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# The Crux

BIMONTHLY FORUM FOR THE LABORATARIANS

CONTENTS



## Editorial

Running in its fifth year (not a toddler anymore!), CRUX has been acclaimed as the most innovative and informative medical diagnostic educational instrument of this decade. Having reached all inhabited continents, CRUX has been appreciated immensely and quite often requests have come in for us to write on particular disorders of our reader's choice. This issue is carrying an important haematologic disorder of global significance - Thalassemia. It is a genetic disorder of defective haemoglobin synthesis. Means are now available to diagnose carriers of the disorder in-utero. Those found positive can be appropriately handled as per one's own religious and scientific beliefs and sentiments. We are still a little away from appropriate genetic engineering techniques to replace and rectify defective genes responsible for the disorder on the chromosomes 11 and 16. DISEASE DIAGNOSIS segment of this issue more than amply considers all clinico-diagnostic aspects of all clinically relevant Thalassemias known to mankind. We still wait for the day when genetic disorders could be (though not wished away) cured like we treat common infections. Virus vehicles carrying the reparative genes could be possibly trained to gently attack and repair only the defective genes leaving the normal genome safe and sound and effectively untouched.

The latest bug rage namely MRSA that was highlighted in the previous issue, has, due to space constraints, spilt over in this issue. INTERPRETATION portion outlines general principles of prevention and infection-control strategies along with MRSA in the workplace while TROUBLESHOOTING defines the exact modalities of debugging the world and clinical practice of the dreaded MRSAs.

Half a page is devoted to intelligent fun as usual. BOUQUET is there, please flip a few pages.

Thanks once again and happy reading!

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# DISEASE DIAGNOSIS

## THALASSEMIA

### Description

Congenital disorders of hemoglobin synthesis. Characterized by deficient synthesis of one or more hemoglobin polypeptide chains. Beta-thalassemia results in an excess of alpha-globins, leading to the formation of alpha-globin tetramers that accumulate in the erythroblast. Alpha-thalassemia results in an excess of beta-globins, which leads to the formation of beta-globin tetramers called hemoglobin H. Hemoglobin H can precipitate, causing damage to the red blood cell membrane and leading to red cell breakage. Clinical classification is by phenotype: thalassemia may be major, intermedia, minor, or silent. Genotypes are far more complex and determine the clinical picture, which is of a spectrum of disease.

**Synonyms:** Cooley's anemia / Mediterranean anemia

**Urgent action:** Transfusion is required in thalassemia major.

**Cardinal features:** Congenital disorders of hemoglobin. Characterized by deficient synthesis of one or more hemoglobin polypeptide chains, leading to an imbalance in numbers of alpha and beta chains. The interaction of alpha- and beta-thalassemia gives rise to a less severe hemolytic anemia. In most thalassemias, globin chains are reduced but are structurally normal. Some structural hemoglobin variants produce thalassemic syndromes; interactions of the different forms of thalassemia and other hemoglobinopathies are common. Clinical classification is by phenotype: thalassemia may be classified as major, intermedia, minor, or silent. Genotypes are far more complex and the clinical disease ranges along a continuous spectrum. Prevalent in the Mediterranean region, Middle East, and southeast Asia. Both alpha- and beta-thalassemia traits are frequent in African-Americans, but symptomatic thalassemia is rare. Microcytic anemia is characteristic. Hemoglobin electrophoresis is usually abnormal, with increased $HbA_2$ and sometimes fetal hemoglobin (HbF). Major forms may benefit from splenectomy. Allogeneic bone marrow transplant is potentially curative if an HLA (human leukocyte antigen) match is available.

### Causes

#### Common causes

**Genetic:** Most of the alpha-thalassemia syndromes result from gene deletions. Most of the beta-thalassemia syndromes result from nucleotide substitutions or deletions in genes that are otherwise intact. The clinical heterogeneity of the thalassemia syndromes is a reflection of the great heterogeneity of mutations that affect the globin genes. Thalassemia intermedia may be produced by a great variety of genotypes.

**Normal hemoglobin:** Adults have mainly hemoglobin A, made up of two alpha and two beta chains, together with $HbA_2$ <2% (two alpha and two delta chains), and no HbF (two alpha and two gamma-globin chains). There are four alpha genes (located on chromosome 16) and two beta genes (on chromosome 11). At birth HbF accounts for 70-90% in normal individuals, and gamma-chain synthesis is only replaced by beta chains gradually. Impairment of beta synthesis leads to the patient being asymptomatic at birth.

**Alpha-thalassemias:** The alpha-thalassemias result from mutations that cause decreased synthesis of structurally normal globin. Two alpha-thalassemia phenotypes are recognized, and are referred to as follows: alpha-thalassemia 1 and alpha-thalassemia 2 (alpha+ thalassemia - low level of alpha chains). Hydrops fetalis has no alpha-globin gene (alpha 0 thalassemia- no alpha chains). Hemoglobin H disease has one alpha-globin gene.

**Beta-thalassemias:** There is only one beta-globin gene, of which there are two alleles (paternal and maternal). Globin chain synthesis in the homozygous state reveals two major types of beta-thalassemia: beta+ type (suboptimal beta chains present) and beta-0 type (total absence of beta chains). The beta-thalassemia syndromes are caused by mutations of the expressed beta+ allele and nonexpressed beta-0 alleles. The mutations affect gene regulation or expression rather than gene deletion, and can result in decreased synthesis of structurally normal globin. In individuals with beta+ thalassemia, the amount of beta-globin messenger RNA in reticulocytes and bone marrow normoblasts is decreased 3- to 10-fold. In patients with homozygous beta-0 thalassemia, beta-globin synthesis is absent.

**Deltabeta-thalassemia:** This disorder is characterized by decreased or absent synthesis of both delta- and beta-globin chains. Most of the deltabeta-thalassemias result from gene deletions.

**Gammadeltabeta-thalassemia:** This rare form of thalassemia is characterized by deletion or inactivation of the entire beta-gene complex. The homozygous state has not been encountered

**Hereditary persistence of fetal hemoglobin (HPFH):** As in deltabeta-thalassemia, delta and beta chain synthesis is decreased or absent in patients with HPFH. Unlike deltabeta-thalassemia, the increase in gamma chain synthesis is sufficient to almost balance alpha chain synthesis. Both deletion and nondeletion forms of HPFH have been characterized.

**Pathophysiology of thalassemia:** How does defective hemoglobin cause disease?

Selective deficiency of one or more polypeptide chains causes decreased hemoglobin synthesis and imbalance between alpha and nonalpha chain production. In the absence of complementary globin chains with which to bind, chains with normal synthesis form aggregates, precipitate within the cytoplasm, damage cell membranes, and lead to premature cell destruction. In patients with alpha-thalassemia, the defect in alpha chain synthesis results in an accumulation of gamma chains in the fetal and neonatal periods and of beta chains thereafter. The excess of beta chains oxidize and precipitate with cell aging. In homozygous beta-thalassemia, a deficiency of beta chain synthesis results in an accumulation of alpha chains. The free alpha chains aggregate to form insoluble inclusions in bone marrow erythroid precursors. In thalassemia syndromes there is often ineffective erythropoiesis and hemolysis, which lead to anemia.

**Contributory or predisposing factors:** Genetic.

### Epidemiology

**Incidence and prevalence:** Most common genetic disorder worldwide.

**Prevalence:** 50-100/1000 in southeast Asia. 30/1000 worldwide. 50/1000 in African-Americans. 150-300/1000 in Italy, Greece, and among Americans of Italian or Greek descent.

#### Demographics

**Age:** Congenital condition. Beta-thalassemia major causes severe anemia and jaundice from age 3-6 months. Alpha-thalassemia causes intrauterine death if all four chains are affected; other forms may not present until later life. Beta-thalassemia minor is usually asymptomatic.

**Gender:** Male=female.

**Race:** 50-100/1000 in southeast Asia. 50/1000 in African-Americans. 150-300/1000 in Italy, Greece, and among Americans of Italian or Greek descent.

**Genetics:** Inherited in an autosomal-recessive pattern. Inheritance of one defective gene causes the mild type of thalassemia; inheritance of two defective genes causes the severe type of thalassemia. Two alpha-thalassemia phenotypes are recognized; one is characterized by thalassemia minor in the heterozygous state and the other is marked by no clinical or hematologic abnormality in the heterozygous state. There are also two major types of beta-thalassemia: one with some residual beta chains (beta+ type) and another with no beta chains (beta0 type). 92% of the beta-thalassemia genes in Italians and Greeks are accounted for by six mutations, more than 90% of those in Sicilians by three alleles, 96% of those in Sardinians by two alleles, and 91% of those in south Chinese and southeast Asia by four alleles.

**Geography:** The distribution of the thalassemias is similar to that of malaria. The purported advantage afforded the thalassemic red cell has been attributed to its low concentration of hemoglobin, an essential nutrient for the malaria parasite. Most common in the Mediterranean and the Middle East, particularly Greece. Hemoglobin H (HbH) disease affects individuals throughout southeast Asia, the Mediterranean islands, and parts of the Middle East; it occurs rarely in populations of African descent. The highest concentration of alpha-thalassemia genes is found in southeast Asia and among those populations who have their origin along the west coast of Africa. In the eastern oases of Saudi Arabia, more than 50% of the population appears to have a clinically silent form of alpha-thalassemia, and HbH disease is recognized with increasing frequency. In African-Americans, alpha-thalassemia is relatively common, but rarely is it of clinical significance. Of African-American infants born in Philadelphia, 3% were found to have the electrophoretic and hematologic characteristics. Two million refugees from Cambodia, Laos, and Vietnam during 1970-1980 led to symptomatic alpha-thalassemia syndromes increasing throughout North America and Europe.

### Diagnosis

Clinical presentation

**Symptoms:** Symptoms of anemia: tiredness, breathlessness, poor exercise tolerance. Abdominal pain due to hypersplenism and splenic infarction may occur. Right upper quadrant pain caused by gallstones may occur.

**Signs:** Thalassemia trait has no signs or symptoms. Other forms of thalassemia may be associated with the following signs: Pallor. Poor growth. Inadequate food intake. Splenomegaly. Jaundice. Maxillary hyperplasia. Dental malocclusion. Cholelithiasis. Systolic ejection murmur in the presence of severe anemia. Pathologic fractures.

**Associated disorders:** Sickle cell anemia trait may be inherited in conjunction with one thalassemia gene.

**Differential diagnosis**

**Iron deficiency:** Anemia secondary to inadequate iron supplementation or excessive blood loss.

**Features:** Usually normal on examination. Skin pallor may be present. Hypochromic microcytic anemia. Red blood cells with central pallor, anisocytosis, and poikilocytosis. Elevated red blood cell distribution width. Elevated reticulocyte count. Absent iron marrow stores. Decreased serum ferritin. Decreased serum iron and increased total iron-binding capacity.

**Other hemoglobinopathies:** Inherited disorders of hemoglobin structure or production. The most common is sickle cell anemia. Sickle cell trait may occur in combination with thalassemia, and the degree to which the patient is affected depends on the thalassemia gene present (i.e. whether there are any normal beta chains present). There are many other hemoglobin variants caused by structural globin chain defects (e.g. hemoglobin E disease, the most common variant in southeast Asia, which causes a mild microcytic anemia). The hemoglobin variants may occur in combination with thalassemia.

**Features:** Diagnosed on electrophoresis. Family studies may be needed to identify genotype of heterozygous forms.

**Other hemolytic anemias:** Hemolysis is premature lysis of red blood cells: the normal lifespan of 120 days may be reduced to <5 days. Hemolytic anemia may be inherited or acquired.

Inherited types: Enzyme deficiencies (e.g. glucose-6-phosphate dehydrogenase (G6PD) deficiency, pyruvate kinase deficiency). Hemoglobinopathies (e.g. sickle cell disease, thalassemia). Disorders of the red cell membrane (e.g. congenital spherocytosis, congenital elliptocytosis).

Acquired types: Immune: alloimmune (e.g. rhesus incompatibility, ABO incompatibility). Nonimmune: infection (especially falciparum malaria, *Clostridium welchii*), drugs, burns, valve prosthesis, and other causes of hypersplenism.

**Features:** Apart from in hemoglobinopathies, hemoglobin electrophoresis is normal. Peripheral blood film may reveal abnormal cell forms. G6PD deficiency: episodic hemolysis, laboratory testing for G6PD assay is low. Pyruvate kinase deficiency is much rarer, causes chronic hemolytic anemia, and the specific enzyme assay is diagnostic.

**Workup**

**Diagnostic decision**

**Symptomatic thalassemia syndromes:** In major thalassemia, diagnosis is obvious from hemoglobin electrophoresis. The symptomatic thalassemia syndromes rarely pose problems in diagnosis.

Alpha-thalassemia major syndromes: Electrophoresis is normal in the absence of hemoglobin H disease.

Hemoglobin H disease: Patients with this condition have a severe anemia, and often require blood transfusions to survive. The diagnosis is confirmed by hemoglobin electrophoresis showing the presence of hemoglobin H. At birth, 20-40% Hb Bart's is found (Hb Bart's is deletion of all four alpha-globin genes). The level of $HbA_2$ is decreased (average 1.55%). A hemoglobin band migrating more slowly than $HbA_2$ is seen in individuals with hemoglobin Constant Spring.

Beta-thalassemia major (Cooley's anemia): Anemia and morphologic alterations of circulating erythrocytes are first detected at 6 weeks and splenomegaly at 8 weeks of age. In the absence of transfusion therapy, the hemoglobin concentration slowly falls to 3-5g/dL. The reticulocyte count is elevated (5-15%). $HbA_2$ is increased variably. Absent or reduced hemoglobin. Increased fetal hemoglobin (HbF).

Thalassemia intermedia: Signs and symptoms of thalassemia intermedia are comparable to those of thalassemia major but of lesser magnitude. The hemoglobin concentration is maintained in the range 6-9g/dL without transfusion. The hemoglobin electrophoretic pattern is highly variable - a reflection of the heterogeneity of genotypes that produce this clinical syndrome.

**Asymptomatic thalassemia syndromes**

Alpha-thalassemia minor: This disorder is suspected in the newborn on the basis of a low mean corpuscular volume (less than 94fL) and an increase in Hb Bart's. Failure to detect Hb Bart's does not exclude alpha-thalassemia. Confirmation of the diagnosis of alpha-thalassemia minor is possible through family studies. In the absence of a specific screening test, a definitive diagnosis can be made only by demonstrating a reduced rate of alpha chain synthesis in reticulocytes.

Beta-thalassemia minor: The diagnosis of heterozygous beta-thalassemia is confirmed by the following: increase in $HbA_2$, red cell microcytosis, hypochromia, target cells, and basophilic stippling. 50% of patients have a mild elevation in HbF of 1-3%. Hemoglobin electrophoresis demonstrates a predominance of HbA, increased levels of $HbA_2$ (3.5-8%), and normal or minimally increased levels of HbF.

**Summary of tests:** The symptomatic thalassemia syndromes rarely pose problems in diagnosis. The hematologic features of the asymptomatic syndromes are subtle, but the following tests should be performed: Complete blood count (CBC). Hemoglobin electrophoresis permits differentiation of the alpha- and beta-thalassemias. Peripheral blood smear: changes in red cell morphology and in the relative amounts of hemoglobin fractions are sufficiently great as to be distinctive and in themselves diagnostic. Hematocrit may be helpful and is part of the standard work-up to assess anemia. Serum ferritin, transferrin, and iron-binding capacity help to distinguish thalassemia from iron deficiency. Serum bilirubin may be raised in hemolysis. Urine urobilin and urobilinogen may be present. Globin gene analysis may be performed by a specialist if other tests and family history do not fully explain genotype. Bone marrow aspiration may be performed by a specialist.

**Tests: Complete blood count**

**Normal:** Hemoglobin: female 12.0-15.0g/dL; male 13.6-17.7g/dL. Mean corpuscular volume (MCV): 76-100mcm$^3$ (76-100fL). Mean corpuscular hemoglobin concentration (MCHC): 33-37g/dL (330-370g/L). Reticulocyte count: 0-1% . Note: in neonate normal reticulocyte count is 1.5-7%, hemoglobin 14.5-23g/dL, MCV 98-119mcm$^3$ (98-119fL). Red blood cell (RBC) count: male 4.3-5.9x10$^6$/mm$^3$ (4.3-5.9x10$^{12}$/L); female 3.5-5.0x10$^6$/mm$^3$ (3.5-5.0x10$^{12}$/L). RBC distribution width (RDW): 11.5-14.5.

**Abnormal:** In symptomatic thalassemias, hemoglobin is markedly reduced, MCV and MCHC are reduced, and reticulocyte count is raised. In thalassemia minor, hemoglobin is variably reduced, and MCV and MCHC are reduced. In hereditary persistence of fetal hemoglobin, hemoglobin may be increased. RBC count is normal or may be increased in alpha-thalassemia (despite a reduced hematocrit/hemoglobin value). RDW may be normal or elevated in thalassemias. Reticulocytes are elevated in hemolysis generally, but often not as elevated in thalassemia as one would expect on the basis of other indices.

**Cause of abnormal result: Thalassemia major:** Anemia usually is pronounced when first documented at age 3-6 months. Before transfusion, the hemoglobin concentration is 2.5-6.5g/dL and the packed cell volume is 0.11-0.24L/L. The anemia is microcytic - MCV is 48-72mcm$^3$ (48-72fL) - and hypochromic - MCHC is 23-32g/dL (230-320g/L). Leukocytes characteristically are increased in number and platelet numbers are normal. In the absence of transfusion therapy, the hemoglobin concentration slowly falls to 3-5g/dL. The reticulocyte count is elevated (5-15%).

**Thalassemia intermedia:** The hemoglobin concentration is maintained in the range of 6-9g/dL without transfusion.

**Thalassemia minor:** Anemia is mild or absent. The RBC count is elevated, and the MCV and MCHC values are reduced; the degree of reduction in the MCV is directly related to the degree of reduction in beta-globin production. The MCHC is normal or only slightly decreased.

**Iron deficiency:** Also causes microcytic hypochromic anemia. Iron deficiency causes reduced levels of $HbA_2$ in thalassemic patients; elevated levels cannot be demonstrated until the iron deficiency is corrected. Iron deficiency also lowers serum ferritin. Iron deficiency is easily confused with thalassemia minor.

**Medications, disorders and other factors that may alter results:** Parvovirus B19 infection may produce 'aplastic crisis' and severe reticulocytopenia in thalassemia. Iron deficiency causes reduced levels of $HbA_2$ in thalassemic patients; elevated levels cannot be demonstrated until the iron deficiency is corrected; iron deficiency also lowers serum ferritin.

**Hemoglobin electrophoresis**

**Description:** Electrophoretic examination of peripheral blood sample.

**Advantages/disadvantages:** Easy to perform as part of standard work-up for unexplained hemolytic anemia. Allows diagnosis of major and intermedia forms and identifies fetal hemoglobin (HbF) and concurrent presence of HbS (sickle

cell hemoglobin).

**Normal:** In the normal adult, hemoglobin A, which is composed of two alpha- and two beta-globins ( 2 2), is the most prevalent, comprising about 95% of all hemoglobin. Two minor hemoglobins also occur: hemoglobin A2, composed of two alpha- and two delta-globins ( 2 2), comprises 2-3.5% of hemoglobin; whereas HbF is composed of two alpha- and two gamma-globins ( 2 2), and comprises less than 2% hemoglobin. HbF is the dominant hemoglobin in the fetus, and begins to decrease after gestational week 30.

**Abnormal: General:** In addition to the more detailed findings given below, the following general features may be observed: Elevated $HbA_2$ levels in beta-thalassemia trait. Elevated $HbA_2$, elevated HbF, reduced or absent $HbA_1$ in beta-thalassemia major or intermedia.

**Alpha-thalassemias:** Normal except for the presence of hemoglobin H (HbH) in HbH disease.

HgH disease: At birth, 20-40% Hb Bart's is found. Hb Bart's is replaced gradually during the first months of life by HbH, which stabilizes at a level between 5 and 40%. The level of $HbA_2$ is decreased (average 1.55%). A hemoglobin band migrating more slowly than $HbA_2$ is seen in individuals with Hb Constant Spring.

**Beta-thalassemias**

**Beta-thalassemia major:** Absent or reduced HbA. Increased HbF. Variable increase in $HbA_2$.

**Thalassemia intermedia:** The hemoglobin electrophoretic pattern is highly variable - a reflection of the heterogeneity of genotypes producing this clinical syndrome.

**Thalassemia minor:** Hemoglobin electrophoresis demonstrates a predominance of HbA, increased levels of $HbA_2$ (3.5-8%), and normal or minimally increased levels of HbF. In Hemoglobin Lepore the concentration of $HbA_2$ is normal or reduced, and that of HbF is normal or elevated. Hemoglobin Lepore is produced at a reduced rate, accounting for only 5-15% of the total concentration of hemoglobin. The most consistent feature of thalassemia minor is an increase in $HbA_2$. $HbA_2$ levels in persons with heterozygous beta+ thalassemia are lower than those in persons with beta 0 thalassemia, and may fall to within the normal range.

Thalassemia minima: The hemoglobin pattern is normal.

**Silent carrier state:** Hematologically normal.

**Alpha-thalassemias in association with structural variants:** The beta chain variants noted in association with alpha-thalassemia include HbS (sickle cell hemoglobin), HbC, HbE, and HbJ Bangkok. The interaction of alpha-thalassemia and HbS trait produces a variable amount of HbS.

HbH disease: At birth, 20-40% Hb Bart's is found. Hb Bart's is replaced gradually during the first months of life by HbH, which stabilizes at a level between 5 and 40%. The level of $HbA_2$ is decreased (average 1.55%).

**Hereditary persistence of fetal hemoglobin (HPFH):** Persistence of HbF into adult life. In the homozygous state HbF constitutes 100% of the hemoglobin concentration; HbA and $HbA_2$ are absent. In the African-American variant the level of $HbA_2$ is low (1.6-2.2%), and HbF is increased to 10-36% (mean 26%). In the Greek variant the relative concentration of HbF in the heterozygous state is lower (15-25%) than that associated with African-American HPFH. Levels of HbF are lower in association with iron deficiency. Greek HPFH in association with heterozygous beta-thalassemia: the major hemoglobin is HbA, and both $HbA_2$ (3.6-5.2%) and HbF (20-40%) levels are increased.

**Cause of abnormal result:** Thalassemias.

**Medications, disorders and other factors that may alter results:** There are a large number of nonthalassemic hematologic disorders that are often associated with an increase in HbF. These include juvenile chronic myelocytic leukemia, the Di Guglielmo syndrome, sideroblastic anemia, pernicious anemia, myelofibrosis, aplastic anemia, the Diamond-Blackfan syndrome, and paroxysmal nocturnal hemoglobinuria.

Peripheral blood film smear

**Description:** Blood test: sample is placed on slide and examined under medium and high-power field. The appearance of red blood cells on smears of the peripheral blood is both striking and characteristic.

**Advantages/disadvantages:** Easy and quick to perform. Will produce diagnostic picture of thalassemia major if present.

**Normal:** Normal morphology without basophilic stippling, distortion, or target cells. **Abnormal:** Abnormal forms.

**Cause of abnormal result:** Alpha-thalassemia minor: Red cell morphology is abnormal with microcytosis, hypochromia, and slight anisopoikilocytosis. Punctate basophilic stippling. High percentage of target cells.

**Beta-thalassemia major:** Anisocytosis is significant, with cells ranging from 3 to 15 m in diameter. They contain little pigment and may be so distorted in shape that they appear to be composed almost exclusively of a thin, nearly colorless membrane. Target cells are numerous, many of them having a bridge joining the central and peripheral zones of pigment. Few cells are fully pigmented. Basophilic stippling is prominent. Poorly pigmented normoblasts are regularly present, their number ranging from 10 per 100 leukocytes to several times the number of leukocytes. Morphologic alterations of circulating erythrocytes are first detected at 6 weeks and splenomegaly at 8 weeks of age.

In thalassemia intermedia, peripheral blood erythrocytes show changes comparable to those of thalassemia major: Significant anisocytosis. Hypochromia. Target cells. Basophilic stippling. Numerous nucleated forms.

**Thalassemia minor:** Morphologic alterations of peripheral blood erythrocytes are prominent. These changes include microcytosis, hypochromia, anisocytosis, poikilocytosis, target cells, and basophilic stippling. Nucleated red cells are not present.

Hereditary persistence of fetal hemoglobin (HPHF): Minor abnormalities of red cell morphology may be seen, including microcytosis (MCV 68-84 $mcm^3$ (68-84 fL)), anisocytosis, and target cells.

**Hematocrit**

**Normal:** Male 39-49% . Female 33-43%.

**Abnormal:** Values below the normal ranges. Keep in mind the possibility of a falsely abnormal result.

**Cause of abnormal result:** 28-40% in alpha-thalassemia trait and beta-thalassemia trait. May fall to less than 10% in beta-thalassemia major. Reduced in iron deficiency, hemoglobinopathies, and any blood loss (acute or chronic).

**Medications, disorders and other factors that may alter results:** Parvovirus B19 infection may produce 'aplastic crisis' and severe reticulocytopenia in thalassemia.

**Serum ferritin, transferrin, and iron-binding capacity**

**Normal:** Ferritin: 18-300ng/mL (18-300mcg/L). Transferrin: 170-370mg/dL (1.7-3.7g/L). Serum iron-binding capacity 250-460mcg/dL (45-82mcmol/L).

**Abnormal:** Plasma iron turnover is increased out of proportion with the increase in erythrocyte iron turnover. Serum iron levels are increased, serum transferrin is often fully saturated, and a nontransferrin-bound iron fraction may be present. Serum iron-binding capacity is decreased in hemolytic anemias.

**Cause of abnormal result:** Transferrin is elevated and ferritin is decreased in iron deficiency. Transferrin is decreased in hemolytic anemias. Ferritin is increased in iron replacement therapy. Serum iron-binding capacity is elevated in iron deficiency and decreased in hemolysis.

**Medications, disorders and other factors that may alter results:** Iron therapy will normalize ferritin levels in iron deficiency. Transfusion will raise ferritin levels in thalassemias.

**Serum bilirubin (indirect)**

**Normal:** 0-1.0mg/dL (2-18mcmol/L).

**Abnormal:** Increased unconjugated bilirubin levels.

**Cause of abnormal result:** Elevated in hemolysis, liver disease, hepatic congestion secondary to congestive heart failure, Gilbert's disease, Crigler-Najjar syndrome, hyperthyroidism (rarely).

**Urine urobilin and urobilinogen**

**Normal:** Absence of urobilin or urobilinogen.

**Abnormal:** Urobilin or urobilinogen present.

**Cause of abnormal result:** In thalassemia and other causes of hemolysis, the urine often contains increased quantities of urobilin or urobilinogen, and may be dark brown because of the presence of dipyrroles and mesobilifuscin. Urobilin or urobilinogen also raised in hepatitis and liver cell dysfunction.

**Clinical Hallmarks:** Iron deficiency is the most common form of anemia and may present similarly to beta-thalassemia. Iron deficiency causes reduced levels of $HbA_2$ in thalassemic patients; elevated levels cannot be demonstrated until the iron deficiency is corrected. The diagnosis of transient aplastic crisis due to parvovirus B19 is often presumptive, based on a falling hemoglobin and a low reticulocyte count in a patient with a hemolytic anemia.

**Treatment: Goals:** Offer genetic counseling and information to whole family to minimize impact of disease on future generations. Minimize impact of disease on life. Minimize impact of disease on growth, development, puberty, and fertility. Minimize impact of transfusion therapy on health. Treat infections promptly and protect against bloodborne diseases. Maintain adequate hemoglobin concentration and suppress erythropoietic response. Avoidance of iron therapy

unless iron deficiency is documented biochemically.

**Immediate action:** Transfusion in acute anemia. Criteria for transfusion in the emergent setting are based on clinical symptoms of anemia.

**Outcomes: Prognosis:** Outlook varies depending on type.

Thalassemia minor: Patients have a normal lifespan.

Thalassemia intermedia: Growth and development during childhood is relatively uncompromised, pubescence takes place normally, and fertility is preserved. Survival into adulthood is the rule, and patients typically enjoy a full lifespan.

Thalassemia major: Effective iron chelation improves longevity. The most important factors associated with survival are the age at which chelation therapy was introduced and the success with which serum ferritin was maintained below 2500ng/mL (2500mcg/L). The natural course of untransfused thalassemia major is of recurrent infections, progressive cachexia, and death by 5 years of age. Aggressive transfusion therapy permits near-normal growth and development in childhood, but itself produces progressive organ damage, with death from iron overload in adolescence or early adult life. Transfusional iron overload is compounded by increased intestinal absorption of iron. The introduction of iron chelation therapy in the 1970s constituted a further therapeutic advance. In the US the mean age of patients with thalassemia major increased from approx. 11 years in 1973 by 80% to a median age of 23 years by 1994. In one series, the median age of survival was 31 years.

**Clinical Hallmarks:** Initiation of iron chelation therapy in a timely manner is key to improving prognosis in patients with thalassemia major and thalassemia intermedia. Liver biopsy with quantitative determination of iron provides crucial information, and cannot be replaced with noninvasive imaging studies.

**Progression of disease**

**Deterioration:** Full diabetes care is required in patients who develop diabetes mellitus. Full supportive care for liver disease is required in patients with hepatic fibrosis or hepatitis, and cirrhosis. Full supportive medical treatment is required for patients with cardiac hemosiderosis leading to congestive cardiac failure.

**Terminal illness:** Most patients with thalassemia major die from complications of iron overload and cardiac hemosiderosis leading to congestive cardiac failure. At a total body iron burden of 40g, organ function begins to fail, and at 60g or more, intractable cardiac failure has its onset. Supportive care should be offered, with symptomatic treatment.

**Clinical complications**

**Beta-thalassemia major:** General: Susceptibility to infections after splenectomy. Infections from blood transfusion. Intercurrent infections. Worsening of anemia during infections. Jaundice. Leg ulcers. Cholelithiasis. Pathologic fractures. Impaired growth rate. Delayed or absent puberty. Hepatic siderosis. Hemolytic anemia. Splenomegaly. Cardiac disease from iron overload. Aplastic and megaloblastic crises.

Skeletal abnormalities: Changes to the skull and facial bones. The outer and inner tables are thin, and perpendicular striations appear between the tables, resulting in an X-ray appearance suggestive of hair standing erect on the scalp. Pneumatization of the sinuses is delayed. Severe malocclusion. Pathologic fractures. Compression fractures of the vertebrae. Premature fusion of a segment of the epiphysis of the proximal end of the humerus or the distal end of the femur is relatively common. The ribs are broad, especially at their sites of articulation with the transverse processes of the vertebrae. Erosion of the marrow through the cortex at this site produces a paravertebral mass, which rarely extends into the spinal column to produce cord compression. In portions of the skeleton where red marrow normally is replaced by fat, lesions produced by thalassemia undergo regression; in portions supporting active erythropoiesis into adulthood, thalassemic changes progress with time.

Effects on growth and endocrine system: Growth retardation in early childhood is a consequence of severe anemia. It can be prevented (although not corrected) by an aggressive blood transfusion program. Even in children optimally transfused the preadolescent and adolescent growth spurt is delayed and curtailed, so that full potential stature is rarely realized. Pubescence is delayed and often is incomplete. In 250 adolescents who had had the benefit of both transfusion and chelation therapy, pubescence was lacking completely in 38% of girls and 67% of boys of age 12-18 years. Only 19% of the girls experienced menarche, and secondary amenorrhea intervened in one-third of this group. Boys may have active spermatogenesis but lack libido. Pituitary response to provocative stimulation is described as normal or deficient, suggesting a failure either of hypothalamic maturation or pituitary function. Overt diabetes mellitus and hypoparathyroidism are well documented. Insulin resistance and increased insulin secretion precede the development of diabetes. Most endocrine abnormalities are noted only in older, chronically transfused patients.

Cardiopulmonary complications: After the first decade, many patients experience one or more episodes of sterile pericarditis, characterized by pain, friction rub, and pericardial effusion without tamponade. The illness is self-limited. Both pericardial iron deposits and infection with rheumatogenic strains of streptococci have been invoked as possible causative factors. Myocardial hemosiderosis is the leading cause of death in transfused patients. Congestive heart failure and arrhythmias may be noted as early as age 6, but these conditions do not usually have their onset until the middle of the second decade. Despite careful medical management, most patients with symptomatic heart disease do not survive more than a few months. Echocardiography and radionuclide cineangiography permit detection of myocardial dysfunction before the development of overt disease.

Hepatobiliary disease: Liver enlargement in early life is related to extramedullary hematopoiesis, but later results from extensive cirrhosis. Iron deposits produce pathologic findings indistinguishable from those of idiopathic hemochromatosis. The incidence of gallstones is determined in large part by the aggressiveness of transfusion therapy. Recent estimates based on ultrasonographic evaluation place the incidence at between 2 and 4% .

Hepatitis: Patients with thalassemia acquire hepatitis most often from viruses contracted with blood transfusions. Advances in detection of bloodborne viruses has greatly diminished the risk of infection with blood transfusion. Patients who have substantial iron overload - ferritin levels >3000ng/mL (3000mcg/L) - have a much greater incidence of active liver injury than those with lesser iron burdens.

**Thalassemia intermedia:** Complications in adult life include pathologic fractures, cholelithiasis, and thoracic masses composed of hematopoietic tissue. The primary cause of premature death is myocardial hemosiderosis. Iron overload is more the result of augmented gastrointestinal iron absorption than of transfusional iron loading. The estimated amount of iron that subjects with thalassemia intermedia absorb on a standard diet is 3-10 times more than normal, and is attributed to a greatly expanded erythropoietic effort. By the third or fourth decades, the iron load may be similar in magnitude to that of transfusion-dependent thalassemic patients in their teens.

**Prevention**

Prenatal information: Genetic counseling. Prenatal diagnosis: study of globin genes performed on fetal cell DNA obtained by amniocentesis after 14 weeks.

Complication prevention: Evaluation for thalassemia by one year of age for offspring of adult thalassemia patients. Avoidance of infections. Prompt treatment of infections (after splenectomy, patients should have a supply of ampicillin to take if symptoms of infection appear). Periodic dental checkups. Avoidance of activities that could result in bone fractures.

Prenatal diagnosis and carrier detection: Family history is critical to detect thalassemia prenatally. Initial attempts to identify fetuses at risk for thalassemia major depended on fetal blood sampling during the second trimester. The application of recombinant DNA technology to carrier detection and prenatal diagnosis greatly enhanced its accuracy and availability. These approaches require that the specific mutation sought first is determined from a study of family members or from population surveys. The spectrum of beta-thalassemia mutations has been determined for most of the world's population at greatest risk, including the Italians, Sicilians, Greeks, Spaniards, Turks, Lebanese, Indians, Chinese, and Melanesians. The global development of prenatal screening programs in the early 1980s was monitored by the World Health Organization's International Registry for Prenatal Monitoring of Hereditary Anemias, providing a mechanism for the rapid dissemination of new knowledge.

**Screening:** The application of recombinant DNA technology to carrier detection and prenatal diagnosis has greatly enhanced its accuracy and availability. The spectrum of beta-thalassemia mutations has been determined for most of the world's population at greatest risk, including Italians and Sicilians, Greeks, Spaniards, Turks, Lebanese, Indians, Chinese, and Melanesians. These screening programs have had a major impact on the incidence of thalassemia major in parts of the world where its prevalence has exceeded available resources. The combined efforts of screening couples at risk and prenatal diagnosis have reduced the birth rate of children with thalassemia major by 70-90% in Sardinia, Greece, Cyprus, and Ferrara. Among patients with thalassemia living in Connecticut, the relative number of children younger than 5 years dropped from 34% to 4% between 1973 and 1985. A corollary of the decline in the birth rate of affected infants is an increase in the reproductive experiences of couples at risk of having children with thalassemia major. For example, Greek Cypriots with thalassemia minor in London, most of whom elected not to have children before the availability of prenatal testing, had children at the same rate as other London Cypriots after the introduction of prenatal diagnosis programs.

# INTERPRETATION

## MRSA (METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS)

....contd.

### Prevention and infection-control strategies

Alcohol, has proven to be an effective surface sanitizer against MRSA. Quaternary ammonium can be used in conjunction with alcohol to increase the duration of the sanitizing action.

The prevention of nosocomial infections involves routine and terminal cleaning. Non-flammable Alcohol Vapor in Carbon Dioxide systems (NAV-CO2 systems) have an advantage, as they do not attack metals or plastics used in medical environments and do not contribute to antibacterial resistance.

*MRSA boil*

In healthcare environments, MRSA can survive on surfaces and fabrics, including privacy curtains or garments worn by care providers. Complete surface sanitation is necessary to eliminate MRSA in areas where patients are recovering from invasive procedures. Testing patients for MRSA upon admission, isolating MRSA positive patients, decolonization of MRSA positive patients, and terminal cleaning of patients rooms and all other clinical areas they occupy is the current best practice protocol for nosocomial MRSA.

At the end of August 2004, after a successful pilot scheme to tackle MRSA, the UK National Health Service announced its *Clean Your Hands* campaign. Wards will be required to ensure that alcohol-based hand rubs are placed near all beds so that staff can hand wash more regularly. It is thought that if this cuts infection by just 1%, the plan will pay for itself many times over.

Mathematical models describe one way in which a loss of infection control can occur after measures for screening and isolation seem to be effective for years, as happened in the UK. In the "search and destroy" strategy that was employed by all UK hospitals until the mid 1990s, all patients with MRSA were immediately isolated, and all staff were screened for MRSA and were prevented from working until they had completed a course of eradication therapy that was proven to work.

Loss of control occurs because colonised patients are discharged back into the community and then readmitted: when the number of colonised patients in the community reaches a certain threshold, the "search and destroy" strategy is overwhelmed. One of the few countries not to have been overwhelmed by MRSA is the Netherlands: an important part of the success of the Dutch strategy may have been to attempt eradication of carriage upon discharge from hospital.

### MRSA in the Workplace

Current US guidance does not require workers in general workplaces (not healthcare facilities) with MRSA infections to be routinely excluded from going to work.

Unless directed by a healthcare provider, exclusion from work should be reserved for those with wound drainage that cannot be covered and contained with a clean, dry bandage and for those who cannot maintain good hygiene practices. Workers with active infections should be excluded from activities where skin-to-skin contact is likely to occur until their infections are healed. Healthcare workers should follow the Centers for Disease Control and Prevention's Guidelines for Infection Control in Health Care Personnel (USA).

To prevent the spread of staph or MRSA in the workplace, employers should ensure the availability of adequate facilities and supplies that encourage workers to practice good hygiene; that routine housekeeping in the workplace is followed; and that contaminated equipment and surfaces are cleaned with detergent-based cleaners or Environmental Protection Agency (EPA)-registered disinfectants.

### Epidemiology

Worldwide, an estimated 5 billion people carry some form of *S. aureus*; of these, up to 88 million (2.7% of carriers) are thought to carry MRSA.

Cystic fibrosis patients are often treated with multiple antibiotics, which must be administered in a hospital setting. Frequent hospital visits can increase exposure to MRSA, potentially increasing the rate of life-threatening MRSA pneumonia in this group.

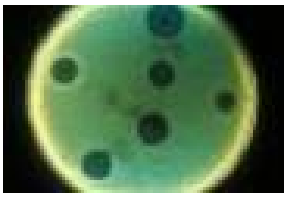
The risk of cross-colonization has led to the increased use of isolation protocols among these patients. In a hospital setting, patients who have received fluoroquinolones are more likely to become colonized with MRSA, this is probably because many circulating strains of MRSA are fluoroquinolone resistant, which means that MRSA is able to colonize patients whose normal skin flora have been cleared of non-resistant *S. aureus* by fluoroquinolones.

MRSA infections through skin contact have occurred in locker rooms and gymnasiums, even among healthy populations. MRSA has also been found in the public school systems. MRSA is also becoming a problem in pediatric settings, including hospital nurseries. A number of healthcare workers are now found to be carrying MRSA.

MRSA causes as many as 20% of *Staphylococcus aureus* infections in populations that use intravenous drugs. These out-of-hospital strains, or CA-MRSA, are more easily treated, though more virulent, than HA-MRSA. CA-MRSA apparently did not evolve *de novo* in the community but represents a hybrid between MRSA that spread from the hospital environment and strains that were once easily treatable in the community.

Most of the hybrid strains also acquired a factor that increases their virulence, resulting in the development of deep-tissue infections from minor scrapes and cuts, as well as many cases of fatal pneumonia.

### Strains

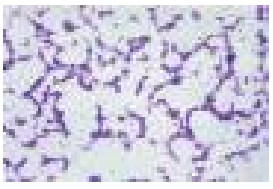


*Growth on culture media*

MRSA are EMRSA15 and EMRSA16. EMRSA16 is the best described epidemiologically; it originated in Kettering, England, and the full genomic sequence of this strain has been published. EMRSA16 has been found to be identical to the ST36:USA200 strain, which circulates in the United States, and to carry the SCC*mec* type II, enterotoxin A and toxic shock syndrome toxin 1 genes. Under the new international typing system, this strain is now called MRSA252. It is not entirely certain why this strain has become so successful, whereas previous strains have failed to persist.

One explanation is the characteristic pattern of antibiotic susceptibility. Both the EMRSA15 and EMRSA16 strains are resistant to erythromycin and ciprofloxacin. It is known that *Staphylococcus aureus* can survive intracellularly, and these are precisely the antibiotics that best penetrate intracellularly; it may be that these strains of *S. aureus* are therefore able to exploit an intracellular niche.

*Growth on culture media*



*Gram Stain*

In the United States, most cases of CA-MRSA are caused by a CC8 strain designated ST8:USA300, which carries *mec* type IV, Panton-Valentine leukocidin, PSM-alpha and enterotoxins Q and K, and ST8:USA400. Other community-associated strains of MRSA are ST8:USA500 and ST59:USA1000.

# TROUBLESHOOTING

## PREVENTION OF MRSA INFECTIONS

....contd.

### FAQs For the Workplace

### Standard Precautions

**1) Hand Hygiene**
Perform hand hygiene after touching blood, body fluids, secretions, excretions, and contaminated items, whether or not gloves are worn. Perform hand hygiene immediately after gloves are removed, between patient contacts, and when otherwise indicated to avoid transfer of microorganisms to other patients or environments. When hands are visibly soiled with blood or other body fluids, wash hands with soap and water. It may be necessary to perform hand hygiene between tasks and procedures on the same patient to prevent cross-contamination of different body sites.

**2) Gloving**
Wear gloves (clean nonsterile gloves are adequate) when it can be reasonably anticipated that contact with blood or other potentially infectious materials, mucous membranes, non intact skin, or potentially contaminated intact skin (e.g., of a patient incontinent of stool or urine) could occur. Remove gloves after contact with a patient and/or the surrounding environment (including medical equipment) using proper technique to prevent hand contamination. Do not wear the same pair of gloves for the care of more than one patient. Do not wash gloves for the purpose of reuse since this practice has been associated with transmission of pathogens.

**3) Mouth, nose, eye protection**
Use PPE to protect the mucous membranes of the eyes, nose and mouth during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions and excretions. Select masks, goggles, face shields, and combinations of each according to the need anticipated by the task performed.

**4) Gowning**
Wear a gown, that is appropriate to the task, to protect skin and prevent soiling or contamination of clothing during procedures and patient-care activities when contact with blood, body fluids, secretions, or excretions is anticipated.

**5) Appropriate device handling of patient care equipment and instruments/devices**
Handle used patient-care equipment soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of microorganisms to other patients and environments. Ensure that reusable equipment is not used for the care of another patient until it has been appropriately cleaned and reprocessed and that single-use items are properly discarded.
Clean and disinfect surfaces that are likely to be contaminated with pathogens, including those that are in close proximity to the patient (e.g., bed rails, over bed tables) and frequently-touched surfaces in the patient care environment (e.g., door knobs, surfaces in and surrounding toilets in patients' rooms) on a more frequent schedule compared to that for other surfaces (e.g., horizontal surfaces in waiting rooms).

**6) Appropriate handling of laundry**
Handle, transport, and process used linen to avoid contamination of air, surfaces and persons.

(to be contd.)

# BOUQUET

## In Lighter Vein

A psychiatrist was conducting a group therapy session with four young mothers and their small children. "You all have obsessions," he observed.
To the first mother he said, "You are obsessed with eating. You even named your daughter Candy."
He turned to the second mom. "Your obsession is money. Again, it manifests itself in your child's name, Penny."
He turned to the third mom. "Your obsession is alcohol and your child's name is Brandy."
At this point, the fourth mother got up, took her little boy by the hand and whispered, "Come on, Dick, let's go home."

Joe has been seeing a psychoanalyst for four years for treatment of the fear that he had monsters under his bed. It had been years since he had gotten a good night's sleep. Furthermore, his progress was very poor, and he knew it. So, one day he stops seeing the psychoanalyst and decides to try something different.
A few weeks later, Joe's former psychoanalyst meets his old client in the supermarket, and is surprised to find him looking well-rested, energetic, and cheerful. "Doc!" Joe says, "It's amazing! I'm cured!"
"That's great news!" the psychoanalyst says. "you seem to be doing much better. How?"
"I went to see another doctor," Joe says enthusiastically, "and he cured me in just ONE session!"
"One?!" the psychoanalyst asks incredulously.
"Yeah," continues Joe, "my new doctor is a behaviorist."
"A behaviorist?" the psychoanalyst asks. "How did he cure you in one session?"
"Oh, easy," says Joe. "He told me to cut the legs off of my bed.

## Wisdom Whispers

- Happiness is an in tray that is out.
- A man's work is rather the needful supplement to himself than the outcome of it.
- Happiness is enjoying your achievements, no matter how small.
- Think happy thoughts all achievements begin with an idea.
- Happiness is the hum of busy concentration in a classroom, like bees in a hive --- everything smacks of honey.
- Our minds are always at the level we believe ourselves to be at. Many a mailroom clerk could run the company if he or she were only asked.
- Being part of a team is better than being a solo contender.

## Brain Teasers

1. What do raised MPV, heightened P-LCR and enhanced PDW on cell counter result formats imply? Raised chances of…
   A. Vaso-occlusive phenomena B. Infections
   C. Arteritis D. Leukemias
2. H5N1 virus is related to the outbreaks of…
   A. Bird flu B. West-Nile fever
   C. Rocky mountain spotted fever D. Dengue fever
3. Phenazopyridium taken orally changes the colour of urine to…
   A. Orange-red, B. Bluish, C. Brownish, D. Reddish brown
4. The Makler, CellVu, and MicroCell methods are all used to count…
   A. Sperms, B. RBCs, C. Platelets, D. WBCs

Answers: 1. A, 2. A, 3. A, 4. A

## TULIP NEWS

# COAstat-1, THE COAGULATION ANALYSER, MAKES A GRAND ENTRY INTO THE HAEMOSTASIS MARKET

Since its launch in the year 2000, Tulip Instrumentation Division, has achieved great strides by introducing a wide range of instruments ranging from semi-automated systems to fully-automated systems.
Clinical chemistry analysers, Turbidimetry analysers, ELISA readers and washers, Coagulation analysers and Matrix gel centrifuges are some of the systems introduced to complement the accuracy, precision and reliability of the *in vitro* diagnostic testing products manufactured by Tulip Group.
Adding another feather to its cap, Tulip Group proudly introduces the launch of


COAstat-1 is a single channel coagulation analyzer engineered with the ideal optomechanical measuring system. COAstat-1 operates with an automatic counter to trigger off as soon as the start reagent is added and stops the moment the clot is formed. COAstat-1 is suitable to perform all routine coagulation tests such as PT, APTT, TT, Fibrinogen, factor assays and clot- based assays.

### SALIENT FEATURES

- The stirring action combined with optical measurement ensures that even the smallest fibrin clot is detected ***because*** of **Optomechanical measuring system.**
- Certainty and Uniformity in INR values ***because*** **COAstat-1 specific ISI values** are provided by the widely used thromboplastin's UNIPLASTIN & LIQUIPLASTIN.
- Optimized reaction environment ***because*** of **controlled incubation block temperature at 37°C ± 1°C.**
- Convenience in testing protocols ***because*** **16 cuvette positions and two reagent positions** are provided in the incubation block.
- Assured Service back up by Tulip's Engineering team ***because*** of **proven track record.**

COAstat-1 is based on the principle of **Reagent- Instrument Synergy** for achieving uniform INR values across the country.

### Importance of REAGENT- INSTRUMENT SYNERGY

The use of INR (International Normalized Ratio) has resulted in greater safety and effectiveness of Monitoring Oral anticoagulant therapy.
It is a well known fact that the ISI (International Sensitivity Index) assigned to a reagent depends on the instrument used for clot detection. When a manufacturer assigns ISI value to their reagent it is based on the instrument they use for clot detection. When the same reagent is used on different instruments the ISI starts to vary and so does INR. This leads to variation in INR reporting. It is therefore recommended that **instrument specific ISI values** be used for INR calculations. The use of COAstat-1 in synergy with Uniplastin/Liquiplastin will benefit the customer in producing uniform INR values.

### Benefits of using **UNIPLASTIN/LIQUIPLASTIN** in synergy with COAstat-1

Well-calibrated, standardized thromboplastin reagent with wide usage experience is classified as a National Reference Thromboplastin reagent by W.H.O. Another essential criteria for a National Reference Thromboplastin is to have a system of uniform reporting of results that are beneficial and safe for mobile patient.
Our Uniplastin, liquid stable PT reagent has virtually become the National Reference Thromboplastin reagent. Uniplastin/Liquiplastin are the mostly used thromboplastin reagents in the country and they provide the ISI specific for COAstat-1.

### Clot detection method of COAstat-1

Coagulometers available in market are based on any of the three clot detection methods

- Optical
- Optomechanical
- Electromechanical

The optical clot detection system is susceptible to interference from lipaemic, icteric or hemolysed samples.

Electromechanical and optomechanical systems such as COAstat-1 are relatively free from such interferences. Secondly, the stirring action combined with optical measurement of the Optomechanical measuring system ensures even the smallest clot is detected.

Therefore COAstat-1 with Uniplastin/Liquiplastin offers a synergistic solution for effective measurement of Haemostasis.

Tulip Group COAstat-1 Coagulation Analyzer

## In Synergy with TULIP'S haemostasis reagents!

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