5. REVIEW OF LITERATURE

1. TRANSFUSION RELATED COMPLICATIONS

a. Risks and factors contributing to transfusion related adverse events

Certain factors may increase the likelihood of a transfusion related adverse effects and these include

- Individual patient characteristics
- Blood component
- Equipment
- Concomitant medications and intravenous fluids

(I) Individual patient characteristics

Patients who have previously been transfused, multiparous women and patients receiving emergency uncross-matched transfusion are at increased risk of immediate and delayed haemolytic transfusion reactions. Febrile, allergic and anaphylactic reactions occur more commonly in multiparous women and in patients with IgA deficiency and anti-IgA antibodies.

(II) Blood component

Platelet and granulocyte transfusions are associated with the highest rates of febrile non-haemolytic transfusion reactions. The incidence of such reactions can be modified by changes to the blood component processed by leucodepletion. All red cell and platelet components produced by the blood service are leucodepleted. Platelets, which require storage at 20–24ºC, are associated with higher rates of bacterial contamination than red cells, which are routinely refrigerated. All platelets are subject to routine bacterial culture and screening for the detection of a bacterial contaminated product. Transfusion of fresh frozen plasma is associated with a higher risk of allergic reactions. Some reactions are mild, but severe life-threatening reactions such as anaphylaxis and Transfusion-related acute lung injury (TRALI) may also occur.

(III) Equipment

All blood components are administered through specifically designed intravenous sets, which incorporate a 170–200 micron filter to remove debris and clots that may have accumulated during storage. All equipment must be specifically designed, and assessed as safe for blood administration and used in accordance with the manufacturer‘s operational procedures.

(IV) Concomitant medications and intravenous fluids

No medication or solutions should be added to or infused through the same tubing with blood or components except 0.9% Sodium Chloride Injection BP. ABO-compatible plasma or 4% Albumin or other suitable plasma expanders may be used as directed by the physician. Crystalloid and colloid solutions containing calcium must never be added to or administered through the same intravenous line as blood

or component collected in an anticoagulant containing citrate, which may interfere with the anticoagulant effect, leading to coagulation.

(V) Procedures

Clear written procedures and adequate staff training are essential for all aspects of the clinical transfusion process— from initial assortment of samples for pre-transfusion testing through to final documentation of the transfusion process and outcome. There are numerous chances for error during this process if procedures are not strictly followed. Recent reports (2005) from the UK indicate that nearly 60% of adverse events associated with transfusion are a result of 'wrong blood to wrong patient. The majority of these errors are the result of failure to follow procedures, or inadequate or unclear procedures (10)

Table 1: Hot spots for errors in the transfusion process(9)

Location	Critical point	Health care professional
Blood donor centre or session	Identification of donor. Assessment of donor for safety of donation. Identification of donation	Donation session staff
Blood centre	Processing and issue	Blood centre laboratory staff
Ward or outpatient clinic	Assessment of recipient and decision to transfuse	Medical and nursing staff
Ward	Prescription request form	Medical and nursing staff
Ward or phlebotomy clinic	Sampling for pre-transfusion testing. Transfer of sample to laboratory	Doctors, midwives, nurses, phlebotomists, Porters
Laboratory	Reception, testing, allocation of component, labeling and issue	Medical laboratory assistants, Biomedical scientists
Blood transfusion laboratory or remote blood refrigerator	Collection from storage site	Porters, Nursing staff
Ward, operating theatre, emergency department	Beside administration checks, monitoring or adverse incidents	Nurses, midwives, doctors, operating department practitioners

b.Errors resulting in 'wrong blood' incidents(11)

(I) Prescription, sampling and request

- Failure to identify correct recipient at sampling
- Correct patient identity at sampling but incorrectly labeled sample
- Selection of incompatible products in an emergency
- Transfusion laboratory
- Took a wrongly identified sample through testing
- Tested the correct sample but misinterpreted the results

- Tested the correct sample but recorded the results on the wrong unit of blood as compatible for the patient
- Incorrect serological reasoning, example: O-positive FFP to non-O-positive recipient

(II) Collection of unit

- Failure to check recipient identity with unit identity.
- Bedside administration error
- Checking of recipient identity through case notes on prescription chart, rather than that on the wristband.
- Wristband missing or erroneous

(III) Prevention of 'wrong blood' incidents(11)

Prevention of multiple errors which can contribute to the transfusion of ABO-incompatible red cells must depend upon the creation of an effective quality system for the entire process, which will involve;

- Adherence to national guidelines and standards
- Local procedures which are agreed, documented and validated
- Training and retraining of key staff
- Regular error analysis and review
- Reporting to local risk management committee
- Reporting to national haemovigilance schemes to contribute to the understanding of the extent and underlying the causes

c.Types of transfusion related complications

Transfusion-related complications can be categorized as acute or delayed, which can be divided further into the categories of noninfectious(Table-2) and infectious. The American Association of Blood Banks (AABB) uses the term "noninfectious serious hazards of transfusion" to classify noninfectious complications. Transfusion-related infections are less common because of advances in the blood screening process; the risk of contracting an infection from transfusion has decreased 10,000-fold since the 1980s. Noninfectious serious hazards of transfusion are up to 1,000 times more likely than an infectious complication. However, there has been no progress in preventing noninfectious serious hazards of transfusion, despite improvements in blood screening tests and other related medical advances. Therefore, patients are far more likely to experience a noninfectious serious hazard of transfusion than an infectious complication.

(I) Non-Infectious Complications

Table 2: Non-infectious transfusion related complications

Acute	Delayed
Acute haemolytic reaction	Delayed haemolytic reaction
Allergic reaction	Iron over load
Anaphylactic reaction	Microchimerism
Coagulation problems in massive transfusion	Over-transfusion or under-transfusion
Febrile non-haemolytic reaction	Post transfusion purpura

Metabolic derangements	Transfusion associated graft-versus-host disease
Mistransfusion (transfusion of the incorrect product to the incorrect recipient)	Transfusion related immunomodulation
Septic or bacterial contamination	
Transfusion associated circulatory over load	
Transfusion related acute lung injury	
Urticarial reaction	

d.Another way of Classification of Transfusion reactions(11)(12) is shown below

Immunologic

- Acute haemolytic transfusion reaction
- Delayed haemolytic transfusion reaction
- Transfusion-related acute lung injury (granulocyte antibody model)
- Allergic (Urticarial) reaction
- Anaphylactic reaction
- Transfusion-related graft-Vs-host disease

Infections

- Septic transfusion reaction (bacterial contamination)
- Viral infection (HIV, HTLV, HBV, HCV, WNV)

Others (Non immunologic)

- Circulatory overload
- Transfusion-related acute lung injury (lipid activators of neutrophil model)
- Febrile non-haemolytic transfusion reaction (cytokine, and other BRM mediated)

(I) Acute reactions

i. Acute haemolytic reaction

Hemolytic transfusion reactions are caused by immune destruction of transfused RBCs, which are assaulted by the recipient's antibodies. The antibodies to the antigens of the ABO blood group or alloantibodies to other RBC antigens are produced after immunization through a previous transfusion or pregnancy.

There are 2 classes of hemolytic transfusion responses: intense and deferred. Non-immune causes of acute reactions include bacterial overgrowth, improper storage, infusion with incompatible medications or inconsistent prescriptions and infusion of blood through lines containing hypotonic solutions or small-bore intravenous tubes.

In acute hemolytic transfusion reactions, there is a destruction of the donor's RBCs within 24 hours of transfusion. Hemolysis may be intravascular or extra-vascular. The most common type is extravascular hemolysis, which occurs when donor RBCs coated with immunoglobulin G (IgG) or complements are attacked in the liver or spleen.Intravascular hemolysis is a severe form of hemolysis caused by ABO antibodies. Symptoms of acute hemolytic transfusion reactions include fever, chills, rigors, nausea, vomiting, dyspnea, hypotension, diffuse bleeding, hemoglobinuria, oliguria, anuria, pain at the infusion site; and chest, back, and abdominal pain.19 Associated complications are clinically significant anemia, acute or exacerbated renal failure, disseminated intravascular coagulation, need for dialysis, and demise secondary to complications. The incidence of acute hemolytic reactions is approxi-mately one to five per 50,000 transfusions. From 1996 to 2007, there have been 213 ABO-incompatible RBC transfusions with 24 deaths. Estimated risk per unit transferred: 1:38,000 to 1:70,000 (11).

ii.Allergic reactions

Allergic reactions vary from mild (urticarial) to life threatening (anaphylactic). Urticarial allergic reactions are outlined by hives or pruritus. Patients experiencing allergic transfusion reactions are susceptible to the antigens within the donor unit. These antigens are soluble, and the associated reaction is dose-dependent. Allergic transfusion reactions occur in 1 to 3 percent of transfusions.

Patients with anaphylactic transfusion reactions, like those with urticarial reactions, may present with hives, however they are distinct in developing hypotension, bronchospasm, stridor, and gastrointestinal symptoms. Anaphylaxis occurs in response to a recipient's presensitization to a range of proteins in donor plasma. For example, anaphylaxis occurs because of donor IgA being infused into a recipient who is IgA deficient and has preexisting circulating anti-IgA. In addition, anti–human leukocyte antigen (HLA) antibodies and anticomplement antibodies have been linked to anaphylactic reactions, which are estimated to occur in one in 20,000 to 50,000 transfusions. Prevention of anaphylactic transfusion reactions includes avoiding plasma transfusions with IgA in patients renowned to be IgA deficient. Cellular products (e.g., RBCs, platelets) may be washed to remove plasma in patients with IgA deficiency. The simplest precaution is observation of the patient throughout the initial quarter-hour of transfusion(11)

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iii.Anaphylactoid/Anaphylactic Reaction

These types of reactions occur when a plasma-containing component is transfused to an individual with preexisting antibody directed at an epitope contained within the donor plasma. The resulting antigen-antibody complex triggers mast cell degranulation and other mechanisms of anaphylaxis (12).Prevention of anaphylactic reactions with future transfusions involve verification that the recipient is IgA deficient with IgA antibody. Some institutions prefer to check first for the presence of IgA in the recipient and then to test individuals who lack IgA for the presence of anti-IgA. In case where anti-IgA can be demonstrated, subsequent transfusion of plasma-containing components (RBCs, platelets, Cryoprecipitated AHF, and FFP) must be from IgA-deficient donors. Because only nanogram amounts of IgA are required to participate in anaphylactoid reaction, conventional washing of cellular blood components will not sufficiently reduce the associated plasma. However, frozen deglycerolized RBCs are acceptable, as which are standard RBC units washed with 3 liters of normal saline.

iv.Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is non cardiogenic pulmonary edema causing acute hypoxemia that occurs within six hours of a transfusion and has a clear temporal relationship to the transfusion. Patients with TRALI do not have any other risk factors for acute lung injury. Antineutrophil cytoplasmic antibodies or anti-HLA antibodies activate the recipient's immune system, resulting in massive pulmonary edema. Activated neutrophils in the lungs may also secrete proteolytic enzymes, leading to more tissue damage. Optimal methods for detecting these antibodies in donated products have yet to be determined.

Aside from the need for prompt cessation of transfusion, the most vital reason for identifying episodes of TRALI is to identify donors who are potentially at the risk of precipitating TRALI in other recipients. If a donor with granulocyte or HLA antibodies can be identified as the cause, that donor should be deferred from donating plasma-containing blood components in future. In addition to referring donors implicated in TRALI, several donor strategies have been proposed to reduce the likelihood of first episodes of TRALI. This include the collection of plasma solely from male donors, deferral of multiparous women from donating plasma and testing of multiparous donors for antibodies, donors found to be antibody positive should be deferred from donating plasma-containing components. Use of pooled solvent/detergent (SD) treated plasma and storage of platelets in additive solution rather than plasma is other alternatives (12). Estimated risk per unit transfused: 1:5000 to 1:90,000 (11).

v. Febrile non-hemolytic transfusion reactions

An FNHTR is defined as a rise in body temperature of at least 1.8°F (1°C) above 98.6°F (37°C) within 24 hours after a transfusion; it may involve rigors, chills, and discomfort. The fever occurs more often in patients who aretransfused repeatedly and in patients who are pregnant. Leukoreduction, which is the removal or filtration of white blood cells from donor blood, has decreased FNHTR rates. FNHTRs are caused by platelet transfusions more often than RBC transfusions and have an incidence that ranges from less than 1 to more than 35 %.

Two mechanisms have been proposed to explain FNHTRs: a release of antibody-mediated endogenous pyrogen, and a release of cytokines. Common cytokines that may be associated with FNHTRs include interleukin-1, interleukin-6, interleukin-8, and tumor necrosis factor.FNHTR could be a diagnosing of exclusion that can be made only after ruling out other causes of fever (e.g., hemolysis, sepsis).

Leucocyte reduction decreases the incidence, however doesn't prevent them entirely (12).Estimated risk per unit transfused: 1:17 to 1:200 (Red blood cells); 1:3 to 1:100 (platelets) (11).

vi. Transfusion associated circulatory overload

Transfusion-associated circulatory overload is the consequences of a rapid transfusion of a blood volume that is more than what the recipient's circulatory system deals with. It is not associated with an antibody-mediated reaction. Those at highest risk are recipients with underlying cardiopulmonary compromise, renal failure, or chronic anemia, and infants or older patients. Signs and symptoms like tachycardia, cough, dyspnea, hypertension, elevated central venous pressure, elevated pulmonary wedge pressure, and widened pulse pressure. Cardiomegaly and pulmonary edema are often seen on chest radiography.

The diagnosis is made clinically, but may also be assisted by measuring brain natriuretic peptide levels, which are elevated in response to an increase in filling pressure. A study comparing patients who have transfusion-associated circulatory overload with patients who have TRALI found significantly greater levels of brain natriuretic peptide in those with transfusion-associated circulatory overload. The treatment is diures is to decrease volume overload and the patient should be placed in an upright position, if possible supplement with oxygen (11,13). As a general guide, infusion should be at a rate not to exceed 2 to 4ml/kg/hour and the rate should be lower (~1ml/kg/hour) for patients with circulatory overload. Estimated risk: Common (14).

vii. Septic Transfusion Reaction (Bacterial Contamination)

Before the 2003 implementation of requirements that blood banks or transfusion service use methods to limit and detect bacterial contamination in all platelet components, it was estimated that between 1 in 1000 and 1 in 3000 platelet units were contaminated with bacteria. Contaminated RBC units are more likely to contain gram negative organisms and thus are typically associated with more severe sepsis, possible even with fatal gram negative septic shock. Platelet units or main contrast, are more often contaminated with gram positive organisms. Mortality rates for platelet associated sepsis are around 25% and for red cell associated are closer to 70% (13). The incidence of bacterial contamination of red cells has been estimated to be 1:31,000 with an overall fatality rate of 1:1,000,000. The incidence of bacterial contamination in platelets may be as high as 1:700 for pooled random-donor platelet concentrates and 1:4000 for single donor platelet concentrates (15, 16). Estimated risk per unit transfused: 1:31,000(red blood cells); 1:700 (pooled random-donor platelet concentrates); 1:4000 (single-donor platelet concentrates) Mediators: endo-toxins produced by gram-negative bacteria (11). Measures to reduce the risk of bacterial contamination includes donor selection procedures, Blood Collection, Components storage times, Pre-transfusion, screening of components, Leukocyte filtration, Phagocytosis, Photochemical determination of cellular blood components (17).

viii.Hypotension Associated with Bedside Leukocyte Reduction Filters (Primary Hypo-tensive Reaction)

A small number of cases have been reported in conjunction with Bedside Leukocyte Reduction by Filtration. The use of pre-storage leukocyte reduced blood components instead of Bedside Filtration will likely reduce the risk of such hypo-tensive reactions now termed “Primary Hypo-tensive Reactions” (12).

ix. Other reactions characterized by haemolysis

Donor units of red cells may also be haemolysed as a result of

- Excessive warming
- Erroneous freezing
- Addition of drugs or intravenous fluids
- Trauma from extracorporeal devises; or Red cell enzyme deficiency.

(II) Delayed Reactions

Signs and symptoms usually appear within 5-10 days following the transfusion, however intervals as short as 24 hrs and as late as 21 days have been recorded. The exact onset may be difficult to define since haemolysis can be initially insidious and may only be appreciated from results of post-transfusion samples. Estimated risk per unit transfused-1:5000 to 1:11,000 (11)

i. Transfusion associated graft-versus-host disease

Transfusion associated graft-versus-host disease is a consequence of a donor's lymphocytes proliferating and causing an immune attack against the recipient's tissues and organs. It is fatal in more than 90 percent of cases. Patients vulnerable to this condition are those who are immunocompromised or immune competent and who are receiving transfusion with shared HLA haplotypes (i.e., donor could be relative).Symptoms include rash, fever, diarrhea, liver dysfunction, and pancytopenia occurring one to six weeks after transfusion.

Risk factors include a history of fludarabine (Oforta) treatment, Hodgkin disease, stem cell transplant, intensive chemotherapy, intrauterine transfusion, or erythroblastosis fetalis. Other probable risk factors include a history of solid tumors treated with cytotoxic drugs, transfusion in premature infants, and recipient-donor pairs from homogenous populations. Gamma irradiation of blood products keeps the donor lymphocytes from proliferating and can prevent transfusion-associated graft-versus-host disease (8) Leukocyte reduction is not effective (12).Estimated risk per unit transfused: rare (11)

ii. Post-transfusion Purpura

PTP is a rare disorder characterized by severe thrombocytopenia occurring in the first 3 weeks after transfusion in a patient with a prior allogenic exposure through transfusion or pregnancy. PTP is caused by anamnestic production of platelet-specific antibody, often directed against the high incidence HPA-1 platelet antigen. The recommendation that plasma-containing transfusions should be avoided in patients with PTP and that, should red cells be required, they be washed to remove soluble platelet antigens and residual platelet membrane fragments (15). Blood components implicated in causing PTP are (18)

- Whole blood
- Packed red calls: and
- Red cell concentrates.

Estimated risk per unit transfused: rare (11).Mediators: platelet-specific antibodies

iii. Transfusion Induced Haemosiderosis

Tissue iron overload inevitably leads to patients who receive regular red cell transfusions for congenital or acquired anaemias. Iron is deposited initially in the liver and monocyte-macrophage (reticuloendothelial) system, but as these tissues become saturated, iron begins to deposit in other organs such as endocrine glands

and the heart. The body lacks an effective means of eliminating this excess iron, and without therapy, cirrhosis, heart diseases, diabetes, and other disorders develop: death is usually the result of cardiac failure (19) The normal body iron concentration is approximately 40-50mg/kg body weight: women have lower amounts and men somewhat higher (20)Oral drugs with Chelation therapy are useful for management of the situation. Estimated risk per unit transfused: is essentially inevitable after transfusion of 100units (11).

Complications of massive and rapid transfusion

Massive transfusion is defined as the replacement of one blood volume within 24-hour period. For adults of average size, this is roughly equivalent to 10 units of RBCs, with any accompanying crystalloid, colloid, platelet or plasma infusions. The possible complications include citrate toxicity, electrolyte imbalance, circulatory overload and hypothermia. Increased risk of FNHTR and allergic reaction are there

Physical/Chemical Haemolysis

Non-immune haemolysis of red cells due to physical or chemical means can occur through a number of mechanisms including improper temperature during storage, during shipment, or before infusion (example: Malfunctioning blood warmers),Improper component preparation(Example: inadequate deglycerolization of frozen cells), mechanical stress, use of non FDA approved equipment (Example: microwave oven) and administration of mixing red cells with intravenous fluids other than 0.9% Sodium chloride or other FDA approved solutions. Asymptomatic haemoglobinuria is the most common symptom. The transfusion should be discontinued and intravascular access maintained with normal saline. The haemolysis can be prevented by strict adherence to the SOPs (11).Estimated risk per unit transfused: rare

(II) Transfusion transmitted infections (TTI)

A virus, parasite, or other potential pathogen that can be transmitted in donated blood through a transfusion to a recipient. The term is usually limited to known pathogens, but also sometimes includes agents such as Simian foamy virus which are not known to cause diseases.

1. Viruses
2. Parasites and specific bacteria
3. Other bacteria (21)

The main diseases transmitted through blood are Hepatitis, AIDS, Syphilis and Malaria (22, 23)

i. Viral Infections

- Hepatitis A

The transmission of Hepatitis A virus through blood transfusion is very rare because the period of viremia is very short and there is no carrier stage. Donors with history of viral hepatitis after the age of 11 are permanently excluded from donation of blood because HBV and HCV are more likely etiologies in older children and adults. The

most recent estimate of risk from HAV transmission through blood components is 1:10 million units (12)

- Hepatitis B

HBV is a DNA virus. There is an incubation period of approx 8 weeks during which the infection will be asymptomatic and undetectable by serologic methods. Blood donation during this sero-negative window period carries the potential of HBV infection in the recipient of blood or blood components. The viral markers that are of use in screening donors for HBV are hepatitis B surface antigen (HBsAg) and antibody against hepatitis B core antigen (anti-HBc, also known as "anti-core"). HBV risk in the setting of blood transfusion can arise in one of two ways: first, during the window-period donation by an infected donor before seroconversion and, second, through blood components collected from a chronic HBV carrier with undetectable levels of HBsAg .(11)

- Hepatitis C

The causative organism of HCV is a genetically diverse RNA virus. The only effective way of deciding whether an individual is infected with HCV is either by serology (detection of HCV antibody) or by NAT [detection of HCV by polymerase chain reaction (PRC)]. There is a sero-negative window period after infection with HCV (3-6 months), during which a donor can be infected while not detectable anti HCV (3-6months). Furthermore, HCV infection is not always characterized by persistent antibody response, even in immuno-competent individuals, because HCV antibodies can disappear over time. The current residual risk ranges from 1:1.9 million for repeat donors in US and 1:791,666 for first time donors(2.4 times greater risk with first time donors).

Testing for serologic markers indicative of infection with hepatitis B virus and hepatitis C virus has significantly reduced the risk of transmission of these diseases through blood transfusion. Each unit is currently tested for hepatitis surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc). Donors who indicate a potential risk factor for hepatitis as part of their medical history are not allowed to donate and donations with repeatedly reactive screening test results for HBsAg, anti-HBc and anti-HCV are not used for transfusion. This coupled with implementation of NAT for hepatitis C virus by blood centers in 1999, has decreased the estimated risk per unit transfused for hepatitis B to 1:63,000 and hepatitis C to 1:1,600,000(12).

- Hepatitis D and G

HDV and HGV are both blood-borne viruses. However neither virus is is considered having explicit significance in transfusion medicine at this time. HDV require co-infection with HBV and HGV is not convincingly associated with human disease (12)

- Human Immunodeficiency Virus

HIV is an enveloped, more or less spherical virus, with two linear, positive sense strands of RNA.All blood components are capable of transmission of HIV-1, Its transmission has been markedly reduced since the introduction, in 1985, of an immunologic assay for anti-HIV-1, In addition, donors at risk for contracting AIDS are excluded from donating blood. HIV-2 is endemic in West Africa and much rarer in elsewhere. In 1999, the major blood collecting organizations implemented HIV NAT on an investigational basis, which is estimated to have further reduced the window

period to 10days(13). The predominant transmission routes are sexual, perinatal and parenteral. Prevalence and incident rates as high as 20% and 1-2% in parts of sub-Saharan Africa. Prevalence in the USA is estimated at about 0.4% and incident rates are about 16 per 100,000 annually. Diagnosis of infection may be based upon tests for antibodies to HIV and/or the presence of HIV RNA in the plasma (24) . It is of interest that two of the five transmission events noted in USA since 1999 have involved infection from a transfusable plasma unit, but not from the accompanying red cell concentrate, suggesting that the sensitivity of nucleic acid testing approaching the infection dose of HIV offered by a red cell concentrate. The AIDS epidemic has been a medical and human disaster. It stimulated the current stringent approach to blood safety and continuous quality improvement. All donors are directly asked about a history of AIDS-related symptoms and about possible exposure to infection. Questions about behavioral risk are asked and individuals acknowledging such risks are permanently or temporarily deferred. Some of the questions, particularly those relating to male-to-male sexual activity, have been challenged as discriminatory, particularly when accompanied by permanent deferral. All donations are, at a minimum, tested for antibodies to HIV and in many areas, also for HIV RNA. Testing for the HIV p24 antigen may be performed as an alternative to testing for RNA, but this approach offers lesser sensitivity (25)

- Human T-cell Lymphotropic Virus

HTLV- I is a retro virus associated with adult T- cell leukemia/lymphoma. The disease is endemic in Southern Japan, certain Pacific islands, sub-Saharan Africa and the Caribbean basin.[22] HTLV II exhibits a high degree of nucleic acid homology with HTLV I. A high prevalence has been reported in Native American populations and intra venous drug users in the United States (12).

- Cytomegalovirus

CMV is transmitted by viable leukocytes in transfused blood. Although the overall prevalence rate for CMV antibodies in the population is between 40% and 90%, only a small percentage (<1%) of these units are capable of transmitting the virus(12).

- West Nile Virus

The causative organism is an arthropod-borne virus transmitted through mosquito bites in birds and appearing in humans as an incidental host. In December 2005, the FDA in US approved the first NAT for WNV. At present, in addition to deferral based on reactive NAT results, donors are also deferred for 120 days if they have symptoms suggestive of illness caused by WNV at the time of collection or within 2 weeks after donation. Donors with low level WNV viraemia may sometimes have false negative results when screened by NAT. Pooled plasma derivatives are unlikely to present WNV risk because WNV is inactivated by heat and by solvent/detergent treatment.(11)

- Human Herpes Virus-8

HHV-8 infection is rarely a problem in immuno-competent individuals, who are unlikely to develop Kaposi's sarcoma unless they become immuno suppressed (12)

ii. Parasitic Infections

- Malaria

There is no effective screening test for detection of this parasite. But donors at high risk of acquiring and therefore transmitting the disease (example: travelers to areas endemic for malaria, donors who emigrate from a malarial area within the past 3 years) are deferred from donating blood for a prescribed period of time. In US, EIA tests for antibodies against *P falciparum* and *P vivax* and PCR tests are being investigated in endemic areas. In France, immunofluorescence antibody (IFA) assays have been used widely in donor screening. In 2002 study, IFA detection was coupled with a dipstick antigen assay to improve sensitivity to 88%.The risk of acquiring malaria from blood transfusion in US and Canada is estimated at 1:4 million (12).

- Chaga's Disease

It is caused by *Trypanosomacruzi*, a protozoan parasite that is transmitted by the bite of an infected reduviid bug. It is endemic in Central and South America and in Mexico. In Mexico, the prevalence of Chaga's disease among blood donors is 1 in 133, which is consistent with earlier figures from Brazil. Of the disease is made possible by the fact that T. cruzi infection is a lifelong illness and most chronically infected individuals are asymptomatic. Transfusion transmission is considered to be most likely with whole blood or platelets, because these components have the highest transmission efficiency. In Dec 2206, the USFDA approved a whole cell lysate ELISA screening test for Chaga's disease. Screening for Chaga's test is not mandated by the FDA (15).

- Babesiosis

It is caused by a protozoan parasite of rodents *Babesiamicroti* and is transmitted through the bite of the *Ixodesscapularis* tick. In the past 20 years there have been approximately 2 dozen reported cases of transfusion associated babesiosis in the United States (25). No serologic assay is available to identify blood donors infected with babesiosis, so prevention relies on excluding donors at risk of having contracted the disease FDA (11).

iii. Other organisms – Syphilis

It is rare for syphilis to be transmitted through a blood transfusion. The causative organism of Syphilis, *T. pallidum,* does not ordinarily survive for more than 72 hours at 1-6^{0}C, so only components stored at room temperature or transfused promptly after collection have any risk of transmitting the disease. AABB standards do not require serologic test for Syphilis be performed on donor blood. However, Syphilis screening tests are required by the FDA (11).

Table 3 shows the estimated risk associated with infectious complications

Table 3: Estimated risk associated with infectious complications(12)

Complications	Estimated risk
Hepatitis B virus	1 in 350000
Hepatitis C virus	1 in 1.8 million
Human T- lymphotropic virus 1 or 2	1 in 2 million
Human immunodeficiency virus	1 in 2.3 million
Creutzfeldt-Jakob disease	Rare*
Human herpes virus 8	Rare*
Malaria and babesiosis	Rare*
Pandemic influenza	Rare*
West Nile virus	Rare**

*- exact risk unknown

The preventable and non preventable adverse events are shown in table 4.

Table 4: Preventable and non preventable adverse events

Type of adverse reaction	Related to the quality and safety of the supplied blood component?	Related to failure in clinical transfusion process?	Means of prevention
Transfusion - transmitted bacterial infection	Yes	Possible due to failure to inspect component before transfusion	Donor skin cleansing Diversion pouch on donation line Pathogen reduction Correct storage conditions
Transfusion-transmitted viral infection • HBV • HCV • HIV-1/2 • Other	Yes	No	Correct handling to avoid damage to containers Donor selection Donation testing Pathogen reduction
Transfusion-transmitted parasitic infection • Malaria • Other	Yes	No	Donor selection Donation testing Pathogen reduction
Haemolysis due to incorrect storage	No	Yes	Quality assured clinical transfusion

			process
Immunological haemolysis due to ABO incompatibility	No	Yes	
Immunological haemolysis due to other alloantibody	No	Yes	
Anaphylaxis or hypersensitivity Posttransfusionpurpura Transfusion-related acute lung injury	No	No	May be unpredictable and unavoidable TRALI risk may be reduced with FFP from male donors
Graft versus host disease	No	Yes Due to failure to select component or failure to recognise patient at risk	Use of irradiated components for at-risk patients Use of amotosalen treated platelets
Transfusion associated circulatory overload	No	Yes Due to failure to recognise patient at risk	Avoid over-infusion.

2. ADVERSE DONOR REACTION

Adverse reactions in donor are the complications observed as a result of the difference in the etiology from those in the recipient. These adverse reactions may be due to donation, selection, and management of donors, which may directly harm the donor or impact the quality of the product, which ultimately influence the recipient. A classification and a set of definitions of complications have been proposed by a joint working group from the International society of blood transfusion (ISBT) and European haemovigilance network (EHN). They are subdivided in local reactions related to needle insertion (vessel injuries, nerve injuries, other), general reactions (vasovagal immediate and delayed type) and other important complications. The severity and imputability of donor complications are graded according to another however comparable scale as used for adverse reactions in recipients. This scale is also internationally accepted (7).

Generally, blood donors tolerate the donation very well, but occasionally adverse reactions of varying severity may occur during or at the end of the collection. The adverse reactions that occur in donors may be local or systemic, mild or severe (26-28). It may occur during or at the end of the procedure of blood collection (29).

Mostly, local reactions occur because of issues concerned with venous access. Usually, they are haematomas caused by extravasation from the veins due to imprecise placement of needle during venipuncture, swelling, pain; hyperaemia and swelling may develop at the site of extravasation. Generally, these are ordinary complications that do not require any treatment. However, local phlebitis and thrombophlebitis are some serious but very rare complications of this category.

In case of systemic reactions, it can be grouped in to mild and severe. Mostly, systemic reactions are vaso-vagal reactions triggered by the pain of venipuncture, by the donor observing his or her own blood or by the donor observing another donor unwell, by the anxiety and state of tension of undergoing the donation, etc. It is characterized by the appearance of pallor, sweating, dizziness, gastrointestinal disorders, nausea, hypotension, and bradycardia. Prompt therapeutic intervention is necessary to avoid the development of vasovagal syncope which may end in convulsive syncope. Systemic reactions can occur during apheresis procedure also. Utilization of anticoagulants such as acid-citrate-dextrose (ACD) during this procedure for the collection of blood components can cause hypocalcemia because of chelation. This hypocalcemia leads to the episodes of paraesthesia of the lips, oral cavity and limbs. Generally, these symptoms get normalized after the interruption of apheresis procedure. But, sometimes, therapeutic intervention may need including administration of calcium gluconate. Tremor, muscle spasms, hypotension, tachycardia, arrhythmia, convulsions and tetany are some rare complications associated with apheresis procedure. Moreover, overdose of Acid-citrate-dextrose (ACD) may leads to acute intoxication rarely (28).

The adverse donor reactions may be

a. Acute (Immediate or delayed - after single donation):

It may be mild or serious. Acute reactions most frequently arise from anxiety about painful venipuncture or susceptibility to blood volume deficit during or after donation. The most common type of reaction is a vasodepressor reaction associated with changes in pulse and blood pressure.

b. Chronic (in response to long term donation):

Long term effects among whole blood donors major concern is iron depletion leading to anemia. Over 200 mg of iron is lost with each donation.

The adverse reactions that occur in donors can be divided into local reactions or systemic reactions.

- Local reactions are related to venous access. They are usually haematomas, needle injury, Pain due to trauma, hyperaemia and swelling, phlebitis and thrombophlebitis.
- The systemic reactions may be of mild or severe and areand may be triggered by the pain of the venipuncture, by seeing his own blood, by seeing another donor not well, by the anxiety and tension regarding the donation, etc. The systemic reactions are characterised by the appearance of pallor, sweating, dizziness, gastrointestinal disorders, nausea, hypotension, and bradycardia are the characteristic of systematic reaction.. Therapeutic intervention must be so fast, otherwise may progress into an episode of syncope and can be complicated by the convulsive syncope associated with vomiting, loss of sphincter control etc.(30).

3. HAEMOVIGILANCE

a. Haemovigilance – Essentiality and terminology

Treating patients with blood or its products emerged as a significant issue in quality care therapeutics. Transfusions are necessary for the management of variety of acquired and hereditary diseases, are indicated by the physicians of almost all specialties, but consists potential threats such as infections and immunological reactions. Hence, the safe blood supply requires a well-organized system of donor selection, blood collection, safety and compatibility evaluation, controlled production and optimal usage of blood and its products at clinical level and monitoring of adverse transfusion events – haemovigilance (31).

The term haemovigilance (he'movigilance in French) was coined in 1990s. This term has evolved from already existing term "Pharmacovigilance". The term haemovigilance is derived from the Greek word "Haema" which means blood and the Latin word "vigilans" which means "watchful" or "paying a specific attention to" (10,32-35).

b. Origin and Developments in Haemovigilance

In the late 1980s, the countries like France, UK, USA, Canada and Japan felt the importance and need for safe transfusion when several haemophilia patients under transfusion of blood and factor concentrates were affected with infections such as Hepatitis C virus (HCV) and HIV that leads to the development of a monitoring system now known as haemovigilance.

In 1991, the France began the pioneer work on haemovigilance with organizing of monitoring systems by blood transfusion committees followed by the establishment of Centre National d' Haemovigilance in 1992. In the year 1994, a complete haemovigilance system was established (33,34).

Later in 1995, a resolution was published by European council with the aim of improving the public confidence in safe blood supply. Hence the haemovigilance system came under the governance of legal authorities. Awareness in the differences and difficulties in regard to blood transfusion, five countries took the initiative in 1998 to work together in the field of hemovigilance: Belgium, France, Luxembourg, Portugal and The Netherlands. The first meeting was organized in Paris on February 10, 1998; the European Haemovigilance Network (EHN) was born. Soon after, Denmark, Greece, Ireland, Finland and the United Kingdom joined the EHN and Switzerland, Norway and Canada were adopted as associate members. Several other countries (inside and outside the European Union) have shown their interest in cooperating with this Network.

The objectives of the EHN are as follows:

- Facilitating close contacts in the field of hemovigilance between countries in Europe
- Enabling rapid and efficient exchange of reliable information and of experience
- Maintaining a rapid alert system

- Developing joint activities (like organizing European Seminars on Haemovigilance) (36)

A system called as 'International haemovigilance network' (IHN) is in functioning. It is an international organisation comprised of national or regional haemovigilance systems. It serves as a forum for sharing best practice and benchmarking of data, as well as providing a resource for existing and new haemovigilance systems. IHN was formed in 2009 from the European Haemovigilance Network (EHN), which itself was founded in 1998.

The membership of the IHN consists of national, operational haemovigilance systems. These organisations join the group on behalf of their country, with a nominated lead member who is usually the head (director, president) of the national haemovigilance system of that country. Individuals working in haemovigilance from member countries are free to participate in all aspects of IHN. The IHN provides a forum for sharing best practice and benchmarking of data, as well as providing a resource for existing and new haemovigilance systems. An annual symposium is held each year in one of the member countries and may be attended by interested professionals.

IHN's vision:

Health services around the world will have effective haemovigilance systems in place.

IHN's mission statements (purpose):

- To promote haemovigilance internationally to improve outcomes for donors and patients
- To support haemovigilance systems worldwide
- To be the leading international haemovigilance resource

IHN's mission statements (organisational):

- IHN shall be a financially sustainable organization
- The governance structure shall be aligned to pursue IHN's mission and meet its strategic goals(37)

The IHN is working along with 'International society of blood transfusion' (ISBT) to ensure a better service (32).

ISTARE

ISTARE stands for International Surveillance of Transfusion-Associated Reactions and Events. It is an INH's online database. Its purpose is to record national haemovigilance data using common definitions. This allows international comparisons, information sharing and benchmarking.

It aims to capture all adverse reactions and incidents (events) in recipients of blood and blood products that can certainly, probably or possibly be imputed to blood transfusion. It also records adverse events in blood donors.

It is important to note that ISTARE is not limited to serious events that represent only "the tip of the iceberg". It also aims to capture less serious events and even "near misses".

ISTARE is absolutely operational in web-based form at present. The authorised person can enter, by following simple steps, their country's haemovigilance data. They can enter data for previous years as well as the most recent data. The country name will not be identified by name in ISTARE output, it can only be recognised by a code which will be known exclusively to the uploader. (38).

ISTARE is supervised by a Working Group of the IHN and captures the following data on general information on structure and coverage of the haemovigilance system, numbers of donors/donations and main categories of blood products, specific types of blood components issued and transfused, whole blood and apheresis donor complications, incorrect blood component transfused (IBCT), adverse transfusion reactions- by blood component, by imputability: "possibly", "probably" and "definitely" and by severity: non-severe, severe, life-threatening and fatal.

At present, the haemovigilance system has been implemented in most of the developed countries to monitor the adverse events/reactions related with donation and transfusion of blood. Such surveillance is now well-recognized as an integral part of quality management system in a blood programme (35). This system is known in different names in different countries (Table 5) (7,9 33,39).

Table 5: Name, abbreviation and year of establishment of some well-known haemovigilance system

Name	Abbreviation	Country	Year of establishment
Serious Hazards of Transfusion	SHOT	United Kingdom	1996
Transfusion Reactions in Patients	TRIP	Netherlands	2002
Transfusion Transmitted Injuries Surveillance System	TTISS	Canada	2002
Haemovigilance	---	France,	1994
		Singapore	2002
Quebec Haemovigilance System	QHS	Quebec	2000
Haemovigilance Programme of India	HvPI	India	2012

Around 107 million units of blood donations are collected globally every year. Nearly 50% of these blood donations are collected in high-income countries, home to 15% of the world's population. In low-income countries, up to 65% of blood transfusions are given to children under five years of age; whereas in high income countries, the most frequently transfused patient group is over 65 years of age,

accounting for up to 76% of all transfusions. Blood donation rate in high-income countries is 39.2 donations per 1000 population; 12.6 donations in middle-income and 4.0 donations in low income countries(40)

The WHO Global Database on Blood Safety (GDBS) was established in 1998 to address global concerns with respect to the availability, safety and accessibility of blood for transfusion. The objective of this activity is to collect and analyze data from all countries on blood and blood product safety as the basis for effective action to improve blood transfusion services globally. A questionnaire has been developed as a standardized tool for the collection of data, is based on the WHO Aide Memoire for National Health Programmes: Blood Safety, which covers the four major components of the integrated strategy for blood safety advocated by WHO. The data collected through the GDBS questionnaire are analyzed and reports are published on the WHO website. The focus of the analysis is to provide information on the current status of blood transfusion services, assess country needs in improving blood safety, formulate strategic recommendations to countries, plan and implement activities and evaluate progress(41,42)

Providing safe and adequate blood should be an integral part of every country‘s national health care policy and infrastructure. WHO recommends that all activities related to blood collection, testing, processing, storage and distribution should be coordinated at the national level through effective organization and a national blood policy. This should be supported by appropriate legislation to promote uniform implementation of standards and consistency in the quality and safety of blood and blood products. In 2011, 68% of countries had a national blood policy, compared with 60% of countries in 2004. Overall, 62% of countries have specific legislation covering the safety and quality of blood transfusion.

WHO has taken some initiatives in order to support and consolidate the haemovigilance program in resource poor countries. The goal of these initiatives is to strengthen and expand national systems for data collection and management, risk assessment, surveillance and vigilance for policy decisions and programme planning for safe blood transfusion. WHO has developed norms, standards, recommendations, guidelines, materials tools and training materials which will be useful for countries in developing haemovigilance systems. This will help in assessment, monitoring and evaluation of national blood programme. WHO has also established a mechanism of collecting and reporting data of blood transfusion services from 194 WHO Member States (annually) based on 20 key quantitative blood safety indicators and (triennially) using a comprehensive data collection tool. In 2007, WHO organized a "Global Consultation on Universal Access to Safe Blood Transfusion". The international experts and participants of this consultation gave recommendations to WHO on developing quality systems throughout the Blood transfusion chain. WHO has recently initiated the establishment of a Global Haemovigilance Network, building on the existing efforts and in collaboration with IHN, ISBT and Federal Govt. of Canada. This initiative will focus on the needs of developing countries in establishing haemovigilance systems and will also explore the possibilities of international data and information sharing. In November 2012, WHO organized a global consultation jointly collaborated with IHN and ISBT in Dubai, United Arab Emirates and laid down recommendations on recent development on haemovigilance(7).

c. Definition of haemovigilance and associated terms

Based on the reports of World health organization (WHO), ISBT and IHN, the haemovigilance is defined as a set of surveillance procedures covering the whole transfusion chain from collection of blood and its components up to the follow-up of its recipients intended to collect and assess information on undesirable or unexpected effects resulting from the use of blood products and to prevent their occurrence or recurrence. (31-36).Alternatively, it can be expressed as a system meant for close monitoring, documenting reporting and analyzing the adverse events occurring in the chain of blood transfusion with the aim to avoid their occurrence (34).

For haemovigilance, there are many other official definitions are also routine. Significantly, the European blood directive (Directive of the European Parliament and the council that establish standards regarding the quality and safety in collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC) define the haemovigilance as a set of organized surveillance procedures relating to serious adverse or unexpected events or reactions in donors or recipients, and the epidemiological follow-up of donors.

The European Blood Directive also gives definition for some terms closely associated with haemovigilance. They are

(I) Serious adverse event:

Any untoward occurrence associated with the collection, testing, processing, storage and distribution of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity.

(II) Serious adverse reaction:

An unintended response in donor or in patient associated with the collection or transfusion of blood and blood components that is fatal, life-threatening, disabling or incapacitating or which results in, or prolongs, hospitalization or morbidity. Adverse Incidents sometimes referred to as “Incorrect blood component transfused” (IBCT), result from avoidable system failures throughout the transfusion chain.

(III) Incident

As per the working group of the International Society of Blood Transfusion (ISBT), an incidentis when the patient receives a blood component that did not meet all the requirements for a suitable transfusion for the patient, or was intended for another patient. It thus includes transfusion errors and deviations from standard operating procedures or hospital policies. It may or may not result in an adverse reaction.

(IV) Near Miss

A near miss is an error or deviation from standard procedure or policy that is discovered before the start of the transfusion. (43) It include those occasions an error was detected, either by chance or as a result of quality checks, and an incident prevented. Sampling errors are common accounting for 56% of near miss reports (44).

d. Blood bank establishment&hospital blood bank

In the EU directives concerning blood products, blood establishments and hospital blood banks are considered two entities. A blood bank establishment is any structure or body that is responsible for any aspect of the collection and testing of human blood or components and their processing storage and distribution. This does not include hospital blood banks.

A hospital blood bankis a hospital unit that stores and distributes and may perform compatibility tests on blood exclusively for use within hospital facilities, including hospital - based transfusion activities.

Some of the definitions were obtained from other areas such as Pharmacovigilance etc. The definition about the types of blood components is based on the council of Europe: Guide on preparation, use and quality assurance of blood components, Recommendation No. R (95) 15, Part C: Blood components.

Some other aspects are based on the guidelines of EHN and the council of Europe: Guide on the preparation, use and quality assurance of blood components, Recommendation No. R(95) 15; Chapter 31 – Haemovigilance (36).

e. Scoring for severity:

Internationally accepted definitions for adverse reactions in recipients have been developed by IHN-ISBT working committee group in order to be able to share information and compare data. An adverse event that results in morbidity or mortality of a recipient is called an adverse reaction and when it affects a donor it is called complication. An internationally accepted scale is used to grade the 'severity' of an adverse reaction in recipient. The likelihood for adverse reaction or imputability can be attributed to the blood component transfused and it is also important to determine whether blood component has been involved or not. Criteria for ‘severity’ and ‘imputability’ of transfusion reactions have been laid down by the ISBT (7).

0 – No sign; 1 – Immediate symptoms without vital risk and complete resolution; 2 – Immediate symptoms with vital risk; 3 – Prolonged morbidity; 4 – Death of the patient

f. Scoring for imputability:

0 – No relationship; 1 – Possible; 2 – Likely; 3 – Sure(36), Clinical and biological symptoms:

- Immediate reaction***:*** haemolysis, non-hemolytic febrile transfusion reaction [NHFTR]; allergic reactions - rash, erythema, urticaria, anaphylaxis, transfusion related acute lung injury (TRALI)
- Delayed reaction after transfusion – hemolysis, graft-versus-host disease (GvHD), post-transfusion purpura (PTP), Microbiological / viral transmission, allo-immunization (against antigens of RBC, WBC and PLT), incorrect blood component transfused (IBCT) and others (36).

g. Objectives and role of haemovigilance in transfusion chain

- monitoring the prevalence and incidence of infectious markers in blood donors

- compiling adverse events / incidents that are suspected or have been confirmed to be associated with blood collection (relating to the donors) or

transfusion of labile components (relating to the recipients), including transfusion errors and product-related side effects

- documenting confirmation of the transfusion of blood components to patients

- offering rapid alert ***/*** early warning procedures, thereby covering the entire blood transfusion chain and the respective activities

From the above all, it was clear that the hemovigilance should cover the whole blood transfusion chain that means it covers each step in the transfusion process, from the donor to the recipient ("from vein to vein")

h. General concept and essential components of haemovigilance system

The definitions of haemovigilance clearly indicates that this system would cover the whole blood transfusion chain, from the donor to recipient. An active haemovigilance system should consist

- Legal framework
- Continuous and guaranteed budgeting and finance facility
- Central evaluation centre setup
- Commonly agreed definitions
- Standardized reporting system
- Development of rapid alert/early warning system
- Established culture of professionalism
- Functional hospital transfusion committees
- Introducing the preventive or corrective procedures
- Creating the international cooperation

Moreover, various potential participants of this system like manufacturers, blood banks, hospital transfusion committees and competent authorities should be ready to work in a constructive and coordinated manner to fulfill the overall objectives of haemovigilance system.

Manufacturers of equipments, reagents and disposable materials for blood centers and hospitals should establish the post marketing survey procedures for the collection and processing of data related directly and indirectly with blood transfusion.

Blood banks are the consumers of equipments, reagents and disposable materials but they provide services associated with transfusion and also importantly they produce various types of labile blood components. Thus on one side, they are consumer and on other side they are producers and play an important role in haemovigilance.

Hospital transfusion committee has a prime role in the designing of guidelines, training administration, ensuring the peer review, reports supervision, taking preventive or corrective actions and auditing concerned with haemovigilance. Physicians and paramedical staff are also playing a key role in haemovigilance.

Competent authorities are essential for the success of haemovigilance system. They play an important role in legislation, inspection, budget designing and ultimately surveying either directly or by delegation. Thus each and every haemovigilance system, whatever form it exists requires the role of competent authorities (36).

i. Requirements of an effective haemovigilance system

A world health organization guideline on adverse event reporting and learning systems emphasized that the effectiveness of an advent reporting system is measured not only by accurate collection and analysis of data, but also by its use to make recommendations that improve patient safety. The guidelines outlined the following core concepts.

- The fundamental role of a patient safety reporting systems is to enhance the patient safety by learning from failures of the healthcare system.
- Reporting must be safe. Individuals who report incidents must not be punished or suffer other ill effects from reporting.
- Reporting is of value only if it leads to a constructive response. At a minimum, this entails feedback of findings from data analysis. Ideally it also includes recommendations for changes in healthcare procedures and systems.
- Meaningful analysis, learning and dissemination of lessons learned require expertise and other human and financial resources. The agency that receives reports must be capable of disseminating information, making recommendations for changes and informing the development of solutions.

Collection of complete data on adverse reactions and events requires local awareness and vigilance and a robust reporting system that is easily understood and user friendly. The scope of the system must be clear to reporters, definitions must be unambiguous and the system must be sufficiently flexible to respond to developments and changes in transfusion practice.

Haemovigilance systems must be flexible, forward looking, responsive to developments in transfusion practice, and, above all, in touch with clinicians prescribing blood, and requirements of patients.

j. Haemovigilance systems, concepts and models

The current HV systems show significant conceptual and organizational differences related to

- What is reported and when
- How is the system organized

(i) What is reported and when:

In most systems, not only adverse reactions (in patients) but also adverse events(AE) are being reported, but in some systems only adverse reactions are reported. Adverse events such as near misses and errors with or without clinical implications occur much more often than adverse reactions. The advantage of also reporting Adverse events is that these reports offer more and relatively cheap(no harms done) learning opportunities.

i. Reporting of all vs. serious adverse reactions only: Reporting of all adverse events results in better for vigilance purposes and raises awareness as serious AR are rare-events. It requires more resources, however.
ii. Only incidents in recipients or also in donors: Donor vigilance may contribute to reduce complications, lead to increased frequency of donation and improve donor satisfaction.

iii. All or only product related adverse reactions and adverse events: Based on EU regulations, each EU member state has to provide the European commission annually with product related incidents. In principle, HV system should cover the whole transfusion chain.

iv. 'Hot' or 'cold' haemovigilance: Hot means immediate reporting allowing immediate corrective measures to be taken. This is very important for product related incidents and corrective actions to be taken in hospital and blood establishments. Most regional or national haemovigilance system deal with 'cold' vigilance, for instance trends on an annual basis or follow-up of corrective measures(45).

v. Passive vs. active: In general HV systems deal with passive HV. Eg of active HV are specific transfusion safety research projects and post-marketing surveillance of new components by manufacturers.

vi. Reporting on a voluntary vs. a mandatory basis: The Haemovigilance reporting may be mandatory as developed in France or voluntary as exemplified by the Serious Hazards of Transfusion (SHOT) scheme in the United Kingdom. Confidentiality of the patients, donors and reporters must be ensured and the scheme must comply with the legislative requirements for data protection.[7] Centralized or decentralized collection of data guarantee its uniformity and thereby comparability. A disadvantage may be that health care professionals may be less motivated to report.

vii. Centralized or decentralized: Collection of data guarantee uniformity and thereby comparability. A disadvantage may be that health care professionals may be less motivated to report.

(ii)How the system is organised.

- Local**:** Hospital and blood establishment together
- Regional**:** Health District, State, Province
- National**:** Blood organizations, Public Health, Regulatory Agency, Professional Bodies
- International**:** Voluntary organizations like EHN, ISBT etc

Governance of a HV system can be organized by a competent authority, a manufacturer, professional organizations or a public health organization

Advantages and disadvantages of the same are listed out in Table 6. Some of the countries and their method of haemovigilance governance are shown in Table 7.

Table 6: Advantages and disadvantages of various types of governance of haemovigilance system

Authority	Advantage	Disadvantage
Competent Authority	Creation of a centralized system, with sufficient resources and manpower and the HV system is embedded in a multidisciplinary organization including pharmaco and materio vigilance (like in France)	Top heavy system, influenced by politics and reporting to a competent authority would result in under reporting of errors
Manufacturer	Availability of qualified people and less fear for error reporting	Manufacturer may have conflict of interest
Professional organizations	High quality reports because they are checked by experts and that the whole transfusion chain is covered	Voluntary and hence dependent on the willingness of the professionals to report. Also, central steering is lacking
Public health authority	One may mention the expertise in surveillance methodology and that the handling and analysis of database can easily be implemented	No prior knowledge of blood transfusion is available

Table 7: Some countries and their method of governance of haemovigilance systems(39)

Regulations	Blood manufacturers	Medical societies	Public health authorities	Public-Private participation
France, Germany, Switzerland	Japan, Singapore, South Africa, Denmark	Netherlands, UK	Canada	USA

The categories of adverse events in the origin of the system are subjected to modification. Eg, SHOT changes (9) are shown in Table 8

Table 8 SHOT reporting categories

Originalreportingcategories 1996	**Expandedreportingcategories2012**
Incorrectbloodorcomponenttransfused(IBCT)	IBCT includes wrong components transfused or one where specific requirements were not met and errors related to information technology from 2007
Acutetransfusionreactions(all,including haemolyticreactionsoccurring within24h)	Acutetransfusionreactions(allergic,hypotensiveandseverefebrile
Delayedhaemolytictransfusion reactions (>24hpost-transfusion)	Haemolytic transfusion reactions(acute or delayed) Alloimmunization(separated out in 2012 and optional)
Transfusion-relatedacutegraft-versus-hostdisease	
Transfusion-relatedacutelunginjury	
Post-transfusionpurpura	Post-transfusionpurpurawithadditionofplatelettransfusions aspossiblecausefrom2012
Bacterialinfection	Transfusion-transmittedinfection
Viralinfection	
Otherinfection	
	Transfusion-associatedcirculatoryoverload Transfusion-associated dyspnoea Adverse incidents related to autologous transfusion and cell salvage Avoidable, delayed or under-transfusion(formerly inappropriate and unnecessary transfusion, introduced in 2000 Right blood right patient Anti-D errors Near miss events

DETAILED REVIEW OF LITERATURE

Jean –Claude Faber in 2003 (36) described about various aspects of haemovigilance. The author elaborated about the history and origin of haemovigilance system. Various definitions associated with blood transfusion and haemovigilance system, general concepts and the components of the haemovigilance system, problems, difficulties, solutions and the future scope of this system was discussed by the author. An overview of haemovigilance system in the European Union countries was provided by the author.

Somnath Mukherjee *et al.,* 2016 (7) approached the haemovigilance in Indian perspective. The authors discussed the history of blood transfusion, need of haemovigilance, its scope and essentiality very clearly. They also described about haemovigilance for receipients, donors, transfusion practices and haemovigilance in developing countries. Importantly the authors made a clear outline about national haemovigilance programme of India.

Paula H. B. Bolton-Maggs*et al.,* 2013 (9) inked about the serious hazards of transfusion (SHOT) scheme of UK. Also, the authors elaborated about the status of haemovigilance system in other European countries and North America. Regarding with SHOT programme, the authors highlighted its achievements in the reduction of unpredictable transfusion reaction and in the area of surveillance of transfusion incidents. They also pointed out the strategies development for the purpose of improving transfusion safety.

Praveen Kumar *et al.,* 2013 (46) carried out a retrospective evaluation of adverse transfusion reactions following the transfusion of blood products. For that all the transfusion reactions reported to the blood bank at the All India Institute of Medical Sciences (AIIMS) New Delhi over a period of four years and five months (From December 2007 to April 2012) were collected and analyzed. In the outcome of the study, the authors states that during the study period a total of 380,658 bloods and blood components were issued. Out of the total 196 adverse reactions reported under the hemovigilance system, the most common type of reaction observed was allergic 55.1% (*n* = 108), followed by febrile non-hemolytic transfusion reaction (FNHTR) 35.7% (*n* = 70). Other less frequently observed reactions were Anaphylactoid reactions 5.1% (*n* = 10), Acute non-immune HTRs 2.6% (*n* = 5), Circulatory overload 0.5% (*n* = 1), Transfusion related acute lung injury 0.5% (*n* = 1), Delayed HTRs 0.5% (*n* = 1). Not a single case of bacterial contamination was observed. From this study, the authors came to a conclusion that the frequency of transfusion reactions in the study subjects was found to be 0.05% (196 out of 380,658). This may be an underestimation of the true incidence because of under reporting. It should be the responsibility of the blood transfusion consultant to create awareness amongst their clinical counterpart about safe transfusion practices so that proper hemovigilance system can be achieved to provide better patient care.

Ashish Jain *et al.,* 2012 (32) reviewed about haemovigilance and blood safety. The authors described about the historical aspects and scope of haemovigilance. Also, they elaborated about recipient as well as donor haemovigilance.

JaspreetKaurBoparai*et al.,*2016 (33) made a brief communication about the haemovigilance programme of India. The authors clearly made an outline in the origin and history of development of haemovigilance system and its beginning and functioning in India. From the conclusion of authors, it came to know that haemovigilance is an essential component of quality management in a blood system and is needed for the continual enhancement of quality and safety of blood products

and transfusion process by monitoring and safeguarding the adverse events associated with the use of blood products.

Satyajeet Singh *et al.,* 2015 (34) reviewed about haemovigilance practice in India. The authors presented the details of origin and history of haemovigilance initially and then outlined about haemovigilance programme of India. They explained various details about HvPI such as objectives, functional units, procedure for the enrollment in the programme etc. The authors also discussed about the roles and responsibilities of medical and nursing staff of the haemovigilance centres. As a conclusion, the authors told that a functional haemovigilance system can act as a backbone to monitor the transfusion practices and be accountable to appropriate documentation, reporting and investigation of transfusion reactions.

SukantaSen *et al.,* 2014 (10) elaborated about haemovigilance and transfusion safety in their review. The authors discussed about origin and developments in haemovigilance system and HvPI in detail. Finally, the authors came to conclusion that the information gained from the haemovigilance and analyses facilitate the corrective and preventive actions to be taken to minimize the potential risks associated with safety and quality in blood processing and transfusion for donors, patients and staff. Such information is also have a key role to introduce required changes in the applicable policies, improve the standards, systems and processes, assist in the formulation of guidelines, and increases the safety and quality of the entire process from donation to transfusion. Developing guidelines, audit and haemovigilance systems in countries with limited resources can be achieved more readily through a stepwise implementation.

Amit P date *et al.,* 2016 (35) evaluated the knowledge attitude and practice of haemovigilance among doctors in tertiary care hospital in Nagpur, Maharashtra, India. For that a cross sectional, questionnaire based study was carried out with a sample size of 120 doctors for a period between July 2014 and December 2014 at NKP salve institute of medical sciences and research centre Nagpur, Maharashtra, India. From the outcome of the study, it was found that 39% and 30% of the responders were aware of the haemovigilance programme and transfusion reaction reporting centre respectively. Reporting of transfusion reaction was poor among the respondents (22%). According to respondents creating awareness about haemovigilance by conducting continuing medical education, and training to healthcare professionals would lead to improvement in reporting of transfusion reactions. Complacency and ignorance were the main factors which discouraged transfusion reaction reporting by doctors. From this study, the authors came to a conclusion that increasing the awareness of haemovigilance among doctors and training on reporting transfusion reactions would likely improve spontaneous reporting and help to strengthen the blood transfusion system.

Sanjeev Sharma *et al.,* 2011 (8) analyzed the indications and complications associated with the transfusion of blood and its products. Initially, the authors states that, blood transfusion can be a life-saving procedure, but it has risks, including infectious and noninfectious complications. There is debate in the medical literature concerning the appropriate use of blood and blood products. Clinical trials investigating their use suggest that waiting to transfuse at lower hemoglobin levels is beneficial. Then the authors discussed about various types of blood products such as RBC, Plasma, Platelets, Cryoprecipitate with emphasize on their preparation, indication and complications associated with their transfusion. Also, the authors discussed in detail about various types of transfusion complications such as acute haemolytic reactions, allergic reactions, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload and transfusion associated graft versus host disease.

A study by **Kumar R *et al.*** , found that the frequency of ATRs was observed to be 0.92%[47].

Sharma DK *et al*. reported that a total of 0.92% ATRs were encountered. Allergic reaction was the most frequent transfusion reaction encountered (65.6%)seen most commonly with PRBC febrile reactions (28.1%), which were seen more commonly with PRBCs Packed red blood cells (PRBCs) and whole blood (WB) were most commonly implicated[48]

Kumar *et al.* observed that the frequency of ATR in their study was found to be 0.05% (196 out of 3,80,658) and the majority of the types of reactions observed were allergic reactions followed by FNHTRs and HTRs Of all the TRs that were reported, 42.8% occurred with packed red blood cells (PRBC), while platelet rich plasma (PRP) and fresh frozen plasma (FFP) transfusions were responsible in 37.7% and 19.3%, respectively. (49).

Agnihotri *et al.* found that Red blood cell units were the most frequently transfused component and thus most commonly involved in an adverse reaction (42.6 %), (50)

As per **Swiss Haemovigilance annual report** febrile non-haemolytic TR (FNHTR)and allergic TR together continue to account for almost 90% of the transfusion reactions reported. Proportion of reported TR accounted for by blood components is Packed red blood cells (PRBC) 75%,Platelet concentrates PC 17% Fresh frozen plasma (FFP) 4%(51). 0.3% of adverse reactions were reported in another case and the most common reaction observed was allergic reaction 55.6% followed by FNHTR 33.3%(52).Bacterial sepsis, although rare(1:12'000 / 1:130'000), can be vigorous (53)

There may be contamination during sample collection, component preparation, or thawing the platelets and also leuko-reduction by using platelet filters and irradiation has reduced infectious TRs to a minimal number(54).

Fabiana M *et al.* reported that PTP is a rare delayed transfusion reaction where a patient develops dramatic, sudden and self-limiting thrombocytopenia (platelet counts $<10 \times 10^9$/L in 80% of cases), typically 7 to 10 days after a blood transfusion. It is caused by alloimmunization against platelet antigens, anti-HPA-1a being the most frequent antibody.(55). **Domen RE *et al.*** reported that. Leukoreduction plays an important role in reduction of FNHTR.(56)

In a report of HvPI by **Akanksha Bisht *et al*.** FNHTRs constituted the most frequently reported transfusion reaction (40.84%). Mild allergic reactions which were reported in “other reaction” category comprised 27.26% of the reactions. Anaphylactic/hypersensitivity reactions were 12.68% and hemolytic transfusion reactions were 4.31% (164 out of 3903). Out of these 164 hemolytic transfusion reactions, 22 (0.56%) were due to ABO mismatch, 58 (1.49%) were due to non-ABO alloantibodies, and 84 (2.15%) were due to nonimmune causes. There was incomplete information on cause/error which led to the ABO mismatch. In 9 out of 22 cases where information was available, 6 cases had a bedside sampling/administration error. Alloantibodies were identified and reported in three patients only. In the rest, immune-hematology workup was not available for review in the TRRF. The nonimmune hemolytic transfusion reactions were mainly due to ward/bedside storage and handling errors as per the available information. The remaining categories of transfusion reactions reported were TAD (2.38%), TACO (0.67%), PTP (0.64%), TTBI (0.46%), TRALI (0.26%), TT malaria (0.03%), and TAGvHD (0.03%). In the category of “other reactions,” majority were mild allergic

reactions (27.26%) and mild FNHTRs (5.02%), and the rest were either not specific or symptoms not possible to classify into a specific reaction(57)

The Australian Haemovigilance report concludes that the frequency of donation-associated adverse events is higher in younger donors and in female donors, especially those under the age of 20 years(58).The AABB donor haemovigilance report 2012 reports that the female donors were twice as likely to experience an adverse reactions to donating blood.(59)

J.C.Wiersum-Osselton *et al.* mentions that the occurrence of vasovagal reactions is associated with young, female donors, smaller estimated blood volume, first-time donor status. A reduction in vasovagal reactions has been documented with use of a water drink before donation, muscle tensing, social distraction and lower collection volume for donors with small estimated blood volume.(60)

In the study by **Subhashish D *et al*.** they observed the AE during blood donation were higher in younger and first time donors. Statically significant association between age and number of donations (1st time & repeat donors)were observed, lesser the age more the adverse effects in both first time & repeat donor(61). Studies conducted elsewhere have already reported association of various factors such as age, gender, weight, donor status, EBV and volume of blood collected with a higher incidence of VVRs.[62-64]

In a survey by **Abhishek *et al.*,** they identified 564 complications among 27719 donations. The overall rate of complications was 2035/100000[95% confidence interval (CI): 1870– 2210/100000].Complications related to vasovagal reactions occurred with a rate of 1151/100000 donations (95% CI: 1023–1279). The local complications caused by insertion of the needle, occurred with a rate of 884/100 000 donations (95% CI: 772–996) Most of the complications were vessel injuries with hematoma (779/100000 donations, 95% CI: 673–885) and extravasations (76/100000, 95%CI: 43-109). The remainder consisted of nerve injuries (29/100000 donations, 95% CI: 9–49)(65).

Crocco A and D'Elia D in their study found only 1.2% of all the volunteers suffered some kind of adverse reaction: 59 (1.08% of the subjects) had mild reactions (agitation, sweating, pallor, cold feeling, sense of weakness, nausea), and only 4 had more severe disorders, including vomiting, loss of consciousness, and convulsive syncope[66].

Thrombophlebitis has a low incidence (1 in 50,000 to 1 in 100,000), and infection at the phlebotomy site is rare. Both are easily treated and have little impact on the donor's health.[67] .