure found to recur after liver transplantation. The exact cause for this storage disorder remains unknown. Another chronic cholestatic disease of North American Indian children of Cree extraction reported from Northern Quebec has been shown to be caused by a mutation of the cirrh1 gene. This causes marked jaundice in the neonate, which gradually fades by 1 year but then is followed by progressive cholestasis and the development of biliary cirrhosis, leading to the need for liver transplantation in early childhood. This is caused by a missense mutation of CIRR1A. The normal function of this gene is not known.

Much better understood are the progressive familial intrahepatic cholestatic conditions PFIC1, 2 and 3. These are caused by mutations of the ATP8B1 transporter, the ABCB4-MDR3 transporter, respectively. A slightly modified polymorphism of the gene mutation responsible for PFIC 1 or Bylers syndrome is responsible for benign recurrent intrahepatic cholestasis, which may not become symptomatic until adulthood. This is a non-progressive form of remitting and relapsing cholestasis whereas Bylers syndrome in childhood leads to progressive liver disease. This same transporter also is present in pancreatic cells, the ileum, and colon, so children with Bylers syndrome, even after liver transplantation, may be left with diarrhea. The bile salt excretory pump transporter, however is present only on the canalicular membrane, thus mutation of this gene causes only chronic cholestasis (PFIC2). Neither PFIC 1 nor 2 are associated with any damage to the canalicular membrane or bile ducts and hence affected children have normal levels of GGT despite being cholestatic, whereas as PFIC3 causes severe damage to the canaliculus and intrahepatic bile ducts and hence the GGT can be very high in affected children. This damage is because PFIC3 is caused by a mutation in the MDR3 gene responsible for transporting phosphotidylcholine across the canaliculus. Without phosphotidylcholine the bile acids in the canaliculus do not form micelles. Hydrophobic bile acids destroy biliary membranes if not embedded in micelles. Subsequent crystallization of cholesterol and the formation of tiny stones in the canaliculus cause considerable hepatocyte damage, requiring the need for liver transplantation.

Other genetic defects may be responsible for damage to the interlobular bile ducts, causing hypoplastic ducts. Alagille syndrome is caused by a mutation in the JAGI gene. This is an autosomal-dominant condition that affects many structures (eg, bile ducts, heart, face, skeleton, kidney and eye). The gene is a ligand for the
notch-family receptor. The notch signaling pathway is very important in development. Clinical presentation of this disease varies greatly and sometimes it may not even be recognized until early adulthood, although most often affected children are jaundices as babies and are noticed to have a prominent forehead, a pointed chin, low-set ears and hypertelorism.

Children with cystic fibrosis caused by mutation of the CFTR gene (the gene product is located on all epithelial cells, thus biliary epithelial cells are involved) now are managed so successfully in terms of their lung disease that the biliary complications of this very common inherited disease are prominent in individuals surviving into adulthood. In cystic fibrosis the bile ducts become plugged with viscous material that initiates an inflammatory condition of the intrahepatic bile ducts leading to focal biliary cirrhosis.

Many of the intrahepatic conditions that cause cholestasis in adults (described later) also may affect children, the most common being PSC, which in children frequently overlaps with autoimmune hepatitis.

### Cholestasis in Adults

Prescription drugs, over the counter drugs and herbal remedies are the most common causes of acute cholestasis in adults, which may sometimes progress to a chronic vanishing bile duct syndrome. Thus, drugs may induce cholestasis at the subcellular, the canalicular or the ductal level.

ICP is also a very heterogenous condition, therefore different biochemical patterns may be observed. It has long been recognized that there is genetic component to ICP because the disease is much more common in Chile and in Scandinavia. Nevertheless, because the incidence of this third-trimester complication of pregnancy is diminishing, there also must be external factors that influence its clinical presentation. The biochemical abnormalities seen in ICP are predominantly high serum transaminase levels and the GGT levels may or may not be increased. However, very high levels of bile acids are present in all cases.8 The condition responds dramatically to treatment with ursodeoxycholic acid by alleviating the pruritus in the mother and reducing the chance of prematurity or stillbirth of the fetus.

### Table 1. CAUSES OF Vanishing Bile Duct Syndrome (Ductopenia)

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Alagille syndrome (and nonsyndromatic)</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Duct plate abnormalities</td>
</tr>
<tr>
<td></td>
<td>PFIC-3</td>
</tr>
<tr>
<td>Infectious</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>Biliary sepsis</td>
</tr>
<tr>
<td>Parasites</td>
<td>Idiopathic malignant</td>
</tr>
<tr>
<td></td>
<td>Cholangiocarcinoma</td>
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<tr>
<td></td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td></td>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Vascular</td>
<td>HA thrombosis</td>
</tr>
<tr>
<td></td>
<td>PNH</td>
</tr>
<tr>
<td></td>
<td>Portal biliopathy</td>
</tr>
<tr>
<td></td>
<td>Vasculitis (PAN)</td>
</tr>
<tr>
<td></td>
<td>Henoch-Schonlein (surgical-localized)</td>
</tr>
<tr>
<td>Toxic</td>
<td>Drugs (after cholestatic hepatitis)</td>
</tr>
<tr>
<td></td>
<td>Formaldehyde</td>
</tr>
<tr>
<td></td>
<td>Floxuridine</td>
</tr>
<tr>
<td>Immune</td>
<td>PBC</td>
</tr>
<tr>
<td></td>
<td>PSC</td>
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<tr>
<td></td>
<td>Sarcoi d</td>
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<tr>
<td></td>
<td>Graft vs host disease</td>
</tr>
<tr>
<td></td>
<td>Allograft rejection</td>
</tr>
<tr>
<td></td>
<td>Overlap autoimmune hepatitis/PSC</td>
</tr>
</tbody>
</table>

In adults, the vanishing bile duct syndrome is the most common cause of chronic intrahepatic cholestasis (Table 1). The diagnosis can be made only by liver biopsy examination and at least 10 portal tracts need to be present, with at least half of them with absent ducts, before a confident diagnosis of vanishing bile duct syndrome can be made. Inherited causes of vanishing bile duct syndrome already have been discussed. Acquired causes include immune-mediated, infectious, malignant, vascular, toxic (including drug-induced), and idiopathic. The most common are immune-mediated, such as PBC, PSC, sarcoidosis,
graft-versus-host disease and allograft rejection. The diagnostic hallmark for PBC, namely the AMA, facilitates recognition of this disease. But there is an entity sample called AMA-negative PBC, such cases in all other ways resemble AMA-positive PBC. Only in those who test negative for AMA is it necessary to show a normal biliary tree via MRCP (or ERCP), to be sure the individual does not have PSC. A beaded appearance caused by structuring and dilatation of the extrahepatic and/or intrahepatic biliary system is the typical pattern of PSC, but there are individuals who manifest cholestasis for many years (even with concomitant inflammatory bowel disease) who remain with a radiologically normal hepatic biliary tree for a long time before overt PSC is seen. Sometimes liver biopsy examination will show typical lesions with onion-skin fibrosis of the small intralobular bile ducts despite normal large ducts. Such cases have been described as having small-duct PSC.

If fibrotic duct lesions typical of PSC are not seen, yet there is a cholangiopathy visible on liver histology despite normal cholangiographic appearances of the larger ducts and AMA are undetectable, this poses a diagnostic dilemma. Fortunately, such unknown cholangiopathies are rare. An overlap of autoimmune hepatitis and PSC is particularly common in children, but may affect adults. There is no evidence to suggest that the outcome of such overlap syndromes is any different from typical PSC, but survival is certainly worse than that of typical autoimmune hepatitis.

**Consequences of Cholestasis and its Treatment**

Treatment both of the consequences of the retention of hydrophobic bile acids within the liver and the effects of diminished quantities of bile acid reaching the bowel is necessary. The retention of bile acids within the hepatocyte has a detergent effect on the intracellular membranes and promotes hepatocyte apoptosis and hepatic fibrosis. Retention of the biliary lipids normally excreted in bile causes hypercholesterolemia and xanthoma. Pruritus is is the most frequent complication of bile retention, but the exact cause of pruritus in cholestasis is much debated.

The reduced micellar concentration of intraluminal bile acids that results from stagnant bile flow causes steatorrhea and weight loss as well as vitamins A, D, E and K deficiency. The consequences of diminished bile acids within the bowel are most pronounced in children; nevertheless, the consequences in adults also may be severe.

**Consequences of Cholestasis and its Treatment**

The most prevalent symptom of cholestasis (even if anicteric) is pruritus, a symptom that often is under appreciated by physicians but when severe may cause marked sleep disturbance and sometimes cause the patient to even contemplate suicide. Thus pruritus should never be ignored. The first line of treatment is the anion-exchange resin, the best-known being cholestyramine. This agent often gives rise to gastrointestinal disturbance and is poorly tolerated by some but is effective in 80%. It needs to be taken appropriately (i.e., before and after breakfast and 4 hours from any other oral medication) and taken on a daily basis to prevent pruritus, not just taken when pruritus is present. The second line of therapy is the antibiotic rifampin. This is effective in 50%; its mechanism of action remains unclear. The usual dose is 150mg twice daily. Patients do need to be monitored for the albeit rare complications of hepatitis, hemolytic anemia, and renal dysfunction. As a third line therapy, opioid antagonists, given in very low doses initially and gradually increasing the dose as the patient is able to tolerate the symptoms typical of withdrawal, is very effective but when used chronically may give rise to the chronic pain syndrome. Recently, treatment with the antidepressant Sertraline has been shown to be effective in some individuals with recalcitrant pruritus. Many notice an improvement in pruritus if they are in the sun (without sunblock). In acute severe cholestasis, for example, ICP with severe pruritus, apheresis, or perhaps even MARS, can be used with tremendous relief of symptoms. In those with chronic cholestasis and unremitting pruritus, liver transplantation may be necessary but partial biliary diversion very effectively eliminates the pruritus of chronic cholestasis in children with PFIC who may have severe pruritus but no liver failure, and thus have no need for liver transplantation.

**Consequences of Cholestasis and its Treatment**

Osteomalacia and/or osteoporosis are associated with severe chronic cholestatic liver disease (eg, that caused by PSC and PSC). Osteomalacia is seen only when there is profound icteric cholestasis with inadequate calcium and vitamin D supplementation.
Calcium supplementation also benefits those with osteoporosis, with the addition of bisphosphonates when necessary. In individuals with chronic (even anicteric) cholestatic liver disease, screening for bone mineral density should be routine at diagnosis and every 1 or 2 years.

Portal hypertension in patients with biliary tract disease may occur before the development of cirrhosis, caused by nodular regenerative hyperplasia and thus the usual screening rules with regard to the platelet count do not apply to those with disease of the portal tracts.

Specific Therapies:

Although many of the genetic mutations responsible for the several forms of congenital cholestatic liver disease have been described, gene therapy is still only a hope for the future. There are a few specific therapies for cholestatic liver disease, they include antibiotics for bacterial cholangitis and corticosteroids for autoimmune cholangitis. Nonspecific therapies that promote bile flow - namely hydrophilic bile acids (eg, ursodeoxycholic acid [UDCA]), make physiologic sense. UDCA leads to improved liver biochemistries, liver histology, and perhaps survival (in patients with PBC). The role of UDCA therapy in the management of PSC is uncertain. Although corticosteroid therapy may play a role in very early PBC, steroids given to individuals with more advanced cholestatic liver disease promote severe osteoporosis and must be avoided. In some children with PFIC3, UDCA may reduced damage to bile ducts. Only when UDCA is given to women with ICP does UDCA lead to a decrease in total serum bile acids and loss of pruritis.

When all strategies have failed and the liver is failing or the consequences of chronic cholestasis are refractory to treatment and intolerable (eg, pruritus), then liver transplantation is curative. Individuals given a liver transplant for chronic cholestatic liver disease have an excellent outcome.

References:

INTRODUCTION:

Status Epilepticus is a medical emergency associated with high morbidity and mortality. The etiology varies among the different age groups, being more common at the extremes of ages. The outcome depends to a great extent on the underlying etiology and the presence of additional medical conditions. Outcome also depends on the rapidity of diagnosis and initiation of appropriate therapy. The goals of therapy include rapid termination of clinical and electrical ictal activity, prevention of aspiration pneumonia, and treatment of complications in anticipation. Every hospital needs to manage SE on the basis of established protocols, and an early decision regarding artificial ventilation.

DEFINITION:

SE is defined as “a seizure that persists for a sufficient length of time or is a repeated frequency enough that the recovery between attacks does not occur. This definition is difficult to use in clinical practice because of lack of specific duration and more recent publications have tried to remedy this by defining SE as a seizure that lasts for 20-30 minutes.(1) This time frame is based on an estimate of duration necessary to cause damage to cerebral neurons (1). Therefore an operational definition is that either continuous seizure lasting at least 5 minutes or two or more discrete seizures between which there is incomplete recovery of consciousness (2)

Clinical Features:

The most common potentially and dangerous forms of status epilepticus are described below.

1. Generalized convulsive status epilepticus is the most common form of status epilepticus. Despite treatment, the mortality associated with this type of status epilepticus is 20%-27% (3). After about 30 minutes, generalized convulsive status epilepticus can degenerate to non-convulsive status.

2. Non-convulsive generalized status epilepticus (subtle status epilepticus) is associated with minimal or no motor activity and requires electroencephalography for diagnosis. As many as 25% of cases of status epilepticus are nonconvulsive, and this condition is responsible for 8% of cases of unexplained coma (4). In fact, the most common seizure recorded during electroencephalographic monitoring of patients with altered mental status is non-convulsive (5). Non-convulsive seizures are often refractory to therapy, and are associated with a 65% mortality (3).

3. Refractory status epilepticus is a seizure that lasts more than 1 or 2 hours or is refractory to therapy with 2 or 3 anticonvulsant agents (6). Almost one-third of cases of status epilepticus are refractory (6).

4. Myoclonic status epilepticus can occur in up to one third of patients with persistent coma following out-of-hospital cardiac arrest. This condition is characterized by sound-induced or spontaneous irregular and repetitive movements of the face and extremities (7). When it persists for 24 hours following resuscitation, myoclonic status is a sign of devastating neurological damage.

Etiologies:

New-onset seizures can be the result of a drug intoxication (e.g. Theophylline), drug withdrawal (e.g., Ethanol), infections (e.g., meningoencephalities,
abscess), head trauma, ischemic injury (e.g., focal or diffuse), space-occupying lesions (e.g., tumor or hemorrhage), or systemic metabolic derangements (e.g., hepatic or uremic encephalopathy, sepsis, hypoglycemia, hyponatremia, or hypocalcemia). In one survey of new-onset seizures in ICU patients, the most common causes were sedative or opioid withdrawal (33%), severe metabolic abnormalities (33%), and drug intoxication (15%). The drugs most likely to cause seizures in ICU patients are listed in Table 1.

**TABLE-1**

<table>
<thead>
<tr>
<th>Drug Intoxication</th>
<th>Drug Withdrawal</th>
</tr>
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<tbody>
<tr>
<td>Pharmaceuticals:</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Imipenem</td>
<td>Ethanol</td>
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<tr>
<td>Isoniazid</td>
<td>Opiates</td>
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<tr>
<td>Lidocaine</td>
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<tr>
<td>Meperidine</td>
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<td>Penicillins</td>
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<tr>
<td>Theophylline</td>
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<tr>
<td>Tricyclics</td>
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<tr>
<td>Drugs of Abuse:</td>
<td></td>
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<tr>
<td>Amphetamines</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
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<tr>
<td>Phencyclidine</td>
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</tbody>
</table>


**Pathophysiology:**

Isolated seizures occur due to the generation and spread of abnormal electrical activity among neuronal networks; the networks are probably abnormal to start with. But several mechanisms come into play with the onset of a seizure, which work to terminate the attack. SE is believed to be due to the failure of these seizure abortive mechanisms.

It is now believed that loss of GABA-mediated inhibitory synaptic transmission in the hippocampus is critical for the emergence of SE, and excitatory synaptic transmission is important in sustaining SE. Experimental studies in rats have shown that the sensitivity of GABA-A receptor to benzodiazepines, and other allosteric modulators decreases over time as SE continues. This may be one of the reasons for the failure of the inhibitory mechanisms.

Prolonged seizures produce CNS damage. The physiologic consequences of SE, such as elevation of body temperature, transient metabolic acidosis, and elevation of hormonal concentrations (such as epinephrine in the arrhythmic range) add to the injury.

Marked rise in pressure in the systemic as well as the pulmonary circulation may have deleterious effects, such as by causing pulmonary edema. Prolonged and repeated seizures themselves cause damage to limbic structures like the hippocampus. This damage is partly due to glutamate-mediated excitotoxicity, and not merely because of increased metabolic demands of repetitive neuronal firing. Continued epileptic activity may lead to relative cerebral hypoxia and hypoglycemia. The seizures compromise cerebral vascular auto-regulation, which in turn compromises hypothalamic autonomic regulation, and intra-cranial hypertension may then supervene. Complications such as cardiovascular collapse, arrhythmias, aspiration pneumonia, acute lung injury, and pulmonary hypertension may further compromise cerebral oxygen delivery. Cerebral and systemic hypoxia and acidosis, hyperthermia, rhabdomyolysis, and DIC may then lead to multiple organ failure and death.
Management

The management of the patient with SE should normally occur at two levels.
1. Management of the seizures themselves.
2. General medical management.

Figure 1 provides the algorithm for the general management of SE presenting to the Emergency Room.

1. Assess and Control Airway.
2. Monitor vital signs (including temperature)
3. Conduct pulse oximetry and monitor cardiac function.
4. Perform rapid blood glucose assay.

↓

Start intravenous infusion

↓

Administer thiamine (100mg)
And glucose (50ml of 50% glucose)

↓

Start anticonvulsant therapy

Take focused history
And examine patient
Known seizure disorder or other Illness ?

Perform laboratory studies.

Complete blood count
Electrolytes and calcium
Arterial blood gas
Renal function
Liver function
Toxicology

Undertake further evaluation to Establish cause

Manage other medical problems.

The patient should be placed in a position to minimize trauma to convulsing limbs from neighbouring hard objects and surfaces. Frequent oro-pharyngeal suctioning may be required. Attempts to prevent tongue bites by placing handkerchiefs and other objects in the mouth between the teeth, have led to choking and death; a towel, folded cylindrically and placed sideways in the mouth may be far safer.

The immediate assessment of breathing and securing the airway is of paramount importance in the actively convulsing patients, as they are highly prone to develop aspiration and all the attendant complications. During the tonic-clonic phase of the convulsion, the patient may stop breathing and become cyanosed; however this is generally short-lasting, and does not create a problem, unless the airway is blocked. Administration of 100% oxygen is usually sufficient,
but the airway patency should be secured with an oral or nasopharyngeal airway tube. If there is respiratory compromise, an emergent intubation may be called for; if neuromuscular blockade is deemed necessary to perform the procedure, then a short-acting agent like 0.1mg/kg of vecuronium should be employed, thereby ensuring that ongoing seizures are not missed by the attending physician.

Alcohol ingestion is a common cause of presentation in the emergency with SE; prompt administration of thiamine is therefore essential, often before it can be ascertained that alcohol has been consumed. Similarly, immediate blood sugar measurement is now routine, and even when initially normal, 100-200ml of 25% glucose are administered in actively convulsing patients, as blood sugar levels tend to fall, and hypoglycemia can add to the complications.

Hyperthermia and metabolic acidosis occur relatively frequently in SE; together with the peripheral blood leucocytosis, they may suggest an infection and lead to the inappropriate use of antibiotics. Later on the patient may actually develop aspiration pneumonia, for which antibiotics may become necessary. On the other hand, the classical symptoms and signs of acute bacterial meningitis may be absent in convulsive SE with fever; a high index of suspicion for acute bacterial meningitis is therefore of paramount importance. The most appropriate management is early parenteral antibiotics and lumbar puncture if there are no contraindications. Metabolic acidosis gets corrected once the seizures are controlled. Hyperthermia should be managed emergently with anti-pyretics and cooling blankets, as continued high fever can have deleterious effects on the central nervous system.

**Control of Seizures : Drug Therapy**

In the management of SE, the response to treatment and the ultimate outcome are very much dependent on the duration of the status before effective anti-epileptic medications are administered. This was amply demonstrated in the study in San Francisco in the 1980s, where the authors found that if the AED was administered within 30 minutes of the onset of SE, the response rate was as high as 80%, whereas in those treated after the 30 minutes period, the response rate fell to 40%. Rapid functional plasticity of GABA\(_A\) receptors has been demonstrated to occur during SE in rats with a substantial reduction of diazepam potency for termination of the seizures, especially as the duration of electrographic seizures increases. (12).

The ideal drug to control status should be easy to administer, should produce the effect immediately, have long-lasting effect, and at the same time should not depress cardio-respiratory function or the consciousness. Benzodiazepines like diazepam and barbiturates carry the risk of respiratory depression and also depress consciousness in a dose-dependant manner. Phenytoin and fosphenytoin can cause hypotension and cardiac arrhythmias if administered too fast; this can be a limiting factor when attempting rapid seizure control, though in practice this is seldom the reason for failing to control seizures. The Figure 2 gives an algorithm for the management of SE in adults and older children that is followed all over the world; the choice of drugs is based on the rapidity of action of the drugs and the duration of action. Lorazepam has an extremely rapid onset of action; in a retrospective analysis comparing the treatment of SE with diazepam and lorazepam, both were found to be equally effective, but there were fewer recurrences with lorazepam, and fewer repeat doses were required. Based on this the authors recommended that lorazepam should be the drug of first choice.

Fig-2- Algorithm for management of status Epilepticus in adults & older children.
LORAZEPAM
(0.1 mg/kg IV at 2 mg/min)

Additional emergency drug therapy may not be required if seizures stop and the
cause of status epilepticus is rapidly corrected.

Seizures continuing

2 Phenytoin 20mg/kg IV at 50mg/min. or
Fosphenytoin 20 mg/kg PE IV at 150 mg/min.

Seizures continuing

3 Phenytoin or Fosphenytoin,
Additional 5-10 mg/kg or 5-10 mg/kg PE

Seizure continuing

Proceed immediately to anaesthesia with propofol or
Midazolam if the patient develops status epilepticus
While in the ICU, has severe systemic disturbances
(e.g. extreme hyperthermia) or has seizures that
Have continued longer than 90 minutes)

4 Phenobarbital
20/mg/kg IV at
50-75mg/min

5 Phenobarbital
(additional 5-10mg/kg IV)

6 Anaesthesia with
Midazolam or Propofol.
Phenytoin has the advantages of the availability of an injectable preparation, and till recently was the only other anti-epileptic drug whose plasma levels could be rapidly brought to the therapeutic range. In addition, it has a long duration of action. In a five-year randomized, double-blind trial comparing the efficacy of lorazepam alone, phenytoin alone, diazepam with phenytoin, and Phenobarbital alone for the treatment of generalized SE, the treatments were equally effective, except that lorazepam alone was more effective than phenytoin alone, when seizures were assessed 20 minutes after the administration began. In the algorithm, lorazepam is followed by Phenytoin if the seizures are not controlled, and this is preferred by neurologists and epileptologists the world over. When the cause of the SE is a reversible one, such as sub-therapeutic drug concentration or an acute metabolic process, then lorazepam alone may be sufficient and obviate the need for phenytoin or Fosphenytoin.

**Pharmacologic Therapy**

**Benzodiazepines**

Intravenous benzodiazepines will terminate 65-80% of convulsive seizures within 2 to 3 minutes. Lorazepam in a dose of 0.1mg/kg IV or diazepam in a dose of 0.15mg/kg IV is equally effective in aborting a generalized seizure. However, the anticonvulsant effects of lorazepam lasts longer than those of diazepam (12-24 hours vs. 15-30 minutes, respectively), so recurrent seizures are less likely following lorazepam. Because of its prolonged effect, lorazepam is the initial agent of choice for treatment of convulsive seizures. If diazepam is used, it should be followed immediately by phenytoin to prevent seizure recurrence.

**Phenytoins**

Intravenous phenytoin has been widely used to treat seizures since 1956. The standard intravenous dose is 20mg / kg in adults; a smaller dose of 15mg/kg is recommended in the elderly. A maximum infusion rate of 50mg/min is advised to reduce the risk for cardiovascular depression (which is due to the drug itself and the propylene glycol diluents used in intravenous preparation). If the initial dose of phenytoin is unsuccessful, additional doses can be given to a total cumulative dose of 30mg/kg. The therapeutic serum level for phenytoin is 10 to 20 microgram/mL.

Phenytoin should not be given in dextrose-containing solutions because it can precipitate, and tissue extravasation must be avoided because the highly alkaline pH of 12 can cause tissue necrosis.

**Fosphenytoin** is a pro-drug that may be preferred to phenytoin because (1) it can be infused faster than phenytoin, (2) it does not contain propylene glycol (which contributes to cardiovascular depression), (3) it is compatible with dextrose-containing solutions, and (4) drug extravasation does not cause skin necrosis (18). Fosphenytoin is rapidly converted to phenytoin (half life is 7-15 minutes), and the therapeutic doses are the same as those recommended for phenytoin. However, the maximum allowable infusion rate for fosphenytoin is 150 mg/min, which is three times faster than phenytoin, so fosphenytoin could produce more rapid suppression of seizures than phenytoin.

**Phenobarbital**

The combination of benzodiazepines and phenytoin will control seizures in 60-90% of cases of convulsive status epilepticus. In refractory cases, intravenous Phenobarbital can be effective when given in a dose of 50-75mg/min. until seizures are controlled or a maximum of 20mg/kg is achieved. The therapeutic serum level for Phenobarbital is 20 to 40microgram/mL. Common side effects include hypotension (usually responsive to IV fluids), respiratory depression, and prolonged sedation (at the higher dose range) Phenobarbital is also the most effective agent available for the initial treatment of nonconvulsive seizures.

**Anticonvulsant hypersensitivity syndrome** is an uncommon (incidence 1:1,000 to 1:10,000) idiosyncratic reaction to phenytoin or Phenobarbital (cross-reactivity is 50%) associated with the triad of fever, rash, and lymphadenopathy. Elevated liver enzymes and lymphocytosis occur in up to two-thirds of cases. Treatment involves immediate withdrawal of the offending agent and seizure control with diazepam at 0.05-0.4mg/kg/hr.

**Treatment of Refractory SE (RSE)**

When SE does not respond to standard treatment with benzodiazepine, phenytoin, and Phenobarbital, then it is considered to be refractory, requiring aggressive management. Patients generally need to be in the intensive care unit, and most require
intubation to prevent aspiration and mechanical ventilation.

This therapy requires a team approach, with the anaesthesiology and intensivist playing vital roles. Infusions with anaesthetic doses of midazolam or propofol are usually required. EEG monitoring is generally necessary, and the aim is suppression of epileptic spikes; the end point is burst-suppression, though occasionally, fall in blood pressure becomes a limiting factor, especially when propofol is used. Midazolam is given in a bolus dose of 0.2 mg/kg slow intravenous push, followed by 0.75 to 10 microgram/kg per minute. Alternatively, propofol at a dose of 1 to 2 mg per kilogram intravenous followed by 2 to 10mg/kg/hr may be used. It directly activates GABA_A receptors. In addition, propofol inhibits the NMDA receptor and modulates calcium influx through slow calcium ion channels. Propofol has a rapid onset of action with a dose-related hypnotic effect; and recovery is rapid even after prolonged use. Propofol decreases cerebral oxygen consumption, reduces intracranial pressure and has potent anti-convulsant properties. It is a potent antioxidant, has anti-inflammatory properties and is a bronchodilator. As a consequence of these properties propofol is being increasingly used in the management of traumatic head injury, SE, delirium tremens, status asthmaticus and in critically ill septic patients. (13) Propofol has a remarkable safety profile; dose dependent hypotension is the commonest complication, particularly in patients who are volume-depleted, or have limited cardiac reserve. Hypertriglyceridemia and pancreatitis are uncommon complications. (13) High dose propofol infusions have been associated with the “propofol syndrome”; this is a potentially fatal complication characterized by severe metabolic acidosis and circulatory collapse.(13) A smaller proportion of patients respond to propofol, than to barbiturates, but the response appears much earlier (2.6 min versus 123 min with barbiturate coma). The plasma concentrations of propofol associated with control of SE were 14 microgram / ml±4(25.5microgram/ml). Recurrent seizures are common when propofol infusions are suddenly discontinued but not when the infusions are gradually tapered. Continuous electroencephalographic monitoring is necessary. The duration of treatment is never certain, but usually, a seizure-free period of about 24 hours is sufficient, and the agent can be gradually tapered thereafter, unless further seizures supervene. Recovery usually takes a long time, depending on the duration of infusion, occasionally taking as long as 36-72 hours. More recently a meta-analysis of 22 studies with original data on the use of propofol in SE, has raised serious doubts about the safety of propofol in refractory SE, because two non-randomized studies and several case reports show an increased risk of mortality. The authors of this meta-analysis advise that guidelines should not recommend the use of propofol as a routine treatment in refractory SE before a proper randomized trial has been performed. Midazolam, on the other hand, appears safer; in a recent report of the treatment of 27 pediatric patients with refractory generalized convulsive SE, midazolam infusion at a rate of 3.1 mg/kg/min was found to be effective and safe in 26, without adverse effects such as hypotension, bradycardia or respiratory depression. In a randomized open-label study in children at the PGIMER, Chandigarh, comparing the efficacy of midazolam and diazepam in refractory SE, both were found to be equally effective, with median time to seizure control of 16 minutes; however in the midazolam group, seizures recurred in more children (57% versus 16% in diazepam group; P<0.05) and the mortality was higher in the midazolam group (38%) as compared to the diazepam group (10.5%), P<0.1>0.05). The maximum dose (mean ± SD) of midazolam and diazepam required was 5.3± 2.6 mg/kg/min and 0.04±2.6mg/kg/min respectively. Thus the experience with midazolam also is varied and mixed, though overall it appears to be equally effective and marginally safer. Benzodiazepines and barbiturates enhance GABA receptor-mediated inhibition. However, patients often become refractory to benzodiazepines when seizures are prolonged, and barbiturates are often then used for these refractory cases of SE.(8) RSE has been treated conventionally with high-dose intravenous barbiturate coma; pentobarbital coma (PBC) was evaluated in a small series of 17 patients with RSE.(14) Seizures were aborted in 16 of 17 patients, but vasopressors were required in 11 for severe hypotension; nine of them died, and among these, new-onset epilepsy, multiorgan failure before or during PBC, age>40 years, and hypotension requiring vasopressors.
during PBC were the causes identified. In a meta-analysis of twenty-eight studies describing a total of 193 patients comparing the efficacy of midazolam (MDL), propofol (PRO), and pentobarbital (PTB) for terminating seizures and improving outcome in RSE patients, PTB treatment was associated with a lower frequency of short-term treatment failure (8 vs. 23%; \( P<0.01 \)), break through seizures (12 vs. 42%; \( p<0.001 \)) and a higher frequency of hypotension (systolic blood pressure <100mmHg; 77 vs 34%; \( P<0.001 \)). The conclusion is that though PB is more effective, midazolam is both safe and effective.

**Sodium Valproate:**

Although sodium valproate is not approved by the US FDA for treatment of SE, it was found to have an overall efficacy of 63.3% in a study in which 63 patients were given a median dose of 31.5 mg/kg of IV valproate. In a multicenter, open-label, prospective, dose-escalation study of IV sodium valproate administered to patients with epilepsy, rates of infusion of upto 6 mg/kg/minute and doses of upto 30 mg/kg were well tolerated, with no clinically significant negative effects on blood pressure and pulse rate and caused only mild-to-moderate, reversible adverse events, even among unstable SE patients with hypotension.

**Topiramate:**

Topiramate is an anticonvulsant with multiple activities at receptors and ion channels that may be more effective than conventional anticonvulsants in treating RSE. Like phenytoin, topiramate exhibits voltage-sensitive, use-dependent, sodium-channel blockade and may have an additive effect at this site. Topiramate potentiates GABA inhibition independently of the benzodiazepine site on the GABA receptor and significantly elevates brain GABA levels; this more likely underlies its effectiveness in RSE. Another action of topiramate is its ability to antagonize excitatory glutamatergic transmission, providing a mechanism for termination of seizure discharges in RSE.(15) Topiramate has been shown to reduce neuronal injury after prolonged SE and may prevent delayed neuronal death. In a series of six cases, topiramate effectively terminated RSE in a variety of clinical settings(16). In cases of RSE unresponsive to sequential trials of multiple agents, a suspension of topiramate administered via nasogastric tube was effective in aborting RSE; effective dosages ranges from 300 to 1,600 mg/d. Except for lethargy, no adverse events were reported.(16)

**Surgery for SE**

Patients with RSE of focal origin may be potentially amenable to respective surgery. The literature is limited to isolated case reports or small case series involving multiple subpial transections, cortical resection, corpus callosotomy, or implantation of a vagus nerve stimulator. At the Jefferson Comprehensive Epilepsy Center, patients with medically intractable SE who fail to respond to three courses of cerebral suppressant therapy for approximately 2 weeks are considered for surgical treatment in the absence of any known remitting etiology. When structural or functional neuroimaging shows a focal lesion, or the EEG displays focal changes, they prefer focal resection and/or subpial transection. Corpus callosotomy is used for patients with generalized or non-localizable intractable SE who fail to respond to three courses of cerebral suppressant therapy for approximately 2 weeks. Bingaman and colleagues at the Cleveland Clinic performed respective surgery in the acute setting for refractory SE in 10 patients with focal epileptogenesis when High Dose Suppressive Therapy (HDST) failed; 7(10%) became seizure-free, and 3(30%) had significant improvement in epilepsy.

**Pre-hospital treatment:**

SE frequently occurs or is identified in settings where it may not be feasible to administer intravenous drugs; in these settings, rectal diazepam, especially in children, and intramuscular midazolam can be used. Rectal diazepam is very easy to administer; a starting dose of 0.5 mg/kg is recommended, with a maximum of 20mg per single dose, this is effective in 67% within 15 minutes. A gel formulation for rectal administration of diazepam is under study for rapid out-of-hospital control of SE. After intramuscular administration of diazepam is under study for rapid out-of-hospital control of SE. After intramuscular administration midazolam is rapidly absorbed (mean time to peak serum concentrations 25 min), and seizures are controlled within 10 minutes.

The mean absolute bioavailability of intramuscular midazolam is 87% and after intramuscular administration, sedation is slower (2-30 min versus less than 1-2 min with the intravenous preparation) and persists for a longer period (20-120 min versus 7-75 min).
Diazepam is administered to children in SE by paramedics in many Emergency Medical Services systems throughout the United States despite the lack of clear evidence that this therapy is safe and effective when employed in the pre-hospital environment. In a retrospective review, published in 1995, (17) pre-hospital diazepam therapy was associated with SE of shorter duration (32 min vs. 60 min; P=0.007) and a reduced likelihood of recurrent seizures in the emergency department (58% vs. 85%; P=0.045). Though these data suggest that pre-hospital administration of diazepam may shorten the duration of SE in children and simplify the subsequent management of these patients in the emergency department, data concerning the safety of such treatment are scanty. Possibly, rectal diazepam or intramuscular midazolam may be considered relatively safe and effective in this setting.

Outcome in SE

The most important factor deciding outcome in SE is the underlying etiology. In the San Francisco study, the best response to anticonvulsants occurred in patients with SE related to tumor, anticonvulsant drug withdrawal, or refractory epilepsy. (18) The poor responders in this study had anoxia, drug toxicity, CNS infection, or other metabolic abnormalities. Aminoff et al found that the outcome of SE worsened with an increase in the duration of status. Towne et al also found that the group with SE lasting <1 h had a lower mortality as compared with seizure duration one hour or more. Hyperthermia, peripheral leucocytosis and CSF pleocytosis are common accompaniments of SE, and even systemic acidosis may occur in a few patients, without necessarily pretending a worse outcome. The overall mortality among adults with SE is 20%, and those with first-time episodes of SE are at substantial risk for more such episodes and for the development of chronic epilepsy. (17) When SE is related to an acute medical problem such as renal failure, sepsis, electrolyte abnormality, CNS infections, stroke, head trauma, drug toxicity, or hypoxia, seizures are especially difficult to control and associated with a higher mortality. (18,19)

The best example of this is the elderly patient who has survived an episode of cerebral hypoxia, and has developed myoclonic SE, which carries a grave prognosis. In a recent study evaluating variables affecting outcome in children with SE, no deaths were due to SE itself; (20) symptomatic etiology (acute or remote) and refractory SE were associated with adverse outcomes, and age <12 months at development of SE, and duration of SE >60 minutes tended to be more frequent among those who developed adverse outcome. (20)

CONCLUSION:

SE should be identified early and treatment initiated as soon as it is clear that a seizure has lasted 5-10 minutes; out-of-hospital administration of intramuscular midazolam or rectal diazepam by paramedics transporting the patient could shorten the duration of SE and hospital stay. Airway, breathing and circulation should be assessed in the emergency department and adequate steps initiated to correct any abnormalities. The appropriate drug in correct doses should be administered; every hospital needs to follow the treatment based on established protocols, and an early decision to paralyze and ventilate the patient in preparation for continuous midazolam or propofol administration should be taken. With the available drugs and the facilities to manage complications, the morbidity and mortality associated with SE can be minimized.

REFERENCES


Psychological Factors in Asthma: A Critical Review
Sangeeta Rath¹, Saadia Alam²

Abstracts
Asthma is a chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm. Recent trends in medical research have led both clinicians and psychologists to reconsider the role of psychological factors in asthma. There is a paradigm shift that reconsiders the overlap between biological determinants and psychological factors by understanding the rising trends in the prevalence and severity of asthma. This review highlights the associations between asthma and life stress as well as asthma and different aspects of personality.

Asthma is among the most chronic medical condition and is a major public health concern in both prevalence and morbidity. It is a chronic inflammatory disease of the airways characterised by variable and recurring symptoms, reversible airflow obstruction and bronchospasm. The Global Strategy for Asthma Management and Prevention Guidelines define asthma as a chronic inflammatory disorder of the airways associated with increased airway hyperresponsiveness, recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night and early morning. Airway inflammation produces airflow limitation through acute bronchoconstriction, chronic mucus plug formation and airway wall swelling. These symptoms may be relieved spontaneously or after treatment. Asthma can develop at any age.

The prevalence of asthma is steadily increasing throughout the world. An estimated, 300 million people worldwide suffer from asthma with 250,000 annual deaths attributed to the disease. The prevalence of asthma increased 75% from 1980 to 1994. Asthma accounts for approximately 500,000 hospitalizations each year. Asthma is thought to affect about 3% of the population in most countries. The highest prevalence (almost 30%) is found in New Zealand. In India, the prevalence of asthma in adult males during 1995-97 was 3.94% in urban and 3.99% in rural areas. In adult females, the prevalence was 1.27% in both urban and rural areas, 34.1 million American have been diagnosed with asthma by health professionals during their lifetime. It is estimated that the number of people with asthma will grow more than hundred million by 2025.

Efforts have been made to define the aetiology risk factor for the development of the disease. It is thought to be caused by combination of genetic and environment factors. Environmental risk factors include allergic reactions, exposure to pollutants like pollen, mites, animal fur, house dust, cold air etc. Asthma is a psychophysiological disorder which is characterised by genuine physical symptoms that are caused or worsened to some extent by psychological factors. Psychological factors such as stress, anxiety and depression can increase susceptibility to asthmatic attacks (Greengrass, 2002, Lebrer et al. 2002). Evidence evolved over the last two decades of important interactions among behavioural, neural, endocrine and immune processes provide fresh insight into means by which psychological stressors may influence the development and expression of the inflammatory disease.

Although consensus has emerged from clinical, psychological, biological and social science literature that psychosocial factors affect asthma morbidity, their role in the genesis, incidence, symptomatology of asthma remains controversial since mechanisms are not well understood. Recent trends in medical and psychological research have led both clinicians and psychologists to reconsider the role of psychosocial stress in
There is a rising trend in the prevalence and severity of asthma all over the world. The traditional environmental risk factors are not able to explain this trend. Over the last two decades there is significant emphasis on the substantial role of the social environment and social integration in health and disease in general. Prospective epidemiological studies have demonstrated the association between life stress, social position or status, quality of social relationship, personality and health. There is a paradigm shift that reconsiders the overlap between biological determinants and psychological factors in understanding the rising of asthma.

**Asthma and Stress**

Stressful life events can trigger asthma exacerbations, but could also contribute to the development of the incident asthma. However, a few studies have investigated the association between stressful life events and adult asthma prospectively. Wisnivesky, Lorenzo et al. (2010) evaluated the relationship between perceived stress and morbidity among inner city adults with asthma. Results indicated that higher perceived stress was significantly correlated with worse asthma control, poor quality of life and decreased medication adherence. It was concluded that among inner city asthmatics, higher perceived stress is strongly associated with increased asthma morbidity. Loerbroks, Apfelbacher, Thayer, Debling and Sturmer (2009) conducted a study on asthma and stressful events like having broken off a life partnership was associated with asthma. Oh, Kim et al. (2004) studied the association between stress and asthma symptoms in the general population of Korea. A database generated by the National Health and Nutrition Examination Survey (in South Korea, 1998) was used for this cross-sectional study. 9263 subjects were selected by stratified random sampling. Subjects were interviewed using a questionnaire. Multivariate analysis showed that the ratios for asthma symptoms increased according to the severity of stress reported by the subjects. The cross-sectional study done showed an association between stress and asthma symptoms in the general population of South Korea.

Some retrospective studies have been reported finding the association between onset of asthma and stressful life events as well as prospective studies showing an increased risk of asthma attacks among children and adults who had experienced negative life events recently.

**Asthma and Personality**

Personality dimensions seem to play an important role in the chronic inflammatory disease. Although patient’s personality has been thought to affect the disease, the association of asthma and psychological factors is still debated.

Earliest to make systematic study of psychosomatic diseases using the concepts of extraversion, introversion and neuriticism was Sainsbury (1960). He found the psychosomatic group to be more introverted than controls and some psychosomatic diseases to be associated with hysterical personality. The findings of Sainsbury have been corroborated by Kanter and Hazelton (1964). Sreedar (1976) studied patients suffering from peptic ulcer, irritable bowel syndrome, hypertension and bronchial asthma. The result of the studies indicated that patients suffering from asthma and peptic ulcer were high in introversion and neuroticism. Shanmugam (1979) made an attempt to verify the findings regarding extraversion, introversion and neurotic factors in bronchial asthma. Asthmatic patients were found to be neurotic.

Oswald et al. (1970) studied the relationship between breathlessness and anxiety in asthma and bronchitis. Four hundred and seventy-one patients who fell within the general diagnostic range of asthma, bronchitis or both completed two personality testing forms that is the Eysenck Personality Inventory form A and Cattell Self Analysis form. Results indicated that all categories of patients showed a tendency towards neuroticism, anxiety and introversion and the scores were slightly higher for bronchitis than for asthmatics. Neuroticism and anxiety increased with increasing respiratory disability. Belloch et al. (1994) study in bronchial asthma examined the relationship among clinical data, baseline lung function and personality traits. It also examined the patients characteristics related to physicians judgement about his or her asthma severity.
measuring anxiety, depression, self-consciousness and subjective symptoms were completed by 51 asthmatic patients. The factor analysis of responses revealed that the physicians severity judgement is based on high scores on depression and longer duration of asthma. Janson et al. (1992) have found an association between reported respiratory symptoms and psychological states. But in case of persons diagnosed with asthma no evidence was found as to whether they suffered from more anxiety or depression than those without asthma. Michel et al (1998) also suggest that atopic patients instead of being typically depressive are characterised by an increased emotional sensitivity.

Neuroticism is widely documented to reflect an exaggerated reporting symptoms, due to an over-sensitive focus on internal stimuli in individuals in this trait. Leorbroks et al. (2009) investigated the association between neuroticism, extraversion, stressful life events and incidence of asthma. 5114 middle aged adults completed the questionnaires. Results indicated that high versus low neuroticism were predisposed to developing asthma but high extraversion did not. Having broken off a life partnership significantly increased asthma risk in contrast to death of a close person or unemployment. It was concluded that high levels of neuroticism may increase the risk of asthma in middle-aged adults. Having broken off a life partnership was the only stressful event which was associated with incident asthma. Synthesised with evidence this could reflect that interpersonal conflicts may increase asthma risk possibly along an immunological pathway.

Huovinen, Kaprio and Koskenvuo (2003) studied asthma in relation to personality traits, life satisfaction and stress. A total of 1154 adults were studied. The researchers specifically studied the association of psychological factors (including extraversion and neuroticism, subjective stress and life satisfaction) and prevalent asthma as well as predisposing effect of these factors on the risk of adult onset asthma among women. It was concluded that the effect of psychological factors is different among men and women. Prevalent asthma decreases life satisfaction and increases neuroticism thus lending further support to the possible association between asthma and depression. A high extraversion score was a strong predictor of incident asthma among women.

**Asthma and Learned Helplessness**

Learned helplessness (Seligman, 1975) refers to beliefs on the part of the individual that they have no control over their outcomes. Such views often develop after exposure to situations in which such lack of control is present but they generalise it to other situations where individuals fate is at least partly in their hands. Depression may develop when people perceive a lack of control over an important event and inappropriately generalise their perception to other aspects of their lives. (Seligman et al 1988).

Calfee et. al. (2000) studied whether psychological factors play an important role in the outcome of asthma. Results indicated that greater perceived control is associated with improved asthma related health states as well as with a decreased prospective risk of severe asthma attacks.

Goldney et. al. (2003) studied the relation between asthma, depression and quality of life. The prevalence of major depression was significantly higher for those who experienced dyspnoea, waking at night with asthma and morning symptoms of asthma. Quality of life scores were also lower for the same group.

In order to study the effect of experimentally induced learned helplessness in older adolescents and young adults with long standing asthma Chaney et al (1999) studied thirty-nine participants with histories of long standing asthma and an age matched healthy cohort of 94 participants. Results indicated that individuals with long lasting asthma may be at increased risk for depression and for learned helplessness deficits, specifically impaired problem solving in response to environmental non contingency.

**Asthma and Self-efficacy**

Perceived self-efficacy refers to beliefs in ones capabilities to organise and execute the courses of action required to manage prospective situations (Bandura, 1996). It reflects the belief of being able to control challenging environmental demands by means of taking adaptive action. It pertains to optimistic self-belief to handle critical demands that tax individual’s resources.
One of the earliest researchers to demonstrate the success of self-management programmes for chronic disease was Thomas Creer in the field of asthma. Creer (1987) linked self-management to the development of self-efficacy and shift in locus of control from external to internal. Palena et. al. (2000) assessed the efficacy of self-efficacy programmes for adult asthmatics and found that it leads to greater behavioural changes than a programme without these guidelines. After self-management programmes patients demonstrated favourable changes in generalised self-efficacy, social support, self-treatment and self-management of behaviour. Martin et. al. (2009) conducted a pilot study to find out whether interventions that improve asthma self-efficacy for appropriate self-management behaviours will improve asthma control. It was found that intervention group improved asthma self-efficacy, self perceived coping skills and asthma quality of life. Campbell et. al. (2006) studied the association between peak expiratory flow rate (PEFR) and high frequency heart rate variability (HFHRV) during periods of negative affect and physical activity in daily life in patients with higher versus lower asthma self-efficacy scores. Lower asthma self-efficacy was associated with increased parasympathetic activity and air flow obstructions during periods of negative affect.

However, only few studies have investigated the association between stressful life events and asthma, but a casual link between stress and asthma has not been established. There are some retrospective studies reporting an association between onset of asthma and stressful life events as well as prospective studies showing an increased risk of asthma attacks among people who had experienced negative life events just before the onset of asthma.

Most of the studies on personality and asthma have indicated the presence of anxiety and depressive disorder and is highly associated with increased asthma symptoms. Still it is questionable to what extent psychological factors may influence asthma. Thus it is possible that asthma itself can change one’s personality.

It is necessary to distinguish the effects of asthma on patient’s psychological condition from the role of psychological factors in the genesis of asthma. It is also highly relevant to do prevalence studies to estimate the relation between asthma and psychological factors and incidence studies to examine the role of stress, life satisfaction and personality traits in the development of asthma in adulthood in a large population based sample.

References:
Anaemia and hypoxia in carcinoma cervix: A Review.
Sanjukta Padhi¹, Lucy Pattanayak²

Background:
Anemia is the most frequent hematological manifestation in cancer patients but often under appreciated and under treated. World Health Organization (WHO) defines anemia as hemoglobin (Hb) level less than 130 gm/l for males and 120 gm/l for females; hematocrit (Hct) level of less than 39 % for males and 36% for females. According to National Cancer Institute (NCI), the normal hemoglobin level for males is 14-18gm/dl and for females is 12-16gm/dl. The severity of anemia has been graded on the level of Hb (¹):

<table>
<thead>
<tr>
<th>Hb(gm/dl)</th>
<th>None (0)</th>
<th>Mild (1)</th>
<th>Moderate (2)</th>
<th>Severe (3)</th>
<th>Life threatening (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>&gt;11</td>
<td>&lt;11-9.5</td>
<td>&lt;9.5-8</td>
<td>&lt;8-6.5</td>
<td>&lt;6.5</td>
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<tr>
<td>EORTC</td>
<td>&gt;12</td>
<td>&lt;12-10</td>
<td>&lt;10-8</td>
<td>&lt;8-6.5</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td>NCI</td>
<td>-</td>
<td>10-normal</td>
<td>8-10</td>
<td>6.5-7.9</td>
<td>6.5</td>
</tr>
</tbody>
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Anemia in cancer patients or cancer related anemia (CRA) is multifactorial and may directly arise from the myelosuppressive effect of radiotherapy and chemotherapy, blood loss during surgery or from the complication of the disease itself. According to the NCCN guidelines in oncology, 30 – 90 % patients experience anemia during their course of treatment (³) and 27-50% of patients have been estimated to have moderate to severe anemia (³). Beyond the symptoms of pedal edema, palpitations, fatigue, dyspnea, nausea, cognitive impairment and dizziness, anemia significantly impairs functional ability and emotional or social well being. (⁴) Most importantly anemia has a negative effect on radiosensitivity and chemosensitivity, thereby decreasing response to treatment and life expectancy or survival rates.

Discussion:
Radiation therapy is an integral component of standard care of cervical cancer and chemotherapy is administered concurrently for enhanced tumor control. In 1999, five landmark papers reported significant improvement in disease free survival and overall survival with the use of concomitant chemoradiation in all patients of advanced cervical cancer. Based on these studies in February 1999 the NCI gave a consensus that “strong recommendation should be given for cisplatin based chemotherapy in all patients who require radiotherapy for cancer cervix” (⁸, ⁹).

Radiation acts by causing lethal or double strand damage of DNA helix. The G2/M phase of the cell cycle is the most radiosensitive while the S phase is most radio resistant. Out of all the factors which enhance radio sensitivity of tumor cells, molecular oxygen is considered to be the most potent radiosensitiser causing DNA damage (¹⁰). The chemotherapeutic agent cisplatin inhibits redistribution and resynchronization of tumor cells, thereby arresting cells in the radiosensitive phase of the cell cycle. Cisplatin is also nephrotoxic and exacerbates CRA by reducing erythropoietin production, decreased life span of RBC and impaired hematopoiesis.

Correction of anemia in solid tumors increases the radiosensitivity and chemosensitivity; the relation between anemia and tumor hypoxia in uterine malignancies being well known. (¹¹) The term oxygen enhancement ratio (OER) frequently used in oncology.
refers to the ratio of the dose necessary to achieve the same effect under hypoxic condition as under normoxic condition \(12\).

Degner and Sutherland devised a mathematical model to predict the relation between hemoglobin level and oxygenation of tumor tissue; increase in Hb level by 20 % could produce a decrease in hypoxic tissue volume by 30 % \(13\).

Hypoxic regions are defined as areas of pO2 values less than 10 mm Hg, the prevalence in cervical cancers being 60 %. Hypoxia may act by direct or indirect means causing resistance to standard radiotherapy, chemotherapy or chemoradiotherapy thereby leading to poor clinical outcome and response \(14\). Directly hypoxia leads to tumor resistance by deprivation of molecular oxygen; therefore all treatment strategies require high intratumoral oxygen concentrations to be cytotoxic. Indirectly hypoxia causes treatment resistance by modulating gene expression and post transcriptional or post translational effects, altering cell cycle position and influencing the number of cells destroyed by radiotherapy or chemotherapy \(14\). Radiation leads to formation of free radicals within the cells. In the presence of oxygen the free radicals are fixed and interact with DNA enhancing cell death whereas in hypoxic conditions the free radicals are not fixed and cell death may not occur.

It is seen that radio sensitivity in carcinoma of uterine cervix decreases rapidly when pO2 is <25-30 mm of Hg \(15\). Numerous clinical trials have explored the prognostic implication of low pretreatment pO2 levels with unresponsiveness of tumors to radiation and chemotherapy. Several studies demonstrate that pretreatment O2 status of tumors predicts OS, DFS and local tumor control in cancer cervix \(11\).

The level of hemoglobin or the severity of anemia is an independent prognostic marker in cervical cancer patients undergoing chemoradiation. Dubray et al \(16\) have shown that pretreatment Hb level of < 12 gm/dl in carcinoma cervix was an independent predictive factor of increased two years loco regional failure and death.

Several new paradigms have emerged for the treatment of CRA and aggressive efforts should be made for restoration of normal Hb level in cancer patients.

Blood transfusion is frequently required due to a drop in Hb because of hemorrhage or disease related factors or treatment (surgery/radiotherapy/chemotherapy) induced. Safe and effective blood transfusion needs to be ensured and maximum operational efficiency has to be maintained. Blood transfusion however leads to short term resolution of symptoms and transmission of infection is a well known risk factor.

Erythropoietin- is a glycoprotein, 90% of which is produced in the kidneys in response to hypoxia and 10 % is produced in the liver. Recombinant human erythropoietin has been produced using recombinant DNA technology having amino acid sequence identical to natural erythropoietin. In 1990, USFDA approved erythropoietin for oncology practice and has been widely used since then.

Oral supplements- are frequently used with chemoradiotherapy in cancer patients, with symptomatic benefit.

\textbf{Conclusion :}

Anemia and the level of hemoglobin is an independent prognostic marker in patients of carcinoma cervix undergoing chemoradiation. Molecular oxygen being the most potent radiosensitiser, hypoxia leads to resistance to standard radiotherapy and chemotherapy with poor response to treatment and clinical outcome. Since compliance to anemia correction is very poor in our region, audits or reviews need to be done frequently by oncologists as well as gynecologists to ensure optimum benefit from chemoradiation.

\textbf{References :}


Morgagni’s Hernia – A Quiet Companion in a Child

Jyoti Patnaik¹, M.R. Das²

Abstract:
A case of Morgagni’s Hernia was found accidentally in a child of 13 years during a radiographic evaluation for asthma. A barium follow through and a CECT Thorax was done to confirm the diagnosis. A laparoscopic repair was then done. The patient is now being managed for asthma and has reported no further complication.

Key words: Morgagni’s Hernia, CDH- Congenital Diaphragmatic Hernia

Case Report:
A young girl, 13 years old presented with cough and dyspnoea and wheezing for 15 days. She had repeated attacks of these episodes since the age of 3 years. Since last 6 months the frequency of these episodes had increased. She was usually relieved with bronchodilators. There were nocturnal exacerbations. There was no family history of asthma.

On examination she was obese, afebrile, with a pulse rate 92/min, blood pressure 110/70 and respiratory rate 24/ min. Her respiratory system examination revealed diminished breath sounds in right mammary area with bilateral rhonchi.

A chest x ray pa view showed an opacity in the the right lower zone

A barium follow through was then done that showed the presence of dye within shadow thus confirming the herniation of abdominal contents into the thoracic cavity

A CECT Thorax confirmed the presence of small intestine and mesentry in the thoracic cage

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Laparoscopic repair of the hernia was performed on this patient.

The patient is now on ICS + LABA combination for asthma and is apparently asymptomatic.

Post op chest x ray PA view is now normal.

Discussion:

Diaphragmatic hernias can be congenital through embryological defect in the diaphragm, or it could be acquired. Giovanni Batista Morgagni in 1761 reviewed CDH and traumatic diaphragmatic hernia. He described classical anterior diaphragmatic hernias and in his honour this was named Morgagni’s Hernia. CDH occurs among in 1 in 3000 children and Morgagni’s Hernia was a rare entity as it was seen only among 5% to 10% of CDH. It is seen in the anterior midline through sternocostal hiatus and in 90% of the cases they are seen on right side. Presentation are usually respiratory distress along with cyanosis. Bowel sounds may be sometimes heard in the thorax in infants. When there is a late diagnosis it may be due to gastric or splenic volvulus or due to large bowel obstruction. The treatment includes laparoscopic reduction of abdominal contents, approximation of edges of diaphragm with nonabsorbable suture along with prosthetic mesh if opening is large.

Conclusion:

This case of asthma had no other symptoms to present clinically as a case of Morgagni’s Hernia and she is now apparently asymptomatic. She is being periodically evaluated for recurrences.

References:


Occipital Meningoencephalocele
M. Panda¹, C. Mohapatra², C.L. Sarangi², R. Satapathy³

ABSTRACT

The very existence of a developmental defect in an ultrasonogram is always shocking to the mother. Knowledge of the embryological basis of these disorders may be of help to the Gynaecologists, Radiologists and so also to the society in order to prevent any neurological handicap outcomes. Meningoencephalocele characterized by herniation of brain tissue along with meninges is a common malformation with an incidence of 1 in 2000 live births. Several embryopathogenic factors leads to this disorder, out of which abnormal sonic hedgehog gene and FOXG1 may be the main initiating factor. One such case is reported here in a term dead male fetus born to an elderly primi, which was dissected, studied histologically and diagnosed to be a case of occipital meningoencephalocele.

Key Words:
Meningoencephalocele, Embryopathogenic factor, Sonic hedgehog, FOXG1

INTRODUCTION

Encephaloceles represent a congenital defect of the cranium through which a portion of the central nervous system herniates out. When there is herniation of meninges along with the neural tissue, it is called as meningoencephalocele. These encephaloceles are classified into six groups depending on the location of the defects in the cranium. They are occipital, occipitocervical, parietal, syncipital, basal & temporal. They account for approximately 10% to 20% of all craniospinal dysraphisms. The prevalence ranges from 0.8 to 4 per 10,000 live births, although the true incidence is greater because, about 70% of them result in loss of pregnancies. Racial and geographic factors also influence both frequency and site of the disorder.

In western hemispherical population 85% are posterior in location, while in south-east Asia there is predominance of anterior lesions. In general, posterior encephaloceles are more common than anterior cranial fossa encephaloceles except in some Asian populations. Almost all meningoencephaloceles are sporadic in nature.

CASE REPORT

An elderly primi aged 32 years from Jagatsinghpur gave birth to a term dead fetus in the Gynaec department of S.C.B. Medical College & Hospital, Cuttack. The fetus presented a projection from the occipital region. The fetal age determined was 36 weeks as per the recorded data. The external features of the tissue were observed, dissection was carried out on the skull and brain and a piece of the protruding mass was subjected to histological study.

OBSERVATION

It was observed that all the skull bones were developed except for an unusual gap at the site of posterior frontanelle through which the mass of tissue protruded out [fig-1]. It measured around 10cm in length and the skin over the mass was mature but atretic because of the large size of the herniated mass. The tissue was cut open and it was seen that, a lobulated bilateral mass of neural tissue which was cystic in nature extended from the occipital pole of the cerebral hemisphere [fig-2]. There was presence of haemorrhages, gliosis and ischemic necrotic tissue [fig-3]. The brain as a whole was intact grossly and no other abnormalities were detected in the spinal cord. Histologically, there was presence of meninges and haemorrhages along with the cerebral tissue. The neural tissue showed dysmorphism with high degree of disorganization [fig-4].

DISCUSSION

At third week of intra-uterine life the midline cells of the ectodermal plate gives rise to the formation of neuroectoderm. Rapid growth of the cells results in folding towards the notochord with gradual formation of the neural groove and thus a neural tube.
Recklinghausen suggested that encephalocele occurs because of defect in primary neurulation which is related to a disorder of the closure of the primitive neural tube at around 4-6 weeks of gestation. Since the meningoencephalocele contains mature brain substance such as cerebral tissue rather than more primitive neural tissue like tectum, it may be related to abnormalities of the overlying mesenchymal development instead of defective neurulation.

Some studies support a theory that there is some disturbance in the separation of neural tissue and the surface ectoderm after neurulation. Because of this there is insufficiency of the paraxial mesoderm which in turn affects the formation of the occipital bone and neurocranium. These abnormalities of the overlying mesenchymal development result in a local “blow-out” of the cranium with thus posterior meningoencephalocele formation. Such a “blow-out” occurs at 8-12 weeks of gestation. This hypothesis supports the fact that the meningeal and neural protrusions are present from the outset, while abnormal skeletal developments occur later.

Another widely accepted theory is that of Geoffrey St. Hillaire [1827] who proposed that cranioschisis occurs after neural tube closure. As the fissure heals, adhesions develop between neuroectoderm and cutaneous ectoderm thereby preventing interposition of the mesoderm which is destined to form the cranium, thus leading to the protrusion through the unusual gap.

From the molecular studies it is determined that the process of neural tube formation is controlled by genes such as sonic hedgehog and their respective proteins which can be transcription factors, membrane receptors or ligands. In the anterior neural ridge [ANR] at the four-somite stage, fibroblast growth factor 8 [FGF8] induces expression of FOXG1, a transcription factor. FOXG1 then regulates development of the telencephalon [cerebral hemisphere]. Any abnormality in this gene may lead to the overgrowth of the cerebral tissue. So also any kind of defect in the bone morphogenic protein (BMP 4 & 7) may give rise to ossification defect in the bones of the skull, the most commonly affected bone being the squamous part of the occipital bone. This defect thus allows the overexpanded neural tissue to protrude out thus leading to the occipital meningoencephalocele.

**CONCLUSION**

Thus we conclude that an occipital meningoencephalocele is seen because of abnormality in the gene FOXG1 which results in over-distention of the primitive neural tube which leads to protrusion of the neural tissue from the normal confines of the cranium through the defect in the occipital bone, which may be formed because of insufficiency of the paraxial mesoderm or by ossification defect induced by the anomalous bone morphogenetic proteins [BMP 4 & 7]. Neurological prognosis in children with posterior meningoencephalocele is in large measure determined by the amount of neural tissue that has herniated through the defect. Still then, newer insight into the molecular basis of the defect will help us to forecast a prognosis, provide genetic counseling and thus formulate prevention of handicapped children.

**References:**

5. Langman’s Medical Embryology 11th edition. By TW Saddler
A Rare Case of Familial Tuberous Sclerosis Complex

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ABSTRACT:
Tuberous sclerosis complex (TSC) is a rare multisystemic genetic disorder with autosomal dominant inheritance. Around 50-80% are sporadic and rest are familial.¹ A 15 yr boy with history of seizure disorder was evaluated and was found to have Tuberous sclerosis complex. Incidentally his mother and younger brother who were attending him were also found to have Tuberous sclerosis and the family were considered to have Familial Tuberous sclerosis complex. Here we report the case with review of literature in view of rarity.

KEY WORDS: Tuberous sclerosis complex, Facial Angiofibroma, ash leaf spots, familial, sporadic, sub-ependymal calcification.

INTRODUCTION:
First complete description of Tuberous Sclerosis (Bournvilles’Disease) was given by DM Bournville (1880) who has coined the term “Tuberous Sclerosis”.² Neurologist Vogt. established a diagnostic triad of epilepsy, idiocy and adenoma sebaceum which was helpful in diagnosis of TSC before USG, CT Scan or MRI were available. Though a 1998 Study estimated the total population prevalence between 7 and 12 per 1,00,000 ³, Familial TSC which accounts for around one third of total cases is still a rarer entity. TSC is an autosomal dominant disorder with variable penetrance for which clinical presentation varies widely among affected individuals. Here we report a family where the mother and two sons are affected to variable extent.

CASE REPORT:
A 15 yr boy presented to us with history of generalised tonic clonic seizures around 4 episodes in 2 days. There was no history of fever, headache, vomiting, head injury or altered sensorium prior to seizure. There was history of seizure at intervals of few months for last 3 yrs and he was on valproic acid irregularly. He had left school from 7th class because of poor performance and joined as helper to a shopkeeper. They are two brothers. None of the parents had history of seizure disorder. But his brother (only sibling) was having seizure disorder and was on irregular treatment. There was no significant perinatal history and developmental milestones were normal.

On examination he was of average body built with pulse rate 73/min, BP 120/70 mm of Hg, afibrile with resp. rate 17/min. There was no pallor, icterus, cyanosis, clubbing or significant lymphadenopathy. There was no goitre and secondary sexual characters well developed. There were angiofibromas over face mostly in butterfly distribution over cheeks and naso labial folds.(Fig 1.) There were multiple hypomelanotic macules (Ash leaf spots) over back. Examination of respiratory system and CVS revealed no significant abnormality. On examination of abdomen there was no organomegally, CNS Examination including fundoscopy was essentially normal.

Routine haematological and biochemical reports were in normal range. X-ray of chest and USG Abdomen-pelvis revealed no significant abnormality. 2D Echocardiogram of heart was normal. Non contrast

Fig 1.Patient himself with Angiofibroma over face

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CT scan of brain showed sub-ependymal calcifications in posterior horn of Rt lateral ventricle and anterior horn of Lt lateral ventricle. (Fig 6) 

Considering seizure disorder, subnormal intelligence, angiofibromas over face, multiple Ash leaf spots and characteristic subependymal calcifications he was diagnosed as a case of Tuberous sclerosis complex (TSC).

His mother and younger brother who were attending him were also having angiofibromas over face and naso-labial folds. (Fig 2 & 3) So detailed medical history of the mother and the brother was collected and they were thoroughly examined. Though the mother had low intelligence there was no history of seizure or any significant medical illness. On general examination she had shagreen patches over trunk, multiple Ash leaf spots on back (Fig 4.) and angiofibromas over face. Systemic examination also revealed no abnormality. The younger brother had history of seizure and was on valproic acid irregularly, doing poor in school. On examination he had classical facial angiofibromas and ash leaf spots but no other significant physical findings. But they didn’t cooperate for further investigation. In view of seizure disorder, facial angiofibroma, Ash leaf spots and low intelligence brother was diagnosed as a case of tuberous sclerosis complex. characteristic adenoma sebaceum over face of mother, Ash leaf spots, low intelligence and shagreen patch over trunk she was also diagnosed as a case of tuberous sclerosis. The patient was put on valproic acid and advised to continue regularly. The younger brother was referred to the paediatrics Dept. for optimisation of antiepileptic therapy. Mother was advised for periodic follow up.

**DISCUSSION:**

Tuberous sclerosis complex is a rare multisystemic genetic disease that causes non malignant tumors in brain and other organs such as kidneys, heart, eyes, lungs and skin. TSC is the result of mutation of two tumor suppressor genes TSC-1 on chromosome 9q34 and TSC-2 on chromosome no 16p13.3 which encodes for proteins hamartin and tuberin respectively.

The physical manifestations are due to formation of hamartia (malformed tissue such as cortical tubers), hamartoma (growth such as facial angiofibromas) and very rarely cancerous hamartoblastomas. CNS manifestations include learning difficulties, autism, pervasive developmental...
disorders, self injurious behaviour, ADHD, behavioural outbursts. Classic intracranial manifestations include subependymal nodules with or without calcifications, cortical / subcortical tubers. Other significant abnormalities include angiomylipomas of kidney, multiple cysts in lungs, rhabdomyomas of heart, retinal phakomas. Skin leisons include facial angiofibromas in butterfly distributions, periungual fibromas, Ash leaf spots, Shagreen patches over trunk and café-au-lait spots.1,2

There are no pathognomonic clinical signs for TSC. A combination of signs classified as major or minor is required to establish a clinical diagnosis. The major signs are Facial angiofibroma, Nontraumatic periungual fibroma, Hypomelanotic macules(>3 in number), Shagreen patch, Cortical tubers, Subependymal nodules, Sub-ependymal giant cell astrocytoma, Retinal hamartomas, Cardiac rhabdomyomas, Renal angiomylipoma and Lymphangiomaromatosis.5,7 The minor signs are Dental pits, Rectal polyps, Bone cysts, Gingival fibromas, Cerebral white matter migration tracts, Renal hamartomas, Renal cysts and cafe-au-lait skin lesions.

According to different signs present cases are considered:

Definite TSC- 2 Major or 1 major with 2 minor signs present

Probable TSC- 1 Major plus 1 minor sign present

Suspect TSC- Either 1 major or 2 minor signs.5,7

Management of TSC includes optimal antiepileptic therapy for effective seizure control. In refractory cases neurosurgical intervention helps. For facial angiofibromas dermabrassion or laser helpfull. Everolimus has been in use for sub ependymal giant cell astrocytoma.2

Prognosis depends on severity of symptoms. Those with mild symptoms do well and live long productive life but individuals with severe symptoms develop serious disabilities. However with appropriate medical care most individuals can look forward for normal life expectancy1,2

REFERENCES:
Multiple Myeloma presenting as proptosis: A diagnostic dilemma
Sanjukta Padhi1, Sagarika Samantaray2, Lucy Pattanayak1, Biswaranjan Routray1

Abstract:

Background: Plasma cell neoplasms are characterized by monoclonal proliferation of plasma cells or terminally differentiated B cells. They may present as solitary plasmacytoma, which can affect bone or soft tissues, or they can manifest with systemic involvement as multiple myeloma. Extramedullary presentation of multiple myeloma is uncommon and the orbit is involved in less than 0.25% cases till date. We describe an unusual case of multiple myeloma that presented to us with proptosis.

Case: A 45-year-old male presented with gradual proptosis of the right eye for a period of 15 days. Local examination revealed a forward and outward protrusion of the eyeball, restricted movements and loss of vision in the right eye. On palpation there was a firm mass 2.5x2.5 cm in size, nontender in the superior orbit of the eye. Hb was 7 gm % and ESR was 110 mm in the 1st hour. Scrape cytology from the mass showed sheets of binucleate and multinucleate plasma cells suggestive of plasmacytoma. Bone marrow aspiration and cytology showed oval cells with pale basophilic cytoplasm, perinuclear halo, nuclei with cartwheel chromatin suggesting plasma cells which were > 30%. Serum Bens-Jones protein was positive and electrophoresis showed a sharp M band in the gamma region confirming the diagnosis of Ig G multiple myeloma. Skeletal survey was normal.

Conclusion: Orbital myeloma with negative skeletal survey is infrequently encountered. Cytological picture from the lesion as well as bone marrow biopsy is confirmatory in the absence of bony lesions. Associated features like anemia help in staging and prognostication.

Key Words: Plasmacytoma, Multiple myeloma, Orbit, Proptosis.

Introduction:

Plasma cell neoplasms constitute a spectrum of disorders characterized by clonal proliferation of immunoglobulin producing terminally differentiated B cells called plasma cells. Multiple myeloma is a monoclonal proliferation of plasma cells, which causes skeletal destruction, bone pain and fractures along with anemia, hypercalcemia and renal failure. Extramedullary disease manifestation is uncommon at presentation and is seen in the setting of advanced disease or relapse after bone marrow transplant, frequently affecting the liver, spleen, lymph nodes and kidneys. Orbital involvement is rare and has been reported in < 50 cases till date. We describe a rare case of multiple myeloma involving the orbit and presenting as proptosis as the only symptom.

Case:

A 45-year-old male presented with painful gradual proptosis of the right eye (Fig 1) for a period of 15 days. It was associated with redness of the eye, watering of conjunctiva for 3 months. He also complained of long standing fatigue, weakness and anorexia. On clinical examination, patient was thin built, emaciated, grossly anemic. There was no significant lymphadenopathy or bony tenderness. Local examination revealed a forward and outward protrusion of the right eyeball, restriction of movements and loss of vision in the right eye. Deep palpation showed a smooth, round, firm mass of about 2.5x2.5 cm in size.
nontender in the superior orbit of the right eye. The posterior extent of the mass could not be reached and it was free from the overlying skin. The proptosis was nonpulsatile, noncompressible, did not protrude with Valsalva maneuver and did not have any postural variation. Periocular skin was normal with only few superficial engorged veins. Funduscopy showed a pale optic disc with clear margin. Biochemical investigations revealed Hb to be 7 gm %, TLC was 10,000/cmm, DC showed N65%, L25%, E3%, B2%, M0%. ESR was 110 mm in the 1st hour. Scrape cytology from the mass showed cellular sheets of mature and immature binucleate and multinucleate plasma cells suggestive of plasmacytoma (Fig 2). Bone marrow aspiration and cytology showed single cells or groups of cells with pale basophilic cytoplasm, cytoplasmic vacuoles, perinuclear halo, eccentrically placed nuclei with cartwheel chromatin clearly suggestive of plasmacytoma.

FNAC from the eye growth showing cellular sheets of mature and immature plasma cells with pale cytoplasm and perinuclear halo.

Bone marrow biopsy showing single cells or groups of cells with pale basophilic cytoplasm, perinuclear halo, eccentrically placed nuclei with cartwheel chromatin clearly suggestive of plasmacytoma.

Serum Electrophoresis showing prominent M band in the gamma region. there was significant reduction of the eye mass and further cycles were continued.

Discussion:

Plasma cell neoplasms are a heterogeneous group of diseases characterized by monoclonal proliferation of terminally differentiated immunoglobulin producing B cells called plasma cells. This spectrum ranges from clinically benign conditions like monoclonal gammopathy of undetermined significance (MGUS), indolent myeloma, smoldering myeloma, osteosclerotic myeloma, nonsecretory myeloma to diffuse and
systemic conditions like multiple myeloma or more aggressive form like plasma cell leukemia. Wills et al classified plasma cell neoplasms as: (i) Multiple myeloma, (ii) Solitary plasmacytoma of bone and (iii) Solitary extramedullary plasmacytoma (soft tissue plasmacytoma). Multiple myeloma accounts for 10% of all hematologic malignancies with the incidence being 5.5 cases in every 100,000 population. Median age of presentation is 60 years only 3.4 % of the population presenting in the age group of 30-50 years. Solitary plasmacytoma is characterized by the following criteria: (i) single histologically confirmed lesion, (ii) negative skeletal imaging, (iii) normal bone marrow biopsy (<10 % monoclonal plasma cells), (iii) no myeloma related organ dysfunction. This may present either as solitary plasmacytoma of the bone (SPB) or solitary extramedullary plasmacytoma (SEMP). SEMP frequently affects upper respiratory tract and paranasal sinuses. Orbital involvement is rare and most commonly presents as unilateral soft tissue mass with extension of the bony deposit associated with bone destruction. The present case reveals a single orbital lesion, negative skeletal imaging or no bony destruction but the presence of >30 % plasma cells in bone marrow biopsy confirms it to be multiple myeloma.

Multiple myeloma is known to involve head and neck – nasopharynx, tonsils, and paranasal sinuses in extramedullary involvement, orbital myeloma is infrequent, the incidence amongst orbital tumors being 0.25 %. From 1906 to 1953 Clarks collected 13 cases of multiple myeloma involving the orbit. Orbital involvement usually presents as a swelling, proptosis and diplopia. Visual improvement may present from minor defects to complete blindness or limitation of eye movement. Invasion of adjacent critical structures is a differential diagnosis for other malignancies like lymphoma, leukemia, plasmacytoma, metastases, malignant lacrimal tumors and other malignancies from adjacent skin. In multiple myeloma, normocytic normochromic anemic picture is observed due to tumor involvement of the marrow. This in turn leads to weakness, fatigue and shortness of breath as seen in our case. In Durie Salmon staging, the level of anemia is one of the criteria for assessing the tumor burden. Treatment policy depends upon whether a bone marrow transplant is desired or not. Oral Melphalan and Prednisolone (MP) reduce the chances of stem cell mobilization whereas VAD can be used if a BMT is planned. Meta analyses of several RCTs have shown no survival advantage with the use of VAD over MP but the advantages include quick response, can be used in patients with impending renal failure and lack of cumulative bone marrow stem cell damage which allows a future BMT. The novel drugs used now are Lenalidomide, a congener of Thalidomide and proteasome inhibitor like Bortezomib.

Conclusion:
Orbital myeloma with negative skeletal survey is infrequently encountered. Cytological picture from the lesion as well as bone marrow biopsy is confirmatory in the absence of bony lesions. Associated features like anemia help in staging and prognostication. The present case highlights a rare clinical presentation of multiple myeloma with proptosis as the only clinical feature.

References:
Gangrenous Mucocele of Appendix – A Rare Presentation. 
Srikanta Kumar Patro

Introduction

Mucocele of the appendix is a rare entity which is characterized by progressive enlargement of the appendix from the intraluminal accumulation of the mucoid substance.¹ Mucocele may be non-neoplastic or neoplastic. There are four histological types of mucocele; retention cyst, mucosal hyperplasia, cystadenomas and cystadenocarcinoma. It is often asymptomatic and occurs as an incidental surgical finding. Sometimes patients with mucocele can present with confusing symptoms. Preoperative suspicion and diagnosis is important. Ultrasonography and computed tomography are useful diagnostic tools. Several complications such as torsion, intussusception and perforation with pseudomyxoma peritonei can occur.³ Only a few cases have been reported so far but present case is unique of its type as there is no torsion or intussusception and also there is isolated gangrene of the mucocele [the tip, base and meso-appendix being non-gangrenous]. The question still remains unanswered regarding the rare presentation.

Case presentation

An Indian Hindu female aged about 45 years reported to the emergency department with complaints of pain in lower abdomen since 3 days which was diffuse dull aching to start with then localized to right iliac fossa since last 24hrs. She was nauseated with history of several bouts of vomiting in last 2 days. On examination temperature was 99°F, pulse 94/min. regular, BP 110/76 mm of Hg. Tenderness elicited all over the abdomen but maximum over right iliac fossa with rebound tenderness and involuntary guarding. Blood investigations reported marked leukocytosis esp. neutrophillic, urinalysis was normal. Ultrasonography of abdomen and pelvis reported acute appendicitis with peri-appendiceal collection. Laparotomy planned after relevant investigations and resuscitation in right lower paramedian incision. Intraoperative picture revealed a gangrenous thin-walled cyst near the base of appendix filled with mucinous material, but distal most part, base and meso-appendix were inflamed but non-gangrenous, and there was no torsion of appendix. Appendectomy was done and wound closed. The specimen is subjected to histopathological study.

Histopathology Report – Grossly it is an appendix with fusiform tumefaction little away from its base. The proximal undilated segment was 8 mm. long and 10mm. in diameter and its lumen was obliterated. Beyond the obliteration there was a dilated mass 50 mm. long and 40 mm. in diameter. The serosa was smooth, glistening gray-purple, mottled with dark red. The mesoappendix was thickened and hemorrhagic. The leathery wall varied from 0.5 mm. to 2 mm. in thickness and contained spicules of calcification. The
gelatinous content was translucent gray to opaque dull white. Microscopic examination of a section, the wall was observed to be composed of compact laminations of hyalinized collagen connective tissue infiltrated with occasional lymphocytes, plasma cells and neutrophilic polymorphonuclear leukocytes. Compressed smooth muscle, present only on the mesoappendical border, was undergoing necrobiosis. Dilated veins and dense extravasations of erythrocytes were noted throughout the wall, particularly in the less compact subserosa. In the undilated proximal segment the lumen was obliterated by dense fibrous connective tissue. There is no evidence of malignancy.

Pathologic Diagnosis: Mucocele of the appendix with gangrene.

Discussion

Mucocele of the appendix is an infrequent entity and is found in only 0.2 – 0.4% of all appendicectomy specimens and 8% of all appendicular tumours. But exact incidence in India has not been reported. Most commonly persons of 4th, 5th and 6th decades are affected with a little preponderance in females than males.2

Most cases of mucocele of appendix are clinically asymptomatic. However, clinical manifestations include right abdominal pain, abdominal mass or gastrointestinal bleeding. Several complications may be associated with mucocele of the appendix such as intussusception, torsion and in case of perforation leading to pseudomyxoma peritonei.

Pre-operative diagnosis can be facilitated by ultrasonography, computed tomography and colonoscopic examination. On ultrasonographic examination, outer diameter threshold for the diagnosis of appendiceal mucocele has been established to be 15mm or more with a sensitivity of 83% and a specificity of 92%. The sonographic cystic mass which is named “onion skin sign” in the right lower quadrant of the abdomen in the presence of a normal ovary is suggestive of the diagnosis.3 Computed tomography is considered an effective diagnostic tool for mucocele of appendix which can also determine its relationship with the neighbouring organs. Appendiceal mucocele on computed tomography appears as a cystic mass with enhancing wall nodularity in region of appendix.

On colonoscopy an elevation of orifice of appendix is seen and yellowish mucous discharge should be visible from appendiceal lumen. Colonoscopy can also diagnose synchronous or metachronous colon tumor which would be as high as 29%.

Treatment of mucocele of appendix is purely surgical. Pseudomyxoma peritonei is the worst complication which is characterized by peritoneal dissemination caused by iatrogenic or spontaneous rupture of the mucocele. Care should be taken to handle the tissues carefully during the surgery to avoid rupture of the mucocele. Open surgery is preferred than laparoscopic approach as the incidence of pseudomyxoma peritonei is more in the latter. Simple appendectomy is the choice of surgical treatment in patients with negative resection margins and without perforation. In our case appendectomy was done. No long term follow up is needed for these patients.1 However, some authors recommend follow-up of all patients, because of association with neoplasms in other locations such as colon and ovary. There is also increased risk of pseudomyxoma peritonei after a long follow up.

References

ABSTRACT

Here we described a 7 year old girl who presented with intermittent nasal bleeding for one month and purpuric spots all over the body for one day. Clinically diagnosed as ITP which was further confirmed by CBC & bone marrow study. The child was initially treated with methyl prednisolone for 3 days but showed no improvement in clinical signs & symptoms subsequent studies showed highly raised ANA & dsDNA with low complement level suggestive of SLE. As it is one of the atypical presentation of SLE we report this case with brief review of literatures.

KEY WORDS
SLE, Purpura, Epistaxis

INTRODUCTION

The word lupus (Latin: wolf) was originally used from 13th to the 19th centuries to describe a dermatitis characterized by recurrent, florid facial ulcerations. That time dermatitis, facial findings were prerequisite for diagnosis for lupus. Later varied systemic manifestations were reported and explained and still the disease is continuing to show its varied presentations, complicating our understanding of its pathogenesis. Its clinical manifestations are extremely variable, and its natural history is unpredictable. SLE presenting with epistaxis & purpura is a rare clinical situation.

CASE REPORT

A 7 year old girl presented with history of intermittent bleeding from nose for past one month which has increased since yesterday with multiple dark red spots all over the body since one day. There is no history of swelling of joints, spontaneous or injury prone bleeding, hematemesis or malena, gingival bleeding, recent viral infection & history of drug intake (eg.: cephalosporins, aspirin, NSAID, cytotoxic drugs), no family history of bleeding disorders & no history of intermittent fever, photosensitive rash, oral ulcer, arthritis. She was born out of non-consanguinous marriage. On examination, she was afebrile, severely pale, bleeding from nose without any nasal pathology, Purpuric spots over neck & all over the body without hepatosplenomegaly & lymphadenopathy. Lab investigations showed, Hb :6.8gm%, TPC: 60,000/cmm, TLC:11,600/cmm, DLC: N:28%,E-1%,L-70%,M-1%, PSC : Normocytic normochromic anemia with thrombocytopenia, normal platelet size,BT:7 min 30 sec with normal PT, aPTT .Bone marrow examination showed normal myeloid & erythroid series with increase in no. of megakaryocytes with normal size-suggestive of Idiopathic Thrombocytopenic Purpura. IV Methyl prednisolone was given for three days. Epistaxis & purpura decreased but persisted. On subsequent investigation :ESR-90mm/hr, CRP-19.7mg/dL, HIV negative, Urine routine microscopy-albumin(+), RBC & pus cell nil, ANA-strongly positive. Anti DsDNA - 40.3 U/ml (positive). C4- 170 mg/L (160-380) & low C3-558mg/L (790-1520). So diagnosis of SLE was done and was discharged with oral methyl prednisolone 15mg b.d. because of non-affordability of staying in hospital. On follow up after 2 weeks, there was improvement in clinical and laboratory findings.

DISCUSSION

Epistaxis & purpura complicating SLE as such is very rare (2%). Still rarer is the epistaxis & purpura as the presenting complaint in SLE (1%). In adults, four criteria have a sensitivity and specificity of 96% but In childhood SLE they have a sensitivity of 75% and a specificity of 96%. However these criteria may not present simultaneously but may present serially. A study in Sweden reported that more than half of patients with “incomplete” SLE fulfilled four or more...
of the ACR criteria after a median time of 5.3 years. Untreated, SLE is often progressive and has a significant fatality rate. Recent literature have advised to start appropriate medical treatment for SLE even with less than four criteria as in this case. So considering SLE as a D/D in a case acutely presenting like a bleeding disorder particularly in a female child is worth consideration.

BIBLIOGRAPHY


Plasma Cell Leukemia Presenting As A Rare Cause of Severe Anaemia

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ABSTRACT
Plasma cell leukemia (PCL) is a rare form of plasma cell dyscrasia characterized by proliferation of plasma cells that account for more than 20 percent of the differential leukocyte count. PCL is a rare yet aggressive form of multiple myeloma (MM) and can either originate de novo (primary PCL) or as a secondary leukemic transformation of MM (Secondary PCL). Secondary PCL occurs as progression of disease in 1-4% of all cases of MM. Here we report a case of secondary PCL in a 50 years old female. The case is presented because of its rarity.

Key words: - Multiple myeloma, primary plasma cell leukemia, secondary plasma cell leukaemia.

INTRODUCTION
PCL is a rare entity characterized by high levels of plasma cells circulating in the blood. The concentration of plasma cells exceeds 2x10⁹/L. The primary form presents with no previous history of MM and usually features a rapid clinical progression and short survival. The secondary type evolves as a terminal event in 1-2% of MM. The clinical presentation of PCL differs from MM and resembles that of acute leukemia.¹ Here we report a case of secondary PCL in a 50 years female who presented with severe anemia & lymphadenopathy.

CASE SUMMARY
A 50 years old female presented with complaints of fever, weakness, easy fatigability, anorexia and loss of weight for 2 months. There was no history of cough, hemoptysis, jaundice or abdominal discomfort. She did not have history of hematemesis, melena or bleeding haemorrhoids. She had attended menopause 2 years back and there was no history of per vaginal bleeding. She was non-diabetic and nonhypertensive. There was no other significant medical or surgical illness.

On examination she was of average body built with weight 42 kg, pulse 96/min, BP 120/70 mm of Hg. There was severe pallor but no icterus, cyanosis, clubbing or pedal edema. JVP was not raised. There were multiple, hard, non tender, mobile supraclavicular lymphnodes. Examination of chest and CVS revealed no abnormality. On examination of abdomen there were no organomegaly or free fluid.

On investigation haemogram revealed hemoglobin of 4.0gm/dl, total leukocyte count of 5.33x10⁹/L and platelet count was 1.40x10⁹/L. Peripheral smear showed marked hypochromia, rouleux formation and mileau of proteinaceous background, differential count of 24% immature plasma cells (fig1). Other abnormal laboratory
studies were high sedimentation rate of 175 mm/1hr. LDH-1130 iu/L, serum urea 43mg/dl, creatinine 2.1mg/dl and serum calcium 10.8mg/dl. Urine analysis was positive with Bence-Jones protein along with albumin. Skull x-ray revealed multiple punched out lesions (fig 3). Bone marrow aspirate was hyper cellular and showed diffuse replacement of marrow elements by 100% plasma cells(fig3). Serum protein electrophoresis showed monoclonal M band & immune fixation studies showed Ig A2 950mg/dl, IgG 628 mg/dl, IgM 16/mg/dl and IgA kappa paraprotein at a concentration of 2.95 g/dl.

DISCUSSION

Although plasma cells are occasionally observed in the peripheral blood of patients with MM, the term PCL is only used when the number of these circulating cells is significant (more than 20%). Because of the low frequency of PCL, most clinical data are collected from case reports and few reviews. Its incidence ranges from 1-2% of all myelomas.

Patients with PCL represent a unique subset of patients with MM. The diagnosis requires that (i) for a blood leukocyte count >10x10^9/L at least 2x10^9/L are circulating plasma cells, or(ii) for PBLC < 10x10^9/L at least 20% of the circulating cells must be plasma cells.

The plasma cell leukemia (PCL) is classified as primary when this is the initial manifestation of MM or secondary when it is seen in the context of refractory or relapsing disease. Secondary PCL occurs as a progression of disease in 1-4 percent of all cases of MM. PCL is associated with a poor prognosis and with a shorter survival than that of patients with typical MM. Clinical distinctions that have been reported between the two forms of MM include a younger age, a higher prevalence of hepatosplenomegaly, lymphadenopathy, thrombocytopenia, a lower serum M protein level, extramedullary involvement and renal failure when leukemia is present. Our patient was a female of 50 years who presented with severe anemia, fever and lymphadenopathy.

The role of conventional chemotherapeutic agents (Novel Agents) in the treatment of PCL remains undefined in contrast to their very good response in MM. In a study of 5 patients with PCL, Thalidomide did not result in a response in any. However, in another study, 4 Thalidomide-treated patients with PCL had a medium reduction in M protein of 80%. One achieving a very good partial response. Lenalidomide has been reported to be effective for the treatment of PCL as a single agent and in combination with melphalan and prednisone.

Bortezomib has shown good effectiveness in the treatment of plasma cell Leukaemia. Bortezomib treatment in PCL has led to restoration of normal peripheral blood counts and eliminations of transfusion dependency. Among 12 patients with PCL who received bortezomib, 5 achieved partial responses, 4 very good partial response, and 2 complete responses for a response rate of 92%. 8 of the patient were alive 6 to 21 months after treatment with bortezomib suggesting that this agent has particular effectiveness.

REFERENCES

(5) Johnston RE, Abdalla SH. Thalidomide in low doses is effusive for the treatment of resistant or relapsed multiple myeloma and for PCL. Leuk Lymphoma.2002;43(2);351-4.
(6) Benton DM JR, Smith MK. Effectiveness of lenalidomide (Revlimid) for the treatment of plasma cell leukemia. Leuk Lymphoma.2007;48(7);14 23-5.
Pretibial Myxedema

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Pretibial myxedema (also called localized myxedema, thyroid dermopathy, or infiltrative dermopathy) is an infrequent manifestation of Graves’ disease. It occurs in almost 5 percent of patients with Graves’ disease, many of whom are older and nearly all of whom have had both hyperthyroidism and ophthalmopathy. Pretibial myxedema is an infiltrative dermopathy that most frequently appears symmetrically on the anterior tibia and dorsal of the feet. The lesions can be morphologically variable, but commonly they consist of pink, flesh-colored to violaceous nodules. The skin can also present with a diffuse brawny edema without the nodules. In Grave’s disease, myxedema tends to occur in the presence of ophthalmopathy at a later stage in the disease. One half of the cases of myxedema occur after the patient becomes euthyroid with treatment.

It results from the accumulation of increased amounts of hyaluronic acid and chondroitin sulfate in the dermis in both lesional and normal skin. The mechanism that causes myxedema is unclear although animal model studies suggest that thyroid hormones affect the synthesis and catabolism of mucopolysaccharides and collagen by dermal fibroblasts. The fibroblasts in the orbital and pretibial dermis share antigenic sites that underlie the autoimmune process that causes Grave’s disease. This cross-reaction may contribute to the development of myxedema occurring long after euthyroid status is achieved through treatment.

Treatment for myxedema is difficult. Systemic or intralesional glucocorticoids, topical glucocorticoids under occlusion.

Various treatment modalities have been employed, including topical and systemic corticosteroids, compression dressings, and local injections. Moderate benefits of short-term topical corticosteroid therapy have been reported.

REFERENCES:

1. Pretibial Myxedema; Jeanie Chung-Leddon, MD, PhD; Dermatology Online Journal 7(1):18; 2001
4. Williams textbook of endocrinology;
Anaemia and Diabetes
Prasanna Kumar Rathor

Anaemia that remains an under recognised and under treated condition in diabetic patients may seriously affect the health and quality of life.

Diabetics are always at risk to develop kidney disease. Almost always kidney damage in diabetes is progressive and there is decline in kidney function. Around one-third to half of the diabetics are hypertensive or develop hypertension during their lifetime. They are at increased risk to develop deterioration in kidney function. The obese people may also have problems in kidney function and its exact cause is not known. Due to progressive damage from diabetes, hypertension and possibly from obesity less erythropoietin is produced. Lower levels of circulating erythropoietin ultimately leads to decreasing haemoglobin level and anaemia.

Anaemia is more common in patients with every stage of chronic kidney disease (CKD). The exact cause of this pathological process is not known.

CKD patients with diabetes, develop anaemia in the early stage of the disease. Anaemia worsens as CKD progresses towards end stage renal disease (ESRD) with 28% patients having anaemia in early stages (1 & 2) and 87% of patients having anaemia in later stages (3-5) Diabetics and prediabetics are at risk for developing CKD. In majority of the newly diagnosed cases of chronic kidney disease and kidney failure, diabetes is the leading cause.

Eventually 35% of diabetics develop nephropathy. This progressively destroys the kidney and reduces production of erythropoietin.

The progression of CKD in diabetes can be significantly reduced by early diagnosis, aggressive treatment of hypertension and tight control of blood glucose. The ideal blood pressure for diabetic hypertensive is always below 130/80 mgHg. For this low salt, appropriate diet, permissible exercise and medication by a clinical diabetologist is essential.

The use of angiotensinogen - converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in these patients protect the kidneys from hypertensive damage but which also contribute to the suppression of erythropoiesis and to development of anaemia.

For diabetic patients the cause of anaemia can be multifactorial resulting from the complication of kidney disease, nutritional deficiencies or inflammation of chronic disease and also associated with thiazolidinedione therapy. Anaemia was reported with 1% of patients treated with pioglitazone. This effect is most likely due to a slight increase in plasma volume. Studies have shown that TZDs do not cause hemolysis or affect red cell mass or erythropoiesis.

Management of Anaemic in diabetes:

CBC is checked for detection of anaemia when proteinuria is detected or eGFR is below 60ml/minute. Patient must take salt restricted diet. Dietary protein restricted to 0.8gm/Kg/day. Therapeutically vitamin B12 and Iron is administered. The response to therapy is monitored. Erythropoietin may be infused. Patient is referred to a Nephrologist for further management.

References:
3. Fonseca, Vivian A Clinical Diabetes 2006 pp. 312-313
CT Signs of Abdominal Aortic Aneurysm Rupture

Sasmita Parida

Abdominal aorta begins at the level of diaphragmatic hiatus and bifurcates at the level of L4 into the common iliac arteries. The normal caliber of abdominal aorta increases with age; at the renal hila, it’s mean diameter varies from about 1.5 cm in women in the fourth decade of life to about 2.0 cms in diameter in men in eighth decade. Abdominal aortic aneurysm is defined as a localized dilatation of the vessel by 50% or more of it’s normal diameter (when the wall to wall diameter is < 3cm in adult). The most dreaded complication of abdominal aortic aneurysm is rupture hence we will discuss few CT signs of impending or contained abdominal aneurysm rupture. This is in fact the most important diagnosis in patients with acute abdominal pain especially back or flank pain.

Primary Signs:
- Peri-aortic Stranding
- Retroperitoneal haematoma

Majority of these cases show posterior periaortic haemorrhage. Massive haemorrhage into posterior perirenal compartments are also seen. Intra peritoneal haemorrhage may be seen. Extravasations of contrast media is noted in contrast CT scans in these cases.

Secondary signs of Abdominal Aortic Rupture:
- Increase in aneurysm sign
- Low thrombus to lumen ratio – Thick circumferential thrombus is protective against aneurysm rupture. In addition enlargement of patent lumen is indicative of partial lysis of the thrombus, which predisposes an aneurysm to rupture. So thrombus to lumen ratio is a good indication of abdominal aortic rupture.
- High attenuation crescent sign – This represents an acute haematoma either within the mural thrombus or the aneurismal wall. It is one of the earliest and most specific sign of aneurysm rupture. It shows the loss of ability of the thrombus to protect the aneurysm against rupture.
- Focal discontinuity of aortic calcification.
- Tangential calcium sign – It looks as if the calcium is pointing away from the expected circumference of the aneurysm.
- Drapped aorta sign – Some area of the posterior aortic wall is not identifiable and posterior aorta follows the contour of spine in one or both sides.

Summary:

Imaging findings of Aortic aneurysm rupture is varied. It may be from small aortic leaks with subtle infiltration of retroperitoneal fat to frank retroperitonel or intraperitoneal extravasations. It occurs most commonly as a consequence of atherosclerotic disease of aorta.

Ruptured abdominal aortic aneurysm: CT scan showing a ruptured but contained abdominal aortic aneurysm. The abdominal aortic aneurysm is outlined circumferentially with calcium (arrow), and the area of contained hemorrhage is seen posterior to the aorta.
Ruptured aortic aneurysm: Contrast CT Scan shows site of leak (white arrow) with retroperitoneal haemorrhage (curved black arrow).

Draped aorta sign: CT Scan shows the posterior wall of the aorta is not distinctly identifiable on right side (arrow) and follows the contract of the adjacent vertebral body.

Hyperattenuating Crescent Sign: CT scan shows a well-defined peripheral crescent of increased attenuation (arrow) within the thrombus of a large abdominal aortic aneurysm.

References:
1. High attenuation crescent in the abdominal aneurysm wall at CT, a sign of acute or impending rupture.
2. Acute abdomen – Aortic aneurysm rupture CT signs of impending Aortic aneurysm rupture, Jay P. Heiken
5. Diagnostic imaging – Cardiovascular abbara – walker – Imbesi – Ng, Roberts, Page II, 5-10 to II 5, 13.
HIV and Anaemia
Sanjay Swain

INTRODUCTION:
Anaemia is the most common haematological complication of HIV infection and associated with a high morbidity and a poor prognosis. HIV infection is associated with a reduction in CD4 + numbers and altered Iron metabolism. Anaemia in HIV infection has a multifactorial aetiology, occurs frequently and is associated with increased disease progression and a shortening of survival time. Direct viral effects, reduced energy and nutrient intake, inflammation and metabolic alterations have been proposed as important biological factors enhancing the risk of anaemia with infection.

INCIDENCE & SIGNIFICANCE:
The yearly incidence of developing anemia in HIV positive individuals increases with disease progression, affecting 3 percent of all patients with asymptomatic HIV infection, 12 percent of asymptomatic patients with CD4 cell counts <200 cells/dL, and 37 percent of patients with an AIDS-related illness [1]. Anaemia is the most common hematologic abnormality associated with HIV infection, affecting 60 to 80 percent of patients in late stage disease. While anaemia may manifest as a mere laboratory abnormality in some individuals, others may experience typical symptoms (eg, fatigue, dyspnea, reduced exercise tolerance, diminished functional capacity) directly related to a reduction in hemoglobin concentration. Shortly after the first description of the acquired immunodeficiency syndrome (AIDS), cytopenias of all major blood cell lines were increasingly recognized in patients with HIV infection. The incidence of erythropenia is noted in approximately 70 percent, lymphopenia in 70 percent, neutropenia in 50 percent, and thrombocytopenia in 40 percent . The incidence of the various cytopenias correlates directly with the degree of immunosuppression.

ETIOPATHOGENESIS:
The pathogenesis of HIV-associated anaemia is poorly understood and may include a direct effect of HIV on erythropoiesis. In vitro studies have suggested that specific HIV strains, like X4 that uses the CXCR4 co-receptor present on erythroid precursors, are associated with diminished erythropoiesis. This co-receptor affinity is determined by changes in the hypervariable loop of the HIV-1 envelope genome.

The other ways leading to anaemia in HIV infection are changes in cytokine production with subsequent effects on hematopoiesis; decreased erythropoietin concentrations; opportunistic infectious agents, such as Mycobacterium avium complex [2] and parvovirus B-19; administration of chemotherapeutic agents such as zidovudine, ganciclovir,[3] and trimethoprim-sulfamethoxazole; and myelophthisis caused by cancers such as lymphosarcoma. Other mechanisms for HIV-associated anemia, although uncommon, include vitamin B12 deficiency [4] and the autoimmune destruction of red blood cells. Direct infection of marrow precursor cells [5] has been hypothesized, but not proven.

The other possible causes of anaemia are bleeding due to gastrointestinal malignancy or severe infection etc.

DRUG INDUCED ANAEMIAS IN HIV INFECTION:
The administration of ZDV is recognized to cause anaemia because of myelosuppression. So prescription of ZDV is positively associated with a diagnosis of drug-related anemia but was protective against a diagnosis of anemia unrelated to drugs. The protective effect may also be explained by the fact that for patients who do not develop anemia related to ZDV and continue to take the drug, ZDV treatment may slow the progression of the HIV disease and the HIV replication rate. Lower viral burden, in turn, may be associated with a decreased incidence of anemia because of less cytokine-mediated myelosuppression.
The prescription of ganciclovir, known to cause myelosuppression, was also associated with the incidence of anemia, whether identified as drug related or unrelated. This suggests that anemia associated with prescription of ganciclovir may be less likely to be recognized or recorded in medical records as drug-related than anemia associated with ZDV prescription.

Fluconazole may cause myelosuppression when taken concurrently with ZDV, because taking both reduces the serum half life of ZDV and increases its serum concentrations.[6]

Administration of TMP-SMX can cause drug-associated aplastic anemia or immune-mediated destruction of specific populations of blood cells although the effect is sporadic. It is likely that the protective effect of TMP-SMX is associated with the prevention of other conditions, such as Mycobacterium avium complex [7]or bacterial septicemia, which are more predictable causes of anemia, or other infections that could promote the development of the anemia associated with chronic disease or with inflammation.

An increased incidence of anemia not recognized as drug related is observed in black persons. This association could be because of several factors or a combination of these factors. A small percentage of black persons have sickle cell anemia. The prevalence of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency may be 4% to 13% for black men[8 ] and 3% for black women.[9].For persons with G-6-PD deficiency, dapsone or sulfamethoxazole, both of which are prescribed for prophylaxis for P carinii pneumonia in patients with HIV infection, may cause hemolytic anemia.Persons with G-6-PD deficiency may also develop hemolytic anemia after infection with certain bacteria (including Salmonella).[10]

DISCUSSION :

It is found that anemia is a frequent complication of HIV infection that is associated with an increased risk of death and that recovery from anemia is associated with decreased risk of death for HIV-infected persons who do develop anemia. For most CD4 strata the median survival for persons who never became anemic was similar to the median survival for those who became anemic but later recovered.

The incidence of anemia was strongly and consistently associated with the progression of HIV disease as measured by diagnosis of an AIDS-defining opportunistic illness and measurement of a CD4 count of <200 cells/dL. This association is most likely explained by the increasing viral burden as HIV disease progresses, which could cause anemia by increased cytokine-mediated myelosuppression. Alternatively, anemia may be a surrogate marker for some aspect of disease progression not captured by controlling for CD4 count and clinical AIDS diagnosis.

Anemia is also associated with thrombocytopenia and neutropenia, perhaps because myelosuppression being caused by chemotherapeutics may affect production of all the cell lineages. The association of anemia with lymphoma may be due to myelophthisis, the secondary effects of therapies administered for lymphoma, or anemia associated with chronic disease. Myelosuppression is commonly observed in patients with bacterial septicemia, regardless of HIV infection status.

The outcomes of drug-related anemia and anemia unrelated to drugs are biased by the effect of ZDV prescription, one of the most recognized causes of anemia in HIV-infected persons. Because these two types of anemia are distinguished only on the basis of physician’s diagnosis as recorded in the medical record,because there is no standard criterion for drug-related anemia. The condition may have been under diagnosed or under documented in medical records or the association between ZDV prescription and drug-related anemia could be overestimated if physicians assume a drug-related cause for anemia in a patient who is taking ZDV.

The definition of anemia chosen for most of the studies (hemoglobin <10 g/dL) is different from clinical reference ranges for hemoglobin concentration in men and women. This cutoff level is chosen for defining anemia in general to exclude hereditary causes for mild anemia, such as thalassemia trait, and to allow for use of a single cutoff that would clearly include the normal hemoglobin concentrations for both men and women. Physicians should consult their local laboratories to determine appropriate reference ranges for clinical interpretation of hemoglobin concentrations. Of course any anemia in HIV-infected persons, regardless of severity, should be investigated and taken care up to improve survival rate.
CONCLUSION:

It has been seen that haemoglobin levels gradually decrease in HIV-infected patients who proceed towards death. Haemoglobin remains a strong independent prognostic marker for death after adjustment for CD4 lymphocyte count and viral load. Therefore, among patients with similar CD4 lymphocyte counts and viral load measures, those patients with a lower haemoglobin level are at a significantly increased risk of death. Further research is needed to determine the impact of newer treatment regimens on levels of haemoglobin.

Anemia in HIV-infected patients, if persistent, is associated with substantially decreased survival. As recovery from anemia is shown to directly increase survival in HIV positive persons, screening for anemia should be aggressive and patients with anemia should be treated with the best possible means.

REFERENCES:
1. DoukasMAHuman immunodeficiency virus associated anemia. Med Clin North Am761992699
2. GroopmanJEManagement of hematologic complications of human immunodeficiency virus infection. Rev Infect Dis121990931
4. FrontieraMMyersAMPPeripheral blood and bone marrow abnormalities in the acquired immunodeficiency syndrome. West J Med1471987157
7. ZauliGReMCVisaniGFurliniGLaPlacaMEvidence for a human immunodeficiency virus type-1 mediated suppression of uninfected hematopoietic (CD34+) cells in AIDS patients. J Infect Dis1661992710
8. ZauliGDavisBReMCVisaniGFurliniGLaPlacaMTat protein stimulates production of transforming growth factor-1 by bone marrow macrophages: A potential mechanism for human immunodeficiency virus-1 induced hematopoietic suppression. Blood8019923036
10. SpivakJBarnesDCFuchsEQuinnTCSerum immunoreactive erythropoietin in HIV-infected patients. JAMA26119893104

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