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The Crux

BIMONTHLY FORUM FOR THE LABORATARIANS

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Editorial

Gone are the days when syphilis was treated with an injection of milk to create hyperpyrexia and thereby affecting the death of the *Treponemes*. Gone are the days also of heating the serum for conducting the VDRL test, now single step Immunochromatographic techniques are available that are most accurate and obviate the need to conduct time-consuming and cumbersome tests of the yesteryears. Diagnostic technology has advanced by leaps and bounds. The DISEASE DIAGNOSIS section of this episode talks in depth about the clinico-diagnostic aspects of a stigma ridden STI known as SYPHILIS. A much more dreaded disease (HIV/AIDS) has attracted all the lime-light and taken the R&D inputs away, however, we at TULIP have forgotten neither and created very specific and sensitive diagnostic platforms for both the STIs.

While the Laboratarians talk about specific tumor markers there is a non-specific tumor marker that can be tested for with a stool sample of a patient suspected of having colorectal neoplasm. FOBT report on a stool sample can be given while the patient waits in the Lab. The first investigation while looking for a colorectal malignancy should always be FOBT. Although non-confirmatory for colorectal neoplasms, it is quite a useful screening tool and on finding a positive test result further investigations can then be planned. INTERPRETATION segment in this issue thoroughly interprets FOBT. The indications, utility, interpretative precautions, investigation schedule and well almost everything about this tumor marker have been discussed. Other investigative methods of conducting biopsy oriented endoscopy or colonoscopy or conducting a CEA estimation should always follow an FOBT.

With increasing usage of anti-coagulants, the importance of properly estimating Prothrombin time/ index or better still International Normalized Ratio (INR) has now been recognized. There are a few variables that can significantly alter the test results and influence the result and hence the treatment wrongly. If INR falls outside the therapeutic range, the treatment being pursued is effectively useless or fatal. TROUBLE SHOOTING portion of this years' last communication delves in depth about INR and related practical problems, which you can trouble shoot yourself.

As always, BOUQUET is presented to you this time too.

Tulip Group

DISEASE DIAGNOSIS

SYPHILIS

Historical

First recognized in 16th century, syphilis (also known as *lues*) currently adds 12 million new cases every year, while about 50 million cases need treatment. Over various periods, therapeutic measures have included causing hyperpyrexia, using bismuth or arsenic. Since the advent of antibiotics, the treatment has become simpler and less dangerous.

Causative organism

Syphilis is caused by *Treponema pallidum*, a spirochete that is a thin spiral or coil shaped bacterium that gains access via breaks in the mucous membranes or the skin. 90% of the cases are STIs. Other means of transfusion include transplacental spread, via kissing, via transfusion of infected blood, and direct inoculation such as by a needlestick. As all donated blood samples are usually refrigerated and the treponemes cannot survive for more than 3 days in such a stored blood, therefore, infection through blood transfusion is usually rare.

Etiology of various treponemal infections

	Syphilis	Bejel - endemic syphilis	Yaws	Pinta
Causative organism	*T. pallidum* subsp. pallidum	*T. pallidum* subsp. endimicium	*T. pallidum* subsp. pertenue	*T. carateum*
Geographic Distribution	Worldwide	Mid. East, Africa	Africa Pacific	Central and South America
Preferred climate	All	Subtropical	Tropical	Warm
Typical age of infection in yrs	15-40	1-10	1-15	10-30
Main mode of transmission	Sexual, Congenital	Skin Contact	Skin Contact	Skin Contact
Late complications				
- skin / mucosa	+	+	+	+
- bone / cartilage	+	+	+	-
- CNS	+	-	-	-
- heart / circulation	+	-	-	-

Clinical Manifestations

Primary syphilis: The entry stage into the body. Incubation period may range from 10-90 days. The first lesion is a chancre (a 10-15 mm blister-like sore that usually develops on the genitals but can also develop in the mouth or on the breasts). Rectal chancres may develop in the homosexuals. Externally invisible, vaginal/cervical chancres may sometimes be overlooked. These lesions are painless and disappear within 3-6 weeks even without treatment. The differential diagnosis at this stage can be lymphogranuloma venereum, herpes simplex virus, or a skin neoplasm. About 70% of cases develop lymphadenopathy in the draining lymph nodes (of the chancre site). Usually painless, the nodes can be firm or rubbery in consistency.

Secondary syphilis: Untreated, the stage between 6 weeks to 6 months is a systemic infection and is termed as secondary syphilis. Chancres may still be present. Cutaneous eruptions/rashes and ulcers in the mucous membranes mark it. These rashes are typically copper colored, do not have pain or itching and occur on the palms of hands and soles of the feet. The differential diagnosis here can be drug reactions, rubella, dermatophytosis, mononucleosis, and pityriasis rosea. Skin eruption may take a few weeks to a year to resolve. The patient may develop condylomata lata, which are wet weeping pinkish or gray areas of flattened skin in the moist zones of the body. The skin rashes, oral and genital ulcers and condylomata lata are all highly infectious.

Approximately half the patients with secondary syphilis develop lymphadenopathy in the axillary, inguinal and neck nodes; about 10% of the cases develop inflammations of the eyes, kidney, liver, spleen, bones, joints or the meninges. Patients may also have flu-like general illness with a low-grade fever, chills, loss of appetite, headaches, running nose, sore throat, and aching joints.

Latent syphilis: Though symptom free, the patient can infect others in this phase. Pregnant women can transmit the disease to their unborn children. During early latency, patients are at risk of spontaneous relapses marked by recurrence of the ulcers and skin rashes of secondary syphilis. In late latency, these reactions are less likely. Late latency may either resolve spontaneously or continue for the rest of the patient's life.

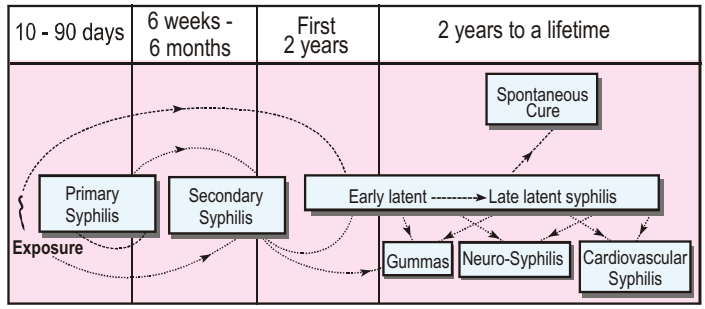
Tertiary syphilis: This is the third stage of untreated syphilis and occurs in about 35-40% of cases. In this stage, patients cannot transmit the disease to others. Symptoms of this stage are thought to be on account of a delayed hypersensitivity reaction to the spirochetes. Some cases develop Benign Late Syphilis that appears 3-10 years after disease acquisition. It is characterized by development of gummas. Gummas are rubbery tumor-like growths that are most likely to involve the skin or long bones but may also develop in the eyes, throat, mucous membranes, liver, or gastric lining. Benign late syphilis is usually rapid in onset and responds well to antibiotic therapy.

Cardiovascular syphilis: 10-15% cases of tertiary syphilis progress to cardiovascular syphilis stage. It occurs along with neurosyphilis usually 10-25 years after infection acquisition. It causes inflammation of the arteries leading from the heart and causes heart attacks, scarring of the aortic valves, congestive heart failure, or the formation of an aortic aneurysm.

Neurosyphilis: About 8% of cases of untreated syphilis will have CNS involvement and exhibit physical as well as psychiatric symptoms. It appears 5-35 years after acquisition of infection. It has 4 subcategories :-

1) Asymptomatic - No symptoms referable to CNS seen. Only CSF may show some abnormality.
2) Meningovascular - There is involvement of brain vessels or meningitis. The patient experiences headaches, irritability, and visual problems. If the spinal cord is involved, the patient may experience weakness of the upper extremities.
3) Tabes dorsalis - This refers to a progressive degeneration of the spinal cord and nerve roots. Patients lose the sense of perception of their body position and orientation in space (proprioception), resulting in difficulties in walking and loss of muscle reflexes. They may also have shooting pains in the legs and periodic episodes of pain in the abdomen, throat, bladder, or rectum. Tabes dorsalis is also referred to as locomotor ataxia.
4) General paresis -This refers to the effects of neurosyphilis on the cortex of the brain. Slowly but progressively the patient looses memory, cannot concentrate and looses interest in self-care. Personality changes include irresponsible behavior, depression, delusions of grandeur, or complete psychosis. General paralysis is sometimes called as dementia paralytica, and is seen in patients over 40 years of age.

Course of untreated syphilis



CLINICAL MANIFESTATIONS IN SPECIAL POPULATIONS

Congenital syphilis

Infants born to untreated primary or secondary syphilitic mothers will have congenital syphilis, while, this infection rate drops to about 40% in births given by early latent stage syphilitic mothers and reduces further to 6-14 % for offspring born to late latent syphilitic mothers. The prognosis for early congenital syphilis is poor: about 54% of fetuses die in-utero or soon after birth. Those who survive may look normal at birth but would show signs of infection between three and eight weeks later.

Diagnostic classification of congenital syphilis

Laboratory criteria for diagnosis

Demonstration of *Treponema pallidium* by darkfield microscopy, fluorescent antibody,or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material.

Case classification

Probable : A condition affecting an infant whose mother had untreated or inadequately treated* syphilis at delivery, regardless of signs in the infant, or an infant or child who had a reactive treponemal test for syphilis and any one of the following:

- Any evidence of congenital syphilis on physical examination
- Any evidence of congenital syphilis on radiographs of long bones
- A reactive CSF VDRL Test
- An elevated CSF cell count or protein (without other cause)
- A reactive fluorescent treponemal antibody absorbed 19S class-IgM antibody test or IgM enzyme-linked immunosorbent assay

Confirmed : A case that is laboratory confirmed

Also includes mother with serologic evidence of relapse or reinfection after treatment or with a documented history of treatment of insufficient serologic follow-up after appropriate treatment.

Infants with early congenital syphilis have systemic symptoms resembling those of adults with secondary syphilis. About 40-60% of the infants will have CNS involvement. The disease may present in these infants as jaundice, splenomegaly, hepatomegaly, anemia, skin rashes, codylomata lata, pneumonitis, snuffles (persistent runny nose, and lymphadenopathy).

Late congenital syphilis

Children who develop syphilis symptoms after 2 years of age are said to have late congenital syphilis. The typical symptoms include facial deformities (saddle nose), Hutchinson's teeth (abnormal upper incisors), saber shins, dislocated joints, deafness, mental retardation, paralysis, and seizure disorders. *All pregnant women must be checked for syphilis at the first ANC visit and later in the third trimester and at delivery (if the lady belongs to a high risk community).* Sero-titers may increase slightly when serofast women who were previously adequately treated for syphilis become pregnant, however, the increase is less than four-fold.

HIV patients

Being an STI, syphilis is closely related with HIV. Syphilis sometimes mimics symptoms of AIDS. Conversely, AIDS appears to increase the severity of syphilis in patients suffering from both the diseases. AIDS also hastens the appearance of neurosyphilis. False negative treponemal and nontreponemal tests for syphilis are known to occur in HIV patients. A conclusive evidence can be clinched from a biopsy of the lesion and spirochetes can be searched for.

Ocular syphilis

Syphilis is the commonest bacterial intraocular infection in HIV-infected patients. Vision loss in these patients can occur because of uveitis or optic nerve disease, which may manifest itself as papillitis, perineuritis or retrobulbar optic neuropathy, although uveitis is the commonest complication.

IMMUNOLOGY OF SYPHILIS INFECTION

Immune response to first infection

Four days after getting infected IgM antibodies are synthesized in the host. At 10-21 days post-infection these antibodies reach titers that are detectable using IgM antibody based assays. IgG antibodies are detectable a few days later. In secondary syphilis, although the body is protected against reinfection during this stage, it is unable to eliminate the causative organisms. The manifestations of the secondary stage, such as recurrent skin eruptions lasting from weeks to months, seem to be related to the development of systemic immunity. If the host has immunological control over the *T. pallidum* infection to the point where no further clinically apparent eruptions occur, the period of late latency is said to be present. During this phase a delayed type of hypersensitivity reaction against the causative organism is detectable. This reaction together with the humoral response, is considered to be crucial for the suppression of infection. After another latency period, which may last more than 20 years, clinical manifestations of tertiary syphilis may occur. The immunological mechanisms leading to this are unknown.

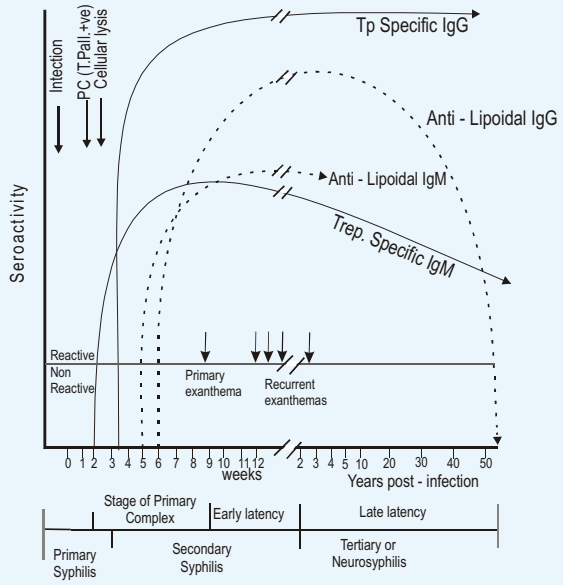
Immune response after specific therapy

Curative therapy of the infection results in disappearance of *T. pallidum* specific IgM antibodies from the patient's serum usually within 3-12 months. The reduction of IgG antibodies depends on the time interval between infection and first antibiotic treatment. If started soon enough, the treatment can make all serologic tests for syphilis turn negative. If not, IgG against syphilis may persist for life.

Immune response after the second or multiple reinfections

Second or multiple contacts with the antigens boost production of pre-formed IgG antibodies. Immediately after infection these antibodies show a steep rise in titer. They also suppress the synthesis of IgM antibodies. These antibodies are either not detectable in serum of patients, or only after a time delay of 2-4 weeks.

Sero-response during various stages of syphilis infection



DIAGNOSIS

Patient history, signs and symptoms

The incubation period, early signs and symptoms of syphilis are all variable and are usually unnoticed. Definite diagnosis, however, depends upon the results of laboratory tests.

Direct visualization of the spirochetes

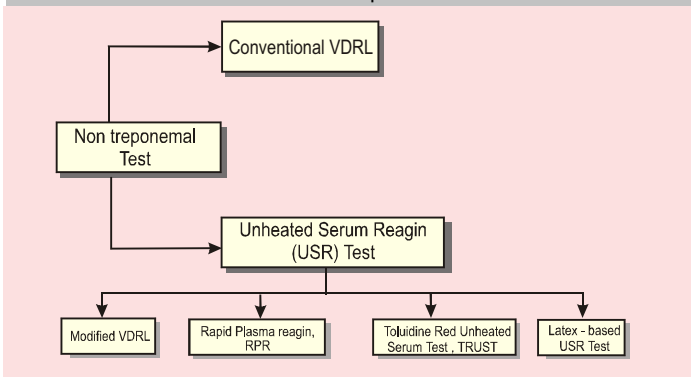
This requires dark-field or electron microscopy. Culture of bacteria has been done in rabbits but the process is not practical, being time consuming and expensive. Bacteria can be demonstrated in a specimen obtained from a typical lesion (can be seen even in the absence of positive serologic tests). Dark field microscopy reveals corkscrew-like organisms moving with a spiraling motion. Oral and anal lesions cannot be used as they harbor similar appearing commensals.

Serologic Tests

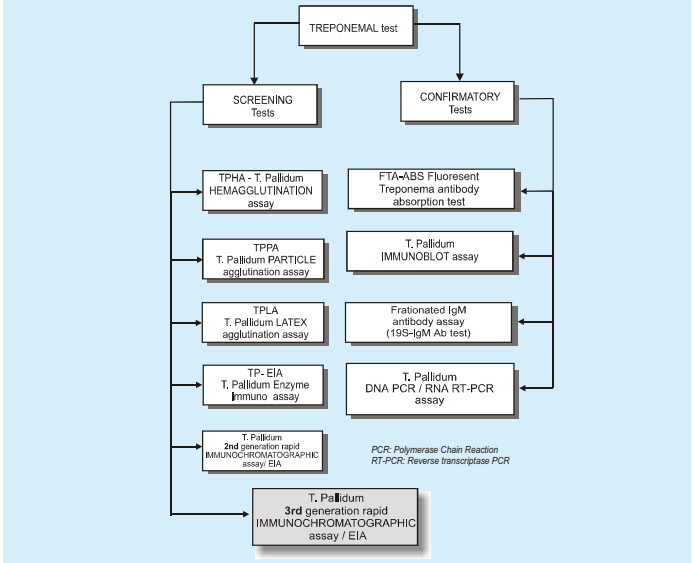
These can be classified into Non-Treponemal and Treponemal tests. They, however, cannot distinguish between the different treponematoses. In practice, serological tests for syphilis are used for:

- Screening asymptomatic individuals with no history suggestive of syphilis, such as pregnant women.
- Screening genitourinary medicine clinic attenders at recent risk of acquiring a sexually transmitted infection.
- Screening blood and organ/tissue donors.
- Detecting or excluding current or past syphilis in patients with HIV infection.
- Testing patients whose history or clinical signs are consistent with syphilis, as in cases of genital ulceration or chronic neurological illness.
- Confirmatory testing of specimens reactive in screening tests for syphilis.
- Assessment of the stage of infection and monitoring the therapeutic response.

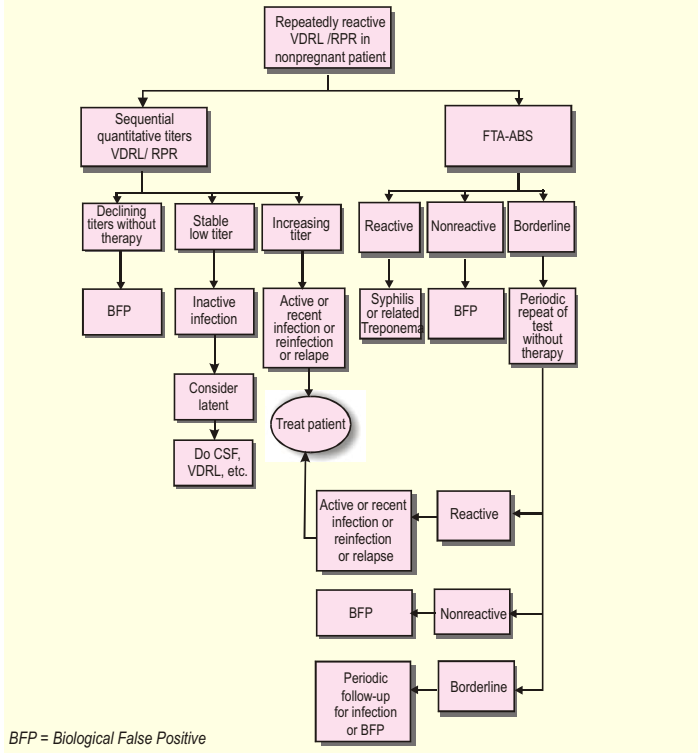
Format for Non-Treponemal Tests



Format for Treponemal Tests



Flow chart for positive serologic test for syphilis



BFP = Biological False Positive

The third generation Rapid Immunochromatographic assay has maximum sensitivity at all stages of syphilis, it is important that tests should detect both IgG and IgM antibodies. The difficulties faced in the second-generation tests on account of prozoning phenomenon necessitating dilution of sample have been obviated in the third generation tests.

Causes of False Positive Serologic Tests For Syphilis

Non-Treponemal Tests

A) Acute Condition (< 6 months): Pneumonia (Viral, Pneumoccal, Mycoplasmal), Hepatitis, Tuberculosis, Mononucleosis, Chancroid, Chickenpox, HIV infection, Measles, Malaria, Immunizations, Pregnancy, Laboratory error.

B) Chronic condition (> 6 months): Hepatic disease, Malignancy, Intravenous drug use, Aging, Connective tissue disorders, Multiple blood transfusions.

Treponemal Tests

A) Acute condition (< 6 months): Mononucleosis, Lyme disease, Leprosy, and Malaria.

B) Chronic condition (> 6 months): Systemic Lupus Erythematosus

SYPHILIS DIAGNOSIS IN DIFFERENT PATIENT GROUPS

Cases	Initially use	If positive, use
Pre-natal/ Ante-natal	Treponemal test	Non-treponemal test for titer
Blood transfusion	Non-treponemal test	Treponemal test to rule out BFP
Random screening	Treponemal test	
Treatment monitoring	Non-treponemal test for titer	
Organ transplantation	Treponemal test	Non-treponemal test for titer
Patients attending VD clinics	Treponemal test	Non-treponemal test for titer
Psychiatric patients (neurosyphilis)	Treponemal test	Non-treponemal test for titer
HIV patients	Treponemal test	Non-treponemal test for titer

TROUBLE SHOOTING

PROTHROMBIN TIME / INR

Oral anticoagulants are used for:

1. Prevention of primary and secondary venous thromboembolism
2. Prevention of systemic arterial embolism in patients with mechanical prosthetic valves or with atrial fibrillation.
3. Prevention of acute myocardial infarction in patients with peripheral arterial disease.
4. Prevention of stroke and recurrent infarction.

Warfarin sodium (a vitamin K antagonist) is the most commonly used oral anticoagulant in use today. Prothrombin time test is used to detect coagulation disorders related to the extrinsic pathway namely II, V, VII, X and fibrinogen and for monitoring oral anticoagulant therapy. Rate of depression of the individual clotting factors is determined by their biological half-life. Factor VII falls most rapidly followed by factors IX, X, and II. As the active clotting factor levels begin to fall, the PT results start to prolong. Factor V and Fibrinogen are not affected by anticoagulants. On the other hand upon withdrawal of the oral anticoagulant therapy these factors return to normal levels in the reverse order and so do the PT results.

Since the individual thromboplastin reagent preparations differ significantly in their sensitivities to the deficiencies of the vitamin K dependent coagulation factors, the use of 'seconds' or PTR (ratio) or PTI (index) as a reporting format has led to confusion among clinicians. In order to correctly dose deserving patients with oral anticoagulants so as to achieve the dual goal of adequate anti-coagulation and reduce the risk of bleeding simultaneously, the WHO introduced a method for monitoring patients stabilized on oral anticoagulant therapy using International Normalized Ratio (INR). The INR normalizes the PT ratio to an International Reference Preparation (IRP) of thromboplastin. This has ensured that a uniform intensity of oral anticoagulant therapy is used world wide.

Factors Influencing Anticoagulant Effects of Warfarin

GUT	PLASMA
Anticoagulated Effect Potentiated • Low vitamin K intake • Reduced vitamin K absorption in fat malabsorption *Anticoagulant Effect Counteracted* • Increased vitamin K intake • Reduced absorption of warfarin by cholestyramine	*Anticoagulated Effect Unchanged* • Displacement of warfarin from albumin binding does not influence anticoagulant effect of coumarins

LIVER	
Anticoagulant Effect Potentiated Drugs: • Phenylbutazone, Metronidazole, Sulfinpyrazone,Trimethoprim, Sulfamethoxazole, Disulfiram, Amiodarone,Erythromycin, Anabolic steroids,Clofibrate, Cimetidine, Omeprazole, Thyroxine, Ketoconazole, Fluconazole, Isoniazid, Piroxicam, Tamoxifen, Quinidine, Vitamin E (megadoses), Phenytoin, Liver disease.	*Anticoagulant Effect Counteracted* Drugs: • Barbiturates, Rifampicin, Griseofulvin, Carbamazepine, Penicillin, Alcohol. *Hypermetabolic States:* • Pyrexia • Thyrotoxicosis

HAEMOSTATIC PLUG	
Impaired Haemostatic Plug Formation *Impaired Coagulation* • Reduced vitamin K dependent coagulation factors • Reduction in concentration of other coagulation factors • Other anticoagulants (heparin, ancrod)	*Impaired Platelet Function* • Thrombocytopenia • Aspirin, Other NSAIDS,Ticlopidine, Moxalactam, Carbenicillin and high doses of other penicillins

Problems in Monitoring Oral anticoagulant therapy

Reporting PT in seconds, or as PTR, or as PTI, or as % activity by using different reagents can give remarkably differing values. By mid 1970s, WHO and other agencies started work towards standardization of PT for monitoring oral anticoagulant therapy. The first step was preparation of IRP's (International Reference Preparations) of thromboplastins. This was done to have an accurate reference reagent which could serve as a standard for calibrating responsiveness / sensitivity of commercial thromboplastin reagents. The IRPs prepared were assigned ISI values of 1.0. The ISI (International Sensitivity Index) indicates the sensitivity of test thromboplastin in comparison to the IRP. When the calibration line has a slope=1.0, the test thromboplastin equates to the IRP in sensitivity and responsiveness. In other words, the ISI is a measure of the responsiveness (prolongation of PT values) of a given thromboplastin to the reduction of the vitamin K dependent coagulation factors. The lower the ISI (more close it is to 1.0) the more sensitive is the thromboplastin. Manufacturers assign ISI value for each lot of thromboplastin by the WHO recommended methods to assist laboratarians in calculation of the INR.

Results are reported by using the formula

$$INR = \left(\frac{\text{Patient PT in seconds}}{\text{Mean Normal PT}}\right)^{ISI}$$

Many automated and semi-automated coagulometers can do the calculation themselves.

Recommended therapeutic ranges for oral anticoagulant therapy

Indications	Desired/ Recommended INR	Intensity
Prophylaxis of venous thrombosis (high risk surgery) Treatment of venous surgery Treatment of pulmonary embolism Prevention of systemic embolism Tissue heart valves Acute myocardial infarction (to prevent systemic embolism) Valvular heart disease Atrial fibrillation	2.0 - 3.0	Low
Mechanical prosthetic valves (high risk) Prevention of recurrent myocardial infarction	2.5 - 3.5	High

Other Factors Influencing the INR

The variability of the responsiveness of the PT reagents, is corrected through the "ISI" calibration, however three additional technical factors influence the INR.

➢ *Derivation of MNPT*: Ideally each laboratory must derive its own MNPT from 20 or more normal patients for a given PT reagent and Lot under use. This corrects within laboratory test variables that influence PT results. If "normal control plasmas" are used in place of patient plasma for arriving at the MNPT it can effect the evaluation of the patients level of anticoagulation. If the control time is greater than the MNPT, the PT ratio for any patient PT will be smaller, potentially leading to over coagulation. If the control time is lesser than MNPT

the ratio for any patient PT will be greater, leading to under coagulation. On the other hand MNPT for a particular laboratory using the same combination of methodology, reagent and instrument would remain constant.

- *Magnitude of difference in the ISI value of test thromboplastin and IRP (ISI=1.0) and Method of clot detection employed during PT test.:* INR looses some precision when comparisons are made with thromboplastins with markedly different ISI values as against the IRP (ISI=1.0) and different methods of clot detection e.g.,manual, mechanical, optical etc. Therefore manufacturers must provide ISI values adapted to the method used for clot detection. Also the reagent used for reporting results should ideally be as close to 1.0 as possible.
- Since all manufactures (for QC and ISI evaluation) and diagnostic community worldwide use 3.2% TriSodium Citrate as the preferred anticoagulant of choice for coagulometry studies, it is imperative that all laboratories also employ the same strength of TriSodium Citrate for their evaluations. This is mandatory to avoid giving falsely high INR results that may be obtained by using 3.8% TriSodium Citrate.

Practical Considerations for Warfarin therapy

Oral administration of Warfarin results in a rapid absorption of the drug, however an observable anticoagulant effect is delayed. This delay is due to the time required for des- -carboxylated (dysfunctional) vitamin K dependent factor to replace the normal clotting factors. Depending upon the dose the delay may range from 1 to 7 days. The early anticoagulant effect is mainly caused by the loss of fully carboxylated procoagulant factor VII which has a half life of approximately 5 hours.

However these oral anticoagulant reagents also cause suppression in the synthesis of natural anticoagulant protein C and protein S. Due to this, in the early phase of initiation of oral anticoagulant therapy there is a potential for initial prothrombotic effect. This event underlines the syndrome of coumadin induced skin necrosis, especially in patients with hereditary deficiencies of protein C and protein S.

Therapy can begin with an anticipated maintenance dose (e.g.,: 5 mg/day). A small loading dose of about twice the average maintenance dose may also be used initially. This dosage achieves a steady state anticoagulant effect in 5-7 days. The use of large loading dose (e.g., 20-40 mg) has little benefit. Such dosing not only produces a marked factor VII deficiency (which alone may not protect against thrombosis) but also an acquired protein C deficiency, which could produce a prothrombotic state.

If the need for antithrombotic effect is more urgent, heparin should be given as indicated. Heparin is then discontinued when INR is in the therapeutic range.

Considerations for frequency of Laboratory tests for monitoring oral anticoagulant therapy

PT monitoring of patients initially should be performed daily for the first 5 days and 2 to 3 times a week for the first 1 to 2 weeks. Depending on the stability of the PT results from the third week onwards frequency of monitoring may be further reduced to every 4-8 weeks. While some patients on long term Warfarin therapy have unexpected fluctuations in dose response, some have unexplained requirement for increase in dosage

The unexpected fluctuations in dose response could be due to: change in diet, undisclosed concomitant drug use, poor patient compliance, surreptitious self-medication, alcohol consumption, intermittent illness or unsuspected changes in the responsiveness of the PT reagent used to perform the PT test.

INR	Recommendations
INR > 3.5 but < 6.0 Patient not bleeding	Rapid reversal not indicated, omit warfarin for a few doses and resume warfarin at lower dose when INR reaches the therapeutic range.
INR > 6.0 but < 10.0 Patient not bleeding	If rapid reversal is required give 1-2 mg sc Vit K ➢Reduction of INR will occur in 8 hours ➢Back in therapeutic range in 24 hours ➢If INR remains high at 24 hrs additional dose of 0.5 mg Vit K may be given ➢Warfarin can be resumed at lower dose when INR returns to therapeutic range
INR > 10.0 Patient not bleeding	Give 3 mg sc Vit K ➢INR will be reduced substantially by 6 hrs ➢Check INR at 6 hours ➢Vit K can be repeated if necessary
INR > 20.0 or Patient bleeding	Give 10 mg sc Vit K supplemented with FFP or prothrombin complex ➢Check INR every 6 hrs ➢Administration of Vit K injection may be repeated every 12 hrs ➢In case of life threatening bleeding or serious warfarin overdose replacement with prothrombin complex concentrate is indicated, supplemented with Vit K 10 mg; repeated as necessary depending on INR.

Advantages of the INR system

- Major advantage of the INR system is that it helps alleviate confusion in the interpretation of PT results. Usually laboratory changes like change in thromboplastin and/ or equipments could go unnoticed by the attending physicians. The INR remains constant even with such changes.
- INR system affords comparison of PT results between laboratories
- INR system provides a more accurate and convenient means of monitoring patients who travel extensively.
- INR therapeutic ranges for different clinical conditions are based on international collaborative studies. Usage of standardized dosage reduces the risk of thrombotic episodes or secondary bleeding.

Disadvantages of the INR system

- The prothrombin time test is always a part of the preoperative screening panels. It is also frequently used to evaluate other hemostatic disorders such as liver disease, DIC, LA, hereditary factor deficiencies and acquired vitamin K deficiency. Since these disorders have been excluded from the derivation of the ISI, INR has a diagnostic and therapeutic value mainly applicable for patients stabilized on oral anticoagulants. Therefore laboratories may prefer to report both the INR and patients time in seconds depending upon the clinical application.
- The INR systems effectiveness would still depend on the calibration of the coagulation instruments as well as thromboplastin reagents used.
- Derivation of the correct MNPT and use of the mean normal range in each laboratory
- Usage of thromboplastin reagents with ISI of preferably 1.0 or as close to 1.0 as possible.
- The correct use of the formula to compute the INR.
- Uniform understanding of the INR system by clinicians as well as laboratarians.

INTERPRETATION

FECAL OCCULT BLOOD (FOBT)

FOBT is both a preventive and diagnostic tool. Normal amount of blood lost is less than 2 ml/day or 2 mg of hemoglobin/gm of stool. The usual card tests employing guaiac detect blood losses of 20/ml day or more. These card tests have a sensitivity of 90% at hemoglobin concentrations of 25 mg (or more) /gm of stool. These devices, in spite of best of protocols for stool collection will give 1-3% false positive results.

Utility of FOBT

- Preventively, FOBT should be done annually and sigmoidoscopy be conducted once every 3 to 5 years after the age of 45 years.
- Screening for asymptomatic ulcerated lesions of GI tract, especially of the colon that is beyond the reach of routine sigmoidoscopy.
- In various screening programs, 2-6% of participants have positive tests; of these, carcinoma is found in 5-10% and adenoma in 20-40%.
- Adenomas < 2 cm in size are less likely to bleed. Upper GI tract bleeding is less likely than lower GI tract bleeding to cause a positive test.
- Long distance running is associated with positive guaiac test in upto 23% of runners.

Recommendations for testing

Feces: Smeared directly on a device (usually paper)
Feces: Approximately 1 ml sample in a special stool collection vial approximately 1 gm.

If the screening is directed to detect colorectal neoplasia, it is recommended to take two samples from three consecutive bowel movements.

If the search is for inflammatory bowel disease, it is sufficient to take two samples from one bowel movement, preferably one from the centre of the stool and other from the periphery. The one from the centre reflects the lower GI tract condition and from the periphery reflects the upper GI tract condition. Test all samples within four days of collection. Do not rehydrate slide prior to development.

For three days before testing, avoid large doses of ascorbic acid, oral iron, aspirin, and other NSAIDs; red meat and certain fruits and vegetables that contain catalases and peroxidases (e.g., cucumbers, horseradish, cauliflower), especially if slides are rehydrated.

Samples from upper GI tract should not be tested for blood using urine dipsticks or stool occult blood test kits (low pH may cause false negative and oral drugs false positive results).Even one positive test should be considered a positive test even without a dietary restriction.

Methods of testing FOBT

Guaiac based tests that detect peroxidase activity. Other methods utilizing fluorescence to assay stool-derived porphyrins are also available but are cumbersome and less sensitive and less specific.

Immunochemical methods specifically detect human hemoglobin and do not require diet restriction (as they do not react with animal heme or foods), are stable up to 30 days and detect as low as 0.3 mg Hb/gm of stool as compared to 5-10 times this amount to cause a positive guaiac test. This is considered to be the method of choice in day-to-day practice. Other methods available are RID, LIA, ILMA, ELISA etc.

Suggested diagnostic strategy for the evaluation of a positive FOBT

1) Inspection - Look for hemorrhoids and fissure or other local disease of the anus
2) Rectal examination - A polyp may be palpable
3) Colonoscopy - Benign or malignant tumors, inflammatory bowel disease, diverticulitis, and angiodysplasia are common findings with a positive FOBT.
4) Gastroscopy - Gastric or duodenal ulcers, tumors, a hiatus hernia or esophageal varices can lead to fecal occult blood.
5) Small intestine - Celiac disease, a Meckel's diverticulum or angiodysplasia are the most common bleeding sources in the small intestine.

GI manifestations of advanced HIV infections may be associated with typical symptoms of inflammatory bowel disease like Crohn's disease or ulcerative colitis

A negative fecal occult blood test does not exclude the presence of a malignant disease; a positive test needs no further verification by an additional positive FOBT. In each case a rapid diagnostic procedure, e.g. endoscopy, ultrasound, X-ray is justified if clinical suspicion persists.

Taking into account the higher prevalence of adenomatous polyps compared to cancer among the population, it is quite obvious that the positive predictive value of a FOBT for polyps is higher than for cancer with equal specificity. Because cancer at the specific site can be prevented by poypectomy the positive predictive value of a FOBT for colorectal cancer prevention purposes should derive from a combination resulting from the positive predictive value for cancer and for polyps.

BOUQUET

In Lighter Vein

An old bishop in the Roman capital was sick to death of socials and the embassy parties, he was to attend every other day. At one of them, he entered wearily, and sank into the nearest chair.The hostess asked coyly, “A pot of tea, bishop?”
“No tea,” roared the bishop.
“A cup of coffee, My Lord?”
“No coffee,” growled the bishop.
An understanding lady, she whispered in his ears, “Shall I serve you Scotch and water?” “No water,” said the bishop brightening.

Teacher: “Who can tell me where we can find mangoes?”
Student: |”I guess everywhere womangoes.”

A signboard before a sharp curve: 'Expect the unexpected.'

Rear of a bus: 'Overtakers, beware of undertakers.'

Wisdom Whispers

- Pay no attention to what the critics say. A statue has never been erected in honor of a critic.
- When you get to the end of your rope, tie a knot and hang on.
- It's not what you look at that matters, it's what you see.
- Shoot for the moon. Even if you miss, you'll land among the stars.
- One courageous thought will put to flight a host of troubles.

Brain Teasers

1.Hella cells are associated with
A.Carcinoma prostate B.Carcinoma cervix C. Burkitt's lymphoma D. CML

2.Glycogen can be confirmed by which of the following stains
A. PAS B. Methyl violet C. Von Kossa D. Sudan Black B

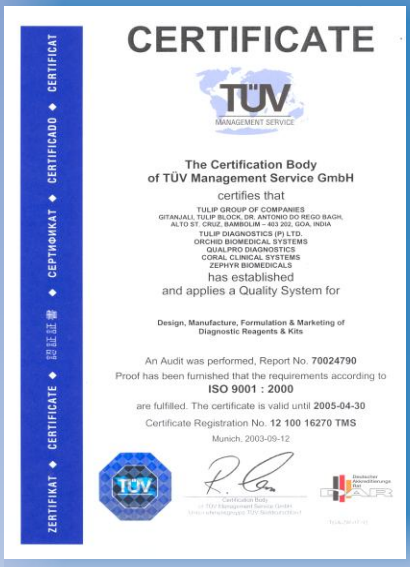
3.What is the colour of hemosiderin?
A. Black B. Golden Yellow C. Greenish D. Red

4. Increased excretion of 5-HIAA in urine is associated with:
A.Carcinoid syndrome B. Synovioma C. Chemodectoma D. Fanconi's syndrome

5. Durck's granulomas are found in:
A.Gout B. Berylliosis C. Sarcoidosis D. Malaria

(Answers: 1) B, 2) A, 3) B, 4) A, 5) D)

TULIP NEWS


CERTIFICATE

TÜV MANAGEMENT SERVICE

The Certification Body
of TÜV Management Service GmbH
certifies that

TULIP GROUP OF COMPANIES
GITANJALI, TULIP BLOCK, DR. ANTONIO DO REGO BAGH,
ALTO ST. CRUZ, BAMBOLIM – 403 202, GOA, INDIA
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ORCHID BIOMEDICAL SYSTEMS
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CORAL CLINICAL SYSTEMS
ZEPHYR BIOMEDICALS

has established
and applies a Quality System for

Design, Manufacture, Formulation & Marketing of
Diagnostic Reagents & Kits

An Audit was performed, Report No. 70024790
Proof has been furnished that the requirements according to
ISO 9001 : 2000
are fulfilled. The certificate is valid until 2005-04-30
Certificate Registration No. 12 100 16270 TMS
Munich, 2003-09-12

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

In today's global marketplace, many organizations are utilizing ISO 9001:2000 as an international standard to provide a uniform quality management system, and for the design, development, production, and servicing of their management system to better meet their customer's needs.

Tulip Group of Companies, comprising of eight independent diagnostic companies has emerged as the leading manufacturer and marketeer of *in vitro* diagnostic reagents, kits and instruments, both nationally and internationally.

The Group companies focus on customer satisfaction and quality management as their prime objective. In recognition of the work towards enhancing the same, **the individual group companies i.e., Tulip Diagnostics (P) Ltd., Orchid Biomedical Systems, Qualpro Diagnostics, Coral Clinical Systems, Zephyr Biomedicals have been awarded the prestigious ISO 9001:2000 by TUV Management Service, Germany.**

ISO: 9001:2000 AND ITS ORIGIN

The International Organization for Standardization (ISO) was founded in 1946. Based in Geneva, Switzerland, it created the first international standards for manufacturing, trade and communications. ISO 9001 was initially published in 1987 and specifies, in broad terms, the necessary components of a quality management system and, in detail, the basic requirements of the quality function for all industries.

The most recent change to the ISO 9001 standard is ISO 9001:2000. This new standard is now in place and includes improvements in three key areas:

- Creating a common structure based upon a process model.
- Creating a method to demonstrate continual improvement and customer satisfaction.
- Developing metrics to determine how effectively internal processes are working with a focus on improving results.

BASIC REQUIREMENTS FOR ISO CERTIFICATION

This International Standard specifies requirements for a quality management where an organization

- Needs to demonstrate its ability to consistently provide products that meet customer and applicable regulatory requirements, and
- Aims to enhance customer satisfaction through the effective application of the system, including processes for continual improvement of the system and assurance of conformity to the customer and applicable regulatory requirements.

ISO 9001 certified companies like TULIP have proof of their commitment to quality and continuous improvement.

HEMOSPOT

A TWO FIELD
FECAL OCCULT BLOOD TEST

Pack Size	Presentation
HEMOSPOT	50 Tests

NON TREPONEMAL TEST

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RPR CARD TEST FOR SYPHILIS

Syphicheck
Treponemal test

SYPHILIS DIAGNOSIS
Screen. Confirm. Report.
TULIP Group

3rd Generation Immunochromatographic assay

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