TULIP NEWS

Tulip Group gets busy again to combat another spell of monsoon related diseases...

After the scorching spell of summer, comes the cool monsoon with a long-awaited relief. However the cool showers also bring with them a lot of diseases which are peculiar to monsoon. In India, more or less the monsoon begins in the 1st week of June. It canbe late or sometimes be earlier. The arrival, period and density of rainfall varies locationwise too.

Diseases that spread during monsoon are mainly water-borne, air-borne or vector-borne.

Some of the water-borne gastro-intestinal diseases like typhoid, paratyphoid , mosquito-borne disease like malaria, dengue fever and other diseases like Weil-Felix disease (rat fever), leptospirosis takes its toll on the population during this monsoon.

Infact last year, there was an upsurge of dengue fever. Collection of water in potholes and stagnation provide breeding grounds for mosquitoes and bring about the spread of diseases like malaria and dengue. Contamination of water due to low levels and unhygenic living conditions in the cities are mainly the cause of many monsoon ailments. Typhoid, paratyphoid fever is spread through contaminated water and food. Water gets contaminated with rat or cat urine containing microorganisms, and persons coming in contact with such water becomes victims of diseases like leptospirosis and rat fever. Climatic variations also aggravate the spread of the above diseases.

Like an eagle quick to react, Tulip Group with its array of rapid diagnostic tests is ready to combat the spread of such diseases

INFECTIOUS DISEASE RANGE

Product	Description	Pack
Enterocheck-WB (Device)	Rapid immunochromatographic tests for detection of IgM antibodies to *S.typhi* in serum/plasma and whole blood	10/25 Tests
Dengucheck-WB (Device)	Rapid immunochromatographic tests for detection of Dengue virus in human Serum, plasma and whole blood	10 Tests
Leptocheck-WB (Device)	Rapid immunochromatographic tests for IgM antibodies to Leptospirosis in human serum, plasma and whole blood	10 Tests

PARASITOLOGY RANGE

Product	Description	Pack
Falcivax (Device)	Rapid tests for Malaria Pv/Pf	1/10/25Tests
Parascreen (Device)	Rapid tests for Malaria Pan/Pf	1/10/25Tests
Parabank (Device)/(Dipstick)	Rapid tests for Malaria Pan	10/25Tests

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

VOLUME - III
ISSUE - XXIII
JUL / AUG 2007

The Crux

BIMONTHLY FORUM FOR THE LABORATARIANS

CONTENTS

Editorial

BioSpectrum the business of Biotech CIOL NETWORK

Extract from a report appearing in BioSpectrum, Volume 5 , Issue 7, July 2007, a widely acclaimed Biotech business magazine published by Cyber media publication, India ,

Tulip is No 1

■ TULIP GROUP IS LEADING THE WAY IN DIAGNOSTICS

Dear Customers,

We wholeheartedly owe this great success to you. This would not have been possible but for your tremendous support and patronage during the last 19 years of our service to you. We assure you that Tulip Group of Companies will continue rendering products and services to the best of your expectations for years to come.

■ THANK YOU CUSTOMERS ■

TÜV MANAGEMENT SERVICE ISO 9001

Tulip Group

DISEASE DIAGNOSIS

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Description

Disseminated intravascular coagulation (DIC) is an acquired coagulation disorder resulting from excessive activation of the coagulation system. It arises as a complication of a variety of life-threatening conditions; sepsis, massive tissue injury, and obstetric complications being amongst the most common. **In** response to cell injury or activation, monocytes and endothelial cells generate tissue factor, which activates the coagulation cascade. In DIC, the normal anticoagulant and fibrinolytic systems are overwhelmed and coagulation activation cannot be contained. The process rapidly becomes systemic, resulting in disseminated microvascular thrombi **Concurrently,** the risk of bleeding is also increased. Coagulation factors and natural anticoagulants are consumed during thrombosis, as are platelets, all of which become depleted. **The** fibrinolytic system is activated to dissolve the fibrin thrombi. As a result, plasminogen is consumed as it is converted into plasmin, which in turn breaks down fibrin clots. Fibrin degradation products (FDP) including D-dimers are formed, which can contribute to bleeding, because they impair fibrin clot formation and interfere with platelet function. **The** most frequent clinical presentation of acute DIC is bleeding, characterized by multiple ecchymoses and mucosal bleeding. Concurrent widespread microvascular thrombosis may lead to tissue ischemia and multiorgan failure. **In** chronic DIC the process is the same, but the activation of the coagulation system is low-grade, prolonged and more controlled, and there is usually time for compensatory responses to take place. The risk of bleeding is consequently lower, but the process gives rise to a hypercoagulable state which may result in venous or arterial thrombosis. **Treatment** is primarily that of the underlying cause, together with supportive measures as necessary (e.g. plasma or platelet replacement). **Mortality** in severe acute DIC exceeds 75%, usually owing to progression of the underlying disease, although DIC increases the risk of mortality beyond that associated with the primary disease.

Synonyms

Consumptive coagulopathy. **Defibrination** syndrome

Immediate action

Patient requires immediate transfer to a tertiary care hospital environment.

Prehospital care:

Monitor vital signs/ **Maintain** airway/ **Assess** and document extent of hemorrhage or thrombosis/ **Correct** hypovolemia as required.

Urgent action

Continue prehospital measures. **Attend** to life-threatening issues such as airway compromise or severe hemorrhage. **Determine** underlying cause of DIC and initiate therapy. **Consult** hematologist if DIC suspected. **Withdraw** specimens for anticoagulant studies. **Replace** blood products as indicated. **Begin** anticoagulant therapy if so advised.

Significant points

The pathogenesis of acute DIC is mediated by the widespread release of thrombin and plasmin into the circulation. Tissue factor is released from damaged tissue, leading to unregulated thrombin formation. **DIC** is always secondary, and increases the risk of mortality beyond that associated with the primary disease. The damage may be the result of sepsis (in 50% of cases), trauma, ischemia, excessive metabolic stress, heat, chemicals, and tumors. **DIC** is mainly a clinical diagnosis. Excessive thrombin release causes symptoms associated with tissue ischemia and multiorgan failure; secondary plasmin release, together with consumption and depletion of coagulation factors and platelets, may cause a range of bleeding phenomena. **Practitioners** should be aware of the clinical settings in which DIC can occur and familiar with the features that warn of its development. **The** importance of recognising the non-overt stage rather than the overt and late stage of DIC is becoming more apparent. **A** pathological degree of bleeding or thrombosis in an ill patient should alert physician to the possibility of DIC. **Confirmation** is by a range of hematological tests. Characteristic findings include prolonged clotting times (prothrombin time, activated partial thromboplastin time) elevated products of fibrin breakdown (D-dimer), low platelet counts, and low fibrinogen**. Recognition** and rapid, effective control of the underlying disease is paramount in ensuring successful management of acute DIC. **Treatment** is mainly that of the underlying disorder, together with circulatory or blood product support (e.g. Platelet replacement) as necessary. Occasionally anticoagulation is indicated. **The** removal of the cause does not necessarily alleviate the process in all cases. This is particularly relevant in patients with sepsis, where clinical deterioration may continue despite antibiotic treatment. **There** is some evidence that specific treatments that modify excess thrombin or plasmin activity (e.g. activated protein C) have reduced mortality in recent years. **Heparin** or low-molecular-weight heparin are often used in the treatment of chronic DIC. Warfarin is sometimes ineffective for long-term control.

Background

Cardinal features

Disseminated intravascular coagulation (DIC) is an acquired thromboembolic disorder arising as a complication of a variety of serious and life-threatening conditions. Consequently the clinical presentation will largely be determined by the underlying cause. **In** acute DIC, normal localised and compensated coagulation processes are overwhelmed and become systemic and maladaptive. **It** may present clinically at any point in the spectrum from bleeding to thrombosis, and organ failure is a common finding. **The** degree of coagulopathy and the dominance of thrombotic or bleeding sequelae depend on genetic and other host related factors. **Patients** are usually critically ill and will demonstrate a variety of signs according the severity of the disorder. **Hemorrhage** is the commonest presentation, presenting as bruising, petichae, mucosal oozing, prolonged bleeding at venepuncture or surgical sites, or bleeding from multiple sites including the gastointestinal tract. Clinical deterioration is noted with the development of hypovolemic shock, impaired consciousness, acute renal failure, hypoxia and progresssive respiratory failure. **Treatment** is essentially that of the underlying cause, together with supportive measures as necessary (e.g. plasma or platelet replacement). **Mortality** in severe DIC is high, exceeding 75%.

Causes

Common causes

DIC is essentially an abnormal response to tissue damage, and represents a complex interaction between the inflammatory and coagulation pathways. **The** normal response to tissue damage is a contained generation of thrombin (initiated by tissue factor release) at the site of the injury. **Thrombin** is pivotal in controlling haemostasis. It balances both procoagulant and anticoagulant activities, by activating the conversion of fibrinogen to fibrin and simultaneously activating the protein C anticoagulant regulatory pathway respectively. **Loss** of controlled thrombin generation and this homeostatic balance is the hallmark of DIC. **Mechanisms** perpetuating the generation of thrombin (intrinsic pathway activation, coagulation factor depletion, and systemic endothelial dysfunction) are pathogenic in its dissemination

Causes of acute DIC:

Severe infection and sepsis: the most common cause of DIC, accounting for > 50% of cases. About 10-20% of patients with Gram-negative bacteremia have evidence of DIC, but Gram-positive infections may also be causative. Systemic fungal infections, malaria, viral hemorrhagic fevers, herpes, and influenza virus are recognized causes. **Trauma:** serious tissue injury and burns can cause endothelial damage and release of tissue factor. Head injury and fat embolism are also causes. **Organ** destruction: DIC is seen in severe pancreatitis. **Obstetric** complications: Placental separation and amnotic fluid embolism may result in release of placental tissue factor, with generation of excess thrombin. **Severe** immunological reactions: e.g. transfusion with ABO incompatible blood cells, transplant rejection. Incompatible transfusion may rapidly cause DIC. Endothelial damage results from antigen-antibody reactions. **Malignancy:** acute promyelocytic leukemia, acute myelomonocytic or monocytic leukemia, disseminated prostatic carcinoma

Causes of chronic DIC:

Carcinoma: Adenocarcinoma is a common cause. Recurrent venous thromboembolism is a particular feature of this form of DIC (Trousseau's syndrome). Carcinomas may cause DIC by invasion of tissues and release of tissue factor, or by direct activation of the prothrombinase complex by a specific cancer procoagulant. Seen in both solid tumors and hematological malignancies, e.g. leukemias. **Liver** disease: DIC is seen in acute hepatic necrosis, fatty liver of pregnancy, insertion of a LeVeen shunt in a patient with chronic liver disease and ascites. **Vascular** abnormalities: e.g. hemangiomas, aortic aneurysm, empyema. DIC may follow localized intravascular coagulation if the local generation of thrombin is so great that coagulation factors and platelets are depleted, leading to a systemic hypocoagulable state with hemorrhagic complications. **Chronic** infection (e.g., tuberculosis, abscesses, osteomyelitis).

Rare causes

Acute DIC: Heatstroke, lightning strike, snakebite, recreational drugs (e.g. cocaine). Due to endothelial damage and release of tissue factor.

Chronic DIC: Retained dead fetus syndrome. Progresses over several weeks. At first the mother can compensate, and production and consumption of fibrinogen are temporarily in equilibrium. But decompensation with severe hypocoagulopathy eventually occurs unless the uterus is evacuated

Epidemiology

Frequency: DIC may occur in 30-50% of patients with severe sepsis.

Mortality: **Overall** mortality rate quoted at 50-75%. Rate depends largely on the underlying disorder, but DIC worsens prognosis of all disorders. **Septic** abortion with shock associated with DIC has a mortality rate of 50%. **Idiopathic** purpura fulminans associated with DIC has a mortality rate of 18%. **In** the setting of major trauma, DIC roughly doubles mortality rate.

Demographics

Age: Occurs at all ages. **Gender**: Occurs equally in males and females. **Race**: Occurs equally in all races.

Genetics: No genetic influence known. **Geography**: No influence known. **Socioeconomic status**: No influence known.

Diagnosis

Clinical presentation: In nearly all cases, the condition causing disseminated intravascular coagulation (DIC) will be apparent. **A** pathological degree of bleeding or thrombosis in an ill patient should alert physician to the possibility of DIC. **Diagnosis** is primarily clinical, with laboratory tests providing confirmation. When the clinical setting is consistent with DIC and results of routine tests (e.g., platelet count, prothrombin time, partial thromboplastin time, fibrinogen level) are all abnormal, a diagnosis can often be made without the need for more extensive testing. **Far** less commonly, bleeding caused by DIC may be the first symptom of the underlying condition, such as an occult malignancy. **Laboratory** tests can be very useful in the diagnosis of non-overt DIC.

Acute DIC: Presentation will be characterized by the underlying disorder (e.g. severe trauma, sepsis, placental abruption). **The** most obvious clinical symptom is bleeding, characterized by multiple ecchymoses and mucosal bleeding. **Insidious** underlying widespread microvascular thrombosis may lead to tissue ischemia and multiorgan failure.

Chronic DIC: An indolent, subacute or chronic disorder. The clinical features and laboratory findings in chronic DIC can be much more subtle than with acute DIC. **Hemorrhage** may not be a feature; thrombosis is most likely the predominant clinical manifestation. **Coagulation** factors may be normal, increased, or moderately decreased, as may the platelet counts. In some vascular and obstetrical disorders, mild to moderate consumption coagulopathy may be present.

Symptoms

Symptoms are predominantly related to those of the underlying disorder: **Widespread** bleeding at operative sites, line sites, and venepuncture sites. **Ischemic** or thrombotic fingers and/or toes. **Sudden** neurological changes due to thrombosis.

Signs

Acute DIC: Hemorrhage is the commonest presentation. Bruising, petichae, mucosal oozing, prolonged bleeding at venepuncture sites, secondary hemorrhage into surgical wounds are common. Bleeding from multiple sites should immediately suggest DIC. **Hypovolemia**, hypotension, shock. Usually associated with bleeding and/or underlying disease. **Skin** signs: Bruising and petichae are common. Purpura fulminans is a particularly severe form of DIC, with hemorrhagic skin necrosis and gangrene that is typically associated with infection. May occur during infection with Gram-negative bacteria or 7-10 days after chickenpox or scarlet fever in children.

Chronic DIC: Peripheral circulation: Frequent evidence of thrombotic disease, e.g. hypertrophy, absent pulses, discoloration. **Renal** signs. Microvascular thrombosis in the kidney is common, leading to acute renal failure. **CNS** signs: Disseminated microvascular thrombosis in the brain leads to generalized cortical and brain stem dysfunction with impaired consciousness and coma. **Respiratory** signs: Thrombosis and hemorrhage in the lungs cause hypoxia and progresssive respiratory failure. **GI** signs: Submucosal necrosis in the GI tract causes secondary hemorrhage.

NB: In chronic DIC the patient may be asymptomatic, with only laboratory abnormalities.

Differential diagnosis

Hemolytic uremic syndrome: Characterized by acute renal failure, microangiopathic hemolytic anemia and fever. Most common in children, often following acute infection.

Features: Most common in children < age 5 (DIC is most common in adults). **CBC** shows anemia (anemia and thrombocytopenia in DIC). **Peripheral** blood smear shows numerous schistocytes-fragmented, deformed or irregular RBCs. **Coagulation** studies usually normal. **Clinical** manifestations predominantly renal. **Prognosis** generally good

Immune (idiopathic) thrombocytopenic purpura: is an isolated thrombocytopenia with normal bone marrow and absence of other causes of thrombocytopenia. Often follows an acute infection.

Features: 40% of patients are < age 10. **Absence** of underlying disorder as in DIC. **CBC** shows isolated thrombocytopenia. **Coagulation** studies are normal. **Prognosis** good. **Schistocytes** are not present

Thrombotic thrombocytopenic purpura: A life-threatening multisystem disorder characterized by microvascular lesions with platelet aggregation. May be associated with pregnancy or diseases such as HIV, cancer, bacterial infections.

Features: Often associated with cancer. **CNS** changes (e.g. neurologic dysfunction, confusion, coma) predominate. **Peripheral** blood smear shows moderate to severe schistocytosis - often considered a defining characteristic. **Coagulation** studies usually normal. **Outlook** is poor if untreated; mortality is 95% in patients not treated with total plasma exchange or steroids.

Vitamin K deficiency: Vitamin K is essential for coagulation. Frequency is greatest in breastfed infants, often due to maternal malnutrition. Uncommon in adults; it usually occurs in association with poor diet, malabsorption, or liver disease.

Features: Easy bruisability. **Mucosal** bleeding, especially epistaxis, GI hemorrhage, menorrhagia, hematuria. **Prolonged** prothrombin time (PT). **Normal** platelet count (usually greatly reduced in DIC), normal fibrinogen level (usually low in DIC). **Activated** partial thromboplastin time (aPTT) usually normal, but may be extended in severe cases (extended in DIC). **Presence** of des-gamma-carboxyprothrombin (DCP), a sensitive marker for vitamin K deficiency, in plasma.

Liver failure: Frequently associated with coagulopathies; diagnosed on clinical signs of liver failure with laboratory confirmation.

Features: Skin signs, e.g. jaundice, palmar erythema, spider angiomata. **Breath** signs (fetor hepaticus). **Abdomen**: hepatolegaly or cirrhosis. **Neurological** signs, e.g. flapping tremor, dysarthria. **Abnormal** LFTs. **Abnormal** PT and aPTT. **Fibrinogen** may be normal (usually low in DIC). **Platelet** count may be low, but rarely drops below 40,000-50,000 even in severely affected patients. **Factors V** and VIII normal (low in DIC). **Schistocytes** are uncommon.

Chemotherapy-induced thrombotic microangiopathy: A thrombotic microangipopathy has been associated with the use of certain chemotherapeutic drugs.

Features: Treatment with mitomycin C can result in a thrombotic microangiopathy similar to thrombotic thrombocytopenic purpura. **Important** to keep in the differential as a trial of stopping the drug may allow the condition to resolve.

Workup

Diagnostic decision

An awareness of the clinical settings in which DIC can occur and the early clinical warning signs associated with its development will facilitate the physician to diagnose and treat DIC appropriately. In nearly all cases, the condition causing DIC will be apparent. **DIC** is primarily a clinical diagnosis; laboratory tests confirm the diagnosis and monitor replacement of blood components. **When** the clinical setting is consistent with DIC and results of routine tests (e.g., platelet count, prothrombin time, partial thromboplastin time, fibrinogen level) are all abnormal, a diagnosis can often be made without the need for more extensive. **The** acute phase response can result in shortening of the activated partial thromboplastin time and increased fibrinogen concentrations. These results may therefore be within the normal range, despite the presence of a significant consumptive coagulopathy. **Below** is the consensual definition of DIC, and diagnostic criteria for DIC, proposed by the Scientific Subcommittee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis

Essential condition: Does the patient have an underlying disorder known to be associated with DIC ? If so, order global coagulation tests (platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, soluble fibrin monomers or fibrin degradation products)

Score global coagulation test results:

Platelet count (> $100x10^9$/L= 0, 51-$100x10^9$/L = 1, < $50 x10^9$/L =2). **Elevated** fibrin-related marker, e.g. fibrin degradation products (no increase= 0, moderate increase = 2, strong increase= 3). **Prolonged** prothrombin time (< 3 sec= 0, > 3 but < 6 sec= 1, > 6 sec = 2) **Fibrinogen** level (>1.0 g/L= 0, < 1.0 g/L= 1)

Score: If 5 or greater, compatible with DIC. **If** <5, suggestive but not affirmative of non-overt DIC; repeat in 1-2 days

Non-overt DIC: Since early detection is vital, recognition of abnormal trends in laboratory results is also important. The ISTH have proposed criteria and guidance for the detection of early, non-overt DIC.

Examination

Cardiovascular system: Hypotension: postural hypotension is common. Check both erect and supine BP. **Tachycardia:** often present, resulting from hypovolemia. **Signs** of spontaneous or life-threatening hemorrhage, e.g hematuria, melena, epistaxis, gingival bleeding. **Signs** of subacute bleeding, e.g. purpura. **Signs** of diffuse or localized thrombosis, e.g. limb or digital ischemia. **CNS: Represent** signs of disseminated thrombosis seen in DIC. **Non-specific** altered consciousness. May range from inattention to stupor or coma. Test recent memory, also orientation for time, place, and person. **Focal signs**. Not always present in DIC. May be evidence of intracerebral bleeding, a grave prognostic sign **Respiratory system: Reflect** pleural thrombosis of bleeding. **Signs** of respiratory distress, e.g. Tachypnea. **Pleural** friction rub sometimes present **Gastrointestinal system: Reflect** pleural thrombosis of bleeding. **Is** there a history or evidence of hematemesis? **Do** stools show evidence of melena or hematochezia (passage of bright red blood)? **Genitourinary system Signs** of azotemia and renal failure (e.g. pallor or yellowish tinge, peripheral edema, ammoniacal breath). **Hematuria**: History or evidence of uterine hemorrhage **Skin: Reflect** pleural thrombosis of bleeding. **Petichae, Purpura. Hemorrhagic bullae. Acral cyanosis (intense, painful erythema of palms and soles, often culminating in vesicles and bullae). Skin** necrosis of lower limbs (purpura fulminans). **Localized** infarction and gangrene. **Wound** bleeding and deep subcutaneous hematomas. **Thrombosis**, evidence of ischemia (e.g. cold skin, hypertrophy). **Bleeding** at venepuncture sites.

Summary of tests

Laboratory tests for DIC fall broadly into two categories - tests of thrombin generation and of plasmin generation.

Thrombin generation:

Complete blood count: Thrombocytopenia due to thrombin generation is an almost universal finding in DIC. Production of platelets by the bone marrow is increased, but platelet survival is so short that thrombocytopenia, often severe, occurs. Blood film may show schistocytosis - fragmented, deformed or irregular RBCs (probably due to RBCs traversing vessels deformed by thrombin deposition)

Prothrombin time (PT) and Activated partial thromboplastin time (aPTT): Both may be prolonged, due to consumptive deficiency of the tenease and prothrombinase complexes and of prothrombin, the thrombin precursor. Times are elevated in 70% and 50% of patients respectively. Fibrinogen concentration: is frequently low (in approx. 50% of patients), owing to high fibrinogen consumption.

Plasmin generation:

Fibrinogen degradation products(FDP). Elevated plasma concentrations reflect generation of plasmin; abnormal levels are found in 85% of patients. The fibrin degradation product D-dimer is generated by plasmin lysis of cross-linked fibrin clots. The D-dimer test has high sensitivity and reliability for diagnosis of DIC, documenting the presence of both thrombin and plasmin. Chest X-ray may show pulmonary thrombosis or hemorrhage

There is no single diagnostic test for DIC. Diagnosis is strongly suggested by a combination of: **A** clinical condition consistent with DIC. **Thrombocytopenia** ($<100x10^9$/L). **Prolonged** PT and aPTT. **Reduced** fibrinogen level. **Elevated** FDP, e.g. presence of D-dimer

Tests

Complete blood count (CBC) Abnormal: The following are characteristic of DIC: **Platelets**$<100x10^9$/L.**Thrombocytopenia**, often severe, is almost universal in DIC. **Schistocytosis**: fragmented, deformed or irregular RBCs. Not always present. Severe schistocytosis might suggest an alternative diagnosis, e.g. thrombotic thrombocytopenia purpura or hemolytic uremic syndrome

Cause of abnormal result: Thrombocytopenia in DIC is caused by reduced platelet survival. **Schistocytosis** in DIC probably results from shearing of RBCs as they traverse platelet-fibrin plugs in arterioles and capillaries

Medications, disorders and other factors that may alter results

Thrombocytopenia is caused by: **Decreased** platelet production, e.g. aplastic anemia, leukemia, viral infections, toxins. **Splenic** sequestration or hypersplenism. Increased platelet destruction, e.g. Thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, drug-induced thrombocytopenia. Schistocytosis is also seen in: **Conditions** of blood flow turbulence, e.g. stenotic vessels, artificial heart valves. **Acquired** small blood vessel disorders, e.g. eclampsia, vasculitis. **Thrombotic** thrombocytopenic purpura, hemolytic uremic syndrome (usually moderate to severe)

Prothrombin time (PT) Abnormal: In DIC > 13.5s, but often > 2.5 times normal laboratory value.

Cause of abnormal result: In DIC, consumptive deficiency of thrombin precursors.

Medications, disorders and other factors that may alter results

Increased by: A number of hemorrhagic disorders, e.g. factor deficiency (fibrinogen II, V, VII, X), vitamin K deficiency, liver disease, primary fibrinolysis. **Anticoagulant** therapy, e.g. heparin, warfarin. Full anticoagulant therapy increases PT to 2-3 times normal laboratory values. **Disorders** with increased red blood cell mass (e.g. polycythemia vera). Excess anticoagulant in serum results in artificially prolonged PT.

Decreased by: Vitamin K supplementation. Thrombophlebitis. Glutethimide. Estrogens. Griseofulvin. Diphenhydramine. Elevated fibrinogen

Activated partial thromboplastin time (aPTT) Abnormal: Any value > 35s.

Schistocytosis In DIC, consumptive deficiency of thrombin precursors.

Medications, disorders and other factors that may alter results

Increased by: **Coagulation** factor deficiency (fibrinogen II, V, VIII, IX, X, XI, XII, high molecular weight kininogen (HMWK), prekallekrein). **Von** Willebrand's disease. Vitamin K deficiency, nephrotic syndrome, primary fibrinolysis, lupus anticoagulant syndrome. **Anticoagulant** therapy, e.g. heparin, warfarin

Fibrinogen concentration Abnormal: < 200mg/dL OR > 400mg/dL

Cause of abnormal result: Level usually decreased in DIC, because of consumptive deficiency of fibrinogen.

Medications, disorders and other factors that may alter results

Elevated: Fibrinogen is also an acute phase reactant, so it may be initially elevated by conditions where there is acute inflammation or damage and which may underlie DIC, e.g. severe infections, burns, carcinoma. **Oral** contraceptives/ Myocardial infarction/ Carcinoma/ Moderate elevations may be seen in pregnancy and cigarette smoking

Reduced: Anabolic steroids/ Androgens/ Phenobarbital/ Streptokinase/ Hereditary afibrinogenemia/ Liver disease/ Primary or secondary fibrinolysis/ Cachexia

D-dimer test Abnormal: Elevated in DIC (refer to local reference values).

Cause of abnormal result: Abnormal clot formation and lysis, indicating both excessive thrombin activity and excessive plasmin activity.

Medications, disorders and other factors that may alter results

The D-dimer test has > 98% specificity for thrombosis, but level may be elevated in other thrombotic disorders, e.g. DVT, pulmonary embolism. Level may be elevated in patients with malignancy. Sensitivity of D-dimer test is reduced in patients taking anticoagulants

Chest X-ray Abnormal: May show areas of thrombosis or hemorrhage in DIC.

Cause of abnormal result: Abnormal fibrin or plasmin activity.

Clinical Hallmarks

Consider DIC in any patient with multiple sites of excessive bleeding or clotting. **The** D-dimer test will often be elevated owing to cancer or liver failure, making it difficult to confirm the diagnosis of DIC in such patients. **The** number of schistocytes per high power microscope field may be rather low (2-4) compared to the much larger number (10-20) in thrombotic, thrombocytopenic purpura. **Chronic** DIC is common in patients with cancer, and may be associated with: non-bacterial thrombotic endocarditis, deep venous thrombosis, or pulmonary embolism.

Follow-up

Plan for review Further inpatient care: **Most** patients with acute DIC will require critical care management appropriate for the primary diagnosis. **Continuing** assessment of severity of DIC and response to treatment are required. The patient's PT, aPTT, platelet count, fibrinogen level and Hcrt should be regularly monitored (usually every 8h) and therapy adjusted accordingly. Effective therapy is indicated by the slowing or cessation of bleeding, normalization of PT, aPTT and decreased FDP or D-dimer levels

Further outpatient care: **Patients** who recover from acute DIC should be followed up by their PCP and/or a hematologist. **Patients** with low-grade or chronic DIC may be managed by a hematologist on an outpatient basis after initial assessment and stabilization. **Outpatient** medication may include anticoagulant and/or antiplatelet agents for those with low-grade DIC and/or antibiotics appropriate to the primary diagnosis

INTERPRETATION

SERUM CALCIUM

Normal Value

Colorimetric method: 8.7 to 11.0 mg/dL

OCPC method

Principle

Calcium in an alkaline medium combines with o- Cresolphthalein Complexone to form a purple coloured complex. Intensity of the colour formed is directly proportional to the amount of calcium present in the sample.

Arsenazo III method

Principle

Calcium combines specifically with Arsenazo III at a neutral pH to form a blue purple coloured complex. Intensity of the colour formed is directly proportional to the amount of calcium present in the sample.

Colorimetric Method

Clinical Relevance

A. Normal levels of total calcium combined with other findings

1. Normal calcium levels with overall normal findings in other tests indicate that there are no problems with calcium metabolism.
2. Normal calcium and abnormal phosphorus indicate impaired calcium absorption due to alteration of parathyroid hormone activity or secretion. In rickets, the calcium level may be normal or slightly lowered and the phosphorus level is depressed.
3. Normal calcium and elevated BUN indicates
   a. Possible secondary hyperparathyroidism. Initially lowered serum calcium results from uremia and acidosis. The lower calcium level stimulates the parathyroid to release parathyroid hormone, which acts on bone to release more calcium.
   b. Possible primary hyperparathyroidism. Excessive amounts of parathormone cause elevation in calcium levels, but secondary kidney disease would cause retention of phosphate and concomitant lower calcium.
4. Normal calcium and decreased serum albumin. This is indicative of hypercalcemia, since there should be a decrease in calcium when there is a decrease in albumin because of the 50% of serum calcium that is protein-bound.

B. Hypercalcemia (increased total calcium).

Hypercalcemia is associated with many disorders, but its greatest clinical importance rests in its association with cancer, including multiple myeloma, parathyroid tumours, nonendocrine tumours producing a parathormone-like substance, and cancers metastasizing to the bone. Increased calcium levels are caused by or associated with

1. Hyperparathyroidism due to
   a. Parathyroid adenoma associated with hypophosphatemia
   b Hyperplasia of parathyroid glands associated with hypophosphatemia
2. Cancer
   a. Metastatic cancers involving bone cancers of lung, breast, thyroid, kidney, and testes may metastasize to bone
   b. Hodgkin's disease other lymphomas
   c. Multiple myeloma in which there is extensive bone destruction
   d. Lung and renal cancers may produce parathormone resulting in symptoms of hypercalcemia
   e. Sarcoidosis due to increased IgG or IgA
   f. Leukemia
3. Addison's disease
4. Hyperthyroidism
5. Paget's disease of bone (also accompanied by high levels of alkaline phosphatase)
6. Prolonged immobilisation
7. Bone fractures combined with bed rest
8. Excessive intake of vitamin D
9. Prolonged use of diuretics, thiazides
10. Respiratory alkalosis
11. Milk alkali syndrome (history of peptic ulcer could indicate excessive intake of milk and antacids)

C. Hypocalcemia (decreased total calcium levels)

Commonly caused by/associated with

1. Pseudohypocalcemia (hypoproteinemia). Actually, what looks like hypocalcemia is really a reflection of diminished albumin (as revealed by a serum protein electrophoresis). It is the reduced protein that is responsible for the low calcium, since 50% of the calcium total is protein-bound. (Excessive use of IV fluids will decrease albumin levels and thus decrease the amount of calcium).
2. Hypoparathyrodism (primary is very rare) may be due to accidental removal of parathyroid glands during a thyroidectomy, irradiation, hypomagnesemia, GI disorders, renal wasting.
3. Hyperphosphatemia
   Due to renal failure, laxatives, cytotoxic drugs
4. Malabsorption
   Due to sprue, celiac disease, pancreatic dysfunction (fatty acids combine with calcium and are precipitated and excreted in the feces).
5. Acute pancreatitis
6. Alkalosis (calcium ions become bound to protein)
7. Osteomalacia
8. Diarrhea
9. Rickets

D. Increased ionised calcium

1. Primary hyperparathyroidism
2. Ectopic parathyroid hormone producing tumours
3. Excess intake of vitamin D
4. Various malignancies

E. Decreased ionised calcium

Primary hypoparathyroidism is associated with low ionised calcium level and low total calcium level

BOUQUET

IN LIGHTER VEIN

WISDOM WHISPERS

- A good marriage would be between a blind wife and a deaf husband.
- The best way to get husbands to do something is to suggest that perhaps they are too old to do it
- When a man steals your wife, there is no better revenge than to let him keep her.
- An archaeologist is the best husband a woman can have; the older she gets the more interested he is in her.
- A sweetheart is a bottle of wine, a wife is a wine bottle.

BRAIN TEASERS

1. Which of the following conditions shows spurious macrocytosis on automated machines?
   A. Auto-agglutination B. Liver Disease C. Hypothyroidism
   D. Reticulocytosis
2. Down's, Fanconi's and Bloom's syndromes can be associated with which of the following disorders?
   A. Acute leukemia B. ITP C. CML D. DIC

Answers: 1. A, 2. A

TROUBLE SHOOTING

GUIDELINES FOR BLOOD GROUPING AND ANTIBODY TESTING IN PREGNANCY (...continued)

Women with immune anti-K, or other Kell system antibodies.

HDN due to anti-K is characterised by low haemoglobin, but amniotic and/or cord bilirubin levels are not generally reported. The fetal anaemia associated with anti-K may be due to the inhibition of K positive erythroid early progenitor cells or to promotion of their immune destruction.

While it has been stated that the severity of HDN due to anti-K is not correlated with titre of the antibody reports of affected pregnancies are associated with antibodies with a titre of at least 32. However, samples from women with anti-K should be titrated by IAT when first identified in the pregnancy, as for any clinically significant antibody.

The majority of cases of anti-K in pregnant women are the consequence of previous K positive transfusions. The incidence of anti-K could be reduced by selecting K negative units for transfusion to females with potential for childbearing. Therefore selecting K-negative units for females under the age of 60 is considered good practice. However urgent transfusions should not be delayed if suitable K-negative units are not immediately available.

The transfusion history of women with anti-K should be established and a sample from the father of the fetus should be K typed. If the woman has not been transfused and the father is K positive, the patient should be referred to a specialist unit and titration of samples should be performed at monthly intervals to 28 weeks, and at fortnightly intervals thereafter. If the father is K negative and a confidential enquiry establishes paternity, no further samples are required until 28 weeks when the antibody should be titrated and further antibodies excluded.

The fetus can be K typed from an amniocentesis sample, but this sampling involves physical intervention with associated risks to the fetus and of stimulating the antibody level.

Recommendation 8:

Cases of anti-D, anti-c and anti-K [unless the father is confirmed K negative] should be assessed at monthly intervals to 28 weeks gestation and at fortnightly intervals thereafter. Such cases must be referred to a specialist fetal medicine unit if the antibody reaches the critical level and/or the level is rising significantly. (Grade B)

Women with other red cell antibodies

Only IgG antibodies are capable of entering the fetal circulation. Red cell antibodies with a significant IgG component are detectable by IAT. 'Cold reactive', IgM and low affinity antibodies to high frequency antigens [e.g. Cr1 and CR4 related antibodies] have not been implicated in HDN.

In addition to anti-D, -c and K, the following specificities are most commonly associated with HDN: anti-C [-Ce], -E [-cE], -Fya, and -Jka. However, many other specificities have been reported as the cause of HDN, and a summary, by blood group system, is given by Daniels et al. In all these cases re-testing at 28 weeks generally provides sufficient information to determine management of the pregnancy. A medical decision should be made regarding the more frequent testing of women with a previous history of children with HDN. Where an antibody has been detected, testing of both booking and 28-week samples should include titration and testing by IAT against reagent cells heterozygous for the corresponding antigen. Careful attention to technique is necessary to minimise the variables in the method and titrating the anti-D standard in parallel, as an internal control, is recommended. Given the wide spread implementation of recommended protocol, prophylactic anti-D may be present in addition to alloantibodies and selecting D negative reagent cells for titration should be considered.

In general, a titre of 32 or greater is likely to cause HDN, although a clear-cut association between titre and HDN has not been established.

The presence of any further antibodies should be established and any clinically significant antibodies should be titrated as above.

Recommendation 9:

Clinically significant antibodies, other than anti-D, -c or K, should be assessed, and other antibodies excluded, at 'first appointment' and at 28 weeks gestation. (level IIb Grade B)

Recommendation 10:

All women who have previously had an infant affected by HDN should be referred before 20 weeks to a specialist unit for advice and for assessment of fetal haemolysis, irrespective of antibody level. (Level IIb Grade B)

PATERNAL TESTING

Where a clinically significant antibody capable of causing HDN, particularly anti-D, anti-c or anti-K, is present in a maternal sample, determining the father's phenotype provides useful information to predict the likelihood of a fetus carrying the relevant red cell antigen. The complexities of paternal testing and the potential for misidentification of the father need to be acknowledged .

FETAL GENOTYPING

When a clinically significant antibody of high concentration is present, and/or the woman has a history of HDN and the father is heterozygous for the relevant antigen, it can be clinically relevant to determine the genotype of the fetus. Until recently fetal DNA for genotyping by PCR assay was obtained by amniocentesis or chorionic villus sampling. These invasive techniques carry a small risk of spontaneous miscarriage and may boost maternal antibody levels.

A technique is now available for the accurate determination of fetal D genotype from samples of maternal peripheral plasma.

The same testing service for fetal c and K type is under development and should be used as it becomes available.

REPORTS OF LABORATORY INVESTIGATIONS

In addition to blood group and specificity of any red cell alloantibodies present, reports must inform the clinician[s] responsible for the woman's antenatal care of the likely significance of the antibody/ies, with respect to both the development of HDN and transfusion problems. Reports should also, where relevant, alert the clinician to the need to refer the woman to a specialist unit.

Details of the timing of further samples required should also be given.

Recommendation 11:

Women with clinical significant red cell antibodies should be issued with a card giving details of the antibody.

Action at the time of birth

D negative women with no immune anti-D

A maternal sample and a cord blood sample should be taken. The cord blood sample should be used to determine the infant's D group, thus identifying women who must receive post-delivery prophylactic anti-D immunoglobulin.

Since there is minimal evidence that DVI on fetal red cells can cause maternal sensitisation, and since detecting DVI on cord samples would require different reagents from those used on adult patients, with the potential for confusion and inappropriate testing of adult patients, testing cord samples for DVI is not recommended, i.e. anti-D reagents for typing cord samples should not react with DVI. Most examples of weak D antigen can be easily detected by selecting high affinity anti-D reagents.

A test should be performed on the maternal blood sample to detect and estimate the volume of fetal cells present, so that additional anti-D immunoglobulin may be given if the feto-maternal haemorrhage [FMH] exceeds 4mL. Samples showing a FMH result of more than 4mL by acid elution technique, should be referred for a more accurate assessment of the volume of bleed by flow cytometry. The dose calculation for prophylactic anti-D is based on the volume of FMH.

Direct Antiglobulin Test [DAT] on cord samples

Routine DAT on the cord samples of D positive infants born to D negative women

This is not recommended. It has been shown that following recommended protocol, anti-D immunoglobulin can cross the placenta, enter the fetal circulation and bind to fetal D antigen sites. Consequently, up to 3-6% of D positive cord samples have been found to have a positive DAT and this may result in unnecessary additional investigations being undertaken and in anxiety for the parents. There is evidence that prophylactic anti-D does not cause destruction of fetal/neonatal red cells .

DAT on infants of women who have IAT reactive red cell antibodies.

Whenever the maternal serum has been found to contain an immune, IAT reactive red cell antibody/ies a DAT should be done on the cord sample. A positive DAT in itself is not diagnostic of HDN. However if it is positive, the infant's haemoglobin and bilirubin levels should be checked to diagnose/exclude HDN. Where the DAT is positive and the infant shows symptoms of HDN, a red cell eluate may be helpful to confirm the red cell antibody specificity. In cases of suspected HDN wherever possible the red cells from the cord should be tested for the corresponding antigen[s].

Infants who have been transfused in utero with units negative for the relevant antigen the DAT may be negative and the baby may type as antigen negative for several months after birth

Recommendation 12:

All infants born to women who have clinically significant antibodies should be closely observed for evidence of HDN. A DAT should be performed and if positive, haemoglobin and bilirubin levels should be measured. (Level IV, Grade C)

Pre and Post delivery testing of maternal samples

Routine antibody screening of immediate pre and/or post delivery samples is not required, as this information does not influence management of the pregnant woman or her infant. Blood grouping and antibody screening of maternal samples other than confirmatory D typing should be undertaken only if pre-transfusion compatibility tests are required.