VOLUME - II
ISSUE - IX
MAY / JUN 2005

The Crux

BIMONTHLY FORUM FOR THE LABORATARIANS

CONTENTS

1 Editorial
2 Disease Diagnosis
5 Interpretation
7 Trouble Shooting
6 Bouquet
8 Tulip News

Editorial

Tulip Group has reached the top of the pyramid. Though it is a unique place to be at, it makes one feel lonely while giving an excellent view of what is going on below. Our intention is to go still higher. Our innovative products have taken India and half the world by storm. We export to the countries from where we used to import diagnostic kits/ reagents/ devices. Name a diagnostic laboratory sub-speciality, we have top of the line products for that. Starting from hemoglobin estimation till ELISA based immunoassays, we make them all.

In our effort to keep busy Laboratarians abreast with the very latest from the diagnostic field, we deliver Technical Notes (available on our Website), Technical Series Monograms (delivered to you) and now The Crux (also delivered in person to you). This is the ninth issue of The Crux and believe us you shall continue to receive them in future too. We have been receiving requests for particular topics and many of them have been covered in our previous issues. If you have anything in particular about which more information/details are sought - please let us know. Trust us, you shall have them.

This issue talks about Sickle Haemoglobinopathies under the DISEASE DIAGNOSIS section. Though, not so common an entity, it does lead to morbidity and mortality and can be easily diagnosed by relatively uncomplicated techniques. All related Clinico-diagnostic aspects of Sickle Haemoglobinopathies have been presented.

Under INTERPRETATION segment we have presented basic facts about tumor markers. The next issue shall carry the overflow of this very important branch with specifics as related to individual tumor markers. The commonly employed (asked for) markers shall be presented. Medium and even small labs now routinely practice this upcoming branch, which hitherto was the sole domain of large laboratories. Quick screening devices can be used at field level settings and are being regularly employed by smaller laboratories even in far-flung peripheral small towns.

A very common problem that medical practitioners face is Fever/Pyrexia of Unknown Origin. The TROUBLE SHOOTING portion considers this and makes the diagnosis making a relatively easy process. FUO/PUO is defined for you. The Differential Diagnosis is presented along with an algorithm that sequentially guides through to the final diagnosis. The process is a multi-speciality exercise.

Amidst these serious articles somewhere within you shall find a BOUQUET to enliven you.

ISO 9001

Tulip Group

DISEASE DIAGNOSIS

SICKLE HAEMOGLOBINOPATHIES

These are hereditary disorders in which the red cells contain HbS. They include the heterozygous (sickle-cell trait) and the homozygous (SS disease) states for HbS, and conditions in which HbS is combined with other haemoglobin structural variants or thalassaemia. In the deoxygenated state, the solubility of HbS is ten per cent of that of HbA. The conformational changes in HbS induced by deoxygenation cause the cells containing the abnormal haemoglobin to become rigid and deformed, assuming a sickle or crescent shape.

The red cell sickling in the circulating blood has two major pathological effects:

i) The distorted and rigid cells block small blood vessels, impairing flow and causing ischaemia and infarction; and

ii) Repeated 'sickle-unsickle' cycles lead to loss of fragments of red cell membrane, and the cells become spherocytic and fragile. They are removed prematurely by the reticulo-endothelial system, and to a lesser extent destroyed in the circulation resulting in both extravascular and intravascular haemolysis.

HbS differs from HbA in the substitution of valine for glutamic acid in the sixth position from the N-terminal end of the β-chain. The precise mechanism by which this seemingly minor change in amino acid sequence leads to such an important rearrangement of the molecule on deoxygenation is not known with certainty. Electron microscopy of sickle cells has shown bundles of long tubular fibers parallel to the long axis of the cell, which is presumed to be of sufficient rigidity to distort the cell membrane. Each fiber consists of 14 or possibly 16 spirally wound filaments, the filaments being composed of HbS molecules like beads on a string.

Red cells containing large amounts of HbS begin to sickle at an oxygen tension of 50-60 mm Hg. The cells in parts of the microcirculation experience this tension, and thus sickling occurs in vivo. If the flow rate is rapid, sickling does not become fully established and the cells resume normal shape when they are swept back to areas of circulation where the oxygen tension is higher. If the flow rate is slow, and the cells are delayed in areas where the oxygen tension is low, the cells sickle and there is further slowing of the circulation. Oxygen tension is further reduced, additional sickle cells accumulate, and finally complete blockage of the vessel occurs. Tissue ischaemia resulting from such vessel blockage is the basis of the painful crises that are a major clinical feature of the sickling disorders.

Several factors influence the degree of deoxygenation required to produce sickling of red cells containing HbS.

- The amount of HbS in the red cell is clearly of importance as the cells of a patient with sickle-cell trait which contain less than 50 per cent HbS are less likely to sickle at a particular level of deoxygenation than the cells of a patient with homozygous sickle cell disease which contain nearly100 per cent HbS.
- The physical properties of the haemoglobin with which HbS is associated in the red cell may increase or decrease the liability of the HbS to sickle. HbC and HbD potentiate sickling, and patients heterozygous for these haemoglobins and HbS have moderately severe sickling disorder. HbF has the opposite effect and tends to diminish sickling.

Red cells of patients with homozygous sickle cell disease have a reduced oxygen affinity, and the oxygen dissociation curve of the blood is shifted to the right. Although this phenomenon assists the release of oxygen at the tissue level, it also results in the occurrence of sickling at a higher oxygen tension than would be the case if the dissociation curve were normal. Acidosis shifts the curve further to the right and similarly enhances the sickling process.

The packed cell volume and proportion of red cells containing HbS are also important in determining the increase in blood viscosity resulting from a fall in oxygen tension.

The sickle gene is the result of a point mutation in the codon for the sixth amino acid of the β globin chain, and is inherited as a mendelian co-dominant.

It occurs mainly in blacks or persons with an admixture of black blood, and is thus seen frequently in Africa and amongst black populations in north and south America and the West Indies. It is also found in certain regions in Greece, southern Italy, Turkey, the middle East, and India. The sickle gene is believed to confer some protection against *Plasmodium falciparum* malaria, and its geographical distribution is in accordance with this concept. The following sickle haemoglobinopathies are prevalent in communities where the sickle gene is found -- sickle-cell trait, homozygous sickle-cell disease, sickle-cell thalassaemia, and sickle-cell HbC disease.

Laboratory Diagnosis

1. Sickle test: HbS cells sickle on being mixed with freshly prepared sodium metabisulphite.

False positive tests may occur in

- Patients who have received recent blood transfusion
- Infected blood sample
- Old reagent

2. Hb solubility test : Reduced HbS is relatively insoluble in concentrated phosphate buffer. Hb added to a solution of sodium dithionite (a reducing agent) containing a phosphate buffer, development of turbidity implies presence of HbS. Whole blood can be used in this test but saponin (a lysing agent) has to be added.

False positive tests may occur in

- Neonates
- Abnormal plasma proteins (If whole blood is used)
- If RBCs contain Heinz bodies
- PCV too high or too low
- Old reagents

3. Hb electrophoresis: Is mandatory. Cellulose acetate (pH = 8.6) is good but if HbD is co-existing; S and D separation would not occur, in that case use Agar gel (pH = 6.0) with citrate buffer for electrophoresis.

SICKLE CELL TRAIT (AS)

Sickle-cell trait, the asymptomatic carrier state for HbS, occurs in about eight per cent of American blacks. In Africa, its prevalence rate in many populations is over 20 per cent, and reaches 50 per cent in some tribes. Sickle cell trait is the heterozygous state for the HbS gene. HbS comprises 38-45 per cent of the total haemoglobin, the rest being HbA, HbA_2 and HbF. The cells do not contain sufficient HbS to undergo sickling at the lowest oxygen tension normally occurring in the body, and the red cell lifespan is normal. In the stained blood film, no sickle cells are present and the red cells appear normal. The MCV and MCH are also normal. However, sickling can readily be demonstrated by the sickle test, and the haemoglobin solubility test is positive. If the patient has a concurrent thalassaemia, the red cells are microcytic with a mild reduction in MCV and an HbS concentration of less than 38 percent. Sickle cell trait does not cause anaemia, and in general is asymptomatic. If anaemia is present, other causes, e.g. iron deficiency, should be sought. A high proportion of affected subjects show defects in urine concentrating ability, and haematuria is an occasional complication. Rare episodes of splenic infarction during flight at high altitude in non-pressurized aircraft have been described, and severe hypoxia resulting from administration of anaesthetic agents and other respiratory depressants may in exceptional cases be associated with in vivo sickling and serious thrombo-embolic sequelae. There is some evidence that sickle cell trait is a risk factor for sudden death during unaccustomed exercise, but most epidemiological studies suggest that no selective morbidity or mortality is attributable to the condition.

SICKLE CELL ANAEMIA

HbS enough for *in vivo* sickling is seen in southern India.
In vivo sickling may cause

- Chronic haemolytic anaemia
- Organ damage
- Episodes of pain

Clinical

- Diagnosis usually made at age less than 2 years
- From birth to 6 months, HbF protects
- Have increased incidences of infections with
  - Pneumococci
  - Meningococci
  - Haemophilus
- Autosplenectomy occurs by 8 years or so
- There is abnormal neutrophilic chemotaxis and phagocytosis
- Hand foot syndrome: microinfarction of medulla of carpal and tarsal bones
- Splenic sequestration syndrome: blood pooling in spleen → hypovolemia → shock → death
- Splenomegaly: evident by 6 th month, autosplenectomy occurs by 8 years or so, even though spleen is enlarged but changes of splenectomy (functional asplenia), e.g.: Howell-Jolly bodies, target cells, failure of spleen to accumulate radioactive colloidal sulphur, are there.
- In adults: clinical severity is variable, although all are anaemic.

Sickle Cell Crises

(Incidence reduces with increasing age)

1. Vaso-occlusive Crises

Are typically recurrent and potentially catastrophic

- Clinical manifestations are sudden in onset and directly attributable to obstruction of the microcirculation by intravascular sickling
- There is little or no change in haematologic values
- Precipitating factors

In adults
- infections

In children
- fever, dehydration and acidosis

Sometimes a history of recent exposure to cold may be obtained. Sudden changes in the altitude and travel in non-pressurized aircraft are less common antecedents.

Hand and Foot Syndrome

The initial episode in young children often involves the small bones of hand and feet. The dorsa of hands and feet are swollen, non erythematous, and very painful. Fever and leucocytosis are common. X-ray changes are limited to soft tissue swelling, cortical thinning and marked destruction of metacarpals, metatarsals and phalanges appear 2-3 weeks after the onset of symptoms. It may recur till the patient is about 3 years of age.

Bone and Joint Crises

After about 3 years of age sludging of blood occurs in the larger bones of the extremities, the spine, rib cage and periarticular structures, producing bone and joint crises. Pain results from ischaemia of bone, bone marrow, periosteum, or periarticular tissues. It is of gnawing character and progress in severity.

Abdominal Crises

These are attributable to small infarcts of mesentery and abdominal viscera and are characterized by severe abdominal pain and signs of peritoneal irritation.

CNS Crises

Occur in children and young adults. There is sudden occlusion of cerebral vessels. Hemiparesis, aphasia, seizures, sensory deficits, and altered sensorium occur single or together. Intracerebral or subarachnoid haemorrhage may result from hypoxic necrosis of vessels. Cerebral angiography demonstrates stenosis and thrombotic involvement of medium and large vessels (in larger vessels the involvement initially is of vasa vasorum).

Pulmonary Crises

Characterised by fever, tachypnoea, chest pain, increased leucocytosis, and pulmonary infiltrates, pulmonary crises are the single most common expressions of sickle cell anaemia requiring hospitalisation. These crises may occur alone or with pulmonary infections.

2. Haematologic Crises

Haematologic crises, characterised by sudden exaggeration of

anaemia, are unrelated to vaso-occlusive crises. If unrecognised, the haemoglobin fall may be so acute as to cause heart failure and death within hours.

Aplastic Crises

Temporary arrest of erythropoiesis usually is associated with or follows a febrile illness. In the early phase of a crisis, peripheral reticulocytes and bone marrow normoblasts disappear or are greatly reduced. The process is self-limited and erythropoiesis usually starts within 5 to 10 days with appearance of reticulocytes and normoblasts in the peripheral blood.

Splenic Sequestration Crises

Characterised by sudden trapping of blood in the spleen. It occurs almost exclusively in infants and young children whose spleens are usually enlarged. The already enlarged spleen rapidly increases in size at the expense of blood volume. Hypovolemic shock and death may occur within hours.

Haemolytic Crises (Hyperhaemolytic Crises)

There is sudden acceleration of the haemolytic process. They have been described in association with G6PD deficiency and with hereditary spherocytosis. These crises also occur following challenge by oxidant drugs and infections.

Megaloblastic Crises

These crises result from the sudden arrest of erythropoiesis by folate depletion. Chronic erythroid hyperplasia imposes a drain on folate reserves. Megaloblastic crises are likely to occur when food consumption is interrupted by illness or alcoholism or when folate requirement is further augmented by rapid growth or pregnancy.

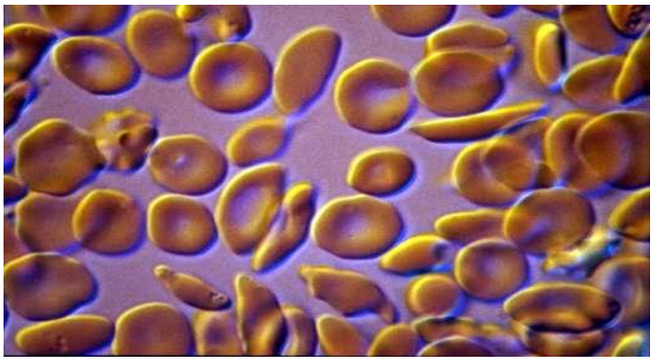
3. Infectious Crises

Infection is the major presenting manifestation of sickle cell anaemia in early childhood. During the first 5 years of life, *S. pneumoniae* is the major offending organism and the blood and spinal fluid (meningitis) are major sites of infection. Incidence of *H. influenzae* infection is also higher in these children. After 5 years of age, gram negative bacteria replace *S. pneumoniae* as the major offenders. Osteomyelitis especially due to *Salmonella* is common in these patients. The pathophysiologic basis for increased susceptibility to aggressive infection is due in large part of the loss of spleen function.

In addition there are a number of other signs and symptoms

- Dorsal kyphosis, lumbar lordosis
- Hypogonadism in males
- Conjunctival icterus and pallor
- Tender hepatomegaly (tender-microinfarctions)
- Cholelithiasis
- Autosplenectomy
- Cardiomegaly
- Pulmonary fibrosis ⟶ pulmonary hypertension ⟶ right ventricular hypertrophy ⟶ right ventricular failure
- Pleuritic pain
- Brain: headache, hemiplegia
- Chronic renal failure, fixed low specific gravity urine
- Renal medullary infarction, papillary necrosis and haematuria
- Eye: infarction of peripheral retina
- In elderly patients - Periosteal thickening
  - Osteosclerosis of long bones
  - Aseptic femoral head necrosis
- Increased susceptibility to *Salmonella* osteomyelitis
- Sterility in females

Blood Picture



Sickle cell anemia, peripheral smear

Anaemia

- Moderate to marked normochromic (MCV and MCH are normal) anaemia
  - It occurs because of reduced RBC life span to about 8 days and in part due to ineffective erythropoiesis
  - Haemolytic and aplastic crises further reduce haemoglobin.
  - Irreversibly sickled cells (RBCs) have a life of 2 days
  - Osmotic fragility is decreased
- ESR is decreased, sickling prevents rouleaux formation
- There is moderate to marked anisopoikilocytosis
- Serum and red cell folate values are decreased
- There is evidence of intravascular haemolysis
- Sickle and solubility tests are positive
- There is irregular distribution of HbF (acid elution test)
- Haemoglobin electrophoresis shows increased HbS

Prognosis

Serious in childhood only.

Treatment

Prophylactic - avoid precipitating factors.
Folic acid - 5 mg daily
Good general nutrition and hygiene
Crises - rest, rehydrate, antibiotics if infection occurs, bicarbonate if patient becomes acidotic. Transfusion in severe anaemia.
Extra care during pregnancy and anaesthesia.

Combination of HbS with other haemoglobinopathies

- **Sickle Cell β Thalassaemia**
- **Sickle Cell HbC Disease**
- **Sickle Cell HbD Disease**

INTERPRETATION

CANCER MARKERS (TUMOR MARKERS)

Features of Tumor Markers

Should be identified by biochemical, immunological or molecular biological methods.

Measured easily, reliably and cost effectively using an assay with high analytical sensitivity and specificity.

Quantitative level of tumor marker reflects tumor burden with diagnostic sensitivity (few False Negatives) and specificity (few False Positives).

Test result influence patient care and outcome.

Clinical Applications of Tumor Markers

Screening

Some tumor markers, such as AFP in serum and occult blood in feces, have been utilized in mass screening programs of asymptomatic individuals, with limited success, in high risk sectors of population. However it is yet to be emphasized that no biochemical tumor marker is yet specific and sensitive enough to be used as a definitive screening test for cancer.

Staging and Grading

The degree of elevation in the concentration of several tumor markers can help to stage tumors. In general, the mean circulating levels of these tumor markers increase with the stage of the cancer. In contrast, placental alkaline phosphatase is a tumor marker related to the grade of cancer, and serum levels of this analyte are higher in grade 1 and 2 tumors than in grade 3 ovarian carcinomas.

Monitoring treatment

One of the most important applications of tumor markers lies in supervising the course of the disease, especially during treatment. Most other clinical procedures lack the sensitivity and convenience for such frequent examinations. The levels of the tumor marker will inform whether the patient is experiencing remission or relapse and will also determine the effectiveness of the treatment.

During the course of chemotherapy, the level of the tumor marker may indicate when there is a need for a redesign of medication, because many a times tumor cells develop drug resistance

Tumor marker profiles usually reflect one of the following classical patterns:

- A rapid decline in the tumor marker level to normal concentration following surgery or other forms of first-line therapy suggests that treatment has been successful.
- The lack of a decline to basal levels following first-line therapy may indicate that treatment has only been partially successful.
- Continued low levels of the tumor marker indicate that remission has been maintained.
- A subsequent rise in the concentration of the tumor marker (from the basal level) suggests a recurrence of the disease. Tumor markers can warn of renewed tumor growth 3-12 months before other methods provide confirmation.
- Decline of the marker levels after an increase has been associated with a recurrence, is suggestive of the responsiveness of a tumor to treatment.
- If tumor marker concentration remains elevated after treatment, the tumor may be resistant to the therapeutic method employed and the prognosis of the patient is poor.

Detection of Recurrence

Monitoring tumor marker for the detection of recurrence following surgical removal of the tumor is an important clinical application. It is desirable to monitor the patient using highly sensitive onco immunoassay tests in order to detect recurrence as early as possible.

While monitoring for recurrence, the slope (the rate of increase of tumor marker concentrations with time) of tumor marker is important. The slope is a major factor guiding therapeutic strategies.

Prognosis

In patients with cancer, tumor markers help in assessing the tumor aggressiveness, which in turn determines how a patient should be treated. Because serum concentration of tumor marker increases with tumor progression and usually reaches the highest levels when tumor becomes metastasized, the serum level of tumor markers at diagnosis are likely to reflect the aggressiveness of the tumor and help predict the outcome for the patient. A low serum level indicates that the tumor is at an early stage or still organ confined.

Diagnosis

Diagnosis is a procedure that determines definitively whether a person has cancer. The frequency of raised levels of an isolated tumor marker in non malignant diseases and the overlap between normal concentrations and the concentrations of tumor markers in patients with proven cancer discourages their isolated usage for diagnosis.

The use of multiple markers simultaneously to observe specific patterns of tumor marker is widely accepted as a reliable tool for diagnosis

Differential diagnosis and classification

Immunoassays for some cancer markers used in clinics to distinguish between clinical conditions with similar symptoms, where one or both could be cancerous. For example measurement of Neuron Specific Enolase (NSE) allows differentiation between neuroblastoma and Wilm's tumor when a child presents with palpable abdominal mass.

Classification of Tumor Markers

Nature	Example
Oncofetal & Oncoplacental antigens	CEA, AFP, hCG
Carbohydrate molecules with epitopes recognizable by monoclonal antibodies	CA 125, CA 19.9 ,CA 15.3, CA 242
Differentiation & proliferation antigens	NSE, PSA, β_2 microglobulin
Ectopically produced hormones	ACTH, calcitonin
Ectopically produced proteins	Bence Jones proteins

Diagnostically Important Tumor Markers

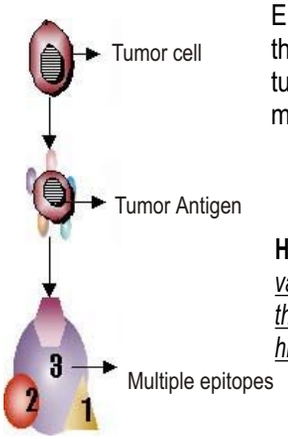
Tumor Marker	Condition
PSA	Prostate cancer
CEA	Colorectal cancer, Breast cancer
AFP	Testicular cancer, Liver cell cancer
hCG	Germ cell tumors,Trophoblast cancer
CA 125	Ovarian cancer
CA 15-3	Breast cancer
CA 19-9	Pancreatic cancer, Biliary tract cancer

Factors Affecting Tumor Marker Diagnosis

Specificity: Most markers are not specific for a tumor.

Single Tumor (Breast Cancer)	Multiple Markers (CA 15-3, CEA)
Single Marker (CA 125)	Multiple Tumors (Ovarian, Lung, Uterine cancer)

Multiple Epitopes:



Epitopes are antibody binding sites on the antigen. Tumor cells have many tumor antigens. Each antigen has multiple epitopes.

Hook Effect: By definition, "*a falsely low value produced by the immunoassay when the actual concentration of the sample is highly elevated is termed as HOOK EFFECT*"

Half Life of Tumor Marker: It refers to the time for the serum concentration of the tumor marker to drop to half its original concentration.

Sensitivity: Many immunoassay techniques suffer from poor sensitivity. Sensitivity of an immunoassay is very important in case of tumor recurrence after surgery, where the levels of the tumor marker should be very low. Increase in values after surgery indicates tumor recurrence. Also detection of very low values may have a prognostic effect.

To be continued……

BOUQUET

In Lighter Vein

- "Doctor, are you sure I'm suffering from pneumonia? I've heard once about a doctor treating someone with pneumonia and finally he died of typhus."
  "Don't worry, it won't happen to me. If I treat someone with pneumonia he will die of pneumonia."

- Outside a muffler shop: "No appointment necessary, we hear you coming."
- Outside a hotel:"Help! We need inn-experienced people."
- On a desk in a reception room: "We shoot every 3rd salesman, and the 2nd one just left."
- In a veterinarians waiting room: "Be back in 5 minutes, Sit ! Stay!"
- At the electric company: "We would be de-lighted if you send in your bill. However, if you don't you will be."
- On the door of a computer store:"Out for a quick byte."
- In a restaurant window: "Don't stand there and be hungry, come on in and get fed up."
- Inside a bowling alley: "Please be quiet, we need to hear a pindrop."
- In the front yard of a funeral home: "Drive carefully, we'll wait."
- In a counsellor' s office: "Growing old is mandatory, growing wise is optional."
- Seen on a bulletin board:"Success is relative, more success, more the relatives."

Wisdom Whispers

- Be true to your work, your word and your friend.
- We do not remember days, we remember moments.
- I have no yesterdays, time took them away. Tomorrow may not be, but I have today.
- Determine to work. Work to stand. Stand to fight. Fight to win.
- You can save time but you can't bank it.
- Time cannot be expanded, accumulated, mortgaged, hastened, or retarded.
- Time is really the only capital that any human being has, and the only thing he can't afford to lose.
- Do not worry about the future. Plan for it.

Brain Teasers

1. Pseudomyxoma peritonei is usually seen with
   A. Phaeochromocytoma B. Mucus secreting ovarian neoplasm
   C. Hypernephroma D. Retroperitoneal fibroma
2. Seminoma, Melanoma, Medullary carcinoma breast and Hodgkin's disease can show infiltration by which of the following cells?
   A. Basophils B. Eosinophils C. Neutrophils D. Lymphocytes
3. Microscopically, normal cells or tissues present in abnormal locations are referred to as:
   A. Choristoma B. Hamartoma C. Chordoma D. Chlamydoma
4. Cystosarcoma phylloides of breast is a type of
   A. Sarcoma B. Fibro-adenoma C. Carcinoma D.Hamartoma

ANSWERS : 1. B, 2.D, 3. A, 4. B

TROUBLE SHOOTING

FUO/PUO (FEVER/PYREXIA OF UNKNOWN ORIGIN)

Fever of unknown origin (FUO) in adults is defined as a temperature higher than 38.3°C (100.9°F) that lasts for more than three weeks with no obvious source despite appropriate investigation. The four categories of potential etiology of FUO are classic, nosocomial, immune deficient, and human immunodeficiency virus related. The four subgroups of the differential diagnosis of FUO are infections, malignancies, autoimmune conditions, and miscellaneous. A thorough history, physical examination, and standard laboratory testing remain the basis of the initial evaluation of the patient with FUO. Newer diagnostic modalities, including updated serology, viral cultures, computed tomography, and magnetic resonance imaging, have important roles in the assessment of these patients.

Classification of Fever of Unknown Origin (FUO)

Category of FUO	*Definition*	*Common etiologies*
Classic	Temperature >38.3°C (100.9°F) Duration of >3 weeks Evaluation of at least 3 outpatient visits or 3 days in hospital	Infection, malignancy, collagen vascular disease
Nosocomial	Temperature >38.3°C Patient hospitalized ≥ 24 hours but no fever or incubating on admission	*Clostridium difficile* enterocolitis, Drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis
Immune deficient (Neutropenic)	Temperature >38.3°C Neutrophil count ≤ 500 mm^3 Evaluation of at least 3 days	Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus
HIV-associated	Temperature >38.3°C Duration of > 4 weeks for Outpatients, > 3 days for inpatients HIV infection confirmed	Cytomegalovirus, *Mycobacterium avium intracellular* complex, *Pneumocystis carinii* pneumonia, Drug-induced, Kaposi's sarcoma, lymphoma

Common Aetiologies of FUO

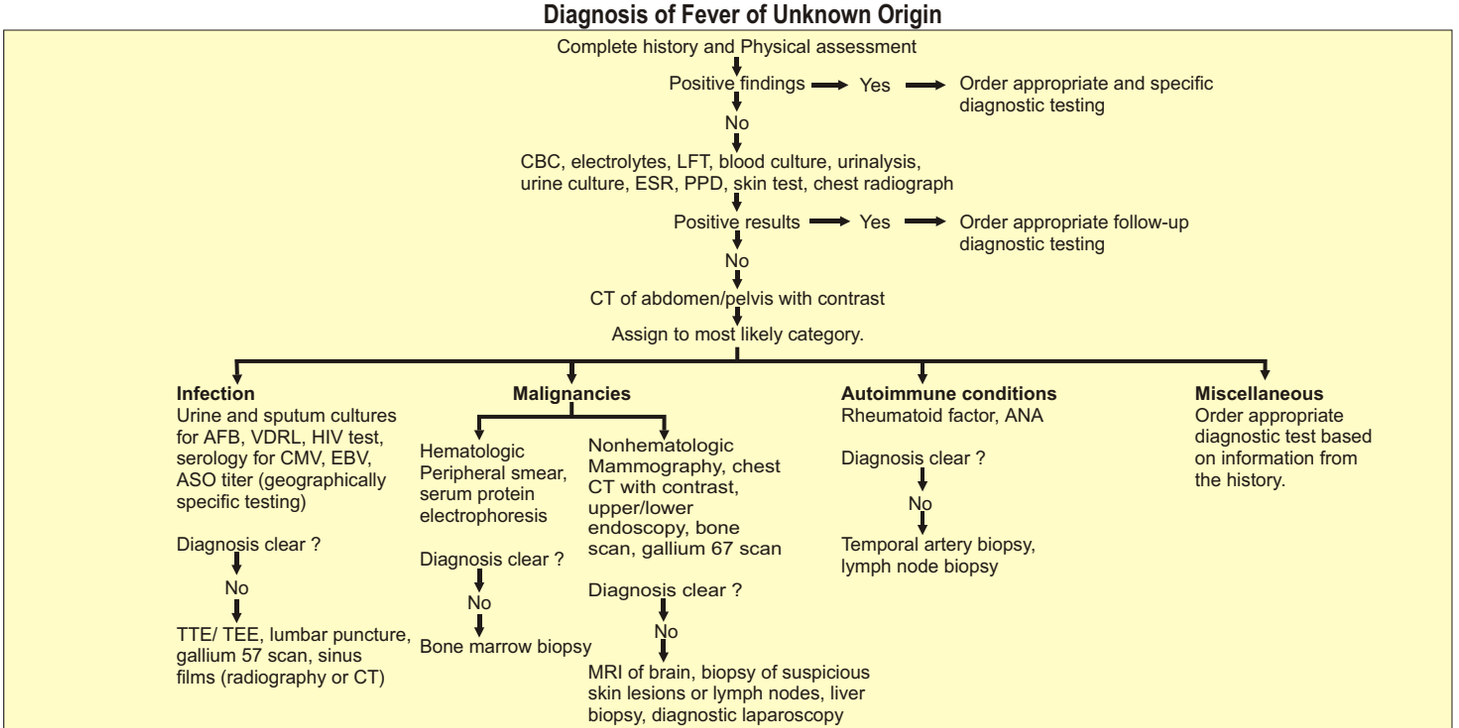
Infections: Tuberculosis(especially extrapulmonary) , abdominal abscesses, pelvic abscesses, dental abscesses, endocarditis, osteomyelitis, sinusitis, cytomegalovirus, Epstein-Barr virus, HIV, Lyme disease, prostatitis, sinusitis, malignancies, chronic leukemia, metastatic cancers, renal cell carcinoma, colon carcinoma, hepatoma, myelodysplastic syndromes, pancreatic carcinoma, sarcomas

Autoimmune conditions: Adult Still's disease, polymyalgia rheumatica, temporal arteritis, rheumatoid arthritis, rheumatoid fever, inflammatory bowel disease, Reiter's syndrome, systemic lupus erythematosus, vasculitides

Miscellaneous: Drug-induced fever, complications from cirrhosis, factitious fever, hepatitis(alcoholic, granulomatous or lupoid), Deep venous thrombosis, sarcodoisis

Agents commonly associated with drug-induced fever - Allopurinol, Captopril, Clofibrate, Erythromycin, Heparin, Hydralazine, Hydrochlorothiazide, Isoniazid, Meperidine, Nifedipine, Nitrofuranatoin, Pencillin, Phenytoin, Procainamide, Quinidine

Diagnosis of Fever of Unknown Origin



Algorithm for the diagnosis of fever of unknown origin
(CBC=complete blood count; LFT= liver function test; ESR= erythrocyte sedimentation rate; PPD= purified protein derivative; CT= computed tomography; AFB= acid-fast bacilli; HIV= human immunodeficiency virus; CMV= cytomegalovirus; EBV= Epstein-Barr virus; ASO= antistreptolysin antibodies; ANA=anti nuclear antibody; TTE= transthoracic echocardiography; TEE= transesophageal echocardiography; MRI= magnetic resonance imaging)

For appropriate diagnosis, the level or generation of tests that may suffice may vary with individual cases. For instance, in an attempt to diagnose tuberculosis, sometimes ppd with X-ray may be sufficient, while in other cases you may need PCR-NAT technologies. Likewise for diagnosing SLE, in a few cases anti- deoxy ribonuclear protein antibodies may be enough while in other cases complete ANA profile may be essential.

TULIP NEWS

TULIP GROUP ON A PRODUCT LAUNCHING SPREE

In the last issue, we had discussed the launch of the two novel HCV products ***FLAVICHECK HCV-WB*** & ***QUALISA HCV.***

Following the successful launch of these products, TULIP GROUP introduced two more indigenous products into the market,

QUALISA HIV1/2 & QUALISA HBsAg

Both are ELISA tests for the detection of the Two Critical Diseases - The HIV (Human Immunodeficiency Virus) and HBV (Hepatitis B virus).

QUALISA HIV1/2, coated with synthetic peptides having highly immunodominant epitopes can detect both HIV1 and HIV2.

QUALISA HBsAg, with monoclonal antibody directed against the 'a' epitope of Hepatitis B virus not only detects all the subtypes of HBsAg but also all sizes of HBsAg (viz, LHBsAg, MHBsAg & SHBsAg) and all the genotypes of HBsAg with 100% Sensitivity & Specificity and with a detection limit as low as 0.025 ng/ml of HBsAg.

Symbiosis/ fusion of Quality & ELISA has delivered a world-class range of ***QUALISA*** products.

QUALISA - UNMATCHED BENEFITS !

Qualpro, a Tulip Group company, has developed ***QUALISA***, a range of Microwell Enzyme Immunoassays (ELISA) with unique **DHS^3** Technology for the detection of **HIV, HBsAg and HCV.**

QUALISA range of products are world class products evaluated by NIB (National Institute of Biologicals) and approved by DCGI (Drug Controller General of India). In an inhouse evaluation the ***QUALISA*** range of products has been found to be way ahead in Sensitivity and Specificity in comparison to the other ELISAs available in the market.

Moreover, for the first time in India, the shelf life is so extended that there is no reagent wastage possible even in the 480T pack. This is possible by uniquely packaging it in (3x8) wells format for all pack sizes. This ensures the shelf life to be almost 1 year instead of just 60 days as in other assays.

Time and again Tulip Group has set trends in the diagnostic field by placing innovative products with proven technology in the market after extensive R&D.

QUALISA marks the beginning of world-class ELISAs to detect and diagnose the most dreaded diseases.

STAND OUT IN A CROWD .... WITH Qualisa

Printed and published by D.G. Tripathi, Edited by Dr. R.J. Sood M.D. (path.) for and on behalf of Tulip Diagnostics Private Ltd, Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh Alto Santacruz, Bambolim Complex Post Office, Goa - 403202, INDIA. Fax: (0832) 2458544, E-mail: tulip@sancharnet.in. Website: www.tulipgroup.com