Dr. Jayashree Sharma
Professor & Head,
Department of Transfusion Medicine
GSMC & KEM Hospital,
Mumbai.
DENGUE … THE CHALLENGES !!!

- Dengue is a self-limiting acute febrile illness followed by a phase of critical defervescence.
  - Broad clinical spectrum
  - Complicated presentations
  - Lack of definitive guidelines

- *Harrison’s Book of Medicine* has “dismissed” Dengue in a short paragraph…!!!!!!
Dengue fever has emerged as a major public health problem in tropical and subtropical regions across the world.
World Health Organization has classified dengue as the most important mosquito borne viral disease in the world in its 2012 report.

- Dengue is now endemic in >125 countries. 75% of the world's population exposed to dengue lives in the Asia Pacific region of the world.

- The incidence of dengue has increased 30-fold between 1960 and 2010.
The Dengue Virus

- Dengue virus (DEN) is a small single-stranded RNA virus comprising four distinct serotypes (DEN-1 to DEN-4).

- These closely related serotypes of the dengue virus belong to the genus Flavivirus, family Flaviviridae.
The Aedes aegypti (Infected Female Mosquito)

- It is transmitted by a mosquito - the *Aedes aegypti*
- It is generally an animal virus
- Man is accidentally infected
- Other vertebrates are the reservoirs
- Day biting – It is an urban mosquito
- Lives in fresh water in homes
- Lays eggs preferentially in jars, discarded containers, coconut shells, old tires etc.
- Year round breeding
- Tropical regions are its favourite zones.
Transmission

Healthy person

Infected mosquito

Infected person

Incubation Period: 3 to 14 days
Most commonly 4 to 7 days
Pathogenesis

Dengue Virus infection

Production of Antibodies

- Antigen antibody reaction with complement activation

  - Deposition on vessels and various tissues and platelets

  - Clinical Manifestations

Activation of T Cells

- Production of various cytokines

  - Increased vascular permeability

  - Clinical Manifestations
Clinical Features

Dengue symptoms

- High fever
- Headache
- Muscle and joint pain
- Pain behind eyes
- Skin rashes
- Vomiting
- Bleeding from mouth and nose
Bleeding manifestations of dengue fever
The WHO Classification (1975, 1997)

Symptomatic dengue infection

Undifferentiated fever

Fever with 2 of the following
- Headache
- Arthralgia
- Retro-orbital pain
- Rash
- Myalgia
- Hemorrhagic manifestations
- Leukopenia
and
- Supportive serology;
or
- Occurrence at the same location and time as other confirmed dengue cases

Dengue fever

Dengue Hemorrhagic Fever

All 4 components must be met
- Fever
- Hemorrhagic manifestations
- Thrombocytopenia
- Evidence of plasma leakage
The WHO Classification (2009)

Symptomatic dengue infection

Dengue -/+ warning signs

Probable dengue
Live in/travel to dengue endemic area.
Fever and 2 of the following:
- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test positive
- Any warning sign

and

- Supportive serology;
or
- Occurrence at the same location and time as other confirmed dengue cases

Warning signs**

- Abdominal pain and tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement > 2 cm
- Laboratory: increase in hematocrit concurrent with rapid decrease in platelet count

**requiring strict observation and medical intervention

Severe dengue

Any of the followings:

- Severe plasma leakage leading to shock or respiratory distress.
- Severe bleeding as evaluated by clinicians.
- Severe organ involvement
  - Liver (AST, ALT ≥ 1000)
  - CNS: impaired consciousness
  - Heart and other organs
**Figure 1: Dengue case classification and levels of severity. Source WHO (3).**

**DENGUE ± WARNING SIGNS**

**SEVERE DENGUE**

1. Severe plasma leakage
2. Severe hemorrhage
3. Severe organ impairment

**CRITERIA FOR DENGUE ± WARNING SIGNS**

Probable dengue
- Live in/travel to dengue endemic area.
- Fever and 2 of the following criteria:
  - Nausea, vomiting
  - Rash
  - Aches and pains
  - Tourniquet test positive
  - Leukopenia
  - Any warning sign

Laboratory-confirmed dengue (important when no sign of plasma leakage)

**Warning signs***
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

* (requiring strict observation and medical intervention)

**CRITERIA FOR SEVERE DENGUE**

Severe plasma leakage leading to:
- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding as evaluated by clinician

Severe organ involvement
- Liver: AST or ALT >= 1000
- CNS: Impaired consciousness
- Heart and other organs
Dengue Fever with bleeding in 7%

Dengue – the dangerous form in 3%

Complete recovery is the rule

Severe weakness may persist for many days after the fever subsides.

Treatment: maintenance of good hydration, IV fluids and vigilant monitoring for warning signs and any bleeding
Thrombocytopenia in Dengue

- Thrombocytopenia: a potential indicator of clinical severity (WHO).

- Definitions generally describe a rapid decline in platelet count or a platelet count less than 150,000 per microliter of blood.

- In the previous studies reported, DHF in adults without shock, platelet counts usually decreases on the 3rd day until the 7th day of illness and reaches normal levels on the 8th or 9th day.
Days of illness

Temperature

Potential clinical issues

Dehydration

Shock bleeding

Reabsorption fluid overload

Organ impairment

Laboratory changes

Hematocrit

Platelet

Serology and virology

Viraemia

IgM/IgG

Course of dengue illness:

Febrile

Critical

Recovery phases

* Source: adapted from Yip (2) by chapter authors.
The pathogenesis of thrombocytopenia in dengue fever is not clearly understood.

The proposed mechanisms include:

a. Bone marrow suppression due to destructive effects of the virus on bone marrow
b. Platelet dysfunction due to exhaustion from platelet activation triggered by immune complexes
c. Platelet destruction due to increased apoptosis, lysis by the complement system and by the involvement of antiplatelet antibodies
d. In addition, DENV infection induces platelet consumption due to disseminated intravascular coagulation (DIC).
Platelet transfusions

- Thrombocytopenia is a common cause of concern in dengue to both patients and attending clinicians.

- No clear guidelines exist for management of thrombocytopenia.

- The natural tendency is to order platelets routinely & transfuse.

- Authors have noted that many times the prescription for the platelet are not based on medical rationale, but as a response to an intense social pressure on the treating physicians by the patients and their relatives.
Kumar et al. (2000) also observed that the demands for platelet transfusion were mostly received as a panic reaction during the epidemic of dengue fever.

Observing a fall in platelet count even if the count were above 20,000 the blood prescribing clinicians send requisition for platelet transfusion without any specific indications.

This leads to flooding of transfusion services with blood and component requests.

Bound to put tremendous strain on the transfusion services during periods of dengue epidemics.
Rightly said by Pallavi P (2011) et al, this ‘syndrome’ of chasing platelet count in dengue patients who are otherwise completely asymptomatic and improving can be labelled as ‘Dengue panic syndrome’.
Prophylactic Vs Therapeutic Tx

Prophylactic platelet transfusions are defined as platelet transfusions given in the absence of clinical bleeding, in contrast to therapeutic platelet transfusions given to patients with clinical bleeding.

- Efficacy of prophylactic platelet transfusion is controversial!!

- Platelet transfusion are said to aggravate the thrombocytopenia by an exalted immune response by presenting a strong antigenic stimulus.
Besides, the short life span of transfused platelets result only in a transient non-sustained elevation of the platelet count.

They also evoke hypersensitivity reactions and fluid overload with complications such as pleural effusion, ascitis and pulmonary oedema.

*Inappropriate platelet transfusions in absence of bleeding have been reported from 13% to as high as 56.2% by various authors.*
INDICATIONS

Prophylactic transfusion (in a non-bleeding patient)
- Platelet count $< 20 \times 10^9/\text{L} (<20,000/\text{mm}^3)$.

Therapeutic transfusion (in a bleeding patient)
- Significant active clinical bleeding with platelet count $< 50 \times 10^9/\text{L} (<50,000/\text{mm}^3)$.
- Proven disseminated intravascular coagulation.

Guidelines issued by the Directorate of national vector borne diseases control program, Government of India

<table>
<thead>
<tr>
<th>Blood component</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>Packed red cells</td>
<td>Loss of blood (overt blood) - 10% or more of total blood volume</td>
</tr>
<tr>
<td></td>
<td>Refractory shock despite adequate fluid administration and declining hematocrit</td>
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<tr>
<td></td>
<td>Replacement volume should be 10 ml/kg body weight at a time and coagulogram should be done</td>
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<tr>
<td></td>
<td>If fluid overload is present packed red cells are to be given</td>
</tr>
<tr>
<td>Platelets</td>
<td>In general there is no need to give prophylactic platelets even at &lt;20,000/cumm</td>
</tr>
<tr>
<td></td>
<td>Prophylactic platelet transfusion may be given at level of &lt;10,000/cumm in absence of bleeding manifestations</td>
</tr>
<tr>
<td></td>
<td>Prolonged shock; with coagulopathy and abnormal coagulogram</td>
</tr>
<tr>
<td></td>
<td>In case of systemic massive bleeding, platelet transfusion may be needed in addition to red cell transfusion</td>
</tr>
<tr>
<td>Fresh frozen plasma/</td>
<td>Coagulopathy with bleeding</td>
</tr>
<tr>
<td>cryoprecipitate</td>
<td>Patient’s clinical condition may be considered or as per the advise of the physician</td>
</tr>
</tbody>
</table>
Dengue patients can be categorized into the four categories based on their platelet count. (Directorate of Health services)

**High risk patient**
- Platelet count $<20,000/cumm$, high risk of bleeding.
- should be receiving prophylactic platelet transfusion.

**Moderate risk**
- Platelet count is in between 21-40,000/cumm.
- should be transfused with platelet only if they have any hemorrhagic symptoms.

**Low risk**
- Platelet count $>40,000/cumm$ but $<100,000/cumm$.
- should be observed and monitored, should not receive unnecessary platelet transfusion due to risk of transmission of blood borne infection.

**No risk category**
- Platelet count $>100,000/cumm$.
- should not be transfused with platelet, should be managed on intravenous fluids and supportive therapy.
Since the pathogenesis of bleeding manifestations and thrombocytopenia is poorly understood, there are no definite guidelines about the use of platelet transfusions in DHF/DSS.

In a study on adults with acute dengue, the authors found prophylactic platelet transfusions to be ineffective in preventing bleeding.

Lack of efficacy of prophylactic platelet transfusions has been reported in literature by various authors.

Preventive transfusions also did not produce improvement in coagulation status.
In a comparative study between patients with dengue shock syndrome who received platelet transfusions and those who did not receive transfusions, there was significant difference in the development of pulmonary edema and the length of hospitalization but no difference was observed in the incidence of bleeding manifestations.

The Trial of Platelet Prophylaxis study of United Kingdom examined the safety of a therapeutic only platelet transfusion strategy with no prophylactic platelet transfusions in thrombocytopenic patients. In dengue shock syndrome patients who received prophylactic platelet transfusion, it was observed that the increment in platelet count was transient and returned to pre transfusion values within 5 h of transfusion.

The study was conducted to evaluate the appropriateness of platelet transfusion done in dengue patients with thrombocytopenia.

Among 343 serologically confirmed cases, the prevalence of platelet count <100,000/cumm was 64.72% (222 patients), bleeding manifestations were recorded in 6.12% (21 patients).

71 (20.7%) patients of dengue cases received platelet transfusion. Among them 34 (47.89%) patients had a platelet count <20,000/cumm, 28 (39.44%) had platelet counts in of 21–40,000/cumm and 9 (12.67%) had platelet count between 41–100,000/cumm. Out of 37 patients with a platelet count <20,000/cumm, 11 patients had bleeding manifestations which necessitates platelet transfusion. However, the remaining 26 patients with platelet count <20,000/cumm with no haemorrhagic manifestations received inappropriate platelet transfusion.

Transfusion of 36.62% of platelet concentrate was inappropriate.
Kulkarni et al conducted this study during dengue epidemic in 2011 to study the effectiveness of platelet transfusion in dengue patients.

- 230 Serologically confirmed cases were included.
- 182 (78%) received platelet transfusion. 118 (51%) patients with platelet count between 20,000-1 lac received single donor plt conc.
- 64(27%) patients with platelet count <20,000 received multiple pl conc transfusions.
- Even with multiple transfusions, platelet count increased by 50000 and did not decrease duration of hospital stay.

Hence concluded that **51% of patients had inappropriate platelet transfusions**.
A 1992 study by the American Association of Blood Banks’ Transfusion Practice Committee reported that over 70% of hospitals transfused platelets primarily for prophylaxis, with an arbitrary transfusion threshold of 20 x 10^9/L or higher in 80% of these hospitals.

This prophylactic platelet transfusion threshold can be traced to published data half a century ago, and was widely adopted for many years despite lack of clinical evidence that 20 x 10^9/L is the appropriate transfusion threshold.

Data from randomized clinical trials suggest that a decrease in platelets counts of up to 10 x 10^9/L may be tolerated without the need for prophylactic platelet transfusion in the absence of major bleeding.
Clinical profile of dengue fever and use of platelets in four tertiary level hospitals of Delhi in the year 2009

KN Tewari*, NR Tuli**, SC Devgun***

- This is a retrospective study of 230 patients admitted in 2009 in four tertiary level hospitals situated at different locations in Delhi.
- 163 cases (70.8%) had dengue fever and 25 cases (15%) had evidence of haemorrhagic manifestations. Severe thrombocytopenia as low as 2,000 was observed in cases of DF and another of DHF – without any bleeding manifestations in DF and minor bleeding manifestations in DHF.
- Fresh blood has been given to one patient of DF and of DHF. Blood and platelet both have been given to one patient of DF and two patients of DHF. Platelet transfusion was given to 48.7% (80) cases of DF cases and 73.5% (50) cases of DHF.
- Minimum unit transfused is one and maximum was 16 units with an average of 4.23 units.
- There is significant difference in the value of p in the average number of days of stay in hospital for those who were given platelet transfusion.
- Two deaths have been reported in cases of DF – one due to atypical presentation, and the other due to gastro-intestinal tract bleeding.
Transfusion of other components

- In cases of shock with declining hematocrit: Blood transfusion is a life saving measure.

- However there is risk of fluid overload due to decompensated cardiac status.

- In massively bleeding patients packed red cells may be transfused.

- FFP & cryo transfusions: for coagulopathy

- Role of Recombinant Factor VIIa
Role of FFP

- Antibody concentrates in the form of FFP could block immune mediated platelet destruction.

- The postulated mechanisms are akin to Fc receptor blockade by intravenous immunoglobulin and the associated inhibition of platelet binding by macrophages.

- This could lead to a reduction in peripheral platelet destruction, and hence an increase in the platelet count.

- In addition, thrombopoietin activator in FFP may also directly stimulate thrombopoietin in the bone marrow.


To test the efficacy of FFP on thrombocytopenia in patients with dengue fever, 109 serologically confirmed dengue patients with platelet counts <40,000/mm³ were randomised into two groups.

Group A (treatment) 53 patients and group B (control) 56 patients.

Group A received 3 units (600ml) of FFP and Group B received equal volume of isotonic saline over the same period.

The primary outcome measure was the difference between pre- and post-interventional platelet counts at 12, 24 and 48 hours.

Results, the mean platelet count was significantly higher in Group A than in Group B at 12 hours (p=0.04; t-test).

The mean platelet counts continued to be higher in Group A than in Group B at 24 and 48 hours post-intervention, but the differences were not statistically significant.

Conclusions in dengue patients with thrombocytopenia, infusion of 600 ml FFP may contribute to a significant increase in platelet count in the first 12 hours, but not thereafter.
• **Thrombocytopenia**: Not the only predictor of severe bleeding.

• **Bleeding during DHF may result from a combination of factors such as thrombocytopenia, coagulation defects and vasculopathy.**

• **Due to multifactorial etiology of bleeding in patients with dengue, it is wise to conduct a coagulation profile in addition to platelet count before giving platelet transfusions.**
CHALLENGES FOR TRANSFUSION SERVICES

- Blood transfusion services constantly face challenges during dengue outbreaks.
- Increasing demand for platelets and FFP.
- Platelet concentrates due to their short shelf life are frequently in limited supply.
- Adverse effects of transfusion.
Transfusion of blood components is associated with many adverse effects.

- Febrile non-hemolytic transfusion reactions
- Alloimmunisation to HLA and HPA antigens and platelet refractoriness
- Sepsis, due to bacterial contamination of the blood
- Allergic reactions,
- Transfusion related acute lung injury,
- Transfusion associated cardiac overload and
- Transfusion Transmitted infections
Case

- 14 yr old boy, k/c/o hemophilia
- Presented with fever, high grade with chills and headache
- Over 48 hrs he had severe hemoptysis and altered sensorium with convulsions
- Was admitted in ICU and intubated for airway protection and was mechanically ventilated.
- Investigations showed *Dengue NS1 positive*
- Platelet count – 40,000 and Factor VIII activity levels were <1%
- He was transfused with 12 units platelet concentrate, 4 units FFP.
- He also received factor VIII injections to keep the activity level 50%.
- Over next 3 days, clinical bleeding stopped and platelet levels normalised.

“It is a deadly combo, almost like a death sentence. Here, you have a patient who can bleed to death at the slightest instance suffering from dengue, whose known complication is to make a patient bleed. Even in a tertiary set-up, such as KEM, we have not treated such a case in the last two decades,”
Haemophilic teen saved from fatal sting of dengue

Less Than Five Such ‘Miraculous’ Recoveries In S Asia: KEM Docs

Sumitra Debroy@timesgroup.com

Mumbai: A 14-year-old boy from Naigaum with a genetic bleeding disorder made a dramatic recovery from the dreaded dengue hemorrhagic fever, making it one of the few known instances in medical literature. Doctors at KEM Hospital in Parel, where Arjun Saroj is being treated, termed his comeback as “miraculous”.

KEM doctors said treating a haemophilia patient for dengue was a huge leap in tackling the dreaded infectious disease. “It is a deadly combo, al-
Cases of dengue after receipt of blood products or donor organs or tissue and after occupational exposure in a health care setting have been reported.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Route of transmission</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue</td>
<td>Percutaneous</td>
<td>Several healthcare workers were infected after needlestick injuries during care of returned travelers who had diagnoses of dengue.</td>
</tr>
<tr>
<td></td>
<td>Mucocutaneous</td>
<td>A healthcare worker became infected with dengue 3 virus after being splashed in the face by blood from a febrile traveler who had a diagnosis of dengue.</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td></td>
<td>A 17-year-old man from Hong Kong, Special Administrative Region, People’s Republic of China, donated blood in July 2002, from which erythrocytes were transfused to a 72-year-old woman, in whom febrile illness consistent with dengue fever developed 3 d later.</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td></td>
<td>A 6-year-old child from Puerto Rico became infected with dengue 4 virus from a bone marrow transplant and died.</td>
</tr>
<tr>
<td>Renal transplant</td>
<td></td>
<td>Dengue hemorrhagic fever developed after a living donor renal transplant.</td>
</tr>
</tbody>
</table>
A 52-year-old, asymptomatic, repeat blood donor gave blood on July 15, 2007. He informed the blood bank that he had had a fever the day after donation. The stored serum sample was positive for dengue virus type 2, as ascertained by means of a polymerase-chain reaction (PCR) assay.

The recipient of the donor’s red cells had fever and myalgia 2 days after transfusion.

The recipient of the donor’s fresh-frozen plasma had fever and worsening pleural effusions the day after transfusion.

The recipient of the donor’s platelets was asymptomatic but had serologic evidence of a recent secondary dengue infection on follow-up.
The PCR-amplified products from the donor and two recipients were cloned. Direct sequencing of all available envelope glycoprotein showed alignment with published sequences for dengue virus type 2 in the GenBank database.

Both recipients were positive for dengue virus type 2 as detected with the use of a PCR assay.

Though a whole-genome sequencing for definitive confirmation could not be done, the timing of the infections, is enough evidence for transfusion-related transmission.

This case illustrates the difficulties encountered when attempting to ensure a safe blood supply in the face of emerging flavivirus threats worldwide.
Why has transfusion-associated dengue not yet been widely recognized as a problem in dengue-endemic countries?

- lack of recognition is likely due to lack of awareness that dengue is transmitted not only by vectors but also by blood products.
- there is no surveillance for such events,
- if a case is suspected, it is difficult to prove transfusion transmission v/s vector-borne transmission in recipients from endemic countries.

Risk is high in endemic areas as most DENV infections are asymptomatic and the viremia is high titered, long lasting, and detectable among asymptomatic individuals.
Characteristics that are necessary for transmission by transfusion are:

- The survival/persistence of the infectious agent in collected blood or components, and its ability to cause infection by the intravenous route.
- Ability of the agent also causes identifiable disease in the recipient.
- The length of the asymptomatic blood-borne period, how often blood is donated during this period.
- The immune status of the recipient population.
- Factors relating both to the infectious agent and the genetic and immunologic makeup of the recipient will determine the frequency and severity of the disease.
Mosquito bite

Virus isolation
Molecular techniques
Dengue antigen capture ELISA

Day of illness

-4  -2  0  2  4  6  8  10  12

Fever
Viraemia
Shock Haemorrhage

Dengue antibodies

Plaque reduction neutralisation test
Haemagglutination inhibition
IgM and IgG ELISA
Rapid tests
### Overview of the problem:- Tip of the Iceberg….KEM MICU data

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Patients admitted in MICU</th>
<th>Fever Patients admitted in MICU (%)</th>
<th>Critically ill Dengue patients (%) of fever cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>728</td>
<td>177 (24.3)</td>
<td>24 (13.6)</td>
</tr>
<tr>
<td>2014</td>
<td>720</td>
<td>188 (26.1)</td>
<td>58 (30.9)</td>
</tr>
<tr>
<td>2015 till 31.10.2015</td>
<td>431</td>
<td>132 (30.6)</td>
<td>27 (20.5)</td>
</tr>
<tr>
<td>Year</td>
<td>No. of Patients Expired in MICU</td>
<td>Fever Patients Expired in MICU (% of deaths)</td>
<td>Dengue Expired (% of Dengue admissions)</td>
</tr>
<tr>
<td>--------------------</td>
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<td>---------------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>2013</td>
<td>322</td>
<td>88 (27.3)</td>
<td>9/24, (37.5)</td>
</tr>
<tr>
<td>2014</td>
<td>286</td>
<td>71 (24.8)</td>
<td>16/58, (27.6)</td>
</tr>
<tr>
<td>2015 till 26.09.2015</td>
<td>166</td>
<td>45 (27.1)</td>
<td>10/27, (37.0)</td>
</tr>
</tbody>
</table>
Conclusion

- Inappropriate platelet transfusions in absence of bleeding have been reported from 13% to as high as 56.2% by various authors.

- The demand for platelets and FFP is increasing due to more number of cases with dengue hemorrhagic fever and dengue shock syndrome.

- Further, lack of knowledge, absence of evidence based guidelines and panic like situation leads to flooding of transfusion services with blood and component requests.

- Hence, it is prudent to consider transfusion only if the benefits outweigh the accompanying risks of transfusion.
Appropriate use of blood components is required to ensure their availability for needy patients as well as to avoid the unnecessary risk of transfusion-transmitted diseases.

Lack of evidence-based guidelines for transfusion support in dengue fever which contributes to inappropriate use of blood components.

Blood centers constantly face the challenge of inventory management during dengue outbreaks.
- Need for development of specific guidelines for transfusion.
- Constant interaction and co-ordination amongst clinicians and transfusion centre for implementation of the guidelines.
- A regular medical audit to review the optimal utilisation of blood components.
Prevention is better than Cure.