

National Board of Examinations

Considering the variations in the level of standards of post graduate and post doctoral examinations in our country and based on the recommendations of an Expert Group set up for maintaining uniform standards, the Ministry of Health & Family Welfare, Government of India, established the National Board of Examinations (NBE) in 1975, with its headquarters at New Delhi.

Objectives of NBE

Conduct postgraduate examinations in the disciplines of modern medicine at the national level.

Maintain a high standard of examination, so as to ensure that candidates have received adequate training and are competent in every way to practice as specialists, in their respective fields.

Constitute Speciality Boards in which the examinations are to be conducted.

Formulate basic training requirements for eligibility to appear for the respective examinations.

Prescribe course curricula for postgraduate studies.

Organize postgraduate courses, workshops, seminars, symposia and training programmes of specialised nature.

Institute professorships, other faculty positions, fellowships, research cadre positions and scholarships etc. for realising the objectives of the Board.

Constitute an Accreditation Committee to approve centers for DNB courses.

Co-ordinate with national and international bodies, agencies, universities for the furtherance of the objectives of the Board.

Vol. III. No.1-2, Jan. Apr. 2008

Journal of Postgraduate Medical Education, Training & Research

National Board of Examinations



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Ravinder Kumar Batra

Department of Anesthesia, All India Institute of Medical Sciences, New Delhi

Anemia is a laboratory diagnosis and is defined as an absolute or relative deficiency of circulating red blood cells or haemoglobin concentration less than normal for age and gender. It is not a disease per se, but a reflection of some other problem. Anaemia occurs when the balance between the normal rates of blood loss and blood production is disturbed. There are three basic mechanisms by which this occurs: (1) blood loss, (2) excessive destruction of red blood cells (haemolysis), and (3) abnormally low production of red blood cells by the bone marrow. Adult patients with haemoglobin concentration of less than 12.5g/dL in males and 11.5% in females are considered anaemic. Depending upon their haemoglobin level, the patients can be classified as having mild anemia (8-10 gm/dL), moderate anemia (6-8 gm/dL) and severe anemia (< 5 gm/dL). Mild anaemic patients coming for surgery are clinically symptom free, whereas moderate to severe anaemic patients will have pallor and complain of lethargy and other symptoms. However the symptoms of anaemia will depend upon duration, severity, concurrent disease and age of the patient. In a healthy person, symptoms do not develop until the haemoglobin level falls below 7g/dL. Anaemia complicates the management of patients by

reducing the oxygen content in circulating blood, which in turn reduces oxygen delivery to the tissues. Knowledge of the haemoglobin level and the cause of anaemia is important to an anaesthesiologist as some of the haemoglobinopathies may precipitate perioperative problems.

Oxygen Delivery and peri-operative transfusion-The delivery of oxygen is calculated by following formula:

$$Do_2 = CO \times (Hb \times SaO_2 \times 1.34 + PaO_2 \times 0.003)$$

Where Do_2 = oxygen delivery;
CO = Cardiac output

Hb = Haemoglobin concentration; SaO₂ = Percent of oxygenated haemoglobin 1.34 = Hufner number (constant 1.34 – 1.36); and 0.003 = dissolved oxygen (ml/mm Hg/dL)

The best haematocrit level at which the oxygen carrying capacity is ideally matched with the rheologic properties is approximately 27%. Gold standard ("10/30 rule" or 10g/dL Hb and haematocrit of 30%) has recently been challenged by different studies. Also there is no evidence in the literature suggesting that patients with mild anaemia have increased adverse events such as poorer wound healing, increased stroke, or myocardial infarction rates. In fact, patients who receive transfusion are at high risk of

peri-operative infection due to the immunomodulating effects of transfusion. So, it is difficult to determine the threshold at which anaesthesiologists should transfuse patient in the peri-operative setting. Also, transfusing red cells solely on the basis of haemoglobin concentration or haematocrit are no longer considered justified. Indications of transfusion of red cells should be based on the oxygen supply/demand ratio in the individual patient. These are decreased mixed venous oxygen concentration, serial measurements of lactate showing progressively increasing concentration and electrocardio-graphic changes suggestive of myocardial ischaemia. The main hesitancy of avoiding transfusions in the perioperative period is the complications associated with it and the complications should always make the clinician weigh benefits against potential risks. One should remember that transfusion should not be given solely to achieve volume expansion or to raise haematocrit to a certain level.

Physiological Effects and compensatory mechanism to increase oxygen delivery in severe and chronic Anaemia- In the absence of preexisting major end organ dysfunction and maintenance of normovolemia, majority of the patients tolerate severe anaemia well due to following changes:

- Blood viscosity is decreased with accompanying vasodilation.
- Blood flow increases due to fall in systemic vascular resistance.
- Augmented stroke volume (increased plasma volume) increases cardiac output, allowing arterial blood pressure and pulse rate unchanged.
- In the absence of coronary artery disease and carotid artery stenosis, coronary and cerebral blood flow increase, that is there is redistribution of blood to vital organs.
- Increase in tissue oxygen extraction as reflected by decrease in venous oxygen saturation

Oxygen Dissociation Curve (ODC) and Anaemia-Chronic anaemia shifts the ODC to right due to increase in 2,3-diphosphoglycerate in red blood cells and increased P-50. This reduces the oxygen affinity for haemoglobin thereby enhancing the oxygen delivery to the tissues. Preoperative transfusion in patients with chronic anaemia should be avoided as the compensatory mechanism for better tissue oxygen delivery may get disturbed.

Types of Anaemia-Anaemia can be classified into following types

Acute - Blood loss and Haemolysis

Chronic - Nutritional/ consumptive (Iron deficiency anemia, Vitamin B₁₂ deficiency, Folate deficiency)

Haemolytic anemias

Corpuscular hemolytic anaemias - Cell membrane defects (Spherocytosis); Hemoglobinopathies (Thalassemia and Sick Cell Anaemia); Enzyme defects (Glucose - 6 - Phosphate Dehydrogenase deficiency, and pyruvate kinase deficiency)

Extracorporeal hemolytic anaemias-Immunologically mediated (Rh incompatibility, ABO transfusion reactions, autoimmune hemolytic anaemia); Result of consumption of certain medications; Caused by infectious diseases; Metabolic derangements (Zieve syndrome) or The result of microangiopathic processes (hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura).

Differential Diagnosis of Anaemia-Differential diagnosis of anaemia can be made by doing following investigations and the results can be interpreted accordingly:

Erythrocyte indices used to categorize anaemia and pin-point probable cause are:

- MCH: Mean Corpuscular hemoglobin
- MCV: Mean Corpuscular volume
- MCHC: Mean Corpuscular Hemoglobin concentration (Hb/Hct)

Serum Iron, Transferrin and Serum Ferritin, Serum Folic acid, Serum Vitamin B₁₂ levels

Iron Deficiency Anaemia-The Iron stores are 50mg/kg and 35mg/kg with daily intake of Iron as 12mg and 15mg in adult male and adult females

respectively. Iron deficiency anaemia is the most commonly occurring anaemia among the surgical patients. It is due to chronic blood loss or to increased requirement in pregnancy or infancy or nutritional. Severe iron deficiency anaemia can result in respiratory distress, congestive heart failure, thrombocytopenia, and neurological abnormalities. Clinical features are Fatigue, breathlessness, koilonychia, hair loss, Plummer-Vinson syndrome

Diagnosis- Peripheral smear will show as microcytic/hypochromic anaemia, with decreased reticulocyte count and decreased MCH/MCV ratio. Serum transferrin is increased. Low serum ferritin and serum iron concentrations. Bone marrow will show low to missing iron deposits.

Treatment- Locating the source of chronic blood loss. Iron supplementation: Oral or intravenous

Anaesthetic Implication-It is always advisable to raise the haemoglobin level by iron supplementation if time permits.

Megaloblastic Anaemia-The two most common forms are vitamin B₁₂ deficiency and folic acid deficiency. Vitamin B₁₂ and folic acid are important cofactors in the synthesis of DNA. The deficiency of these leads to insufficient amount of DNA which results in reduction in production of adequate amount of red cells by bone marrow. This, in turn leads to very large blood cells, each packed with an abnormally high amount of haemoglobin. Vitamin B₁₂

deficiency leads to pernicious anaemia. It is most commonly caused by an autoimmune disease. Other causes are strict vegetarian diet, malabsorption syndrome, blind loop syndrome and tapeworm infection. Symptoms: Dyspnoea on exertion, anorexia, weight loss, weakness., easy fatigability, palpitation, syncope, headache and angina pectoris. Other symptoms of vitamin B₁₂ deficiency are neurologic (degeneration of the lateral and posterior spinal cord columns leading to peripheral neuropathy and gait ataxia) and gastroenterologic (atrophic tongue or Hunter's glossitis). These patients may suffer from depression or psychotic symptoms. Early warning sign is loss of sensation to vibration. Liver and spleen may be palpable. Congestive heart failure, cardiac arrhythmias, and murmurs may be noted.

Diagnosis-Peripheral smear and bone marrow will show oval, egg-shaped or tear-drop form macrocytic, hyperchromic cells with normal reticulocyte count and normal serum iron, whereas MCH/MCV ratio is increased. Plasma vitamin B₁₂ concentration is low.

Treatment - Parenteral vitamin B₁₂

Folic acid deficiency-Folic acid deficiency is the most common cause of anaemia in pregnancy due to increased requirement. It is also seen in alcoholic, patients with abnormal diet habits and patients taking methotaxate and phenytoin. It does not produce

any neurologic sequelae in an adult but may produce neural tube defects in early pregnancy. Diagnosis is made by peripheral smear and measurement of plasma folic acid concentrations. Treatment by oral folic acid.

Anaesthetic Implication - Proper neurological evaluation should be done before planning for peripheral nerve blocks and regional anaesthesia. Use of succinylcholine controversial if significant muscle wasting is present. The clinical significance of effects of nitrous oxide on vitamin B₁₂ metabolism is controversial but it should be avoided in these patients as nitrous oxide converts the cobalt from the monovalent form to the bivalent form. As a result, methionine synthase activity is inhibited.

Spherocytosis-It is one of the most common inherited haemolytic anaemia in which there is a defect in the erythrocyte membrane. This causes increased permeability to sodium and water giving erythrocyte its typical spherical form. This spherical erythrocyte is susceptible to phagocytosis in the spleen at an early stage. Due to this, patients are prone to haemolytic crises and released bilirubin subsequent to haemolysis causes gallstones formation.

Diagnosis-Normocytic, normochromic anaemia, Normal MCH/MCV ratio and normal serum iron, whereas reticulocyte count is increased. Signs of haemolysis (increased indirect bilirubin, increased dehydrogenase, increased reticulocytes). Osmotic testing confirms the diagnosis

Anaesthetic Implications- Patients are more prone for infections and septicemia may set in early as some of these patients may have undergone splenectomy for recurrent haemolytic crises. So prophylactic vaccination must be advised for these patients.

Haemoglobinopathies- Haemoglobinopathies result from the abnormal haemoglobin molecules which in turn results from exchange of only one amino acid to another on α or β chains of globin molecule. The important and most common haemoglobinopathies are Sickle Cell Anaemia and Thalassemia.

Thalassemia-This is a group of inherited disorders resulting from inability to produce structurally normal globin chains. This produces abnormal haemoglobin molecule which results into subsequent haemolysis. This disorder can affect both α and β globin chain synthesis. It is divided into major thalassemia if the bearer is homozygous and minor thalassemia if the disease is heterozygous. β -thalassemia major (Cooley's anaemia) is rare and carries poor prognosis. α -thalassemia is incompatible with life.

Diagnosis-There are three prominent features of thalassemia : anaemia, hamolysis, and marked hyperplasia. Anaemia is microcytic and hypochromic. Clinically patients will have prehepatic jaundice, hepatosplenomegaly and an increased susceptibility to infections. Patients may have retarded growth, fractures and facial dysmorphism due to bone marrow hyperplasia. Extramedullary marrow develops in the

pleura, sinuses, epidural space, and pleural cavity. Spontaneous bleeding from these can cause haemothorax, epidural haematoma, and epistaxis. Due to multiple blood transfusions, patient may develop secondary haemochromatosis and may die of complications like arrhythmias, congestive heart failure, or cardiac haemochromatosis.

Diagnosis-Minor thalassemia may show mild anaemic states with microcytic/hypochromic, reduced MCH/MCV ratio, decreased reticulocyte count and increased serum iron. The diagnosis is confirmed by electrophoresis.

Treatment-Based on severity of anaemia, thalassemia major must be treated aggressively to reduce complications and prolong life. Bone marrow transplantation may cure thalassemia. Repeated transfusion will be required if bone marrow transplantation fails.

Anaesthetic implications-Cardiac evaluation to rule out effect of haemochromatosis. Evaluation of the airways and anticipate difficult intubation. Epidural, spinal, and intrapleural anaesthesia or analgesia relatively contraindicated.

Sickle Cell Anaemia-In Sickle Cell Anaemia, there is a mutation in the sixth amino acid in the α -chain of the haemoglobin molecule. In this glutamic acid is replaced by valine. The deoxygenated form, haemoglobin S (HbS) has the tendency to precipitate, causing the erythrocytes to lose their normal

biconcave form and to take on a sickle like structure. This leads to sludging and occlusion of the microvasculature resulting to end organ infarction. The diagnosis of Sickle cell anaemia is based on microscopic sickle cell test or by haemoglobin electrophoresis. Depending upon this, Sickle Cell Anaemia is divided into heterozygotic (HbSC), when HbS is less than 50% or homozygotic (HbSS). Heterozygotic carriers are generally asymptomatic, whereas homozygotic carriers can have sickle cell crises subsequent to triggering agent and as early as infancy. Anaesthetic management is focused on prevention of sickling or sickle cell crises during the perioperative period. Although heterozygotic carriers do not present much problem but all the patients should be kept well hydrated, warm and well oxygenated. Any episode of acidosis should always be prevented in these patients. Although tourniquet have been successfully used in some cases whereas exchange transfusion to improve HbS <30% is no longer considered proper standard of care. General anaesthesia is still believed by many investigators as a better choice for complex sickle cell anaemia over neuraxial anaesthesia. Cytotoxic agents such as hydroxyurea stimulate the production of fetal haemoglobin and are being studied in the prevention of vaso-occlusive crises. Inhaled nitric oxide has shown promise in being able to reduce the sickling process and even to unsickle cells.

Enzyme Deficiency Anaemia-Glucose-6-phosphate dehydro-

genase (G6PD) deficiency and pyruvate kinase deficiency are the most commonly seen enzyme defects within the erythrocyte leading to haemolysis.

G6PD Deficiency - G6PD deficiency is one the groups of congenital hemolytic anaemia, and its diagnosis should be considered in children with a family history of jaundice, anemia, splenomegaly, or cholelithiasis, especially in those of Mediterranean or African ancestry. The enzyme defect is inherited recessively on the X-chromosome. Oxygenation injury of the erythrocyte occurs as these contain reduced amount of glutathione. Infections or ingestion of some drugs or chemicals may precipitate haemolytic crises. These drugs are phenacetin, high doses of aspirin, penicillin, streptomycin, chloramphenicol, sulfacetamide, sulfanilamide, sulfapyridine, nalidixic acid, isoniazid, primaquine, quinidine, doxorubicin, methylene blue, and nitofurantoin. The diagnosis of G6PD deficiency is made by a quantitative spectrophotometric analysis or, more commonly, by a rapid fluorescent spot test detecting the generation of NADPH from NADP. The test is positive if the blood spot fails to fluoresce under ultraviolet light. In field research, where quick screening of a large number of patients is needed, other tests have been used; however, they require definitive testing to confirm an abnormal result. Tests based on polymerase chain reaction detect specific mutations and are used for population screening, family studies, or prenatal diagnosis.

Anaesthetic implications-

Anaesthetic drugs have not been implicated as haemolytic agents. Since these patients are unable to reduce the methaemoglobin produced by sodium nitrate, therefore sodium nitroprusside and prilocaine should not be administered. Early postoperative evidence of haemolysis might indicate G6PD deficiency.

Treatment-The main treatment for G6PD deficiency is avoidance of oxidative stressors. Rarely, anemia may be severe enough to warrant a blood transfusion. Splenectomy generally is not recommended. Folic acid and iron potentially are useful in hemolysis, although G6PD deficiency usually is asymptomatic and the associated hemolysis usually is short-lived. Antioxidants such as vitamin E and selenium have no proven benefit for the treatment of G6PD deficiency. Research is being done to identify medications that may inhibit oxidative-induced hemolysis of G6PD-deficient red blood cells

Pyruvate Kinase (PK)

Haemolysis - PK is a glycolytic enzyme of glycolysis (Embden-Meyerhof) pathway. It is most common defect due to autosomal recessive pattern of inheritance. The normal erythrocyte does not have mitochondria and relies on glycolysis to produce adenosine triphosphate to maintain cellular integrity. A deficiency of PK produces potassium leak from red blood cells, increasing their rigidity and accelerating destruction in spleen. Homozygous carriers present with haemolytic anaemia, premature

cholelithiasis, and splenomegaly. The degree of anaemia varies from mild to severe, transfusion dependent anaemia. No special anaesthetic consideration other than those for any patient with chronic anaemia.

Antibody – induced Haemolysis -

Haemolysis and agglutination are two major reactions which result from antibodies. Antibodies directed against erythrocytes are either IgM and IgG in structure. IgM antibodies with molecular weight of 900,000 daltons are larger (complete) and can act like a bridge between two erythrocytes. Examples of IgM antibodies are ABO isoagglutinins and cold agglutinin. IgG antibodies are smaller in size (150,000 daltons) and cannot form a bridge between two erythrocytes (incomplete antibodies). Examples of IgG antibodies are Rhesus (Rh) agglutinins and warm antibodies. The Coombs test is used to diagnose the presence of incomplete antibodies either already attached to the surface of erythrocytes (direct Coombs test) or in the patient's serum (indirect Coombs test).

Autoimmune Haemolytic

Anaemia-It is caused by either warm (IgG) or cold (IgM) antibodies. Seventy percent of all autoimmune haemolytic anaemia are caused by warm antibodies and these are seen in patients with Non-Hodgkin's lymphoma, systemic lupus erythromatosus, viral infections, and after ingestion of certain drugs (penicillin, á-methyl dopa). These antibodies bind to surface of

erythrocytes at body temperature without causing haemolysis. The erythrocytes undergo phagocytosis in spleen thereby diminishing the survival time to only a few days. This increases erythropoiesis to ten fold.

Fifteen percent of all patients with autoimmune haemolytic anaemia present with cold antibodies. These antibodies are seen in patients after Mycoplasma pneumoniae or mononucleosis. These antibodies lead to acrocyanosis and haemolysis as soon as intravascular temperature decreases below 25° to 30°C.

Anaesthetic implications-

Maintain a warm environment essential for prevention of haemolysis. Plasmapheresis to reduce the titre of cold antibody is recommended in hypothermic procedures such as cardiopulmonary bypass.

Traumatic Haemolysis-

This is seen in patients with mechanical cardiac valves, intra-aortic balloon pumps or after severe physical exertion specially extreme hiking, runner anaemia.

Renal Anaemia-

These patients have normocytic, normochromic anaemia due to inadequate production of erythropoietin. The severity of anaemia may vary with degree and duration of renal failure. The causes of anaemia in renal failure are due to decreased erythropoietin, haemolysis, bleeding from gastric ulcer and retention of toxins. It can also be associated with iron deficiency due to decreased absorption of iron from intestine and folic acid deficiency due to loss of folate

in dialysate and as a result of decreased folate intake. Haemoglobin concentration varies from 7 to 9g/dL. Packed cells to be transfused if there are signs of ischaemia. Recombinant human erythropoietin is given to raise haemoglobin level.

Anaesthetic Implications-Uraemic patients with chronic anaemia tolerate anaesthesia well, probably because they have a normal or higher than normal plasma volume. It is therefore recommended not to set a specific rule as to an acceptable haematocrit, but rather to evaluate each patient individually.

Acute blood loss or Haemorrhagic shock - It is one of the most challenging situations since the compensatory mechanism conceal the laboratory values until one loses half of the circulating blood volume. Haemoglobin value falls only with concomitant administration of intravenous fluid. Anaemia will develop within hours by shift of interstitial fluid in the absence of intravenous fluid administration. So the haemoglobin and haematocrit may not correctly represent the amount of blood loss in acute stages. For this anaesthesiologist should assess these patients clinically preoperatively by signs of hypovolemia like orthostatic hypotension, tachycardia, narrowing of pulse pressure, alteration of cerebral function, and low urine output.

Diagnosis - Normocytic, normochromic anaemia, MCH/MCV ratio normal, increased reticulocyte count but normal serum iron

Anaesthetic Implications-The blood volume should be replaced by crystalloid, colloid or RBCs as guided by central venous pressure measurement. Avoid myocardial depressant and vasodilator anaesthetic agent if blood volume not properly replaced.

Anaemia due to Hepatic Failure-Anaemia due to hepatic failure is associated with chronic severe liver insufficiency. This may or may not be related to deficiency of folic acid or bleeding from oesophageal varices, gastritis, duodenal or gastric ulcers. Thrombocytopenia and decreased levels of coagulation factors may contribute to increase bleeding.

Anaesthetic Implications-Routine preoperative transfusion may not be required and these patients tolerate anaesthesia well with low haematocrit levels.

Aplastic Anaemia-Certain drugs like antimicrobials, analgesics, anticonvulsants, antihistamins, anti-inflammatory agents, tranquilizers, a thyroid drugs, hypoglycemics and chemicals such as benzene, carbon tetrachloride, and glue can cause depression of bone marrow. This results in defective erythropoiesis.

Diagnosis-Normocytic, normochromic anaemia, MCH/MCV ratio normal, reduced reticulocyte count but normal serum iron

Treatment-Avoidance of potentially incriminating drugs or chemical. Steroids.

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Ravindranath R. Tongaonkar

DR. Tongaonkar Hospital, Dondaicha, Dhule

Now rural surgery is accepted as a specialty. Many Surgeons are going to remote areas and setting their practice in small towns. It is mandatory for them to know what is expected of them in rural areas and what common basic surgical skills they should possess before going to these areas. National Board of Examination has recently launched a pilot project to impart special training to rural surgeons under the title of 'DNB (rural surgery)'. The Association of Rural Surgeons of India is helping the National Board in this venture. This article is based on author's personal experience of 41 years working in a small remote town and 3 Surveys. The article gives an over all view of what is expected of a rural surgeon and what basic surgical skills he must possess when he decides to go to rural areas. Based on analysis of 20100 surgical procedures¹ carried out by the author, in a small rural hospital over 30 years period from 1967 to 1997, ENT & Head and neck (9.92%), Genito-Urinary (10.11%), Abdominal including Hernias(17.05%), Extremities including fractures (25.95%), OBG (27.1%), others (9.86%) .

In the initial period of practice more frequently performed operations were- tonsillectomies, appendectomies, hernias and

hydroceles, supra - pubic cystolithotomies, ano-rectal procedures like piles, fistulae and fissures. Tubectomies, lower segment caesarean sections, and D & Cs (Dilatation and curettage of uterus) were common gynaec procedures. Less frequent, but not uncommon major, planned operations were, thyroidectomies, radical and simple mastectomies, intestinal resections, hemicolectomies, hysterectomies, nephrectomies and pyelolithotomies, prostatectomies, ovarian cystectomies and lumps and bumps all over body and pediatric surgery procedures like meningoceles & Ramstad's operations. In the initial periods Emergencies were much more common, 44% as compared to 36% in a series from Sassoon Hospital Pune² But later the incidence of emergencies reduced to 31%³ Among the emergency procedures fractures and dislocations were most-common. Next common were traumatic and septic affections of the extremities. Obstructed labor due to all sorts of causes, many times needing caesarean section was very common. Sometimes author had to use obsolete procedures like craniotomies, internal podalic version or evisceration. The common abdominal emergencies were acute appendicitis, intestinal obstructions, and perforations, ruptured ectopic pregnancies and

acute retention of urine mostly due to enlarged prostate. One more notable feature the author faced during his 41 years of practice. In absence of any assistant like registrar or house surgeon even at the age of 68 he has to do all minor surgical work himself, like incising abscesses, suturing CLWs, doing circumcisions and removing sebaceous cysts and lipomas.

The second method is based on surveys done by sending questionnaire to rural surgeons across the country³

- First survey was carried out in 1988 by the Rural Health Care committee of Association of Surgeons of India (ASI) under the chairmanship of Dr. R.D. Prabhu (author was also one of the members of that committee). There were 151 respondents out of these 142 were working in the rural areas. According to this study 80% of rural surgeons were doing gynaec surgery. As regards paramedic work, the analysis showed that more than 90% rural surgeons had their own X-ray machine and 77% had their own laboratory. Regarding anesthesia 45% did not have qualified anesthetist and 60% had to give anesthesia to their own

patients at some time or the other.

- Second study and survey was carried out jointly by Dr J. K. Banerjee and the author himself in 1995. There were 75 respondents. Out of these 71 i.e. 94% were doing gynaec and obstetric work.
- Third study was author's own survey with specific questions. There were 48 replies and 45 eligible rural surgeons. Besides many questions relating to their work, hospital, equipment, problems & difficulties & family life, few questions were pertaining to their actual clinical work. One question was regarding whether they treat medical patients like cardiac patients, unconscious patients and fever patients - 16 out of 48 surgeons were treating cardiac patients, 26 were treating unconscious patients and 36, fever patients. Regarding gynaec practice 27 (60%) were doing medical termination of pregnancy (MTP), 32 (71%) were performing lower segment caesarean section and 41 (91%) were doing hysterectomies. Answering the question regarding major general surgical procedures like radical mastectomies, vagotomy, gastro-jejunosotomies, intestinal resections, cholecystectomies and kidney operations, around 50% rural surgeons reported that they were performing these procedures.

The nature of rural surgical practice is entirely different as compared to city practice. A study on Intermediate Technology in Surgery carried out by the International Federation of Surgical Colleges had concluded that 'Most of the surgery of third world will be carried out in district hospitals and every doctor in such hospitals must be prepared to under take surgery as part of a much wider range of duties⁴. In our experience, the rural patients do not differentiate between a physician, a surgeon or gynecologist so there is more work of consultation taking major part of the surgeon's time. In the analysis of author's first 18 years practice there were 75060 O.P.D. patients as compared to only 5769 operations⁵. Emergencies are much more common in comparison to city practice and disturb the sleep of the surgeon almost daily. As there are no pathologists or radiologist the surgeon has to keep his own laboratory and blood transfusion service, and a small X-ray machine. He also must have an ultra-sonography machine & knowledge to handle it and do scans¹. There are no facilities for frozen section biopsies. In absence of special investigations, clinical judgment is the most important armamentarium in diagnosis. Qualified anesthetist and qualified staff and paramedical personnel are not available and the rural surgeon has to have knowledge of all the procedures done by these personnel⁶. On the operation table the rural surgeon has to perform procedures from all

branches of surgery including gynecology and obstetrics. The three specialties, i.e. Orthopedic, ENT and Gynaec form almost 65% of rural surgical practice. Besides surgery, the rural surgeon has to admit all cases needing hospitalization like pediatric patients, unconscious patients, patients with high fevers, convulsions, status asthmatics, heart attacks and some times even schizophrenics. Thus the rural surgeon has to be 'Jack of all but Master of Surgery' and for this he must have special training⁷. Prof. Ram Murthi in his presidential address and personal communication has raised a question regarding whether there should be a different training program for 'professorial surgeons' (teaching in Medical colleges) and practicing surgeons (like rural surgeons)⁸. We, the members of Association of Rural Surgeons of India (ARSI), were insisting on such type of special training for rural surgeons in many of our meetings and presentations. According to a study carried out in Canada the most common surgical procedures in communities of 10,000 people or less are hernias, tubal ligations, appendectomies, breast biopsies, closed fracture reductions, anorectal surgery, varicose vein procedures, cholecystomy and hysterectomy⁹. South African medical schools train GP's with advanced surgical skills. The most common surgeries performed by South African GP-surgeons are tonsillectomy, D&C, appendectomy, closed fracture reduction, caesarean section, tubal ligation, breast lumps, and

hysterectomies¹⁰. In a draft prepared by a Working Group of the Society of Rural Physicians of Canada for training for family physicians in general surgery, a curriculum for a national training program in advanced surgical skills for rural family physicians has been prepared¹¹. The draft suggests following basic skills to be learned by a prospective rural surgeon:

- Abscesses, hematoma
- Acute abdominal pain
- Abdominal trauma
- Abdominal masses
- Acute gynecological problems - PID, ovarian cyst, ectopic pregnancy
- Breast lumps and infections
- Burns - with and without skin grafting
- Caesarean section
- Circumcision - adult and child
- Chronic tonsillitis, tonsillar abscesses
- Compartment syndrome
- Facial injuries - zygomatic fractures, nasal bone fracture
- Hand injuries - extensor tendons, flexor tenosynovitis, partial amputations, metacarpal fractures
- Hand pain - ganglion, trigger finger, carpal tunnel syndrome
- Ingrown toenails
- Leg ulcers
- Groin lumps and pain
- Neck lumps
- Nerve and tendon entrapment
- Pilonidal abscess/sinus
- Scrotal swelling
- Sterilization - male, female
- Laparoscopic skills
- Endoscopic skills
- GI bleeding, altered bowel habits
- Hemorrhoids, rectal pain

- Z-pasty, full and split thickness skin grafts
 - Repair and treatment complex wounds and infections
 - Venous incompetence
 - Abnormal uterine bleeding
- Almost similar but more comprehensive curriculum has been prepared by the National Board of Examinations with the help of senior rural surgeons for the course of DNB (rural surgery) which the student must acquire, before getting that qualification. Thus if a surgeon decides to practice in rural areas he must have knowledge and possess all the basic skills discussed in the article. Later if he wants to develop more advanced and more sophisticated skills, not only in surgery but in any specialty, no body can prevent him or her. There is ample scope for improvement even in rural areas and 'Sky is the limit' provided he or she knows the limitations in the rural areas!¹²

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Commentary

Sanjivni Khanna, J.Anupama

Department of OBG, Maharaja Agrasen Hospital, Delhi

Cancer of the cervix is the commonest cancer in Indian women. India accounts for 1/5th of the world's burden of cervical cancer. India's age-standardized incidence ratio of 30.7/100,000 women and age-standardized mortality rate of 17.4 / 100,000 women for cervical cancer is the highest in South Asia. In a low resource setting, the lifetime risk of a woman developing cervical cancer is 2-4%. Annually, 85% of deaths due to cervical cancer all over the world occur in poor-resource countries. ¹Organized cytology-based screening programs have reduced the incidence of cervical cancer in developing countries. ² Implementation of such screening programs in low-resource settings is a challenging task for the following reasons:

- logistics involved for cytology based screening of a large population can put a lot of stress on existing scant resources
- requirement of trained personnel to perform the test and interpret the result
- need for multivisit approach
- paucity of centers with facility for colposcopy and histopathology, both of which are integral to the management of abnormal cytological smears.³

Alliance for Cervical Cancer Prevention (ACCP)- The ACCP was formed in 1999 to develop innovative and alternative approaches for cervical cancer screening. Efforts were made to put into operation, non – cytology-based screening techniques that will conquer the aforesaid hurdles. ⁴

Rationale for screening in cervical cancer- Screening programs for cervical cancer are feasible because of the following reasons:

- It is a significant health burden with high morbidity and mortality
- It has a long latent phase
- Effective treatment for precancerous lesions is available
- Easy accessibility of the cervix during routine gynecological examination
- Simple, safe, effective and culturally acceptable screening techniques are available.

Approaches to screening ⁵

Camp Approach-This approach is temporary. It can sensitize the population for screening though it does not make any impact on incidence and mortality.

Hospital-based screening- This is also temporary as it is sanctioned for a specific time frame and cannot be incorporated into the system due

to poor resources. In India, this is restricted to urban areas .

High-Risk screening-As the name implies, it refers to screening of high-risk individuals. High risk factors for cervical cancer include:

- Onset of intercourse before the age of 15 years
- Multiple sexual partners
- History of sexually transmitted disease
- Early age at first delivery
- Multiparity
- Unhealthy appearance of the cervix on gross examination

Frequency of screening ⁵- In 2007, ACCP has laid down recommendations regarding frequency of screening in low-resource settings. Every woman has the right to cervical screening at least 'once in a lifetime'. In India, 'once in a lifetime' screening would result in reduction of 20-30% in the lifetime risk of cervical cancer.

Screening programs in low resource settings should fulfill the following criteria:

- Use less resource intensive screening techniques
- Use screening techniques with good accuracy
- Based on the country specific information, formulate protocol for age of initiation of screening, frequency of screening and recommendation for follow-up & treatment.

- Educate women and motivate them to seek screening facilities

Proposed screening techniques in low resource settings

Unaided visual inspection (UVI) - It is referred to as “Downstaging” by WHO. Downstaging for cervical cancer is defined as “the detection of the disease in an earlier, curable stage, in asymptomatic women, using a simple speculum for visual examination of the cervix”. Downstaging brings down the case fatality rate by detecting disease at an earlier stage. The aim of unaided speculum examination is to differentiate a normal from abnormal cervix and refer the patients with abnormal cervix for further evaluation.

The appearance of the cervix on UVI is classified into:

- Normal
- Abnormal-hypertrophy, redness, polyp, nabothian follicles, simple erosion, distortion, irregular surface, abnormal discharge, prolapsed uterus
- Suspicious of malignancy- an erosion that bleeds on touch, an irregular growth

Paramedical workers can be trained to perform a UVI. A good agreement in the interpretation of UVI has been noted between the doctor and paramedical staff.^{6, 7} The sensitivity of UVI has been reported to be 90% and specificity as 40- 50% for detection of invasive cancer.^{6,8}

Visual inspection after acetic acid (VIA)- It is also referred to as cervicoscopy or direct visual

inspection or Acetic Acid test. It involves naked eye examination of the cervix to detect abnormal areas after application of 3-5% acetic acid.

Equipment required for performing VIA include

- examination table with stirrups
- sterile speculum and gloves
- source of light
- cotton swabs and forceps
- syringe for acetic acid lavage and acetic acid in dilution of 3-5%
- stationery to record examination findings

Principle of acetic acid test-

Acetic acid dissolves mucus, induces intracellular dehydration and causes coagulation of the protein. Due to these factors cells with increased nuclear cytoplasmic ratio & nuclear density and cells with chromosomal aneuploidy turn opaque and are seen as acetowhite areas and the acetic acid test is considered positive.

Findings on VIA

- **VIA negative** - No acetowhite lesions; polyps with bluish-white acetowhite areas; nabothian cysts that appear as button-like areas, as whitish acne; dot-like areas in the endocervix, which are due to grape-like columnar epithelium staining with acetic acid; streak-like acetowhitening in the columnar epithelium
- **VIA positive** - distinct, well defined, dense (opaque, dull- or oyster-white) acetowhite areas with regular or irregular margins, abutting the squamocolumnar junction in

the transformation zone or close to the external os if the squamocolumnar junction is not visible; strikingly dense acetowhite areas seen in the columnar epithelium; ondyroma and leukoplakia

- **VIA positive, suggestive of invasive cancer** - clinically visible ulcero-proliferative growth on the cervix that turns densely white after application of acetic acid and bleeds on touch-Like UVI, VIA can also be conducted by paramedical staff though studies have reported a higher false positive rate leading to more referrals. VIA has been shown to have a higher sensitivity (56.1-93.7% range across studies) and lower specificity (65-85%) when compared to cytology - sensitivity (28.9-76.9%) and specificity (85-95%).⁵

Visual inspection after acetic acid with magnification (VIAM)-

It is the visualization of the cervix after application of 3-5% acetic acid under low magnification. The role of magnification in improving the test parameters of VIA is still not clear. Basu et al and Sankaranarayanan et al have shown that VIAM is not superior to VIA. The sensitivity of VIAM has been reported as 60.7 -64.2% while the specificity is 83.2-86.8%.^{9,10}

The instrument used for magnification is a hand -held device with built-in light source called gynoscope. This device is useful in rural areas where there is no supply of electricity.¹¹

Visual inspection with Lugol's iodine (VILI)-It is also known as Schiller's test. Equipment required is the same as for VIA except that it utilizes 50% lugol's iodine instead of acetic acid.

Principle of VILI-Squamous epithelium contains glycogen in contrast to normal columnar epithelium, precancerous and cancerous lesions. Iodine stains a glycogen rich epithelium mahogany brown, as it glycophilic. Normal columnar epithelium, precancerous and cancerous lesions being glycogen deficient appear yellow or mustard in colour.

Advantage of VILI over VIA-easy recognition of yellow colour changes of a positive test by health care staff.

VILI negative - squamous epithelium that turns mahogany brown; columnar epithelium that does not take up stain; scattered, irregular, partial or non-iodine uptake areas; associated with inflammation.

VILI positive- non -iodine uptake areas that touch the transformation zone(TZ) or are close to external os if TZ not seen or cover the entire cervix

VILI positive, suspicious of cancer - visible ulcerative, cauliflower like growth which bleeds on touch.

The sensitivity of VILI ranges from 76-97% while specificity has been reported as 75-85%.¹²

Management in case of positive Visual test-In low-resource settings, the role of 'see and treat' policy following a

positive visual test is being evaluated to eliminate the need for colposcopy and multiple visits.⁴ However, where facility is present, patient should be referred for cytology and further workup.

Advantages of visual tests

- Safe, effective, practical, affordable, easily available
- Easy to perform
- High sensitivity and high negative predictive value (99%)
- Low start-up and sustaining costs
- Technique is easy to master and can be performed by paramedical staff
- Test results available immediately
- Decreased loss to follow-up
- Can be followed up with treatment in the same sitting

Disadvantages of visual tests

- Low specificity
- No universally accepted standard definition of tests results
- Less accurate in postmenopausal women
- Interpretation dependent on the performer

HPV screening in low resource settings-The strong association between HPV infection and cervical cancer has been established beyond doubt and this has been the rationale behind use of HPV DNA tests for screening of cervical cancer. HPV DNA testing has better sensitivity and specificity than visual tests and cytology.¹³ It is being used as an adjunct to cytological screening in

developed countries. However, technical and infrastructural requirements limit its use in low-resource settings. A cost-effective HPV DNA test needs to be developed before it can be incorporated into the screening programs in low-resource settings.

Screening program for cervical cancer can be successful if

- Women's awareness regarding the screening program is increased and they are encouraged to seek them.
- Screening should be followed by treatment if required. Appropriate counseling regarding future visits should be given
- Systematic appraisal of the program and the providers is done at regular intervals

Every problem has the seed of its own solution. Considering the vastness of our country, only an organized screening program that can be applicable even in the far-flung rural areas devoid of any facility may help curtail the menace of monstrous cervical cancer.

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Ancient masters of human anatomy and healing



The Ancient Egyptians were advanced medical practitioners for their time. They were masters of human anatomy and healing mostly due to the extensive mummification ceremonies. This involved removing most of the internal organs including the brain, lungs, pancreas, liver, spleen, heart and intestine. The Egyptians had a basic knowledge of organ functions within the human body (save for the brain and heart which they thought had opposite functions).

The practices of Egyptian medical practitioners ranged from embalming to faith healing to surgery and autopsy. Among the curatives used by the Egyptians were all types of plant (herbs and other plants), animal (all parts nearly) and mineral compounds. The use of these compounds led to an extensive compendium of curative recipes, some still available today. For example, yeast was recognized for its healing qualities and was applied to leg ulcers and swellings. Yeast's were also taken internally for digestive disorders and were an effective cure for ulcers.

Though the Egyptians were effective healers, they did not have a clear knowledge of cellular biology or of germ theory, so it would be inappropriate to attribute the use of Yeast's as an antibiotic; as the curative effects behind the use of antibiotics were not known until well into modern times.

Review Article

A. Devadoss

Institute of Orthopedic Research and Accident Surgery, Madurai

The iliac crest autologous bone graft remains the gold standard through out the world for timely healing of fractures and to fill voids and gaps. But the morbidity of autograft from iliac crest has its own problems and this has caused orthopaedic surgeons to enhance bone healing with bone graft substitutes. The purpose of this paper is to give the basic fund of knowledge on bone graft substitutes, an opinion on the levels of evidence in the current literature. The bone graft substitutes are categorised as Osteoinductive, Osteoconductive or Osteogenic.

Osteo inductive bone substitutes - Osteoinduction is defined as a process that supports the mitogenesis of undifferentiated mesenchymal cells leading to the formation of osteoprogenitor cells with the capacity to form new bone. The Osteoinduction concept was introduced by Urist in 1965¹. Urist et al identified the Bone Morphogenetic Protein (BMP). Wozney et al (1988)² identified at least fifteen BMP's and they were part of the larger transforming growth factor β (TGF- β) super family of molecules. Demineralised Bone Matrix is produced by acid extraction of allograft. It contains type I collagen, non collagenous proteins and Osteoinductive growth factors (Friedlander -1983)³. It is

available as freeze dried power, granules, gel, putty or strips. Dynagraft II is available in India as DBM. DBM is mainly used as bone graft extender along with autograft. There is no level - I study to show that DBM alone is useful in humans. At present two recombinant BMPs, rh BMP-2 and rh BMP -7 (also known as Osteogenic protein -1(OP-1) are available for clinical use. McKee et al (2002)⁴ investigated the use of OP -1 in the treatment of open tibial fractures. There was a significant decrease in the rate of secondary interventions for delayed union and non unions in the OP -1 treated group.

Osteoconductive bone substitutes - The term Osteoconduction refers to a process in which the three dimensional structure of substance is conducive for the on growth and / or ingrowth of newly formed bone. During Osteoconductive bone ingrowth, capillaries, perivascular tissue, and osteoprogenitor cells migrate into the bone graft substitute; newly formed bone is produced within its porous spaces. Inter connectivity and pore sizes are important factors in determining the Osteoconductive properties of a substance. Research indicates that the optimal pore size for bone ingrowth is in between 150 and 500 μm (Gazdag 1995)⁵. Apart from mechanical buttress these

Osteoconductive scaffolds may prevent soft tissue from occluding the space, thereby possibly precluding subsequent bone formation. Very often they are used as autogenous bone graft extenders.

Indications - For filling bone voids and defects, it will assist in, but there are not essential to bone stability. These substitutes are most commonly used following trauma to fill metaphyseal voids eg. Tibial plateau, distal radius, and neck of humerus. Because of their limited mechanical properties must be used along with internal or external fixation. Although most products are designed to be used instead of autogenous bone graft, collagen based matrices are to be used in conjunction with a bone marrow aspirate.

Contraindications-

Presence of Osteomyelitis, children with open growth plates and associated vascular injuries.

Coralline Hydroxyapatite-

This is available extensively in our country as G. Bone. It is produced from marine coral exoskeletons that have a very regular pore structure resembling cancellous bone. The coral is subjected to high pressure and heated in an aqueous phosphate solution, thus correcting the calcium carbonate coral skeleton into hydroxyapatite ($\text{C}_{10}[\text{P04}]_6[\text{OH}]_2$) (Roy et al 1974)⁶. Animal

and human experiments show that vascular and fibrous tissue invade the pore structures and are subsequently converted to mature lamellar bone, similar to the process seen in autogenous bone grafts (Cornell et al 1998)⁷ Coralline hydroxyapatite is marketed in our country as G. Bone (Surgiwear Co). It is available as granules and blocks of various sizes. The material is brittle and fragmentation into many very small particles.

Resorption is very limited. Blocks of implanted coralline hydroxyapatite may remain apparent on radiograph for 10 years or longer. Coralline hydroxyl apatite has a long track record as an effective bone graft substitute for metaphyseal defects. Block material are particularly useful when the defect is non constrained. Granules and injectable products are difficult to maintain in non constrained defects.

Collagen based matrices -

Xenografts consisting of sponge like strips of purified bone fibrillar collagen (Primary TypeI) that is combined with hydroxyapatite alone or with both hydroxyapatite and Tricalcium phosphate . These are marketed as collagraft (Zimmer) and Healos (Depuy). These matrices are designed to be used in conjunction with either autogenous bone marrow or Autogenous bone graft. They do not offer any significant mechanical properties and not ideal to be used in metaphyseal defects. But may be used as onlay graft when the cortex is deficient and in the presence of significant

periosteal stripping that may preclude fracture healing.

Collagenbased matrices should not be used in patients with severe allergies or known allergies to bovine collagen .

Calcium Phosphate cement -

It is available as Norian SRS(Skeletal Repair System) . It is an injectable paste of inorganic calcium and phosphate that hardens insitu and cures by a crystallisation reaction to form dehilite, a carbonate apatite similar to that found in the mineral phase of bone. Calcium phosphate cement offers the highest mechanical compressive strength of any of the Osteoconductive bone graft substitutes. Generally earlier weight bearing is possible. It is useful in elderly patients with severe osteoporosis.

Calcium Sulphate -

Calcium sulphate is used as bone graft substitutes as early as 1892 (Pettiar 1959). Available as “ Stimulan” in our country. When the hemi hydrate form of calcium sulphate is mixed with water, a dehydrate known as Gypsum is formed. Calcium sulphate is available as either as individual pellets or as a powder that can be mixed in solution to form an injectable paste. Calcium sulphate resolves in 4 to 12 weeks. Walsh et al (2003)⁸, hypothesized that the mechanism of bone regenerative action of calcium sulphate is related to the local acidity produced during its resorption. They postulated that in a confined cancellous defect, this local acidity results in demineralisation of the adjacent bone, with a release

of matrix bound bone morphogenetic proteins that have a stimulatory effect on bone formation. This may represent another possible in-vivo mechanism of action for the resorption and rapid regeneration of bone defects by calcium sulphate. It has been shown that osteoclast attach to calcium sulphate. (Sidqui et al 1995)⁹. In animal studies done by Turmer et al [2001&2003] show that the trabecular bone following the surgically created bone defects is qualitatively similar to that seen after autogenous bone grafting . But it does not have any Osteoinductive property. [Petrus Kevicius 2002]¹⁰. Watson (2004)¹¹ reported satisfactory reports using injectable calcium sulphate in tibial plateau and pilon fractures. The calcium sulphate has completely resorbed by 3months. Of the available Osteoconductive bone graft substitutes, calcium sulphate is the most rapidly resorbed . Because of its rapid resorption rate and low mechanical strength it is more useful as a bone graft extender rather than as a filler for metaphyseal defects

Tricalcium Phosphate (TCP)-

It is available in India as ChronOS (Synthes). TCP is available in either granular or block form. TCP assume either á - TCP has a polygonal shape, where â TCP is spherical, has a higher porosity . TCP undergoes resorption by dissolution and fragmentation over 6 to 18 months. Buchholz et al (1987)¹² reported excellent results using TCP as a bone graft substitute.

Allograft -Allograft is an attractive alternative to autogenous bone as it avoids donor site morbidity, is relatively abundant and can be used off the shelf. Frozen allografts are stored at temperature below -60°C which decreases enzyme degradation and host immune response. The risk of disease like HIV -2 and HCV transmission is there .The use of allograft has become widespread .Potential applications in the trauma setting include reconstruction of skeletal defects, augmentation of fracture repair especially in periprosthetic fractures, augmentation of fracture repair and treatment of non union

Bone Morphogenesis cascade

-Osteogenesis begins with a stem cells that gives rise to progenitor cells. Bone marrow aspirate is another way to supply connective tissue progenitors to enhance bone growth and repair. Connolly et al (1986 and 1998)^{13,14} were the first surgeons to use bone marrow aspirate as a clinical alternative to autograft. This is done intra operatively with ease and is associated with a low morbidity rate. Use of platelet rich plasma is in practice due to the factor derived from platelets stimulates the formation of osteogenesis , the invasion of pluri potential mesenchymal stem cells, monocytes and macrophages and the further aggregation of platelets . As a result , these molecules do not directly stimulate bone formation, but they have been referred to as osteopromotive factors – (Slater et al 1995, Marx et al 1998)^{15,16}.

Conclusions-Clinical evidence for the use of currently available bone graft substitutes ranges from level –I to level IV. The Orthopaedic Trauma Association Orthobiologies Committee (2007)¹⁷ has given the levels of recommendations regarding various bone graft substitutes as given in the table.

bone graft substitutes. Most available studies are non randomized case series in which their efficacy cannot be proved. No direct comparisons of the different type of Osteoconductive bone graft substitutes have been done. Indiscriminate use without clear indications results in unnecessary financial

Bone Graft Substitutes	Grade of Recommendations
Osteoinductive Allograft bone Deminerlized Bone Matrix Purified Human BMP OP – 1 Device Infuse	I C C A A
Osteoconductive Tricalcium Phosphate Calcium Sulphate Allograft Hydroxyapatite	A B C A
Osteogenic& Osteopromotive Bone Marrow aspirate injection Platelet – Rich plasma and Blood concentrates	B I

Grades of recommendation

- A. Good evidence (Level -1 studies with consistent findings)
- B. Fair evidence (Level II or III studies with consistent findings).
- C. Poor Quality evidence (Level IV or V studies with consistent findings.
- I. There is insufficient evidence not allowing a recommendation for or against intervention.

Only limited clinical information is available on this use of most

costs Depending on the product chosen, the resorption rate may be too fast or too slow for the desired out come .The orthopaedic surgeon must know the properties of various types of bone graft substitutes to enable him to use the right type of bone graft substitute, in the right type of case to get the desired good result.

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Review Article

Rajeev Chawla

Maharaja Agrasen Hospital, Delhi

The prevalence of Type-2 Diabetes mellitus is rising to epidemic proportions. DM is feared most for morbidity & mortality associated with its chronic complications. Since the introduction of new oral agents, insulin devices & better patient care fortunately both Type-1 & Type-2 diabetics now enjoy significant longevity but unfortunately with that we are witnessing rising pool of micro & macro vascular complications. This is going to put enormous financial & manpower burden on the total health care system & medical fraternity since the cost of treating complications happens to be even more than five times then treating diabetes mellitus itself. Although all diabetic patients are prone to microvascular complications namely – Diabetic Neuropathy, nephropathy, retinopathy, which can impede their quality of life but it is macrovascular complications which most increase morbidity and mortality¹ Vascular complications are one of the most serious consequences of diabetes and are responsible for most of the excess mortality observed in diabetic patients. It is likely that all blood vessels both small & large are abnormal in diabetic patients with long standing disease. Although there is a generalized microangiopathy but microvascular blood vessel in

retina, renal glomeruli & microvessels of large nerves seem to have significant pathology. Similarly, of the large vessels, the arteries of the lower limbs are particularly affected, although the carotid & coronary vessels are also involved. Statistics for vascular disease in patients with Type-2 diabetes are alarming. The risk of coronary artery disease or stroke is increased 2-4 folds compared with general population, and the risk of peripheral vascular disease is increased four times^{2,3} Diabetic microvascular complications can occur in patients with either Type-1 or Type-2 diabetes despite improvements in management of glucose, blood pressure and lipid levels. As many as 37% of patients with diabetes suffer at least one microvascular complication, and at least 13% have more than one⁴ In a study of 3010 diabetics by Ramachandran A.⁵, the prevalence of microvascular complications was – Retinopathy – 23.7%, Nephropathy-5.5%, Neuropathy-27.5% & Prevalence of CHD-11.4% & PVD was 4%. In our own study from North Delhi Diabetes Centre⁶ comprising 720 type-2 diabetics, Retinopathy was seen in 21.2%, Microalbuminuria in 41%, Peripheral Neuropathy in 15.3%, CAD in 7% & PVD was seen in 7.4% of patients.

Screening for microvascular complications-There is no

perfect way to predict which patients with diabetes will develop microvascular complications, nor the severity and at what stage will microvascular complications shall manifest^{7,8} Infact, many studies have established beyond doubt that about 20% patients do have atleast one or more microvascular & macrovascular complications at the time of diagnosis of Type-2 Diabetes⁹ (UKPDS). In our own study¹⁰ the prevalence of various microvascular and macrovascular complications at onset was – NPDR 10%, peripheral neuropathy – 20%, microalbuminuria.- 16%

Diabetic Nephropathy Screening – As per ADA Clinical Practice Recommendations 2006 – perform an annual test for the presence of microalbuminuria in Type-1 diabetic patients with diabetes duration of > 5 years and in all type-2 diabetic patients, starting at diagnosis and during pregnancy¹¹ Serum creatinine should be measured at time of diagnosis and at least annually for the estimation of glomerular filtration rate (GFR) in all adults with diabetes regardless of the degree of Urine albumin excretion^{12,13}

Diabetic Retinopathy Screening – ADA recommends that adults & adolescents with type-1 diabetes should have an initial dilated and comprehensive eye

examination by an ophthalmologist or optometrist within 3-5 years after the onset of diabetes¹⁴ Patients with type-2 diabetes should have an initial dilated and comprehensive eye examination shortly after the diagnosis of diabetes and subsequently every one year. Less frequent examination (every 2-3 years) may be considered in the setting of a normal eye exam & more frequent exam will be required if retinopathy is progressing¹⁵ However, women who are planning pregnancy or who have become pregnant should have a comprehensive eye examination during 1st Trimester with close follow up during pregnancy & should be counseled on the risk of development or progression of diabetic retinopathy¹⁶

Neuropathy Screening - Patients with diabetes should be screened for Distal symmetric polyneuropathy (DPN) at diagnosis using tests such as pinprick sensation, temperature and vibration perception (Using a 128 Hz tuning fork), 10 gm monofilament pressure sensation at the dorsal surface of both great toes, just proximal to the nail bed and ankle reflexes^{17,18} Combinations of more than one test have > 87% sensitivity in detecting DPN. Loss of 10 gm monofilament perception and reduced vibration perception predict foot ulcers. A minimum of one clinical test should be carried out annually, and the use of two tests will increase diagnostic ability. Focal & multifocal neuropathy assessment requires clinical

examination in the area related to the neurological symptoms. Similarly screening for autonomic neuropathy (AN) should be instituted at diagnosis of Type-2 diabetes. Cardiovascular autonomic neuropathy may be indicated by resting tachycardia > 100 bpm, orthostasis (a fall in systolic blood pressure > 20 mm upon standing) or other disturbances in autonomic nervous system function involving the skin, pupils or gastrointestinal and genitourinary systems¹⁹. Special electrophysiological testing for DPN & AN is rarely needed & may not effect management and outcomes. Once the diagnosis of DPN is established a referral for preventive specialist or podiatrist for special footwear is appropriate. Early recognition and appropriate management of neuropathy in diabetics is important because upto 50% of DPN may be asymptomatic and these patients are at risk of insensate injury to their feet. Moreover, autonomic neuropathy may involve every system in the body and especially cardiovascular autonomic neuropathy causes substantial morbidity and mortality.

Screening for Macrovascular Complications

Foot Screening - A comprehensive foot examination should be performed at diagnosis and subsequently annually using a monofilament, tuning fork, palpation of foot vessels and a visual examination for skin colour, nail changes, callous or foot ulcers²⁰ Consider obtaining

an ankle brachial index (ABI), as many patients with PVD or lower arterial disease (LEAD) are asymptomatic, moreover, presence of PVD or LAED should be taken as a corrugator marker for presence of simultaneous Coronary artery disease (CAD)²¹ A multidisciplinary approach is recommended for patients with diabetic foot or foot ulcers and all patients with significant PVD, foot ulcers or neuroischaemic foot should be referred to foot specialist or podiatrist because foot ulceration and ultimate amputation are most common consequences of diabetic neuropathy and neuroischaemic foot contributing to major morbidity and mortality in patients with diabetes²² The risk of ulcers or amputations is significantly increased in people who have diabetes > 10 yrs, are male, have poor glycemic control or have cardiovascular, retinal or renal complications.

CVD-CVD is the major cause of mortality for individuals with diabetes. It is also a major contributor to morbidity and direct and indirect costs of diabetes. Type-2 Diabetes itself is an independent risk factor for macrovascular disease, and its common co-existing conditions (e.g. Hypertension and dyslipidemia) are also risk factors.²³ Various studies have shown the efficacy of reducing cardiovascular risk factors in preventing or slowing CVD. Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure >

130 mmHg or diastolic blood pressure > 80 mmHg should get it confirmed on a separate day & if found Hypertensive should be treated to a blood pressure < 130/80 mmHg.²⁴ Dyslipidaemia – In Type-2 Diabetics a detailed lipid profile should be done at onset & subsequently annually at least & more often at times to achieve the following goals-LDL < 100 mg/dl; HDL > 50 mg/dl; Tgs < 150 mg/dl. Lifestyle modification focusing on the reduction of saturated fats & cholesterol intake, weight loss (if indicated), and increased physical activity has been shown to improve the lipid profile in patients with diabetes. Lipid management aimed at lowering LDL cholesterol, raising HDL cholesterol, and lowering Tgs has been shown to reduce macrovascular disease and mortality in patients with Type-2 diabetes, particularly in those who have had prior cardiovascular events.²⁵

CHD Screening - In asymptomatic patients consider a risk factor evaluation at least annually to stratify patients by 10 yr. risk and treat risk factors accordingly.²⁶ These risk factors include dyslipidaemia, hypertension, smoking, a positive family history of CAD & the presence of micro or macroalbuminuria. Candidates for a diagnostic cardiac stress test include those with -Typical or atypical cardiac symptoms and An abnormal resting ECG. The screening of asymptomatic patients remains controversial although studies have demonstrated that a significant

percentage of patients with diabetes who have no symptoms of CAD have abnormal stress tests, either by ECG or echo and nuclear perfusion imaging.²⁷ It is also demonstrated that patients with silent myocardial ischaemia have a poorer prognosis than those with normal stress tests. Their risk is further accentuated if cardiac autonomic neuropathy coexists.²⁸ Approximately 1 in 5 will have an abnormal test & >1 in 15 will have major abnormality. However, more information is needed concerning prognosis, and the value of early intervention (invasive or noninvasive) before wide spread screening is recommended as there are no large controlled prospective trials with adequate control groups to shed light on approach towards diabetic patients with silent ischaemia. A recent report indicated that only 37% of adults with diagnosed diabetes achieved on HbA_{1c} < 7%, only 36% had a blood pressure < 130/80 mmHg and just 48% had a cholesterol < 200 mg/dl. Most distressing was that only 7.3% diabetic subjects achieved all three treatment goals.²⁹ Both DCCT³⁰ & UKPDS³¹ trials have proven that at any given time about 35% à 65% diabetic patients having hyperglycemia shall develop some or the other microvascular or macrovascular complication with conventional treatment. Several lines of evidence suggest that the increased risk of vascular disease in diabetes starts about 10 years earlier – possibly even from birth or even from womb. As many as 50% of patients with newly diagnosed Type-2 Diabetes

already have evidence of some macrovascular disease,³² hence, inspite of great strides in the management of diabetes death rate continues to rise largely from vascular disease.³³ Hence, message is very clear that having type-2 diabetes is like having had an MI in the past. So diabetics are considered to be CAD equivalent.

Hence, approach to a patient with diabetes requires a multidisciplinary approach with special emphasis on early screening for various vascular complications first at the time of diagnosis & subsequently at least once a year to retard or check the further propagation of complications.

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Medical Trivia

- In 2003, 2,500,000,000 Paracetamol tablets were sold over the counter in the UK.
- The left testicle hangs lower than the right in 85% of men.
- There have been more babies born in the 10 years after the world population conference in 1992, as there were people alive on the planet 2000 years ago.
- Hepatitis C is 4000 times more infectious than HIV
- Around the world, about 1600 people are infected with HIV-AIDS every day.
- Around the world, 50 people a day are blown up by land mines.
- In the UK there was 100 times more research money spent on AIDS than on Prostate cancer last year, but 100 times more men died from Prostate cancer than from AIDS.
- The mosquito is the most dangerous animal in the world. 3000 people die each day from Malaria. World wide, 515 million people are infected.
- 15% of the UK NHS budget is spent on treating sufferers from Diabetes and its related complications.
- Properly performed, CPR delivers less than 30% of the hearts normal flow of oxygenated blood to the brain.
- Last year in the UK, 2500 people died in traffic accidents, 3000 died from hypothermia and cold related problems, mostly in their own home.
- The average red blood cell lives for 120 days.
- A red blood cell can circumnavigate your whole body in 20 seconds.
- There are 2.5 trillion red blood cells in your body, which means about two and a half million new ones need to be produced every second by your bone marrow. That's the same as reproducing the population of the city of Toronto every second. That's 100 billion every day.
- If you look at all the cells and tissues in your body, about 25 million are reproduced every second, which is like reproducing almost the entire population of Canada every second!
- Nerve impulses travel at over 400 km/h. When we touch something, we send a message to our brain at 124 mph.
- In one square inch of our hand we have nine feet of blood vessels, 600 pain sensors, 9000 nerve endings, 625 sweat glands, 36 heat sensors and 75 pressure sensors.
- A sneeze explodes out of the body at 166 km/h.
- A cough travels at 100 km/h.
- The average heart beats at 100,000 times a day.
- Your blood is on a 600,000 mile journey.
- Your eyes can distinguish up to one million colour surfaces and take in more information than the largest telescope known to man.

J. K. Sahni

Department of ENT, Lady Hardinge Medical College New Delhi

Foreign body has been defined as an object or substance foreign to the location where it is found (Jackson & Jackson). These can be further divided into exogenous and endogenous. There are numerous types of foreign bodies which can be either ingested or swallowed by children of different age groups. The symptoms produced depend upon the nature of foreign body, its size, site of lodgement and the duration for which it lodged. Foreign bodies in tracheobronchial tree are more common in small children than the foreign bodies of Oesophagus. This is because of poor reflexes of the respiratory passages making them more prone for lodgement of foreign bodies. Children try to keep many unwanted objects in their mouth and vary often these are coughed out or swallowed without coming into the knowledge of the patients. Occasionally the foreign body gets impacted in the food or air passage causing symptoms.

Foreign bodies in food passages -Numerous types of foreign bodies are encountered in food passages in children. The commonest being coins, others are bones, safety pin, glass bead, all pin, buttons, metallic nails. A bolus of food may also become a foreign body if it gets held up above a stricture. There are 4 anatomical constrictions of Oesophagus where the foreign body may get lodged. There are

at the level of cricopharynx, at the arch of aorta, where the left main bronchus crosses the oesophagus, at the cardiac end. There is a positive history of ingestion of the foreign body in most of the cases. The child complains of pain the neck or chest depending upon the site of foreign body. There is difficulty in swallowing and if the foreign body is big there might even be absolute dysphagia. The clinical examination does not reveal anything. Since a small child will not cooperate even for indirect laryngoscopy. A radio opaque foreign body can be detected by x-ray examination of neck and chest. Both AP and lateral views are advisable since at times it is clinically difficult to differentiate a foreign body bronchus which is not producing any respiratory symptoms from the one in oesophagus. (Sahni and Kohli, 1984). In a non radio opaque foreign body e.g. denture (in adults) unless there is a wire hook attached to it, seeds or a bolus of food or meat, patient is asked to swallow a cotton plug soaked in Barium sulphate. It will get stuck over the foreign body and can be visualized on x-ray examination. It is always advisable to have x-ray examination a little before endoscopy because the foreign body may shift its position and may even go into stomach which makes endoscopy attempt of no use. This is very well illustrated by a case we had recently under our care.

A 2 year old female child come to ENT OPD with history of

ingestion of some foreign body while playing a few hours ago. Xray chest showed a radio opaque foreign body impacted just below the level of cricopharynx. Due to some reason oerophagoscopy could not be performed till the next morning. X-ray chest was repeated before taking of the child for endoscopy and it was seen that the foreign body had come down into the stomach. Then it was decided that laparotomy needs to be done and the surgeons were consulted. They were also of the opinion that such are big foreign body could not traverse whole of gastrointestinal tract without getting impacted on the way. To our surprise the foreign body was expelled out in the stool of the patient, the next day when she was to be taken up for surgery. This case demonstrated that even such a large foreign body (metallic strip 3.5 cm long and 2.5 cm wide) with very sharp and curved edges could negotiate the constrictions of the gastrointestinal tract without getting impacted on the way. Such a clinical course is more common in cases of coins than of foreign bodies of this nature. Certain enzymes have been used to treatment e.g. pepsin has been used to dissolve impacted bolus of meat. More than 60 cases have been reported and there were 2 fatal complications proving this technique to be dangerous (Ritter 1974). Whenever a diagnoses of F.B.

Oesophagus is made patient is admitted and foreign body is removed with appropriate forceps after doing Oesophagoscopy under G.A. It is very safe procedure these days and in expert hands. There hardly any complication except when the foreign body is impacted for a very long duration and it has caused extensive necrosis all around. The longest duration for which the foreign body remained impacted is for seven years. It was a coin in hypopharynx (Kulkarni SS, 1968). More recently alkaline batteries are increasingly seen as being ingested by children. These batteries cause lot of tissue necrosis because of chemical reaction. Patient needs a careful follow up to ensure that there is no stricture formation (Bajaj Y et al 2000). Chakrabarti A et al 2005 have reported a child presenting with retropharyngeal abscess caused by mutton bone impacted in pharynx of a 7 year old child.

Foreign bodies in Tracheo-bronchial tree -Foreign bodies in larynx and tracheobronchial tree have a more serious out come and need a very urgent attention because their presence can cause respiratory embarrassment. Again these foreign bodies can be of various types e.g. peanuts, almond seed, groundnut, plastic beads, pins, nails, hooks, broken tracheostomy tube, buttons etc. Out of these the vegetative foreign bodies are the commonest and have got a more serious prognosis because if small they go unnoticed for quite some time till the patient lands up with unresolving pneumonitis. But if

these are big they produce immediate sign and symptoms necessitating urgent endoscopic removal. The removal of these foreign bodies also is a tedious procedure since these tend to break down into small pieces and have to be removed piece meal. Whenever, a foreign body inhaled child has repeated bouts of irritating cough, respiratory distress and even cyanosis. Child complains of pain on the affected side of chest. On examination there is increased respiratory rate, ronchi and creptitation, decreased air entry on the affected side. The child may not have any sign indicating foreign body though history of foreign body is positive (Sahni et al, 1984). Indirect laryngoscopy is of great help in diagnosis of foreign body of larynx in a cooperative child. Foreign bodies in right bronchus are twice as common as those in the left. This be cause right bronchus is short, wide and more in line with the trachea than the left bronchus. The lodgement of foreign body in a bronchus can give rise to 4 types of valvular obstruction namely check valve, stop valve, ball valve and by-pass valve, each with their own characteristic pathophysiological changes in the lungs and media stinum (Chatterjee and Chatterjee 1972). Apart from clinical examination, x-ray of chest PA and lateral views give valuable information both in radio opaque and radiolucent foreign bodies of tracheobronchial tree. Lateral view is of immense help in diagnosing a foreign body which has got deeper and got lodged in one of the lower lobe braches. X-ray chest might be normal or it may show collapse of lungs with

or without consolidation or there may be emphysematous changes in the lungs. Subcutaneous emphsama can also occur but it is quite rare. Any shift in position of trachea is noted. Tracheal foreign bodies and less commonly bronchial foreign bodies have a tendency to shift their position. So it is very important to examine the "normal" lung also before the completion of the endoscopic procedure. In removal of foreign bodies from the respiratory passage bronchoscopy with an open rigid ventilating endoscope in the treatment of choice. Certain first aid measures which are generally tried to relieve the obstruction are to be discouraged since these are dangerous and should be avoided unless there is no choice because of obstruction of the airway which is not relieved by patient own reflexes. These are pounding the back postural drainage. Bronchodilators, finger probing of the throat and Heimlich procedure. These techniques may result in further impaction of foreign body causing total obstruction not present earlier. These efforts may also delay transferring the child to a proper medical center.

Foreign bodies of larynx need to be treated with utmost urgency since the child is in respiratory distress. In some cases emergency tracheostomy has to be done before attempting direct laryngoscopy for removal of the foreign body. Routine radiography of chest when combined with fluoroscopy gives the highest results, other wise there is 34% failure rate of plain x-ray film. Also a positive history of foreign body dictates endoscopy

with or without radiologic confirmation. A 24 hrs. interval prior to endoscopy, during which the patient is investigated in hospital serves as safely zone prior to endoscopy. The safely zone insures adequate gastric emptying, availability of the most qualified surgical team, skilled anaesthetist and the essential preparation of the equipment. Rigid endoscopy under general anesthesia is the treatment of choice for removal of tracheobronchial foreign bodies. It is desirable to have the ventilating bronchoscopies to minimize the complications and to give enough time to surgeon for the procedure. Endoscopy should ordinarily be lesser than an hour's duration otherwise chances of subglottic oedema are more.

Flexible fiber optic bronchoscope too has been tried for foreign body removal more so in mentally retarded adult. The advantage described are:

- because of its flexibility it is easily introduced in the presence of severe deformities of cervical spine or the pharynx
- It offers greater range of visualization and easier manipulation.

But still in many cases open rigid bronchoscope is the instrument of choice (Cunanan 1978). Cohen (1981) is of the view of that open rigid endoscopy is the only appropriate form of treatment of foreign bodies in children. According to Wood & Gauderer (1984) flexible bronchoscope is safe, definitive and cost effective technique for diagnosis of foreign bodies of tracheobronchial tree in children. The authors strongly discourage attempt to remove foreign bodies with flexible bronchoscope

except under very unusual circumstances. They suggest the use of both techniques – flexible instruments for diagnostic purposes and open tube instrument foreign body's removal – provides optimum cost effective care for children with suspected foreign bodies. There are very few complications of bronchoscopy in skilled hands. The complications which have been described are :

- Subglottic Oedema. This is directly proportional to the time spent in endoscopy.
- Slipping of the foreign body to the periphery of bronchi and even impaction in lung parenchyma. It may necessitate thoracotomy.
- Reversible cardiac arrest.
- Irreversible cardiac arrest

Factors which are responsible for reduced mortality and morbidity are (Adler and Fuller 1953) :

- Adequate anaesthesia
- Utilisation of smallest bronchoscope compatible with the age of patient.
- Drugs like antibiotics, antihistamine and aminophylline.
- Advent of thoracic surgery.

To conclude, foreign bodies of Aerodigestive tract are a very common problem in children. We have treated more than 60 cases over a period of one year in Lady Hardinge Medical College and Smt. S. K. Hospital, New Delhi.

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Review Article

Manoj Sharma, Raksha Arora, Reva Tripathi, Vijay Zutsi

Departments of Radiation Oncology, Obstetrics and Gynecology

Maulana Azad Medical College, New Delhi

The problem of gynecological malignances with special reference to the cancers of Uterine cervix, body uterus and ovaries has to dealt in totality. The understanding of modern trends and recent advances that have taken place are not to be restricted to the treatment methodologies or strategies but the challenge has to be taken in its totality. The reader shall have to concentrate on all the aspects with the help of reviews of literature from various sources such as journals and web sites. The following chapters shall only give the authors view point and a panoramic glimpse of the over all problem. The reader has to make a basic concept about these three malignancies and hence a comprehensive presentation of all the three malignancies is being given separately. The recent advances that have taken place in the gynecological malignancies are mostly related to the development in molecular oncology and marker studies that prognosticate the doctor and the patient about the disease, methods of early detection, doctor patient cooperation, the systematic documentation of the patients details and protocolisation of the treatment strategy such as combined modality treatments and the developments in the radio

therapeutic gadgetry or chemotherapeutic molecules. The molecular oncology that can help in decision taking in the treatment and prognosis, understanding the biochemical behavior of the disease and targeting the therapy towards the tumors. Preventing the destruction of normal tissue functions and hence providing greater relief to the patients and uneventful radiation therapy. One has to be a cautious lot also with the name of modern trends, a mix of new molecular oncological discoveries, technological development in gadgetry and discovery of a new “effective cancer chemotherapy molecule” that is overshadowed by the manufacturers propaganda machinery that involves luring the oncologists for large scale sales of them to the oncological institutions is the “recent trends of worry and concern” of the ethical committees associated with this specialty all over the world.

The Molecular Oncology Versus Prognostication in gynecological malignances- The recent advances with regards to the gynecological malignancies and molecular oncology are applied to the occurrence of the tumors and hence understanding their biological behavior, clinical presentation and treatment response in form of drug

sensitivity or drug resistance. The early detection with the help of marker and public awareness of the same shall go a long way in over all cancer care. Some of the main issues that have to be understood are : Micro-satellite instability; Oncogenes; Hormone related tumors; Clonality; BRCA 1 and BRCA 2 genes; Growth Factors; Molecules involved in adhesion, motility, angiogenesis, invasion and metastasis .

Some Facts- Augmentation of DNA repair at several level seems to offer resistance to platinum. In the Platinum resistant ovarian tumours addition of antibodies to HER-2 /Neu enhances chemosensitization of platinum in ovarian cells. Elevated intracellular levels of glutathion which lead to increased intracellular detoxification of platinum generally correlates to platinum resistance and confer poor survival. Overexpression of BAX in association with chemo sensitivity to platinum and paclitaxel as well as to improved disease free survival rates in ovarian tumors so does IL-1 Alpha through inhibition of DNA repair. Cell adhesion molecules CD44, E-cadherin both are expressed to peritoneal mesothelium but such expressions are lost when cancer cells have made their presences in ascitic cells. This can be a tool that can prognosticate about an

apparently looking early ovarian tumor.

Cervical Cancers Vis-À-vis understanding the Etiopathogenesis of Cervical and Vulvar Carcinoma by Human Papilloma Virus - The development of HPV vaccine has been an intense focus of investigation. Prophylactic HPV vaccination strategies have used non infective non viral DNA containing antigenic papilloma virus like particles. Development of therapeutic HPV vaccine has been somewhat more problem-atic in that sustained cellular immunity against E6 and E7 proteins has been difficult to achieve. New approaches include the use if autologous dendritic cells pulsed with HPV specific tumor antigen as E7 to stimulate tumor specific cytotoxic Lymphocytes (CTLs) Dendritic cells are thought to be effective stimulators not only to produce and maintain primary CTLs but also to stimulate established CTL levels.

Molecular Cofactors important to Cervical Carcinogenesis - It seems that HPV infection alone is not sufficient for cervical carcinogenesis hence attention is also drawn towards molecular cofactors such as infection by Herpes Simplex virus and presence of activated Ha-ras. Many negative and positive regulators of oncoproteins E6 & E7 transcription have been identified that effect the progression or regression of cancer cells. The immune response is likely to be the key in determining malignant transformation of HPV infected

cervical epithelium. As we see with the consequences of infection with dramatic increase in risk of cervical neoplasia and invasive cancer- the degree of which correlate with level of immuno-suppression. Another method to know the prognosis of cervical cancer is to understand the HPV DNA presence or absence. While 90% HPV positive tumors seems to do well where rarely P53 mutations are seen with the HPV negative tumors with more common P53 mutations appear to be of worst prognostic nature.

Cervical Adenocarcinoma- Presence of HPV16 and 18 has been demonstrated in cervical adenocarcinoma dominated by HPV18. HER - 2 / neu over expression is seen in 25% of cases that is associated with the poor prognosis.

Non HPV related molecular abnormalities in cervical cancers-Expression of cell cycle genes such as bcl-1 and bcl-2 is strongly correlated with radio resistance and poor prognosis. Over expression of epidermal growth factors is also associated with poor prognosis. Proteinases capable of degrading extracellular matrix may underlie the propensity of cervical cancer to invade adjacent tissue. Expressions and activity of metalloproteinases of MMP-2 & TIMP-2 are associated with advanced stage and poor survival. Morphologic and immunohistochemical markers of angiogenesis correlate with poor prognosis many cervical cancers secrete significant levels of VEGF, the adenocarcinoma in particular. In Indian context the

strategies of treatment planned in the background of these markers and hence aggression in treatment strategies can certainly improve the outcome of gynecological cancers- cervical cancers in particular. This shall be quite similar to what we see now in breast cancers and PNET with compulsive investigations such as ER, PR & HER-2/ neu studies or immuno-histochemistry for PNET.

Cellular Perturbations-It is now evident that in addition to DNA damage and cell death linked to mitosis, radiation produces a variety of other relevant cellular perturbations. Among the most important are the effects on growth factors and signal-transduction pathways, apopt-osis, and changes in the regulation of the cell cycle.

Effects on Growth Factors and Signal-Transduction Pathways-Within minutes after irradiation, signal-transduction pathways mediated by protein kinase C and tyrosine kinase are stimulated. Such stimulation is probably critical to the induction of many genes and proteins, including a number of early-response genes such as c-fos, c-jun, and NF-B. These early-response genes, in turn, activate other genes, including those for tumor necrosis factor, basic fibroblast growth factor, and transforming growth factor. In addition, new proteins, such as tissue plasminogen activator, are synthesized. It is theorized that this cascade of gene activation, gene transcription, and protein synthesis in response to radiation is related to key cellular functions that permit the cell to survive a

dose of radiation. In addition to radiation-induced stimulation of growth factor production, growth factors affect the response to radiation. Perhaps the most dramatic example is the protection of mice from hematologically lethal irradiation by the cytokines interleukin-1, recombinant granulocyte colony-stimulating factor, and granulocyte macrophage colony-stimulating factor. Another important modulator of the effects of radiation is basic fibroblast growth factor, which increases the resistance of normal endothelial cells to radiation by stimulating damage repair. Thus, these signal-transduction pathways and growth factor responses are attractive targets for protecting normal bone marrow, vasculature, and possibly other structures from the short- and long-term toxic effects of radiation and will be the subject of considerable research in coming years for radiation dose enhancement, over all curtailment of radiation therapy duration and aggressive chemosensitization for stubborn primary or recurrent inoperable tumors. Chemotherapy for cervical cancer has been described as the most important improvement in the treatment of this disease in the past 40 years. A Cochrane meta-analysis of all known randomised controlled trials has shown a reduction in the risk of death by 29%. Not only was there a significant increase in local control (odds ratio 0.61, $P < 0.0001$) but there was also a marked decrease in distant metastases (0.57, $P < 0.0001$).

Acute toxicity, particularly haematological and gastrointestinal, was increased by combined treatment. No increase in late toxicity has been reported, although this was poorly described in many studies. The details of this can be read in the chapters dedicated separately for these three cancers.

Patients' participation in care-

Access to information on the internet means that many patients are now well informed about treatment options. Some ask for treatments that may not be available in their regional cancer center, and because of the variable quality of the information they access, patients may gain an exaggerated or distorted view of the value of new developments. Following the introduction of cancer units and 30 odd regional cancer centers in India, more patients are referred to an oncologist. As a consequence more patients now receive radiotherapy/chemotherapy. The management of most patients is now discussed and decided in multidisciplinary meetings. Such a meeting usually consists of at least an oncologist, a surgeon, a radiologist, a pathologist, and often nurse specialists the patient does not attend the meeting. Increased participation by patients in decision making is illustrated by a cross sectional survey in several of these regional centers showing that most wanted to know the diagnosis, treatment options, likely side effects of treatment, and chance of cure. To some extent the need for more information can be partially met by pointing patients to reliable

websites and by booklets (those produced by Directorate of Health Services Govt. of NCT of Delhi and written by Dr. Manoj Sharma are helping several cancer treatment centers in North India and can be obtained free of cost from the Radiotherapy OPD of Lok Nayak Hospital). The major role of pamphlets and online information, however, should be to reinforce adequate oral communication. Most patients want more time to talk to their consultant. This can be difficult to schedule in busy units with large workloads. The average Indian oncologist sees ten times as many new patients a year as his or her European or North American counterpart. This is specially so when gynecological malignancies all together top the quantum of bulk when compared to other cancers in India. The interesting development that is yet to come in India is the active involvement of the electronic and print media and a perpetual and massive contribution by the oncologist for rendition of programmes related to the diseases and patients problems. Thus through these effective methods of communication an awareness and sensitivity for such problems in the minds of general public, patients and their relatives can be created.

The Preventive Oncology -

Before we go to the advances in the modern trends in the treatment technologies and the strategies one cannot be bereft with the knowledge of Preventive Oncology in all kinds of cancer and cervical,

endometrial and ovarian cancers are also the target for cancer prevention and early detection. This should be very clearly borne in the minds of the reader that the talk of cure, organ conservation and long term survival fails if one is not able to bring these cases to the hospital in conservable stages. The proper awareness and propaganda should start at home i.e. at the level of the general practitioners clinic level and to a great extent at the OPD level of an oncologist. This is one important factor that reader should understand and try to implement. Samples of literature are provided by the author free of cost on self examinations of seven sites of the body, cancers commonly found in Indian females (including oral, breast, cervix endometrial and ovarian) and methods of their early detection, scientific advances that can be educated to lay public and the information education and communication materials for grassroots level that is school level. Indeed it is there the initiatives for cancer cure start in India.

Radiation Therapy -Modern advances in computers have fueled parallel advances in imaging technologies. The improvements in imaging have in turn allowed a higher level of complexity to be incorporated into radiotherapy treatment planning systems. As a result of these changes, the delivery of radiotherapy evolved from therapy designed based primarily on plain (two dimensional) x-ray images and hand calculations to three-dimensional x-ray based

images incorporating increasingly complex computer algorithms. More recently, biologic variables based on differences between tumor metabolism, tumor antigens, and normal tissues have been incorporated into the treatment process. In addition, greater awareness of the challenges to the accuracy of the treatment planning process, such as problems with set-error and organ movement, have begun to be systematically addressed, ushering in an era of so-called **F o u r - D i m e n s i o n a l** Radiotherapy. Two-dimensional (2D) radiotherapy consisted of a single beam from one to four directions. Beam setups were usually quite simple; plans frequently consisted of opposed lateral fields or four-field "boxes". Three-dimensional (3D), or CT-based, planning was a major advance because it took into account axial anatomy and complex tissue contours such as the hourglass shape of the neck and shoulders or a slant from umbilicus towards the fourchette in pelvic radiation. While 3D planning allowed for accurate dose calculations to such irregular shapes, we were still limited in the corrections we could make. As its name implies, intensity-modulated radiation allows us to modulate the intensity of each radiation beam, so each field may have one or many areas of high intensity radiation and any number of lower intensity areas within the same field, thus allowing for greater control of the dose distribution with the target. By modulating both the number of fields and the intensity of radiation within each

field, we have limitless possibilities to sculpt radiation dose. Advanced treatment planning software has furthered our ability to modulate radiation dose. Instead of the clinician choosing every beam angle and weighting, computer optimization techniques can now help determine the distribution of beam intensities across a treatment volume, which often include a nonintuitive distribution of "beamlets," or 1-cm² areas of iso-intensity. For a more in-depth review of IMRT, the reader is referred to the IMRT Collaborative Working Group paper.¹ Despite the capability of planning and calculating doses accurately to within millimeters, we are limited by our inability to identify microscopic disease with such accuracy. We are also limited by the logistic difficulties of immobilizing a patient for the duration of an IMRT treatment (typically 15–30 minutes). Patients and tumors move both as a result of voluntary movement and visceral motion such as respiration and digestion. Additionally, when we're successful, tumors shrink with treatment. Patients may lose weight over the course of the treatment, which will further alter their geometry and therefore dosimetry.^{3,4} The next direction in radiation oncology is to account for this movement and is being called four-dimensional (4D) conformal radiotherapy (CRT), a logical progression from 3D CRT. Researchers have recently developed megavoltage cone-beam CT (MVCT) for clinical use. MVCT will allow the reconstruction of the actual daily-

delivered dose based on the patient's anatomy in real time. This will lead to "adaptive radiotherapy," the modulation of prescription and delivery based on the actual daily delivered dose, as opposed to planned dose.

Hyperfractionation-Standard radiation fractionation is a course of 1.8 to 2.0 Gy/day in single daily doses. Accelerated fractionation refers to delivering the same total dose over a shortened treatment time, most often through the use of twice or thrice daily fractions. Hyperfractionation refers to the same total delivered dose over the same treatment time but in an increased number of fractions; smaller fractions are delivered more frequently than once daily. Multiple different schemes have been used in the cervical cancer, most notably 1.1 to 1.2 Gy twice daily, 1.6 Gy twice daily with a planned 2 week break, and accelerated fractionation with concomitant boost, which delivers 1.8 Gy daily, 5 days a week to a large field, with a 1.5 Gy "boost" field as a second daily dose during the last 12 days. Early in vitro work showed the potential to expand the therapeutic ratio by altering radiation fractionation, and early trials confirmed the clinical benefit of altered fractionation in head and neck cancers, gynecological cancers and other sites, most notably lung. The hyperfractionated regimen showed a significant improvement in local control over the control arm with no increase in long term toxicities despite an increase in acute toxicities. More advanced cancers should be

treated with a combination of chemotherapy and radiotherapy.

Cervix Brachytherapy-It is for those patients who cannot accommodate standard applications. The results with such methods of treatment are encouraging and are statistically significant in terms of their survival. Taking the advantage of the placement of brachytherapy implants the hyperthermia probes have also been utilized to achieve greater results specially when the brachytherapy includes paracervical and parametrial areas utilizing templates such as Syed Niblet templates. A novel approach to sensitize even the LDR/MDR brachytherapy radiation with the help of chemosensitizing agents as infusion has been tried by several workers to achieve an effective local control of the disease and lesser incidence of local recurrence that happen in certain percentage of cases even after optimal brachy and teletherapy dose has been delivered. This method tried for the first time in the advance cancer cervix patients by the author in India shall certainly be the answer to several of the radiation therapy centers who can offer only a basic treatment and expertise facility.

The para aortic concurrent chemoradiation- Despite accepting the statistical fact of higher nodal positivity in locally advance stage cervical cancers, the issue of para aortic radiation has been debatable for too long and it was almost discarded at one stage with little or no alternative to it. The reason being the inability of the radiation

therapist either to rationalize it or to handle the complications of this intricate method of treatment. The recent studies (Devita) has shown that concurrent chemo radiation has given better recurrence free rates and response rates in the patients who had positive para aortic nodes or had high propensity for microscopic mets due to a large primary tumor volume. The logic that has been ignored for so long while planning a goal for long term survival in these late stage cases.

Concurrent Chemotherapy and Radiation-During the past 5 years, prospective randomized trials involving patients with locoregionally advanced cervical cancer have provided compelling evidence that the addition of concurrent cisplatin-containing chemotherapy to standard radiotherapy reduces the risk of disease recurrence by as much as 50% and thereby improves the rates of pelvic disease control and survival. Based on the results of five large randomized trials (3 GOG, 1 RTOG, 1 SWOG), the National Cancer Institute issued an alert in 1999 stating that strong consideration should be given to adding chemotherapy to radiation therapy in the treatment of invasive cervical cancer. A meta-analysis published by Green et al⁴ showed chemoradiation to improve overall and disease-free survival, and reduction in risk of local or distant recurrence, albeit with a higher incidence of grade 3 or 4 hematological and gastrointestinal toxicity. Most studies included in the meta-analysis used cisplatin, either as a single agent or in combination

with fluorouracil, vincristine or bleomycin.

Neoadjuvant Chemotherapy with Radiotherapy-Several investigators have explored the role of neoadjuvant chemotherapy before radiotherapy for locally advanced cervical carcinoma and shown a local response rate of 50 to 80%. Seven prospective trials comparing neoadjuvant chemotherapy followed by radiotherapy with radiotherapy alone have been reported but none has shown superiority of the neoadjuvant approach in terms of survival. Only one small trial, published by Sardi et al⁵ in 1998, appears to have demonstrated improved survival with neoadjuvant chemotherapy in patients with stage IIIB disease. No trial has compared neoadjuvant chemotherapy with concurrent chemoradiation. Combinations of neoadjuvant plus concurrent chemotherapy have not been tested in randomized trials; such combinations should probably be avoided outside of investigational trials because neoadjuvant chemotherapy could compromise patients' tolerance of subsequent chemoradiation.

Biologic Targeted Therapy-The epidermal growth factor receptor (EGFR) has been an attractive target for therapy because of its upregulation in nearly two-thirds of solid tumors and its association with malignant phenotypes. Preclinical models demonstrated enhancement of radiation sensitivity with blockade of the EGFR, and it was hypothesized that a combination

of anti-EGFR therapy with radiation would lead to improved outcome in epithelial cancers such as those of the uterine cervix cancers also. Patients with advanced head and neck cancer were randomized to received radiation alone or with cetuximab (also know as C225, or Erbitux), a monoclonal, chimeric murine-human antibody. The addition of cetuximab increased two-year survival from 55% to 62%, with a near doubling in median survival from 28 to 54 months. Skin toxicity was increased, however, with Grade 3 to 4 skin reactions in 34% of patients on the cetuximab arm versus 18% on the radiation alone arm. While these results need to be confirmed by further studies, cetuximab is now a reasonable option for radiation patients with advanced cancer who are unsuitable for or unable to receive chemotherapy. The combined role of chemotherapy and hyperfractionation is unknown. This question is being addressed by the ongoing RTOG study 01-29, which randomizes patients to concurrent cisplatin with standard fractionation radiation or concurrent cisplatin with the concomitant boost regimen or accelerated fractionation. A question for future trials is the role of cetuximab with concurrent chemoradiation.

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Review Article

Abhishek Srivastava

Department of Psychiatric & Neurological Rehabilitation
National Institute of Mental Health & Neuro Sciences, Bangalore

Stroke is a leading cause of long term disability in community as about 30-50% of the patients are left with considerable residual deficits¹. A hospital based study done at NIMHANS showed that 57% of subjects with stroke had moderate to severe disability at the time of discharge². Thrombolytic therapy and stroke care units led to restriction of tissue injury following stroke. However, due to narrow time window, thrombolysis is applicable only to a small proportion of people who sustain a stroke. Recent report from Pondicherry reported that only 29.5% of all stroke patients reached hospital within 3 hours and only 16% satisfied criteria for thrombolysis³. The magnitude of post stroke disabilities has led to a renewed interest in techniques to facilitate recovery and restore functions. Restorative neurology deals with techniques to restore disordered nervous system to a level of optimal function⁴. There are three approaches to enhance neuronal restoration after stroke. They are pharmacological agents, physical techniques and neural transplantation. This article reviews the current status of the pharmacologic interventions in restoring function after stroke.

Biological basis of neural recovery-The degree of natural recovery after stroke is variable.

The deficits generally decline in frequency by about one third to half⁵. There are two different but related ways that patient improve after stroke⁶. The first type of recovery, a reduction in the extent of neurological impairment can result from natural spontaneous recovery, which usually account for early spontaneous improvement after stroke within first 3-6months. This form of recovery manifests as improvement in motor control, language ability or other primary neurological functions⁷. The underlying mechanisms include resolution of local edema, resorption of local toxins, restoration of circulation in ischemic penumbra, and recovery of partial damaged ischemic neurons⁸⁻¹⁰. This sequence of recovery however can stop at any stage. The second type of recovery demonstrated in stroke patients is the improved ability to perform daily function in their environment, within the limitation of their physical impairment^{11,12}. The underlying mechanism to explain the second type of recovery is neuroplasticity. Brain plasticity is the ability of nervous system to modify its structure and functional organisation. The two most plausible forms of plasticity are collateral sprouting of new synaptic connections and unmasking of previous latent pathways. Other mechanisms of

plasticity include assumption of function by undamaged pathways, reversibility from diaschisis, denervation supersensitivity, remyelination, and regenerative proximal sprouting of transected neuronal axons¹³⁻¹⁶. Experimental evidence suggests that this plasticity can be altered by several external conditions, including pharmacological agents, electrical stimulation and environmental manipulation¹⁷. The ability to perform the task can improve through adaptation and training, in spite of presence or absence of natural neurological recovery. It is element of recovery on which rehabilitation is believed to exert the greatest effect.

Pharmacological strategies-Pharmacological interventions affecting neuronal restoration following stroke include dopaminergic drugs (L-Dopa and Bromocriptane), noradrenergic drugs (L-DOPS, Amphetamine and Methyl Phenidate), serotonin reuptake inhibitors, gangliosides and nootropics, and neurolytic agents.

Dopaminergic drugs-Lesions of ascending dopaminergic pathways induce neglect in animals and dopaminergic drugs and dopamine receptor agonists; decrease the magnitude of neglect in rats. Dopaminergic drugs are used in the treatment of aphasia and neglect following

stroke. Fleet et al reported that 15 mg of bromocriptine daily for 3 to 4 weeks improved performance on tests for neglect in two subjects with stroke¹⁸. However, in patients with damage of putamen dopamine agonists may over stimulate the normal side and increase neglect¹⁹. Bromocriptine may promote recovery in stable chronic non-fluent aphasia. A prospective double blind randomized control trial showed that L-dopa in combination with physiotherapy resulted in better motor recovery following stroke²⁰. However, a Cochrane review did not find sufficient evidence to support the use of dopamine agonists in treatment of post stroke aphasia²¹.

Noradrenergic drugs Few studies have suggested that pharmacological enhancement of noradrenergic activity promotes functional recovery after stroke²². Amphetamine facilitates pre synaptic release and inhibits reuptake of norepinephrine, dopamine and serotonin. It helps in resolution of diaschisis involving cerebellar hemispheres following stroke. Motor training results in use-dependent plasticity of the brain, and contributes to functional recovery after brain injury and D-amphetamine facilitates development of this use-dependent plasticity. The beneficial effect of amphetamine in stroke may be due to resolution of cerebral diaschisis and facilitation of use dependent plasticity. Nishino et al reported that norepinephrine precursor L- threo-3, 4-Dihydroxy phenyl Serine (L-

DOPS) improved motor power, and gait and cerebral blood flow in 27 subjects with stroke²³. Walker-Baston et al reported that d-amphetamine facilitated the effect of speech therapy for post stroke aphasia. In a study involving 22 subjects with stroke²⁴, Grade et al compared the effect of methylphenidate, another noradrenergic agent, with placebo in 22 patients with stroke²⁵. This drug improved the mood, motor functions and activities of daily living. However, these results were not reproduced in several other trials. Sonde et al did not find any significant difference in outcome between people with stroke who received 10mg of d-amphetamine before each session of physiotherapy for 10 sessions and controls, who received physiotherapy alone²⁶. Similarly, Knecht et al found that d-amphetamine did not improve outcome of somatosensory training²⁷. A placebo-controlled trial by Treig et al also failed to show any beneficial effect of D-amphetamine on post stroke recovery²⁸. The role of noradrenergic agents in treatment of established deficits after stroke is still not clear. A recent Cochrane review found seven studies involving 172 subjects addressing this issue. While there was a trend towards improvement in motor and language functions, evidence was not sufficient to recommend its use and further studies are required²⁹.

Serotonergic drugs -Modulation of Serotonergic neurons may help in restoration of motor

functions after stroke. Dam et al reported that 20 mg of fluoxetine improve motor functions and activities of daily living, independent of their effect on depression³⁰. Functional imaging with MRI showed that single dose of fluoxetine significantly increased blood to flow to ipsilateral cortex during active motor task with affected limb in stroke subjects. This was associated with improvement of motor functions of affected side³¹. Some authors recommend 20mg/day fluoxetine in subjects with stroke, even in those with only subtle signs of depression. SSRIs may increase the spasticity³². Currently only limited evidence is available regarding the effect and of SSRIs on motor function after stroke. We need further evidence before they can be recommended for restoration of motor function.

Gangliosides and Nootropics- Several experimental studies have shown enhanced neuronal sprouting and neuro-protective effects of gangliosides in ischemic stroke. However, Meta analysis of over 2000 subjects in clinical trials showed that this agent did not improve outcome and caused GB syndrome as an adverse event³³. Nootropic drugs like Piracetam and Ergoloids are also tried in stroke rehabilitation. A Cochrane review found non-significant benefit of piracetam in post stroke aphasia and also cautioned that there was a trend towards early death among subjects on this drug²¹.

Drugs interfering with recovery-Several drugs adversely affect natural recovery after

stroke³⁴. Drugs like phenobarbitone, phenytoin, clonidine, alpha methyl dopa, prazosin, haloperidol and phenoxybenzamine delay recovery. Drugs that antagonize the norepinephrine and dopaminergic systems impair recovery after stroke. Gamma amino butyric acid (GABA) and serotonin are major inhibitory transmitters in CNS. Levels of both GABA and serotonin increase following cerebral ischaemia. Drugs like benzodiazepines, which facilitate GABA system, interfere with recovery following stroke³⁵. Use of these drugs should be minimized in patients with stroke.

Conclusion-Stroke is a common neurological disorder with complex process of recovery. Survivors of stroke are often left with permanent disabilities. Approaches for functional restoration include use of drugs, physical techniques and neural transplantation. Amphetamines, methylphenidate, fluoxetine and L- Dopa may assist in neuronal recovery but further evidence is required regarding efficacy of these drugs. Some of the pharmacologic agents can be detrimental for neuronal recovery following stroke and should be used only in unavoidable circumstances.

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Review Article

Ravinder Kumar Batra, Kajari Roy

Department of Anesthesiology, All India Institute of Medical Sciences, New Delhi

Anesthesiologists often come across infants and children with various malformation syndromes. Some of these are lethal and lead to death in early life, however, a working knowledge of the malformation syndromes in childhood is essential for anaesthetic management of such cases. The existing published information on syndromes, especially the rare ones, is meagre. More common syndromes, that are clinically relevant and the ones with significant anaesthetic implications are being discussed under various subheadings. A malformation syndrome is a recurring pattern of anomalies occurring due to certain genetic defects. Some of these are very important to an anaesthesiologist, eg.

- Airway malformations
- Cardio pulmonary malformations
- Central nervous system and neuromuscular anomalies
- Renal anomalies
- Skeletal malformations
- Endocrine disorders
- Haematological disorders and neoplasms

Airway malformations-Airway anomalies are of great importance to the anaesthesiologist as they can cause difficulty in bag-and-mask ventilation or intubation. Lower airway

abnormalities, such as tracheal fistulas and bullae, can lead to difficulty in ventilation under anaesthesia and pneumothorax respectively. Some of these may lead to chronic problems, like obstructive airway disease, aspiration, recurrent pneumonia etc. Any superimposed acute respiratory tract infection or enlarged tonsils can further aggravate the problem. Many anomalies of the airway might not be evident by routine clinical examination. Thus, a consultation with a paediatrician is advisable in case of confrontation with a child with an unfamiliar syndrome. The paediatric airway examination remains more subjective than in adults due to uncooperativeness of the children- tongue size and neck extension usually cannot be assessed accurately. However, presence of a retracted mandible, submental pad of fat, protruding tongue, mouth-breathing or history of stridor, snoring or obstructive sleep apnoea predicts difficulty in ventilation. A number of paediatric syndromes are associated with airway malformations. Some commonly encountered such syndromes are as follows:

Antley Bixler -Craniostenosis, Frontal bossing, Raised intracranial pressure, choanal stenosis/atresia, proptosis.

Craniostenosis, Frontal bossing, Raised intracranial pressure, choanal stenosis/atresia, proptosis. Anaesthetic implications- Early tracheostomy (in Choanal atresia), Eye protection, Avoid nasal intubation.

Apert's -Craniostenosis, Midfacial hypoplasia, Tracheal stenosis +/-, Congenital heart disease, Mental retardation, Raised intracranial pressure, Syndactyly, Renal and pulmonary anomalies, Cervical vertebral fusion. Anaesthetic implications- Difficult intubation (midfacial hypoplasia, Tracheal stenosis, Cervical vertebral fusion). Possibly raised intracranial pressure, Associated congenital heart disease.

Beckwith-Wiedemann -Birth weight > 4,000 gm, Macroglossia, Visceromegaly, Exomphalos, Intra-abdominal tumors, Polycythemia, hyperinsulinism, Congenital heart disease +/- . Anaesthetic implications- Persistent severe neonatal hypoglycaemia, Airway problems.

Caffey's -Infantile cortical hyperostosis, Painful thickening of membrane mandible, Clavicles, and shafts of long bones, Fever. Anaesthetic implications- Difficult intubations.

Crouzon's Crouzon's - Craniosynostosis, Proptosis, Hypoplastic maxilla, Elevated ICP +/- . Anaesthetic implications- Possibly difficult intubation, Severe blood loss with cranial operation, Eye protection.

Di-George's (Catch-22)- Abnormalities of thymus, Parathyroids and great vessels, Choanal atresia, Micrognathia, Short trachea, Congenital heart disease, Hypocalcemic seizures in neonates, Cellular immunodeficiency. Anaesthetic implications - Difficult intubation, Pre-operative cardiac evaluation, Avoidance of nasal tubes, Monitoring of calcium, Irradiation of blood products.

Down's (trisomy 21)- Macroglossia, Pharyngeal hypotonia, Smaller trachea, Obstructive sleep apnoea, Recurrent lung infections, Congenital heart disease, Atlantoaxial instability, Duodenal atresia, Congenital hypothyroidism, Mental retardation. Anaesthetic implications- Airway obstruction during induction and recovery, Neck X-ray pre-op if symptomatic, Subluxation after intubation, Pre-op cardiac evaluation, Bradycardia after inhalational induction.

Edward's (trisomy 18) - Prominent occiput, Microcephaly, Micrognathia, Congenital heart disease, Short sternum, Clenched hands, Rocker-bottom feet, Renal anomalies. Anaesthetic implications- Difficult intubation, Pre-operative cardiac evaluation, Pre-operative renal function.

Fabry's (Lipid storage disease)- Tempero-mandibular joint involvement, Ischemic heart disease, Hypertension, Valvular heart disease, Cerebrovascular disease, Extremity pain, Lymphoedema, Renal failure, Hyperhydrosis, Angiokeratomas. Anaesthetic implications- Pre-op cardiac evaluation for cardiac function. Pre-op evaluation of renal function, in renal failure - care with drugs excreted through kidney. Difficult airway

Goldenhar (Oculo- or facio-auriculo-vertebralsyndrome)- Unilateral facial hypoplasia (hemifacial microsomia), Congenital heart disease, Mandibular hypoplasia, Microtia with deafness, Renal anomalies, Hydrocephalus +/-, Radial anomalies. Unilateral facial hypoplasia (hemifacial microsomia), Congenital heart disease, Mandibular hypoplasia, Microtia with deafness, Renal anomalies, Hydrocephalus +/-, Radial anomalies. Anaesthetic implications- Difficult ventilation and intubation, Increased ICP, Pre-operative cardiac and renal function evaluation.

Hurler (mucopolysaccharidosis IH) - Coarse facial features, oral soft tissue stiffness, Joint stiffness, Coronary artery narrowing, Hydrocephalus, Mental retardation, Pulmonary hypertension. Usually die before 10 years from respiratory and cardiac failure. Anaesthetic implications- Extremely difficult intubation, may require fibre-optic. Pre-operative cardiac evaluation. Careful positioning.

Klippel-Feil- Congenital fusion two or more cervical vertebrae leading to neck rigidity, Micrognathia, Congenital heart disease, Renal anomalies. Anaesthetic implications- Difficult intubation, Pre-operative cardiac evaluation Difficult intubation, Pre-operative cardiac evaluation

Pallister-Hall- Hypothalamic hamartoblastoma, Panhypopituitarism, Imperforate anus, Cleft lip/palate, Micrognathia, Dysplastic tracheal cartilage, Hypoplastic lung, Congenital heart disease, Thyroid hypoplasia. Anaesthetic implications- Difficult intubation, smaller size of endotracheal tube, Pre-operative evaluation of cardiac status and hypothalamo-pituitary axis, steroids may be needed intra-operatively.

Peutz-Jegher's - Gastro-intestinal polyposis, Skin pigmentation. Anaesthetic implications- May have airway obstruction due to polyps in the larynx and pharynx.

Pfeiffer's - Acrocephalosyndactyly, Coronal / sagittal synostosis, Midfacial hypoplasia, Proptosis, Obstructive sleep apnoea, Congenital heart disease, Big thumbs and great toes, Fused elbows. Anaesthetic implications- Difficult intubation, Increased ICP, Pre-operative cardiac evaluation.

Pierre-Robin- Micrognathia, Glossoptosis, Airway obstruction, Cleft palate +/- . Anaesthetic implications- Difficult intubation- fibre-optic/ Bullard's or tongue suture to

displace tongue forward may be required, LMA may be used.

Treacher-Collin (mandibulo-facial dysostosis)- Downsloping palpebral fissures, Low-set ears, Malar hypoplasia, Microphthalmia, Microstomia, Micrognathia, Obstructive sleep apnoea, Congenital heart defects. Anaesthetic implications- Difficult intubation, Pre-operative cardiac evaluation.

Choanal atresia: Bony tissue is the usual cause of obstruction, and mouth should be kept open to prevent total airway obstruction. Unilateral obstruction is associated with chronic unilateral nasal discharge. Many craniosynostoses (Antley Bixler syndrome, Apert's syndrome, Crouzon's syndrome, Marshall-Smith syndrome, Saethre-Chotzen syndrome, Treacher-Collin syndrome) are associated with choanal atresia due to abnormal bony growth of the head and face. If associated with other airway anomalies, as in Treacher-Collin syndrome, both ventilation and laryngoscopy are very difficult.

Micrognathia: It is present in 25% of all malformation syndromes, and can pose severe difficulty in laryngoscopic visualization of vocal cords in severe cases. It forms a part of Pierre-Robin syndrome, Treacher-Collin syndrome, Goldenhar syndrome, Edward's syndrome and many others.

Microstomia: It is less common than micrognathia, but laryngoscopy and intubation

become impossible in severe cases, or if combined with macroglossia or poor neck extension. eg. Treacher-Collin syndrome, Edward's syndrome and many others.

Macroglossia: It may be present in chromosomal disorders, as Down's syndrome, trisomy 4p syndrome etc or storage disorders, as gangliosidoses (Caffey's syndrome), mucopolysaccharidoses (Hurler's syndrome, Scheie's syndrome), or others, as Beckwith-Wiedemann syndrome. The most severe of these is Beckwith-Wiedemann syndrome, where the tongue may be large enough to cause nearly complete airway obstruction, and laryngoscopy is rarely successful.

Laryngeal and tracheal malformations: TEF (tracheoesophageal fistula) is the commonest of this class of anomalies. Others are laryngeal or tracheal stenosis, laryngeal web, laryngeal cleft, dysplastic tracheal cartilage or rings, small epiglottis, short trachea, agenesis of one lung and tumors of the airway. They are often associated with facial deformities, abnormalities of the cervical spine or cardiovascular defects. e.g., Pallister-Hall syndrome, Shprintzen's syndrome, CHARGE association, VATER association, Di-George sequence, trisomy 18 syndrome. Obstruction due to tumor is seen in multiple neuroma syndrome and Peutz Jegher's syndrome, and due to deposits of abnormal tissue in chondrodysplasia punctata, pachyonychia congenita syndrome and Fabry's

syndrome. A short trachea may be present in Di-George sequence, skeletal dysplasias and congenital rubella syndrome.

Cervical spine anomalies: These may lead to decreased cervical spine mobility due to a bony deformity or a muscle contracture, cervical spine subluxation or spinal cord or nerve root compression. Reduced mobility is seen in Klippel-Feil syndrome and Goldenhar's syndrome, and direct laryngoscopy may be difficult, or even impossible in these children, and fibre-optic, lightwand or Bullard's laryngoscope may be alternatives. Cervical spine anomalies are frequently seen in osteochondroplasias and glycogen storage disorders, and odontoid hypoplasia is the most commonly encountered anomaly. Subluxation of the atlanto-axial joint is most commonly encountered in Down's syndrome (20% of these children have this anomaly), and some anaesthesiologists recommend routine radiographs of the cervical spine for these children. Any unnecessary twisting, extension or positioning of the head during airway manipulation should be avoided. Fibre-optic intubation, light-wand etc may benefit these children and help in minimizing spinal cord damage during intubation.

Cardiopulmonary malformations-The syndromes in paediatric age group are often associated with malformations of the heart and great vessels, which are very commonly encountered, or pulmonary hypoplasia, which

is rarely seen in routine anaesthetic practice because of high mortality of these children at an early age.

Pulmonary hypoplasia and chest cavity anomalies- This is usually associated with a small chest cavity, which hinders and prevents the normal growth and maturation of the lungs in-utero. They usually have vertebral or rib anomalies also, and if not lethal in infancy, they present with chronic respiratory tract infections. The anaesthetic management depends on the severity of pulmonary hypoplasia. There is impaired gas exchange due to reduced pulmonary surface area and excessive airway pressures during ventilation can lead to pneumothorax. Some of these syndromes are also associated with cardiac malformations, e.g., Apert's syndrome, Ellis-van Creveld syndrome, Pallister-Hall syndrome and Meckel-Gruber syndrome. Table-1, describes some common syndromes associated with pulmonary malformations and their anaesthetic implications in brief.

Cardiovascular malformations- These are very common in the paediatric population with congenital syndromes, and sometimes there might not be the time to investigate them thoroughly prior to an urgent surgical procedure. They are extremely common in children with chromosomal disorders, and any abnormality detected during history or examination of such children immediately warrants an echocardiogram e.g., Down's syndrome is associated with

endocardial cushion defects, and Turner's with coarctation of aorta. Connective tissue malformation syndromes are usually associated with vessel wall anomalies or valvular defects e.g., Marfan's syndrome is commonly associated with aortic regurgitation and dissection of aorta, Homocysteinuria with medial necrosis of arteries, Osteogenesis imperfecta type I with mitral valve prolapse. Storage disorders are also frequently associated with cardiac defects, eg, Hurler's, Morquio's and Scheie's syndromes are all associated with valvular abnormalities, and Hunter's disease with cardiomyopathy. Maternal exposure to teratogenic agents and drugs are associated with cardiac problems. In case of a child with a malformation syndrome who comes for an emergency surgery which precludes an echocardiogram, a thorough history and physical examination is essential to rule out dysrhythmias (indicated by palpitations and an irregular heartbeat), hypoxemia (indicated by cyanosis, low SpO₂ and polycythemia) and cardiac failure (characterized by decreased weight gain, failure to thrive, pallor, diaphoresis, cardiomegaly, wheezing, hepatomegaly, peripheral oedema and cyanosis). If cardiac failure is suspected, the preload should be optimized by blood or fluids, inotropes should be used intra-operatively to improve contractility and anaesthetic drugs that depress the heart to the minimum extent should be used, and arrangements for post-operative ventilation and ICU care should

be made. In cases of hypoxemia, it is important to maintain the mean arterial pressure at normal or elevated levels to minimize right-to-left shunting of blood, and it might not be possible to increase the SpO₂ above 90% intra-operatively. In case of arrhythmias, they should be treated as usual, and haemodynamic stability should be maintained. Table-2, lists some of the commonly seen cardiovascular malformations and describes their anaesthetic implications. All these children should be subjected to a complete cardiac evaluation pre-operatively.

Some other syndromes might be rarely associated with cardiac defects, eg, Apert's syndrome, Carpenter's syndrome, neurofibromatosis, Sturge-Weber syndrome, tuberous sclerosis sequence, Fabry's disease, Beckwith-Wiedemann syndrome and Fragile X syndrome.

Central nervous system (CNS) and neuromuscular anomalies- Most of the anomalies involving the CNS involve structural anomalies of the brain, and survival beyond childhood is rare in some of these. Many of these are associated with severe airway malformations, and some with cardiac defects. The commonest of structural defects include hydrocephalus and encephalocele. Some of these patients may be on anticonvulsant medication, which may significantly affect metabolism of opioids and neuromuscular blocking agents.

Hydrocephalus- It forms a part of osteochondrodysplasias and

craniosynostoses, usually due to obstruction to the flow of CSF due to bony compression e.g., Achondroplasia, Antley-Bixler syndrome, Apert's syndrome and Pfeiffer's syndrome. It can also be a feature of storage disorders. Eg. Tuberosus sclerosis, neurofibromatosis. The anaesthetic management includes management of a difficult airway and increased intracranial pressure.

Encephalocoele- It means herniation of cerebral tissue and meninges through a bony defect in the skull, and is of three types- anterior, basal or posterior (most common). The presentation differs according to type, as nasal obstruction and recurrent meningitis in the anterior, and hydrocephalus and blindness in the posterior type. Surgical correction is usually impossible in the basal type to involvement of major structures. These syndromes usually have low life expectancy. Survival past infancy is seen in few, e.g., Robert's SC phocomelia syndrome, facioauriculovertebral syndrome.

Abnormal muscle tone- Hypotonia is more common, and lack of movement in-utero may lead to limb and skeletal malformations. It may be associated with a CNS disorder, as in Zellweger's syndrome, or neuromuscular disorders, or due to disorders of the muscle itself. They may be associated with recurrent respiratory infections or feeding problems, and the severity may change with age. They may be associated with cardiac or airway defects. The dosage of muscle relaxants has to be reduced only slightly in

CNS disorders, while it may be drastically reduced in children with neuromuscular anomalies. The neuromuscular monitor should be used with caution in these cases, as it may not indicate accurately if there is enough muscle strength for satisfactory ventilation and prevention of aspiration. Care should be taken during positioning as they may be associated with joint laxity and joint contractures. Down's syndrome and achondroplasia are associated with hypotonia and cervical spine compression or subluxation.

Hypertonia is usually secondary to CNS anomalies, and relatively rare. Positioning of these patients may be difficult, and muscle relaxant requirements are usually unchanged.

Table-3 describes the common CNS malformations and their anaesthetic implications.

Renal malformations - Structural anomalies of the renal system are not important for the anaesthesiologist unless they are associated with functional disturbance. Various syndromes belonging to other classes may be associated with renal anomalies, and renal function in such patients should be tested. Appropriate precautions should be taken during anaesthetic management in case of compromised renal function. Table 4 contains a list of the common syndromes associated with renal anomalies.

Skeletal malformations-The vertebral anomalies important for the anaesthesiologist include hemivertebrae, fused vertebrae, kyphosis, scoliosis, spina bifida, osteoporosis, subluxation of the

atlanto-occipital joint and a narrow caudal space. Nearly all vertebral anomalies are seen with osteochondrodysplasias. Apart from these, joint laxities and contractures and fragile bones warrant care during positioning for laryngoscopy and intubation and also for surgery. Contractures might make even placement of intravenous, arterial and central venous lines extremely difficult. Table -5 describes the anaesthetic considerations in some of the common skeletal malformations

Endocrine disorders - The common endocrine disturbances associated with congenital malformation syndromes include diabetes mellitus, diabetes insipidus, fasting hypoglycaemia, adrenal hypoplasia, pituitary dysfunction, hypothalamic dysfunction, hyper- or hypothyroidism and hyper- or hypocalcemia. Table- 6 describes the anaesthetic implications of some of these common syndromes.

Haematological disorders and neoplasms - These include anaemia, thrombocytopenia or immunodeficiency and an increased risk of infections. Many of these are associated with an increased risk of malignancies, specially the hamartoma malformation syndromes. Such patients should be treated for anaemia, and have pre-operative testing of haematocrit, total leukocyte count and platelet count. The common syndromes involving disorders of the haematological system are described in Table-7.

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Table-1, Common syndromes associated with pulmonary malformations and their anaesthetic implications

Description	Anaesthetic implications
Achondrogenesis Types I & II- severe defect in the development of bone and cartilage, Micrognathia, Chest wall deformities, Short stature, Large cranium, usually lethal.	Difficult airway, Difficult intravenous access, Care with positioning.
Achondroplasia Premature osseous fusion, Macrocephaly, Sleep apnoea, Chest wall deformities (scoliosis, small rib cage), Spine stenosis and fusion, Brainstem compression, Short stature, obesity.	Difficult airway, Cervical cord compression during positioning, Restrictive lung disease due to chest wall deformity.
Ellis-van Creveld Dwarfism, Micrognathia, Short trachea, Congenital heart disease, Restrictive lung disease.	Difficult intubation, Endobronchial intubation, Pre-operative cardiac evaluation.
Meckel-Gruber Microcephaly, Short neck, Micrognathia, Pulmonary hypoplasia, Congenital heart disease, Occipital encephalocele +/-, Hydrocephalus, seizures, Renal anomalies.	Difficult intubation, Pre-operative cardiac and renal evaluation, Anticonvulsant medication may affect metabolism of neuromuscular blockers and opioids.
Osteogenesis imperfecta type II Hearing loss, Kyphoscoliosis, Fragile bones, Multiple fractures, Hyperextensibility, Short stature.	Care in positioning and intubation.

Table-2, Common cardiovascular malformations and their anaesthetic implications

Description	Anaesthetic implications
Zellweger' Micrognathia, Congenital Heart Disease, Hypotonia, Adrenal atrophy, Contractures, Respiratory insufficiency, Renal dysfunction.	Steroid administration, Care during positioning, Pre-operative renal evaluation.
Noonan Short stature, Webbed neck, low set ears, Micrognathia, Mental retardation, Congenital Heart Disease esp pulmonary stenosis, Coagulation disorders, Hydronephrosis or Hypoplasia of kidneys, Lymphoedema.	Difficult intubation, Haemorrhage, Preoperative renal function testing and titration of drugs excreted through renal route, Difficult venous access.

<p>Turner's (single X chromosome) Micrognathia, Short webbed neck, Short stature, Hypothyroidism, Hypertension, Lymphoedema, Coarctation of aorta, Renal anomalies.</p>	<p>Difficult intubation, Difficult I/v cannulation, Preoperative renal function testing and titration of drugs excreted through renal route.</p>
<p>Cri-du-chat Abnormal cry, Microcephaly, Micrognathia, Congenital Heart Disease, Mental retardation, Hypotonia.</p>	<p>Difficult intubation, may have stridor or laryngomalacia, Recurrent aspiration.</p>
<p>Ehler-Danlos' Collagen abnormality with hyperelasticity and fragile tissues, Dissecting aneurysm of aorta and Aortic regurgitation, Vascular fragility, Lung cysts.</p>	<p>Spontaneous pneumothorax, i/v line difficult to maintain due to haematoma formation, Bleeding diathesis, Poor wound healing.</p>
<p>Homocystinuria Intimal thickening, Ectopia lentis, Osteoporosis, Kyphoscoliosis.</p>	<p>Thromboembolic phenomena including CVAs</p>
<p>Marfan's Connective tissue disorder, Dilatation aortic root leads to aortic regurgitation, Aortic and pulmonary aneurysm, Mitral valve prolapse, Kyphoscoliosis, Pectus excavatum, Lung cysts, Joint instability, Lens dislocation.</p>	<p>Pneumothorax, Joint dislocations during positioning, Aortic dissection.</p>
<p>Fetal alcohol syndrome Growth and developmental delay, Micrognathia, Short neck, Congenital Heart Disease.</p>	<p>Difficult intubation.</p>
<p>Fetal hydantoin syndrome Microcephaly, webbed neck, Midfacial hypoplasia, Congenital Heart Disease, Mental retardation, Growth delay, Hirsutism.</p>	<p>Difficult intubation.</p>
<p>Fetal rubella syndrome Microcephaly, Congenital Heart Disease, Mental retardation, Deafness, Cataract, Glaucoma, Anaemia and Thrombocytopenia in neonate.</p>	<p>Preoperative haematological evaluation.</p>
<p>Fetal warfarin syndrome Microcephaly, Congenital Heart Disease, Mental retardation, Convulsions.</p>	<p>Upper airway obstruction, anticonvulsants.</p>
<p>Valproate effects Congenital Heart Disease, Radial anomalies, Meningomyelocele.</p>	<p>Cardiac evaluation.</p>
<p>Hunter's syndrome Pulmonary hypertension, Usually die before ten years from respiratory and cardiac failure, Developmental delay.</p>	<p>Severe coronary artery disease at early age, Valvular and myocardial involvement, Abnormal tracheobronchial cartilages.</p>

<p>Morquio's syndrome Short neck with decreased mobility, Spine and thoracic anomalies, Atlantoaxial instability, Aortic valve pathology.</p>	<p>Difficult intubation, Cervical spine evaluation, Careful positioning.</p>
<p>Scheie's syndrome Corneal clouding, Hernias, Joint stiffness especially hands and feet, Aortic valve involvement.</p>	<p>Care in positioning.</p>
<p>Holt-Oram syndrome (heart-hand syndrome) Congenital Heart Disease, upper limb defects.</p>	<p>Cardiac evaluation.</p>
<p>TAR syndrome Thrombocytopenia, Absent radius, Congenital Heart Disease.</p>	<p>Check preoperative platelet count.</p>
<p>LEOPARD (multiple lentiginos) syndrome Lentiginos, ECG conduction defects, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, retarded growth, deafness.</p>	<p>Problems associated with pulmonary stenosis.</p>
<p>Alagille's syndrome Biliary hypoplasia, Congenital Heart Disease, Hypertension, Renal artery stenosis, vitamin K deficiency.</p>	<p>Cirrhosis, Portal HT, Prolonged PT, Preoperative renal function testing.</p>
<p>CHARGE association Coloboma of eyes, Heart defects (TOF), Atresia of choanae, Retardation of growth, Genital underdevelopment, Ear deafness.</p>	<p>Difficult intubation, Respiratory distress.</p>
<p>Kartagener's syndrome Dextrocardia, Situs inversus, Sinusitis, Bronchiectasis, Immobile cilia.</p>	<p>Chronic respiratory infections, Chronic sinusitis may preclude nasal intubation, Reverse placement of ECG electrodes and defibrillator pads.</p>
<p>VATER association Vertebral anomalies, Congenital Heart Disease (VSD), Anal atresia, Tracheo-esophageal fistula, radial and Renal anomalies.</p>	<p>Pre-operative renal function testing, caution in central neuraxial blocks.</p>
<p>Progeria syndrome (Hutchinson-Giford syndrome) Premature ageing, Micrognathia, Beaked nose, Premature coronary artery disease, Cerebrovascular disease, Hypertension, Diabetes mellitus.</p>	<p>Difficult intubation due to micrognathia and stiff joints, pre-operative cardiac evaluation.</p>
<p>Weill-Marchesani syndrome Congenital Heart Disease (aortic subvalvular stenosis), Glaucoma, blindness.</p>	<p>Pre-operative cardiac evaluation, increased intraocular pressure.</p>

Table-3 common CNS malformations and their anaesthetic implications

Description	Anaesthetic implications
Albers-Schonberg syndrome (osteopetrosis) Brittle bones, Pathological fractures, Hepatosplenomegaly, Anaemia, Muscle dystonia.	Care in positioning
CHILD syndrome Congenital hemidysplasia, ichthyosiform erythroderma, Limb defects, Congenital heart disease, Hypomelia, Renal agenesis.	Pre-operative renal function testing, Difficult intravenous access.
Gorlin's syndrome Skin pigmentation, Oral papillomas, Congenital Heart Disease, Renal dysplasia, Reflux esophagitis.	Anti- aspiration prophylaxis, Difficult ventilation / intubation due to papillomas, Care during positioning, Pre-operative renal and cardiac evaluation.
Lowe's syndrome Cataract, Mental retardation, Rickets, Renal failure.	Pre-operative renal and function evaluation.
Menke's kinky hair syndrome Seizures, Cerebral degeneration, Microcephaly, Kinky hair, Reflux oesophagitis (due to abnormal copper transport)	Anticonvulsant medication, difficult ventilation and intubation.
Neurofibromatosis (von Recklinghausen disease) Multiple neurofibromas involving CNS and PNS, Café-au-lait spots, Bone lesions, may be associated with pheochromocytoma.	May involve airway and central neuraxial space, increased sensitivity to succinylcholine and non-depolarising muscle relaxants.
Osler-Weber-Rendu syndrom Multiple telangiectasias, Pulmonary arteriovenous fistula with right-to-left shunts, CNS AV fistulae and aneurysms, GI bleed, Paradoxical emboli.	Haemorrhage from nose, lung, brain and GIT, Pre-operative hematocrit, careful laryngoscopy and intubation, avoid nasal intubation, Avoid centra neuraxial blocks.
Prader-Willi syndrome Neonate - hypotonia, Poor feeding, absent reflexes. Second phase - hyperactive, Uncontrollable polyphagia, Mental retardation, Obesity, Hypogonadism, Diabetes mellitus.	Extreme obesity and related problems like Cardiopulmonary failure, Difficult ventilation and intubation, Perioperative glucose monitoring, Respiratory complications.
William's syndrome Elfin facies, Congenital Heart Disease, Sudden death (common), musically gifted, Renal malformations, Mild developmental delay.	Pre-operative cardiac and renal evaluation.

Table- 4, Common syndromes associated with renal anomalies

Description	Anaesthetic implications
Bardet-Biedl syndrome Obesity, Retinopathy, Polydactyly, Mental retardation, Renal failure, Hypogonadism.	Pre-operative renal function testing, problems associated with obesity.
Nail-patella syndrome Glaucoma, Scoliosis, Renal malformations, Poorly developed nails and patellae.	Raised intraocular pressure, pre-operative renal function testing.

Table -5, Anaesthetic considerations in some of the common skeletal malformations

Description	Anaesthetic implications
Hecht's syndrome Trismus, Pseudocamptodactyly (difficulty in straightening fingers when wrist is flexed).	Difficult intubation.
Maffuci's syndrome Enchondromatosis and Cavernous haemangiomas with malignant change.	Care during positioning, orthostatic hypotension and sensitivity to vasodilator drugs, GI bleed.
Maroteaux-Lamy syndrome Heart failure by third decade, Obstructive sleep apnoea, Short stature, Recurrent respiratory infections, Decreased joint mobility, Anaemia and thrombocytopenia.	Pre-operative cardiac evaluation, Difficult intubation, Care during positioning, Pre-operative check of haemoglobin and platelet count.
McCune Albright syndrome Fibrous bony dysplasia, Café-au-lait spots.	Care during positioning.
Ollier's disease Multiple enchondromatosis, usually unilateral.	Care during positioning.
Rokitansky's sequence Congenital aplasia of uterus, renal, vertebral, cardiac, auditory defects.	Pre-operative cardiac, renal evaluation.
Weaver's syndrome Microcephaly, large tongue, short neck, mental retardation, seizures, skeletal anomalies.	Anti-seizure medication, difficult intubation.

Table- 6 , Anaesthetic implications of common endocrinal syndromes

Description	Anaesthetic implications
Albright's syndrome Pseudohypoparathyroidism (lack of renal responsiveness to <u>parathyroid hormone</u>), Hereditary osteodystrophy, Short stature, short fourth and fifth metacarpals, rounded facies.	Low serum calcium, High serum phosphate, and appropriately high serum parathyroid hormone; thus, prolonged action of neuromuscular blocking agents.
Klinefelter's syndrome Developmental delay, hypogonadism, infertility.	Difficulty in communication an peri-operative period.
Tuberous sclerosis Mental retardation, Seizures, adenoma sebaceum, Hamartomata of lung, Rhabdomyoma of heart, Endocrinopathies.	Anticonvulsants.
Wermer's syndrome (MENI) Hyperparathyroidism, Tumours of pituitary and pancreatic islet cells, Gastric ulcer.	Renal failure due to stones, hypoglycaemia.

Table-7, common syndromes involving disorders of the haematological system

Description	Anaesthetic implications
Ataxia telangiectasia Cerebellar ataxia, skin and conjunctival telangiectasia, decreased serum IgA and IgE, may develop reticuloendothelial malignancy	Recurrent lung infections, aseptic techniques, glucose intolerance, hyperkalemia may occur with succinylcholine.
Chediak-Higashi syndrome Partial albinism, immunodeficiency, hepatosplenomegaly, Platelet abnormalities, Peripheral neuropathy.	Recurrent infections, aseptic precautions, Bleeding diathesis, Pre-operative platelet function testing.
Gardner's syndrome Multiple polyposis, Bony tumours, Sebaceous cysts, Fibromas.	May have difficult ventilation / intubation if airway has polyps.
MEN type IIB (Sipple syndrome) Medullary carcinoma of thyroid, Pheochromocytoma, mucosal and gastrointestinal neuromas.	Pre-operative evaluation for phaeochromocytoma, thyroid function tests.
Sturge-Weber's syndrome Port-wine staining of face, Haemangiomas, Seizures, Mental retardation, Congenital glaucoma.	Difficult intubation, Increased intraocular pressure, Anticonvulsant medication.
Von-Hippel-Lindau syndrome CNS, retinal and GI haemangioblastomas; Cysts in liver, kidney or pancreas; Cerebellar tumors; may have phaeochromocytoma.	Pre-operative evaluation for phaeochromocytoma, increased intracranial pressure.

Traumatic Lumbar Hernia

Lumbar hernias are rare presentation of blunt abdominal trauma. They are caused by sudden increase in intra abdominal pressure which causes disruption of muscular layers of abdominal wall. Because of the risk of strangulation & incarceration the diagnosis should be done with vigilance and should be recognized at the earliest.

A 38 years old female who presented with diffuse bulge on left side of abdomen since two years after a runover accident with fracture of superior and inferior pubic rami on both sides. Since then she gradually had swelling on lateral aspect of abdomen. She was giving history of gurgling sound after food intake. There was no bladder / bowel complaints. Plain radiograph taken which shows bowel loops outside the abdominal cavity. CT was performed using oral barium contrast and IV Omnipaque. It revealed barium filled bowel loops outside the abdominal cavity. They are herniating through a defect in muscular layer of abdominal wall through the Petit's triangle. The hernial sac contained small and large bowel greater omentum and mesentery.

Discussion -Acute blunt abdominal trauma is a rare cause of acquired lumbar hernia occurring either the Grynfelt –

Leeshaft triangle or in Petit's triangle. Both areas are of relative weakness in posterolateral abdominal wall. Most hernias through these occur either spontaneously or after surgical procedures, such as flank incisions or iliac bone graft procedure¹. Lumbar hernias are also known as hernia of Petit and Grynfelt, occur through the defect in parietal abdominal wall in any area of lumbar region². Two lumbar triangles are the superior lumbar triangle (Grynfelt–Leeshaft) and inferior lumbar triangle (Petit's triangle). Superior lumbar triangle is an inverted three sided space that is bordered by 12th rib superiorly, internal oblique muscle laterally and medially by quadratus lumborum muscle. The roof of the triangle is formed by Latissimus dorsi and floor is formed by transversalis fascia aponeurosis fascia. The inferior lumbar triangle is an upright triangle, bounded by iliac crest inferiorly, external oblique muscle anteriorly and latissimus dorsi posteriorly. The roof consists of skin and superficial fascia and internal oblique muscle lies in the floor. Clinical manifestations include backache, flank pain, occasional nausea and a feeling of weight or dragging sensation. These hernias have a natural history of gradual increase over time³. C.T. can accurately show the anatomy of disrupted muscular layers, show the presence of herniated

abdominal viscera or retroperitoneal fat and show associated abdominal injuries. Careful attention should be given to the patients with a h/o seat belt restraint to the abdominal wall layers. CT can be useful in patient with suspected or having traumatic lumbar hernias. It can reveal the muscular and fascial layers, show the presence of defects and reveal the contents of hernia before repair. It can also allow differentiation of a hernia from haematoma or abscess both common entities after blunt trauma⁴. Presence of acute traumatic lumbar hernia is alone an indication for laparotomy because of high incidence of associated hollow viscus and mesenteric injuries⁵.

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A.M. Deodhar
A. P. Deshmukh

R.M. Chopade
Shubhangi Gulve
Chirag Kale
Department of Radio-
diagnosis, Vivekanand
Hospital, Latur

Choroidal osteoma in a male patient: a rare condition

Choroidal osteoma is a clinical rarity, found mostly in female patients^{1,2}. We here report a case

of unioocular choroidal osteoma in a healthy young male. The age of presentation is youngest in any male patient in Indian subcontinent according to the Medline search on Internet. The condition causes significant diminution of vision due to osseous deposition in the choroid and further the patients may develop choroidal neovascularization with time, which adds further to the diminution of vision¹.

Case History-A healthy young male aged 19 years presented to the OPD with complaints of diminution of vision discovered about a month back. There were no other complaints. There was no history of trauma or any symptoms suggestive of any inflammatory disease in the past. Systemic examination was unremarkable. Ocular examination revealed VA of 6/6 OD, 6/60 OS. BCVA was 6/6 OD, 6/24 OS. The anterior segment examination revealed no abnormality. The intraocular pressure was 16mm of Hg by applanation tonometer. Fundus examination in left eye revealed clear media and normal optic disc. There was a large subretinal slightly elevated yellowish white mass, involving whole of the posterior pole and macular area. Differential diagnosis of

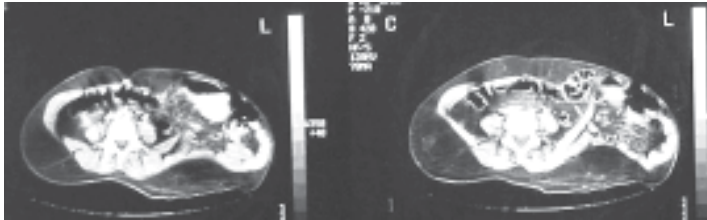


Fig 1 : Herniation through Petits Triangle



Fig 2 : Plain Radiograph :
Bowel outside abdomen



Fig 3 : Radiograph after CECT
abdomen

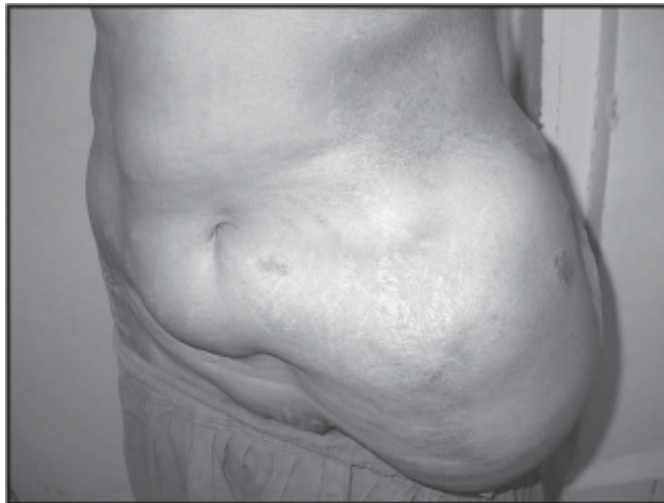


Fig 4 : Diffuse bulge over abdomen

chorioretinal scar or choroidal osteoma was made and a b-scan was ordered. B scan revealed [fig 1] a focal, slightly elevated, highly echo-reflective lesion merging with the retino-choroidal complex. The mass persisted at lower scanning sensitivity. B-scan ultrasonography also showed a distinct acoustic shadowing of the retro-ocular structures posterior to the mass giving the classical appearance of a pseudo-optic nerve. The corresponding a scan showed a high peak at the level of the retina choroid, which persisted even at lowest gain (48 Db) [fig 2], behind this was rapid attenuation of the waves. Fundus picture is depicted in the coloured photograph [fig 3]. Although the diagnosis was nearly certain but a FFA was ordered to look for any CNVM. FFA revealed irregular hyperfluorescence in the area of the lesion with no evidence of any choroidal neovascularization. CT scan or MRI was not indicated hence was not ordered and the diagnosis of choroidal osteoma was confirmed. There was no CNVM detected hence no treatment was given, however because the lesion is known to develop choroidal neovascularization, thus the patient was instructed to report for evaluation every 6 months.

Discussion-The choroidal osteoma is an uncommon benign acquired bony tumour of the choroid with an unknown aetiology. It usually makes its appearance in the second decade or the end of third decade². 90% of these lesions are seen in females; however no endocrinal or hormonal factors have yet

been proved to be a causative factor. 20% of the lesions are bilateral. The patients present with the painless progressive unioocular loss of vision which has been there for many years. Few patients may present with rapid or sudden reduction in vision due to secondary changes in the lesion like serous sensory detachment of the macula, choroidal neovascularization, subretinal bleeding. The tumour commonly involves the posterior pole surrounding the disc and involving the macular area. The tumour appears orange in early stages and later on it turns cream to yellow in colour because of overlying retinal pigment epithelium atrophy and visibility of the calcified tumour mass. The size ranges from one disc diameter to several disc diameters. The borders are sharp, in contrast to choroidal hemangioma. In larger lesions there may be blood vessels running over the lesion mimicking an amelanotic melanoma. Diagnosis is made on history of progressive painless diminution of vision for long time, the appearance on fundus evaluation and ultrasonography. The A Scan shows high peak at the retinochoroid junction with rapid attenuation of spikes posterior to the lesion even at low gain settings. On B Scan mode the lesion appears as a highly reflective plate at the retinochoroid plane which is seen highlighted at lower gain settings. There is presence of double optic nerve sign because of the acoustic shadow posterior to the lesion appearing just like normal optic nerve shadow.

Osteomas are characterised as bone on plane CT scan. However on MRI they appear hyperintense to vitreous on T1-weighted images and hypointense on T2-weighted images⁴. We did not order these investigations to prevent unnecessary radiation exposure and added expenses as the sonographic picture and clinical picture are confirmatory for making the diagnosis⁵. FFA is indicated to differentiate the osteomas from other intraocular tumours like Amelanotic melanoma, choroidal haemangioma, choroidal metastasis, or idiopathic choroidal calcification. The tumour has variable prognosis as one third of the patients develop choroidal neovascularization and associated complications. These patients should be managed for the choroidal neovascularization just like other patients with CNVM.

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Ajai Kumar Gupta

J. P. Gupta

Sanjiv K Gupta

Jan Kalyan

Eye Hospital, Lucknow

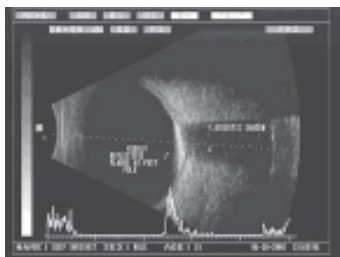


Fig.1

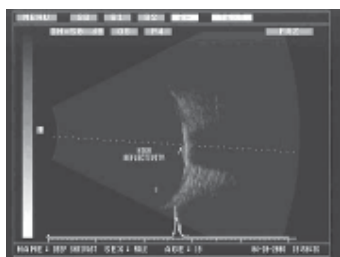


Fig.2

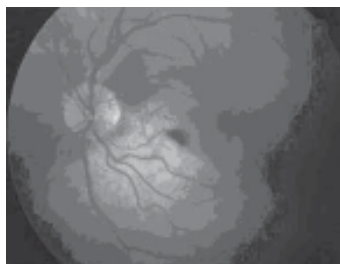


Fig.3

Boerhaave's Syndrome Diagnosed After 36 hours and Treated - A Case Report

Boerhaave syndrome is an uncommon finding requiring prompt diagnosis and immediate surgery because of its high mortality rate. Without surgical intervention, spontaneous perforation of esophagus is virtually incompatible with life. The classic history is of a patient who vomits and experiences epigastric or substernal pain. This pathology is best treated with definitive repair and mediastinal and / or pleural drainage procedures. We describe a case of a 55 years old obese male patient with classic above mentioned history who was referred to us after 36 hours. This patient had undergone aggressive surgical treatment and the postoperative period was stormy. The unusual cause, aggressive management and interesting post operative course is described. Herman Boerhaave first described this entity in 1724. Boerhaave's syndrome is the spontaneous rupture of esophagus usually after vigorous vomiting. Many time associated with excessive alcohol ingestion when a dramatically raised pressure may develop in the esophagus as a result of failure of cricopharyngeal relaxation. It is important to recognize this complication early because of its fatal consequences.

Case report-A 55 year old obese, smoker, alcoholic male patient presented with history of

ingestion of heavy meal followed by severe bout of vomiting and onset of breathlessness. His X-ray chest showed left hydropneumothorax and collapsed lung for which intercostal drainage tube (ICD) was inserted. Patient was referred to our institute after 36 hours since it was draining turbid fluid along with food particles. After resuscitation, CT scan thorax with oral contrast was done which showed spillage of oral contrast into left pleural cavity with left pleural effusion confirming esophageal rupture. Emergency thoracotomy (left posterolateral) through 8th rib bed was performed. There was about 3 cm long tear at left anterior wall of lower esophagus with gross contamination in pleural cavity and pus flecks deposited extensively over pleura. After thorough pleural toilet esophageal tear was repaired in 2 layer with interrupted sutures (Polypropylene). A midline laparotomy for decompressing gastrostomy and feeding jejunostomy was also done. Post operative care included ICU care, nasoesophageal aspiration, mechanical ventilation, antibiotics and chest physiotherapy. Patient's condition was stable till 6th day but ventilatory requirements persisted for failed weaning. On 7th day he developed tachycardia, tachypnoea, leucocytosis and increased ventilatory requirements, which was suggestive of septicemia. There was increased output of turbid fluid through chest drain. CT scan with oral contrast showed significant leak from lower esophagus. Emergency reexploratory surgery was

carried out. At surgery, esophageal mucosa was pouting out along the entire length of tear, with the stitches having loosened up considerably. Entire length of esophageal mucosal tear was well exposed by cutting the left dome of diaphragm. A meticulous, two-layered closure (Polypropylene 3-0), with reinforcement from fundus of stomach was performed. Post operatively (POP) patient continued to need ventilatory support. CT scan was done on 8th POP day, which revealed no leak with good passage of contrast into stomach but pneumonitis with effusion and moderate pericardial effusion suggesting mediastinitis. Gradually oral feeds were instituted, with persistent ventilatory and antibiotic requirement for 3 weeks due to poor respiratory and general condition. He was successfully extubated as his consolidation and septicemia cleared. During this treatment he lost about 15 kgs of weight. At 8 months of follow appointments he is doing well.

Discussion-Boerhaave's syndrome is a barogenic injury to esophagus resulting from sharp increase in intraluminal pressure during vomiting. Perforation resulting from barogenic trauma is most commonly located in the lower third of esophagus on the left side¹. This condition is most commonly seen in men between age of 35 and 55. The Mackler triad consisting of vomiting, chest pain and cervical emphysema is seen in about 50% of cases. Boerhaave's syndrome is an uncommon life threatening

condition demanding early diagnosis with high index of suspicion. Patients who are diagnosed early are treated easily and have better prognosis than those diagnosed late (after 24-48 hrs). Management includes resuscitation and prompt surgical treatment. Principles of esophageal repair include proper exposure of entire length of the mucosal injury and a meticulous two-layer closure is performed². Reinforcement or buttressing of the repair is an important adjunct in reducing the incidence of postoperative suture line disruption. A variety of tissues have been used to buttress esophageal repair including parietal pleura, gastric fundus, intercostal or diaphragmatic muscle and omentum. Wide pleural drainage is mandatory in addition to the repair³. Esophageal perforation is most lethal perforation of GI tract. The mortality rate is high due to pleural sepsis, mediastinitis and attending shock. Survival contingent is largely based early diagnosis, prompt surgical treatment, nutrition and good critical care⁴. Meticulous primary repair of esophageal perforation, regardless of the duration is an established principle in the management with 80% success rate and 14% mortality rate⁵.

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**Nitin R. Patel,
V. P. Joshipura
Bhavin Patel,
S. Chandra**

**Sukumar Mehta
Harjit Dumra**

Department of
Gastrointestinal and
Laparoscopic Surgery
Sterling Hospital
Ahmedabad

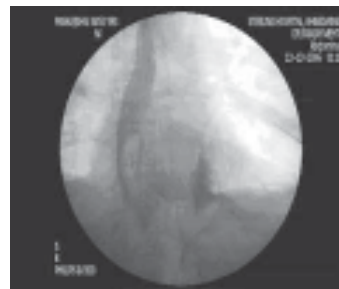


Fig 1:- Leakage of contrast in cavity



Fig 2:- site of perforation (forceps) pleural

Fibrous dysplasia involving skull base & paranasal sinuses

Fibrous dysplasia is a developmental anomaly which is characterized by the progressive replacement of normal bone elements by fibro-osseous tissue. Lichtenstein in 1938 coined the term fibrous dysplasia¹. It is typically seen in adolescents and young adults. The disease can involve any bony in the body. In the head and neck, the skull and facial bones are involved in 10-25% of cases of monostotic fibrous dysplasia and in 50% cases of polyostotic variety². We here report a case of monoostotic fibrous dysplasia involving cranium, skull base, facial bones and paranasal sinuses.

A 22 years old male patient referred for MRI brain with complains of giddiness and blackouts since 2 months. On examination there was minimal facial disfigurement seen (figure 1). There was no swelling elsewhere on the body. MRI revealed widening of vault bones with soft tissue mass involving bilateral frontal region, more on left. It was extending to involve the skull base and clivus (figure 2, 3). Involvement of bilateral ethmoid sinuses, sphenoid sinuses and left nasal cavity also seen. There was deformation of left nasal turbinate (figure 4, 5). The lesion was hypointense on T1WI and heterogeneous hypointense on T2WI. There was

minimal mass effect on left frontal lobe, however brain parenchyma appeared normal in signal intensity pattern. Relevant C.T. sections of paranasal sinuses and cranium taken. It revealed hyperdense components with ground glass appearance figure 6, 7. For academic interest radiographs of skull taken, revealing similar findings (figure 8, 9).

Discussion -Fries reviewed the radiographic features of fibrous dysplasia of skull and facial bones and described three patterns³. The pagetoid or ground-glass, sclerotic and cystic pattern. The pagetoid pattern is most common (56%) and consists of mixture of dense and radiolucent areas of fibrosis. The sclerotic lesions are second most common variety (23%) which are homogeneously dense. The cystic variety (21%) consist of a spherical or ovoid lucency surrounded by a dense bony shell, is least common. This appearance is based on histological component within the lesion. Pagetoid type result from equal mixture of fibrous tissue and woven trabecular bone where as osseous elements show opaque sclerotic type. Similarly the cystic type results from an abundance of fibrous elements. Fibrous tissue is seen as hypointense on both T1 & T2WI magnetic resonance imaging⁴. The signal intensity of fibrous dysplasia on T1 & T2WI and the degree of contrast enhancement on T1WI also depends upon the amount and degree of bony trabeculae,

cellularity, collagen and cystic and haemorrhagic changes⁵. In particular T2WI MR images show variations of signal intensity and T1WI MR images show a homogeneously hypointense signal. CT scanning is the primary mode for radiographic evaluation of fibrous dysplasia which in best way displays the bony changes. MR imaging is a useful adjuncts, particularly in cases of cystic fibrous dysplasia. It is useful to assess the soft tissues and fibrous components and to evaluate the effect of these bony lesion on adjacent soft tissue structures.

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A.M. Deodhar, Atul P. Deshmukh
 R.M. Chopade
 Shubhangi Gulve
 Chirag Kale
 Department of Radiodignosis,
 Vivekanand Hospital
 Latur, Maharashtra



Fig : 1 Minimal Lt. facial disfigurment

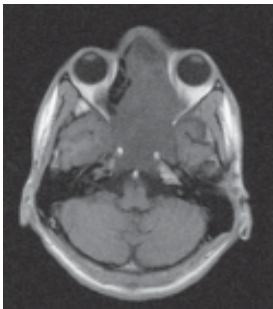


Figure-2 - T1 WI MRI

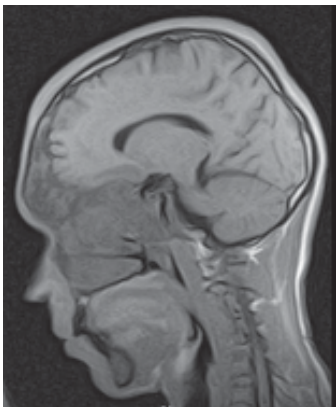


Figure-3 - T1 WI MRI



Figure-4, Fig : 4, 5 : T2 WI MRI coronal

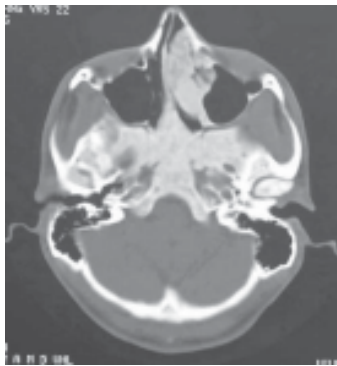


Figure-5

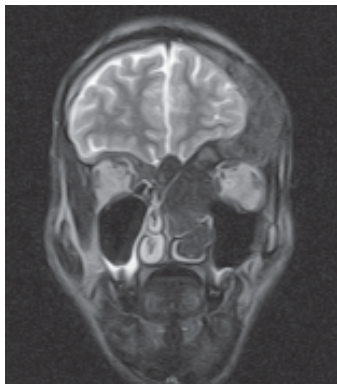


Figure-6, Fig :6,7 : Coronal, Axial CT Scan

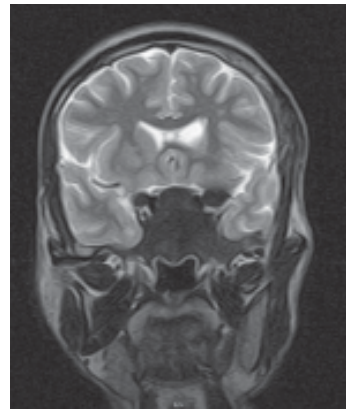


Figure-7



Figure-8 , Fig : 8,9 : X-Ray skull AP,Lat



Figure-9

Recent Advances

V. P. Joshipura, N. R. Patel, H. N. Soni, S. P. Haribhakti

Department of GI and Laparoscopy Surgery, Sterling Hospital, Ahmedabad

Ulcerative colitis (UC) is an inflammatory bowel disease involving colon and sometimes-terminal ileum and rarely involves other systems. UC is predominantly a mucosal disease of yet undetermined etiology. Chronic watery and then bloody diarrhoea are its characteristic features with acute exacerbations and remissions. Extra-intestinal manifestations like sacroileitis, rheumatoid arthritis may be present. UC is a potential pre-malignant condition and the risk of colonic malignancy increases especially after 10 years of disease. Treatment of UC is predominantly a medical treatment. However, surgery is required either in a complicated UC, disease not responding to any drug therapy or steroid dependent disease or in malignant transformation. 5-Amino Salicylic Acid derivatives such as sulfasalazine, mesalazine etc. are the first line of treatment. The disease not responding to these drugs require either topical steroids or addition of azathioprine or 6-mercaptopurine. Acute exacerbations of the disease require either intravenous steroids or cyclosporine or surgical intervention alone or in combination. There is new surge of interest in pharmacotherapy on identification of role of Tumor Necrosis Factor- μ (TNF- μ) in causation of mucosal inflammation noted in UC.¹

Developments in genetic engineering lead to a new class of drugs namely targeted monoclonal antibodies. Infliximab is a chimeric monoclonal antibody targeted against TNF- μ and has proved its efficacy in other inflammatory diseases such as Rheumatoid Arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's Disease. Now since the year of 2005, US Food and Drug Authority (US FDA) has approved its use in UC too.²

Tumor necrosis factor- μ and its role in UC-TNF- μ is proinflammatory cytokine released by cells of monocyte-macrophage system, T cells and mast cells on stimulation by various antigens including bacterial antigens and lipopolysaccharides. It is present in either transmembrane or soluble form in the body. All most of all the cells of the body have receptors [Type I (55 kD) & II (75 kD)] for TNF- μ .³ Soluble form of TNF- μ binds to these receptors and generates a cascade of intracellular events that leads to generation of inflammatory response by the cell. Human and animal studies have shown that TNF- μ has pivotal role in development of mucosal inflammation noted in UC. High levels of TNF- μ are noted in serum, urine, stool and mucosa of the patients of UC and its degree of elevation correlates with the disease activity.⁴ Knowledge of the role

of TNF- μ in the inflammatory disease prompted use of monoclonal antibodies against it to treat the disease. As efficacy of infliximab was proved in non-fistulizing and fistulizing Crohn's disease, logically research initiated to investigate its role in UC.^{5,6}

Infliximab- structure and pharmacodynamics-Infliximab is a genetically engineered, 149,100-d, chimeric monoclonal IgG1 antibody that has two components 25% mouse and 75% human antibody. It specifically binds to the transmembrane or soluble form of TNF- μ and leads to its dysfunction or immune mediated &/or programmed death of the cells containing it.⁷ Complete human monoclonal antibody, adalimumab is also developed, which is under investigation at present. Route of metabolism and excretion of infliximab is unknown. However, its clearance is very slow as it has high and specific affinity for the TNF- μ . Its serum half-life is 9.5 days.

Use of infliximab in Ulcerative Colitis- Till date there are six randomized, double blind, controlled trials have been performed for the use of infliximab in UC. Though some of the trials did not show its efficacy, larger multicenter trials have shown it to be significantly better to placebo in terms of response and maintenance of remission. Sands et al were the first to study infliximab in

randomized controlled manner on 11 patients of steroid refractory severe ulcerative colitis.⁸ They used Truelove and Witts score of > 10 to define severe disease. Single dose of infliximab (5mg/kg in 3, 10mg/kg in 3 and 20mg/kg in 2 patients) was compared with placebo. They showed encouraging results of infliximab as compared to placebo in terms of decrease in severity index, Erythrocyte Sedimentation Rate, C-Reactive Protein and requirement of colectomy. In a study of 43 patients of oral steroid resistant UC, Probert et al showed that there is no significant difference between two doses of infliximab and placebo in terms of achieving clinical and endoscopic remission.⁹ However, patients selected for infliximab had higher oral prednisone requirement as compared to patients selected for placebo at the initiation of the study. Ochsenkuhn et al compared single dose of infliximab versus oral prednisone in 13 moderate UC patients. They showed that both regimes have equal response.¹⁰ However, this study had very less number of patients in each treatment arm. In 2005 Jarnerot et al¹¹ compared single dose of infliximab versus placebo in 45 patients of parenteral steroid refractory UC. They showed that requirement of colectomy was significantly less in infliximab group. Median time to surgery was also significantly more in infliximab group as compared to placebo group. Above-mentioned smaller studies showed conflicting results but the larger well-designed Active Ulcerative Colitis (ACT) I and II trials showed good evidence in favor of infliximab. In ACT I trial

¹², 364 patients of moderate to severe UC were included who had not responded to either steroids, azathioprine or 6-mercaptopurine or in their combinations. Patients received either placebo or infliximab 5mg/kg or infliximab 10mg/kg at 0, 2 and 6 and then every 8 weeks until week 46. They were followed up for 54 weeks. There was significant improvement in clinical response, maintenance of remission and mucosal healing in infliximab groups as compared to the placebo group. However, this study also showed that there is no additional advantage of dose of 10mg/kg as compared to 5mg/kg infliximab. ACT II trial was performed on another 364 patients of moderate to severe UC.¹³ This trial also showed the superiority of infliximab as compared to placebo in terms of clinical response, maintenance of remission and mucosal healing rate. Results of these large well designed ACT I and II trials lead to the US FDA approval for the use of infliximab in patients of UC who does not respond to or intolerant to 5-aminosalicylates, steroids, 6-mercaptopurine or azathioprine.

Adverse effects of infliximab- Infection is the commonest complication of infliximab. Upper respiratory tract and urinary tract are the commoner sites for the infections. However, other bacterial, fungal and viral infections are also documented in the literature. It is not clear that the whether the infections developed are due to infliximab alone or due to previous use of steroids and immunomodulators or due to chronic disease itself. Reactivation of latent tuberculosis is also a major adverse effect of infliximab. It is

estimated that risk is 4 times higher as compared to other drugs and the pattern and nature of tuberculosis is also unusual. All the patients should be screened for latent tuberculosis in form of detailed history, tuberculin test and x-ray chest before starting infliximab. If patient is found to have latent tuberculosis on these tests then 9 months of isoniazide treatment should be completed before infliximab.¹⁴ As 25 % of the structure of infliximab is of murine immunoglobulin, it has potential to generate immune reactions. Acute infusion reactions are defined as any adverse event occurring during or within 2 hours of an infusion while delayed reactions can occur up to 14 days after infusion. Acute reactions can be from nausea, chills, fever to severe anaphylactic reactions. Delayed reactions are serum sickness like reactions characterized by headache, myalgia, polyarthralgia, rash and sore throat.¹⁵ New onset and worsening of already existing congestive heart failure is reported in numerous reports with the use of infliximab.¹⁶ Similarly, demyelinating neural diseases like multiple sclerosis is also noted with the use of infliximab.¹⁷ Hepatotoxicity is reported in some cases so infliximab should not be prescribed to the patients who have liver enzyme levels five times higher than the normal levels.¹⁸ As other immunosuppressive therapies are associated with the increased risk of lymphoma it is possible that infliximab may also lead to lymphoma and there are reports published for the same. However, still the issue of development of lymphoma & other malignancies

is not yet settled.¹⁹ Infliximab is classified into category B medication for the pregnant females and it is not yet known whether it is secreted in breast milk or not.¹⁸

Conclusion-Infliximab - a chimeric monoclonal antibody against TNF- μ , is a new class of drug have proved its usefulness against rheumatoid arthritis and Crohn's disease. It is now approved for the use in patients of ulcerative colitis who are resistant to or intolerant to 5-ASA derivatives, azathioprine, 6-mercaptopurine and steroids in moderate disease. Its use is also justified in patients of severe, steroid resistant ulcerative colitis before considering cyclosporin or surgery. However, cost of therapy and possible adverse reactions should be considered.

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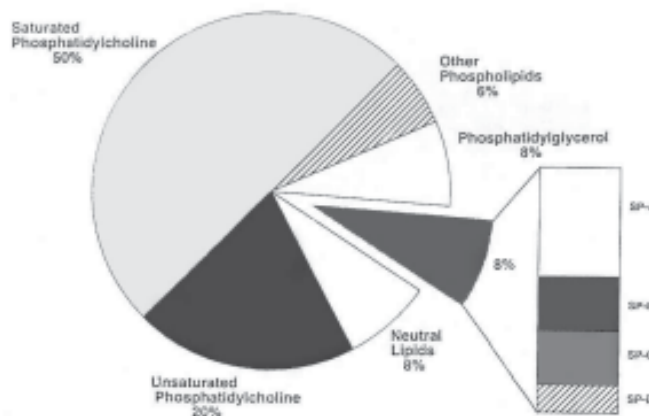
Nivedita Mondal, B.Vishnu Bhat

Department of Pediatrics, JIPMER, Puducherry

The development of surfactant therapy for the treatment of respiratory distress syndrome (RDS) in preterm babies is considered one of the greatest achievements of neonatology. Encouraged by the success of surfactant therapy in RDS due to primary surfactant deficiency, this treatment modality is now being tried in a variety of conditions ranging from Meconium aspiration syndrome to Adult respiratory distress syndrome. The story of surfactant began with von Neergard's observation that surface forces play a role in the mechanical properties of the lung. Pattle and Clements reported a substance that was needed to maintain the lung in a state of inflation at low transpulmonary pressures^{1,2}. Avery and Mead, in 1959 described the deficiency of surfactant in the lungs of infants who died of RDS³. The first clinical application of surfactant was done by Fujiwara et al, who in 1980 successfully treated preterms with a liquid preparation of bovine surfactant⁴. Since then innumerable number of trials have been conducted which have established the role of surfactant in RDS. At present trials are on to determine the possible role of surfactant in other conditions and in creating newer surfactants which resemble natural surfactant more closely.

Composition-Human pulmonary surfactant consists of 90% lipids (70-80% phospholipids and about 10% neutral lipids primarily cholesterol) and 10% proteins. The main lipid fraction which is also the main surface active component is saturated lecithin dipalmitoyl phosphatidylcholine. There are 4 proteins found to be associated with surfactant, named as Surfactant proteins – SP A , SP B , SP C and SP D.SP-A is a hydrophilic calcium binding glycoprotein which reduces protein mediated surfactant inactivation and binds and enhances the uptake of a number of microorganisms like *â-hemolytic streptococcus*, *Staphylococcus aureus*, *E.coli*, *Klebsiella*, fungi and RSV and therefore has immunoprotective function .Patients with deficiency

of SP-A have not been identified. SP-B is a hydrophobic polypeptide which enhances the rate of surface film formation and prevents surfactant inactivation. Babies with genetic absence of SP-B have lethal RDS after term birth⁵. SP-C is a hydrophobic polypeptide which works along with SP- B to enhance the adsorption and spreading of phospholipids to form the surfactant monolayer. Deficiency of SP-C has recently been reported in infants with progressive interstitial lung disease⁶. SP-D is a hydrophilic protein with immunoprotective role similar to that of SP-A and its deficiency has not been described in humans.

Fig.1. Constituents of surfactant⁷

Synthesis and secretion-

Surfactant is synthesized by alveolar type II cells and extruded in the form of lamellar bodies by exocytosis into the alveolar spaces. These lamellar bodies are first seen within the type I cells by 22 weeks of gestation. Surfactant appears in the future air spaces by 23-24 weeks and mature levels are reached after 35 weeks.

Mechanism of action-Surface tension results from intermolecular attractive forces like Van der Waals forces, hydrogen bonds and electrostatic forces. If the air spaces were to be lined by fluid alone then due to the high surface tension the compliance of the lung would be low, requiring high pressures to inflate it and at end expiration the alveoli would collapse. Surfactant is a surface active agent, the molecules of which get dispersed on aqueous surfaces and reduce surface tension. The reduction in surface tension is proportional to the number of surfactant molecules incorporated into the surface area. Before the advent of surfactant therapy, RDS was treated with CPAP or ventilatory support. High levels of oxygen, high tidal volumes and inspiratory pressures were used, all of which caused damage to the lung (oxytrauma, volutrauma and barotrauma) Lung damage led to leakage of plasma into the alveolar spaces resulting in surfactant inactivation. Surfactant treatment if given at the appropriate time prevents and partially reverses all these processes.

Clinical uses

Respiratory distress syndrome -RDS occurs due to deficiency of surfactant leading to diffuse alveolar collapse. The alveoli get lined with an eosinophilic membrane consisting of fibrinous material derived from blood and cellular debris, so the condition is otherwise known as hyaline membrane disease. The risk factors are those that affect the lung maturation like prematurity, diabetes in the mother, lung hypoplasia due to diaphragmatic hernia and genetic factors - male sex, white race, history of RDS in sibling⁸. Recently genetic deficiency of SP-B and mutations of ABCA3 gene have been described in infants with fatal RDS⁹. The other set of risk factors include those that affect production, release or function of surfactant like perinatal asphyxia and cesarean section. The condition presents within 6 hours of birth with tachypnea, subcostal and intercostal retractions, nasal flaring and grunting. The symptoms progressively worsen over the next 2 to 3 days and then start recovering. Chest X ray typically shows low volume lungs, reticulogranular pattern, air bronchogram and in the most severe cases complete white out lungs.

Time of therapy-Prophylactic therapy refers to the administration of surfactant in the first few minutes of life before overt signs of RDS have developed. Rescue surfactant treatment refers to administration of surfactant after the signs and symptoms of RDS

have appeared. Both the approaches have been subjected to several trials, in which reduction in mortality and air leaks have been found. However no significant reduction in the incidence of bronchopulmonary dysplasia has been reported. Early rescue i.e. administration of surfactant within 2 hours of birth is preferable to delayed treatment but in spite of having conducted comparative trials it is rather unclear if prophylactic treatment has any advantage over early treatment. Though most babies born at less than 37 weeks gestation will be deficient in surfactant, prophylactic surfactant administration may result in many infants being intubated and exposed to surfactant, both of which are associated with certain risks and expenses which may be unnecessary especially if the mother has already received antenatal steroids.

Natural vs Synthetic surfactant -Though both natural and synthetic surfactant have proven benefits, direct comparison between the two have shown that natural i.e. animal derived, protein containing preparations (most natural surfactant contain both SP-B and SP-C) have more rapid action and are associated with a significant decrease in pneumothorax and lower mortality. This has been shown in the meta-analysis done by Soll and Blanco. Their study also supports a marginal decrease in the risk of bronchopulmonary dysplasia associated with the use of natural surfactant preparations. An increase in the risk of intraventricular

hemorrhage was seen with natural surfactant extract administration, but it is only reflected in the lesser grades of hemorrhage. The analysis recommended natural surfactant extracts as a more desirable choice than synthetic surfactants¹⁰.

Comparison of natural surfactants - Bloom and colleagues carried out a double blind multicentric trial to compare the efficacy and safety of Infasurf and Survanta in the prophylaxis and treatment of RDS. The treatment arm included infants of ≤ 2000 g birth weight with established RDS who were randomly assigned to receive Infasurf or Survanta in a dose of 100 mg/kg, 22% of those who received Infasurf and 33% of those who were given Survanta required a fourth dose. The interval between doses was significantly longer for Infasurf, suggesting an increased duration of treatment effect. The inspired oxygen concentration and mean airway pressure were lower in the Infasurf treated group during the first 48 hours. Among the babies who had received the surfactant prophylactically there were no differences noted with respect to the number of doses. After the second dose, the intervals between doses were longer for Infasurf treated infants. During the first 72 hours no difference in inspired oxygen or mean airway pressure was seen. There were no significant differences in the incidence of air leaks, complications associated with dosing, complications of prematurity, mortality, or survival without chronic lung disease in

the prevention or treatment arm. The study concluded that infants treated with Infasurf have a modest benefit in the acute phase of RDS and that Infasurf seems to produce a longer duration of effect than Survanta¹¹. Speer and colleagues conducted a randomized control trial to study the outcomes of treatment with two natural surfactants Curosurf and Survanta in preterm babies of birth weight 700 gm – 1500 gm with RDS on ventilatory support with FiO_2 requirement of ≥ 0.4 . One group received an initial dose of Curosurf (200 mg/kg); the other group Survanta (100 mg/kg). Patients who remained on ventilator with an FiO_2 of ≥ 0.3 received up to two extra doses of Curosurf (each of 100 mg/kg) after 12 and 24 hours or up to three additional doses of Survanta (each of 100 mg/kg) between six and 48 hours after the initial dose. Improvement in oxygenation and reduction in ventilatory requirement occurred in both the groups. However, infants who received Curosurf had lower ventilator requirements (lower peak inspiratory pressure and mean airway pressure) and higher arterial:alveolar oxygen tension ratio within the first 24 hours of treatment. The incidences of pneumothorax, grade 3-4 intracerebral hemorrhage and mortality were lower in the group treated with Curosurf but these differences were not significant¹². A comparison of the outcomes of neonates treated with Infasurf and Survanta was done by Clarke et al over a period of one year between January and December 2000 in which the records of

5169 neonates of gestational age $< \text{or} = 36$ weeks were studied retrospectively. 22% of the infants received Infasurf and the remaining 78% received Survanta. Logistic regression analysis showed that the type of surfactant did not significantly influence the incidence of neonatal death, intraventricular hemorrhage, or necrotizing enterocolitis¹³. Therefore though significant differences have been found between the performance of natural and synthetic protein free preparations, comparisons of different natural surfactant have revealed only minor differences.

Method of delivery-Ensure endotracheal tube is properly positioned and give suction if needed. Warm Surfactant to room temperature and instill it intratracheally through the ET tube. Current guidelines call for administration of surfactant in aliquots through a side hole adapter connected to the endotracheal tube. Earlier recommendations of giving surfactant with the infant in different positions to ensure uniform delivery to all areas of the lungs are now often not followed.

Dosage-The dosage of surfactant ranges from 2.5 to 5 ml/kg body weight or 50 to 200 mg/kg. It is advisable to follow the manufacturer's recommendation. Retreatment is often necessary sometimes up to 4 times in the first 24 hours. Multiple dosing is believed to help because it may overcome the inactivation of surfactant by soluble proteins and other factors in the alveoli.

Surfactant	Initial dose	Maximum dose	Cost/ml	Cost/kg for maximum dose
Poractant (Curosurf)	2.5ml/kg	5ml/kg	\$254.00	\$1270.00
Calfactant (Infasurf)	3ml/kg	9ml/kg	\$122.02	\$1098.18
Beractant (Survanta)	4ml/kg	16ml/kg	\$101.68	\$1626.88

In India the cost of an 8 ml vial of Survanta is around Rs.11,000 and that of 10 ml Surfact is about Rs 4900.

Response to surfactant administration-Within minutes of administration of surfactant the requirement for positive pressures and high FiO_2 start falling. The positive inspiratory pressure and FiO_2 must be reduced to avoid barotrauma and oxytrauma. After administration of surfactant, if the ventilator settings are not changed for more than 30 minutes, though a remarkable improvement in oxygenation occurs it is not accompanied by an immediate improvement in $PaCO_2$, this suggests that rather than a rapid improvement in lung compliance it is an improved matching of ventilation and perfusion which is the primary mechanism by which surfactant improves PaO_2 in preterm infants with RDS. However some infants do not have the expected response. The possible reasons for an unfavourable response include insufficient dose, inactivation of surfactant activity by proteins or other substances like meconium, incorrect ventilatory strategy, alternative diagnosis or additional lung pathologies like congenital deficiency of surfactant protein, pulmonary hypoplasia, pneumonia, pulmonary edema etc and associated complications like intracranial bleed. According to Hamvas et al unresponsiveness to surfactant therapy has been seen

to be associated with higher morbidity and mortality in newborn respiratory distress syndrome. Pulmonary interstitial emphysema occurred more frequently in the nonresponsive group¹⁵.

Monitoring-The infants heart rate, color, chest expansion, SPO_2 should be monitored during and after administration of surfactant. Close observation should be done for the first half an hour to make necessary changes in the ventilator settings to compensate for the rapid changes in compliance that occur soon after the administration of surfactant. Reduction in inspiratory pressures should be done in time or else air leaks may occur.

Surfactant therapy for meconium aspiration syndrome - Meconium damages the lung by causing mechanical obstruction of airways, chemical injury and also by inactivation of surfactant. Several studies have now reported the beneficial role of surfactant replacement in MAS. Forty term infants receiving mechanical ventilation for MAS were enrolled in a trial, in which the infants in the study group (n = 20) received multiple doses of Survanta. Oxygenation improved cumulatively after the second and third dose of

surfactant. After three doses of surfactant, persistent pulmonary hypertension had resolved in all but one of the infants in the study group whereas no improvement occurred in the control group. No air leaks developed in the study group whereas air leaks developed in 5 of the 20 infants in the control group. Only 1 infant of those which received surfactant required extracorporeal membrane oxygenation while in the control group 6 underwent ECMO. The duration of mechanical ventilation, oxygen therapy, and admission was remarkably shorter in the surfactant group as compared to the control group. The study concluded that surfactant replacement therapy, if started within 6 hours after birth, improves oxygenation and reduces the incidence of air leaks, severity of pulmonary morbidity and hospitalization time of term infants with MAS¹⁶.

Surfactant therapy for group b streptococcal infection with Respiratory failure-Surfactant deficiency is believed to play a role in the respiratory distress seen in GBS infection which is a common cause of systemic and pulmonary infections in the neonatal period. Clinically, respiratory failure due to GBS infection and HMD present in

the same manner. Although laboratory parameters like leukocytopenia, increased I:T ratio, and elevated serum CRP may help to make a diagnosis of GBS infection within the first 24 hours, there is no way to distinguish with certainty between HMD and pneumonia in a premature infant during the first hours after birth, i.e., at the time when surfactant therapy should be considered. Herting et al investigated the effects of surfactant treatment in term and preterm neonates with GBS infection and respiratory failure, in comparison with corresponding data from a control population of noninfected infants treated with surfactant for respiratory distress syndrome (RDS). The results showed a higher percentage of nonresponders, a slower reduction in oxygen demand, and an increased incidence of complications i.e. mortality, pneumothorax, intracranial hemorrhage in the GBS-infected patients¹⁷.

Other uses of surfactant-Other conditions where surfactant may find a role include congenital diaphragmatic hernia, RSV pneumonia, pulmonary hemorrhage, bronchopulmonary dysplasia, bronchiolitis, asthma and ARDS¹⁸.

Complications -The instillation of 3 – 5 ml/kg of surfactant intratracheally may cause oxygen desaturation requiring transient increase in inspired oxygen, inspiratory pressures or tidal volume or even interruption of administration of surfactant.

Bradycardia is also known to occur due to desaturation or vagal stimulation. It may require temporary interruption of administration of surfactant. The ET tube may become blocked by the surfactant requiring suction or change of ET tube. The ET tube may be placed in the right main bronchus resulting in delivery of surfactant to the right side only which may cause the right lung to become hyper inflated and the left lung to collapse. Though data has suggested a slight increase in the incidence of pulmonary hemorrhage it still remains controversial.

Recent advances-Berggren et al conducted a study on nebulized surfactant therapy for neonatal respiratory distress syndrome. Thirty-four newborns with respiratory distress syndrome were included in the study. All the babies were first supported by nasal CPAP. The treatment group received nebulized Curosurf. The control group received no nebulized material. There were no significant differences between the groups in a/A PO₂ 1-12 h after randomization, number of infants needing mechanical ventilation, time on ventilator or CPAP. Therefore no beneficial effects of aerosolized surfactant were demonstrated in the trial¹⁹. Hafner and co workers tested the effect of surfactant containing recombinant surfactant protein -C (rSP-C) in a rat lung lavage model, their work showed that surfactant containing rSP-C is at least as effective as natural bovine-derived surfactants. Furthermore,

their data also implied that the difference between plain phospholipid surfactant preparations with no surfactant proteins and bovine-derived surfactant preparations containing both SP-B and SP-C can be overcome by addition of SP-C²⁰

Conclusion-Though we have come a long way in the application of surfactant in a variety of clinical conditions yet much remains to be known. Surfactant administration unequivocally reduces the mortality and morbidity in RDS. The benefits in other conditions like meconium aspiration syndrome and GBS infection are encouraging, yet inconclusively. A reduction in the cost and more easy availability of surfactant is needed to allow more number of clinicians to use it.

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