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**COURSE LEVEL:** Intermediate
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# COURSE OBJECTIVES

This Course:

**Implications of HLA in Transfusion Related Immune Complications**:

1.) Discusses TRALI, the mechanisms for development, and its diagnosis after platelet transfusion.

2.) Describes Platelet Refractoriness, its causes, and discusses Eplet matched platelet transfusions.

**Early Transfusion vs. Delayed Transfusion in Cirrhotic Patients with Active Bleeding**

3.) Discusses the Coagulopathies found in Cirrhosis.

4.) Discusses the transfusion of various blood products.

5.) Review the RBC transfusion guidelines for cirrhotic patients.

**Zoonotic Babesiosis – A Growing Concern in Blood Transfusion**

6.) Recalls the background of Babesia, the three major types, its symptoms, and the problems it poses with blood donation.

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MINI REVIEWS IN IMMUNOHEMATOLOGY-19

**Categories:** Immunohematology | **Contact Hours:** 1 | **Course Code:** IH020

## ARTICLE 1 – IMPLICATIONS OF HLA TRANSFUSION RELATED COMPLICATIONS:

**1.)** The causative antibodies in TRALI may be directed against class I or II human leukocyte antigens (HLA) or human neutrophil antigens (HNA).

**A.** True
**B.** False

**2.)** A recent study has demonstrated that donors serum positive for HLA class II antibodies, may induce monocytes and possibly platelets to secrete a variety of inflammatory mediators which subsequently activate neutrophils.

**A.** True
**B.** False

**3.)** Platelet refractoriness is:

**A.** the appearance of light staining platelets on a blood smear
**B.** the constant clumping of platelets, causing micro clots to occur
**C.** the repeated failure to obtain acceptable responses to platelet transfusions

**4.)** Human leukocyte antigen (HLA) mismatches are important risk factors for HLA alloimmunization and cause an increase in the interval of platelet transfusions.

**A.** True
**B.** False

## ARTICLE 2 – EARLY TRANSFUSION VS. LATE TRANSFUSION IN CIRRHOTIC PATIENTS:

**5.)** Increased transfusion of RBCs in patients with cirrhosis is associated with a poorer outcome, since it further increases the portal pressures and promotes additional bleeding.

**A.** True
**B.** False

**6.)** Thrombin production is compromised in cirrhotic patients only when the platelet amount declines to less than 100 x $10^9$/L.

**A.** True
**B.** False

**7.)** Fresh frozen plasma (FFP) is transfused in patients with cirrhosis both therapeutically and prophylactically to correct altered coagulation parameters (PT/INR).

**A.** True
**B.** False

## ARTICLE 3 – ZOONOTIC BABESIOSIS: A GROWING CONCERN IN BLOOD TRANSFUSIONS:

**8.)** Babesiosis is a zoonosis, transmitted primarily by:

**A.** cat bite
**B.** tick vector
**C.** contaminated water

**9.)** There are _____ major types of Babesia involved in human Babesiosis.

**A.** two
**B.** three
**C.** five

**10.)** The major risk factor is the asymptomatic donors and lack of a sensitive and specific test to detect the parasite in the erythrocytes of the donors.

**A.** True
**B.** False

******END OF QUIZ******

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# Implications of HLA in Transfusion Related Immune Complications Like TRALI and Platelet Refractoriness

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**Submission:** February 01, 2018; **Published:** February 09, 2018

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**Keywords :** Trali; Platelet refractoriness; Lung injury; Neutrophils

**Abbreviations :** TRALI: Transfusion-Related Acute Lung Injury; ALI: Acute Lung Injury; HLA: Human Leukocyte Antigens; HNA: Human Neutrophil Antigens; PRA: Panel Reactive Antibodies; MFI: Mean Fluorescence Intensity; CCI: Corrected Count Increment; DIC: Disseminated Intravascular Coagulation; eMMs: eplet Mismatches; HIMMs: Highly Immunogenic Mismatches; FNHTR: Febrile Non-Haemolytic Transfusion Reactions

## TRALI

Transfusion-related acute lung injury (TRALI) is defined as a new acute lung injury (ALI) that develops during or within 6 hours of transfusion and is a leading cause of transfusion-related morbidity and mortality [1]. The causative antibodies in TRALI may be directed against class I or II human leukocyte antigens (HLA) or human neutrophil antigens (HNA). It may also be caused by lipid products from the cellular breakdown, which accumulates in stored blood products and prime, activate neutrophils. TRALI can occur in patients undergoing repeated platelet transfusions and has mortality rates between 6-20%. Thus, it is important to identify these cases and address the issues related to the patients and implicated donors.

### Mechanism for the development of TRALI

There are two working hypotheses - the 'two hit' model and leukocyte antibodies (HLA antibodies). The 'two-hit' model mentions neutrophil priming as an initial requirement which can be a consequence of hematologic malignancy [2]. The introduction of neutrophil-binding antibodies, cytokines, and bioactive lipids from the transfused product, may lead to activation of the primed and sequestered neutrophils. Silliman et al. [3] mentioned that the patients with acute leukemia undergoing induction chemotherapy appeared to be at greater risk of developing TRALI. Another hypothesis suggests that transfused HLA antibodies may induce TRALI by direct contact with susceptible endothelial cells of the lung capillaries. It has been postulated that the transfused HLA Class I antibody binds to its cognate antigen present on the pulmonary endothelium. Passively transfused HLA Class II antibodies are also known to cause TRALI by activation of monocytes which lead to neutrophil activation [4]. A short duration of the clinical episode may reflect the paucity of entrapped neutrophils. A recent study has demonstrated that donors serum positive for HLA class II antibodies, may induce monocytes and possibly platelets to secrete a variety of inflammatory mediators which subsequently activate neutrophils [5].

### TRALI after platelet transfusion

Previously, we have reported a 35 years old female with acute myeloid leukemia with prolonged neutropenia and thrombocytopenia secondary to chemotherapy-induced marrow suppression [6]. She was transfused with multiple platelets (single donor platelets) as she had prolonged thrombocytopenia and developed dyspnoea after one such transfusion. TRALI was diagnosed after excluding other causes of ALI. The Panel reactive antibodies (PRA) of the patient revealed HLA Class I and Class II antibodies. The implicated donor was a registered voluntary platelet donor with the hospital and his sample was sought immediately after this event for laboratory workup. The donor-specific antibody test between recipient and donor pair was positive with a high mean fluorescence intensity (MFI) value for Class I antibodies 10370 and class II antibodies 3454. The HLA typing of the implicated donor was A*02,*03; B*51,*58; DRB1*03,*04. Serum of implicated donor demonstrated HLA Class I antibodies and HLA class II antibodies. Therefore, the mechanism in the patient was a combination of the above factors. The patient had a haematological malignancy with superadded entercolitis which made her susceptible to TRALI by the two-hit model. The donor-derived HLA-A*02 antibodies by binding the pulmonary capillary endothelium may have facilitated the sequestration and activation of neutrophils despite a low ANC. A short duration of the clinical episode may reflect the paucity of

entrapped neutrophils. There was also an evidence of HLA Class II antibodies in the implicated donor.

Based on this observation it is suggested that the laboratory workup of all cases of TRALI should be performed to reduce the potential for further cases due to the implicated donor. Baseline PRA of repeat male donors should be studied to prevent TRALI due to passive transfer of antibodies. It is also important to perform PRA status of oncology patients at their 1st hospital visit to enable provision of epitope matched platelet transfusions to prevent the development of refractoriness.

## Platelet Refractoriness

Platelet refractoriness is the repeated failure to obtain acceptable responses to platelet transfusions [7]. Two consecutive platelet transfusions with corrected count increment (CCI) below 7,500 within 10-60 minutes after transfusion is an evidence of refractoriness [8].

Patients who are refractory as a result of HLA alloimmunization are given HLA-matched or crossmatched platelets. But these HLA matched donors can be potential candidates for stem cell harvest in future and patients can develop antibodies to minor antigens causing graft rejection. Another alternative is to provide platelets from donors matched at HLA-epitope level. This is based on the concept that HLA antibodies are produced for epitopes that can be structurally defined as eplets, which are present on different HLA alleles.

### Causes of platelet refractoriness

The causes of platelet refractoriness can be subdivided into immune and non-immune. Alloimmunization against HLA Class I antigens has remained the major immune cause of refractoriness of thrombocytopenic patients to random donor platelet (PLT) transfusions. Non-immune platelet consumption is associated with fever, sepsis, disseminated intravascular coagulation (DIC), splenomegaly and intravenous antibiotics (especially antifungal drugs such as amphotericin B) etc.

### Eplet matched platelet transfusions

HLA epitope matching is expected to benefit platelet transfusion outcome and increase the number of compatible donors for refractory patients. It could lead to new strategies for HLA mismatch permissibility to reduce alloimmunization and thus increase platelet survival. Human leukocyte antigen (HLA) mismatches are important risk factors for HLA alloimmunization and cause an increase in the interval of platelet transfusions. It is known that HLA antibodies recognize epitopes instead of antigens, thus it has become evident that donor-recipient compatibility should be assessed at the epitope level [9]. A computer algorithm called HLA Matchmaker considers each HLA antigen as a series of small configurations of polymorphic residues, referred to as eplets, as essential components of HLA epitopes. By quantifying the total number of antibody-accessible eplet mismatches (EMMs) between donor and patient, the probable success of the donor-recipient mismatch can be estimated [10]. The program evaluates the total number of triplet mismatches between the donor and recipient HLA collection. The triplet algorithm has helped to define the relative immunogenicity of mismatched triplets by analysis of serologic reactivity patterns of highly allosensitized patients. The program can identify the subset of highly immunogenic mismatches (HIMMs) [11]. Validation of this algorithm has been done previously for the prediction of kidney transplant survival [12]. It is hypothesized that platelet donors matched at the epitope level must be considered compatible, even if donor HLA antigens appear mismatched by conventional criteria. Hence, HLA Matchmaker should be applied at the time of HLA matching at epitope level rather than after failure of HLA-matched platelet transfusion. This hypothesis can be best tested by a prospective follow-up of platelet increments. The number of mismatched eplets (EMMs) has been shown to correlate with the CCIs of PLT-refractory patients with lesser; the mismatch more is the CCI [10].

HLA epitope matching approach in immune refractory patients can have very impressive 1 hour CCI results. It can be expected to benefit platelet transfusion outcome and increase the number of compatible donors for refractory patients. Because the HLAMM algorithm provides a quantitative method to measure donor-recipient mismatches, this method can be used for donor selection which will expand the available donor pool while improving PLT transfusion outcomes.

## Summary

HLA plays a crucial role in certain aspects of Transfusion Medicine. The main function of the HLA molecules is to present antigenic peptides to the immune system and thus regulate the induction of immune responses. HLA antigens and antibodies are responsible for some of the serious clinical complications of blood transfusion. HLA alloimmunisation, TRALI, platelet refractoriness, Febrile Non-Haemolytic Transfusion Reactions (FNHTR) etc are some of the complications of blood transfusion where HLA plays a crucial role [13]. This article highlights the HLA related immune mechanisms responsible for complications of transfusions and ways to detect and avoid the same.

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# Early Transfusion vs. Delayed Transfusion of Blood and other Blood Components in Cirrhotic Patients with Active Bleeding

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**Submission:** January 12, 2019; **Published:** March 07, 2019

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**Keywords:** Gastro intestinal; Bleeding; Cirrhosis Blood components; Blood transfusion; Fibrinogen levels; Portal pressures; Platelet transfusion; Bleeding tendency; Blood transfusion evaluations; Variceal bleeding; Haemostatic imbalance

**Abbrevations:** FFP: Fresh Frozen Plasma; UGIB: Upper Gastro Intestinal Bleeding; PT/INR: Pro-Thrombin Time and International Normalized Ratio

## Introduction

Upper gastro intestinal bleeding (UGIB) due to varices in patients with cirrhosis is a major medical problem in the emergency department [1]. It is also a most important indication for resuscitation with blood components. It is important to follow safe and effective blood transfusion strategies in acute variceal bleed patients with cirrhosis, as the concept of early blood transfusion in these patients is questioned nowadays. Over a period of time, the understanding of the coagulopathy in cirrhosis has evolved, as has the management protocol.

## Coagulopathy in Cirrhosis

Cirrhosis is considered as a global multifaceted acquired disorder in hemostasis since; all the blood coagulation products (coagulation factors, platelets and hemoglobin) are deficient in cirrhotic. Because of alteration in hemostasis, normal coagulation pathway is affected at various levels in cirrhosis. There is imbalance between increased yield and decreased production of fibrinogen. Cirrhosis is deliberated as an acquired coagulation disorder in haemostasis rather than a bleeding disorder since fibrinogen levels are also significantly reduced in patients with cirrhosis. Increased transfusion of RBC in patients with cirrhosis is associated with poorer outcome, since it further increases the portal pressures and promotes additional bleeding.

## Transfusion of Individual Blood Components

Application of transfusion strategies in patients with cirrhosis remains puzzling since different guidelines are formulated differently in patients with compensated cirrhosis with mild/clinically significant portal hypertension, with or without varices. Thrombin production is compromised in cirrhotic patients only when the platelet amount declines to less than 50 x 109/L [2]. Platelet transfusion is usually advocated when platelet count drops below 30 x 109/L [3]. No specific recommendations for platelet transfusion exist for patients with cirrhosis. The consequence of fresh frozen plasma (FFP) transfusion has not been assessed during active variceal bleeding and no proposals exist now. It is essential to comment that pro-thrombin time and International Normalized Ratio (PT/INR) are reflected as indicators of liver function and not of coagulation ailments [4]. Baveno VI [5] guidelines state that PT/INR do not represent the bleeding tendency in cirrhotic patients and it cannot be used to monitor blood transfusion evaluations.

Fresh frozen plasma (FFP) is transfused in patients with cirrhosis both therapeutically and prophylactically to correct altered coagulation parameters (PT/INR) [1]. In many studies, it has been reported that FFP transfusion does not show any signifi-

cant improvement in INR in patients with cirrhosis [6]. Hence FFP transfusion in cirrhotic patient had a negligible influence in revising INR below 1.7 [6]. It may be due to a continuing depletion of pre and anti-coagulation factors, altered endothelial function, portal hypertension, sepsis and renal failure in bleeding cirrhotic patients. In view of potential side effects and unspecified efficacy, prophylactic transfusion of FFP based on altered PT/INR values is not suitable in cirrhotic patients. However, FFP transfusion is being transfused in many centers to cirrhotic patients with active bleeding or prior to invasive endoscopy procedures. However, other blood component transfusion necessities are not reduced in patients with cirrhosis [6].

Only few studies have assessed the influence of recombinant factor VII transfusion during active variceal bleeding [7]. No significant conclusions have been gained across various studies. Significant efficacy was achieved only in patients with severe cirrhosis (Child Pugh C) with active bleeding. Recommendation for therapeutic administration is not available for other group of cirrhotic patients. Amending coagulation factors is not considered as part of the variceal bleeding treatment. Transfusion of individual blood components should be customized precisely according to individual patient cirrhotic conditions.

## RBC Transfusion Guidelines

Elliot et al. published a report on the response to transfusion in the management of massive UGIB. They inferred that there was no point in transfusing a patient beyond 48 hours [6]. This can probably be considered as an early pointer towards a restrictive transfusion strategy. In 2003, Barkun et al. [2] in the non-variceal UGIB consensus conference group came forward with the consensus guidelines. The indications for transfusion of blood as per those guidelines were severe bleeding and haemoglobin less than 10g/dL. A current blood transfusion concept in patients with cirrhosis depends on consensus expert opinion. The recent Baveno VI [5] and UK guidelines recommend blood transfusion to be started when the hemoglobin is between 7-8g/dL [8]. For bleeding due to portal hypertension, the guidelines also recommended maintaining a target hemoglobin level of about 8g/dL [9]. These guidelines also recommend considering further patient factors like cardiovascular status, hemodynamic status, age and active bleeding.

## Conclusion

Patients with cirrhosis have an altered haemostatic imbalance. Before resuscitation of bleeding cirrhotic patients, treating surgeon should understand the coagulopathy and bleeding risk in cirrhosis. FFP and platelets transfusion in correcting mild to moderate liver coagulation parameters remains uncertain. RBC transfusion should not be immediately given to a cirrhotic patient with active UGIB. In view of increased transfusion complications and less mortality, delayed transfusion is better than the early one. Further randomized trails comparing early vs. delayed transfusion in bleeding cirrhotic patients are required to substantiate our opinion.

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# Zoonotic Babesiosis- A Growing Concern in Blood Transfusion

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**Abstract**

A common vector borne disease in animals has become a threatening zoonotic disease in man that has even taken transmission through blood. So a growing concern has been pointed out briefly in this paper.

**Keywords:** Babesiosis; Zoonosis; Blood transfusion

## Introduction

Babesiosis is a zoonosis caused by vector borne, intra erythrocytic protozoa of the *Phylum Apicomplexa* transmitted to hosts primarily by tick vector. The disease mostly occurs in the USA, but cases have also been reported in several European countries, in Egypt, India, Japan, Korea, Taiwan, and South Africa. Cattle tick fever and red water fever are common conditions in animals but Babesia spp. have recently emerged as a growing public health concern for humans in many parts of the world. The main pathological event is lysis of erythrocytes resulting in hemolytic anemia, which in severe cases may lead to organ failure and death, particularly in immune compromised patients. The two groups of parasites involved, Babesia microti-like and Babesia sensustricto (s.s.) species, are very much different in their life cycle and susceptibility to anti babesial drugs.

Though there are effective measures to prevent the disease, infection from blood transfusion is particularly difficult to prevent. More over increasing deer populations, wider distribution and greater abundance of ticks are important in causing a major hike in disease occurrence. The growing numbers of immune compromised patients and closer proximity of man-animal habitats also have increased the number of cases. Though previously unreported or under reported, improved medical awareness has resulted a hike in the number of reported cases.

The three major types of Babesia involved in human Babesiosis are *B. microti, B. divergens* and *B. duncani*. The routes of transmission are vector borne (*Ixodid tick*), congenital and through blood transfusion. The nymphs and adult of ticks commonly known as deer tick or black legged tick (*Ixodes scapularis*) are the main vectors of B. microti. The white-footed mouse (*Peromyscus leucopus*), serves as the reservoir host for the parasite. The white-tailed deer (*Odocoileus virginianus*), acts as a maintenance host for adult ticks and there by transports the infected ticks to previously uninfected areas. Cattle are the definitive hosts for B. divergens and Roe deer seems to be the wild reservoir host.

In the last three decades there was tremendous increase in the reported cases of transfusion transmitted Babesiosis caused by *B. microti*. The major risk factor is the asymptomatic donors and lack of a sensitive and specific test to detect the parasite in the erythrocytes of the donors. Incubation period in both natural and transfusion transmitted are same as one to nine weeks. There are reports of Babesiosis in recipients of solid organ transplants (renal and cardiac). The transmission of babesia has occurred during blood transfusion in these cases [1].

There is wide spectrum of diseases that follows Babesia infection which vary from asymptomatic to extremely fatal as in the case of immune compromised and aged patients. The common symptoms noticed are fever, drenching sweat, head ache, chills, myalgia, malaise and hemolytic anemia. Infected animals show varying clinical symptoms such as anorexia, high fever, coffee colored urine and recumbency in severe cases leading to death.

Early diagnosis is the best way to save the patients. In acute cases ring shaped trophozoites can be seen in the peripheral blood smear stained by Geimsa or Wright stain in the erythrocytes or even extra cellular. Serological examination of antibodies in blood plasma, Polymerase chain reaction for

parasitic antigens and animal inoculation are other diagnostic tests. The gold standard for diagnosis of *B. microti* is indirect immune fluorescent antibody test (IFAT) to detect Ig G and Ig M antibodies to this organism [2].

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