Blood Transfusion Practices in Dengue Fever: A Cross Sectional Single Center Study During a Dengue Outbreak in Pakistan

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ABSTRACT

Introduction: Dengue fever (DF) is a global health problem in tropical and subtropical regions across the globe. Pakistan has become one of the countries which are hit by its outbreaks for the past two decades with the first outbreak reported in 1994.It is a mosquito-borne infection which is transmitted to humans from the mosquito bite. Characteristics of dengue fever are thrombocytopenia, coagulopathy and increased capillary permeability. The disease spectrum ranges from mild fever to life threatening hemorrhagic shock syndrome; hemorrhagic manifestations are the most feared complications of the disease. Guidelines regarding fluid management in dengue fever have been established by Center for Disease Control (CDC) and local national bodies in Pakistan however comprehensive data regarding blood product usage is lacking. Understanding the rationale use of blood products can reduce burden on blood bank inventories as well as reduce unnecessary blood product exposure to the patients in dengue outbreak.

Aims & Objectives: Assessment of compliance of physicians and transfusion provision authorities regarding blood products usage with local and international guidelines in managing dengue outbreak.

Place and duration of study: This study was conducted at Chughtai Institute of Pathology, Lahore from September 2021 to November 2021.

Material & Methods: It was a cross sectional study. Total 107 patients who were non-structural antigen1(NS1) positive confirmed dengue infection presented at Chughtai Blood Bank for request of any blood product were included in the study; individuals with existing cytopenia (known cases) unrelated to Dengue (NS1 antigen positive) were excluded. Data was recorded on a pre-designed Performa/questionnaire. Statistical analysis was performed using SPSS 23.0. Frequencies were calculated and expressed as percentages.

Results: Mean Age of 107 patients was 53 years (±19.05) out of which 63(58.9%) were males and 44(41.1%) were females. Blood products requested were platelets in 93(86.9%) patients, platelets and fresh frozen plasma in 3(2.8%), platelets and whole blood in 9(8.4%) and whole blood in 2(1.9%) patients. Therapeutic platelet transfusions were done in 35(32.7%) patients and prophylactic platelet transfusions were done in 72(67.3%) patients.

Conclusion: Lack of practicing evidence-based guidelines and inappropriate usage of blood products during dengue epidemic overburdens health care facilities and adds to the stress and panic. A well-coordinated centralized management system for dengue outbreak can play pivotal role in guiding rationale use of blood products.

Key words: Dengue fever (DF); center for disease control and prevention (CDC); non-structural antigen1(NS1)

INTRODUCTION

Dengue fever presents as a wide spectrum mosquito-borne viral illness which may produce only mild flu-like illness or progress into potentially lethal dengue hemorrhagic shock syndrome. Severe disease was first reported in 1950s during dengue outbreak in Philippines and Thailand. According to World health organization (WHO) it affects tropical and sub-tropical regions of the world.[1]

In recent past years dengue has become endemic in south-east Asia, Africa, America, Eastern Mediterranean and Western Pacific. Most serious outbreaks are seen in South East Asia and Western Pacific.[2]

Disease risk is influenced by increasing urbanization, monsoon, temperature and humidity variations. Dengue virus belongs to Flaviviridae family of viruses and has four distinct serotypes i.e., DENV1, DENV2, DENV3, DENV4. Illness from one of the subtypes produces lifelong immunity against that subtype and cross-immunity to other subtypes is partial and temporary. Secondary infections with other subtypes increase the risk of developing severe illness.[1]
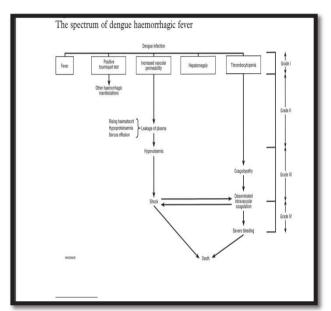
According to WHO bleeding complications of dengue illness has 4 grades (Fig-1).

GRADE I: Thrombocytopenia<100,000 per mm^3.

GRADE II: Increasing hematocritof 20% or more the normal.

GRADE III: Coagulopathy leading to disseminated intravascular coagulopathy (DIC).

GRADE IV: DIC leading to severe bleeding and death.[7]

Fig-1: Spectrum of dengue hemorrhagic fever[3]

Activated immune response leads to lymphocytosis, leukopenia and neutropenia.[8]

Hemorrhagic complications are due to abnormal immune response which releases cytokines, chemokines, activated T-lymphocytes and leads to disturbance of hemostatic system.[2]

Endothelial cells play important role in coagulation response to severe systemic inflammation. Increased peripheral vascular permeability leads to vascular leakage in Dengue hemorrhagic fever and Dengue shock syndrome. Dengue viral Nonstructural protein (NS-1) binds to endothelial cells of lungs and liver cells; this leads to pulmonary vascular and peritoneal leakage.[9]

Guidelines regarding blood products transfusion in dengue fever are limited, several studies show prophylactic platelet transfusions without bleeding manifestations has limited/ no role in management. Despite this the practice of prophylactic platelet transfusions has increased in the dengue outbreak regions of the world. Rationale approach to transfuse platelet is based on platelet count and function, presence of coagulopathy and evidence of bleeding diathesis. For severe bleeding manifestations whole blood, fresh frozen plasma or cryo precipitates can be used in patients with deranged coagulation profile.[2]

TRANSFUSION OF PLATELETS AND OTHER BLOOD COMPONENTS:

Low platelet counts are a common finding in Dengue fever which is attributed to immune mediated destruction.[4] during outbreaks of the disease thrombocytopenia with or without bleeding manifestations creates concern/ panic in both patients and managing physicians. Platelet transfusions in the absence of bleeding manifestations are called "prophylactic platelet transfusions"; whereas in the presence of bleeding manifestations are called "therapeutic platelet transfusions". Several studies have shown that there is no benefit of prophylactic platelet transfusions in preventing bleeding manifestations or reducing severity /duration of bleeding.[10]

Platelet count of <20,000/mm^3 without bleeding manifestation is not an indication of prophylactic platelet transfusion. Another observation is the lack of response to platelet transfusions in patients with thrombocytopenia; this may be due to circulating immune complexes destroying platelets. Health ministries in neighboring countries i.e., Sri Lanka and India have discouraged prophylactic platelet transfusions even when platelet counts are as low as <10,000/mm^3 .[11]

Another important consideration is economic burden in managing dengue patients increases due to unindicated use of platelet transfusions.[11, 12]

Effect of use of fresh frozen plasma (FFP) in bleeding manifestation of dengue has been noted in different studies. One Randomized control trial study done in Sri Lanka showed increase in platelet counts in patients who received FFPs during bleeding manifestation in first 12 hours not after that; however, it did not correlate with the prevention of bleeding episodes,[13] A study from Malaysia showed no reduction in bleeding manifestations after platelet of FFP transfusion rather it increased the risk of pulmonary edema.[14]

Latest Center for Disease Control and prevention (CDC) guidelines recommends do not give platelet transfusions for low platelet counts as they do not reduce bleeding risk and can lead to fluid overload. They recommend transfusing red cell concentrate or whole blood for significant bleeding manifestations and dropping hematocrit (HCT) in vitally unstable patients. (Fig-2)

In addition, CDC also recommends transfusion support of 5-10ml/kg packed red cells OR 10-20ml/kg whole blood immediately in case of compensated and hypotensive shock. (Fig-3, 4)[15]

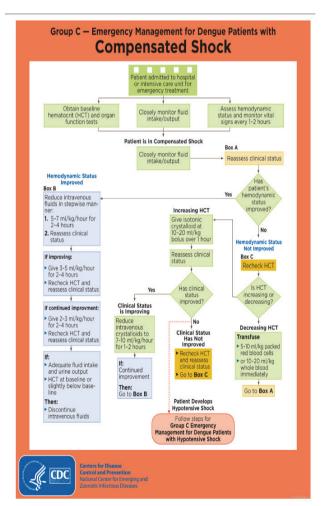**Fig-2**: Dengue management guidelines CDC[15]

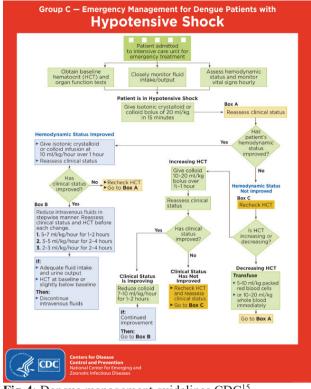**Fig-3**: Dengue management guidelines CDC[15]

Fig-4: Dengue management guidelines CDC[15]

Ministry of National Health Services Pakistan has formed an advisory for the prevention and control of dengue fever in Pakistan. In its clinical management recommendation, they have advised that the platelet transfusions are not recommended for prevention of bleeding but may play role in active bleeding OR severe thrombocytopenia of <10,000/mm^3. They also recommend the transfusion of whole blood in significant bleeding and dropping hematocrit (HCT).[16]

Dengue Expert Advisory Group (DEAG) is another local body working under Government of Punjab for preparing management protocols for dengue fever in Punjab, Pakistan. DEAG's latest guidelines revised in October 2021 suggests monitoring of hematocrit (HCT) of patients while managing compensated / decompensated shock; it recommends if there is a drop of >10 points of HCT from the baseline initiate transfusion with whole blood / packed red cells.[17]

MATERIAL AND METHODS

It was a cross sectional study conducted at Chughtai Institute of Pathology from September 2021 to November 2021. Ethical permission was taken vide IRB number CIP/IRB/1096. Total 107 patients who were NS1 positive confirmed dengue infection presented at Chughtai Blood Bank for request of any blood product were included in the study; individuals with existing cytopenia (known cases)

unrelated to Dengue (NS1 antigen positive) were excluded. Data was recorded on a pre-designed proforma/questionnaire. Statistical analysis was performed using SPSS 23.0. Frequencies were calculated and expressed as percentages.

RESULTS

Characteristics	Values
Mean age (years)	53.06±19.05
Male	63 (58.9%)
Female	44 (41.1%)

Table-1: Age and gender characteristics of 107 patients are shown.

Blood products requested	Values
Platelets	93 (86.9%)
Platelets and fresh frozen plasma	3(2.8%)
Platelets and whole blood	9 (8.4%)
Whole blood	2(1.9%)

Table-2: Blood products requested are shown.

Type of transfusion	Values
Therapeutic	35(32.7%)
Prophylactic	72 (67.3%)

Table-3: Therapeutic and prophylactic transfusion frequency is shown.

Bleeding episodes	Values
Gum bleed	14(13.1%)
Nosebleed	7 (6.5%)
Hematuria	3 (2.8%)
Hematemesis	2(1.9%)
Cranial bleed	2(1.9%)
Malena	3(2.8%)
Hemorrhagic shock	2(1.9%)
Multiorgan failure and DIC	1(0.9%)

Table-4: Bleeding episodes and their frequency is shown.

Platelet count	Values
Low <1	1(0.9%)
Low <5	14(13.1%)
Low <10	50(46.7%)
Low <15	33(30.8%)
Low <20	7(6.5%)
Low <25	1(0.9%)
Low <30	1(0.9%)

Table-5: All 107 patients had thrombocytopenia following are the frequencies of dengue patients with low platelet count.

Outcome	Values
Recovered	102(95.3%)
Expired	5(4.7%)

Table-6: Outcome of the dengue patients who received blood products is shown.

DISCUSSION

Dengue outbreaks in our country have increased in severity over the past decades due to increase in urbanization, climate change, secondary infections with other subtypes of virus. In addition to that in past year diverted efforts from government and health care sector towards corona virus pandemic i.e., reduced insecticide spray campaigns for dengue, stagnant water drainage campaigns and overburdened health care system all had contributed to the increase in poor outcome of the disease in the latest outbreak of dengue in year 2021.

During a period of dengue outbreaks in dengue endemic areas such as Pakistan blood banks are facing constant challenge as the demand of blood products increases due to increase in severity of illness over the period of years. The situation complicates due to lack of practices of evidence-based guidelines on the behalf of treating physicians as well as transfusion provision authorities. Unjustified use of blood products can have many adverse effects; moreover, they add to the financial burden on health care system and suffering of the patients.

Prophylactic platelet transfusions are not recommended as many studies have shown no added benefit in reducing disease severity or preventing bleeding manifestations. All 107 patients in our study had thrombocytopenia (Table-5) and most common bleeding manifestation was gum bleed in 14(13.1%) patients (Table-4) However, 67.3% of platelet transfusions were prophylactic while 32.7% were therapeutic transfusions (Table-3). A study conducted in four tertiary level hospitals

of Delhi observed that 73.5% of patients with dengue fever were given "therapeutic platelet transfusions" and 48.7% of patients were given "prophylactic platelet transfusions".[18] Guidelines issued by health ministry of Sri Lanka has discouraged use of prophylactic platelet transfusion as it cannot prevent hemorrhagic complications in dengue patients and leads to unnecessary exposure to blood products.[19]

Most common blood product requested in our study was platelets 93(86.9%) whereas whole blood was requested in only 2(1.9%) patients (Table-2). A case report from our neighboring country India reported a 24-year-old student dengue patient who received unindicated blood products transfusion and developed transfusion related lung injury (TRALI), multi-organ failure and subsequently expired.[20]

Outcome of dengue patients in our study show recovered 102(95.3%) and expired 5(4.7%)(Table-6)

Comparison of transfusion practices in our neighboring countries shows our blood product usage practices needs to be changed and justified in each case scenario.

As this is a single center study it can give only a glimpse to the current blood product usage practices; so, more studies including larger number of patients and multiple centers might provide more insight to the scenario and improve the practices.

CONCLUSION

Lack of practicing evidence-based guidelines and inappropriate usage of blood products during dengue epidemic overburdens health care facilities and adds to the stress and panic. A well-coordinated centralized management system for dengue outbreak can play pivotal role in guiding rationale use of blood products. Regular awareness programs through continuous medical education (CMEs) sessions, media advertisements, handouts in hospitals and social media campaigns can change/ improve management practices in dengue patients. This can go long way in reducing disease related morbidity, mortality, panic and financial burden.

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